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An investigation of cardiac dysfunction and hypoxaemia during epileptic seizures

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Declaration

I have composed this PhD by Research thesis entitled 'An investigation of cardiac dysfunction and hypoxaemia during epileptic seizures' and all non-referenced contents represent entirely my own work.

Ruth Brotherstone
20th February 2012.

Acknowledgements & Dedication

After working in Neurophysiology for 20 years as a physiologist I had some research questions I wanted answers to. Family and work commitment has meant that this study has been accomplished on a university part time basis and entirely in my own time. Initially, the first two years was a masters degree by research, the University of Edinburgh agreed re-registration of this work to PhD.

Being given the opportunity to research my own questions has been both a privilege and a sacrifice and has required selflessness and selfishness in achieving it.

Acknowledgements

I am grateful for the opportunity of this research and would like to sincerely thank Dr Ailsa McLellan, Consultant Neurologist at the Royal Hospital for Sick Children in Edinburgh for her time, direction and support in this work from the beginning. I would also like to thank Professor Peter Sandercock, Western General and Professor Robert Minns, Child Life & Health, Edinburgh for their academic supervision. I am indebted to Dr Stig Hansen, Clinical Scientist at the Southern General in Glasgow for converting my data by NeuroScope software for me to analyse cardiac vagal tone during sub-clinical seizures. Without Dr Hansen's goodwill, this part of the study would not have been possible. I would like to thank Dr Neil Grubb, Consultant Cardiologist at the Royal Infirmary in Edinburgh for his guidance on cardiac corrected Q-T. I am also grateful to my colleague Bethia Blackhall, physiologist/cardiographer for her time and expertise in measuring data for inter-observer analysis and Cat Graham, Bio-statistician, Wellcome Trust & Jenny Leishman, Edinburgh for their time, expert advice and patience in giving me guidance in performing statistical analyses.
I would like to thank my family and colleagues for their support and to the Department of Clinical Neurophysiology, Area Service in Edinburgh for NHS Lothian for access to electroencephalographic data for this study. I am particularly grateful to Katie Alps who provided the opportunity for me to embark on this study.

Dedication

I would like to dedicate this thesis to the victims and their families who have suffered from sudden unexpected death in epilepsy.

Forward

Epilepsy and Sudden Unexpected Death in Epilepsy

Epilepsy is defined as 'recurrent (two or more) epileptic seizures, unprovoked by any immediate identifiable cause. The epileptic seizure is defined as the clinical manifestation of an abnormal and excessive discharge of a set of brain neurones. The manifestation is a sudden transient phenomenon that may include alteration of consciousness, motor, sensory, autonomic or psychic events which are perceived either by the individual or by an observer '(International League Against Epilepsy 1989).

Classification of epilepsy is grouped into generalised epilepsies and focal epilepsies. Seizures can begin as a focal seizure and then become generalised (secondary generalised). Focal seizures can affect any part of the brain and may or may not lead to impairment of consciousness (simple or complex focal seizure) or complete loss of consciousness. Classification tables have changed over the years in the attempt to arrive at an internationally agreed description of all seizure types known. (International League Against Epilepsy 2005 appendix). For the purposes of this study for seizure alarm trigger levels, distinction is made for simple focal and complex focal seizures and are further categorised into temporal or frontal seizures and laterality.

Depending on which area of brain is involved during the epileptic discharge various clinical manifestations occur. The semiology of the seizure can sometimes provide indications as to what seizure type is involved. Electroencephalographic changes can also give supporting evidence in determining the seizure type.

The prevalence of seizure disorders in children is estimated at 15-20 per thousand of the general population (Wheless et al. 2002) compared to that of 7 per thousand of adults (Brown et al. 1991).

Each year several children are admitted to hospital having been found by their parents in the morning after convulsing for an unknown time in the night. Undetected prolonged nocturnal seizures can be fatal or result in significant morbidity due to hypoxic brain damage (Brown et al 1991). Parents have a constant dread of their children having seizures in the night, which are undetected and they have voiced the need for a reliable alarm system.

The diagnosis of epilepsy carries an excess mortality that is 2-3 times higher than the general population (Cockerall et al 1994) and official statistics report around 1000 deaths due to epilepsy in the UK each year. In chronic epilepsy sudden unexplained death in epilepsy (SUDEP) is a major cause of excess mortality and risk of premature death from SUDEP in individuals with intractable epilepsy is 1:200/year (Nashef et al 1995). The following definition of sudden unexpected death in epilepsy (SUDEP) has been proposed. 'Sudden, unexpected, witnessed or un-witnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicological or anatomical cause of death' (Nashef 1997).

Reported risk factors for SUDEP include young age, uncontrolled epilepsy and seizures occurring in sleep (Shorvon 1997). Death in epilepsy can occur because of SUDEP, due to intrinsic factors and in most witnessed cases

attempts of resuscitation are unsuccessful (Nouri 2011). Death can also occur because of unfortunate body positioning as a consequence of the seizure and an obstructed airway and in these cases timely assistance can prevent fatality (Langan et al 2000).

The reliability of seizure detection from several commercially available alarm systems revealed a high incidence of false alarms, with false alarms demonstrating a ratio of approximately 1 positive: 10 false alarms and accurate seizure detection of only 17% of clinical seizures (Brotherstone 1992) The high incidence of false alarms was due to normal physiological events which is a potential source of anxiety for parents. Furthermore, parents will ignore an unreliable alarm system if they do not believe that the device is accurate. No recent systematic review of the reliability of the different types of seizure alarms has been evaluated in the literature. However, each manufacturer claims reliability of their product.

Autonomic symptoms frequently occur during epileptic seizures and range from subtle to life threatening manifestations (Baumgartner et al 2001). Causes of SUDEP are unknown at this time, despite continued investigation by researchers for over one hundred years (Nashef 2000). The cause of SUDEP is believed to be multifactorial involving intrinsic respiratory, cardiac and autonomic mechanisms (Hirsch et al 2011, Nouri 2011, So et al 2000, Nei et al 2004).

Central apnoea is considered to be one of the main contributing factors of SUDEP and is the immediate event before death. In witnessed SUDEP cases, seizures had stopped and in some cases the victims regained consciousness, before then having difficulty breathing, followed by respiratory arrest

(obstructive and central) and attempts of cardiopulmonary resuscitation were unsuccessful (Nouri et al 2011).

Post-ictal apnea is described in a case study by So et al, 2000, where the patient had been monitored with electroencephalographic videotelemetry during a convulsive seizure that been followed by a period of central apnoea and then cardiac arrest. Cardio-respiratory resuscitation was successful in this case and there had been no evidence of obstructive apnoea. Successful resuscitation in patients with cental apneoa is very rare (Dashief & Dickinson 1986). The authors proposed a SUDEP mechanism of postictal central apnoea.

Central apnoea is believed to be the result of epileptic seizure activity directly or indirectly affecting brainstem respiratory centres via an intense discharge of electrical activity constituting a type of channelopathy (Nashef et al 1997). In a series of witnessed cases of SUDEP, 67% of victims had breathing difficulties following the seizure and cyanosis Nouri et al 2011.

In cases of obstructive apnoea from seizures, Dr Devinsky, Director of the Comprehensive Epilepsy Center, New York University reported by Garuchin from The New York Times in July, 2010 explained that most victims are found face down following a seizure. If someone has an obstructed airway, normally they would roll over but following a seizure they don't because of their "reflexes are reduced." This is why timely assistance is so important to prevent fatalities in these cases of obstructive apnoea.

Hypoxia is the commonest cause of cardiac arrest in infants and children (Carter 1993). A theory of neuro-modulation of respiration is affected during

a seizure discharge altering central mechanisms of regulating phrenic activity (Williams 1989).

Monitoring respiration was not included in this study as patients would have had to wear nasal and mouth thermistors plus two chest strain gauges (one monitoring chest and one monitoring abdominal respiration) in addition to a full set of 23 scalp electrodes and oxygen saturation and modified lead II ECG. Ideally respiration should have been monitored but this was not practical or would have been tolerated by most patients. Instead oxygen saturation was monitored throughout to analyse hypoxia whether it was resultant from central or obstructive apnoea. This was important to assess for the purposes of the study as to whether oximetry would be an important parameter to include in a seizure detection device

Fatal cardiac arrhythmias are also believed to be another main contributing factor in SUDEP (Nouri 2011, Cheung et al 2000). A 'channelopathy' or sudden excessive ion transmission triggered by neural seizure activity is proposed causing an 'electrical accident' of the myocardium, particularly on waking. This 'channelopathy' has been described as a possible cause of instability in cardiac rhythm, particularly during nocturnal seizures, where predominant vagal tone and bradycardia exists during sleep which is suddenly replaced by sudden and extreme sympathetic tone and tachycardia, hypothetically potentially inducing a cardiac arrhythmia in pre-disposed individuals (Nouri 2011, Ansakorpi et al 2004). At autopsy, for some victims of Sudden Unexplained Death in Epilepsy, evidence of excessive amounts of catecholamines have been found in myocardium suggesting massive sympathetic activity around the time of death. This change from vagal tone to sudden sympathetic tone is greatest in young

adults in their 20's as their baseline vagal tone is higher compared to young children and older adults. This may explain why the incidence of SUDEP is highest in young adults (Nei et al 2004).

It is with these factors in mind that I decided to analyse heart rate changes and alteration of oxygen saturation during different types of seizures in a wide age range of patients.

Abstract of Thesis

Epileptic seizures are often un-witnessed and can result in hypoxic brain damage or can be fatal due to injuries, status epilepticus or sudden unexpected death in epilepsy (SUDEP). The first aim of this thesis was to investigate some of the physiological parameters that accompany an epileptic seizure and may be useful in a seizure alarm system. The second aim was to investigate aspects of cardiac dysfunction during clinical and sub-clinical seizures that may be potential contributing factors in SUDEP. Percentage heart rate change and oxygen saturation were studied prospectively during 527 epileptic seizures in 50 patients aged from one-day full term neonate to 60 years with a variety of seizure types (absences, generalised tonic clonic seizures, myoclonic seizures, tonic seizures and focal seizures) and in normal physiological events (e.g. coughing, turning in bed). Higher percentage heart rate change occurred during epileptic seizures (21.8%) than during normal physiological events (16.4%) $p<0.001$. Diagnostic testing of clinically significant seizures i.e seizures that could potentially lead to serious consequences if left undetected (n=61) had a sensitivity of 91% and specificity of 75% when percentage heart rate change and hypoxaemia parameters were combined. Percentage heart rate change and oxygen saturation could be used as reliable indicators of a seizure when set at specific levels and distinguish clinically significant seizures from normal physiological events. These parameters can now be used to develop a reliable alarm system to detect epileptic seizures at night. Prolongation of QTc and increased vagal tone may be possible mechanisms underlying SUDEP. Corrected Q-T cardiac re-polarisation time 5 minutes before and throughout 156 epileptic seizures were analysed using four corrective formulae (Bazett, Hodge, Fridericia and Framingham). All formulae indicated statistically significant lengthening of the corrected Q-T during epileptic seizures ($p<0.001$) compared to pre-seizure values. All formulae agreed that the greatest lengthening of the corrected Q-T beyond normal limits occurred during right temporal lobe seizures in two patients. Reflex and tonic vagal activity utilising R-R intervals was assessed in 33 sub-clinical seizures occurring during stages 3 or 4 sleep and was compared to matched counts of R-R interval non-ictal baseline studies from the same stage of sleep in each patient. Altered vagal activity occurred during total sub-clinical seizures compared to baseline studies ($p<0.001$). Lengthening of the corrected Q-T and changes in cardiac vagal tone during epileptic seizures may have a role in the patho-physiology of SUDEP.

Introduction

The diagnosis of epilepsy carries an excess mortality that is 2-3 times higher than the general population (Cockerall et al 1994) and official statistics report approximately 1000 epilepsy-related deaths occur in the UK each year (Hanna et al 2002).

Death in epilepsy can occur due to unfortunate circumstances at the time of the seizure, for example someone having a seizure while bathing and then drowning while unconscious. If the unfortunate circumstance of bathing at the time of the seizure had been avoided then death may also have been avoided. However, death in epilepsy can also occur due to Sudden Unexpected Death in Epilepsy (SUDEP) where there are no obvious circumstances. The causes of SUDEP are unknown at this time but believed to be multi-factorial involving altered autonomic and cardio-respiratory control. In chronic epilepsy sudden unexpected death in epilepsy is the main cause of excess mortality and risk of premature death from SUDEP in individuals with intractable epilepsy is 1:200/year (Nashef et al 1995). Reported risk factors for SUDEP include young age, uncontrolled epilepsy and seizures occurring in sleep (Shorvon 1997).

The aim of this thesis is to make a contribution to knowledge by firstly investigating whether a seizure alarm system could be reliably based on percentage heart rate change and oxygen saturation parameters. Secondly, two areas of cardiological dysfunction were investigated that may underlie SUDEP mechanisms.

A reliable seizure alarm could be used to identify nocturnal seizures and alert family/ carers to assist in providing rescue medication during

prolonged seizures and allow repositioning of the body following the seizure. A reliable alarm system would be of benefit to those people who have seizures that are amenable to intervention.

Each year several children are admitted to hospital having been found by their parents in the morning after convulsing for an unknown time in the night. Undetected prolonged nocturnal seizures can be fatal or leave the child brain damaged due to hypoxia (Brown et al 1991). Parents have a constant dread of their children having seizures in the night, which are undetected and they have voiced the need for a reliable alarm system.

In an increasingly elderly population and the increased incidence of seizures in the elderly (Sander et al 2004), proportionally more elderly people living alone are at risk of having undetected seizures in the home. A seizure alarm system that could be worn as a wrist watch style device and could wirelessly alert a central care centre similar to the community alarm call system would be an additional improvement to what is available at the moment.

Sections two and three of this thesis investigates two possible underlying cardiological mechanisms involved in SUDEP. Section two is the analysis of cardiac re-polarisation during seizures and whether lengthening of the corrected Q-T occurs which could be identified as a cardiac risk. Section three is the investigation of cardiac vagal tone during sub-clinical seizures where reduced heart rate variability may also be considered to be a separate risk factor contributing to sudden death in epilepsy.

SUDEP is rare and it is difficult to determine what the causes are without evidence during the event. The purpose of this study is to observe and report two physiological findings during epileptic seizures that are considered risk

factors of sudden cardiac death in other diseases and compare these findings to people with epilepsy. By increasing our knowledge in these areas then we may come a little closer to identifying possible causes of SUDEP. Research in lengthening of corrected QT during seizures and vagal tone during sub-clinical seizures is new ground and no large epidemiological studies have been performed as yet. The findings from sections two and three in this study are indicative that larger studies may be important.

In section one, XLTEK Digital 32 Channel Electroencephalography (EEG) Videotelemetry system with simultaneous modified lead II electrocardiography (ECG) and pulse oximetry were used to identify seizures clinically and electrographically. Fifty patients with epilepsy were monitored with an age range of a one-day full term neonate to 60 years and 3 months, with a mean age of 14 years 7 months calculated for the group. Percentage heart rate change was analysed during 527 seizure events over 9 second epochs with group statistical significance of $p<0.001$. Oxygen saturation changes were measured over matching epochs during 494 seizure events, again with group statistical significance of $p<0.001$. The total seizure group was then divided into "clinically significant" seizures (61) and "clinically insignificant" seizures (466). Total seizures consisited of generalised seizures (164), subdivided into generalised tonic-clonic seizures (11), tonic seizures (90), absences (35) and myoclonus (28). Complex focal seizures (260) consisting of frontal lobe (229) & temporal (31). Simple focal seizures (102) seizures could not be diagnostically tested as a separate group as the majority of data came from one patient but were included in the total data. In addition to the total seizures neonatal seizures (10) and sub-clinical seizure activity (83) were analysed seperately. Each category, group and sub-divided groups of seizure type were analysed using one sample t-tests for

percentage heart rate change during each event. Paired t-tests were applied for oxygen saturation change comparing values before and during each event.

A total of 496 normal physiological events were identified using the video-telemetry system. Percentage heart rate and oxygen saturation were analysed using one sample t-tests and paired t-tests respectively. High statistical significance of $p<0.001$ was calculated for both parameters. Sub groups of arousal (190), coughing (34), crying (15), laughing (22), sneezing (10), stretching (36) turning over in bed (141) and yawning (48) were measured and statistically analysed.

Diagnostic testing of percentage heart rate change and percentage oxygen saturation was used to compare changes during epileptic seizures to that of normal events. This type of testing was performed for total seizures, clinically significant seizures (sensitivity 79%, specificity 75%) clinically insignificant seizures (sensitivity 45%, specificity 49%) and each type of seizure group. Impressive diagnostic testing results are calculated for generalised tonic-clonic seizures with sensitivity of 88% and specificity of 85%.

An average oxygen saturation level of 86.9% was recorded during (49) clinically significant seizures compared to an average oxygen saturation level of 97.2% during 430 clinically insignificant seizures. When diagnostic testing is based on combined percentage heart rate change and oxygen saturation, with one/ other/ both parameters reaching their trigger levels, the sensitivity improves further to 91% and specificity stays the same at 75%. This result indicates that if a seizure alarm was triggered because of either percentage

heart rate change or oxygen saturation parameters triggered either independently or together then 91% of clinically significant seizures would be detected. As before, one triggered alarm in every four would be false.

Further research development is envisaged for the future in developing a seizure alarm device. A scientific paper has not been submitted for this section of work because of the intention of further research and patency.

In section two, one hundred and fifty nine (159) seizures were analysed for changes in corrected Q-T from thirty-nine (39) patients from the original study group before and during the seizure and analysed using Bazett, Hodge, Fridericia and Framingham corrective formulae. All formulae agreed statistically significant lengthening of the corrected Q-T ($p<0.001$) occurred during total seizures compared to pre-seizure values. Maximum changes in corrected Q-T occurred during generalised tonic-clonic seizures (403 milliseconds increased to 490 milliseconds) and during focal seizures arising from the right temporal lobe with increases of up to 512 milliseconds corrected Q-T according to Bazett's formula.

Correcting Q-T for heart rate values are dependent on which formula is used. Bazett's formula identified 21 seizures from 9 patients, Hodge's formula identified 7 seizures from 4 patients, Fridericia's formula identified 6 seizures from 4 patients and Framingham identified 3 seizures from 3 patients that lengthened the corrected Q-T beyond clinically normal limits. However, all formulae agreed on the identification of two patients as prolonging their corrected Q-T during a right temporal lobe seizure and a sub-clinical right temporal lobe seizure.

A scientific paper was reviewed, accepted and published in Epilepsia medical journal Epilepsia, 51(2):221–232, 2010 (doi: 10.1111/j.1528-1167.2009.02281.x) based on section two entitled "Lengthening of corrected QT during epileptic seizures" (appendix).

Section three grew from observations during section one of this research. Individual heart rate and oxygen saturation profile graphs were plotted for every patient of their seizures. It became apparent that heart rate appeared "stereotyped" during the tonic phase of a generalised tonic clonic seizure, then accelerating during the clonic phase. This compared to a gradual increase in heart rate during focal seizures. There appeared to be a difference in heart rate control during a generalised tonic clonic seizure and a focal seizure and this then posed the question whether heart rate variability was affected differently in the two types of epileptic seizures.

My initial interest was investigating heart rate variability during clinical seizures but discovered that interpreting results using these measures would be impossible due to the physical element of the seizure directly affecting sympatho-vagal balance. It also became apparent that no epidemiological studies have been performed in people with epilepsy and therefore no normative data was available to compare results to. However, the NeuroScope offers a general range of normal values to initially compare the study results to. Sub-clinical seizures were identified and analysed instead of clinical seizures to eliminate any distortion of results due to physical effect on vagal tone measurements.

In section three cardiac vagal tone/parasympathetic activity and heart rate variability were analysed during 33 sub-clinical seizures from 11 original

study group patients. Sub-clinical seizure data was compared to resting data with patients acting as their own controls. Strict criteria was used in selecting the 33 sub-clinical seizures in that they all had to occur during slow wave sleep so that breathing rate was constant throughout and would not influence results. Forty-five sub-clinical seizures were excluded from this study, as they did not meet the criteria of sub-clinical seizures occurring during slow wave sleep.

Clear altered cardiac vagal tone/parasympathetic activity occurred during total sub-clinical seizures in both Cardiac Index of Parasympathetic Activity (CIPA) $p<0.001$ and 5minute Heart Rate Variability (HRV) HF% $p=0.026$ compared to matched baseline data. Generalised sub-clinical seizures resulted in increased cardiac parasympathetic activity and low coefficient of variation of R-R intervals compared to a decrease in cardiac parasympathetic activity and high coefficient of variation of R-R intervals during temporal lobe seizures. Decreased heart rate variability is used as risk stratification for cardiac death in post-myocardial infarction patients. Decreased heart rate variability occurred during generalised sub-clinical seizures compared to focal seizures and reduced heart rate variability may be an underlying risk factor for SUDEP in predisposed individuals with lowered physiological thresholds compared to others.

A scientific paper has been submitted and accepted for publication in February 2012 by Seizure medical journal based on section three entitled "Parasympathetic Alteration during Sub-clinical Seizures" (appendix)

To conclude, percentage heart rate change and oxygen saturation percentage can be used as physiological parameters to reliably distinguish clinically

significant seizures especially generalised tonic-clonic seizures from normal events. Lengthening of the corrected Q-T, increased vagal tone and decreased heart rate variability may be contributing factors in the physiological mechanisms underlying SUDEP in pre-disposed individuals.

LIST OF CONTENTS

Chapter 4: Results: Generalised Seizures

Statistical results and diagnostic testing in percentage heart rate and oxygen saturation percentage for:

1.4.1 Generalised Tonic Clonic Seizures.
1.4.2 Tonic Seizures.
1.4.3 Absences.
1.4.4 Myoclonus
1.4.5 Summary

Chapter 5: Results: Focal Seizures

Statistical results and diagnostic testing in percentage heart rate and oxygen saturation percentage for:

1.5.1 Frontal Lobe Seizures.
1.5.2 Temporal Lobe Seizures.
1.5.3 Simple Focal Seizures
1.5.4 Neonatal Seizures.
1.5.5 Sub-clinical Seizures.
1.5.6 Summary.

Chapter 6: Results: Normal Physiological Events

Statistical results in:-

1.6.1 Total Normal Physiological Events
1.6.2 Arousal
1.6.3 Coughing.
1.6.4 Crying.
1.6.5 Laughing.
1.6.6 Stretching.
1.6.7 Sneezing.
1.6.8 Turning over in bed.
1.6.9 Yawning.
1.6.11 Maximum, mean and minimum values.

Chapter 7: Results

1.7.1 Intra and Inter-observer Analyses.
1.7.2 Proposed Device Characteristics
1.7.3 Epileptic Seizure Alarm Epoch Analysis Method.
1.7.4 Proposed Trigger Levels for Seizure Detection.

Chapter 8: Section One Discussion and future studies.

1.8.1 Discussion.
1.8.2 Further Studies
1.8.3 Section One Conclusions.

Section Two

Lengthening of Corrected Q-T during Epileptic Seizures

Chapter 9: Introduction

Chapter 10: Methodology

Chapter 11:Results

According to Bazett's Formula

Chapter 12: Results

According to Hodge's Formula

Chapter 13: Results

According to Fridericia's Formula

2.5.1 Total Seizure Group
2.5.2 Generalised Seizures
2.5.3 Complex Focal Seizures
2.5.4 Sub-clinical Seizures
2.5.5 Right and Left Hemisphere Focal Seizure Comparison
2.5.6 Corrected Q-T Prolongation exceeding 60 milliseconds
2.5.7 Summary

Chapter 14: Results

According to Framingham's Formula

2.6.1 Total Seizure Group
2.6.2 Generalised Seizures
2.6.3 Complex Focal Seizures
2.6.4 Sub-clinical Seizures
2.6.5 Right and Left Hemisphere Focal Seizure Comparison
2.6.6 Corrected Q-T Prolongation exceeding 60 milliseconds
2.6.7 Summary

Chapter 15: Inter and Intra-observer Analyses

2.7.1 Results
2.7.2 Kappa

Chapter 16: Comparison of results according to Bazett's, Hodge's, Fridericia's and Framingham's Formulae.

2.8.1 Total Seizure Group
2.8.2 Formulae Identified Corrected Q-T Prolongation Seizure types and Patients
2.8.3 Characteristic Differences and Similarities of Corrective Formulae
2.8.4 Sensitivity and Specificity of Hodge's, Fridericia's and Framingham's Formulae in comparison to Bazett's Formula
2.8.5 Summary

Chapter 17: Linear Regression Plots

2.9.1 Temporal Lobe Seizures
2.9.2 Sub-clinical Seizures
2.9.3 Limitations

Chapter 18: Multivariate Analysis on Corrected Q-T and Anti-Epileptic Drugs

2.10.1 Total patients.
2.10.2 Monotherapy. Polytherapy and QTc.
2.10.3 Anti-Epileptic Drug & QTc in relation to Seizure Duration.
2.10.4 Anti-Epileptic Drug & QTc in relation to Gender.

Appendices

Publications
Brotherstone R.E, Blackhall B, McLellan A. Lengthening of the Corrected Q-T during Epileptic Seizures (2010) *Epilepsia* 51(2):221-232
doi 10.1111/j.1528-1167 2009.02281x

Authorisation for Corrected Q-T paper

Accepted for publication (February 2012)
Brotherstone R.E, McLellan A. Parasympathetic Alteration during Sub-clinical Seizures

Aurhorisation for vagal tone paper

ILAE Epilepsy Classification Table.
Adult Patient Information Sheet.
Parent Information Sheet.
Paediatric Senior Information Sheet.
Paediatric Junior Information Sheet.
XLTEK Mobee 32 Equipment Specification Table.
Masimo specifications
Patient Questionnaire.
Ethical Approval Certificate.

Abbreviations & Units

Abbreviations

ACTH	Adrenocorticotropic Hormone.
Bd	Bi-daily (medication dosage frequency).
B-adrenergic	Beta- adrenergic
Ca^{2+}	Calcium ions
CPVT	Catecholaminergic Polymorphic Ventricular Tachycardia
Co.	Company.
ECG	Electrocardiograph.
EEG	Electroencephalograph.
e.g.	For example.
EKG	Electrocardiograph.
EMG	Electromyography.
H^{+}	Hydrogen ions.
Hb	Haemoglobin.
HbO2	Oxyhaemoglobin.
HR	Heart Rate.
Ltd.	Limited.
Mins.	Minutes.
N	Number.
Na^{+}	Sodium ions.
Na/CaX	Sodium/ Calcium Exchanger
NHS	National Health Service
P value	Statistical probability value.
P wave	Electrocardiographic pacer waveform.
PO2	Oxygen percentage.
QRS	Electrocardiographic complex waveforms.
Q-T	Q-T component parts of electrocardiographic waveform
Q-Tc	Corrected Q-T.
ROC	Receiver Operator Curve.
R-R	Electrocardiographic interval.
RyR2	Ryanodine Receptors
SA node	Sino-atrial node.
SAO2	Oxygen saturation.
SAO2A	Actual Oxygen Saturation.
Secs.	Seconds.
SE Mean	Standard Error of Mean.
SPSS	Statistical Package for Social Sciences.
SR	Sarcoplasmic Reticulum
Std.	Standard.
St.Deviation	Standard deviation.
SUDEP	Sudden Unexplained Death in Epilepsy
Tdp	Torsades de Pointes

Tdur	Time during event.(epoch).
T wave	Electrocardiographic re-polarisation waveform.
TC	Time Constant (high pass filter).
VideoEEG	Electroencephalographic Videotelemetry
Yrs.	Years

Units

Hz	Hertz (cycles per second)
30 mms^{-1}	30 millimetres per second
kohms	kilo-ohms
kPa	kilo-pascals
%	Percentage
+ve	Positive electrode
-ve	Negative electrode
nm	nanometres.
<	Less than.
>	Greater than.
$\sqrt{}$	Square root.
uv	microvolts
uv/mm	microvolts per millimetre

Section One

Can Heart Rate changes and Oxygen Saturation parameters be used to Reliably Distinguish Epileptic Seizures from Normal Physiological Events?

Section One List of Figures

Section One List of Figures Page

Section One List of Figures

Section One List of Figures Page

Section One List of Tables Page

Section One List of Tables Page

Section One List of Tables Page

Section One List of Tables Page

1.1.1 Overview of Existing Seizure Alarms

Several types of seizure alarm systems are currently commercially available. Nine different types of seizure alarm systems provided by various manufacturers or charities are considered. Systematic reviews on the reliability of these types of seizure alarms are not found in the literature. Each manufacturer advertising an epileptic seizure alarm claims reliability.

'Support Dogs' is a registered charity, which was established in 1992 and is based in Sheffield. They train rescued dogs to alert their owner of an imminent seizure and to warn them in a positive manner, by raising a paw or barking twice. This allows the person to get into a safe place (Strong 1999). Incredibly, some dogs can sense a seizure between 20-45 minutes prior to it taking place and this gives people living with epilepsy the confidence to lead more independent lives (Stephens 1997). It is believed that the dogs sense chemical changes which are unique to seizure activity. They are trained to alert their owners of these chemical changes, which warn them that a seizure is about to occur.

The cost of training a dog to detect a seizure and warn their owner of an imminent seizure is around £1500. The cost of this training is funded from donations and sponsorship and is not charged to the person who needs the trained dog.

However, the charity does not provide dogs for every person with epilepsy. Generally, children are not included because they are not old enough to be responsible for the dog. The prospective owner also has to be old enough to work closely with the charity and the dog in residential training for a minimum of 170 hours (Support Dogs 1997).

Commercially, two devices tend to be used in detecting seizures in the home. The first is a baby monitor, so that parents or carers can hear a seizure occurring. Seizure detection then depends on the parents not sleeping through the seizure or the seizure not being silent.

The second type of seizure alarm most commonly used is a bed movement alarm. Various manufacturers make this type of alarm e.g. Medpage Ltd, Emfit by Safety Systems Distribution Ltd and Sensorium providing the Sensalert (www.sensorium.co.uk) and the sensor can be adjusted to what the parents believe so it would not miss true seizures or collect unwanted false alarms from child restlessness. A similar type of bed movement alarm system called Epson alarm (no longer available) but used the same technology was found to have a high level of false alarms of 10:1 (Brotherstone 1992). This type of monitor assumes that the seizure would cause a lot of shaking motion. This type of monitor would not be appropriate for someone who has restricted physical movement or has the type of seizures that does not result in clonus.

A similarly intended device measures electromyographic activity (EMG) via sensory electrodes placed on one arm and one leg. The attached device then indicates a seizure by the increased EMG activity, particularly oscillatory activity. This again assumes clonic action during the seizure. It may also be unpleasant being wired up every night or restrictive on changing position during sleep. Detection of shaking (frequency 2-5Hz) using gyroscopes, accelerometers and computer algorithms have been developed for a mobile phone App called "EpDetect" can be downloaded free onto a compatible mobile phone. If it detects shaking of the wearer for more than 10 seconds, it will send a message to carer's re-set phone numbers and give a GPS location

of the person who triggered the EpDetect App (www.EpDetect.com, 2012). Another similar device is the "SmartWatch" from SmartMonitor that detects abnormal movements within 7-10 seconds and alerts carers by mobile phone (www.Smart-Monitor.com, 2012).

Oxygen saturation monitoring seems to be rarely used in the home, yet clinically our attention is often drawn to a patient having a seizure on the ward because of this type of monitor.

Another type of commercially available system is the 'wristcare' monitor, which collects data for pulse, skin temperature, movement and sweat. It is largely used for the elderly in sheltered accommodation and detects cardiac events, hypothermia and epileptic seizures. When triggered it automatically sends a signal to a warden who can then go and assist or call for emergency back up. The accuracy of this device in detecting seizures will depend on pulse during the seizure.

An apnoea monitor is sometimes used in detecting seizures and it will alarm if the person stops breathing for at least 10 seconds. False alarms can be problematic if the body position moves off the pressure sensor mat. In a previous study the apnoea monitor detected 21% of seizures and had a high false alarm rate of 5:1 (Brotherstone 1992).

The remaining devices commercially available are the enuresis alarm supplied by Alert-it.co.uk and a pressure mat placed on the floor. The enuresis alarm assumes that incontinence occurs during every seizure, which is clearly not the case. Finally, the pressure mat is dependent on the person rolling out of bed during a seizure and landing conveniently on the placed

mat! Alert-it monitors also supply bed movement with breathing sensor and bed vacation sensors.

1.1.2 Investigation of Local Utilisation of Existing Seizure Alarms Methodology

Fifty patients completed a questionnaire (appendix) prior to taking part in the study. For comparison, a cross section of 50 patients attending a seizure clinic also completed the questionnaire.

The purpose of the questionnaire was to assess how many people were aware of and had tried to use a seizure alarm device and if so, how useful they found it.

The questionnaire compared age range, seizure frequency, occurrence and clinical manifestations during seizures. The study group and non-study group were then compared. This then established whether the study group was representative of a cross section of people with epilepsy attending the seizure clinic. This is a relevant measure of whether the results from the study group could be representative of a cross section of people attending clinic.

1.1.3 Results

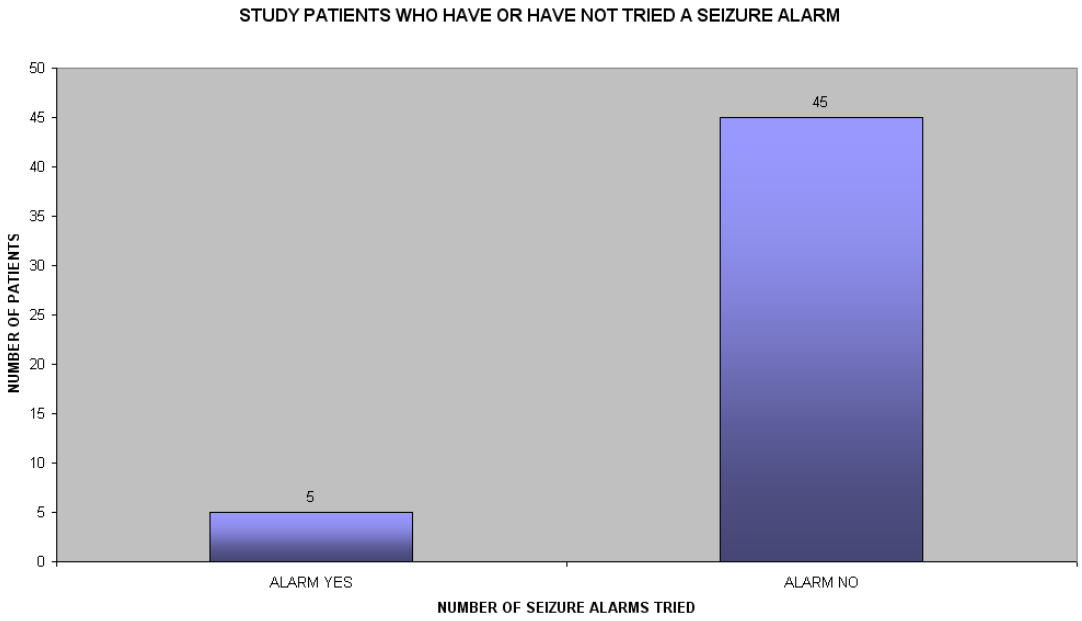


Figure 1 Questionnaire Results: Alarm system for Study Patients Utilisation Graph.

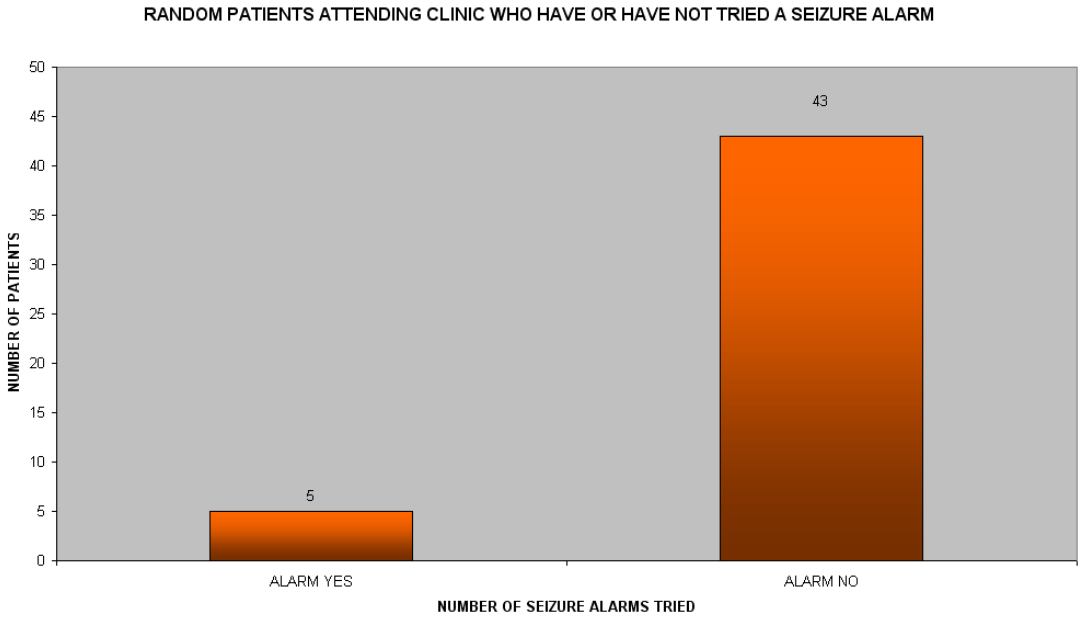


Figure 2 Questionnaire Results: Alarm system for Clinic Patients Utilisation Graph.

Very few people (10%) have tried to use a seizure alarm system (Figures 1&2). Additional comments on the questionnaire indicated that people perhaps were not aware that these devices are available. The devices that were used were either a baby monitor or a bed movement alarm. Those using the baby monitor could only use it because their child made noises during seizures. The accuracy of this device has been described earlier but it also assumes that the child will always make a noise independent of body and cover position. The other consideration is that of brain maturation and the inherent changes in seizure manifestation.

A few people had only recently tried a bed movement device, one person said that it was not suitable and the others commented that they had only recently acquired the system and therefore could not comment on its usefulness at that stage.

Section One

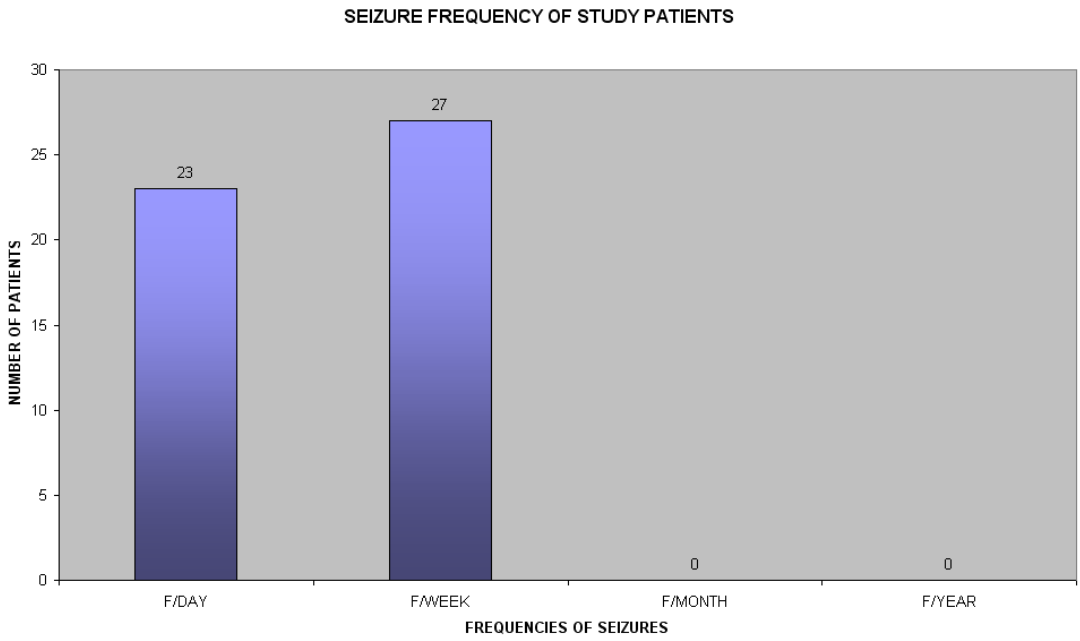


Figure 3 Questionnaire Results: Study Patients Seizure Frequency Graph

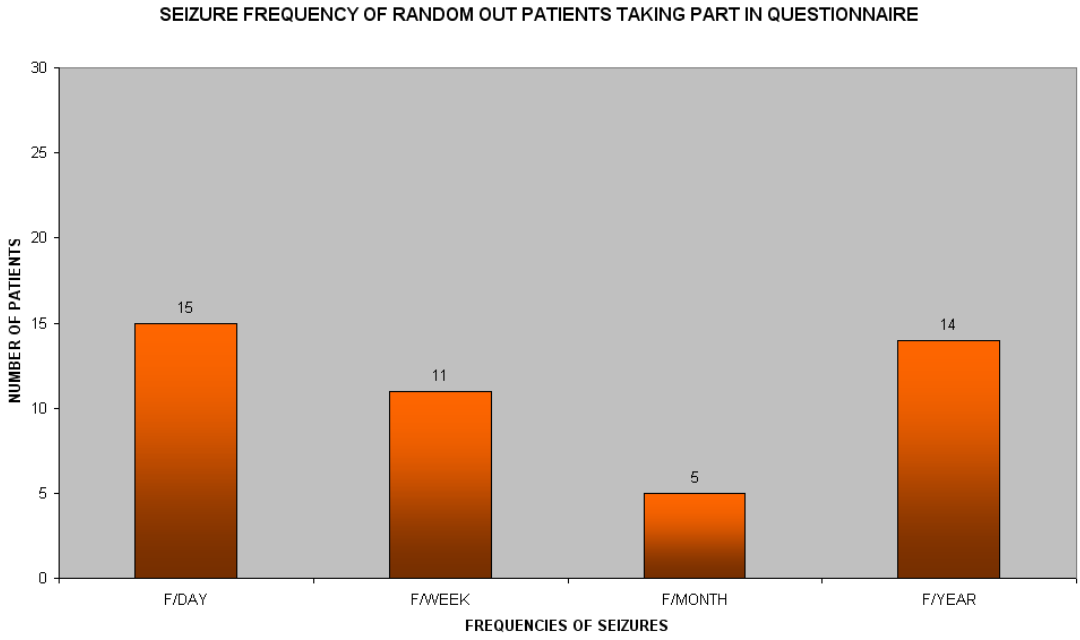


Figure 4 Questionnaire Results: Clinic Patients Seizure Frequency Graph.

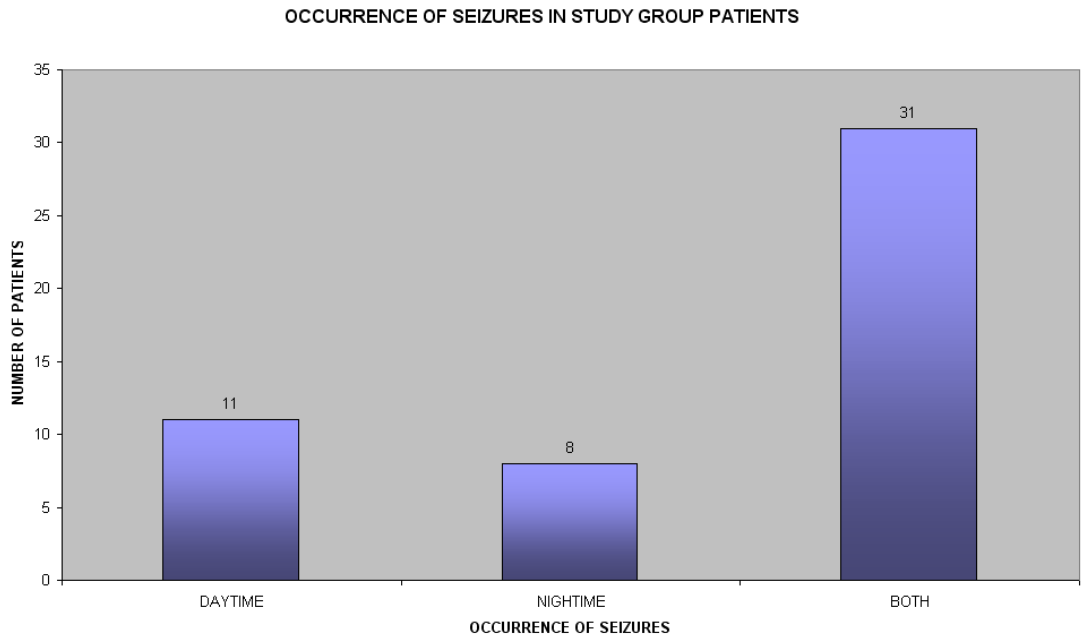


Figure 5 Questionnaire Results: Study Patients Occurrence of Seizures

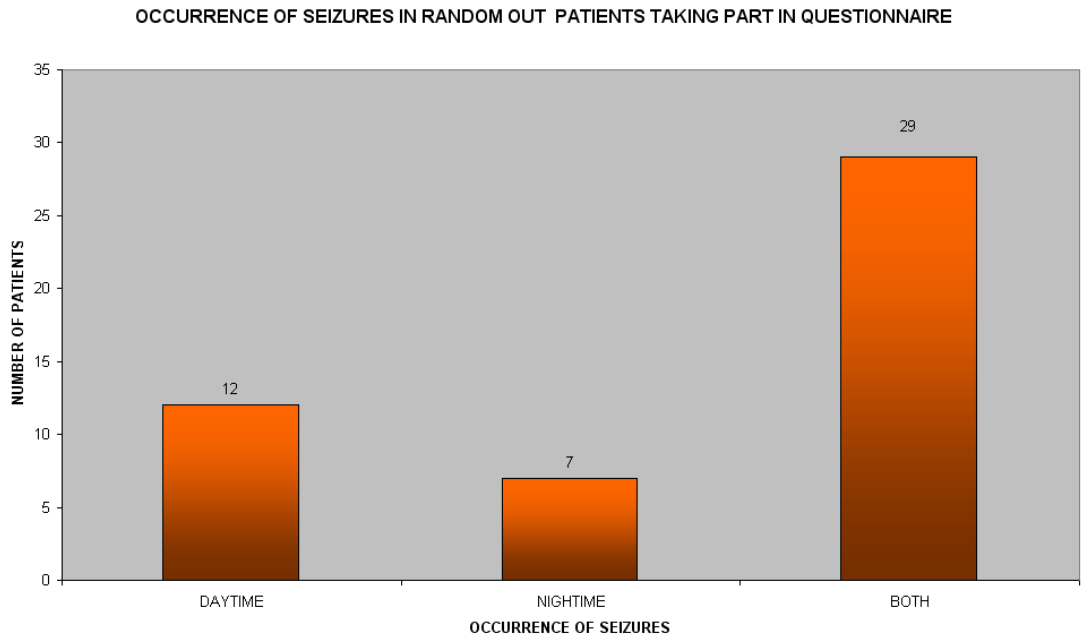


Figure: 6 Questionnaire Results: Clinic Patients Occurrence of Seizures

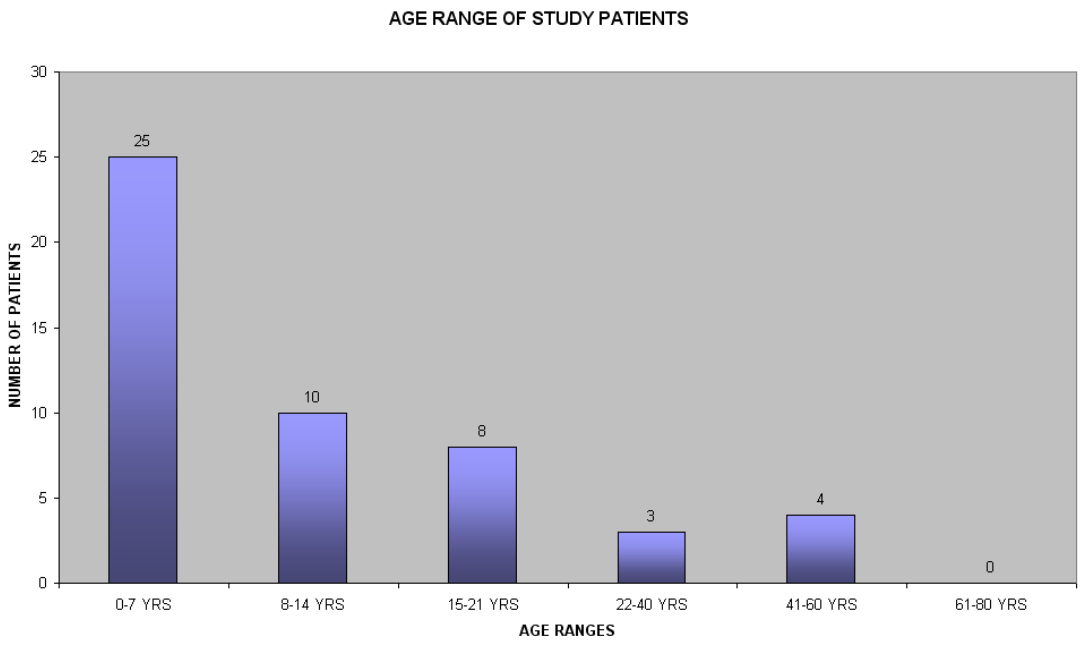


Figure 7 Questionnaire Results: Age Range of Study Patients

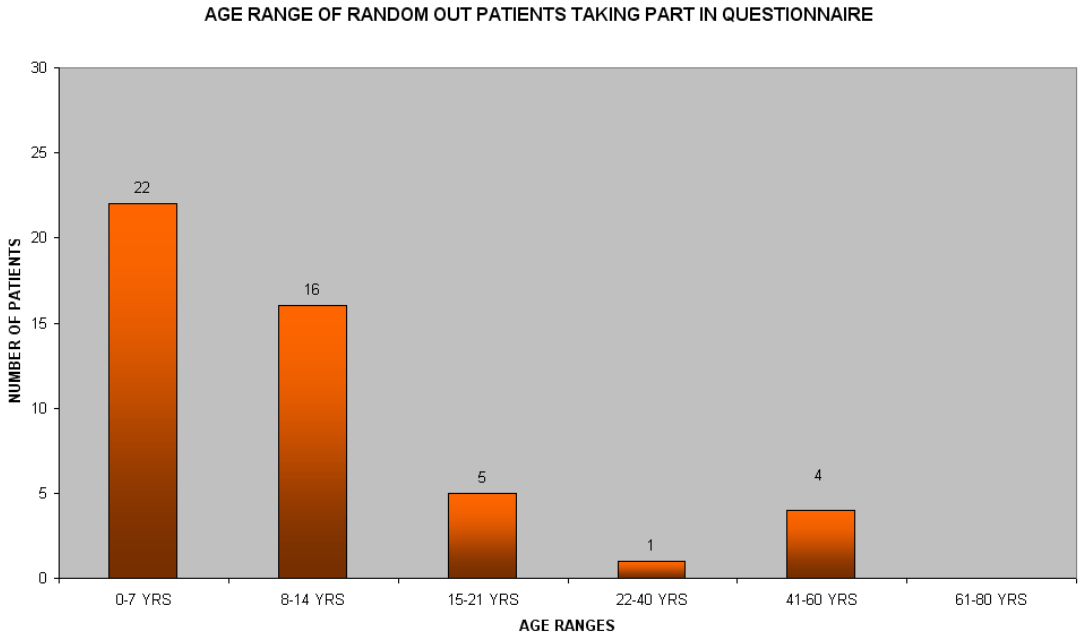


Figure 8 Questionnaire Results: Age Range of Clinic Patients

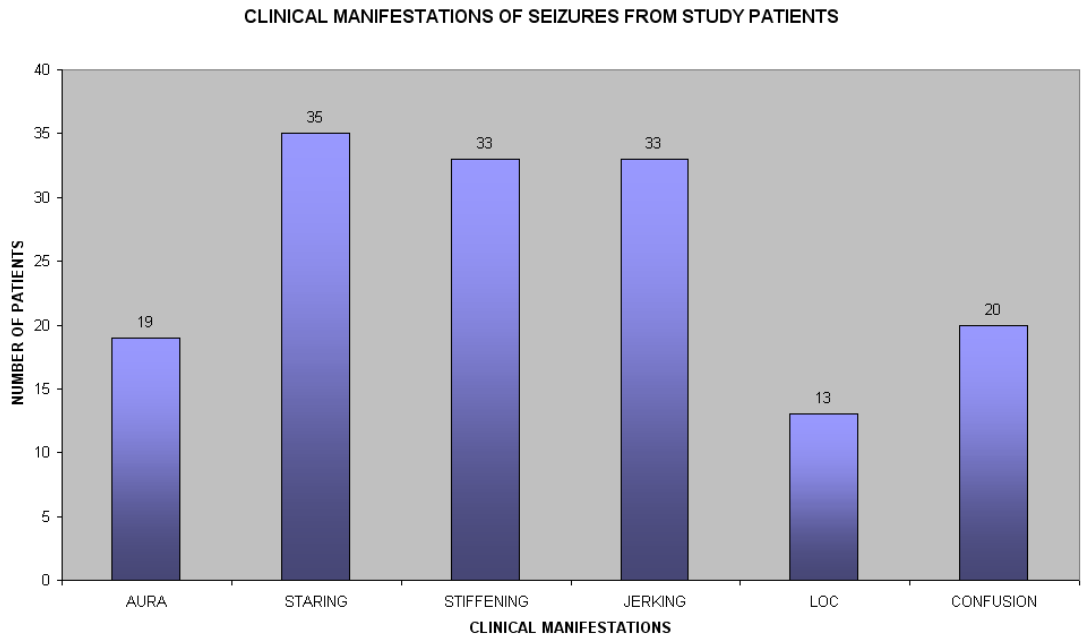


Figure 9 Questionnaire Results: Clinical Manifestations of Study Group Graph

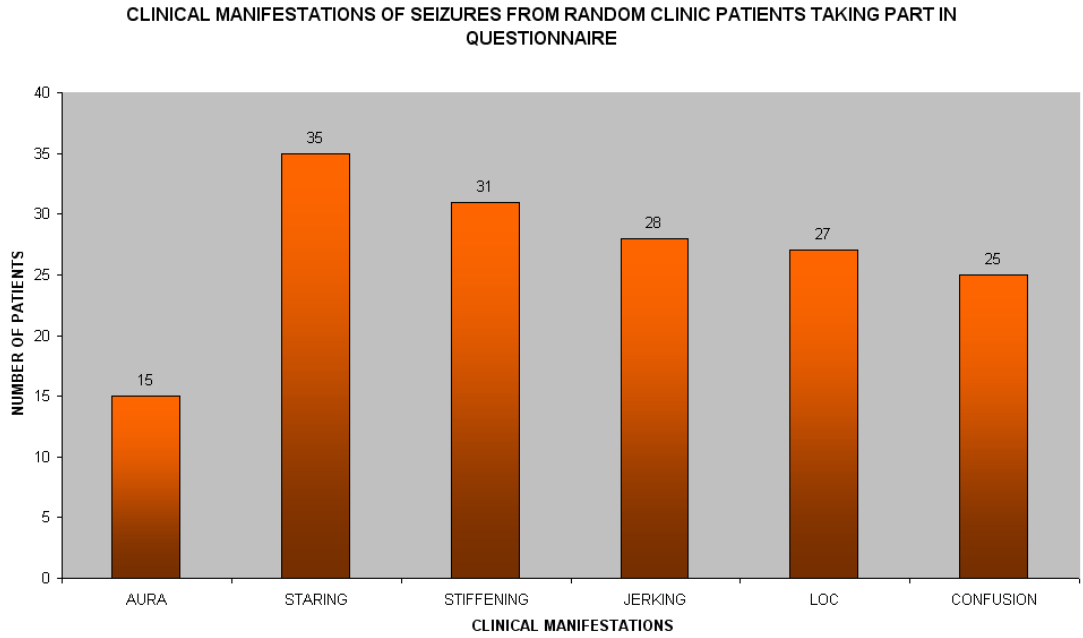


Figure 10 Questionnaire Results: Clinical Manifestations of Clinic Patients Graph.

Occurrence (Figures 5 & 6), age-range (Figure 8) and clinical manifestations (Figures 9 & 10) had similar distribution and therefore suggest that the study group is well matched with a cross section of people attending a seizure clinic.

The only distribution difference is that of seizure frequency (Figures 3 & 4). Those in the study group had seizures either daily or weekly. The non-study group demonstrated a better seizure control with less than half of them having seizures monthly or yearly. The explanation for this difference is because those taking part in the study were included for two main reasons. Firstly, the study group patients were being ethically monitored on the ward primarily for clinical evaluation as their seizure control was not optimal and they were not being monitored solely for the purposes of research. Secondly, if someone is not having a seizure frequency of at least one seizure per week, the likelihood of capturing a seizure while being monitored electrographically is minimal.

The questionnaire has highlighted that perhaps people with epilepsy or their families may not be aware that seizure alarm devices do exist. Perhaps this information is not advertised because generally, the alarm systems are not as reliable as professionals would like them to be. Seizure alert dogs would appear to be the main exception but are not generally available to everyone in need. The study group patients and the cross section of patients attending seizure clinic are similar in distribution of seizure occurrence, age range and clinical manifestations and so the changes seen in this study may be fairly representative of seizure clinic patients generally and not exclusive to this particular group of patients within the study.

Chapter 2 Investigation of Percentage Heart Rate Change & Oxygen Saturation during Epileptic Seizures

ABSTRACT

Objective: To calculate the percentage heart rate change and oxygen saturation during epileptic seizures compared to normal events and to determine accuracy of these parameters for application in an epileptic seizure detection device. ***Methods*** Fifty patients with epilepsy were monitored with an age range of one-day full term neonate to 60 years and 3 months adult. Electroencephalographic video-EEG telemetry monitoring of epileptic seizures with integrated simultaneous modified lead II electrocardiography and pulse-oximetry were used to identify and classify epileptic seizures and a range of normal events. Heart rate was calculated over the proceeding 9 seconds of the event and used as a baseline. The start of each event was identified by clinical changes on the video and simultaneous electrographic changes. Averaged heart rate, percentage heart rate change and oxygen saturation were calculated for each consecutive 9 seconds epoch during each event. The maximum percentage change in heart rate and lowest oxygen saturation value were recorded for each seizure and for each normal event and applied to one-sample Wilcoxon t-testing for percentage heart rate change and paired t-testing for oxygen saturation and diagnostically tested using receiver operator curves for each seizure group. ***Results:*** 527 seizures were analysed for the total seizure group compared to baseline measurements $p<0.001$. Absences (36), simple focal (102), frontal lobe seizures (229), generalised tonic-clonic seizures (11), myoclonus (28), temporal lobe seizures (31) and tonic seizures (90) were identified. A total of 496 normal physiological events were identified and compared to baseline measurements $p<0.001$. Arousal (190), coughing (34), crying (15), laughing (22), sneezing (10), stretching (36), turning over in bed (141) and yawning (48) were measured and statistically analysed. Impressive diagnostic testing results were calculated for generalised tonic-clonic seizures with sensitivity of 88% and specificity of 85% for percentage heart rate change at a specific trigger level. Clinically significant seizures gave a sensitivity of 79% and specificity 75%. When one/ other/ both parameters were diagnostically tested an improved sensitivity to 91% with specificity of 75%. ***Conclusion:*** Percentage heart rate change and oxygen saturation can be used as reliable indicators of seizures when set at specific levels and can distinguish clinically significant seizures especially generalised tonic-clonic seizures from normal events.

1.2.1 Video-Electroencephalography.

Since 1924 when Hans Berger made the first recordings of human electroencephalography, it has been widely accepted that electro-encephalographic activity is generated by postsynaptic potentials. The vertically orientated pyramidal neurons have apical dendrites extending toward the surface and then branch horizontally in the superficial layers of cortex. The dendrites are connected to thousands of excitatory (depolarizing) and inhibitory (hyperpolarizing) synaptic endings (Dinner et al, 1985). The fluctuation of these postsynaptic potentials result in a flow of local currents and it is this electrical activity that is detected by electroencephalography at the scalp surface or invasively from the cortex.

Advances in technology have seen paper electroencephalography machines being replaced by digital systems and now incorporate simultaneous video of the patient. On review, the data can be accurately correlated with what is happening clinically with the patient. Once the data has been recorded referentially, it can be reviewed on any montage selected. The digital system is dynamic with the ability to filter, compress or decompress data and change gain sensitivity retrospectively.

1.2.2 Aims & Objectives

Aims

The aim of section one is to determine whether percentage changes in heart rate and oxygen saturation can be used as reliable indicators in identifying clinically significant seizures, distinct from normal physiological events or

clinically insignificant seizures that could be used in a seizure alarm device in the future.

Objectives

1. Record, measure and analyse changes in percentage heart rate and oxygen saturation during different types of seizures, identified by the use of electroencephalographic video EEG telemetry.

2. Record, measure and analyse changes in percentage heart rate and oxygen saturation during different normal physiological events identified by the use of electroencephalographic video EEG telemetry, to enable comparison of that measured during seizures.

3. To assess these changes in a wide range in age of patients with epilepsy.

4. To analyse results in terms of sensitivity and specificity for heart rate percentage change and oxygen saturation for all clinically significant seizures & clinically insignificant seizures.

5. To analyse results in terms of sensitivity and specificity for heart rate percentage change and oxygen saturation for each seizure classification included in the study (International League Against Epilepsy 2005) of epilepsy monitored in this study for focal seizures and generalised seizures. However, the seizures are further analysed in terms of "complex focal" for seizures with patient loss of awareness and "simple focal" seizures without patient awareness. This further analysis is important for

differentiating "clinically significant seizures" from "clinically insignificant seizures" for the purposes of determining trigger levels for a seizure alarm.

Null Hypothesis

No distinction can be made between epileptic seizures and normal events using percentage heart rate change and oxygen saturation.

1.2.3 Methodology

Patients were invited to take part this prospective study whom most of them were already familiar with having electroencephalographic studies on previous occasions and had agreed to receive this type of monitoring as part of their clinical management of their epilepsy at the Royal Hospital for Sick Children or Western General hospitals, Edinburgh.

Ethical and Management Approval was given before the study commenced. (Ethical Approval reference number LREC/2003/6/22).

Patient information sheets were sent prior to ward admission to give patients and parents an opportunity to ask questions. A junior patient information sheet was appropriately worded for age comprehension to explain the study to children aged 5-12 years (appendix) and a senior information sheet (appendix) was designed for an age range of 13-17 years. Separate parent information sheet and consent form were also included (appendix).

During patient preparation, 23 stick-on surface silver silver-chloride 9 mm electrodes (supplied by Specialised Laboratory Equipment) (Figure 11) were placed on the scalp using the International 10:20 system (Cooper et al) (Figure 13). This ensured that the potential difference recorded between pairs of bi-polar connections (Tables 1 & 2) were symmetrically comparable for each hemisphere. This provided full coverage of all accessible scalp areas, including surface sphenoidals. Prior to electrode application the scalp electrode site was scarified by gently abrading the scalp using a cotton bud with 'Nuprep' (supplied by UniMed Electrode Supplies).

Figure 11 Stick-on 9 mm silver silver-chloride electroencephalographic electrodes. Supplied by Specialised Laboratory Equipment.

The electrodes were attached to the scalp using collodion glue and dried with an air compressor. Spectra conducting saline gel were introduced via a disposable blunted needle (Figure 12) and syringe through the electrode access point. Further scarification using the disposable blunted needle was not usually required to achieve impedances below 10 kilo-ohms (kohms). The collodion glue, spectra gel and disposable blunted needles were supplied by Specialised Laboratory Equipment Ltd.

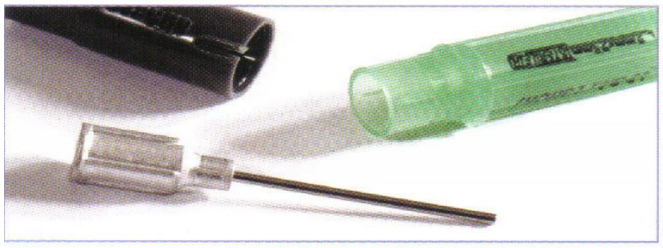


Figure 12 Disposable blunted needle.

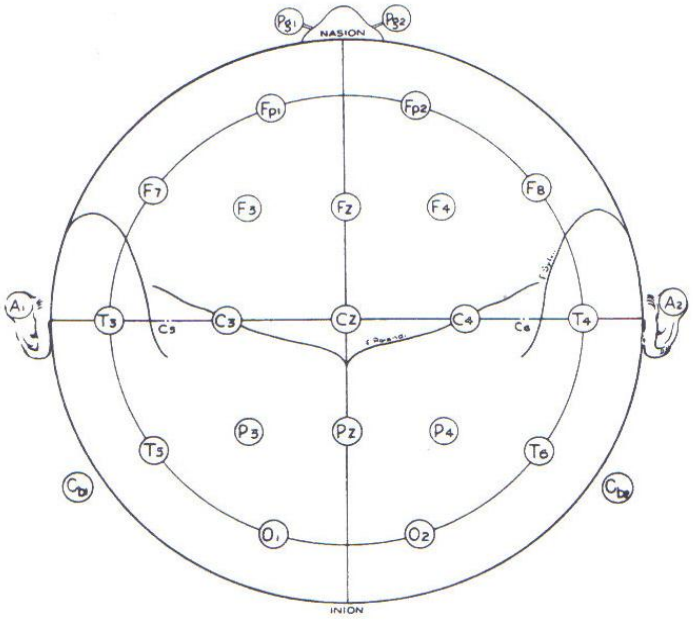


Figure 13 Diagram of International 10:20 System (Cooper et al.2003).

The electrocardiograph (ECG or EKG) is an electrographic record of the heart's electrical activity or conduction, which is recorded from the skin surface. Voltage changes occurring in the heart can be detected at the skin surface because of capacitance properties of the body (Thibodeau et al, 1993)

Modified lead II electrocardiography (ECG) was recorded from disposable ECG electrodes (supplied by Ambu Ltd) (Figure 14) with one electrode placed on the right sub-clavical position and the other electrode placed on

the left abdomen. All wires were tied together to minimise electrical noise pick up from the ward environment and to provide comfort and maximum mobility to the patient. Electrocardiography (ECG) was recorded simultaneously with Video Electroencephalography The filter settings used in acquiring Lead II ECG were a high frequency filter (low pass filter) 70Hz and low frequency filter (high pass filter) of 0.5Hz or Time Constant filter of 1 second with a system sensitivity of 7uv/mm (uv microvolts) and a sampling rate of 500Hz was used in XLTEK EEG systems. High sampling rates of data are necessary to give high resolution and a good reproduction of original physiological signals. The ECG electrodes were replaced every 24 hours so as to ensure minimum skin irritation.

Figure 14 ECG disposable sensory electrodes supplied by Ambu Ltd.

1.2.4 Pulse Oximetry

Masimo SET pulse oximetry was used in this study. The oximeter internally calibrates within the XLTEK EEG (Electroencephalography) video telemetry system and is displayed as a numeric value using adaptive filters, plotted from 1-100% in 0.5 percent increments every 0.4 seconds and is displayed simultaneously with real time EEG and ECG (Electrocardiography) data.

Masimo Sensor Device

Oxygen saturation was monitored using a 'Masimo' forehead sensor (supplied by Artemis Medical), secured by an elasticated headband (Figure 15). The sensor position was changed to either temple or mid-forehead regularly. This was recommended by the manufacturer to minimise any possible irritation from prolonged infrared to one site. In the study the sensor device used was a reusable 'LNOP Forehead Sensor'. This sensor works on reflectance or 'back-scatter' of red and infra-red signal from the sensor placed on the forehead and held in place by a comfortable stretch band encircling the head.

This sensor was well tolerated by all ages of patients. The cable was collected with the surface EEG electrodes and neatly tied together to minimise inconvenience and to maximise freedom of movement for the patient. The forehead sensor was preferable in case of the delay effect in detecting hypoxaemia due to lung / periphery circulation time when recording from finger sensors.

Oxygen saturation measurement is digitally displayed every second on the videotelemetry polygraphy and was recorded before and during each seizure and normal event During the 3 second epoch, the lowest oxygen saturation value was selected to represent maximal de-saturation within each epoch measurement and entered onto the Excel spreadsheet.

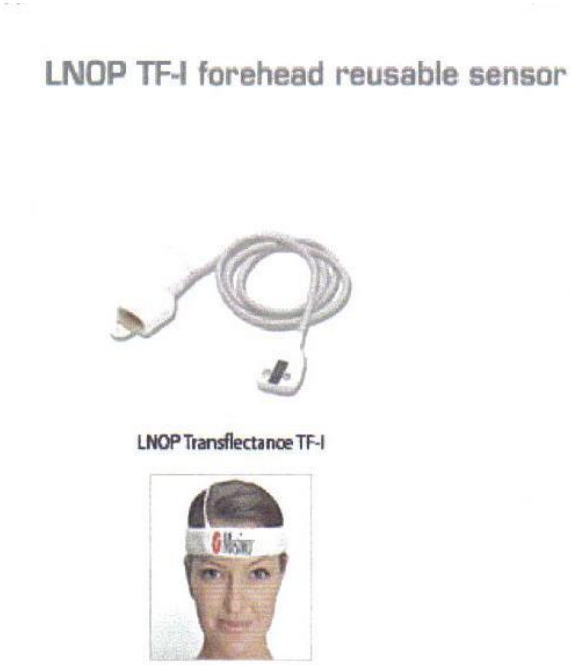


Figure 15 Masimo Forehead Pulse Oximetry Sensor Device

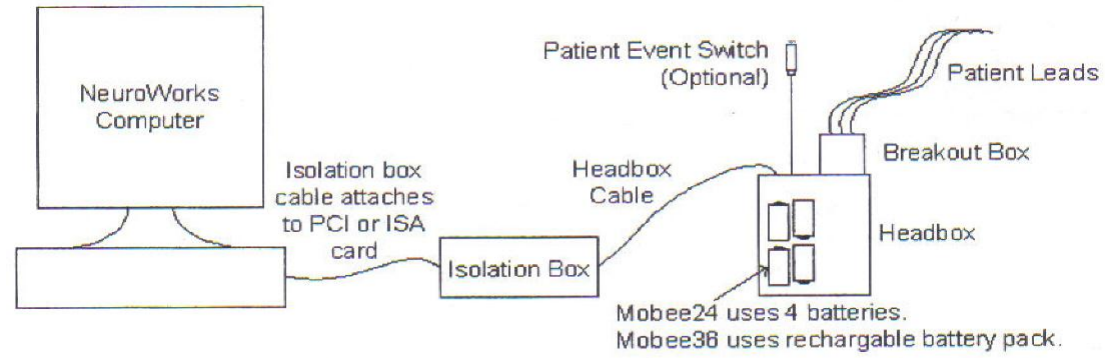
The electroencephalographic electrodes, oxygen saturation cable and the electrocardiographic leads were all plugged into an XLTEK Mobee 32 channel headbox. The Mobee headbox networked the data to a main computer server with simultaneous video of the patient. (Mobee specifications are in the appendix). The XLTEK videotelemetry system via the Mobee 32 headbox recorded these physiological signals continuously, even when disconnected from the server. When reconnected it automatically uploaded the data from the Mobee headbox which has a local memory capacity of 4 hours of disconnection (Figure 16). This allowed for patient disconnection from the network to go to the toilet etc.

The recording commenced at 16:30 hrs and the patient was provided with meals, a variety of board games, colouring books and children's videos / DVDs for their entertainment until their usual bedtime. The patient was observed all night by nursing staff or a parent, if they desired to stay, who

documented any normal events such as sneezing, coughing, yawning, stretching, turning over in bed and any seizures onto a diary. All parents were enthusiastic about their child taking part in the study, as they felt that it was a good opportunity for a detailed assessment of their child overnight. The following morning, the monitoring was ceased and the equipment was disconnected. The electrodes were removed using collodion remover (supplied by Specialised Laboratory Equipment). The child was ready to go home by 10:30 am.

The adult cohort were sometimes monitored for up to 5 days as they were often being clinically assessed for suitability for epilepsy surgery and therefore maximum data was required in those cases. Consent forms (appendix) were completed for wider publication and for the use of video. They were encouraged to bring in books and videos / DVDs of their choice for their stay. A daily ward service of magazines and papers was operated in the hospital.

Video EEG telemetry digital data review was performed using a dedicated XLTEK software computer network system. The system displayed 'raw' physiological electrographic data for electroencephalography and electrocardiography. Pulse oximetry was displayed as a numerical value every second, which was time-synchronised with the data and simultaneous video. The videotelemetry review displayed a maximum of 32 channels of data depending on selected montage (Tables 1 & 2) on full screen of 12 seconds display or 10 seconds display using a chart speed of $30mm^{-1.}$



Mobee Hardware Connections

Figure 16 XLTEK Mobee 32 Hardware connections & Headbox

Section One

Channel	Electrode +ve	-ve	Sensitivity	High Frequency Filter	Low Frequency Filter (TC)	Paper Speed.
1	Fp2	F4	10uv/mm	70Hz	0.5Hz	30mms^{-1}
2	F4	C4	10uv/mm	70Hz	0.5Hz	30mms^{-1}
3	C4	P4	10uv/mm	70Hz	0.5Hz	30mms^{-1}
4	P4	O2	10uv/mm	70Hz	0.5Hz	30mms^{-1}
5	Fp1	F3	10uv/mm	70Hz	0.5Hz	30mms^{-1}
6	F3	C3	10uv/mm	70Hz	0.5Hz	30mms^{-1}
7	C3	P3	10uv/mm	70Hz	0.5Hz	30mms^{-1}
8	P3	O1	10uv/mm	70Hz	0.5Hz	30mms^{-1}
9	Fp2	F8	10uv/mm	70Hz	0.5Hz	30mms^{-1}
10	F8	Sp2/T4	10uv/mm	70Hz	0.5Hz	30mms^{-1}
11	Sp2/T4	T6/A2	10uv/mm	70Hz	0.5Hz	30mms^{-1}
12	T6/A2	O2	10uv/mm	70Hz	0.5Hz	30mms^{-1}
13	Fp1	F7	10uv/mm	70Hz	0.5Hz	30mms^{-1}
14	F7	Sp1/T3	10uv/mm	70Hz	0.5Hz	30mms^{-1}
15	Sp1/T3	T5/A1	10uv/mm	70Hz	0.5Hz	30mms^{-1}
16	T5/A1	O1	10uv/mm	70Hz	0.5Hz	30mms^{-1}
17	ECG1	ECG2	7uv/mm	70Hz	1.0Hz	30mms^{-1}
18	SAO2		20%/mm	Off	Off	30mms^{-1}
19	Pulse Rate		20%/mm	Off	Off	30mms^{-1}

Table 1 Electroencephalographic Montage: Anterior-Posterior Medial & Temporal Derivations.

Channel	Electrode +ve	-ve	Sensitivity	High Frequency Filter	Low Frequency Filter	Paper Speed
1	F8	F4	10uv/mm	70Hz	0.5Hz	30mms^{-1}
2	F4	Fz	10uv/mm	70Hz	0.5Hz	30mms^{-1}
3	Fz	F3	10uv/mm	70Hz	0.5Hz	30mms^{-1}
4	F3	F7	10uv/mm	70Hz	0.5Hz	30mms^{-1}
5	A2/Sp2	T4	10uv/mm	70Hz	0.5Hz	30mms^{-1}
6	T4	C4	10uv/mm	70Hz	0.5Hz	30mms^{-1}
7	C4	Cz	10uv/mm	70Hz	0.5Hz	30mms^{-1}
8	Cz	C3	10uv/mm	70Hz	0.5Hz	30mms^{-1}
9	T3	A1/Sp1	10uv/mm	70Hz	0.5Hz	30mms^{-1}
10	T6	P4	10uv/mm	70Hz	0.5Hz	30mms^{-1}
11	P4	Pz	10uv/mm	70Hz	0.5Hz	30mms^{-1}
12	Pz	P3	10uv/mm	70Hz	0.5Hz	30mms^{-1}
13	P3	T5	10uv/mm	70Hz	0.5Hz	30mms^{-1}
14	F8	T4	10uv/mm	70Hz	0.5Hz	30mms^{-1}
15	T4	O2	10uv/mm	70Hz	0.5Hz	30mms^{-1}
16	F7	T3	10uv/mm	70Hz	0.5Hz	30mms^{-1}
17	T3	T5	10uv/mm	70Hz	0.5Hz	30mms^{-1}
18	ECG1	ECG2	7 uv/mm	70Hz	0.5Hz	30mms^{-1}
19	SAO2		20%/mm	Off	Off	30mms^{-1}
20	Pulse Rate		20%/mm	Off	Off	30mms^{-1}

Table 2 Electroencephalographic Montage: Transverse

Electroencephalography videotelemetry was used to identify both clinical seizures and sub-clinical seizures. If the electroencephalograph showed changes prior to the clinical onset, the start of the seizure was measured at the start of the electrical ictus. If the clinical manifestations appeared prior to the electrical discharge, then the start of the seizure was taken at the start of the clinical onset. Time synchronised video telemetry was necessary to be as accurate as possible in identifying seizure type both electrographically and clinically. Sub-clinical seizures are defined as "electroencephalographic ictal-like patterns without any disturbance of motor, sensory and conscious functions in the wake patient and without any movemeor arousal during the sleep patient" (Zangaladze et al 2008). The electro-cerebral changes and video accompaniment of all seizures were interpreted and discussed with a Consultant Paediatric Neurologist or Consultant Neurologist/ Neurophysiologist for seizure classification.

Electroencephalographic epileptiform activity is an interpretative term applied to electrographic transients of spike and sharp wave activity, distinguished from the background activity occurring in a proportion of patients with epilepsy (Dinner et al. 1985). Seizure activity on the electroencephalograph is a sudden distinctive pattern of electrical change usually in amplitude and rhythmicity.

The entire electroencephalographic videotelemetry study was reviewed, measured and analysed. A report was then created detailing frequencies (Hz) and amplitudes (uv) of the awake trace, asleep trace and any seizures. Measurements were manually selected using XLTEK software cursors. All seizures were identified and annotated to the nearest second at the start of the seizure, whether they were electrical, clinical or both presenting

simultaneously. Heart rate percentage change and oxygen saturation were also measured prior to the seizure. From the onset of the seizure, these parameters were measured 5 minutes (T-5m), 4 minutes (T-4m), 3 minutes (T-3m), 2 minutes (T-2m), 1 minute (T-1m) and 9 seconds (T-9s) before the seizure.

1.2.5 Heart Rate Percentage Change

The videotelemetry records the EEG/ECG/SAO2 and Video signal simultaneously, identifiable to the exact time of day at which it was originally acquired. The seizure onset was identified by electroencephalographic changes and clinical semiology. The data was annotated to the nearest second. Using dedicated software cursors consecutive measurements of R-R intervals were measured in milliseconds over consecutive 3 second epochs and entered onto a spreadsheet. The mean R-R intervals were calculated over each 3 second epochs and converted to seconds by dividing milliseconds by 1000. Heart rate was then calculated by dividing 60 by the converted value to calculate beats per minute. For example, an R-R measurement of 930 milliseconds, when divided by 1000 becomes 0.93 seconds. When 60 is divided by 0.93, a heart rate of 64.5/min is calculated. Continued measurements of each R-R intervals were manually measured throughout each seizure and normal event. Mean heart rate was entered onto an excel spreadsheet and percentage change was calculated using subtraction of the 1st epoch (seconds 1-3) from the 3rd epoch (seconds 7-9) of each subsequent 9 second epoch. Intra and inter-observer analyses are presented in chapter 1.7.1 Oxygen saturation were entered onto the same spreadsheet for each epoch. Continued measurements were made until the

event ended clinically and once the electroencephalograph had resumed the pre-event trace.

The time of seizure onset was entered onto a spreadsheet and subsequent 3 seconds epochs were identified throughout the seizure as well as analysis of 5 minutes prior to the seizure. With this methodology, the data can be checked and re-measured, if necessary for any given 3 second epoch of an epileptic seizure or normal event for any patient measured in this study. Oxygen saturation measurement was digitally displayed every second. During each 3 second epoch, the lowest value was selected and a mean oxygen saturation value was calculated over each 9 second epoch and entered onto the spreadsheet.

Changes in heart rate and oxygen saturation during normal events were necessary to compare any changes to that of seizures. Normal events e.g. sneezing, coughing stretching, yawning, crying, laughing, arousal and turning over in bed were all identified using indications on the electroencephalograph of electromyographic activity and movement artefact correlated with the video evidence and diary annotation. Arousal was identified by the on-going sleep trace being interrupted by the return of awakened activity on the electroencephalograph for at least 5 seconds. The trace was documented to the nearest second on the electroencephalograph.

Using the electroencephalograph and synchronised video, each normal event for every patient was identified and annotated onto the electroencephalograph to the nearest second. A baseline measurement of heart rate was analysed over an epoch of 9 seconds to get a mean average heart rate (T-9). Heart rate was then analysed during the normal

physiological event over the selected 9 seconds epoch (Tdur) and the percentage heart rate change was calculated during subsequent 3 seconds epochs and calculated in the same way as for seizure heart rate methodology.

Inter & Intra-observer Analysis

For inter and intra-observer error analysis, a qualified Electrocardiographer / Electroencephalographer re measured the same raw data in one patient. A mean value for R-R measurements was calculated for each 3second epoch. Mean R-R intervals were calculated over each 3second epoch and converted to seconds by dividing milliseconds by 1000. Heart rate was then calculated by dividing 60 by the converted value to calculate beats per minute and entered onto an Excel spreadsheet. Percentage change in heart rate was calculated by subtracting heart rate of the 1st epoch (seconds 1-3) from the 3rd epoch (seconds (7-9) of each consecutive 9 second epoch.

Observer 1 and Observer 2 measured the same data twice as Run 1 and Run 2. Consistency of each observer's measurements were analysed by comparing Run 1 and Run 2 for intra-observer analyses. Inter-observer analyses were performed by comparing results for Observer 1 and Observer 2 with each run.

1.2.6 Statistical Methods

Minitab (version 14) statistical analysis software was used in analysing one sample t-tests for percentage change of heart rate before and during seizures and by the same method for normal event data. Non-parametric Wilcoxin one sample t-test of percentage change is used as percentage represents different proportions. *Percentage change* of heart rate is presented instead of

comparing absolute heart rate "before" and "during" events to give a proportional change instead of an absolute change. Heart rate is very different depending on age whereas a proportional change from baseline is applicable for all ages. As the age range of patients range from a 1-day old infant to a 60 year old adult, I have made the assumption of independence of data between patients. In addition, due to high levels of intra-subject variation as well as inter-subject variation, I have also made the assumption of independence of data within the same patient.

Paired t-tests were applied for oxygen saturation levels and compared before and during seizures and for normal events. Parametric paired t-tests are appropriate in this case as the t-tests compare the oxygen saturation before the seizure with the oxygen saturation during the seizure. Although there is a maximum ceiling of 100% oxygen saturation, the data difference produced is of normal distribution. Minimum oxygen saturation values during the seizure are presented in each seizure category for the purposes of identifying a useful trigger level for a seizure alarm device.

Diagnostic testing was used to calculate sensitivity and specificity for grouped data for heart rate percentage change and oxygen saturation using Statistical Packages for the Social Sciences (SPSS) version 12.

Diagnostic testing was used to indicate trigger levels that might be used in a seizure alarm if percentage heart rate and oxygen saturation were used as parameters. From diagnostic testing, the sensitivity gives us two results; firstly, it gives the 'true positive' (correctly identified seizure) proportion and the 'false negative' (missed seizure) proportion.

The specificity of each possible trigger level also gives us two results. Firstly, it shows the 'true negative' (correctly identified normal event) proportion and the 'false positive' (false alarm) proportion.

Statistical Package for Social Sciences (SPSS) software uses these co-ordinates to produce a 'Receiver Operator Curve' (ROC). In an ideal situation, the curve should run closest to the top left corner of the graph. This would be possible if the sensitivity and specificity were close to the value of '1'. In order for the graph to produce this curve, specificity is calculated as 1-specificity.

1.3.1 Study Group Characteristics

Fifty patients were invited to take part in this prospective and ethically approved study (Table 3). All patients were having EEG videotelemetry monitoring as part of their clinical management of their epilepsy. Not all patients in the study had seizures captured during their monitoring. The patients had an age range of 1 day (full term) to 60 years and 3 months with a mean age of 13 years and 4 months ± 13.45 years was calculated for the group. The median age of 8 years 6 months indicates that most of the patients in the group tend towards the younger paediatric age range. The gender mix was 33 Males and 17 females.

Eleven patients had structural abnormalities (not including mesial temporal sclerosis or sclerosis of the hippocampus); 1 patient had Rassmussen's Syndrome, 3 patients had a history of stroke, 2 patients had space-occupying lesions, 1 patient had a double cortex (or sub-cortical band heterotopia), two patients had a history of an encephalitis with subsequent cortical damage, 1 patient was microcephalic and one patient was a neonate with a severe ischaemic encephalopathy.

Several different syndromes were included in the group. One patient had Ohtahara's syndrome, 2 patients were Aicardi syndrome, 2 patients were Austistic Spectrum Disorder, 2 patients had Lennox Gastaut syndrome, 1 patient had progressive polymorphic epilepsy of Dravet and 1 patient had Myoclonic Astatic Epilepsy (MAE).

The general seizure type of the group in this study were as follows; 21 patients had a history mainly of complex focal seizures, 24 patients had a history of mainly generalised tonic-clonic seizures and 5 patients had a history purely of focal seizures.

Anti-convulsant medication was used either as a monotherapy or in combination with other anti-convulsants in the attempt to control frequent seizures. In this group of patients, the most commonly used anti-convulsant was Sodium Valproate, which was prescribed for 17 patients (34%). The next most commonly used anti-convulsant was Carbamazepine, which was prescribed for 13 patients (26%) of the study group. Lamotrigine (9: 18%), Topiramate (8: 16%), Phenytoin (6: 12%) and Phenobarbitone (5:10%), were used less commonly. The least commonly used anti-convulsant therapies prescribed for the group were Nitrazepam (2: 4%), Keppra (2: 4%), Vigabatrin (2: 4%) and Ethosuximide (1: 2%). Rescue medication (Diazepam) is not included in this analysis.

The videotelemetry provided valuable information for the clinical management for all patients. Based on the results, 10 (20%) patients had their medication changed or were commenced on anti-convulsants for the first time because of evidence of epilepsy.

From the adult cohort, videotelemetry supported complex focal seizures consistent with neuro-imaging in two patients being assessed for epilepsy surgery.

Patient	Age	Gender	Aetiology/ Epilepsy	Anti-Epileptic Drugs
1	10 months	M	Ohtahara syndrome. Frequent daily myoclonus	Vigabatrin. Phenobarbitone, Diazepam PR
2	14 years 5 months	F	Head injury. Daily frequent complex focal seizures.	Phenytoin. Carbamazepine
3	3 years 5 months	M	Motor developmental delay. Weekly complex focal seizures.	Carbamazepine, Lamotrigine.
4	3 years 7 months	M	Mild motor delay. Weekly Generalised Tonic Clonic Seizures.	Clobazam, Sodium Valproate, Phenytoin.
5	10 years 10 months	F	Mild learning disability. Right hemiparesis. Weekly secondary generalised seizures.	Sodium Valproate, Topiramate.
6	3 years 6 months	M	Mild motor delay. Weekly complex focal seizures.	Carbamazepine, Lamotrigine.
7	14 years 5 months	M	Rassmussen's encephalitis. Daily frequent simple focal seizures.	Clobazam, Sodium Valproate, Carbamazepine.
8	9 years 11 months	M	Progressive polymorphic epilepsy of Dravet. Daily seizures.	Sodium Valproate.
9	3 years 1 month	M	Autistic spectrum disorder. Weekly complex focal seizures.	Nil. (Seizures not previously diagnosed).
10	15 years 11 months	F	Aicardi syndrome. Cerebral palsy with left hemiparesis. Weekly tonic, Generalised Tonic Clonic & myoclonic seizures.	Phenytoin.
11	15 years 2 months	M	Lennox Gastaut syndrome. Daily absences, weekly Generalised Tonic Clonic Seizures.	Topiramate, Clobazam, Propanolol. Midazolam rescue medication.
12	10 years 11 months	M	Stroke, left dystonic hemiplegia. Daily complex focal seizures.	Topiramate.
13	5 years 4 months	F	Sub-cortical band heterotopia. Daily epileptic spasms.	Sodium Valproate.
14	7 years 6 months	M	Global motor delay. Nocturnal seizures occurring weekly.	Carbamazepine.
15	6 years 7 months	M	Lennox Gastaut syndrome. Generalised Tonic Clonic	Sodium Valproate, Topiramate, Clobazam.

			Seizures daily.	
16	5 years 9 months	F	Aicardi syndrome. Epileptic spasms daily.	Vigabatrin, Lamotrigine.
17	49 years 7 months	M	Daily complex focal seizures. One nocturnal Generalised Tonic Clonic Seizure.	Carbamazepine, Lamotrigine, Topiramate.
18	5 years 9 months	M	Normal development. Absences, drop attacks & nocturnal Generalised Tonic Clonic Seizures.	Sodium Valproate, Clobazam.
19	60 years 3 months	F	3 year history of funny turns. Complex focal seizures.	Nil. Commenced on AED after EEG Videotelemetry.
20	20 years 9 months	M	Epilepsy since childhood. Polymicrogyria. Complex focal seizures.	Carbamazepine.
21	17 years 11 months	F	Complex focal seizures, occasional Generalised Tonic Clonic Seizures.	Topiramate, Keppra.
22	11 years 3 months	F	Normal development. Recent weekly focal seizures.	Carbamazepine.
23	11 years 5 months	M	Normal development. Weekly complex focal seizures with secondary generalisation.	Sodium Valproate.
24	27 years 9 months	F	Recent focal seizures.	Nil. Commenced on AED after EEG Videotelemetry.
25	21 years 3 months	F	Daily absences. Generalised Tonic Clonic Seizures every two months.	Sodium Valproate, Phenobarbitone, Lamotrigine.
26	4 years 9 months	M	Mild developmental delay. Weekly nocturnal seizures.	Topiramate, Sodium Valproate.
27	6 years 6 months	F	Previous viral encephalopathy. Cortical visual impairment & learning disability. Atonic seizures and absences.	Phenobarbitone.
28	6 years 1 month	M	Magille's syndrome. Myoclonic absences.	Nil. To be commenced on Ethosuximide.
29	16 years 11 months	M	Normal development. Daily absences.	Sodium Valproate.

30	16 years	M	Frequent daily episodes resembling torticollis & retrocollis. Complex focal seizures.	Carbamazepine
31	4 years 11 months	M	Developmental delay. Nocturnal seizures.	Topiramate, Sodium Valproate.
32	4 years 7 months	M	Complex focal seizures	Carbamazepine, Lamotrigine
33	22 years 7 months	F	Complex focal seizures	Nil. Commenced on AED after EEG Videotelemetry
34	41 years 9 months	F	Myoclonic epilepsy	Nil
35	2 years 5 months	M	Prolonged febrile convulsion. Nocturnal Generalised Tonic Clonic Seizures.	Sodium Valproate.
36	3 years 9 months	M	Autistic spectrum. Weekly Generalised Tonic-Clonic Seizures.	Clobazam, Sodium Valproate, Lamotrigine.
37	4 years 3 months	M	Right temporal lesion extending to parahypocampal gyrus. Focal seizures.	Sodium valproate, Carbamazepine.
38	5 years 11 months	M	Myoclonic Astatic Epilepsy. Absences, atonic, tonic, Generalised Tonic-Clonic Seizures. Periods of non-convulsive status epilepticus.	Phenobarbitone, Topiramate.
39	12 years 4 months	F	Normal development, 18 month history of absences, single Generalised Tonic-Clonic Seizure.	Carbamazepine.
40	30 years 11 months	M	Focal seizures (sensory induced by music)	Lamotrigine
41	5 years 4 months	M	Microcephaly, Cerebral Palsy. Seizures.	Nitrazepam.
42	5 years 4 months	F	Cerebral Palsy. Shunted hydrocephalus. Severe visual impairment. Seizures.	Sodium Valproate, Nitrazepam, Phenytoin.
43	43 years 11 months	M	Encephalitis post typhus vaccination. Complex focal seizures with secondary generalisation since, occurring 2-3/month	Keppra, Lamictal.

44	22 years 8 months	F	Complex focal seizures with secondary generalised seizures.	To be commenced on AEDs
45	2 years	M	Episodes of epilepsia partialis continuans involving the right side of face.	Nil. To be commenced on Phenytoin.
46	4 months	M	Non-accidental injury. Right hemiplegia. Left focal seizures.	Phenytoin, Midazolam.
47	2 days (Full term)	F	Focal structural lesion. Focal seizures.	Nil. To be commenced on AEDs.
48	34 years 11 months	M	Nocturnal frontal lobe seizures.	Carbamazepine.
49	1 day (Full term)	M	Severe hypoxic ischaemic encephalopathy.	Nil. To be commenced on phenobarbitone.
50	10 years 7 months	M	Learning disability. Complex focal seizures.	Nil

Table 3 Total Patient Demographics

1.3.2 Total Seizure Group.

527 seizures were analysed in the total seizure group. This was composed of 36 absences (4 patients), 102 simple focal (6 patients), 229 frontal lobe seizures (10 patients), 11 generalised tonic-clonic seizures (6 patients), 28 myoclonus (5 patients), 31 temporal lobe seizures (11 patients) and 90 tonic seizures (7 patients). In addition, 83 sub-clinical seizures (7 patients) and 10 neonatal seizures were analysed.

A mean difference of 21.8% in heart rate is calculated for the total seizure group (Table 4) during seizures compared to baseline measurements and is highly statistically significant ($p<0.001$). Mean differences in oxygen

saturation are small (2.1) dropping mean oxygen saturation to 96.1, which is clinically not significant but is statistically significant (*p<0.001*).

One sample t-test/paired t-test	n	Mean	St.Deviation	SE Mean	*p*<
%HR	527	21.8	29.7	1.3	0.001
SAO2 BEFORE DURING Difference	 494 494 494	 98.2 96.1 2.1	 1.9 5.3 4.9	 0.1 0.2 0.2	0.001

Table 4 Descriptive Statistics using one sample t-test for Percentage Heart Rate Change and Paired t-test for Oxygen Saturation for the Total Seizure Group.

Overall, both the changes in heart rate and oxygen saturation for total seizures in the study show high statistical significance. This does not however explain how clinically relevant the result is or what the accuracy of an alarm system might be if it was to detect seizures based on heart rate change and oxygen saturation percentage at various trigger levels.

It is therefore necessary to investigate the sensitivity and specificity in diagnostic testing of these parameters for this group.

Diagnostic Testing for the Total Seizure Group.

Diagnostic testing was used to compare the percentage changes in heart rate during seizures with percentage changes in heart rate during normal events. It was also used to compare oxygen saturation percentage values of seizures

to that of normal events. All possible trigger levels in heart rate percentage change and oxygen saturation that may be considered for an alarm system device are derived from ROC co-ordinates.

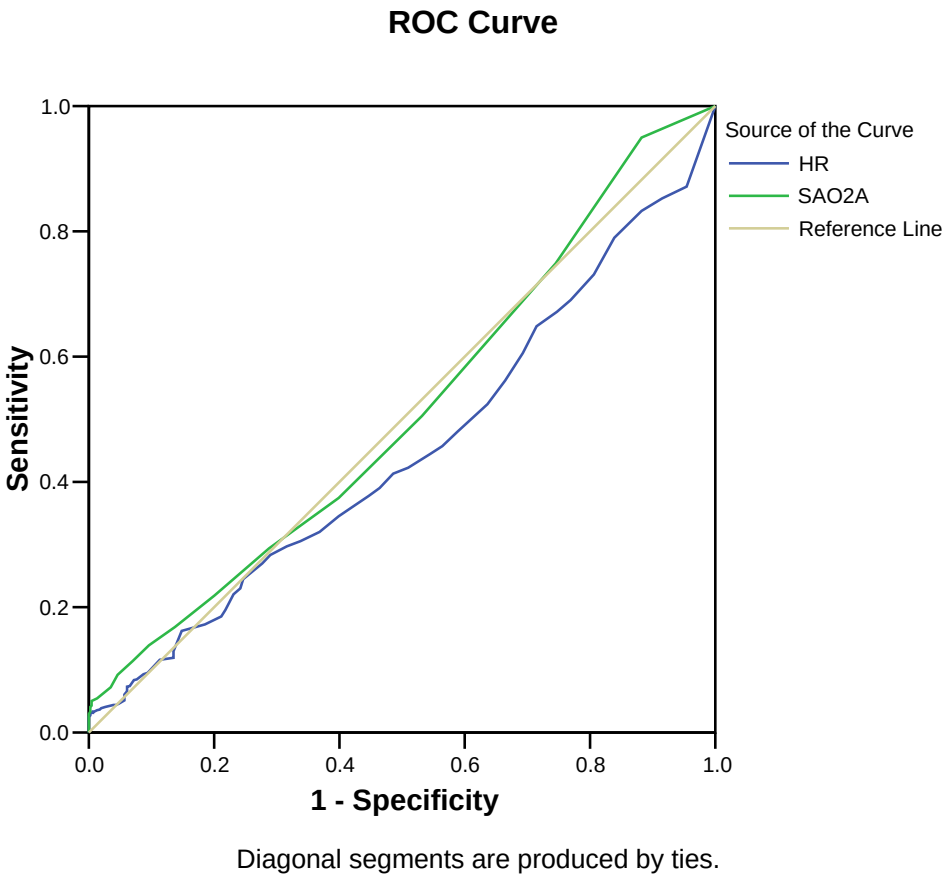


Figure 17 Receiver Operator Curve for Diagnostic Testing of Heart Rate Percentage Change and Oxygen Saturation During Total Seizure Group.

During seizures and normal events, a wide range in percentage heart rate is seen (Figure 17). If a trigger level of a device is set to alarm at the smallest change in heart rate of 0.5% it would correctly identify 87% (sensitivity of 0.871) of seizures (true positives). However, it would also incur many false alarms (false positives). Specificity is calculated as 1-specificity from the co-

ordinates. With a heart rate percentage change of 0.5, specificity is calculated as 1-0.954, which when rounded up, equates to 0.05 (5%). The level of false alarms is calculated as 1- specificity value, which in this case is 0.95 (95%).

At this small alteration in heart rate percentage change, most seizures would be identified but there would be a very high level of false alarms. If a better specificity rating is considered of 0.95 (95%) with a heart rate trigger level of 45.5%, the sensitivity value of 0.046 (5%) is very poor with 95% of seizures missed (false negatives).

In this situation, the best compromise is a trigger level of 14.5%. This still remains poor with only 42% of seizures correctly identified (0.423 true positives) and a specificity of 1-0.510 (49%) true negatives (correctly identified normal events) with a resultant level of 51% false positives (false alarms). In short, an alarm system based on this trigger level has the same chance of the alarm being due to a normal event or a seizure, which would render the system pointless.

Using an oxygen saturation trigger level of 90.5%, specificity of 1-0.045 (0.95 or 95%) is shown. This would result in very few false alarms of 5% but the sensitivity of correctly identifying true seizures as true positives is poor at 0.092 (9%).

To conclude, the sensitivity and specificity values for the total seizure group compared to normal events are poor. The percentage changes in heart rate and oxygen saturation percentage overall, during total seizures, cannot be distinguished from that seen during normal events.

However, this result indicates a poor sensitivity and specificity because many epileptic seizures in the group include very brief clinically insignificant seizures e.g. absences and myoclonus, which perhaps do not show significant changes in heart rate or oxygen saturation. This has possibly numerically 'devalued' the results from changes in heart rate percentage change and oxygen saturation encountered during more clinically significant seizures.

It is therefore important to consider sensitivity and specificity of clinically significant seizures and clinically insignificant seizures and compare the heart rate percentage changes and oxygen saturation to that of normal events. The logic of this is dictated by the fact that a reliable seizure alarm system would be more clinically useful if it identified clinically significant seizures like generalised tonic-clonic seizures and was not triggered because of an absence attack or single myoclonus.

1.3.3 Clinically Significant Seizure Group.

All seizures in this study were self-resolving and did not require rescue medication intervention to stop any prolonged seizures. However, some seizures were more clinically significant than others and required re-positioning into recovery position after the seizure. The seizures that were categorised as being 'clinically significant' were seizures that were considered harmful to the patient and could potentially lead to serious consequences if left undetected and included generalised tonic-clonic seizures, prolonged frontal lobe seizures with clinically significant hypoxia and some temporal lobe seizures that caused cardiology changes e.g. diminished T-wave etc. Therefore seizures that posed an obvious clinical

threat to the patient and where an alarm system would be beneficial in alerting assistance to the individual having the seizure were included in this group.

Sixty one clinically significant seizures were analysed from 28 patients (Table 5) consisting of 13 frontal lobe seizures (7 patients), 2 simple focal (2 patients), 27 temporal lobe (9 patients) 11 generalised tonic-clonic seizures (6 patients), 9 tonic seizures (3 patients) and an acute period of epileptic spasms in one patient.

One sample t-test/paired t-test	n	Mean	StDeviation	SE Mean	*p*<
%HR	61	40.6	33.8	4.4	0.001
SAO2 BEFORE DURING Difference	 49 49 49	 97.2 86.9 10.3	 2.7 11.0 11.3	 0.3 1.5 1.6	0.001

Table 5 Descriptive Statistics for one sample t-test for Percentage Heart Rate and paired t-test for Oxygen Saturation in Clinically Significant Seizures.

This result shows a high statistical significance of $p<0.001$ but again, it does not explain how useful these parameters would be in the use of a seizure alarm device. Diagnostic testing is required to discover how many seizures would be correctly identified and how many false alarms would occur in this group.

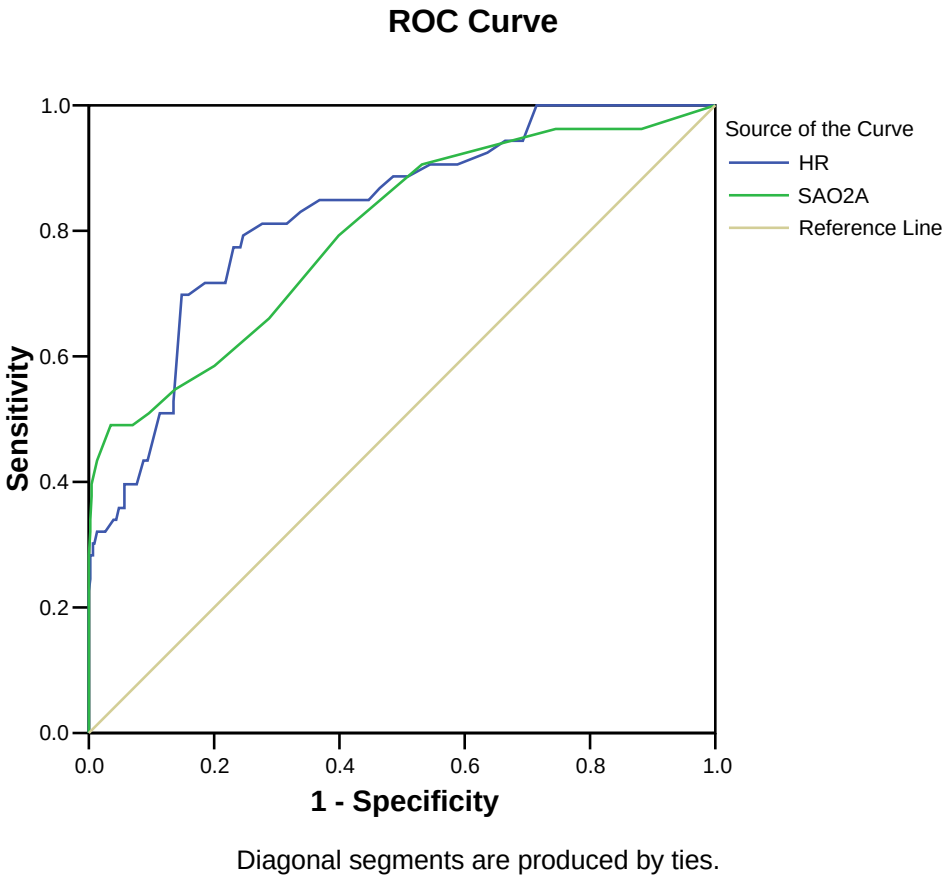


Figure 18 Receiver Operator Curve for Diagnostic Testing of Percentage Heart Rate Change and Oxygen Saturation during Clinically Significant Seizures.

Immediately, a very different trend on the Receiver Operator Curve is observed (*Figure 18*). Both traces are closer to the top left corner for the clinically significant seizure group compared to that seen for the total seizure group (*Figure 17*). The ROC indicates better sensitivity and specificity values in percentage heart rate change and oxygen saturation during clinically significant seizures.

The best compromise between the best level of correctly identified seizures (sensitivity) and keeping false alarms to a minimum due to normal events

(false positives) appears to be when the trigger level is set to a percentage heart rate change of 25.5% (Figure 18). This level gives a sensitivity of 0.792 (79%), which is almost 80% accurate seizure detection. This trigger level gives a specificity of 1-0.246 (75%), which will correctly identify heart rate changes due to normal events that would not trigger the alarm. This leaves a false alarm rate of 25%, which is possibly a little excessive, i.e. 1:4 ratios of false alarms.

To minimise the proportion of false alarms, a lower sensitivity of true positive seizure detection would occur. If parents were given the choice they would probably ask for better seizure detection rate and accept that 1 alarm out of 4 may be a false alarm.

1.3.4 Combined Analysis (Percentage Heart Rate Change and Oxygen Saturation during Clinically Significant Seizures).

Depending on both percentage heart rate change at 25.5% and oxygen saturation of 85% reaching these trigger levels together lowers the sensitivity to 24% but improves specificity to 99%. Oxygen saturation on its own can only identify 38% of seizures but correctly ignores non-events to 99.5%. However, when the data is combined with one/ other/ both parameters reaching their trigger levels, the sensitivity improves further to **91%** and specificity stays the same at 75%. This result indicates that if a seizure alarm was triggered because of either percentage heart rate change or oxygen saturation parameters triggered either independently or together then 91% of clinically significant seizures would be detected. As before, one triggered alarm in every four would be false.

1.3.5 Clinically Insignificant Seizure Group.

Many epileptic seizures are very brief in nature. For example, bystanders may not even be aware that someone has had an absence seizure. These types of seizures can interrupt concentration and affect school performance. However, in terms of a seizure alarm device it would neither be useful to the parent or beneficial to the patient if it triggered every time an absence seizure occurred.

However, some people may have a mixture of absence seizures and generalised tonic-clonic seizures with their generalised seizure disorder. In this situation, it would be useful for an alarm system to trigger during the tonic-clonic seizure but not during an absence.

It would be very useful if an alarm system could not distinguish 'clinically insignificant seizures', which include epileptic seizures like absences from normal events and not trigger in either situation.

466 epileptic seizures were included in the clinically insignificant seizure group. This group was composed of 214 frontal lobe seizures (2 patients), 1 atonic seizure (1 patient), 95 simple focal seizures (I patient), 16 temporal lobe (4 patients), 35 absences (5 patients), 27 myoclonus (5 patients) and 78 tonic seizures (4 patients).

One sample t-test/paired t-test	n	Mean	St.Deviation	SE Mean	*p*<
% HR	466	14.7	16.5	0.7	0.001
SAO2 BEFORE DURING Difference	430	98.4 97.2 1.2	1.7 2.6 2.1	0.1 0.1 0.1	0.001

Table 6 Descriptive statistics for one sample t-test for percentage heart rate change and paired t-test for oxygen saturation for clinically insignificant seizures.

Statistical significance *(p<0.001*) occurs in both heart rate percentage change and oxygen saturation (Table 6) during clinically insignificant seizures. Insignificant seizures have a mean heart rate change of 14.7% compared to baseline with a standard deviation of 16.5%. The mean oxygen saturation of 97% and is a normal value and not clinically significant for a patient but is statistically significant in this group because the majority of clinically insignificant seizures have a slight alteration in oxygen saturation during the seizure of around 1%.

Statistical significance does not equate to clinical significance in this instance and diagnostic testing is required to assess whether insignificant seizures can be distinguished from normal events using percentage heart rate and oxygen saturation as parameters for a seizure alarm.

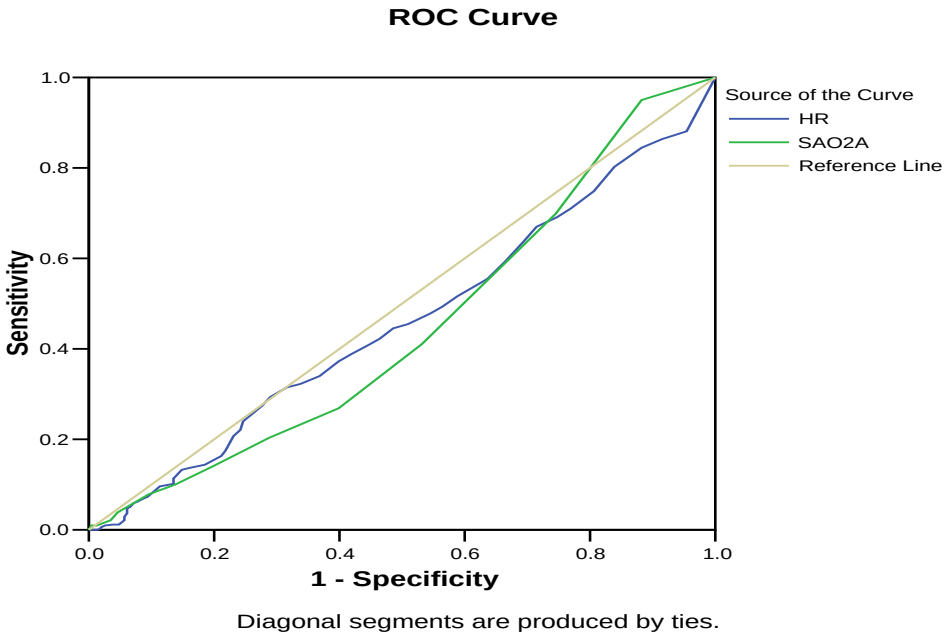


Figure 19 Receiver Operator Curve for Diagnostic Testing of Percentage Heart Rate and Oxygen Saturation during Clinically Insignificant Seizures.

Overall, percentage heart rate change during clinically insignificant seizures, are not distinguishable from normal events. The best compromise seen from diagnostic testing (Figure 19) is a trigger level of 14.5%. This gives a sensitivity of 45% of identifying true positives with 55% missed seizures. A similar specificity is seen of 1-0.51 (49%) true negatives (correctly identified normal events) and a high level of false alarms at 51%. This means that when the alarm triggers, it could either be almost equally due to a clinically insignificant seizure or a normal event. This trigger level is similar to the mean heart rate percentage change for the group of 14.7% seen from statistical analysis of one sample t-tests.

Oxygen saturation percentage for this group shows a similar result in diagnostic testing to heart rate percentage change and it cannot distinguish

clinically insignificant seizures from normal events either. The level of sensitivity and specificity that show the best compromise is a trigger level of 97.5%. This results in a sensitivity of 41% true positives and a specificity of 1-0.53 (47% true negatives). The level of false positives (false alarms) is 53%. Again an alarm system triggering at this level may or may not be a seizure with an almost equal probability.

This is an encouraging result. An alarm system based on percentage heart rate change and oxygen saturation which is set at a trigger level specific in detecting clinically significant seizures, will be unlikely to be triggered due to a clinically insignificant seizure or normal event.

1.3.7 Summary of Changes in Percentage Heart Rate Change and Oxygen Saturation during Clinically Significant and Clinically Insignificant Seizures.

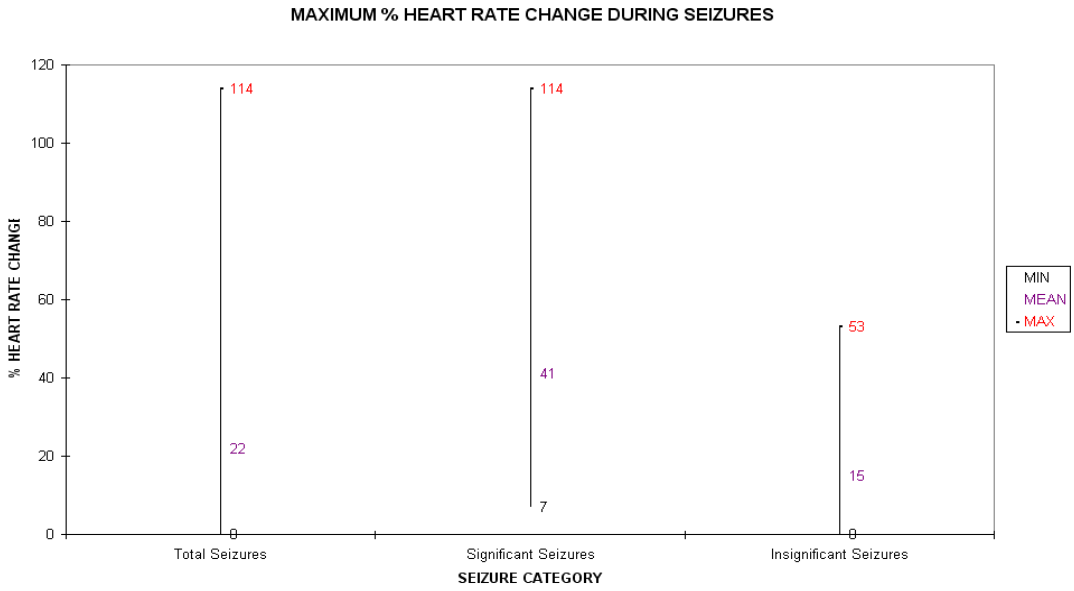


Figure 20 Maximum, Mean and Minimum % Heart Rate Change during Clinically and Clinically Insignificant Seizures.

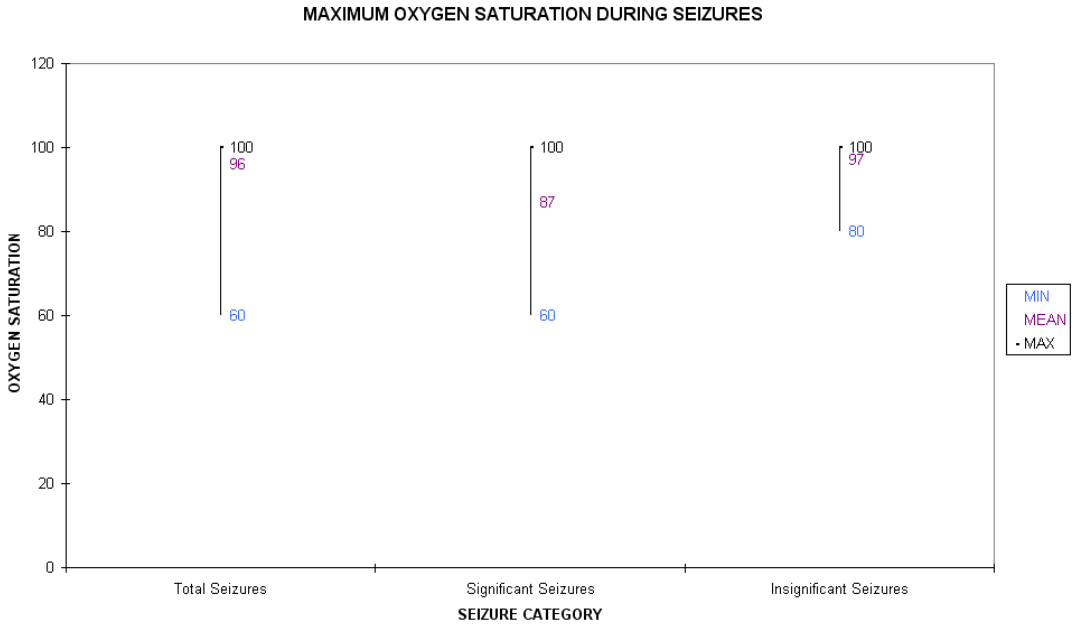


Figure 21 Maximum, Mean and Minimum Oxygen Saturation during Clinically and Clinically Insignificant Seizures.

Chapter 4 Results: Generalised Epilepsy.

1.4.1 Generalised Tonic Clonic Seizures

One sample t- test / paired t-test.	n	Mean	St.Deviation	SE Mean	*p*</=
%HR	11	53.3	24.1	7.2	0.001
SAO2					0.018
BEFORE	8	96.6	1.8	0.6	
DURING	8	91.2	5.2	1.8	
Difference	8	9.3	4.9	1.7	

Table 7 Descriptive Statistics for one sample t-test of percentage heart rate change and paired t-test for oxygen saturation during Generalised tonic-clonic seizures.

High statistical significance ($p<0.001$) is seen for percentage heart rate change during eleven generalised tonic-clonic seizures (Table 7). A mean heart rate change of 53.4% is calculated for the group. A standard deviation of 24.1% indicates that heart rate change distribution for the group can show much higher heart rate changes than the mean value. Despite the small sample size and large standard deviation, statistical significance shows that these high heart rate changes are unlikely to occur by chance.

Statistical significance for oxygen saturation ($p=0.018$) is still considered to be significant measured in eight generalised tonic clonic seizures but is not as highly significant as that seen with heart rate change. The sample size is

smaller for oxygen saturation than the sample size for heart rate change. This may account for a difference in statistical probability calculation.

To consider how useful an alarm device might be in detecting generalised tonic-clonic seizures we need to analyse the sensitivity and specificity of heart rate and oxygen saturation parameters during these seizures.

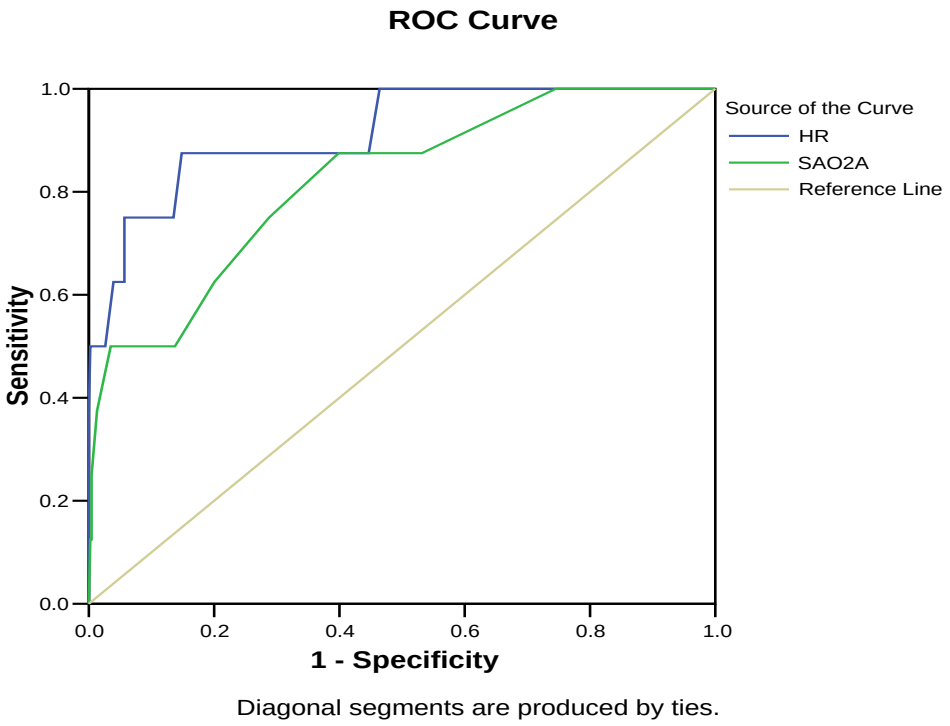


Figure 22 Receiver Operator Curve for diagnostic testing of percentage heart rate and oxygen saturation during Generalised Tonic-clonic Seizures.

Diagnostic testing indicates that generalised tonic-clonic seizures can be distinguished from normal events by using a device based on percentage heart rate change (Figure 22). Oxygen saturation is not always as useful with a sensitivity of 50% at a trigger level of 90.5% oxygen saturation. However,

very few false alarms would occur (5%) with a high specificity of 1-0.046 (95%).

Sensitivity of detecting generalised tonic-clonic seizures, based on a trigger level of 32.5% heart rate change will correctly identify 88% of seizures. This trigger level also provides a high specificity of 1-0.148 (85%) of correctly identified normal events, which would be ignored by the alarm system providing a low false alarm rate of 15%.

1.4.2 Tonic Seizures.

One sample t-test/paired t-test	n	Mean	St.Deviation	SE Mean	*p*<
%HR	90	18.9	15.4	1.6	0.001
SAO2					0.001
BEFORE	89	98.4	1.9	0.2	
DURING	89	94.7	4.3	0.4	
Difference	89	3.7	3.8	0.4	

Table 8 Descriptive Statistics for one sample t-test in Percentage Heart Rate Change and paired t-test for Oxygen Saturation during Tonic Seizures

Tonic seizures (n=90) produce highly significant changes in percentage heart rate change and oxygen saturation (n=89) of $p<0.001$ (Table 8). This indicates that these changes are very unlikely to be due to chance and they must show consistent or similar changes during most tonic seizures. The mean percentage increase in heart rate (18.9%) is not as high as that seen during generalised tonic-clonic seizures (53.4%). The standard deviation of 15.4% is also smaller than that seen during generalised tonic-clonic seizures of 24.1%.

The mean oxygen saturation value for the group during the seizures is 94.7%, which is not clinically significant. High statistical significance of $p<0.001$ indicates that most tonic seizures in the group must show consistent or similar changes in oxygen saturation with mean values dropping by almost 4%. To consider the accuracy of an alarm system, diagnostic testing of percentage heart rate change and oxygen saturation is analysed during tonic seizures

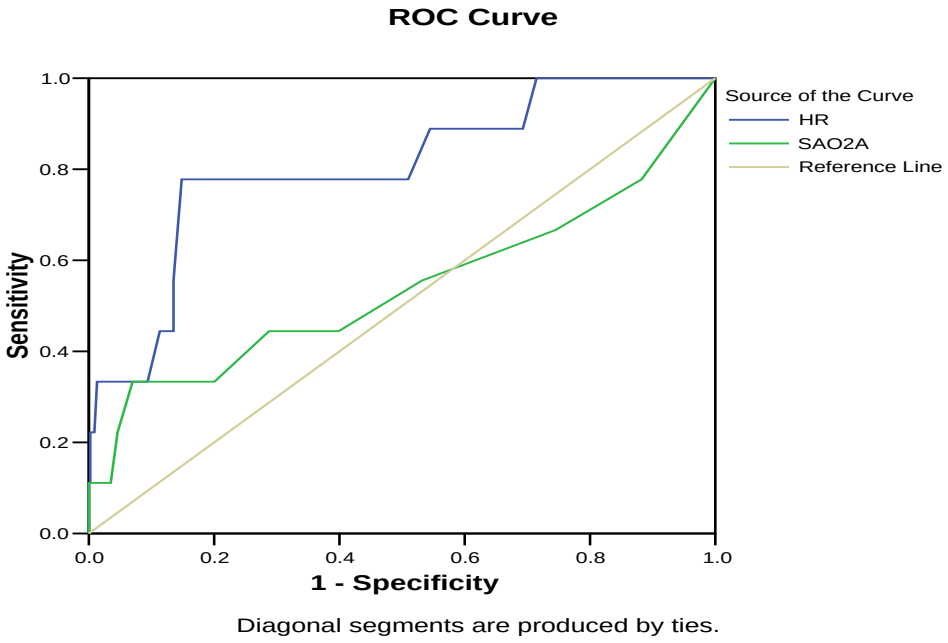


Figure 23 Receiver Operator Curve for diagnostic testing of percentage heart rate change and oxygen saturation during Tonic seizures.

A percentage heart rate change trigger level of 32.5% gives the best balance between sensitivity and specificity proportions (Figure 23). At this level a sensitivity of 78% (true positives) would identify a high proportion of tonic seizures. A specificity of 1-0.148 (85%) would correctly identify most normal events with a false alarm rate of 15%. As suggested by the mean oxygen

saturation paired t-tests, this parameter is more limited in detecting this type of seizure. At a trigger level of 95.5% oxygen saturation, a sensitivity of 44% is poor with 56% of tonic seizures being missed. A false alarm rate of 29% and specificity of correctly detecting normal events is 71%. This result is not surprising given that 95.5% oxygen saturation is not clinically significant.

An alarm system based on percentage heart rate alone may be sufficient in detecting this type of seizure.

1.4.3 Absences

One sample t-test/paired t-test	n	Mean	St.Deviation	SE Mean	*p*</=
%HR	35	3.4	7.1	1.1	0.008
SAO2					0.378
BEFORE	35	95.0	3.4	0.5	
DURING	35	94.8	3.5	0.5	
Difference	35	0.2	1.3	0.2	

Table 9 Descriptive statistics for one sample t-test of percentage heart rate change and paired t-test for oxygen saturation during absence seizures.

Statistical significance is shown for percentage heart rate change during thirty-five absence seizures of p=0.008 (Table 9). The mean percentage change in heart rate is very small (3.4%) with variability of 7% standard deviation. Overall, heart rate changes are small during these seizures. Paired t-tests describe oxygen saturation changes as being insignificant. A small change in oxygen saturation is seen for the group. Diagnostic testing is required to

assess whether absence seizures can be distinguished from normal events using percentage heart rate and oxygen saturation in a seizure alarm.

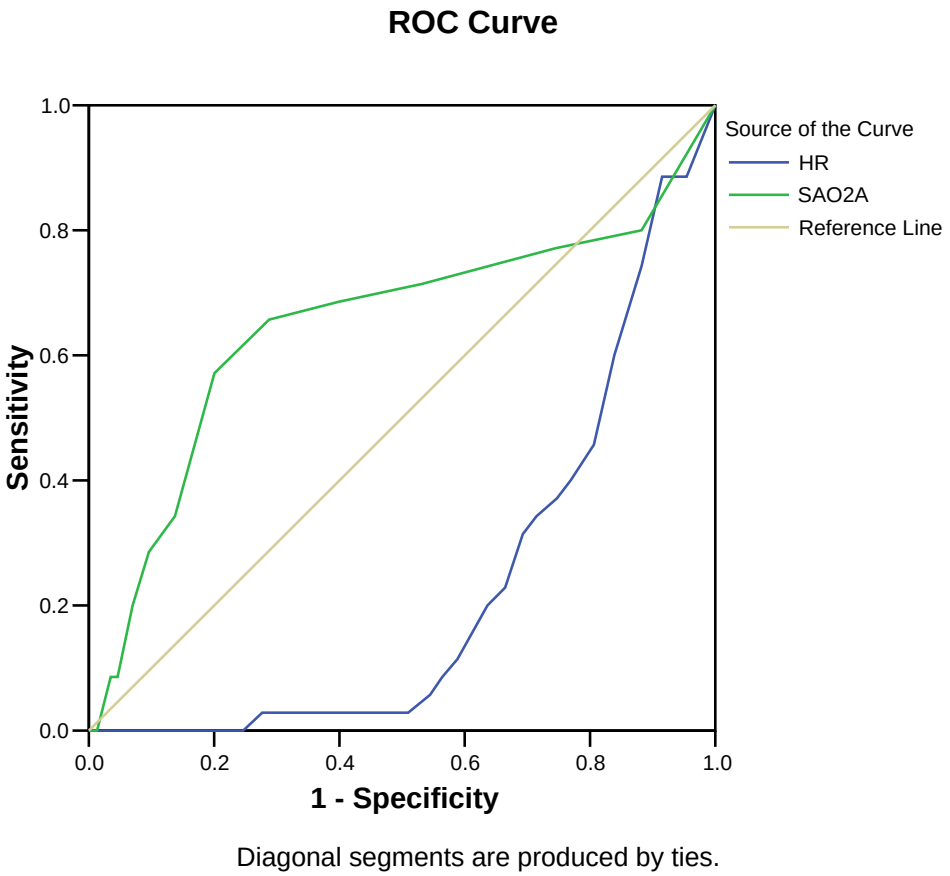


Figure 24 Receiver Operator Curve for diagnostic testing of percentage heart rate change and oxygen saturation during absence seizures.

Diagnostic testing demonstrates very poor results in distinguishing absences from normal events (Figure 24). The best compromise is seen at a trigger level of 8.5%. At this level, we have a sensitivity of 31% with many missed absence seizures with 69% false negatives. A specificity of 31% of true negatives (1-0.69) is seen with a high level of false alarms of 69%. In short, less than one third of absences would be detected and over two thirds of

alarms would be false alarms. Therefore, an alarm system based on percentage heart rate change would be a poor indicator in detecting absences at this level. If the alarm system were set to a higher trigger level to target clinically significant seizures e.g. generalised tonic-clonic seizures, it would be less likely that the alarm would be triggered due to an absence. This is an encouraging result.

Oxygen saturation optimum trigger level setting is 95.5%. At this level, 66% of true seizures would be detected with a similar specificity of 71% (1-0.288) correctly identifying normal events. A false alarm rate of 29% would occur at this level.

Although oxygen saturation shows better sensitivity and specificity than that seen for percentage heart rate change (*Figure 26*), 95.5% oxygen saturation is not considered to be clinically significant.

1.4.4 Myoclonus

One sample t-tests/paired t-test	n	Mean	St.Deviation	SE Mean	*p*</=
%HR	28	2.2	12.3	2.3	0.359
SAO2					0.001
BEFORE	28	96.1	1.9	0.3	
DURING	28	93.2	4.4	0.8	
Difference	28	2.9	4.0	0.7	

Table 10 Descriptive Statistics for one sample t-test of percentage heart rate change and paired t-test for oxygen saturation during myoclonus

Statistical significance is poor for percentage heart rate change during myoclonus (n=28) with a probability of 0.359 (Table 10). This indicates that there is a lot of variability in the data with a relatively high standard deviation of 12.3% to the mean heart rate change of 2.2%. The variability is nearly 6 times that of the mean heart rate change. Therefore statistically, there is a fairly high probability that the heart rate change could occur by chance.

This is not a surprising result because myoclonus is so brief that a consistent change in heart rate would be unlikely.

It is surprising that paired t-test analysis of oxygen saturation during myoclonus show more of a consistent change for such a brief event with statistical significance of $p<0.001$. The mean oxygen saturation percentage during myoclonus is 93.2%.

Diagnostic testing will indicate whether a seizure alarm would identify myoclonus and give the optimum trigger level. However, it would be more beneficial if an alarm system did not trigger during brief myoclonus.

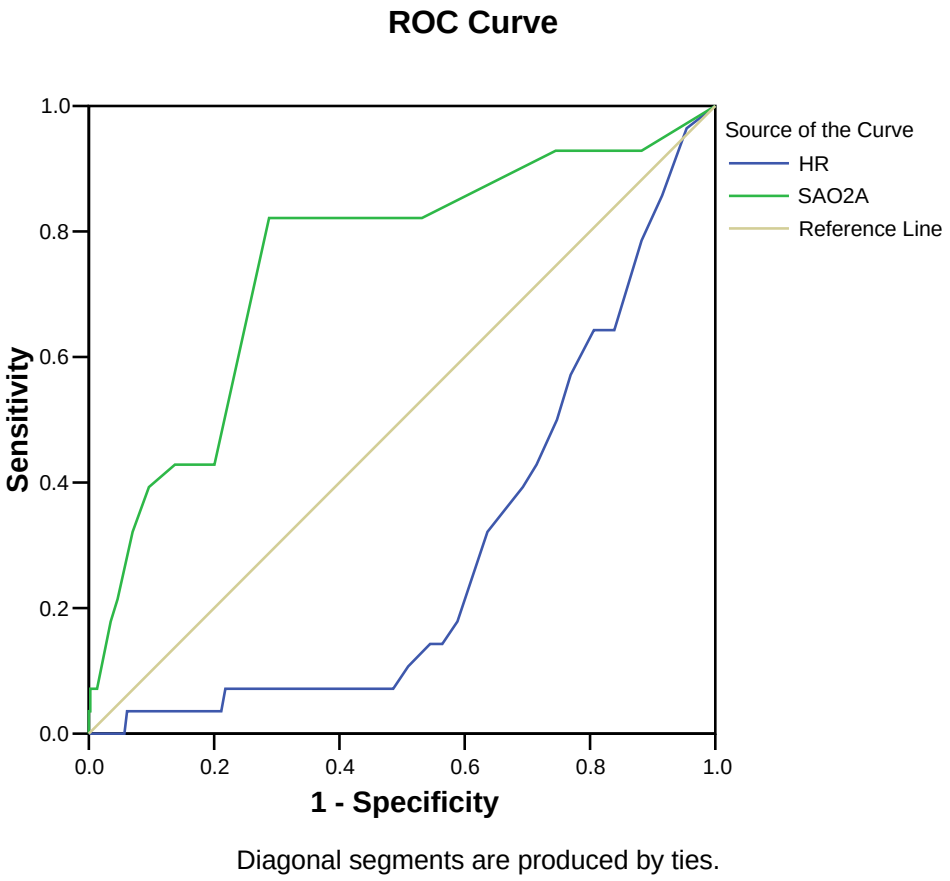


Figure 25 Receiver Operator Curve for diagnostic testing for percentage heart rate change and oxygen saturation during Myoclonus.

Sensitivity and specificity of percentage heart rate change is poor as indicated with the mean changes from the one sample t-test. The best compromise appears to be a trigger level of 9.5% (Figure 25). This offers a sensitivity of true positives of 36% with 64% of missed myoclonus (false

negatives). A specificity of 1- 0.664 (34%) is poor with a high level of false alarms in the order of 66%.

For oxygen saturation, a trigger level of 93.5% indicated as the mean value from paired t-testing for the group gives a poor sensitivity of 43% with 57% of missed seizures. Even though the proportion of false alarms of 14% (false positives) is quite low, an alarm system based at this trigger level would be poor in detecting myoclonus. It is likely that a seizure alarm system based on oxygen saturation would be set at a level of clinical significance i.e 85%. At this level there would not be any false alarms due to myoclonus with an extremely poor sensitivity of 7% myoclonus detection, with 93% missed myoclonic episodes.

This is an encouraging result because it is would be an advantage for a seizure alarm system not to trigger during brief myoclonus.

1.4.5 Section 1 Results Summary.

Seizure Type	n	Mean	St.Deviation	SE.Mean	*p*</=
Generalised Tonic-Clonic Seizures	11	53.3	24.0	7.2	0.001
Tonic Seizures	90	18.9	15.4	1.6	0.001
Absences	35	3.3	7.1	1.1	0.008
Myoclonus	28	2.1	12.3	2.3	0.359

Table 11 Summary of Descriptive Values of one sample t-tests for Percentage Heart Rate during Generalised Seizures.

Seizure Type	n	Mean	St.Deviation	SE.Mean	*p*</=
Generalised Tonic-Clonic Seizures Difference	8	91.2	5.2	1.8	0.018
Tonic Seizures Difference	89	94.7	4.3	0.4	0.001
Absence Seizures Difference	35	94.8	3.5	0.5	0.378
Myoclonus Difference	28	93.2	4.4	0.8	0.001

Table 12 Summary of Descriptive Values of paired t-tests for Oxygen Saturation during Generalised Seizures.

Seizure Type	Proposed Trigger Level	Sensitivity True Positives	Sensitivity False Negatives	Specificity True Negatives	Specificity False Postives
Generalised Tonic-Clonic Seizures	32.5%	88	12	85	15
Tonic Seizures	32.5%	78	22	85	15
Absences	8.5% (or higher to miss events)	31	69	31	69
Myoclonus	9.5% (or higher to miss events)	36	64	34	66

Table 13 Summary of Diagnostic Testing of Percentage Heart Rate during Generalised Seizures

Seizure Type	Proposed Trigger Level.	Sensitivity True Positives	Sensitivity False Negatives	Specificity True Negatives	Specificity False Positives
Generalised Tonic-Clonic Seizures	90.5%	50	50	95	5
Tonic Seizures	95.5%	44	56	71	29
Absence Seizures	95.5% (or higher to miss events).	66	34	71	29
Myoclonus	85% (to miss events).	7	93	100	0

Table 14 Summary of Diagnostic Testing of Oxygen Saturation level during Generalised Seizures.

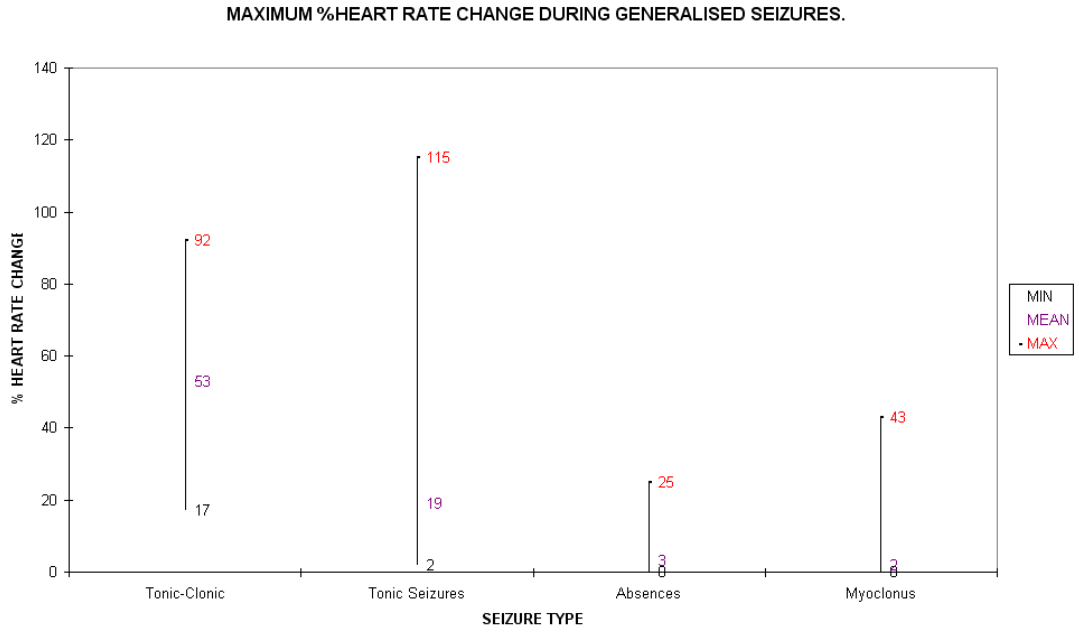


Figure 26 Maximum Percentage Heart Rate Changes during Generalised Seizures.

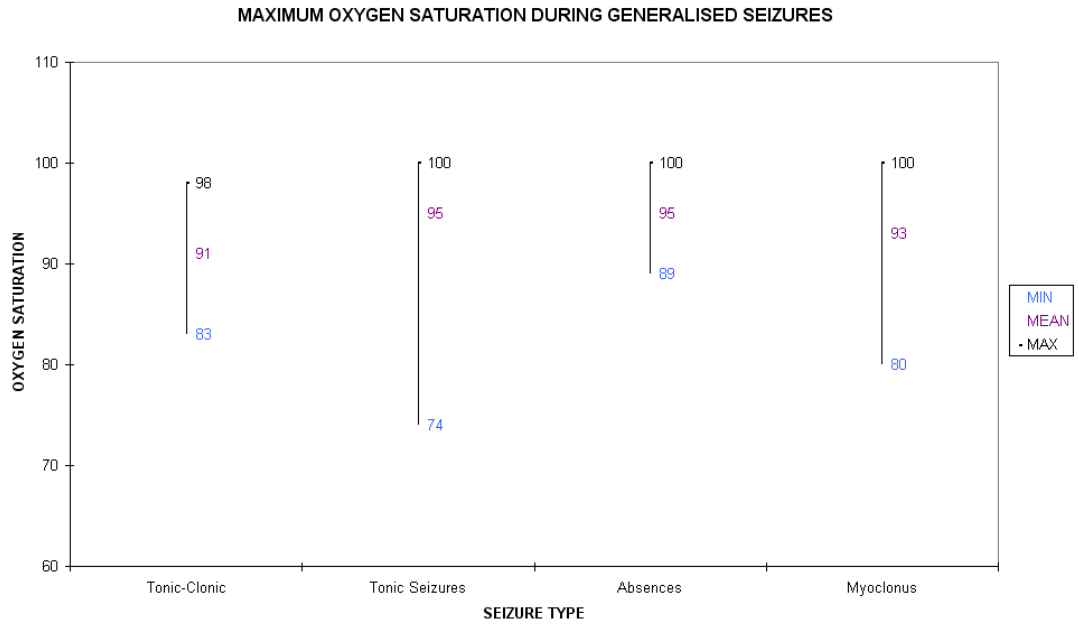


Figure 27 Maximum Oxygen Saturation during Generalised Seizures.

Chapter 5 Results: Focal Seizures

1.5.1 Frontal Lobe Seizures.

One sample t-test/paired t-test	n	Mean	St.Deviation	SE Mean	*p*<
%HR	229	28.3	15.4	1.1	0.001
SAO2					0.001
BEFORE	215	98.9	1.1	0.1	
DURING	215	97.4	4.4	0.3	
Difference	215	1.5	4.3	0.3	

Table 15 Descriptive Statistics for one sample t-test applied to percentage heart rate change and paired t-tests for oxygen saturation during frontal lobe seizures.

High statistical significance $p<0.001$ (Table 15) is seen in both heart rate percentage change (n=229) and oxygen saturation during frontal lobe seizures (n=215). The mean heart rate percentage change of 28.3% is lower than that seen during generalised tonic-clonic seizures but higher than tonic seizures. Many of the frontal lobe seizures have similar changes in heart rate because even though the sample size (229) is large, the standard error of mean is small (1.1).

Oxygen saturation changes demonstrate high statistical significance but the mean oxygen saturation for the total frontal lobe seizure group of 97.4% is not clinically significant.

Section One

Differences in percentage heart rate and oxygen saturation during right and left hemisphere complex focal seizures were tested to analyse differences in the effect of laterality of focal seizures. Data was split into right and left frontal lobe seizures. One sample t-tests of heart rate percentage change and paired t-tests for oxygen saturation before and during seizures were analysed for laterality of seizure. Assumptions of independence are made due to intra and inter-subject variation. Therefore statistical analysis is analysed in terms of seizures and not patients.

Right Frontal Lobe Seizures

One sample t-test/paired t-test	n	Mean	St.Deviation	SE Mean	*p*</=
%HR	13	53.6	39.8	11.0	0.001
SAO2					0.005
BEFORE	12	97.3	3.6	1.0	
DURING	12	83.6	12.1	3.5	
Difference	12	13.6	13.3	3.8	

Table 16 Descriptive Statistics for one sample t-test applied to percentage heart rate change and paired t-test for oxygen saturation during Right Frontal Lobe Seizures.

One sample t-test/paired t-test	n	Mean	St.Deviation	SE Mean	*p*<
%HR	214	26.9	11.1	0.8	0.001
SAO2					0.001
BEFORE	201	99.1	0.5	0.1	
DURING	201	98.3	0.7	0.1	
Difference	201	0.7	0.8	0.1	

Table 17 Descriptive Statistics for one sample t-test applied to percentage heart rate change and paired t-test for oxygen saturation during Left Frontal Lobe Seizures.

Interesting and major differences are seen when data is divided into right (n=13) and left (n=214) frontal lobe seizures in terms of percentage heart rate changes and oxygen saturation. Parameter changes are more marked for right hemisphere frontal lobe seizures (Table 16). The mean percentage heart rate change for the right hemisphere is twice (53.6%) the mean heart rate change seen from the left hemisphere (26.8%), (Table 17).

Mean oxygen saturation percentage changes from the right hemisphere (n=12) are clinically significant (83.7%) compared to the mean oxygen saturation percentage (98.3%) from the left hemisphere (n=201).

High statistical significance is present in all categories of frontal lobe seizure parameter change.

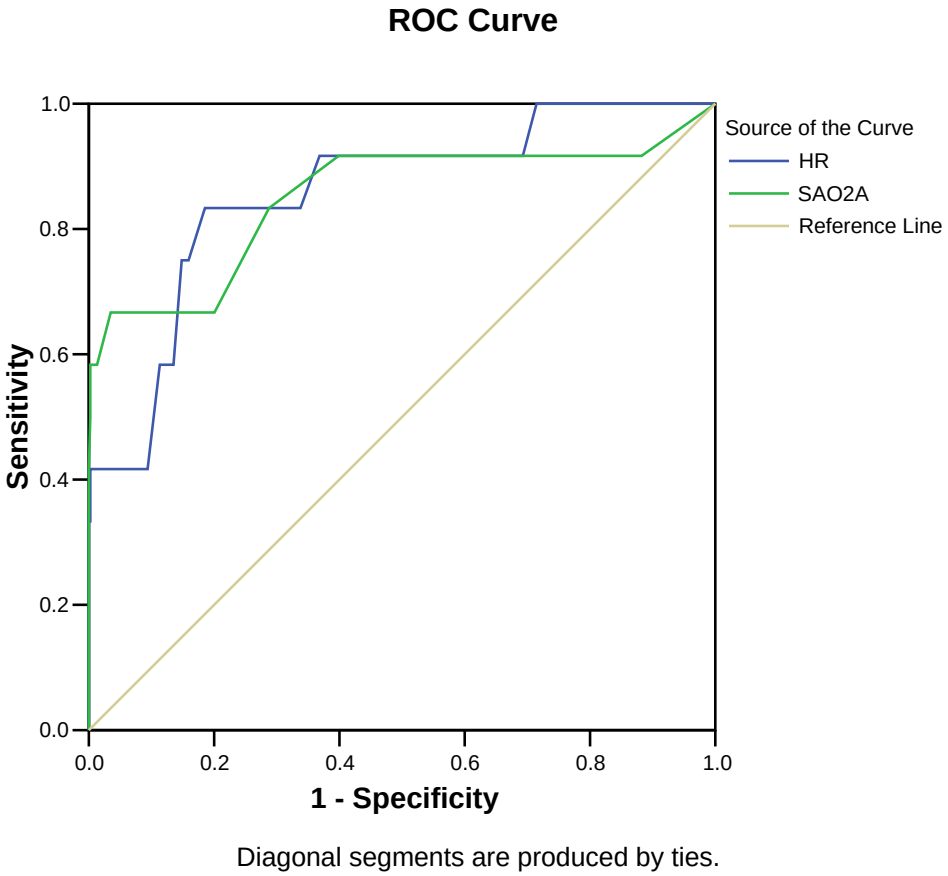


Figure 28 Receiver Operator Curve for diagnostic testing of percentage heart rate and oxygen saturation during frontal lobe seizures.

The optimal trigger level correctly identifying the maximum number of true positives and true negatives without incurring too many false positives during frontal lobe seizures is 30.5% (Figure 28). At this level, it is very close to the mean percentage heart rate change seen for the total group of frontal lobe seizures (28.3%), (Table 15). The specificity value is very slightly better (82% compared to 78%) with the chosen trigger level with slightly less false alarms (18% compared to 22%). With a trigger level of 30.5% a sensitivity of 83% of true seizure detection is very high considering that the sample is

weighted towards left frontal lobe seizures (n=214) which do not tend to show as much percentage heart rate change compared to the right hemisphere (n=13).

The chosen trigger level for oxygen saturation is 89.5% for the best balance in detecting as many frontal lobe seizures without incurring too many false alarms. The sensitivity of 67% is not as high as that seen with percentage heart rate of 83% but a very low level of false alarms would occur of only 3%. It is also worth bearing in mind that not all frontal lobe seizures result in hypoxia so the fact that the sensitivity of detecting frontal lobe seizures using oxygen saturation is not as high as percentage heart rate change is more acceptable especially if both parameters are used in one seizure alarm device.

1.5.2 Temporal Lobe Seizures.

One sample t-tests/paired t-test	n	Mean	St.Deviation	SE Mean	*p*<
%HR	31	28.5	30.1	5.4	0.001
SAO2					0.001
BEFORE	30	96.8	2.5	0.5	
DURING	30	88.9	10.6	1.9	
Difference	30	7.9	10.4	1.9	

Table 18 Descriptive Statistics for one sample t-test applied to percentage heart rate change and paired t-test for oxygen saturation during Temporal Lobe Seizures.

High statistical significance of $p<0.001$ is seen for both parameters during temporal lobe seizures (n=31) (Table 18). Mean percentage heart rate of 28.5% during temporal lobe seizures is a very similar result to that obtained from the total frontal lobe seizure group. A larger standard deviation of 30.1% is seen with the temporal lobe seizure group than that of the frontal lobe group, which would suggest that there is a greater range in heart rate change during temporal lobe seizures. Mean oxygen saturation changes for the group are more clinically significant with values down to 88.9% during temporal lobe seizures (n=30) compared to the frontal lobe seizure group mean oxygen saturation value of 97%. Data for temporal lobe seizures were divided into right and left temporal lobe seizures and statistical analysis for percentage heart rate change and oxygen saturation were analysed.

Section One

Right Temporal Lobe Seizures

One sample t-test/paired t-test	n	Mean	St.Deviation	SE Mean	*p*</=
%HR	15	43.5	22.9	5.9	0.001
SAO2					0.072
BEFORE	15	97.1	3.4	0.9	
DURING	15	91.8	10.9	2.8	
Difference	15	5.2	10.5	2.7	

Table 19 Descriptive Statistics for one sample t-test applied to percentage heart rate change and paired t-test for oxygen saturation during Right Temporal Lobe Seizures.

Left Temporal Lobe Seizures

One sample t-test/paired t-test	n	Mean	St.Deviation	SE.Mean	*p*</=
%HR	16	14.4	29.8	7.4	0.072
SAO2					0.001
BEFORE	15	96.5	1.2	0.3	
DURING	15	86.1	9.8	2.5	
Difference	15	10.5	10.1	2.5	

Table 20 Descriptive Statistics for one sample t-test applied to percentage heart rate change and paired t-test for oxygen saturation during Left Temporal Lobe Seizures.

Very different mean percentage heart rate changes are seen when results from the right (n=15) (Table 19) and left hemisphere (n=16) (Table 20) are compared. A higher change in mean percentage heart rate (43.5%) occurs with right temporal lobe seizures, compared to much smaller mean percentage heart rate change (14.4%) seen from left temporal lobe seizures. High statistical significance is present in percentage heart rate change from both hemispheres with the right hemisphere showing a marginal higher statistical significance ($p<0.001$) compared to the left hemisphere ($p<0.007$). Sample size is equally matched in both groups.

More clinically significant changes in mean oxygen saturation (86.1%) occurred in the left temporal lobe seizure (n=15) group with a high statistical significance of $p<0.001$. Mean oxygen saturation changes appear less clinically significant with values of 91.8% from right temporal lobe seizures (n=15).

Group mean percentage heart rate changes are higher from the right hemisphere for frontal lobe seizures and temporal lobe seizures.

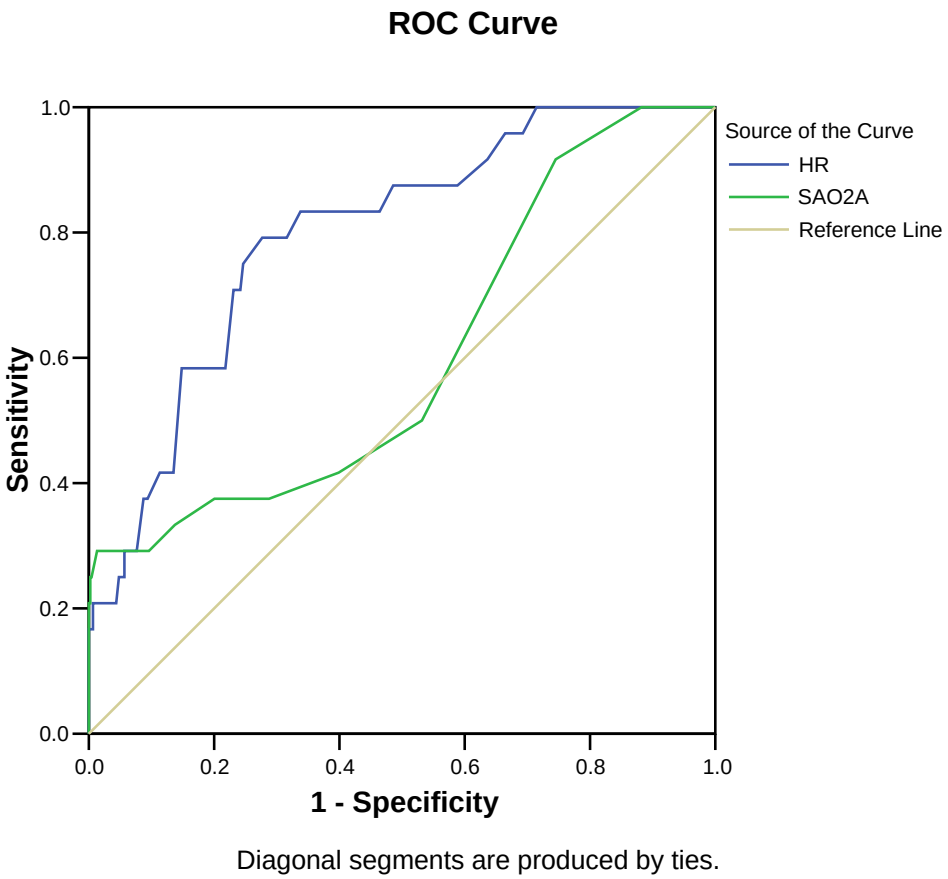


Figure 29 Receiver Operator Curve for diagnostic testing of percentage heart rate change and oxygen saturation during temporal lobe seizures.

From diagnostic testing of percentage heart rate change, the best trigger level of 25.5% is determined with a sensitivity of 75% (Figure 29). At this level the same specificity value is met (1-0.246) at 75%, with 25% false alarm rate.

A mean value of 28.4% was calculated by one sample t-testing for the group for percentage heart rate change (Table 18). If this value were selected as a trigger level, it would result in a lower sensitivity of 58% with more missed

seizures. A slightly higher specificity is encountered of 78% (1-0.218) with a slightly less false alarm proportion of 22%.

A chosen trigger level for oxygen saturation in the detection of temporal lobe seizures is more difficult. Sensitivity falls substantially long before clinically significant oxygen saturation levels are reached. A reasonable trigger level may be 88.5%. Sensitivity is only at 29% but specificity is high (99%) with only 1% false alarm rate. This level may be acceptable for a seizure alarm system if oxygen saturation parameter is used in conjunction with percentage heart rate change, considering that not all temporal lobe seizures result in hypoxia but 29% seizures would be detected by this parameter.

1.5.3 Simple Focal Seizures

One sample t- test / paired t-test.	n	Mean	St.Deviation	SE Mean	*p*</=
%HR	102	-3.6	8.6	0.8	0.001
SAO2					0.442
BEFORE	98	98.3	0.9	0.1	
DURING	98	98.2	1.9	0.2	
Difference	98	0.1	1.8	0.2	

Table 21 Descriptive statistics for one sample t-test applied to percentage heart rate change and paired t-test for oxygen saturation during simple focal seizures.

A small mean percentage change in heart rate is seen in simple focal seizures with a high statistical significance $p<0.001$ (Table 21). Compared to other

seizure types this group shows similar changes to absences. Simple focal seizures tend to show a small decrease in percentage heart rate (-3.6%) rather than an increase. It is due to this consistency and small standard error around the mean that has lead to high statistical significance.

Oxygen saturation is not clinically significant or statistically significant $p=0.442$ in simple focal seizures.

Due to a small change in percentage heart rate and oxygen saturation it is unlikely that trigger levels on a seizure alarm device would identify simple focal seizures from normal physiological events.

Diagnostic testing of simple focal seizures was not possible as 95 of the 102 seizures were derived from one patient. This disproportion would skew results and even calculating descriptive statistics for this type of seizure is more reflective for an individual rather than a group of people. Diagnostic testing could also not be performed on this subset of data as only a few physiological events were captured for the patient who had 95 simple focal seizures.

1.5.4 Neonatal Seizures.

One sample t-test/ paired t-test	n	Mean	St.Deviation	SE.Mean	*p*</=
%HR	10	8.1	13.9	4.4	0.098
SAO2					1.0
BEFORE	7	98.0	0.0	0.0	
DURING	7	98.0	0.0	0.0	
Difference	7	0.0	0.0	0.0	

Table 22 Descriptive Statistics for one sample t-test applied to percentage heart rate change and paired t-test for oxygen saturation during Neonatal Focal Seizures

In the neonatal group (n=10), only a small change in mean percentage heart rate (8.1%) is seen (Table 22). Statistically, the results are also less significant than seen in previous seizure groups and demonstrate a poor significance of $p = 0.098$. This indicates that this small change in percentage heart rate is quite likely to have occurred through chance.

No change was seen when comparing the oxygen saturation (n=7) before the neonatal seizure to the oxygen saturation during the neonatal seizure. This result is unique to this group.

Statistical indications of mean percentage heart rate change and oxygen saturation during these seizures make it unlikely that useful trigger levels provided by diagnostic testing will be available for the neonatal seizure group.

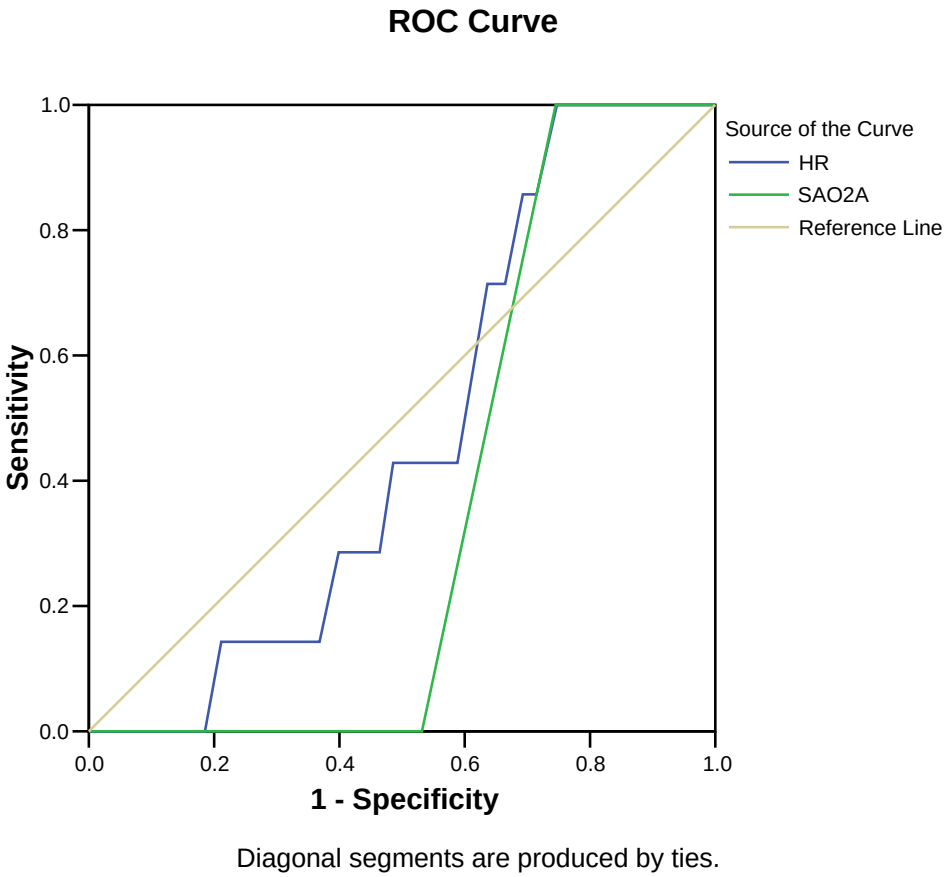


Figure 30 Receiver Operator Curve for diagnostic testing of percentage heart rate change and oxygen saturation during neonatal seizures

With a trigger level of 8.5% (representing the mean percentage heart rate change) gives a sensitivity of 86% true positives are shown in diagnostic testing (Figure 30) of neonatal seizures. However, it also gives a poor specificity of only 31% (1-0.693) and a resultant high false alarm rate of 69%.

The compromise necessary in this case is a trigger level of 15.5%. This remains a very poor option however with sensitivity of 43% and specificity of 51%. This leaves a high false alarm rate of 49%, so if the alarm triggered, it may or may not be because of a seizure as it has equal proportions.

Oxygen saturation trigger level of 98% (mean value of the group) presents an interesting cut off for diagnostic testing. At a trigger level of 98.5%, 100% of seizures would be identified but with very high false alarm rates of 74%. At a trigger level of 97.5%, zero sensitivity is displayed with no identification of seizures and 53% of false positives.

Realistically, oxygen saturation is a very poor indicator for detecting neonatal seizures in this group. Percentage heart rate change is also poor where it may or may not indicate a seizure is occurring in equal proportions.

1.5.5 Sub-clinical Seizures

One sample t-tests/paired t-test	n	Mean	St.Deviation	SE.Mean	*p*</=
%HR	83	2.3	9.3	1.0	0.025
SAO2					0.004
BEFORE	72	96.7	1.8	0.2	
DURING	72	96.3	1.9	0.2	
Difference	72	0.4	1.2	0.1	

Table 23 Descriptive Statistics for one sample t-test applied to percentage heart rate change and paired t-test for oxygen saturation during Sub-clinical Seizures.

Barely statistical significance (p=0.025) for percentage changes in heart rate occurred during eighty three sub-clinical seizures for the group with small mean heart rate percentage changes of 2.3% (Table 23). The standard deviation of the mean percentage heart rate is proportionally large (9.3%) which has led to poor statistical significance.

Oxygen saturation (n=72) changes show more consistent values of 96.3% during sub-clinical seizures with very minimal variation indicated by the standard deviation of 1.9%. This has resulted in a high statistical significance of p=0.004 which does not reflect clinical significant oxygen saturation levels of 96% that are well within normal range.

It would be useful to perform diagnostic testing on this group to determine whether a seizure alarm system would be likely to be affected by changes in heart rate and oxygen saturation during sub-clinical seizures.

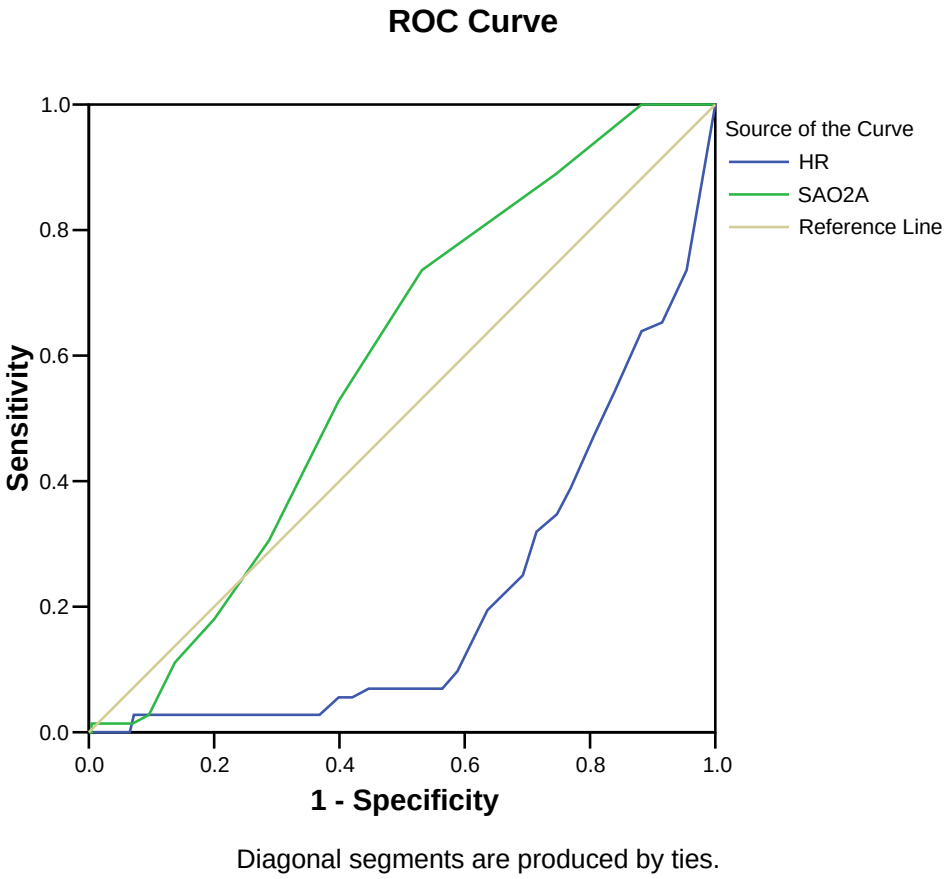


Figure 31 Receiver Operator Curve for diagnostic testing of percentage heart rate change and oxygen saturation during Sub-clinical Seizures.

As the receiver operator curve suggests (Figure 31), a poor sensitivity and specificity rating is seen in percentage heart rate change and oxygen saturation for sub-clinical seizures.

A trigger level of 8.5% offers a sensitivity of 25% with 75% missed sub-clinical seizures. The specificity of 31% (1-0.693) results in a false alarm proportion of 69%. Ideally however an alarm system should ignore sub-clinical seizures and therefore a trigger level of 25.5% or higher would reduce sensitivity to 3%.

The closest balance of sensitivity and specificity for oxygen saturation is a trigger level of 96.5%. At this level, a sensitivity of 53% is seen with 47% missed sub-clinical seizures. A specificity of 60% results in a false positives of 40% . This may seem better but this level of oxygen saturation is not likely to be used in an alarm device, as this level is not clinically significant.

If the trigger level was set to 86.5% oxygen saturation level, then no sub-clinical seizures would be detected with a sensitivity of 0 and no false alarms would be triggered.

This is an encouraging result as it would be preferable if sub-clinical seizures were unlikely to trigger a seizure alarm system.

1.5.6 Summary

Seizure type	n	Mean	St.Deviation	SEMean	*p*</=
Frontal Lobe	229	28.3	15.4	1.0	0.001
Right Frontal Lobe	13	53.6	39.8	11.0	0.001
Left Frontal Lobe	214	26.9	11.1	0.8	0.001
Temporal Lobe	31	28.5	30.1	5.4	0.001
Right Temporal Lobe	15	43.5	22.9	5.9	0.001
Left Temporal Lobe	16	14.4	29.8	7.4	0.072
Simple Focal	102	-3.6	0.9	0.1	0.001
Neonatal	10	8.1	13.9	4.4	0.098
Sub-clinical	83	2.3	9.3	1.0	0.025

Table 24 Summary of Descriptive Values of One Sample t-tests for Percentage Heart Rate Change during Focal Seizures.

Seizure type	n	Mean	St.Deviation	SEMean	*p*</=
Frontal Lobe	215	97.4	4.4	0.3	0.001
Right Frontal Lobe	12	83.6	12.1	3.5	0.005
Left Frontal Lobe	201	98.3	0.7	0.1	0.001
Temporal Lobe	30	88.9	10.6	1.9	0.001
Right Temporal Lobe	15	91.8	10.9	2.8	0.072
Left Temporal Lobe	15	86.1	9.8	2.5	0.001
Simple Focal	98	98.2	1.9	0.2	0.442
Neonatal	7	98.0	0.0	0.0	1.0
Sub-clinical	72	96.3	1.9	0.2	0.004

Table 25 Summary of Descriptive Values of Paired t-tests for oxygen saturation during Focal Seizures

Seizure type	Proposed Trigger Level	Sensitivity True Positives	Sensitivity False Negatives	Specificity True Negatives	Specificity False Positives
Frontal Lobe Seizures	30.5%	83	17	82	18
Temporal Lobe Seizures	25.5%	75	25	75	25
Neonatal Seizures	15.5%	43	57	51	49
Sub-clinical Seizures	>25.5 % (to miss events)	3	97	75	25

Table 26 Summary of Diagnostic Testing for Percentage Heart Rate in Focal Seizures.

Seizure type	Proposed Trigger Level	Sensitivity True Positives	Sensitivity False Negatives	Specificity True Negatives	Specificity False Positives
Frontal Lobe Seizures	89.5%	67	33	97	3
Temporal Lobe Seizures	88.5%	29	71	99	1
Neonatal Seizures	98.5%	100	0	26	74
Sub-clinical Seizures	86.5% (to miss events)	0	100	100	0

Table 27 Summary of Diagnostic Testing for Oxygen Saturation levels in Focal Seizures

Summary of Maximum Changes in Percentage Heart Rate Change and Oxygen Saturation during Focal Seizures.

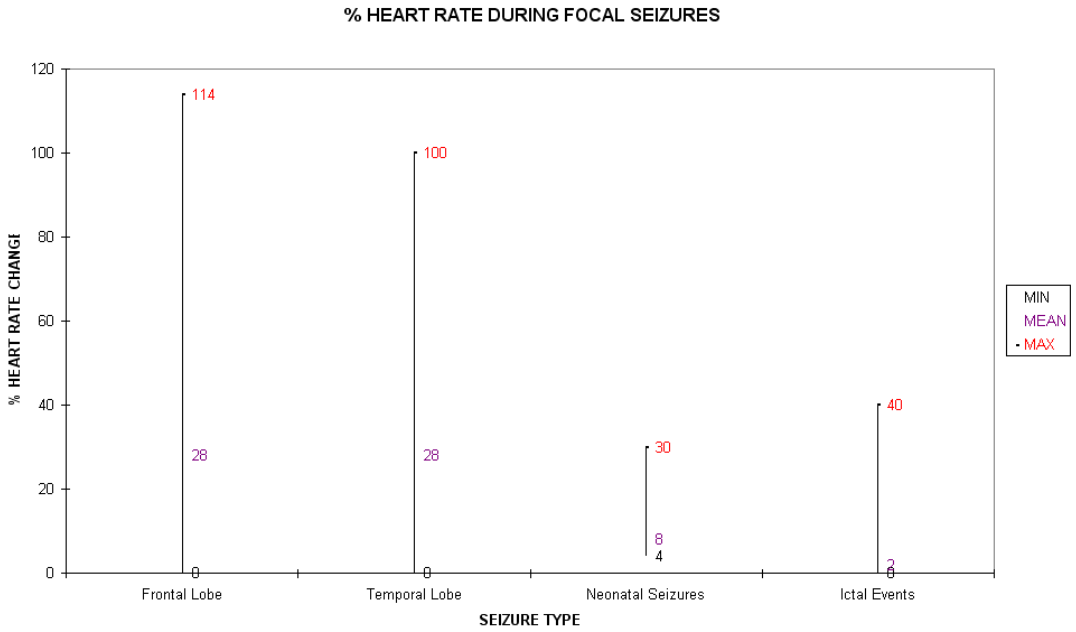


Figure 32 Minimum, Mean and Maximum Values of Percentage Heart Rates Changes during Focal Seizures.

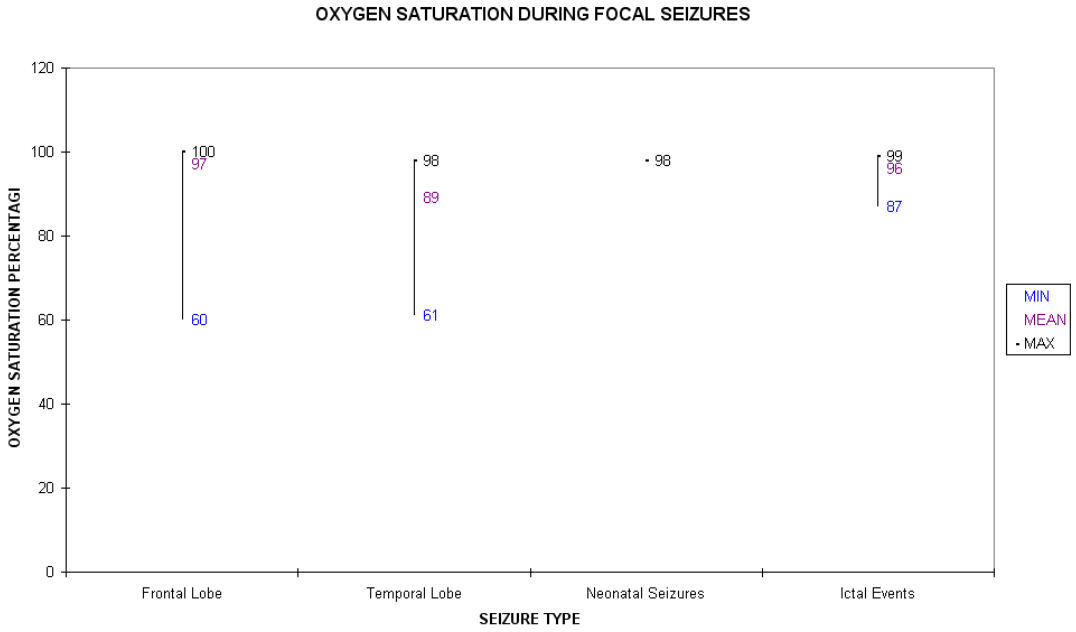


Figure 33 Minimum, Mean and Maximum Values for Oxygen Saturation during Focal Seizures

Summary of Maximum Changes in Percentage Heart Rate Change and Oxygen Saturation during Right / Left Focal Seizures.

Figure 34 Minimum, Mean and Maximum Values of Percentage Heart Rates Changes during Right / Left Focal Seizures.

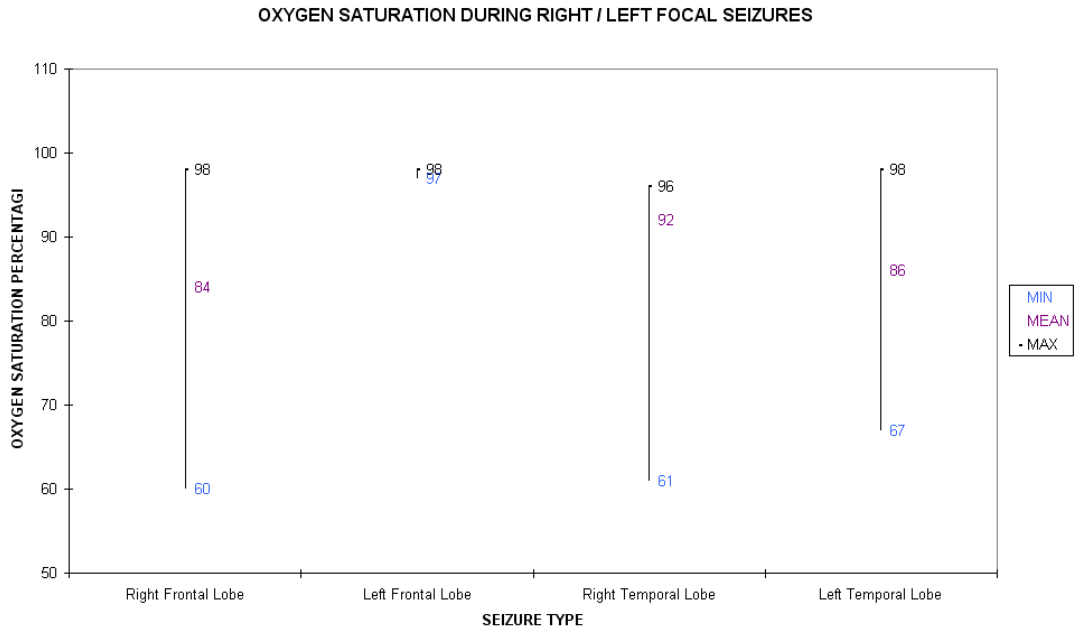


Figure 35 Minimum, Mean and Maximum Values for Oxygen Saturation during Right / Left Focal Seizures

Chapter 6 Results: Normal Physiological Events.

One sample t-tests were applied to percentage heart rate changes during the total normal physiological events group (n=496) and then were analysed for each sub-group of normal physiological event. Paired t-tests of oxygen saturation values were calculated for the total normal physiological events group (n=462) and separately for each sub-group of normal physiological event.

1.6.1 Total Normal Physiological Events.

Both percentage heart rate change and oxygen saturation changes from baseline to during events show high statistical significance of $p<0.001$. This indicates that the recorded changes overall are very consistent and are unlikely to be due to chance.

One sample t-test/paired t-test	n	Mean	St.Deviation	SE.Mean	*p*<
%HR	496	16.5	14.4	0.6	0.001
SAO2					0.001
BEFORE	462	96.7	2.7	0.1	
DURING	462	96.4	3.1	0.1	
Difference	462	0.3	1.6	0.1	

Table 28 Descriptive Statistical Analysis of One Sample t-test for Percentage Heart Rate change and Paired t-test for Oxygen Saturation during Total Normal Physiological Events.

The mean percentage change in heart rate for the group of 16% (Table 28) is less than the mean percentage change in heart rate seen during the total seizure group of 21.8%. (Table 4) The total seizure group also demonstrates a much higher level of standard deviation (30%) compared to this normal data of 14%. The oxygen saturation change during normal events overall is only slight (0.3%) and mean values are not clinically significant at 96%. A small standard deviation (3%) during the events indicates that most of the data is close to the mean value.

1.6.2 Arousal.

The mean average heart rate percentage change of 190 arousal events is 21% (Table 29). This represents data from a wide age range of patients and the changes indicate consistency to result in a high significance of $p<0.001$. Oxygen saturation is barely significant with $p=0.05$ and very little change in oxygen saturation occurs during these events (n=174).

One sample t-test/paired t-test	n	Mean	St.Deviation	SEMean	*p*</=
%HR	190	21.0	13.5	0.9	0.001
SAO2					0.049
BEFORE	174	96.4	2.9	0.2	
DURING	174	96.2	3.2	0.2	
Difference	174	0.2	1.2	0.1	

Table 29 Descriptive Statistical Analysis of One Sample t-test for Percentage Heart Rate change and Paired t-test for Oxygen Saturation during Arousal.

1.6.3 Coughing.

Thirty-four events of coughing were analysed for statistical significance for change in percentage heart rate and oxygen saturation. A small mean change in percentage heart rate of 6.4% is calculated for the group (Table 30), which shows statistical significance of $p<0.001$. Oxygen Saturation change (n=33) is neither clinically or statistically significant.

One sample t-test/paired t-test	n	Mean	St.Deviation	SE.Mean	*p*</=
% HR	34	6.4	9.5	1.6	0.001
SAO2					0.513
BEFORE	33	96.1	2.7	0.5	
DURING	33	96.0	2.9	0.5	
Difference	33	0.1	1.0	0.2	

Table 30 Descriptive Statistical Analysis of One Sample t-test for Percentage Heart Rate change and Paired t-test for Oxygen Saturation during Coughing.

1.6.4 Crying.

A mean percentage heart rate change of 13% is calculated for the group (n=15) during crying (Table 31), with high statistical significance of $p<0.001$. Oxygen saturation of 97% is not clinically significant (n=11) and demonstrates a poor statistical significance of $p=0.132$.

One sample t-test/paired t-test	n	Mean	St.Deviation	SE.Mean	*p*</=
%HR	15	13.0	12.5	3.2	0.001
SAO2					0.132
BEFORE	11	97.7	0.5	0.1	
DURING	11	97.1	1.4	0.4	
Difference	11	0.6	1.3	0.4	

Table 31 Descriptive Statistical Analysis of One Sample t-test for Heart Rate Percentage change and paired t-test for Oxygen Saturation during Crying

1.6.5 Laughing

A small percentage change in heart rate of 5% is calculated for the group (Table 32), A small variability of 4% standard deviation indicates that overall heart rate changes are small during laughing events (n=22). Similarly, very little change is seen in oxygen saturation.

One sample t-test/paired t-test	n	Mean	St.Deviation	SEMean	*p*</=
%HR	22	5.0	4.1	0.9	0.001
SAO2					0.732
BEFORE	22	97.2	1.4	0.3	
DURING	22	97.1	1.1	0.2	
Difference	22	0.1	1.2	0.3	

Table 32 Descriptive Statistical Analysis of One Sample t-tests for Heart Rate change and paired t-test for Oxygen Saturation during laughing.

1.6.6 Stretching.

Percentage heart rate change of 14.8% is calculated for the group (n=36) (Table 33). This is a similar change to that seen during sneezing (15.3%) and crying (13%). It produces a medium change in percentage heart rate during normal physiological events. Statistical significance of $p<0.001$ for percentage in heart rate change occurs during stretching for the group. This high statistical significance indicates that there is a consistent change in heart rate during the event.

One sample t-test/paired t-test	n	Mean	St.Deviation	SE.Mean	*p*</=
%HR	36	14.8	12.2	2.1	0.001
SAO2					0.258
BEFORE	36	96.3	2.9	0.5	
DURING	36	96.2	3.0	0.5	
Difference	36	0.1	0.8	0.1	

Table 33 Descriptive Statistical Analysis of One Sample t-tests for Heart Rate change and Paired t-test for Oxygen Saturation during Stretching.

1.6.7 Sneezing.

A higher mean percentage heart rate change of 15% is seen during sneezing (Table 34) compared to that produced by coughing (6.3%) (Table 30), crying (13%) (Table 31) and laughing (5%) (Table 32) but is not as high as that seen from arousal (21%), (Table 29). Very little oxygen saturation change occurs during a sneezing event.

One sample t-test/paired t-test	n	Mean	St.Deviation	SE.Mean	*p*</=
%HR	10	15.3	10.0	3.2	0.001
SAO2					0.177
BEFORE	10	96.5	3.8	1.2	
DURING	10	97.0	3.7	1.2	
Difference	10	0.5	1.1	0.3	

Table 34 Descriptive Statistical Analysis of One Sample t-test for Heart Rate change and paired t-test for Oxygen Saturation during Sneezing

1.6.8 Turning over in bed.

The same mean percentage change in heart rate (21%) is seen during turning over in bed (n=141) (Table 35) to that occurring during arousal (Table 29). The standard deviation indicates that this percentage change in heart rate during this event can increase further by 14%. Oxygen saturation effectively remains the same during this normal event (n=133).

One sample t-test/paired t-test	n	Mean	St.Deviation	SE.Mean	*p*</=
%HR	141	20.9	14.1	1.2	0.001
SAO2					0.132
BEFORE	133	96.9	2.4	0.2	
DURING	133	96.7	2.7	0.2	
Difference	133	0.2	1.9	0.2	

Table 35 Descriptive Statistical Analysis of One Sample t-tests for Heart Rate change and Paired t-test for Oxygen Saturation during Turning Over in Bed.

1.6.9 Yawning.

In this group, the percentage heart rate change 0.5% (n=48) and oxygen saturation (n=44) show a low statistical significance (Table 36). This suggests that the changes are so variable during yawning, that there lacks consistency and similar results may have been recorded by chance.

One sample t-test/paired t-test	n	Mean	St.Deviation	SE.Mean	*p*</=
%HR	48	0.5	9.9	1.4	0.728
SAO2					0.269
BEFORE	44	97.9	1.5	0.2	
DURING	44	97.7	1.8	0.3	
Difference	44	0.2	1.2	0.2	

Table 36 Descriptive Statistical Analysis of One Sample t-tests for Heart Rate change and paired t-test for Oxygen Saturation during Yawning.

1.6.10 Summary of Mean Values (during normal events).

Normal Physiological Event Group	Mean % Heart Rate Change	n	One sample t-test *p</=*	Mean Oxygen Saturation (during)	n	Paired t-test *p</=*
Total	16.5	496	0.001	96.4	462	0.001
Arousal	21.0	190	0.001	96.2	174	0.049
Coughing	6.4	34	0.001	96.0	33	0.513
Crying	13.0	15	0.001	97.1	11	0.132
Laughing	5.0	22	0.001	97.1	22	0.732
Stretching	14.8	36	0.001	96.2	36	0.258
Sneezing	15.3	10	0.001	97.0	10	0.177
Turning over in bed.	20.9	141	0.001	96.7	133	0.132
Yawning	0.5	48	0.728	97.7	44	0.269

Table 37 Summary of Mean Values during Normal Events

1.6.11 Maximum, Mean and Minimum Values

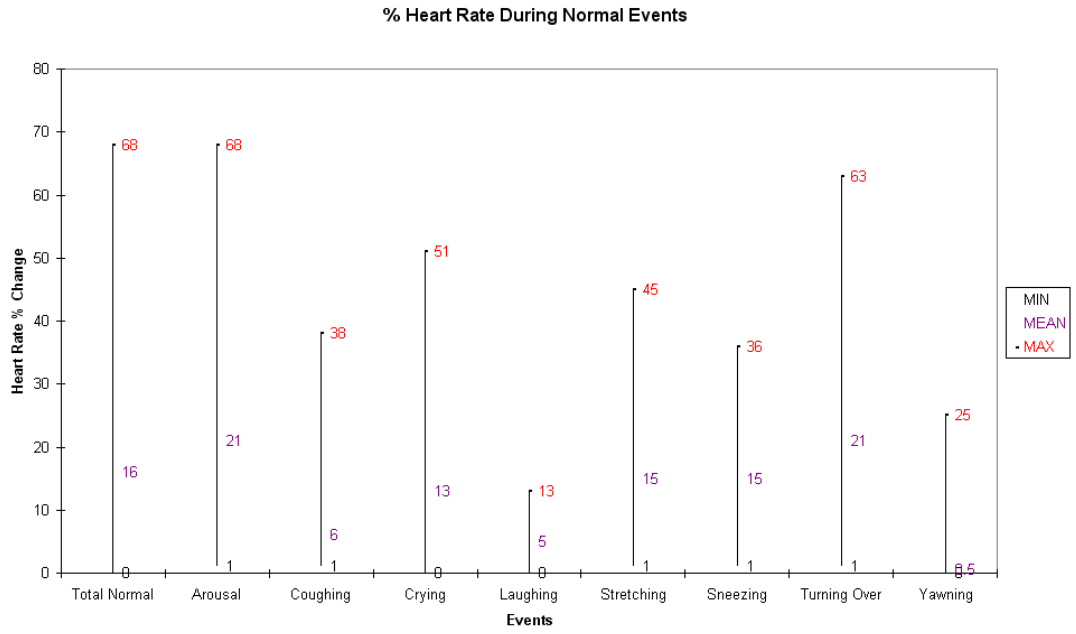


Figure 36 Minimum, Mean and Maximum values of Percentage Heart Rates Changes during Normal Events.

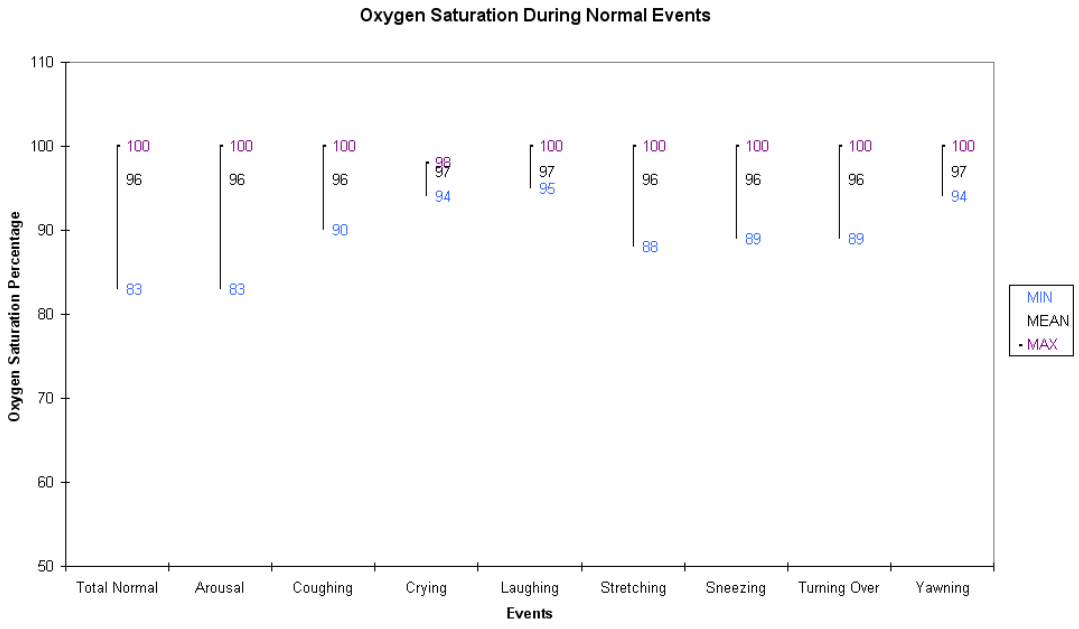
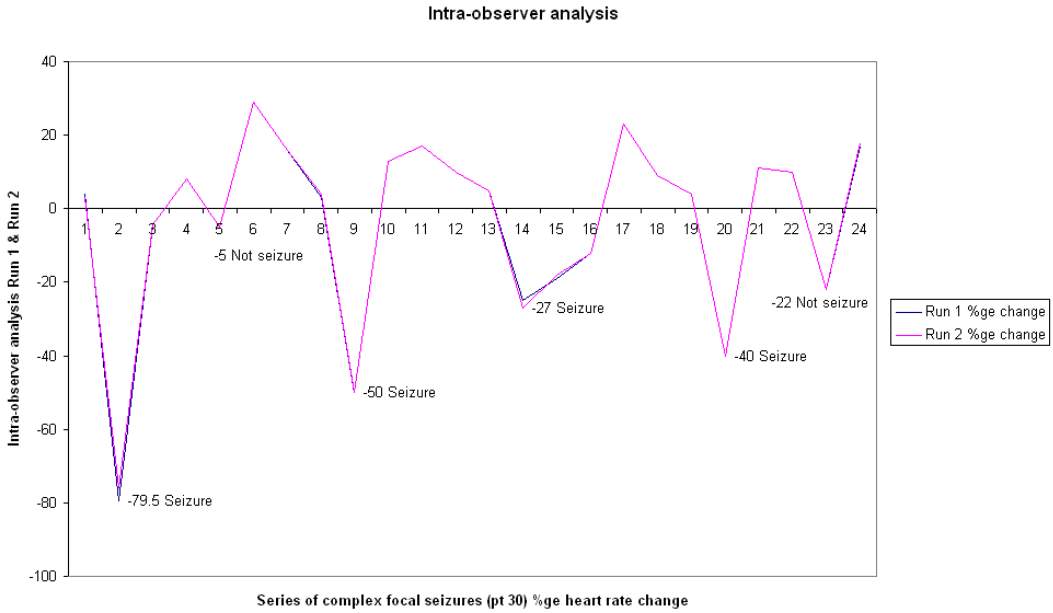


Figure 37 Minimum, Mean and Maximum values for Oxygen Saturation during Normal Events

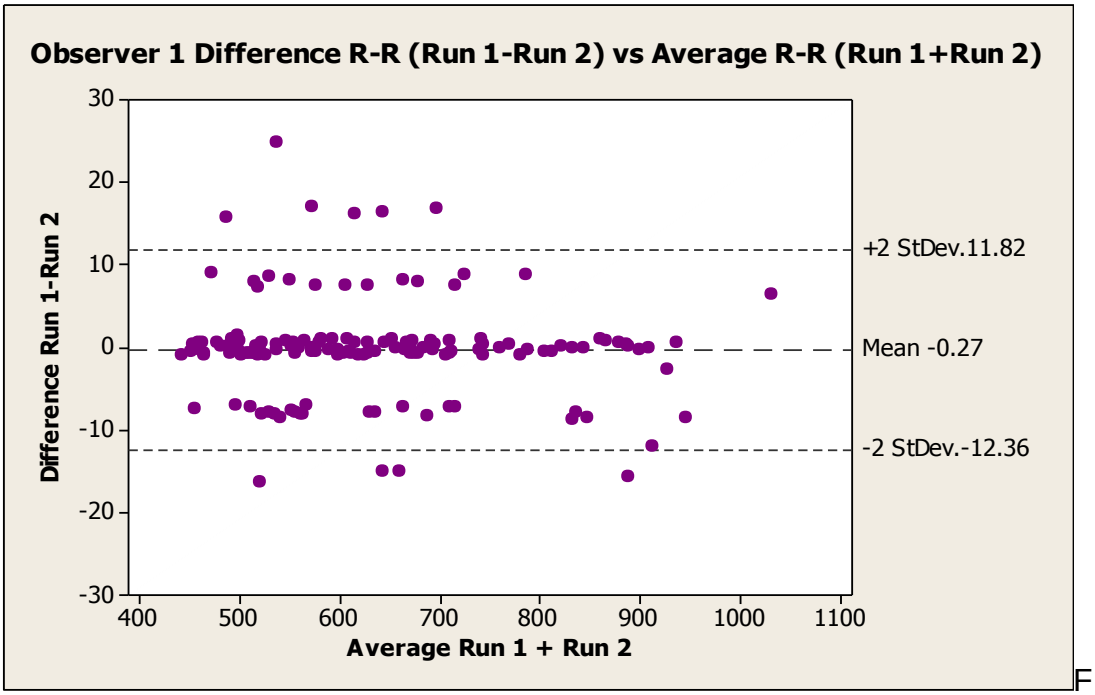
Chapter 7 Results

1.7.1 Intra-observer Analysis



F

Figure 38 Time series plot of consecutive 9 second epochs comparing Run 1 & Run 2 (Observer 1)



F

Figure 39 Bland & Altman plot for Observer 1 R-R Measurements. Limits of agreement of Difference between Run 1 and Run 2 are 8 and -12 msec. (± 2 standard deviations)

Observer 1 (Ruth)	Run1 (msec)	Run 2 (msec)	Difference (msec)	Average (msec)
Total count n (R-R intervals)	146	146	146	146
Mean	631.1	631.4	-0.267	631.2
Standard Error of Mean	11.0	11.0	0.5	11.0
Standard Deviation	132.5	133.1	6.045	132.8
Minimum	448	448	-16.0	448
Q1	520.0	520.0	0	519
Median	608.0	608.0	0	608
Q3	712.0	706.0	0	709
Maximum	1030.0	1024.0	24	1027
Range	582.0	576.0	40	579

Table 38 Descriptive statistics Observer 1 Run 1 and Run 2 (Observer 1)

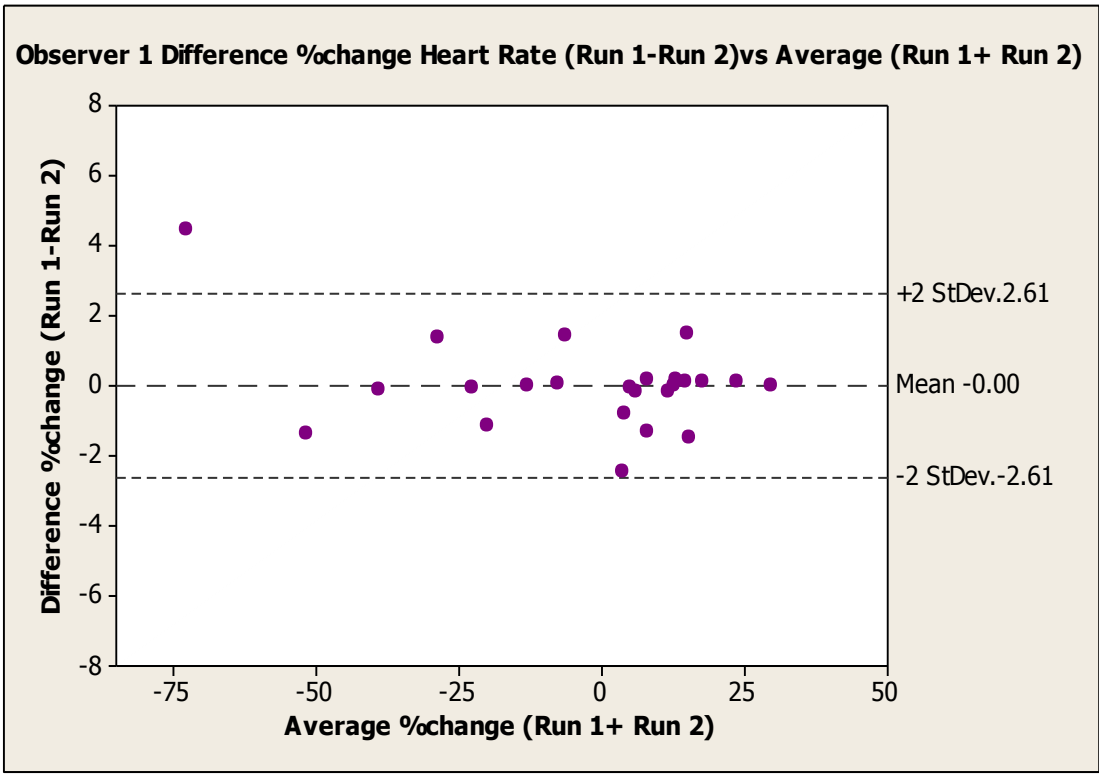


Figure 40 Bland & Altman plot Observer 1 Limits of Agreement on Difference in heart rate percentage change between Run 1 and Run 2 are 1.6% and -2.4% (± 2 standard deviations).

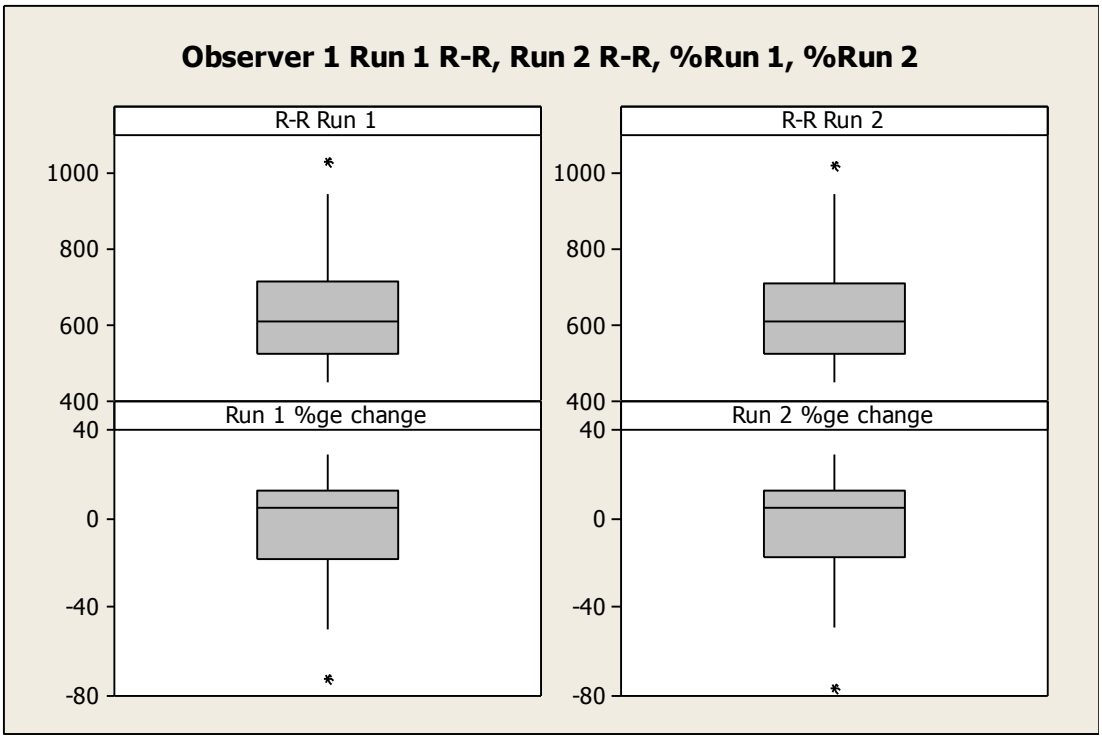


Figure 41 Box plot comparison of observer 1 R-R interval measurements and heart rate percentage change analysis of Run 1 and Run 2.

Observer 1 (Ruth)	Run1 (% change)	Run 2 (% change)	Difference	Average
n	24	24	24	24
Mean	(-3.01)	(-3.01)	0	-3.01
Standard Error of Mean	5.04	5.15	0.266	5.1
Standard Deviation	24.7	25.2	1.3	24.9
Minimum	(-72.5)	(-76.8)	-2.4	-74.6
Q1	(-17.9)	(-17.0)	-0.6	-17.4
Median	4.8	4.8	0	4.8
Q3	12.7	12.7	0	12.7
Maximum	29.2	29.2	4.3	29.2
Range	101.6	105.9	6.8	103.8

Table 39 Descriptive statistics Observer 1 percentage change Run 1 and Run 2.

A close relationship is found between Run 1 and Run 2 for observer 1 measurements (n=146) (Table 39) with a mean difference of 0 milliseconds and mean percentage change difference of (-0.001) % Limits of agreement are 8 msec and (-12) msec, 1.6% and (-2.4) % (±2 standard deviations).

Section One

Observer 2

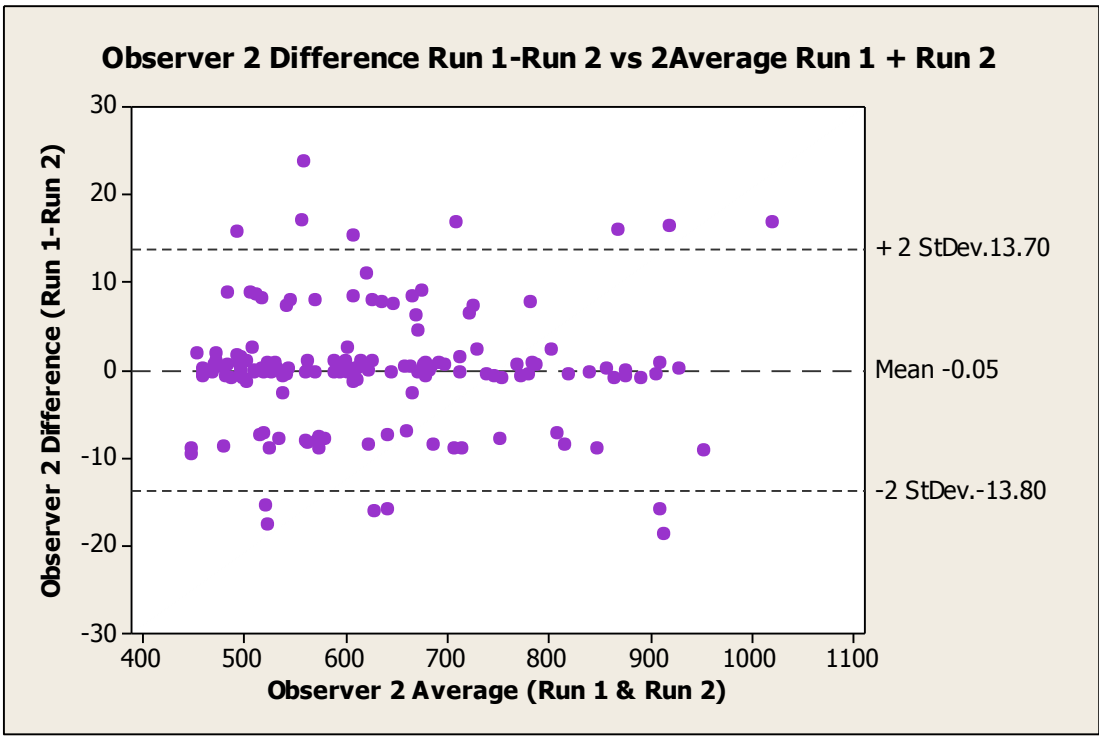


Figure 42 Bland & Altman plot Observer 2 Limits of Agreement between Run 1 & Run 2. Limits of Agreement of difference are -10 and 10 msec.(± 2 standard deviations).

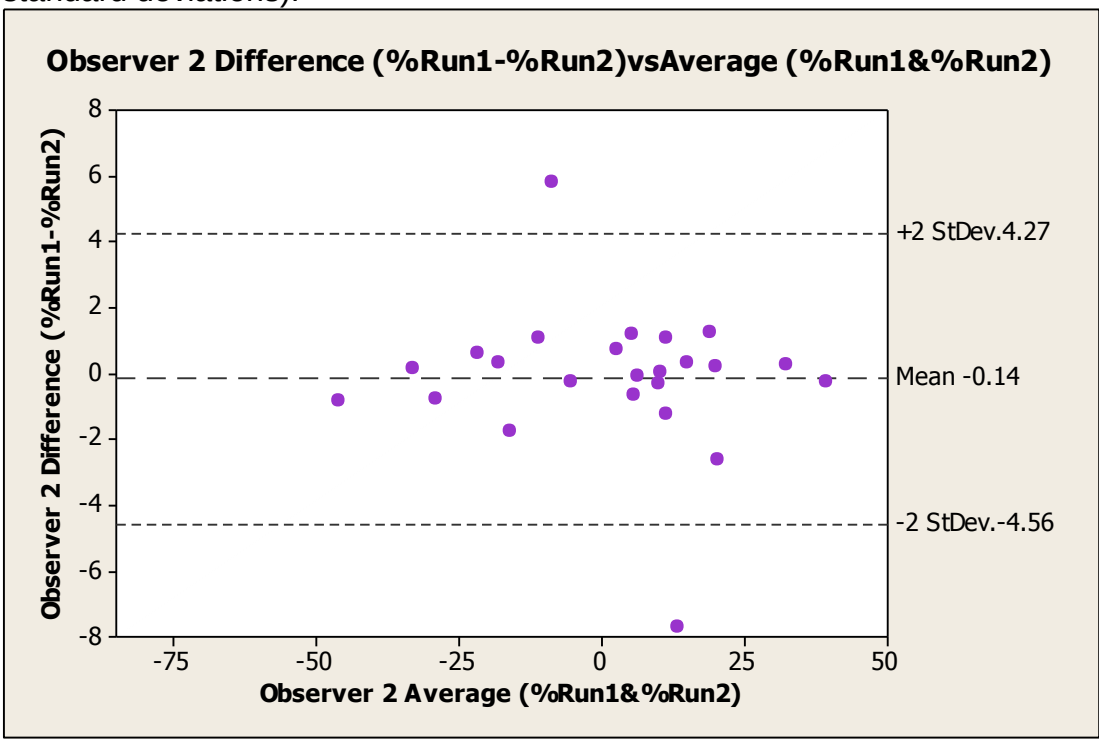


Figure 43 Bland & Altman plot Observer 2 Difference in heart rate percentage change between Run 1 and Run 2. Limits of Agreement of Difference is 1.04% and -2.32% (± 2 standard deviations)

Observer 2 (Thea)	Run1 (msec)	Run 2 (msec)	Difference (msec)	Average (msec)
Total count n (R-R intervals)	146	146	146	146
Mean	630.8	630.9	-0.1	630.9
Standard Error of Mean	11.0	11.0	0.5	11.0
Standard Deviation	133.2	133.1	6.875	133.1
Minimum	448	448	-18	448
Q1	520	520	-0.25	516
Median	608	608	0	608
Q3	712	707	0.5	709.5
Maximum	1040	1024	24	1032
Range	592	576	42	584

Table 40 Descriptive statistics Observer 2 Run 1 and Run 2.

Observer 2 (Thea)	Run1 (% change)	Run 2 (% change)	Difference	Average
n	24	24	24	24
Mean	1.7	1.8	-0.1	1.7
Standard Error of Mean	4.2	4.3	0.4	4.2
Standard Deviation	20.8	21.1	2.2	20.9
Minimum	(-44.3)	(-43.4)	(-7.5)	(-43.9)
Q1	(-15.1)	(-14.0)	(-0.8)	(-14.5)
Median	5.5	5.0	0	5.3
Q3	14.6	16.2	0.8	14.5
Maximum	41.2	41.2	6.1	41.2
Range	85.5	84.6	13.7	85.1

Table 41 Descriptive statistics for Observer 2 percentage change Run 1 and Run 2.

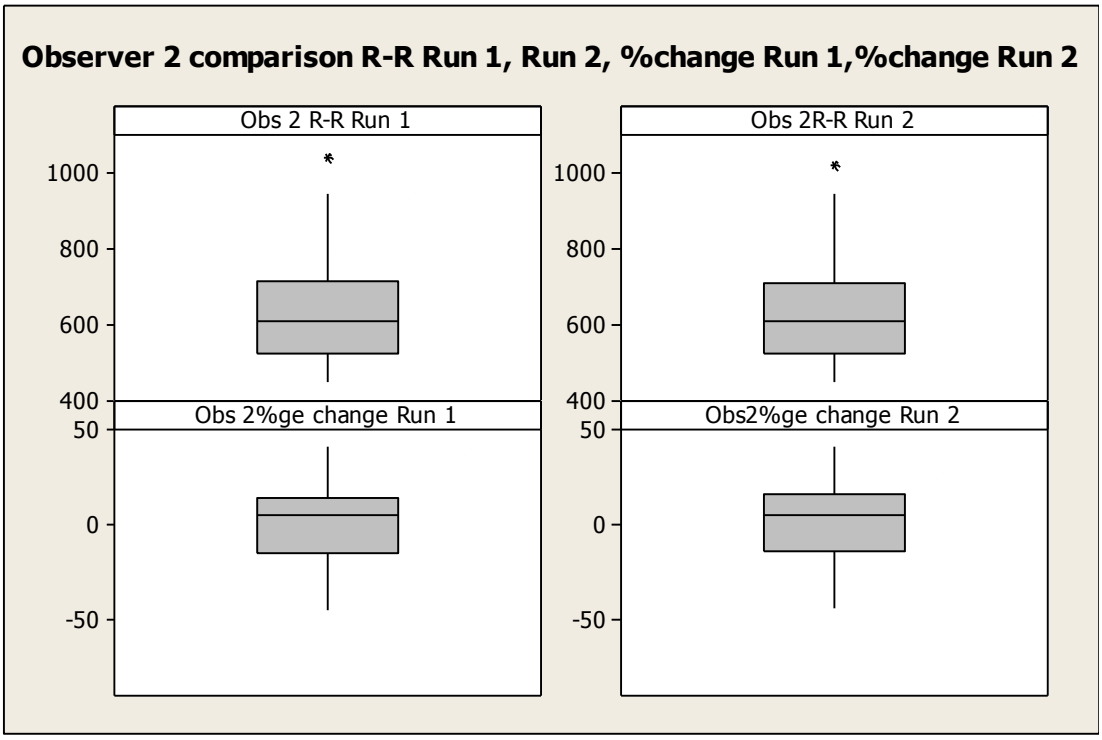


Figure 44 Boxplot Observer 2 R-R Run 1, R-R Run 2, percentage changes Run 1 and percentage change Run 2.

A close relationship is also found between Run 1 and Run 2 for Observer 2 measurements (n=146) (Table 43) with a mean difference of (-0.1) milliseconds and mean percentage change difference of (-0.144) % Limits of agreement are very similar to Observer 1, at 10 msec and (-10) msec and 1.04% and (-2.32) % (±2 standard deviations).

Inter-observer Analysis

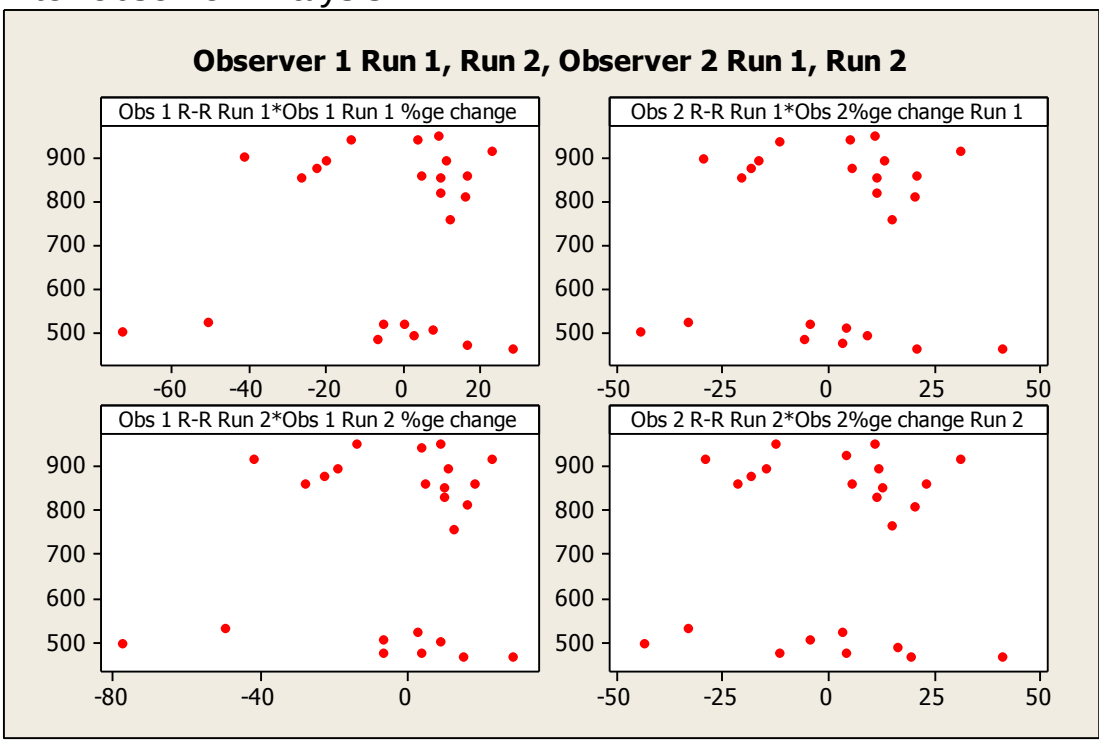


Figure 45 Scatterplot Observer 1 Runs 1 & 2 and Observer 2 Runs 1 & 2 (R-R vs percentage heart rates change).

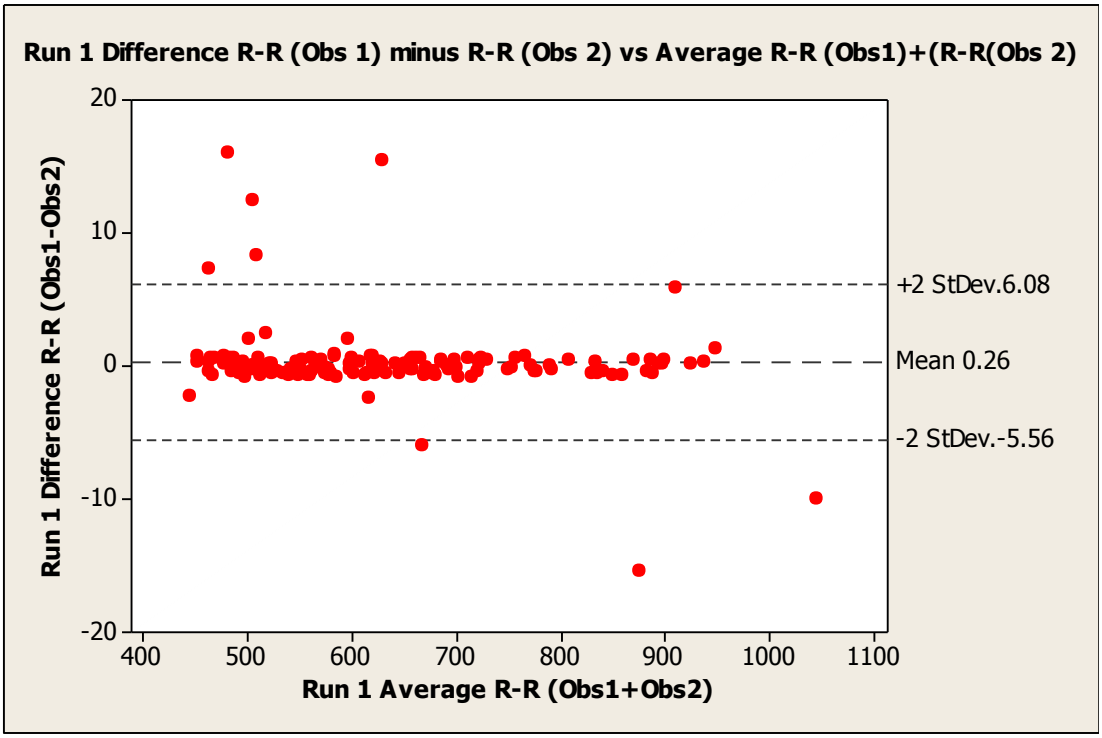


Figure 46 Bland & Altman plot Inter-observer difference in Run 1 R-R measurements. Limits of Agreement of Difference are 6 and -2 (± 2 standard deviations).

Inter-observer	Run 1 Difference Observer 1 minus Observer 2	Run 1 Average Observer 1 plus Observer 2	Run 2 Difference Observer 1 minus Observer 2	Run 2 Average Observer 1 plus Observer 2
Total count n (R-R intervals)	146	146	146	146
Mean	0.3	631.0	0.5	631.1
Standard Error of Mean	0.2	11.0	0.3	11.0
Standard Deviation	3.0	132.8	3.2	133.1
Minimum	(-16.0)	448	(-12.0)	448
Q1	0	520	0	520
Median	0	608	0	608
Q3	0	712	0	706.5
Maximum	16.0	1035	18.0	1024
Range	32	587	30	576

Table 42 Descriptive statistics for Inter-observer analyses.

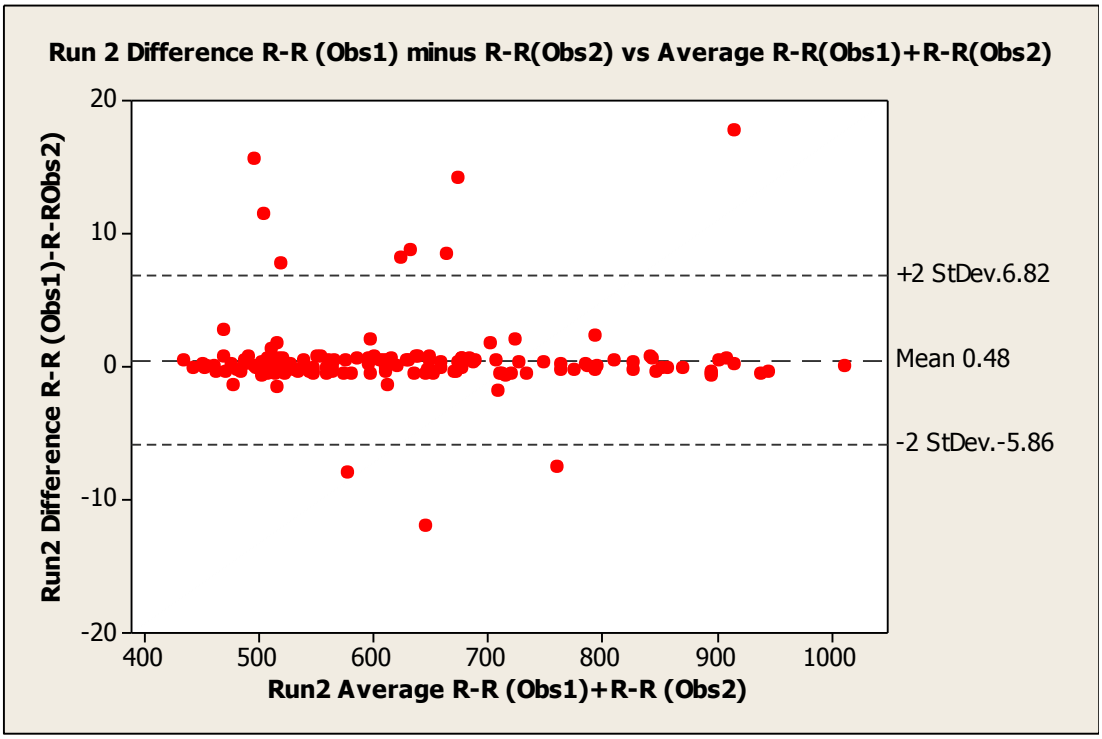


Figure 47 Bland & Altman plot Inter-observer difference Observer 1 and Observer 2 in Run 2 R-R measurements. Limits of Agreement are between 2 and (-2) msec (± 2 standard deviations).

Inter-observer analysis demonstrates a close relationship with a mean difference of 0.3 msec between observer 1 and observer 2 for Run 1 and 0.5 msec mean difference for Run 2 (Table 42). Narrow limits of agreement for Run 1 of 6 msec and (-2) msec mean 95% differences between observer 1 and observer 2 are within 8 msec range.

Similarly, Run 2 shows narrow limits of agreement of 2 and (-2) msec with 95% of inter-observer agreement within 4 msec range.

1.7.2 Proposed Device Characteristics

- Data is stored as heart rate analysed over consecutive 3 second epochs.

- Data extraction and analysis of 1st and 3rd (consecutive 3 sec. epoch) values are used to determine percentage change, calculated by subtracting the 1st epoch (1-3 sec) from the 3rd epoch (7-9 sec) during each 9 sec. analysis epoch, updated every 3 seconds by a moving window technique.

- If the percentage change in heart rate (increase or decrease) exceeds 25%, a trigger mechanism is activated to produce a visual, audible and radio page signal to a remote receiver to indicate a seizure. It would be beneficial if the trigger level could be adjustable to suit individual types of seizure detection. This proposed trigger level may need to be revised during clinical testing and data from larger patient populations.

- An additional fixed trigger level of an absolute heart rate of 30/min that cannot be disabled or altered is required as a 'safety net' to indicate a life-threatening situation.

- Two alarm trigger levels are required to indicate oxygen saturation levels. The first level is a trigger if oxygen saturation drops below 85% to indicate a seizure. The second 'safety net' trigger level is 60% for life threatening situations.

- For validation processes of the device all triggered events should be a signal-relayed to the XLTEK video-telemetry head-box to 'flag' events via a patient event socket for a clinical trial process.

- Data stored onto an internal hard-drive capable of storing logged data for up to 24 hours that can be downloaded via a USB connection. This would be necessary to perform continual assessment of optimum trigger levels and validation for off-line analysis onto Excel, 'Labview or 'Matlab' software.

- The device would resemble a wrist watch and the pulse oximeter would be attached to D2 finger sensor. The device would be light weight and easily tolerated by all patients.

1.7.3 Epileptic Seizure Alarm Epoch Analysis Method.

Analysis is performed first of all by calculating heart rate over consecutive 3 seconds epochs. Percentage change analysis is then performed by calculating heart rate change by comparing the 1st and 3rd heart rate epochs of data (this is data over 9 seconds from the start of the monitoring i.e. there needs to be 3 seconds to lapse in order to calculate the first epoch). Effectively, the calculation analysis is performed every 6 seconds via a 'moving window' analysis technique, updating analysis every 3 seconds (Figure 48).

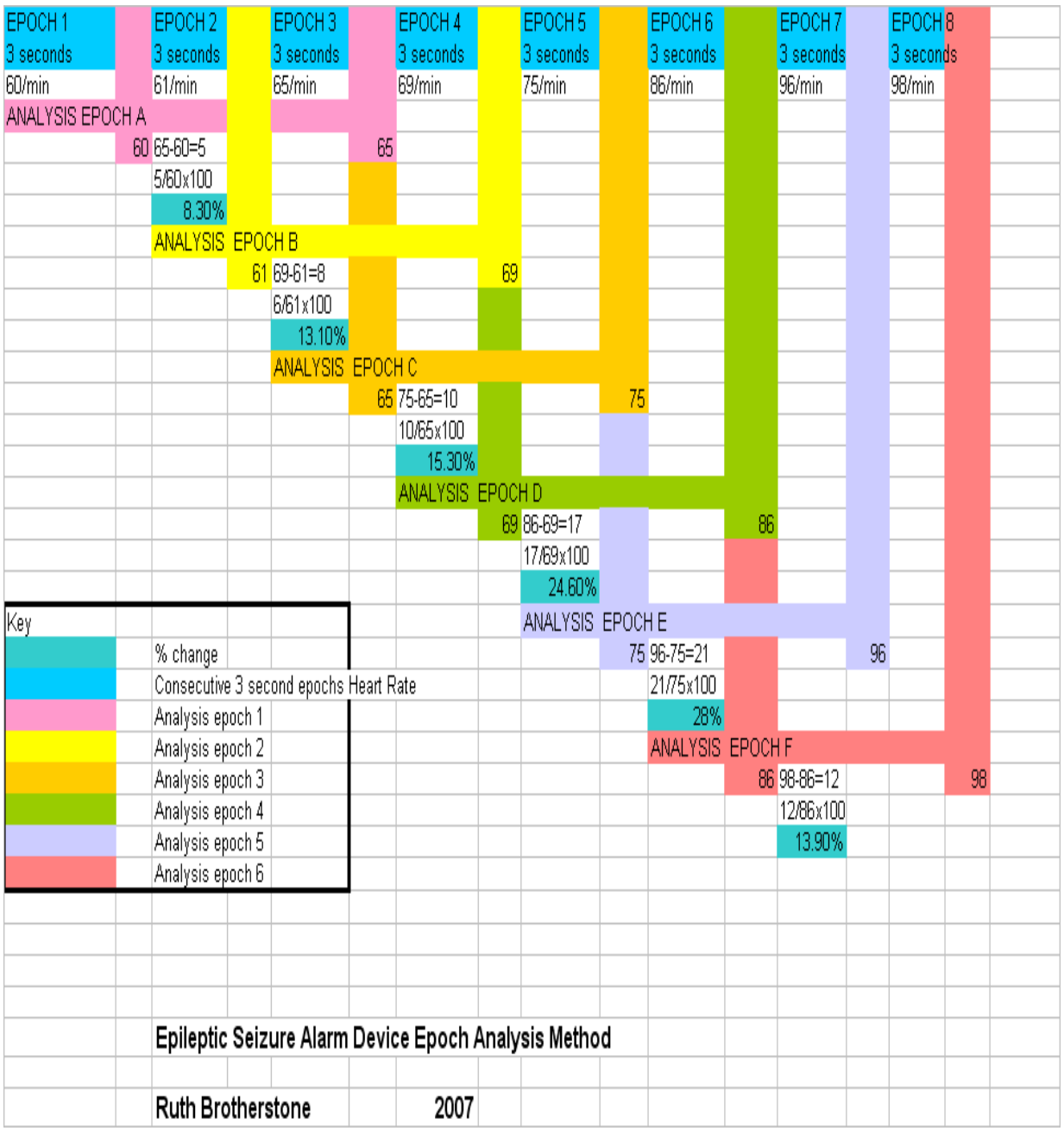


Figure 48 Schematic diagram of percentage change analysis method of data handling of proposed seizure alarm device.

1.7.4 Proposed Trigger Levels for Seizure Detection

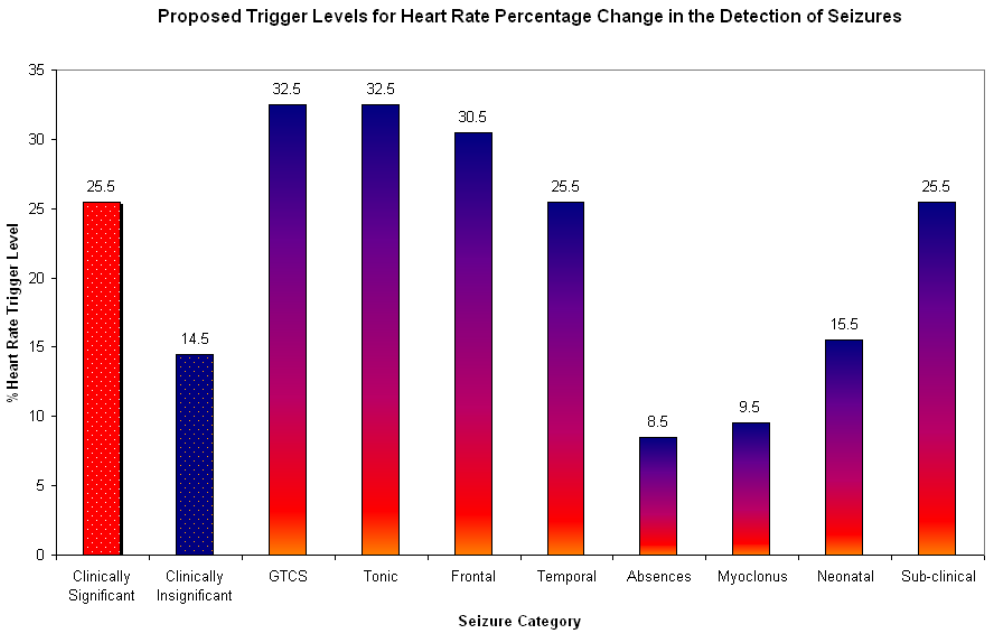


Figure 49 Proposed Trigger Levels in the Detection of Seizures.

N.B Neonatal seizures detected using a trigger level of 15.5% still provides a poor sensitivity of 43% seizure detection. Sub-clinical seizures to be deliberately missed require a trigger level of 25.5% and will only have a sensitivity of 3%.

A summary of proposed trigger levels are presented in tables in section one for generalised and focal seizures.

Chapter 8

Section One Discussion and Future Studies

1.8.1 Section One Discussion

The diagnosis of epilepsy carries an excess mortality that is 2-3 times higher than the general population (Cockerall et al 1994) and official statistics report around 1000 deaths due to epilepsy in the UK each year. In chronic epilepsy sudden unexplained death in epilepsy is the main cause of excess mortality and risk of premature death from SUDEP in individuals with intractable epilepsy is 1:200/year (Nashef et al 1995). Reported risk factors for Sudden Unexplained Death in Epilepsy include young age, uncontrolled epilepsy and seizures occurring in sleep (Shorvon 1997).

Despite these statistics, inadequate seizure alarms are commercially available for identifying nocturnal seizures. This remains a problem for people with epilepsy and their families or carers. The incidence of seizures occurring at night are probably under-estimated because so many attacks are un-witnessed and the person having the seizures may not remember having them due to post-ictal amnesia, are unable to communicate the problem if they have age related communication difficulties or who may be learning disabled, or experience loss of consciousness following the seizure. It is well documented that sleep itself increases the occurrence of seizures. 'Surveys suggest that in 10-45% of patients [with epilepsy] overall, have seizures that may occur predominantly or exclusively in sleep or in relation to sleep deprivation' (Walker et al 2004).

Undetected prolonged nocturnal seizures can be fatal or result in significant morbidity due to hypoxic brain damage. This leaves an indescribable burden of guilt on families living with epilepsy and they have voiced the need for a reliable alarm system. In a professional capacity, 'one still sees the catastrophe of the child who is found by his parents in the morning having convulsed half the night in compensated status and who is left with permanent hemiplegia' (Brown et al 1991). Compensated status epilepticus is continual convulsive status where the body compensates to cope with oxygen and glucose demands metabolically by switching to anaerobic respiration physiological mechanisms. This usually occurs after 30 minutes of continual seizure activity. The brain requirements for oxygen are very high especially during a seizure. During convulsive status, blood flow increases by approximately 400% to meet oxygen and glucose demands of neuronal activity. Areas of brain structures most damaged by status epilepticus are the hippocampal regions, Purkinje cells in the cerebellum, thalamus and then resultant laminar necrosis of the cortex (Brown et al 1991).

Some seizures resulting in death are accidental and death could have been avoided if someone was alerted to the situation and intervened with rescue medication and body re-positioning to prevent an obstructed airway (Langan et al 2000).

Other seizures resulting in death due to SUDEP may not have been prevented even with intervention (Dashief et al 1986). Whether in cases of SUDEP or seizures amenable to intervention, if parents were given the choice of having an alarm system which would alert them of a seizure taking place or not having an alarm system, I am certain that parents and carers would prefer to know when a seizure was occurring. A reliable alarm system would

result in carers doing everything possible to prevent bodily injury, brain damage or even a fatality.

The knowledge that we are dealing with two separate problems, of death in epilepsy namely 'extrinsic factors' of circumstantial compromise e.g. suffocation due to obstructive apnoea or drowning and 'intrinsic factors' of SUDEP, have been considered for over one hundred years. 'Epileptologists at the turn of the century were well aware of the dangers from seizures and recognised that seizure deaths could be accidental or due to intrinsic mechanisms during a single seizure or serial seizures and status' (Nashef 2000). However, very little is understood of what exactly these 'intrinsic' mechanisms are and much research is active in this area.

An increased risk of SUDEP is reported in a young age group. These patients are most vulnerable at night when seizures are most likely to be un-witnessed. A high percentage of nocturnal seizures occur in this age group. 'More nocturnal seizures recur in children, adolescents and young adults than daytime seizures (82%). The most likely timescale for recurrent GTCS are within 6 months of first seizure' (Martinovic et al 1997).

Another risk group for undetected nocturnal seizures are the elderly, often living alone with no immediate assistance during a seizure event. The incidence rate is 1 per 1000 of the general population but this figure is set to rise with the growing elderly population of recent times and is regarded as a significant public health issue with epilepsy being the third most common neurological disorder in old age after dementia and stroke (Sander et al 2004).

There is already a need to understand the physiological mechanisms involved during seizures and a necessity to devise a reliable alarm system. A reliable alarm system may not prevent true SUDEP cases but many seizures that are amenable to intervention, if detected, will be prevented from causing bodily injury, hypoxic brain damage and in some cases death. My view is supported by others ' timely assistance at the time of a seizure is likely to reduce the risk of death or injury' and 'unwitnessed seizures carry a higher risk of death' (Nashef 2000) and 'positioning of the patient or stimulation of respiration may prevent a fatal outcome in some cases. This raises the important issue of supervision' (Langan et al 2000).

A wide age range of patients, were recorded in this study from a 1 day old neonate to a 60 year old pensioner. A baseline heart rate in a neonate is generally much higher e.g. 210/ min compared to that of an elderly person with a heart rate generally of around 60/min. It is because of this age dependant heart rate fundamental that I have chosen to analyse heart rate 'percentage change' instead of absolute heart rate. Any changes in heart rate before an event and during an event were calculated as a proportional change and can be compared for all ages.

An alarm system based on percentage heart rate would have to show a significant proportional change during an epileptic seizure for all ages. In a neonate or young child who has a resting heart rate of 200/min, a 20% increase in heart rate would result in a rate of 240/min. In an adult with a resting heart rate of 60/min, a 20% increase in heart rate would result in a rate of 72/min. Both analogies show a mild proportional change in both patients. If we were to consider an absolute heart rate increase of 40/min of a neonate or young child and add that to an adult rate of 60/min, we would see

a significant tachycardic state of the adult at 100/min. Clearly, this would be a significant increase in heart rate for the adult, not a mild change. Therefore, absolute heart rate changes are not appropriate or offer an ideal measurement when considering and comparing heart rate changes during a wide age range of patients.

In section one of this study, I chose to examine the changes in percentage heart rate and oxygen saturation during epileptic seizures, which were identified and clinically categorised using electroencephalographic videotelemetry. The rationale for choosing to examine these parameters is based on the general belief amongst researchers that there is a fundamental involvement of cardiac and respiratory changes during a seizure. These changes in heart rate and respiratory changes resulting in possible hypoxaemia may either be a centrally driven channelopathy effect or simply the physiological response to physical effort during the seizure with heart rate increase. An alarm system based on heart rate change and oxygen saturation could also measure vital signs and alarm if someone's life was threatened.

Percentage Heart Rate Changes and Oxygen Saturation in Seizures.

The results of percentage heart rate changes during clinically significant seizures in this study are distinctly different from those of clinically insignificant seizures and normal events. This is an encouraging result with good sensitivity (79%) and specificity values (75%) when a proposed trigger level of percentage heart rate change of 25.5% is used. This would suggest that a device based on percentage heart rate and oxygen saturation would identify the type of seizures, which ought to attract assistance. It also

suggests that the alarm would have a minimal number of false alarms due to normal events (1:4 ratios). A factor to bear in mind with these results is that none of the 'clinically significant' seizures required medication intervention and were self-resolving. I would postulate that the sensitivity and specificity values may even be higher during more clinically prolonged seizures.

The results for detecting generalised tonic-clonic seizures give a higher sensitivity of 88% and specificity of 85%. This means that most tonic-clonic seizures would be identified and very few false alarms would occur. A proposed percentage heart rate change trigger level for detecting generalised tonic-clonic seizures is 32.5%. In this group oxygen saturation was only useful in detecting 50% of this type of seizure but is a useful additional trigger parameter with very few false alarms (5%) when a trigger level of 90.5% is used.

When data is combined with one/ other/ both parameters reaching their trigger levels, the sensitivity improves further to 91% and specificity stays the same at 75%. This result indicates that if a seizure alarm was triggered because of either percentage heart rate change or oxygen saturation parameters triggered either independently or together then 91% of clinically significant seizures would be detected. As before, one triggered alarm in every four would be false.

Changes in percentage heart rate occurring during epileptic seizures showed statistical significance of $p<0.001$ for generalised tonic-clonic seizures, tonic seizures, frontal lobe seizures and temporal lobe seizures. Statistical significance was slightly lower in absence seizures ($p=0.008$) and not significant during episodes of myoclonus ($p=0.359$).

Analysis of statistical significance for oxygen saturation was high for tonic seizures (p<0.001) and slightly lower for generalised tonic-clonic seizures (p=0.018). Absence seizures did not show statistically significant changes in oxygen saturation (p=0.378).

Statistical significance does not necessarily equate to clinical significance. Although statistical significance of p<0.001 is also seen for percentage heart rate change during many types of normal events; arousal, coughing, crying, laughing, sneezing and turning over in bed, the maximum percentage heart rate changes are distinctly lower than that seen during seizures. Changes in oxygen saturation as a group reached high statistical significance (p<0.001) but generally were less statistically significant when analysed separately; arousal p=0.049, coughing p=0.513, crying p=0.132, laughing p=0.732, sneezing p=0.177, turning over in bed p=0.132 and yawning p=0.269.

The alarm system based on these parameters would be ideally pre-set to trigger appropriately to the type of seizure the patient is known to have. It may be necessary to collect data individually for that patient to build their own unique range of normal values so the device could be as accurate as possible.

An ideal system would analyse percentage heart rate change and oxygen saturation using an epoch data sampling time of 9 seconds. This would be necessary to average out any normal sinus arrhythmia, which can be marked in children. A separate safety trigger level within the device (which should not be altered) would act as a 'safety-net' to indicate life-threatening vital signs. This trigger would be based on minimum pulse rate and oxygen

saturation. If levels dropped to this level then the safety net trigger would indicate that life may be threatened.

Hemisphere Lateralisation Effects on Percentage Heart Rate and Oxygen Saturation.

A difference is seen when comparing percentage heart rate changes during seizures arising from the right hemisphere and seizures arising from the left hemisphere. Major differences are seen when data is divided into right and left frontal lobe seizures in terms of percentage heart rate changes. The mean percentage heart rate change for the right hemisphere is twice (53.6%) the mean heart rate change seen from the left hemisphere (26.8%). Similarly, more dramatic data of mean oxygen saturation changes are seen from seizures derived from the right hemisphere (83.7%) compared to the left hemisphere (98.3%). High statistical significance is seen ($p<0.001$) for heart rate changes occurring in frontal lobe seizures derived from either hemisphere.

A similar difference is seen when percentage heart rate changes are examined separately for right and left temporal lobe seizures. Much higher changes in mean percentage change occurs from seizures arising from the right temporal lobe (43.5%) compared to the mean percentage heart rate changes from seizures arising from the left temporal lobe (14.4%). High statistical significance ($p<0.001$) is seen for heart rate change from right temporal lobe seizures. A marginally lower statistical significance is seen from heart rate changes during left temporal lobe seizures ($p=0.072$).

Reports of sinus arrest have been secondary to seizures arising from the right temporal region. Other reports have been cases of severe bradycardia secondary to seizures arising from the left temporal lobe (Vaughn et al 1997).

A different result is obtained however when the oxygen saturation changes are studied for right temporal lobe seizures and left temporal lobe seizures. Clinically significant changes in mean oxygen saturation (86.1%) occurred from left temporal lobe seizures with a high statistical significance of $p<0.001$. Mean oxygen saturation changes appear less clinically significant with mean values of 91.8% from right temporal lobe seizures was not statistically significant ($p=0.072$).

The general differences in heart rate change recorded when comparing seizures arising from the right and left hemispheres in this study are explained by other studies on physiological differences of innervation pathways. 'There is clinical evidence of lateralization in neurocardiac control' Intra-operative stimulation of the insula and amygdala has demonstrated that the right cerebral hemisphere mainly modulates sympathetic activity (Cheung et al 2000).

The insular cortex is the continuation of cortex between the frontal/parietal and temporal lobes forming the in-going C-shape on either hemisphere. Historically, many seizures arising from the insular cortex are mistaken for temporal lobe seizures as they share similarities of auras described as a 'rising sensation from the stomach' (Brotherstone 2002). Chronotopic organization studies of the insular cortex have shown that the anterior portion is more likely to cause tachycardia compared to any other cortical area (Opherk et al 2002). Lateralisation of effect on heart rate is documented.

'Stimulation of the left anterior insula causes a bradycardia whereas stimulation of the right insular cortex induces tachycardia' (Nouri et al 2004).

Accuracy of oxygen saturation technology.

In 1989, Diab and Kiani at Masimo Corporation invented signal extraction pulse oximetry. They used adaptive filters to separate the arterial signal from the non-arterial 'noise' or venous blood movement during patient motion. Previous technology had problems because it was not possible to distinguish between arterial and venous blood at these times resulting in error. Masimo adaptive filters isolate the venous signal and then 'cancel' it. This allows continuous data of true arterial oxygen saturation only. Masimo has been scientifically and clinically proven to be accurate during patient motion and during low perfusion. Validation of Masimo's technology has been performed in over 50 independent clinical studies with impressive results of accuracy with Sensitivity of 99% and Specificity of 97% (Barker SJ. in Radical "SatShare" White Paper). This technology has been commercially available since 1998 and to date more than 60% of the world's manufacturers have licensed Masimo SET technology to make signal extraction pulse oximetry.

Masimo uses Discrete Saturation Transform (DST) algorithim. This system comprises of a 'Reference Signal Generator', an 'Adaptive Filter' and a 'Peak Picker' (appendix). The Reference Signal Generator builds a 'noise reference' from the incoming red and infra-red signals for each percent gauged from 1-100. This data (S-Signal and N-Noise) is then passed through the Adaptive Filter, which cancels the correlated frequencies between the Reference Signal and the incoming infra-red signal. Arterial blood has the highest oxygen

saturation and the Peak Picker algorithim displays the highest oxygen saturation monitored.

Masimo disposable finger probes were not used as these are less well tolerated and restrictive for the patient's normal use of their hand. The forehead sensor was preferable in case of the delay effect in detecting hypoxaemia due to lung / periphery circulation time when recording from finger sensors. In a study by Hamber et al a delay of 51 seconds was reported when comparing detection time of hypoxaemia at the finger compared to detection of hypoxaemia at the ear.

Seizures with associated hypoxia.

Hypoxia occurs during some seizures and not others. In the study, hypoxia occurred with clinically significant levels of 71%. A wide range of seizure types of focal and generalised seizures, were associated with hypoxia. A focal seizure involving the right frontal lobe resulted in oxygen saturation levels down to 71%. Hypoxia was also recorded during a left temporal lobe seizure with oxygen saturation levels down to 75%. Several generalised seizures were associated with hypoxia. One period of hypoxia was recorded during a series of epileptic spasms with oxygen saturation recorded down to 81%. Another generalised epileptic myoclonic drop attack resulted in oxygen saturation level of 84%.

One group that did not show any change in oxygen saturation at all in this study group, were the neonates demonstrating focal seizures. A possible explanation for this is that the neonate has a very high concentration of red blood cells. In the womb, the baby depends on oxygen supply via the umbilical cord, which provides comparatively lower oxygen than that

obtained during spontaneous respiration. The high concentration of red blood cells maximise the absorption of all available oxygen molecules. Therefore, the neonatal haemoglobin copes better with low oxygen availability compared to the older infant, child and adult. During a neonatal seizure, the baby may have a suppressed respiratory effort but it would take much longer for oxygen saturation levels to drop significantly. In animal studies, 'immature animals appear to tolerate hypoglycaemia and anoxia better than the more mature' Young animals have a 'higher energy reserve' and a 'lower metabolic rate' (Mayman 1971).

Accidental death during seizures can result from suffocation. The prevalence figures of this cause is somewhat disputed but various reports indicate that suffocation has either occurred due to unfortunate body position and obstructive apnoea or simply the possibility that after a seizure in an unconscious state, the person has suffocated because they have been unable to turn over or move their face to breathe and have consequently suffocated. This is distinctive from death during seizures (SUDEP) where the person has happened to be in a prone position during a sudden 'electrical accident' and that respiratory failure was secondary to another main cause of death.

Several reports describe people being 'found face down onto his pillow' the following morning (Martin 2005). Clearly, there may be several factors involved in determining the fundamental cause or combinations of factors why death can occur during seizures. However, anti-suffocation ventilated pillows may prevent suffocation in some instances and are advertised on the 'The National Society for Epilepsy' website. An alarm system based on oxygen saturation would also alert someone to a seizure and allow intervention.

A more common reason for respiratory problems during seizures appears to be an 'intrinsic' one. ' There is strong evidence in favour of hypoventilation being a common occurrence in epileptic seizures and this is likely to be a significant mechanism in SUDEP' with ' central apnoea observed commonly during seizures, including complex partial seizures' (Nashef 2000).

Mechanically many seizures cause a change in breathing pattern particularly during generalised tonic-clonic or tonic seizures where not just the limbs are involved in tetanic contraction but the intercostal respiratory muscles are also contracted which leads to cyanosis (James 1991). In this study most of the patients having apparent generalised tonic-clonic seizures had a reduction of oxygen saturation down to 85.5%.

Apnoea and hypoxia during seizures are described during many types of seizures by several authors (Brown & Hussain 1991, James et al 1991, Jallon 1997, Langan et al 2000, Nashef et al 1997 and Opherk et al 2002). Seizures may cause a physical restriction to the respiratory muscles by tetanic contraction but others appear to be caused by an'intrinsic' mechanism. Langan et al 2000 reports, 'hypoventilation, which was primarily central in nature, occurred in the context of both generalised and partial seizures.' Animal studies may give some insight as to possible mechanisms of seizure related apnoea and hypoventilation. A study by Williams et al 1989, concentrated on stimulation of sites within the fastigial nucleus of anaesthetised cats. Stimulation rates of 20Hz, 50Hz and 200Hz caused respiratory inhibition and apnoea. They found that the higher the frequency of stimulation the longer the period of apnoea occurred.

Electroencephalographic high frequency spike activity is recorded from surface electrodes during the tonic phase of clinical seizures in humans and animals. The recordable band-width of frequencies we use routinely in Neurophysiology nationally is 0.5Hz-70Hz. This has been continued from the filter settings used on conventional paper machines that were unable to cope with frequencies higher than this due to the friction/striction characteristics of pen writers and paper collection with speeds of 30mm/second. Theoretically with the common use of digital machines it is now possible to increase the bandwidth to record higher frequencies during seizures. This would only be of interest on research grounds as the traditional bandwidth is adequate for investigative and diagnostic purposes.

The use of depth electrodes reveals higher frequencies and amplitude of signal than compared to scalp recordings. The frequencies of spike activity recorded during electrocorticography appear faster than scalp recordings due to the fact that signals are not reduced by having to travel through meninges and skull. Theoretically, an epileptic seizure especially during the tonic phase produces high frequency discharges at the cortex. This discharge could travel to brainstem respiratory centres and as seen with the study of the anaesthetised cats (Williams et al 1989) demonstrating that high frequency discharges can cause apnoea. This hypothetically is an intrinsic channelopathy.

The effect of repeated seizures on cardiac muscle and the response to hypoxia have been indicated as further risk factors of SUDEP. Opherk suggests that repeated autonomic stimulation because of frequent seizures could structurally damage the heart leaving it more susceptible to arrhythmias or ischaemia. A study in piglets showed an attenuated

hyperventilatory response to hypoxia following regular periods of hypoxia (Moss 2002). Maturation in the response to hypoxia may be a factor.

Pathological effect on neural networks is also a consideration. 'The most common abnormalities found on computerised tomography are hippocampal sclerosis, malformations of cortical development, vascular malformations, tumors and acquired cortical damage' (Duncan 2004). For example, atrophy of the hippocampus and amygdala and other mesial temporal areas which are susceptible to tissue shrinkage due to neuronal loss subsequent to damage from temporal lobe seizures may be a participant to channelopathies during seizures as 'evidence exists that seizures involving the amygdala and its adjacent areas may result in serious cardiac arrhythmias' (Ansakorpi et al 2004).

It has been suggested that SUDEP includes a 'heterogenous group of patients' which are more susceptible to lethal cardiac arrhythmias compared to people who demonstrate cerebral dysrhythmias leading to nonlethal cardiac arrhythmias (Dasheiff et al 1986).

1.8.2 Further Studies

A UK patent on method has been submitted by NHS Lothian for a seizure alarm device based on this study 2011. No other seizure alarm device has been found through patent searches that use percentage heart rate change and oxygen saturation.

The next stage in this research is to apply for research funding to build a prototype device to test proof of concept before clinical trials can then take place.

1.8.3 Section One Conclusions

Undetected prolonged nocturnal seizures can result in hypoxic brain damage or death. The cases of death during these seizures are believed to be either due to extrinsic factors of obstructive apnoea and suffocation or intrinsic factors due to sudden excessive discharges affecting autonomic pathways resulting in central apnoea or lethal cardiac arrhythmias. This means that some seizures are amenable to intervention and some are not. The prevalence of nocturnal seizures is probably higher than estimated due to many seizures being undetected. This figure is set to rise due to the aging population and increased risks of undetection with more people living on their own. The emphasis is on detecting seizures and calling for assistance 'studies also need to focus on avoidable mortality' (Nashef 1997). The majority of cases of SUDEP occur during sleep with evidence of marked increases in sympathetic tone and surges of catecholamines and autonomic instability (Nei et al 2004). The need for seizure detection is clear and the results of this study indicate that an alarm system based on percentage heart rate change and oxygen saturation can distinguish many seizures from normal events. Experts in this specialty believe that 'timely assistance by positioning of the patient or stimulation of respiration may prevent a fatal outcome in some cases' (Langan et al 2000).

In this study, I have analysed percentage heart rate change and oxygen saturation before and during 527 epileptic seizures and 496 normal events. Diagnostic testing of this data gives a sensitivity of 79% and specificity of 75% of distinguishing epileptic events from normal events with a trigger level of 25.5% percentage heart rate change. The same trigger level is optimum for the detection of temporal lobe seizures with a sensitivity of 75%

and specificity of 75%. Frontal lobe seizure detection trigger level is optimum at 30.5% percentage heart rate change to give a sensitivity of 83% and specificity of 82%. For the detection of generalised tonic clonic seizures, the trigger level is 32.5% percentage heart rate change. Diagnostic testing suggests a sensitivity of 88% and specificity of 85%.

The results for oxygen saturation during seizures are less sensitive but a useful addition to the percentage heart rate trigger. For the group as a whole a trigger level of 90.5%, gives a sensitivity of 49% and specificity of 54%. This result would indicate that an alarm triggered at this level may or may not actually be a seizure. A similar sensitivity of 50% with the same trigger level of 90.5% oxygen saturation is seen with generalised tonic clonic seizures however the specificity is higher at 95%, which would indicate very few false alarms. Diagnostic testing of oxygen saturation of frontal lobe seizures has a higher sensitivity of 67% and specificity of 97% with a trigger level of 89.5%. Oxygen saturation is least sensitive in the detection of temporal lobe seizures with a sensitivity of 29% and specificity of 99% with a trigger level of 88.5% oxygen saturation.

An alarm system based on these parameters can be set to trigger for individual seizure types depending on the patient's habitual seizures. A second trigger level is proposed which is not adjustable and would indicate a life threatening status of the patient if pulse is lost and oxygen saturation drops to severe hypoxic levels. Abnormal pulse and reduced pulse oximetry are listed as part of the identified risk factors for cardiac arrest (Hodgetts et al 2002). This second trigger level would act as a 'safety net' and both types of alarms would alert parents or carers via an audible alarm and/or a radio page receiver unit.

Section Two

Lengthening of Corrected Q-T during Epileptic Seizures

Section Two List of Figures Page

Section Two List of Figures Page

Section Two List of Tables Page

Section Two List of Tables Page

Section Two List of Tables Page

Section 2

ABSTRACT

Objective: To measure the corrected Q-T cardiac re-polarisation time before and during epileptic seizures. ***Methods*** Thirty-nine video-EEG/ECG/SAO2 telemetry patients were included in this prospective study. Epileptic seizures were identified both clinically and electrographically. R-R intervals and associated Q-T intervals were measured 5 minutes prior to the onset of the identified seizure. Consecutive R-R and associated Q-T intervals were then measured from the seizure onset until the seizure had ended and the electroencephalograph had resumed its pre-seizure trace. Averaged R-R and Q-T intervals over 9 consecutive beats were applied to Bazett's, Hodge's, Frederica's and Framingham's Formulae to compare the corrected Q-T values before and during the seizures. ***Results*** A total of 156 seizures had corrected Q-T analysis performed. 9 generalised tonic-clonic seizures (5 patients), 34 absences (6 patients), 12 tonic seizures (6 patients), 27 temporal lobe seizures (14 patients), 58 frontal lobe seizures (4 patients) and 16 sub-clinical seizures (4 patients). All formulae reported a statistically significant difference in corrected Q-T ($p<0.001$) during total seizure data compared to total pre-seizure data. According to Bazett's formula, 21 seizures (9 patients) transiently increased their corrected Q-T beyond normal limits with maximum corrected Q-T of 512 milliseconds during a right temporal lobe seizure. ***Conclusion*** Significant lengthening of corrected Q-T cardiac re-polarisation time occurred during some epileptic seizures in this study. Prolonged corrected Q-T may have a possible role in Sudden Unexplained Death in Epilepsy (SUDEP).

Chapter 9

Introduction

2.1.1 Sudden Unexpected Death in Epilepsy and Corrected Q-T.

SUDEP has been recognised for over one hundred years but there still remains little evidence to explain what mechanisms are involved (Nashef 2000). Several hypotheses have been postulated mainly concerning respiratory, cardiac and genetic involvement (Nashef et al 2007).

SUDEP has been defined as 'sudden, unexpected, witnessed or un-witnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, where post-mortem examination does not reveal a toxicological or anatomical cause of death' (Nashef 1997).

Cardiac arrhythmia is considered to have a possible role in SUDEP (Soonhak et al 2003, Tavernor 1996). Prolonged corrected Q-T re-polarisation time can lead to fatal cardiac arrhythmias (Morganroth and Pyper 2001, Tavernor et al, 1996). The Q-T interval by definition represents the time required for depolarization and re-polarization of the ventricular musculature (Yu et al 1950). Autonomic symptoms frequently occur during epileptic seizures and range from subtle to life threatening manifestations (Baumgarter et al 2001). An increase in re-polarisation time can lead to cardiac arrhythmias with any combination of a slow heart rate, atrial fibrillation, hypokalemia, hypomagnesemia, hypoxia, congestive heart failure or ischaemia resulting in an induced polymorphic ventricular tachycardia (Morganroth 2001). Some seizures are associated with various levels of hypoxia and ischemic changes,

potentially contributing to a prolonged corrected Q-T, cardiac arrhythmia and sudden death.

A study of patients with severe epilepsy and learning disabilities showed that 60% had abnormalities on the electrocardiogram raising the question whether underlying cardiac rhythm disturbance increases the risk of SUDEP (Jeffrey 2006). Measurements of the corrected Q-T during inter-ictal electroencephalographic discharges indicated that the corrected Q-T (QTc) increased during inter-ictal epileptic discharges and it was proposed that a prolonged QTc could be a possible risk factor of SUDEP in patients with epilepsy (Tavernor et al 1996). One previous study by Nei et al (2006) examined the corrected Q-T during epileptic seizures. This study however only considered using a total mean average for group data and did not analyse individual seizures in each subject. They reported that no corrected Q-T lengthening occurred during seizures based on a grouped mean average. When total data is averaged for all patients in this study a normal mean value of 427 milliseconds is calculated. However, when the data is analysed for individual seizures for each subject, lengthening of the corrected Q-T does occur during some epileptic seizures, and I hypothesize that this may be one of the possible intrinsic mechanisms involved in SUDEP.

The Q-T interval represents the time period of ventricular depolarisation and re-polarisation from the beginning of the QRS complex and ending where the T-wave returns to an iso-electric baseline. An increase in re-polarisation time can lead to cardiac arrhythmias, notably Torsades de Pointes but other types of arrhythmias are also known to occur. Torsades de Pointes is recognised on the electro-cardiograph as a continuous twisting of the vector around the

baseline. An increase in Q-T interval is measured in the supraventricular beat preceding Torsades de Pointes and this can either spontaneously recover or degenerate into ventricular fibrillation (Figure 1) and lead to sudden death (Dept. of Health & Human Services 2004). Syncope in adults and children is described in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) who demonstrate a normal resting Q-T interval and no identified heart disease but collapse, often with clonic movements following exercise or emotion. In some of these cases, epilepsy has been given as a misdiagnosis and care must be taken in clearly identifying CPVT treatable with Beta-blockers. Sudden death can occur in 50% of these cases before the age of 20 years (Leite et al 2001). Circulating adrenaline can produce lengthening of the corrected Q-T by a direct effect on the myocardium (Lee et al 2003). During epileptic seizures increased adrenaline occurs and may produce a combined effect with a sudden and sustained increase in heart rate, hysteresis and changes in ionic flux during hypokalaemia, hypomagnesemia physiological conditions that may be compounded by hypoxia, congestive heart failure and active ischemia leading to increased risk factors of producing cardiac arrhythmias in some individuals.

Evidence of excessive sympathetic activity around the time of seizures are noted from autopsy reports of SUDEP victims, which describe 'post-mortem examination may show neurogenic pulmonary oedema, oedema of various organs and scattered microscopic injury of the heart, possibly due to increased levels of catecholamines, reflecting excessive sympathetic function but the primary cause of SUDEP is unknown' (Ansakorpi et al 2004). Excessive levels of catecholamines at autopsy would suggest Beta-adrenergic activity around the time of death. Heart rate changes during seizures are

common and can be dramatic. Hypothetically, the effects of sudden arousal from sleep compounded with the effect of a seizure may result in excessive cardiological demands resulting in lengthening of the corrected Q-T and possible fatal arrhythmias.

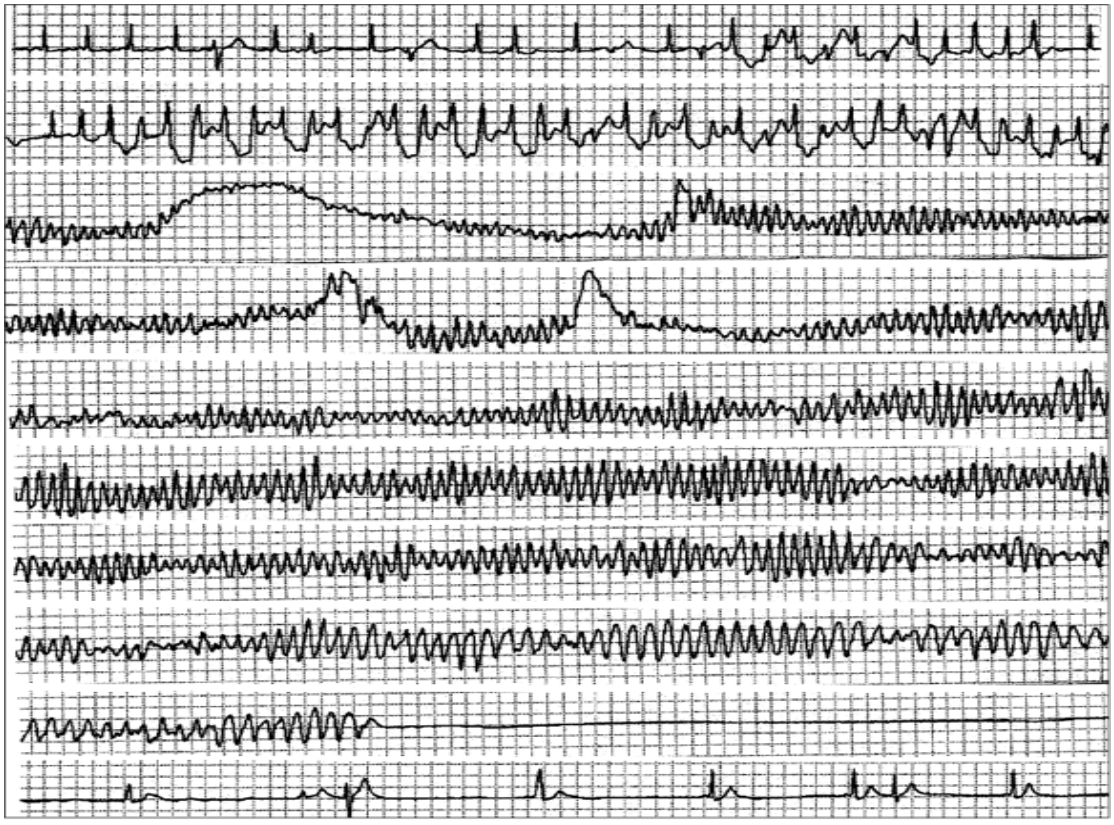


Fig. 1 - Holter recording (V1 lead) during a syncopal episode and convulsion. Tracing shows polymorphic VT initiation preceded by isolated VEB and nonsustained VT.

Figure 1 Catecholaminergic Polymorphic Ventricular Tachycardia. An important diagnosis in children with syncope and normal heart (Leite et al 2001).

Over the last ten years, the identification of ion channel mutations causing a wide variety of inherited disorders has been discovered in clinical Neurology and Cardiology. It is anticipated that many new target channels will emerge in the next few years (Kullmann 2002). As yet no single mutation of either voltage-gated or ligand-gated ion channelopathies has been identified that singularly affects neuronal activity and the cardiac myocyte. So far, however,

two closely related potassium channels KCNQ2 and KCNQ3 which are associated with benign familial neonatal convulsions are homologous with KCNQ1 channel which is known to cause mutations of two inherited cardiac arrhythmias; autosomal dominant long QT syndrome and Jervell and Lange-Nielsen syndrome-autosomal recessive long QT syndrome associated with bilateral deafness.

QTc prolongation exceeding 60 milliseconds from baseline is considered to be a possible risk factor of a patient developing a fatal arrhythmia (European Agency for the Evaluation of Medicinal Products 2005, Fenichel et al 2004, Morganroth and Pyper 2001, Pater 2005). Some seizures are associated with various levels of hypoxia and ischemic changes, which could theoretically contribute to a prolonged QTc and potentially cardiac arrhythmia and sudden death.

Tavernor et al (1996) measured the corrected Q-T during inter-ictal electroencephalographic discharges and indicated that the corrected Q-T increased during some epileptic discharges and proposed that prolonged corrected Q-T could be a possible risk factor of SUDEP in patients with epilepsy.

It was with this hypothesis in mind that I decided to measure the corrected Q-T before and during many different types of epileptic seizures and in a wide age range of patients.

2.1.2 Aim and Objectives.

Aim

The aim of this study is to calculate and analyse the corrected Q-T during different seizure types. This is to determine whether any lengthening of the corrected Q-T occurs during seizures and if there are some seizure types resulting in more Q-T lengthening than others indicating a higher risk of cardiac arrhythmia and possible involvement in SUDEP.

Objectives

- To analyse the corrected Q-T before and during epileptic seizures.
- Compare results using the following formulae:
    1. Bazett's Q-T correction formula.
    2. Hodge's Q-T correction formula
    3. Fridericia's Q-T correction formula
    4. Framingham's Q-T correction formula.
- Analyse Q-T data using linear regression plots on selected data.
- Apply statistical analysis to results.

2.1.3 Null Hypotheses

- No lengthening of the corrected Q-T occurs during seizures according to Bazett's corrective formula.

- No lengthening of the corrected Q-T occurs during seizures according to Hodge's corrective formula.

- No lengthening of the corrected Q-T occurs during seizures according to Fridericia's corrective formula.

- No lengthening of the corrected Q-T occurs during seizures according to Framingham's corrective formula.

- Seizure-derived laterality does not effect lengthening of the corrected Q-T.

- There is no difference in lengthening of the corrected Q-T in focal seizures or generalised seizures.

- The results are the same for each corrective formula in terms of sensitivity and specificity using normal values dependent on heart rate according to Luo et al.

- No lengthening of the corrected Q-T occurs during sub-clinical seizures.

- Oxygen de-saturation is not associated with lengthening of the corrected Q-T.

Chapter 10: Methodology.

2.2.1. Methodology of corrected Q-T analysis.

Thirty-nine patients from the original study group took part in this ethically approved prospective study LREC/2003/6/22. Patients diagnosed with any seizure type were accepted as part of the inclusion criterion. No restrictions on data inclusion were made due to patient pharmacology. All patients were in sinus rhythm and none demonstrated a conductance disturbance during the pre-event resting trace. The study was inclusive for all ages except for neonates. The predicted observer error of Q-T measurement was considered to be too high to reliably measure the corrected Q-T in this group due to high heart rates in neonatal tachycardia. Paediatric age in this study is defined as 3 months to 16 years Data resulted in excessive electromyographic (EMG) artefact and obscuring the electrocardiographic (ECG) signal with 371 seizures being excluded from the study.

Lead II ECG (Tavernor et al 1996, Benatar et al 2001, Pater 2005) was recorded from disposable ECG electrodes (Ambu Ltd). Twenty three silver silver-chloride electroencephalographic electrodes where applied using collodion glue, saline conducting gel with impedances below 10 kilo ohms in accordance to the International 10:20 system (Cooper et al 1980). All wires were tied together to minimise electrical noise pick-up from the ward environment and to provide comfort and mobility to the patient. The electroencephalographic, electrocardiographic and oxygen saturation leads were connected to an XLTEK Mobee 32 channel headbox. Continuously integrated Masimo oxygen saturation monitoring was recorded via a Masimo forehead transducer and all signals were networked via a Mobee

Headbox to a main computer server with simultaneous integrated video of the patient. Electrographic physiological signals were sampled at 500Hz (Rijinbeek et al 2001) and displayed on review using a maximum of 32 channels depending on selected montage on full screen of 12 seconds display using a chart speed of $30mms^{-1}$.

The electroencephalograph with simultaneous video was used to identify all epileptic events, both clinical seizure events and sub-clinical seizure activity. If the electroencephalograph showed changes prior to the clinical onset, the start of the event was measured at the start of the electro-graphic change. If the clinical manifestations appeared prior to the electrical event, then the start of the event was taken at the start of the clinical onset. The data was annotated to the nearest second. Q-T intervals were measured manually (Morganroth et al 2001, Benatar et al 2001, Pater 2005, Fossa et al 2005, Malik 2004) from modified lead II ECG. Consecutive measurements of Q-T intervals and their preceding R-R intervals were measured over a 9 seconds epoch (Tavernor et al 1996, Benatar et al 2001, Luo et al 2004). The QT interval was measured at the start of the QRS complex, to the end of the T-wave, defined as the intersection of iso-electric line and the tangent of maximal downward limb of the T-wave (Lepeschken et al 1952, Surawicz et al 1998, Benatar et al 2001) and entered onto a Microsoft Excel spreadsheet. Careful measurement of the T-wave did not include the U wave as the final Q-T measurement (Lepeschken et al 1952, Surawicz et al 1998, Bazett 1920). The mean average values of 9 consecutive R-R and Q-T intervals were calculated over a 9 seconds epoch to average out the effect of normal sinus arrhythmia (Benatar et al 2001, Luo et al 2004, Malik 2004). During the seizure, the 9 seconds epoch with the longest QTc was chosen to compare

with pre-seizure values. Clinically significant hypoxia was considered to be below 85% oxygen saturation in this study. Corrective formulae were applied to each consecutive 9 seconds epoch from Excel formulae computation. Effectively every heartbeat was manually measured during every event until the event ended clinically and once the electroencephalograph had resumed its pre-event trace. Data were also measured and analysed prior to the seizure event. From the onset of the seizure, data was measured 5 minutes (T-5m), 4 minutes (T-4m), 3 minutes (T-3m), 2 minutes (T-2m), 1 minute (T-1m) and 9 seconds (T-9s) before the event. During the seizure, the 9 seconds epoch with the longest QTc was chosen to compare with the pre-seizure QTc value calculated 9 seconds prior to the seizure (T-9).

2.2.2 Intra & inter-observer analysis

A qualified Electrocardiographer / Electroencephalographer was asked to independently re-measure the same raw data that had been previously measured in three different patients in order to analyse the inter-observer error. The Q-T interval was corrected for rate using Bazett's Formula. Consecutive Q-T and R-R measurements over a 9 second epoch were listed onto an excel spreadsheet. Mean values for the Q-T and R-R measurements were calculated for consecutive 9 seconds epochs. The mean values were then applied to Bazett's Formula to calculate the Corrected Q-T. The mean Q-T and R-R measurements are recommended in cardiology literature to minimise the effect of normal sinus rhythm. In children in particular, normal sinus rhythm can show marked variation. On inspiration, the heart rate

speeds up with a shortened Q-T. On expiration, the heart rate slows down resulting in a longer Q-T.

Inter-observer analysis is important particularly in this calculation as measurements exceeding 450 milliseconds are considered to be clinically significant in paediatric patients and in adult males with a heart rate less than 60/min. Therefore if measurements are consistently over estimated then this may lead to an unrealistically long Q-T. Conversely, if measurements are consistently under estimated a genuinely long Q-T measurement could appear to be normal.

2.2.3 Multivariate analysis of effects of Anti-Epileptic Drugs on QTc

Multivariant analysis was performed on QTc, according to Bazett's formula derived from patients receiving different anti-epileptic medication, monotherapy, polytherapy and those patients not receiving any anti-epileptic drug (AED). Analysis was performed using One-way Analysis of Variation (ANOVA) for comparisons of QTc means in each AED, nil AED, monotherapy, polytherapy and analysed in terms of age, gender and seizure duration using Minitab statistical software, version 14.

2.2.5 Q-T Correction Formulae

Four commonly used correction formulae were applied to all data:
Two nonlinear formulae:-

Bazett (Bazett HC 1920) $QTc=QT/\sqrt[2]{RR\ interval}$.

Fridericia (Fridericia LS 1920) $QTc=QT/\sqrt[3]{RR\ interval}$

Two linear formulae:-

Hodges (Hodges M 1997, Hodges et al 1983) QTc=QT+1.75(heart rate –60)
Framingham (Sagie et al 1992) QTc=QT+0.154(1-RR)

Statistical analysis was performed using Minitab version 14 paired student t-tests comparing the maximum corrected Q-T value prior to the epileptic seizure with the maximum corrected Q-T value during the epileptic seizure. Paired t-testing was considered appropriate for the analysis method to compare the corrected Q-T prior to the seizure with the corrected Q-T during the seizure. Linear regression is applied to a few cases for comparison to results from corrective formulae. Cross tabulation of data comparing all formulae were analysed to give sensitivity and specificity values for each formula. Bazett's formula was used as the 'gold standard' to enable uniformity and comparison to other studies (Yu et al 1950, Morganroth et al 2001, Pater 2005, Fossa et al 2005). The Pearson Chi-Square (Chernoff et al 1954) was applied to determine statistical significance in the comparison of the corrected Q-T during generalised seizures, right hemisphere focal seizures and left hemisphere focal seizures. Fishers Exact Test was applied to the number of patients in each of the aforementioned categories. Normal

limits of corrected Q-T during a seizure were considered to be comparable to corrected QT values during exercise. In children the normal limit of corrected QT during exercise is 440 milliseconds (Rijnbeek et al 2001, Benatar et al 2001). Adult male and adult female corrected QT limit is dependent on formulae upper normal limits for all heart rate summarised in Table 1 (Luo et al, 2004), which are heart rate and gender specific. Increases in corrected QT from the baseline exceeding 60 milliseconds are considered to present a small risk of a fatal arrhythmia (European Agency for the Evaluation of Medicinal Products 2005, Fenichel et al 2004, Morganroth and Pyper 2001, Pater 2005). Patients in this study were also investigated for corrected Q-T increases exceeding 60 milliseconds during epileptic seizures and categorised into seizure types.

		Upper normal limits (98% in ms)			
Gender	**HR**	**QTcB**	**QTcFri**	**QTcFra**	**QTcH**
Both (10,303)	All HR	**483**	**460**	**457**	**457**
	HR<60	454	459	459	466
	HR 60 to 99	483	461	458	456
	HR >99	492	445	436	451
Male (5,420)	All HR	**480**	**457**	**454**	**454**
	HR<60	450	455	455	465
	HR 60 to 99	480	457	454	452
	HR>99	490	445	436	450
Female (4,883)	All HR	**486**	**463**	**461**	**460**
	HR<60	460	463	463	470
	HR 60 to 99	486	465	462	459
	HR>99	492	448	434	452

Table 1 Upper limit of normal values for corrected Q-T in adult males and adult females using Bazett's (QTcB), Hodge's (QTcH), Fridericia's (QTcFri) and Framingham's Formulae (QTc Fra) Luo et al 2004.

Chapter 11 : Results

2.3.1 Study group characteristics

The subject gender mix was 25 males and 14 females. The age range was 2 years 5 months to 60 years 3 months. The mean age was 17 years 2 months with a median age 11 years 5 months. The patients included in corrected Q-T analysis are from the original patient group analysed in the percentage heart rate change and oxygen de-saturation study in section 1.

Study Patient	Section Two Patient	Age	Gender	Aetiology/Epilepsy	Anti-Epileptic Drugs
3	1	3 years5 months	M	Motor developmental delay. Weekly complex focal seizures	Carbamazepine, Lamotrigine.
4	2	3 years 7 months	M	Mild motor delay. Weekly Generalised Tonic Clonic Seizures.	Clobazam, Sodium Valproate, Phenytoin.
6	3	3 years 6 months	M	Mild motor delay. Weekly complex focal seizures.	Carbamazepine, Lamotrigine.
9	4	3 years 1 month	M	Autistic spectrum disorder. Weekly complex focal seizures.	Nil. (Seizures not previously diagnosed).
10	5	15 years 11 months	F	Aicardi syndrome. Cerebral palsy with left hemiparesis. Weekly tonic, Generalised Tonic Clonic & myoclonic seizures.	Phenytoin.
11	6	15 years 2 months	M	Lennox Gastaut syndrome. Daily absences, weekly Generalised Tonic Clonic Seizures.	Topiramate, Clobazam, Propanolol. Midazolam rescue medication.

13	7	5 years 4 months	F	Sub-cortical band heterotopia. Daily epileptic spasms.	Sodium Valproate.
14	8	7 years 6 months	M	Global motor delay. Nocturnal seizures occurring weekly.	Carbamazepine.
15	9	6 years 7 months	M	Lennox Gastaut syndrome. Generalised Tonic Clonic Seizures daily.	Sodium Valproate, Topiramate, Clobazam.
16	10	5 years 9 months	F	Aicardi syndrome. Epileptic spasms daily.	Vigabatrin, Lamotrigine.
17	11	49 years 7 months	M	Daily complex focal seizures. One nocturnal Generalised Tonic Clonic Seizure.	Carbamazepine, Lamotrigine, Topiramate.
18	12	5 years 9 months	M	Normal development. Absences, drop attacks & nocturnal Generalised Tonic Clonic Seizures.	Sodium Valproate, Clobazam.
19	13	60 years 3 months	F	3 year history of funny turns. Complex focal seizures.	Nil. Commenced on AED after EEG Videotelemetry.
20	14	20 years 9 months	M	Epilepsy since childhood. Polymicrogyria. Complex focal seizures.	Carbamazepine.
21	15	17 years 11 months	F	Complex focal seizures, occasional Generalised Tonic Clonic Seizures.	Topiramate, Keppra.
22	16	11 years 3 months	F	Normal development. Recent weekly focal seizures.	Carbamazepine.
23	17	11 years 5 months	M	Normal development. Weekly complex focal seizures with secondary generalisation.	Sodium Valproate.

24	18	27 years 9 months	F	Recent focal seizures.	Nil. Commenced on AED after EEG Videotelemetry.
25	19	21 years 3 months	F	Daily absences. Generalised Tonic Clonic Seizures every two months.	Sodium Valproate, Phenobarbitone, Lamotrigine.
26	20	4 years 9 months	M	Mild developmental delay. Weekly nocturnal seizures.	Topiramate, Sodium Valproate.
27	21	6 years 6 months	F	Previous viral encephalopathy. Cortical visual impairment & 22learning disability. Atonic seizures and absences.	Phenobarbitone.
28	22	6 years 1 month	M	Magille's syndrome. Myoclonic absences.	Nil. To be commenced on Ethosuximide.
29	23	16 years 11 months	M	Normal development. Daily absences.	Sodium Valproate.
30	24	16 years	M	Frequent daily episodes resembling torticollis & retrocollis. Complex focal seizures.	Carbamazepine
31	25	4 years 11 months	M	Developmental delay. Nocturnal seizures.	Topiramate, Sodium Valproate.
32	26	4 years 7 months	M	Complex focal seizures	Carbamazepine, Lamotrigine
33	27	22 years 7 months	F	Complex focal seizures	Nil. Commenced on AED after EEG Videotelemetry
34	28	41 years 9 months	F	Myoclonic epilepsy	Nil

35	29	2 years 5 months	M	Prolonged febrile convulsion. Nocturnal Generalised Tonic Clonic Seizures.	Sodium Valproate.
36	30	3 years 9 months	M	Autistic spectrum. Weekly Generalised Tonic-Clonic Seizures.	Clobazam, Sodium Valproate, Lamotrigine.
37	31	4 years 3 months	M	Right temporal lesion extending to parahypocampal gyrus. Focal seizures.	Sodium valproate, Carbamazepine.
38	32	5 years 11 months	M	Myoclonic Astatic Epilepsy. Absences, atonic, tonic, Generalised Tonic-Clonic Seizures. Periods of non-convulsive status epilepticus.	Phenobarbitone, Topiramate.
39	33	12 years 4 months	F	Normal development, 18 month history of absences, single Generalised Tonic-Clonic Seizure.	Carbamazepine.
40	34	30 years 11 months	M	Focal seizures (sensory induced by music)	Lamotrigine
41	35	5 years 4 months	M	Microcephaly, Cerebral Palsy. Seizures.	Nitrazepam.
42	36	5 years 4 months	F	Cerebral Palsy. Shunted hydrocephalus. Severe visual impairment. Seizures.	Sodium Valproate, Nitrazepam, Phenytoin.
43	37	43 years 11 months	M	Encephalitis post typhus vaccination. Complex focal seizures with secondary generalisation since, occurring 2-3/month	Keppra, Lamictal.

44	38	22 years 8 months	F	Complex focal seizures with secondary generalised seizures.	To be commenced on AEDs
45	39	2 years	M	Episodes of epilepsia partialis continuans involving the right side of face.	Nil. To be commenced on Phenytoin.

Table 2 Section Two Study Patients Demographics.

Results According to Bazett's corrective formulae

Introduction

Henry Cuthbert Bazett was born in Gravesend, England. He was educated at Oxford (B.A., 1908; M.B., 1911; B.Ch., 1911; M.S., 1913; and M.D., 1919). After service as a medical officer in the British Army during World War I, he accepted a professorship in physiology at the University of Pennsylvania in 1921. Bazett's formula QTc= QT/$^{2}\sqrt{}$R-R interval is used to compare Hodge's, Fridericia's and Framingham's formulae to in this study as Bazett's formula is considered to be the 'gold standard' for comparison to other studies. Bazett's formula is found in most cardiology equipment software in the UK (Yu et al 1950, Morganroth et al 2001, Pater 2005, Fossa et al 2005). Bazett's study was based on 39 subjects.

2.3.2 Total seizure group.

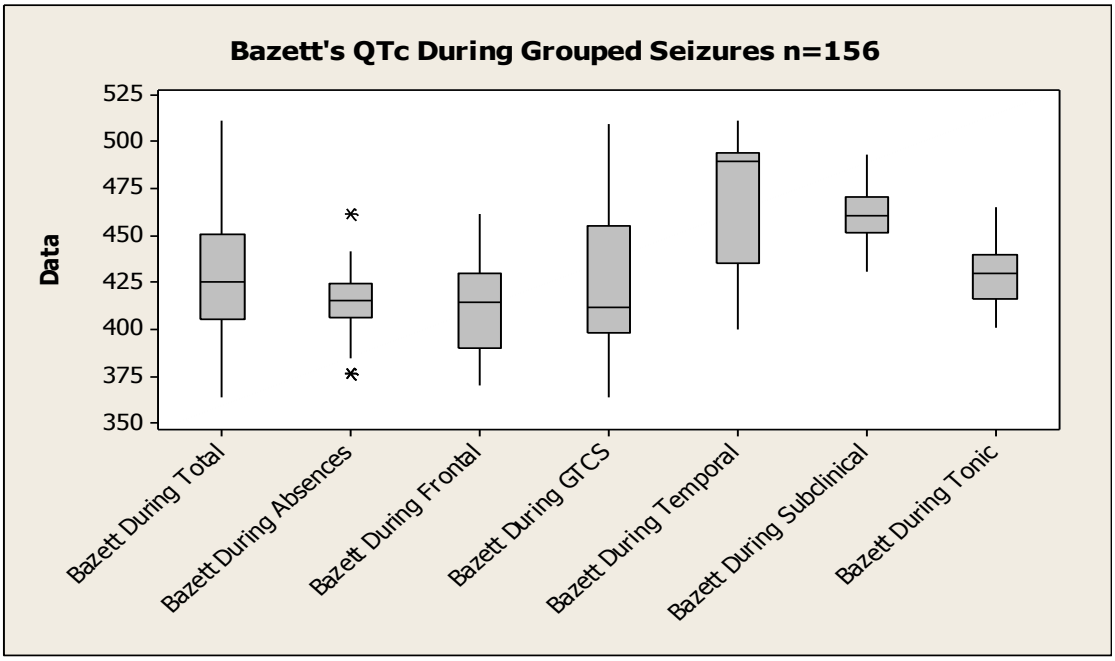


Figure 2. Boxplot of Bazett's corrected Q-T values during grouped seizures.

The subject gender mix was 25 males and 14 females (Table 2). The age range was 2 years 5 months to 60 years 3 months. The mean age was 17 years 2 months with a median age 11 years 5 months. A total of 156 seizures had corrected Q-T analysis performed (370 seizures had to be excluded from the study due to EMG artefact obscuring the ECG trace) The 156 analysed seizures were composed of: 9 generalised tonic-clonic seizures (5 patients), 34 absences (6 patients), 12 tonic seizures (6 patients), 27 temporal lobe seizures (14 patients), 58 frontal lobe seizures (4 patients) and 16 sub-clinical seizures (4 patients) were clinically and electrographically identified.

According to Bazett's formula, nine patients were identified as prolonging their corrected Q-T during seizures, representing 23% (9/39) of the total study group. The longest QTc value from a 9 seconds epoch was selected to compare re-polarisation values prior to the seizure and during the seizure. Of these nine patients 21 seizures when analysed prolonged their corrected Q-T beyond normal values (Luo et al, 2004) according to Bazett's formula. The 21 seizures identified were:

- 5 right temporal lobe sub-clinical seizures (1 paediatric patient).
- 1 left temporal lobe sub-clinical seizure (1 paediatric patient).
- 11 right temporal lobe seizures (3 patients).
- 2 left temporal lobe seizures (2 patients).
- 1 generalised tonic-clonic seizure (1 paediatric patient).
- 1 myoclonic absence seizure (1 paediatric patient).

The proportion of seizures identified by Bazett's formula as resulting in a prolongation of the corrected Q-T of total seizures in the study is 13% (21/156 seizures). The number of patients identified as prolonging their corrected Q-T during seizures is 23% (9/39), (Table 3, Figure 3).

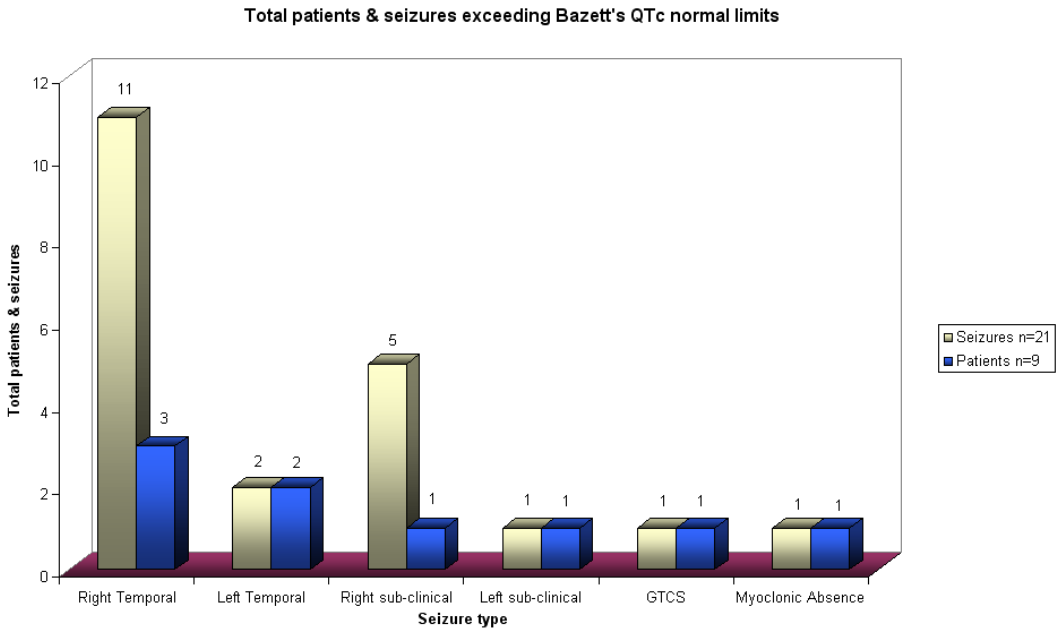


Figure 3 Bar chart of total patients & total seizures with applied Bazett's corrected Q-T formula and exceeding normal QTc limits (according to Luo et al 2004).

Patient Study Identification Number & Gender	Heart Rate During Bpm	Bazett's QTc Before (msec.)	Bazett,s QTc During (msec.)	Bazett's QTc Change (msec.)	Seizure Type
9M(paediatric)	119.5	441	492	51	Right Sub-clinical Temporal
9M(paediatric)	111.9	444	474	30	Right Sub-clinical Temporal
9M(paediatric)	109.1	390	471	81	Right Sub-clinical Temporal

9M(paediatric)	120	376	493	117	Right Sub-clinical Temporal
9M(paediatric)	140.5	445	472	27	Right Sub-clinical Temporal
22F(paediatric)	72.2	425	454	29	Left Sub-clinical Temporal
20M	66.7	396	495	99	Right Temporal
20M	119.5	412	501	89	Right Temporal
20M	100.6	410	494	84	Right Temporal
20M	100.8	421	493	72	Right Temporal
20M	88.4	401	490	89	Right Temporal
20M	102	411	502	91	Right Temporal
20M	100.3	436	494	58	Right Temporal
20M	110	390	512	122	Right Temporal
20M	102	410	492	82	Right Temporal
21F	101	413	494	81	Right Temporal
24F	110.1	420	505	85	Right Temporal
19F	109	396	494	98	Left Temporal

17M	76.8	433	491	58	Left Temporal
18M(paediatric)	148.1	403	490	87	Generalised Tonic-clonic
28M(paediatric)	117.6	440	462	22	Myoclonic Absence

Table 3 Summary of Bazett's corrected Q-T values for patients during seizures exceeding normal limits (according to Luo et al 2004).

Paired t-testing using minitab version 14 was performed on the total seizure group n=156 data according to Bazett's formula and shows a statistically significant difference (*p<0.001)* between the corrected Q-T value prior to the seizure and during the seizure. The mean corrected Q-T value for the group is within normal limits of 427 milliseconds. When the data is divided into seizure types, high statistical significance is seen in frontal lobe seizures, generalised tonic-clonic seizures and temporal lobe seizures. Tonic seizures show a moderate statistical significance and absence seizures present a poor statistical significance when analysing changes in corrected Q-T before the seizures with during the seizures (Table 4)

		Mean msec	St. Dev. msec	StError Mean msec	95% CI msec	*p value*
Bazett's Total Seizure Data n=156	During	427.6	34.0	2.7		
	Before	399.9	35.2	2.8		
	Difference	27.7	32.0	2.6	22.6, 32.7	<0.001
Bazett's Absence Seizure Data n=34	During	414.5	18.4	3.2		
	Before	417.9	19.0	3.3		
	Difference	-3.3	19.3	3.4	-10.2, 3.5	=0.329

Bazett's Frontal Lobe Seizure Data n=58	During	411.2	25.0	3.3		
	Before	379.5	31.4	4.1		
	Difference	31.7	17.7	2.3	27.0, 36.3	<0.001
Bazett's GTCS Data n=9	During	417.8	42.1	14.0		
	Before	365.6	58.5	19.5		
	Difference	52.2	34.9	11.6	25.4, 79.1	=0.002
Bazett's Temporal Lobe Seizures n=27	During	463.0	34.6	6.7		
	Before	408.9	20.8	4.0		
	Difference	54.1	36.9	7.1	39.5, 68.7	<0.001
Bazett's Right Temporal Lobe Seizures n=17	During	481.4	28.5	7.6		
	Before	405.0	21.4	5.7		
	Difference	76.4	23.4	6.2	62.9, 89.9	<0.001
Bazett's Left Temporal Lobe Seizures n=10	During	444.5	32.4	9.8		
	Before	412.7	21.9	6.6		
	Difference	31.8	36.5	11.0	7.2, 56.3	=0.016
Bazett's Tonic Seizures n=12	During	429.2	19.3	5.4		
	Before	414.6	34.5	9.6		
	Difference	14.6	25.4	7.0	-0.7, 29.9	=0.06
Bazett's Sub-clinical Seizures n=16	During	467.5	18.2	4.5		
	Before	435.6	23.1	5.8		
	Difference	31.9	30.2	7.5	15.8, 48.0	<0.001

Table 4 Paired T-testing Statistical Analysis for Bazett's Corrected Q-T Formula Data.

2.3.3 Generalised seizures

Generalised tonic clonic seizures

Changes in the corrected Q-T were analysed before and during nine generalised tonic clonic seizures (*p<0.001).* One seizure resulted in corrected Q-T beyond normal limits with a maximum increase of 87 milliseconds from 403 to 490 milliseconds (Table 3). Three generalised tonic clonic seizures (33%) from 2 patients increased corrected Q-T values exceeding 60 milliseconds during the seizure. Two of these seizures (2 patients) although they demonstrated an increase in corrected Q-T exceeding 60 milliseconds, remained within normal QTc limits for age and gender (Table 7). This seizure type represents one of the highest proportions (33%) of increased corrected Q-T exceeding 60 milliseconds compared to other seizure types in this study (Table 8). Patient 43M became hypoxic during a seizure with oxygen saturation dropping to 67% during the de-saturation period of 87 seconds and total seizure duration 165 seconds. This seizure was a secondary generalised left temporal lobe seizure. The corrected Q-T increased by 130 milliseconds but stayed within normal limits (Table 5). None of the remaining six patients in the study who had generalised tonic clonic seizures became hypoxic

This seizure group was the smallest group in the study n=9 but shows high statistical significance (*p<0.001)* because the standard deviation is relatively large at 34.9 milliseconds indicating one of the largest change in corrected Q-T than any other seizure group. The mean corrected Q-T during generalised tonic-clonic seizures is however still within normal range for this group at 417 milliseconds (Table 4).

An interesting observation is seen in the standard deviation before the seizures being much higher at 58.5 milliseconds compared to 42.0 milliseconds during the generalised tonic clonic seizure group of seizures. This suggests that the corrected Q-T values stay much closer to the mean during the seizure than they did before the seizure indicating a more stereotyped heart rate, re-polarisation time or some characteristic difference autonomically during the seizure compared to before the seizure. This reduction in standard deviation during the event is dramatically different in this seizure type compared to any others.

Absence seizures

Seventy four percent (26/35) of absence seizures either showed no increase in corrected Q-T or slightly shortened the corrected Q-T and as a group did not reach statistical significance (*p=0.329),* (Table 4). One myoclonic absence without hypoxia demonstrated corrected Q-T lengthening by a small amount of 20 milliseconds resulting in corrected Q-T prolongation of 460 milliseconds in a child (Table 3, Figure 3). The remaining 8 events only increased the corrected Q-T by 10 milliseconds.

Corrected Q-T during absences shows the least statistical significance of *p=0.329* compared to other seizure groups, with the least amount of change (-3 milliseconds) measured in the corrected Q-T for the group n=34. The corrected Q-T during absences collectively is well within normal limits of 414 milliseconds with one of the tightest standard deviation of 19.3 milliseconds during the seizure, similar to frontal lobe seizures at 17.6 milliseconds.

Tonic seizures

Small increases in corrected Q-T from 10 up to 50 milliseconds occurred during fifty eight percent (7/12) of tonic seizures with maximum values of 440 milliseconds (*p=0.06), (*Table 4). According to Bazett's formula none of the tonic seizure events increased the corrected Q-T values beyond normal limits. Oxygen saturation dropped to 86% in one patient 15M but remained within clinically normal range.

Corrected Q-T changes seen during tonic seizures n=12 in this study hardly scrape statistical significance at *p=0.06*. The mean corrected Q-T for this group is within normal limits at 429 milliseconds with a standard deviation difference of 25.3 milliseconds slightly larger to that seen in absences and frontal lobe seizures indicating a less tight variation about the mean. The 95% confidence interval seen during tonic seizures is small at (–0.7), 29.9 milliseconds which is slightly wider than that seen during absences at (-10.1), 3.5 milliseconds (Table 4).

2.3.4 Complex focal seizures.

Frontal lobe seizures

Fifty-eight frontal lobe seizures were analysed (2 derived from the right hemisphere and 56 derived from the left hemisphere). Generally, slight increases in corrected Q-T lengthening were observed in sixty four percent (37/58) of frontal lobe seizures resulting in high significance (*p<0.001),* (Table 4). However, the QTc lengthening was not clinically lengthened with values remaining within normal limits. Three left frontal lobe seizures resulted in corrected Q-T lengthening exceeding 60 milliseconds during the seizure but

again remained well within normal limits Table 8. Overall, this result represents a small proportion of five percent (3/58) of total frontal lobe seizures demonstrating this increase (Table 9).

The frontal lobe seizure group n=58 was the largest grouped seizure type data. Changes in corrected Q-T in this group was statistically significant (*p<0.001)* however, this is surprising given that the mean corrected Q-T during seizures is shorter (411 milliseconds) than that of absences (414 milliseconds). The standard deviation is smaller at 17.6 milliseconds compared to of absences at 19.3 milliseconds. Both standard deviation values for frontal lobe seizures and absences are smaller than that seen in temporal lobe seizures and generalised tonic-clonic seizures. No hypoxia occurred during frontal lobe seizures in this study.

Temporal lobe seizures

Seventy percent (19/27) of temporal lobe seizures measured an increase in corrected Q-T during the seizures (*p<0.001), (*Table 3). Bazett's formula indicated forty eight percent (13/27) of these seizures exceeded normal limits (Table 3, Figure 3) with the most dramatic corrected Q-T lengthening occurring from 390 milliseconds to 512 milliseconds during a right temporal lobe seizure lasting 1 minute 27 seconds.

Of the twenty-seven temporal lobe seizures recorded, 13 seizures measured an increase in corrected Q-T beyond normal limits according to Bazett's formula. Eleven of the temporal lobe seizures that showed this increase in corrected Q-T were derived from the right temporal lobe compared to only two left temporal lobe seizures.

Temporal lobe seizures n=27 demonstrate high statistical significance (*p<0.001)* comparing the corrected Q-T value before the seizure and during the seizure. This group gives the longest corrected Q-T mean value for the group at 462 milliseconds during the seizure compared to other seizure types. When this group is sub-divided into right temporal lobe seizures n=17 and left temporal lobe seizures n=10 more interesting statistics emerge. The right temporal lobe seizure group is more highly statistically significant (*p<0.001)* compared to the left temporal lobe seizure group (*p=0.016).* Additionally, the mean corrected Q-T during right temporal lobe seizures is 481 milliseconds compared to 444 milliseconds for the left temporal lobe seizure group. The 95% confidence interval for the right temporal lobe seizure group is the largest compared to any other groups at 62.9, 89.9 milliseconds indicating that 95% of data in this group has the largest range in corrected Q-T compared to other groups (Table 3). Four patients (8 seizures) became hypoxic during their temporal lobe seizures. During two right temporal lobe seizures (1 patient) oxygen saturation dropped to 71% during the de-saturation period lasting up to 81 seconds but the corrected Q-T remained within normal limits. During one of the left temporal lobe seizure, oxygen saturation dropped to 75% during the de-saturation period lasting 78 seconds. The corrected Q-T lengthened to 494 milliseconds, with an increase of 98 milliseconds (Table 5).

2.3.5 Sub-clinical seizures.

Sixteen sub-clinical temporal lobe seizures were recorded and QTc analysed from 4 patients (6 derived from the right hemisphere and 10 derived from the left hemisphere) compared to baseline measurements (*p<0.001)*. Six sub-clinical temporal lobe seizures from 2 patients were found to lengthen the corrected Q-T beyond normal limits according to Bazett's formula, with a maximum increase of 117 milliseconds during one sub-clinical seizure from 376 milliseconds to 493 milliseconds. Five of these sub-clinical seizures (1 patient) were derived from the right temporal lobe compared to one sub-clinical seizure from the left temporal lobe (1 patient).

The standard deviation of 30.2 milliseconds is the third largest calculation after temporal lobe seizures (36.9) and generalised tonic clonic seizures (34.9) milliseconds. A long mean corrected Q-T during sub-clinical seizures for the group is 467 milliseconds which is longer than that seen during generalised tonic clonic seizures (417 milliseconds) and comparable to that seen during temporal lobe seizures (462 milliseconds). The 95% confidence interval of 15.7, 47.9 milliseconds calculate a difference of 32.1 milliseconds, which is one of the largest intervals seen from each seizure group.

2.3.6 Seizures associated with hypoxia.

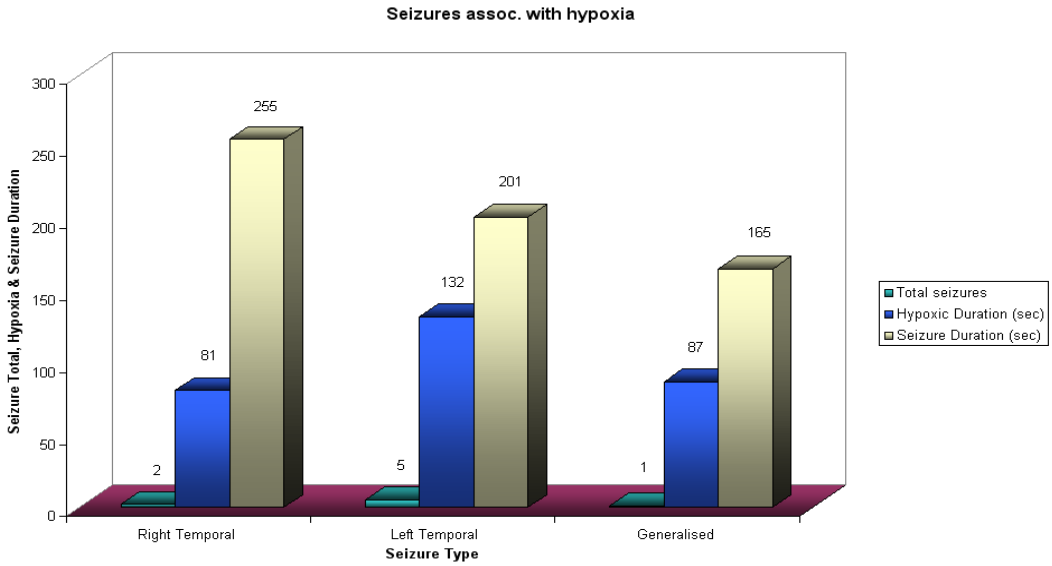


Figure 4 Seizures associated with hypoxia.

Hypoxia occurred in 8 seizures (4 patients).

- 2 right temporal lobe seizures (1 paediatric patient).
- 5 left temporal lobe seizures (3 patients).
- 1 generalised tonic-clonic seizure.

During the right temporal lobe seizures, oxygen saturation decreased to 71%, with a hypoxic duration of up to 81 seconds. The seizure lasted 255 seconds and was the longest seizure in the study. However the corrected Q-T remained within normal limits of 440 milliseconds in a paediatric case.

One of the left temporal lobe seizures (patient 43M) had the longest period of hypoxia lasting 132 seconds with oxygen saturation down to 72% with no change in corrected Q-T. Patient 19F became hypoxic lasting 78 seconds during a left temporal lobe seizure lasting 111 seconds. This patient increased the corrected Q-T by 98 milliseconds to a prolonged 494 milliseconds during the seizure. The T-wave also diminished at the start of the electrical discharge, slowly returning during the second half of the seizure.

The single secondary generalised seizure, originating from the left temporal lobe (43M) increased the corrected Q-T by 130 milliseconds during hypoxia of 67%, lasting 87 seconds and seizure duration of 165 seconds but the QTc remained within normal limits

Patient	Minimum %Oxygen Saturation During Seizure	Period of Oxygen De-saturation (seconds)	Seizure Duration (seconds)	Heart Rate During (Bpm	Bazetts QTc Before (msec)	Bazetts QTc During (msec)	Bazetts QTc Change (msec)	Seizure Type
31M Paediatric	71	81	252	101.5	421	431	10	Right Temporal
31M Paediatric	71	57	255	118.8	411	440	29	Right Temporal
19F	75	78	111	109	396	494	98	Left Temporal
43M	67	87	165	79.8	264	394	130	Left Temporal progressing to GTCS
43M	72	132	201	54.5	400	400	0	Left Temporal
43M	76	48	150	59.4	386	417	31	Left Temporal
44F	74	33	120	103.8	410	470	60	Left Temporal
44F	75	39	102	73.2	390	440	50	Left Temporal

Table 5 Seizures associated with oxygen de-saturation during seizures

2.3.7 Right and Left Hemisphere Focal Seizure Comparison

Patients who had temporal lobe seizures or sub-clinical seizures derived from the right hemisphere that produced a prolongation in corrected Q-T demonstrated a tendency to have multiple seizures compared to those patients experiencing left hemisphere seizures.

A total of twenty-seven temporal lobe seizures (14 patients) were recorded and analysed (17 right temporal lobe seizures (7 patients) and 10 left temporal lobe seizures (7 patients)). Thirteen temporal lobe seizures were found to lengthen the corrected Q-T beyond normal limits according to Bazett's formula. Eleven of these events (11/13) from 3 patients were derived from the right temporal lobe compared to two events (2/13) from 2 patients from the left temporal lobe. Sixteen sub-clinical temporal lobe seizures (4 patients) were recorded and analysed (six derived from the right hemisphere (2 patients) and ten derived from the left hemisphere (2 patients)). Six sub-clinical temporal lobe seizures were found to lengthen the corrected Q-T beyond normal limits according to Bazett's formula. Five of these seizures (1 patient) were derived from the right temporal lobe compared to one seizure from the left temporal lobe (1 patient).

Although it appears that lengthening of the corrected Q-T occurs more often from seizures derived from the right hemisphere there is no statistical significance when comparing right and left hemisphere seizures when the analysis is performed in terms of number of patients.

Lengthening of the corrected Q-T exceeding 60 milliseconds occurred in nineteen seizures of different seizure types (ten right temporal lobe seizures,

one left temporal lobe seizure, three generalised tonic-clonic seizures, three left frontal lobe seizures and two right temporal sub-clinical seizures). Ten (10/19) were derived from the right temporal lobe compared to one (1/19) derived from the left temporal lobe. Two (2/19) right temporal lobe sub-clinical seizures were identified compared to no seizures from left temporal sub-clinical seizures (Table 8).

Analysis of Effects of Laterality both in terms of Number of Seizures and in terms of Number of Patients

When the data is analysed in terms of number of seizures, a bias is introduced because of multiple seizures occurring from a few patients, giving the impression that there is a statistically significant difference in the lengthening of the corrected Q-T from seizures derived from the right hemisphere compared to the left hemisphere. When the data is analysed in terms of number of patients, there is no statistical difference in data derived from right and left hemisphere seizures.

Analysis of Laterality effect in terms of Number of Seizures

Corrected Q-T data using Bazett's formula was grouped into three seizure categories: generalised seizure, right hemisphere seizures and left hemisphere seizures and tested using Pearson Chi-Square analysis (Chernoff et al 1954) which makes the assumption that 'all things are equal.' The Pearson Chi-Square displays a strong statistical significance ($p< 0.001$) of prolonged QTc during right hemisphere seizures compared to both left hemisphere and generalised seizures (Table 6).

	Normal QTc	Abnormal QTc	All
1.Generalised Seizures	53 96.36%	2 3.64%	55 100.00%
2.Right Hemisphere Seizures	8 33.33%	16 66.67%	24 100.00%
3.Left Hemisphere Seizures	74 96.10%	3 3.90%	77 100.00%
All	135 86.54%	21 13.46%	156 100.00%
Pearson Chi-Square = 68.925, DF = 2, P-Value < 0.001			
Likelihood Ratio Chi-Square = 50.172, DF = 2, P-Value < 0.001			

Table 6 Pearson Chi-Square analysis comparing Bazett's corrected Q-T grouped data derived from generalised, right hemisphere and left hemisphere seizures.

Analysis of Laterality effect in terms of Number of Patients

However, when the data is analysed in terms of number of patients instead of number of seizures, the bias is eliminated. Again, corrected Q-T data using Bazett's formula was grouped into three seizure categories: generalised seizure, right hemisphere seizures and left hemisphere seizures but the number of patients were substituted instead of seizures and tested using Pearson Chi-Square analysis. Although patients with seizures arising from the right hemisphere showed more frequent lengthening of the corrected Q-T there is no statistical significance when comparing right and left hemisphere

seizures when the analysis is performed in terms of number of patients. (*p=0.422), (*Table 7).

	Normal QTc	Abnormal QTc	All
1. Generalised Sz Patients	12 85.71	2 14.29	14 100%
2. Right Hemisphere Sz Patients	7 63.64	4 36.36	11 100%
3. Left Hemisphere Sz Patients	11 78.57	3 21.43	14 100%
All	30 76.92	9 23.08	39 100%
Pearson Chi Square=1.725, DF=2,P-Value=0.422			
Likelihood Ratio Chi-Square=1.684, DF=2, P-Value=0.431			

Table 7 Pearson Chi-Square analysis comparing Bazett's corrected Q-T data for number of patients derived from generalised, right hemisphere and left hemisphere seizures.

2.3.8 Corrected Q-T prolongation exceeding 60 milliseconds.

It is considered that when the corrected Q-T lengthens by more than 60 milliseconds there is a small risk of a fatal arrhythmia. (European Agency for the Evaluation of Medicinal Products 2005, Fenichel et al 2004, Morganroth and Pyper 2001, Pater 2005). In this study, nineteen (19) seizures demonstrated an increase in corrected Q-T lengthening exceeding 60 milliseconds. Ten (10) seizures (3 patients) demonstrating this increase were right temporal lobe seizures, representing 59% (10/17) of all right temporal lobe seizures in the study. This compares to only one left temporal lobe seizure increasing the corrected Q-T exceeding 60 milliseconds during the seizure from a total of ten (1/10) left temporal lobe seizures. The patient (19F) who had the left temporal lobe seizure increased the corrected Q-T by 98 milliseconds to a prolonged measurement of 494 milliseconds and was hypoxic with an oxygen saturation of 75%.

Sixteen sub-clinical temporal lobe seizures were recorded and analysed. In two of these sub-clinical seizures ((1 patient) the corrected Q-T lengthened by more than 60 milliseconds. Both of these seizures were right temporal sub-clinical seizures (Figure 5, Table 8).

Patient Study Identification Number & Gender	Heart Rate During (Bpm)	QTc Before (msec.)	QTc During (msec.)	QTc Change (msec.)	Seizure Type
9M(paediatric)	109.1	390	471	81	Right Sub-clinical Temporal
9M(paediatric)	120	376	493	117	Right Sub-clinical Temporal
20M	119.5	412	501	89	Right Temporal
20M	100.6	410	494	84	Right Temporal
20M	100.8	421	493	72	Right Temporal
20M	88.4	401	490	89	Right Temporal
20M	102	411	502	91	Right Temporal
20M	110	390	512	122	Right Temporal
20M	102	410	492	82	Right Temporal
20M	66.7	396	495	99	Right Temporal
21F	101	413	494	81	Right Temporal
24F	110.1	420	505	85	Right Temporal
19F	109	396	494	98	Left Temporal
30M	98.1	336	417	81	Left Frontal
30M	105.2	333	413	80	Left Frontal
30M	90.9	330	401	71	Left Frontal
18M(paediatric)	148.1	403	490	87	Generalised Tonic-clonic
18M(paediatric)	123.9	351	421	70	Generalised Tonic-clonic
43M	79.8	264	394	130	Generalised Tonic-clonic

Table 8.(above) Summary of patients demonstrating an increase in corrected QT exceeding 60 milliseconds during a seizure according to Bazett's Formula.

Of these 19 seizures, 5 seizures identified as having an increase from baseline by 60 milliseconds were still within normal QTc limits of which 2 where generalised tonic clonic seizures and 3 were left frontal lobe seizures. The types of seizures resulting in maximum increases in corrected Q-T lengthening occurred in a generalised tonic clonic seizure (130 milliseconds), right temporal lobe seizure (122 milliseconds) and right temporal sub-clinical seizure (117 milliseconds). This result is consistent with the grouped analysis of seizure types that demonstrated maximum increases of corrected Q-T exceeding 60 milliseconds in this study of 3/9 generalised tonic clonic seizures (33%) from 2/5 patients, 10/17 right temporal lobe seizures (59%) from 3/7 patients and 2/6 right temporal sub-clinical seizures (33%) from 1/2 patients compared 10% (1/10) of left temporal lobe seizures from 1/7 patients and 5% (3/56) of left frontal lobe seizures from 1/2 patients (Table 9 Figure 5).

Seizure Type	Total Seizures	No. Seizures with Bazett's QTc > 60 milliseconds.	% Seizures with Bazett's QTc > 60 milliseconds.
Right Temporal	17	10	59
Left Temporal	10	1	10
Right Temporal Sub- clinical	6	2	33
Left Temporal Sub-clinical	10	0	0
Right Frontal	4	0	0
Left Frontal	54	3	5
GTCS	9	3	33
Tonic	12	0	0
Absences	34	0	0

Table 9.Percentage of corrected Q-T lengthening exceeding 60 milliseconds during epileptic seizure types according to Bazett's Formula.

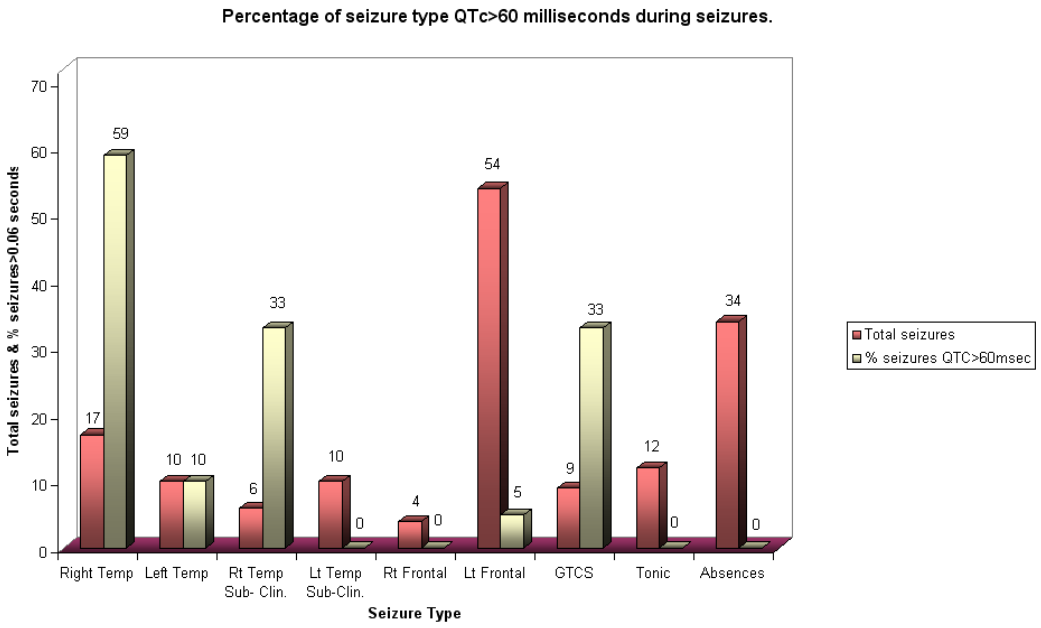


Figure 5 Total seizures and percentage of each seizure type increasing Bazett's QTc >60 milliseconds during the seizure.

2.3.10 Summary

Nine patients (23%) of the study group were identified as prolonging their corrected Q-T during seizures. Twenty-one seizures (13% of total seizures) prolonged their corrected Q-T during 5 right sub-clinical temporal lobe seizures (1 patient), 1 left temporal lobe seizure (1 patient), 11 right temporal lobe seizures (3 patients), 2 left temporal lobe seizures (2 patients), 1 generalised tonic clonic seizure and 1 myoclonic absence seizure.

Bazett's formula shows a statistically significant difference (*p<0.001)* between the corrected Q-T value prior to the seizure and during the seizure for the total seizure group. When the data is divided into seizure types, high statistical significance is seen in frontal lobe seizures, generalised tonic-clonic

seizures, temporal lobe seizures and sub-clinical seizures. Tonic seizures show a moderate statistical significance and absence seizures present a poor statistical significance when analysing changes in corrected Q-T before the seizure with during the seizure.

A right temporal lobe seizure resulted in the most prolonged corrected Q-T of 512 milliseconds. No distinction is found when comparing corrected Q-T lengthening during right temporal lobe seizures with left temporal lobe seizures when analysed in terms of number of patients. Nineteen seizures demonstrated an increase in corrected Q-T lengthening exceeding 60 milliseconds. Ten (10) seizures demonstrating this increase were right temporal lobe seizures, representing 59% (10/17) of all right temporal lobe seizures in the study. This compares to only one left temporal lobe seizure increasing the corrected Q-T exceeding 60 milliseconds during the seizure from a total of ten (1/10) left temporal lobe seizures.

Three patients (4 seizures) became hypoxic during their seizures with oxygen saturation dropping to 67% during a generalised tonic-clonic seizure whereupon the corrected Q-T lengthened by 130 milliseconds but stayed within normal limits. Patient 19F prolonged the corrected Q-T beyond normal limits and de-saturated to 75% during a hypoxic period lasting 78 seconds.

Chapter 12: Results: According to Hodge's corrective formula

Introduction:

Dr Morrison Hodges, Minneapolis introduced a relatively new heart rate correction formula in 1983 (Hodge et al 1983). QTc=QT+1.75(heart rate –60).

Luo et al 2004 recommends Hodge's Formula instead of Bazett's when considering all heart rates, as it is less correlated with heart rate.

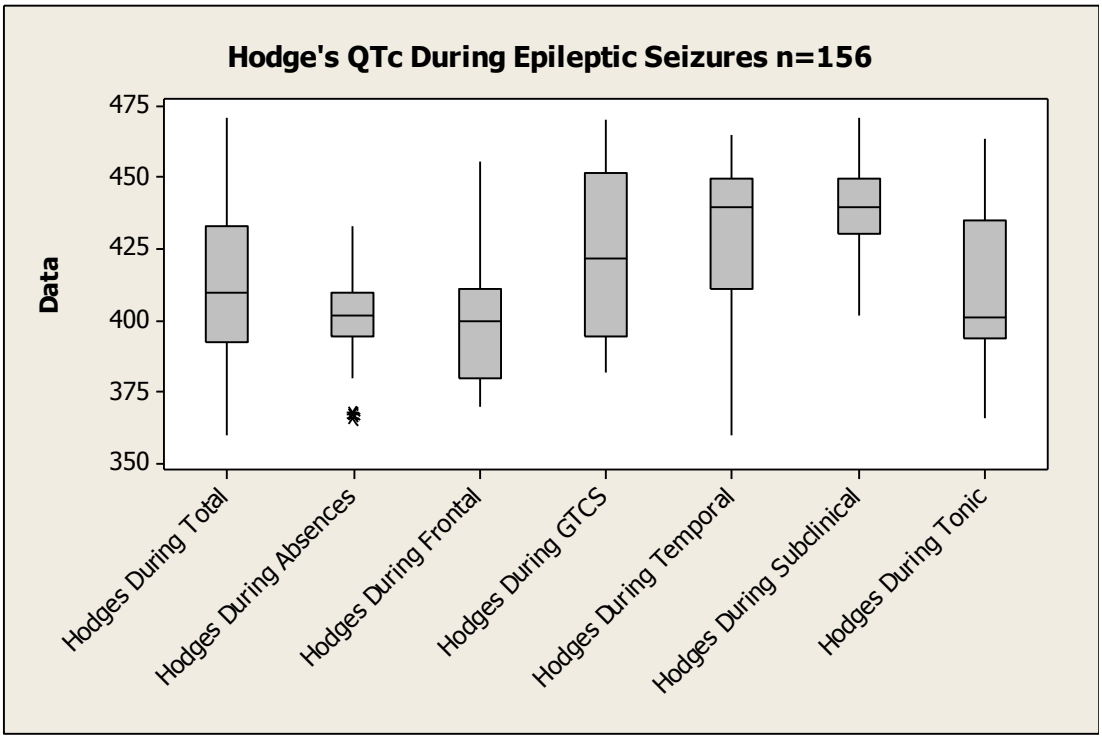


Figure 6 Boxplot of Hodge's corrected Q-T values during grouped seizures.

2.4.1 Total seizure group

The subject gender mix was 25 males and 14 females. The age range was 2 years 5 months to 60 years 3 months (Table 2). The mean age was 17 years 2 months with a median age 11 years 5 months. A total of 156 seizures had corrected Q-T analysis performed (370 seizures had to be excluded from the study due to EMG artefact obscuring the ECG trace) The 156 analysed seizures were composed of: generalised tonic-clonic seizures (9), absences (34), tonic seizures (12), temporal lobe seizures (27), frontal lobe seizures (58) and 16 sub-clinical seizure events were clinically and electrographically identified.

Fewer seizures resulting in lengthening of the corrected Q-T according to Luo et al were identified using Hodge's formula compared to Bazett's results. Seven seizures were derived from four patients.

- 2 Tonic seizures (1 paediatric patient).
- 1 Generalised tonic-clonic seizure (1 paediatric patient)
- 1 right temporal lobe seizure (1 patient).
- 3 right temporal lobe sub-clinical seizures (1 paediatric patient)

When Hodge's formula is applied to the data, 10% of total patients (4/39) were identified as prolonging their corrected Q-T during seizures. The

proportion of seizures demonstrating this increase is 4% (7/156) of the total seizure group (Figure 7, Table 10).

Patient No & Gender	Heart Rate During Bpm	Hodge's QTc Before (msec)	Hodge's QTc During (msec)	Hodge's QTc Change (msec)	Seizure Type
9M(paediatric)	119.5	420	450	30	Rt Temp Sub-clinical
9M(paediatric)	111.9	420	450	30	Rt Temp Sub-clinical
9M(paediatric)	127.5	405	475	70	Rt Temp Sub-clinical
15M(paediatric)	169.6	420	452	30	Tonic
15M(paediatric)	170.5	404	464	60	Tonic
18M(paediatric)	120.4	343	463	120	GTCS
20M	66.7	439	479	40	Rt Temp

Table 10 Summary of Hodges corrected Q-T values for patients during seizures exceeding normal limits according to Luo et al 2004.

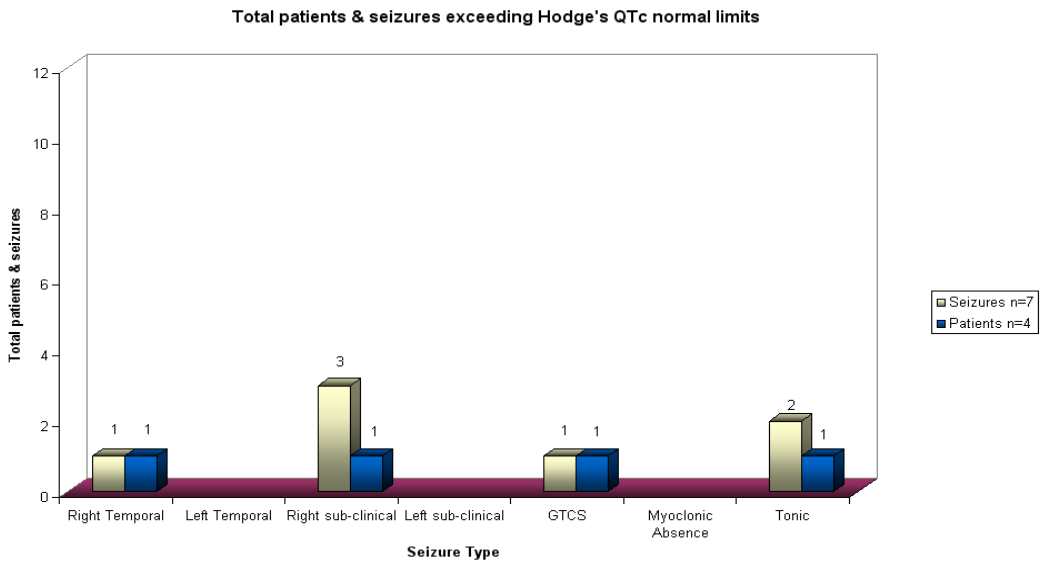


Figure 7 Bar chart of total patients & total seizures exceeding Hodge's corrected Q-T normal limits (according to Luo et al 2004).

Paired t-testing using minitab version 14 was performed on the total seizure group n=156 data according to Hodge's formula and shows a statistically significant difference (*p>0.001)* between the corrected Q-T value prior to the seizure and during the seizure. The mean corrected Q-T value for the group is within normal limits of 409 milliseconds. This mean average is 16 milliseconds shorter than that presented using Bazett's formula.

According to Hodge's corrective formula the total seizure group shows a highly statistically significant change in corrected Q-T during seizures (*p<0.001)*. Frontal lobe seizures and temporal lobe seizures show significance values of *p<0.001* (Table 9). Hodge's formula attaches equally high statistical significance (*p<0.001)* to temporal lobe seizures when sub-divided into right temporal lobe seizures and left temporal lobe seizures. This compares to Bazett's formula which gave less significance to left temporal lobe seizures (*p=0.016).* Hodge's formula also indicates tonic seizures as having a higher statistical significance (*p=0.002)* compared to that of Bazett's formula (*p=0.06).*

Absence seizures still rank poorest with statistically significance in corrected Q-T with a value of *p=0.191* Sub-clinical seizures have a slightly less significant result of *p=0.006* from Hodge's formula compared to Bazett's formula of *p<0.001*.

		Mean msec	St. Dev. msec	St.Error Mean	95% CI msec	*p value*
Hodges Total Seizure Data n=156	During	409.9	26.9	2.1		
	Before	388.4	29.0	2.3		
	Difference	21.5	24.3	1.9	17.7, 25.4	<0.001
Hodges Absence Seizure Data n=34	During	399.8	14.7	2.5		
	Before	402.3	15.1	2.6		
	Difference	-2.5	11.0	1.9	-6.4, 1.3	=0.191
Hodges Frontal Lobe Seizure Data n=58	During	397.6	19.8	2.7		
	Before	372.0	20.8	2.8		
	Difference	25.6	15.1	2.0	21.5, 29.7	<0.001
Hodges GTCS Data n=9	During	422.9	32.2	10.7		
	Before	358.8	44.3	14.8		
	Difference	64.1	41.6	13.8	32.1, 96.1	=0.002
Hodges Temporal Lobe Seizure Data n=27	During	432.7	26.1	5.0		
	Before	401.7	23.6	4.5		
	Difference	31.0	17.6	3.4	24.0, 38.0	<0.001
Hodges Right Temporal Lobe Data n=17	During	437.8	26.6	7.1		
	Before	405.0	23.8	6.3		
	Difference	32.8	13.3	3.5	25.2, 40.5	<0.001

Hodges Left Temporal Lobe Data n=10	During	424.5	23.0	6.9		
	Before	390.9	22.1	6.7		
	Difference	33.6	20.6	6.2	19.8, 47.5	<0.001
Hodges Tonic Seizures n=12	During	411.8	28.6	8.3		
	Before	388.6	20.0	5.8		
	Difference	23.2	20.3	5.9	10.4, 36.2	=0.002
Hodges Sub-clinical Seizures n=16	During	442.2	14.7	3.7		
	Before	426.6	19.5	4.9		
	Difference	15.6	19.6	4.9	5.1, 26.1	=0.006

Table 11 Statistical analysis of Corrected Q-T Data from Epileptic Seizures according to Hodge's Formula.

2.4.2 Generalised seizures

Generalised Tonic-Clonic Seizures.

The generalised tonic-clonic seizures group (n=9) is the smallest group in the study. Hodge's formula differs slightly in statistical significance of *p=0.002* compared to Bazett's formula (*p<0.001)*. The mean corrected Q-T remains within normal range at 422 milliseconds, which is actually longer than that using Bazett's formula at 417 milliseconds. According to Hodge's formula, the generalised tonic-clonic seizure group has the largest standard deviation at 41.6 milliseconds compared to all other groups. Bazett's formula by comparison calculated the longest standard deviation of 36.9 milliseconds to temporal lobe seizures.

The 95% confidence interval of Hodge's formula is wider for generalised tonic clonic seizures at 32.1, 96.1 compared to that seen using Bazett's formula of 25.4, 79.1 milliseconds. Therefore, 95% of generalised tonic-clonic seizure data according to Hodge's formula fell over a wider range of measurement i.e. 64.0 (96.1-32.0) milliseconds compared to Bazett's results of 53.7 (79.1-25.4) milliseconds. This result explains why in this instance, Hodges formula calculates a longer mean corrected Q-T value of 421 milliseconds than Bazett's formula of 417 milliseconds for this seizure group (Table 11).

An interesting observation is that the standard deviation of the before seizure data is larger at 44.3 milliseconds than the during seizure data of 32.2 milliseconds which indicates that the data stays closer to the mean value during the seizure than before the seizure. It is the only seizure type that this occurs suggesting that during generalised tonic clonic seizures heart rate becomes more stereotyped, less variable re-polarisation time or autonomically different during this type of seizure group compared to any other seizure types. This is the same finding as seen using Bazett's formula.

Absence Seizures

The mean corrected Q-T for the absences group is one of the shortest values of 399 milliseconds during the seizure. Hodge's formula attaches slightly more statistical significance (*p=0.191)* to changes in corrected Q-T during absence seizures (n=34) than Bazett's formula (*p=0.329), (*Table 10). This indicates that the results have a large probability of 'chance' and not particularly related to any single event. Absences show the smallest standard deviation from the mean in the group of 11.0 milliseconds compared to all

other groups. The 95% confidence interval is also very small with 95% of data between (-6.4), 1.3 milliseconds.

Tonic Seizures

Hodge's formula considers tonic seizures to indicate a higher statistical significance of *p=0.002* than Bazett's (*p=0.06)* when comparing changes in corrected Q-T before tonic seizures with during tonic seizures. The mean corrected Q-T using Hodge's formula during the seizure is shorter at 412 milliseconds than that seen using Bazett's formula at 429 milliseconds. The difference in standard deviation of Hodge's calculation is smaller at 20.3 milliseconds compared to Bazett's difference in standard deviation in corrected Q-T at 25.4 milliseconds. The 95% confidence interval difference is smaller 25.8 (36.2-10.3) milliseconds for Hodge's results compared to Bazett's results of 30.7 ((-0.7), 29.9-(-0.7)) milliseconds.

2.4.3 Complex Focal Seizures.

Frontal Lobe Seizures

It remains surprising that frontal lobe seizures show high statistical significance (*p<0.001)* as was the case using Bazett's formula. The mean corrected Q-T for the group (n=58) was similar (397 milliseconds) to that seen during absence seizures (399 milliseconds) but the standard deviation is slightly larger at 15.1 milliseconds and a narrow 95% confidence interval of 21.5, 29.7 milliseconds. The mean corrected Q-T for frontal lobe seizures according to Hodge's formula 397 milliseconds is only slightly shorter than that determined by Bazett's formula at 411 milliseconds.

Temporal Lobe Seizures

High statistical significance (*p<0.001)* occurred in the changes of corrected Q-T during temporal lobe seizures (n-27) and in the sub-divided groups of right temporal lobe seizures (n=17), (*p<0.001)* and left temporal lobe seizures (n=10), (*p<0.001),* (Table 11). Hodge's formula attaches a higher statistical significance to left temporal lobe seizures than Bazett's formula of *p=0.016*. The mean corrected Q-T value during temporal lobe seizures is calculated to be 432 milliseconds which is within normal range and compares to Bazett's mean corrected Q-T of 462 milliseconds. Although the left temporal lobe seizure group show high statistical significance (*p<0.001*) using Hodge's formula, they still show the shorter mean corrected Q-T value of 424 milliseconds compared to right temporal lobe seizures at 437 milliseconds.

Temporal lobe seizures have a much smaller standard deviation of 17.6 milliseconds compared to generalised tonic clonic seizures (41.6 milliseconds). This also compares quite markedly with Bazett's standard deviation of 36.9 milliseconds.

2.4.4 Sub-clinical seizures.

A total of 16 sub-clinical seizures recorded and analysed (*p=0.006),* (6 derived from the right hemisphere and 10 derived from the left hemisphere), three right temporal sub-clinical seizures showed an increase beyond normal QTc limits defined by Luo et al 2004 when Hodge's formula is applied with no left temporal sub-clinical seizures identified (Figure 7, Table 10).

A mean corrected Q-T for the group is 442 milliseconds compared to Bazett's mean value of 467 milliseconds. A narrower 95% confidence interval is seen from Hodge's

formula for the sub-clinical group (5.1, 26.1) with a range of 21 milliseconds compared to Bazett's formula (15.8, 48.0) with a range of 32.2 milliseconds.

2.4.5 Right and Left Hemisphere Focal Seizure Comparison.

Three right sub-clinical temporal lobe seizures and one right temporal lobe seizure are identified using Hodges corrective formula as prolonging the corrected Q-T during the seizure according to normal limits (Luo et al 2004). This compares to no seizures identified from the left hemisphere as prolonging the corrected Q-T. Surprisingly, Hodge's formula attaches equally high statistical significance ($p<0.001$) to temporal lobe seizures when sub-divided into right temporal lobe seizures and left temporal lobe seizures (Table 11).

2.4.6 Corrected Q-T prolongation exceeding 60 milliseconds

A total of five seizures where identified from five patients as increasing the corrected Q-T during seizures according to Hodge's formula. Only one seizure exceeded normal corrected Q-T limits (Luo et al 2004) of 470 milliseconds during a right sub-clinical temporal lobe seizure. Three generalised tonic clonic seizures exceeded the corrected Q-T by 60 milliseconds. One generalised tonic clonic seizure in particular increased QTc values by 130 milliseconds but stayed within normal corrected Q-T limits. This seizure was identified by Bazett's formula as exceeding 60 milliseconds. Bazett's formula also identified all of Hodge's seizures exceeding 60 milliseconds except patient 35M who demonstrated an increase of 70 milliseconds according to Hodge's formula (Table 12).

Patient No. & Gender	Heart Rate During Bpm	QTc Before (msec)	QTc During (msec)	QTc Change (msec)	Seizure Type
30M	100.1	331	403	72	Left Frontal
18M paediatric	120.4	343	463	120	GTCS
35M paediatric	180	352	422	70	GTCS
43M	78.8	270	400	130	GTCS
9M paediatric	127.3	405	475	70	Rt Sub-Clinical Temporal

Table12. Summary of patients demonstrating an increase in corrected QT exceeding 60 milliseconds during a seizure according to Hodge's Formula.

2.4.7 Summary

When Hodge's formula is applied to all seizure data, seven seizures derived from four patients exceeded corrected Q-T normal limits according to Luo et al 2004 (Table 11, Figure 8). Hodge's formula identified 2 tonic seizures, 1 generalised tonic-clonic seizure, 1 right temporal lobe seizure and 3 right temporal lobe sub-clinical seizures.

Five patients demonstrated an increase in corrected Q-T exceeding 60 milliseconds during seizures with a right sub-clinical seizure resulting in QTc prolongation of 475 milliseconds. A generalised tonic clonic seizure increased the corrected Q-T by 130 milliseconds but remained within normal limits of 400 milliseconds.

Hodge's formula shows a statistically significant difference (*p<0.001)* when comparing the corrected Q-T value prior to the seizure and during the seizure. Frontal lobe seizures and temporal lobe seizures both show significance values of *p<0.001*. Hodge's formula attaches equally high statistical significance (*p<0.001)* to temporal lobe seizures when sub-divided into right temporal lobe seizures and left temporal lobe seizures. This compares to Bazett's formula giving less significance to left temporal lobe seizures (*p=0.016).* High statistical values are still seen in generalised tonic clonic seizures (*p=0.002),* tonic seizures (*p=0.002)* and sub-clinical seizures (*p=0.006)*. Poor significance is found in the absence seizure group (p=*0.191)*.

Chapter 13: Results: According to Fridericia's Formula

Introduction:

Dr L.S Fridericia was professor of medicine and physiology in Copenhagen, Denmark (Moss 2003) in the early 1900s and published his paper on the duration of electrical systole in 1920. His formula was based on the data of 50 patients. Despite the technological difficulties described in his paper (translation 2003) of using aluminium string galvanometers and photographic plates, his results are impressively accurate measuring very similar corrected Q-T values that we use today. In drug trials, Fridericia's formula is considered to have a more accurate correction factor than other traditional correction formulae in subjects with tachycardia (Pater 2005). Fridericia's paper was published the same year as Bazett's paper. However, although both corrective formulae have been used widely, Bazett's has always been the most commonly used formula and both formulae have been debated over the last 80 years.

Fridericia's corrective formula is $QTc = QT / \sqrt[3]{\text{RR interval}}$

2.5.1 Total Seizure Group

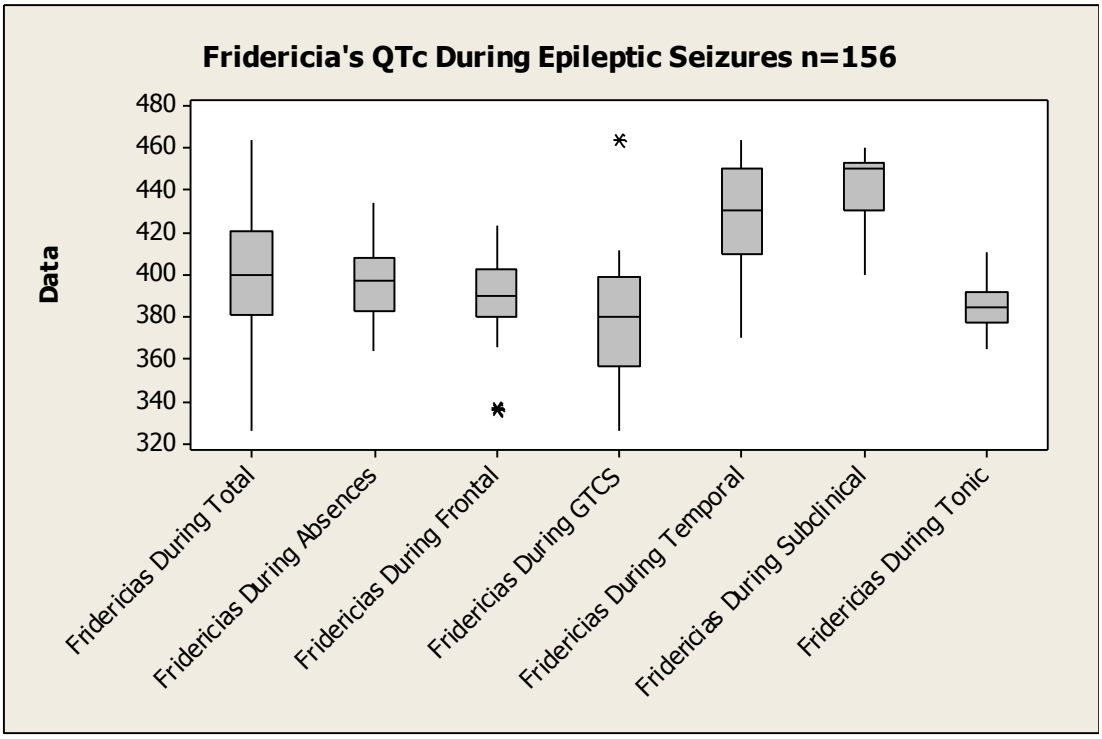


Figure 8 Boxplot of Fridericia's corrected Q-T values during grouped seizures.

The subject gender mix was 25 males and 14 females (Table 2). The age range was 2 years 5 months to 60 years 3 months. The mean age was 17 years 2 months with a median age 11 years 5 months. A total of 156 seizures had corrected Q-T analysis performed (370 seizures had to be excluded from the study due to EMG artefact obscuring the ECG trace) The 156 analysed seizures were composed of:- generalised tonic-clonic seizures (9), absences (34), tonic seizures (12), temporal lobe seizures (27), frontal lobe seizures (58) and 16 sub-clinical seizure events were clinically and electrographically identified.

From a total of 156 epileptic seizures analysed in this study according to Fridericia's corrective formula, 6 seizure events were identified as lengthening the corrected Q-T values beyond normal limits of QTc during exercise (Luo et al 2004). The seizures identified were:

- 1 right sub-clinical temporal lobe seizure (1 paediatric patient).
- 1 generalised tonic clonic seizure (1 paediatric patient).
- 1 left temporal lobe seizure (1 patient).
- 3 right temporal lobe seizures (1 patient)

These results represent 4 patients (10%) from the total of 39 patients in the study. Fridericia's formula identified 6 seizures as prolonging the corrected Q-T, which is 3% (6/156) of the seizure total in this study (Table 13, Figure 9).

Patient No &Gender	Heart Rate During Bpm	Fridericia's QTc Before (msec)	Fridericia's QTc During(msec)	Fridericia's QTc Change(msec)	Seizure Type
9M(paed)	92.8	370	454	84	Rt Temp Sub-clinical
16F(paed)	130	442	464	20	GTCS
17M	75.6	424	463	39	Lt Temp
20M	65.9	440	463	20	Rt Temp
20M	119.5	430	450	20	Rt Temp
20M	110	430	460	60	Rt Temp

Table13. Summary of Fridericia's corrected Q-T values for patients during seizures exceeding normal limits according to Luo et al 2004.

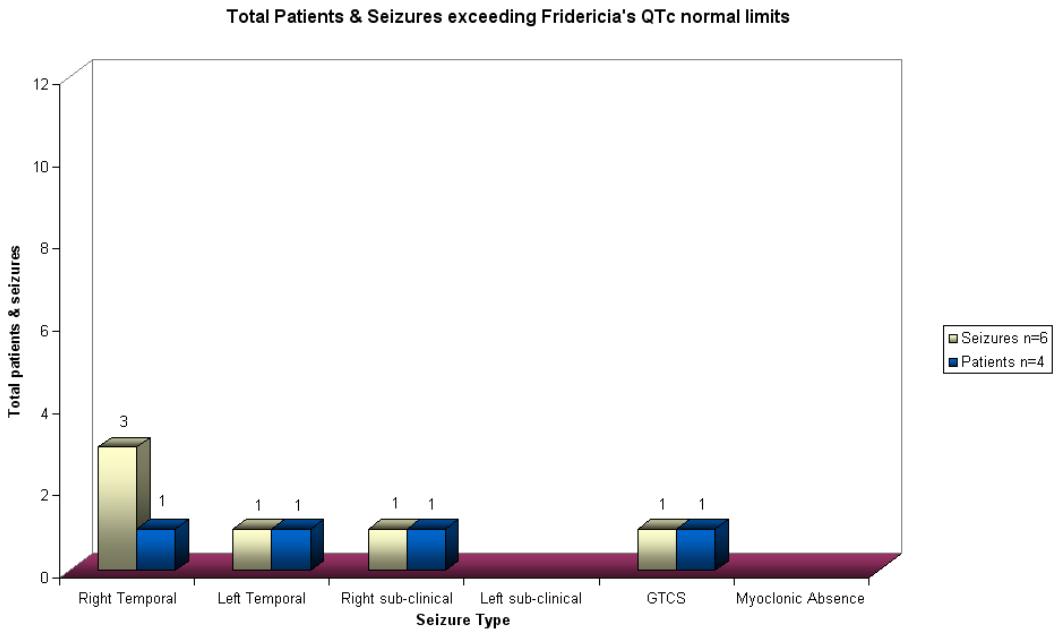


Figure 9 Bar chart of total patients & total seizures exceeding Fridericia's corrected Q-T normal limits (according to Luo et al 2004).

Paired t-testing using minitab version 14 was performed on the total seizure group n=156 data according to Fridericia's formula and shows a statistically significant difference (*p<0.001)* between the corrected Q-T value prior to the seizure and during the seizure (Table 13). The mean corrected Q-T value for the group is within normal limits of 399 milliseconds. This mean average is 28 (427-399) milliseconds shorter than that presented using Bazett's formula and 10 (409-399) milliseconds shorter than Hodge's formula.

Fridericia's corrective formula results in highly statistically significance (*p<0.001)* in corrected Q-T changes the during total seizure group. The formula also agrees with Bazett's and Hodge's formulae in high statistical significance (*p<0.001)* during frontal lobe seizures, temporal lobe seizures and right temporal lobe seizures. It disagrees with Bazett's (*p<0.001*) and Hodge's (*p=0.002*) for generalised tonic clonic seizures of high statistical significance and instead calculates a lower statistical significance of *p=0.07*.

Fridericia gives a lower statistical significance to tonic seizures (*p=0.846*) compared to Bazett's formula (*p=0.06*) and Hodge's formula (*p=0.002*). Sub-clinical seizures are statistically significant when using Fridericia's formula (*p=0.002*), similar to Bazett's (*p<0.001*) and Hodge's (*p=0.006*). Fridericia's formula results agrees generally with Bazett's (*p=0.329*) and Hodge's (*p=0.191*) that absence seizures have a lower statistically significance in corrected Q-T during seizures (*p=0.856).* Fridericia's formula agrees with Bazett's formula (*p=0.016*) in attaching a slightly lower statistical significance to left temporal lobe seizure (*p=0.008)* compared with Hodge's formula (*p<0.001*).

		Mean (msec)	St. Dev. (msec)	St.Error Mean	95% CI (msec)	*p value*
Fridericia's Total Seizure Data n=156	During	399.4	29.5	2.4		
	Before	386.3	30.0	2.4		
	Difference	13.0	21.7	1.7	9.6, 16.4	<0.001
Fridericia's Absence Seizure Data n=34	During	391.8	16.2	2.8		
	Before	392.1	15.7	2.7		
	Difference	-0.3	9.4	1.6	-3.6, 2.9	=0.856
Fridericia's Frontal Lobe Seizure Data n=58	During	385.9	17.8	2.3		
	Before	371.0	23.9	3.1		
	Difference	14.8	17.9	2.3	10.1,19.5	<0.001
Fridericia's GTCS Data	During	378.9	39.2	13.1		
	Before	356.7	47.7	15.9		

n=9	Difference	22.2	32.0	10.6	-2.3,46.8	=0.07
Fridericia's Temporal Lobe Seizure Data n=27	During	429.6	26.8	5.4		
	Before	402.8	24.1	4.8		
	Difference	26.8	24.4	4.9	16.7,36.9	<0.001
Fridericia's Right Temporal Lobe Data n=17	During	434.3	26.8	7.2		
	Before	411.4	24.1	6.4		
	Difference	22.9	16.8	4.5	13.1,32.6	<0.001
Fridericia's Left Temporal Lobe Data n=10	During	423.7	26.9	8.1		
	Before	391.8	19.9	6.0		
	Difference	31.8	31.9	9.6	10.4,53.2	=0.008
Fridericia's Tonic Seizures n=12	During	383.1	18.0	5.0		
	Before	384.6	27.0	7.5		
	Difference	-1.5	27.9	7.7	-18.4,15.3	=0.846
Fridericia's Sub-clinical Seizures n=16	During	444.2	15.7	3.9		
	Before	425.6	22.8	5.7		
	Difference	18.6	20.4	5.1	7.7, 29.5	=0.002

Table 14 Paired T-testing Statistical Analysis for Fridericia's QTc Formula Data.

2.5.2 Generalised seizures

Generalised Tonic-Clonic Seizures

According to Fridericia's corrective formula, the generalised tonic clonic seizure group (n=9) shows less statistical significance (*p=0.07)* than that determined by Bazett's (p=0.002) and Hodge's (p=0.002) corrective formulae.

The reduction in statistical significance may reflect that some of the 9 seizures did not all show the same trend in changes in corrected Q-T during seizures. Fridericia's corrective formulae is said to underestimate corrected Q-T at fast heart rates and this may have some bearing on the statistical results emphasized by a small data group (Table 14).

The mean corrected Q-T is 378 milliseconds which is well within normal range and has the shortest mean value compared to any other seizure group. As seen with previous formulae analysis, the standard deviation of the corrective Q-T value is larger before the seizures (47.7 milliseconds) than that seen during the seizures (39.2 milliseconds) indicating a much tighter range of corrected Q-T values during generalised tonic clonic seizures.

The 95% confidence interval is one of the largest compared to other seizure groups (-2.3, 46.8 milliseconds) with a difference of 49.1 milliseconds compared to that of frontal lobe seizures (10.1, 19.5 milliseconds) of 9.4 milliseconds and temporal lobe seizures (16.7, 36.9 milliseconds) of 20.2 milliseconds.

Absence Seizures

According to Fridericia's formula absences (n=34) have the poorest statistical significance of *p=0.856* compared to all other groups. This result indicates a high probability that the corrected Q-T measurements occurring before and during absence seizures are not distinctly different from chance (Table 14). The mean corrected Q-T 391 milliseconds is shorter than the total mean of 399 milliseconds and is within normal range. Absences have the smallest 95% confidence interval of (-3.6), 3.0 compared to any other seizure group, with a difference of 6.6 milliseconds.

Tonic Seizures

Fridericia's formula calculates the lowest statistical significance of Q-T changes during tonic seizures (*p=0.846)* compared to Bazett's formula (*p=0.06*) and Hodge's formula (*p=0.002*). There is very little difference between mean corrected Q-T before the seizures (384.6 milliseconds) and during the seizures (383.1 milliseconds). The 95% confidence interval (-18.4,15.3 milliseconds) appears to have a reasonable range of 33.8 milliseconds however it also indicates almost equal proportions of values decreasing as well as increasing, resulting in a lower statistical significance (Table 14).

2.5.3 Complex Focal Seizures.

Frontal Lobe Seizures

Frontal lobe seizures (n=58) produce highly statistical results (*p<0.001)* using Fridericia's corrective formula for corrected Q-T change during this seizure

group as with all formulae (Table 14). The mean corrected Q-T during the seizures is 385 milliseconds, which is well within normal limits and is shorter to the mean corrected Q-T for this group using Bazett's (411 milliseconds) and Hodge's (397 milliseconds). The difference in mean corrected Q-T before the seizures and during the seizures is small at 14.8 milliseconds compared to other seizure groups. Fridericia's formula calculates frontal lobe seizures as having the same level of statistical significance as Bazett's and Hodge's formulae. The 95% confidence interval is narrow at 10.1, 19.5 milliseconds with a difference of 9.4 milliseconds and therefore in order for this group of data to show highly statistical results most events would have to show consistent changes albeit small changes during the seizure to distinguish the results from chance. The other weighting factor is that this group has the largest set of data, which strengthens statistical significance if consistent changes are seen even if the amount of change is minimal.

Temporal Lobe Seizures

Temporal lobe seizures (n=27) as a group show high statistical significance (*p<0.001)* in corrected Q-T changes during seizures. When this group is sub-divided into right temporal lobe seizures n=17 and left temporal lobe seizures n=10, the results are similar to Bazett's formula results. Left temporal lobe seizure corrected Q-T changes become less statistically significant (*p=0.008)* compared to right temporal lobe seizures (*p<0.001),* (Table 14).

The mean corrected Q-T difference in left temporal seizures is the largest in any seizure group according to Fridericia of 31.8 milliseconds but the lowest statistical significance for this group suggests that not all left temporal lobe

seizures measure an increase in corrected Q-T during seizures and an element of chance is considered. There are also fewer cases of left temporal lobe seizures (n=10) to use in the analysis compared to right temporal lobe seizures (n=17).

The 95% confidence intervals using Fridericia's formula for temporal lobe seizures (16.7, 36.9 milliseconds) has a larger difference of 20.2 milliseconds than frontal lobe seizures (10.1, 19.5 milliseconds) of 9.4 milliseconds. Interestingly, temporal lobe seizures have a smaller 95% confidence interval than sub-clinical seizures (7.7, 29.5 milliseconds) with a difference of 21.8 milliseconds.

2.5.4 Sub-clinical seizures.

16 sub-clinical seizures were recorded and analysed (*p=0.002),* (6 derived from the right hemisphere and 10 derived from the left hemisphere), one right temporal sub-clinical seizures showed an increase beyond normal QTc limits defined by Luo et al (2004) when Fridericia's formula is applied with no left temporal sub-clinical seizures identified (Table 13, Figure 9).

A mean corrected Q-T of 444 milliseconds was calculated for the group using Fridericia's formula, compared to Bazett's formula (467 milliseconds) and Hodge's formula (442 milliseconds). The group shows a smaller standard deviation of 30.2 compared to temporal lobe seizures of 36.9 milliseconds but sub-clinical seizures show a slightly larger 95% confidence interval of 7.7, 29.5 milliseconds with a difference of 21.8 milliseconds compared to temporal lobe seizures 16.7, 36.9 milliseconds with a difference of 20.2 milliseconds. This analysis added to the group size difference of sub-clinical

seizures (n=16) and temporal lobe seizures (n=27) has lead to a slight reduction in statistical significance (*p=0.002)* for sub-clinical seizures compared to temporal lobe seizures (*p<0.001)*.

2.5.5 Right and Left Hemisphere Focal Seizure Comparison.

Three right temporal lobe seizures (1 patient) and one right sub-clinical temporal lobe seizure were identified as prolonging the corrected Q-T beyond normal limits compared to one left temporal lobe seizure when Fridericia's formula is applied. Right temporal lobe seizures show a slightly higher statistical significant corrected Q-T change during seizures (*p<0.001)* compared to left temporal lobe seizures (*p=0.008).*

In contrast to results from Bazett's and Hodge's formulae, more left temporal lobe seizures increase the corrected Q-T exceeding 60 milliseconds when applying Fridericia's corrective formula.. Three left temporal lobe seizures derived from two patients are identified by Fridericia's formulae compared to one right sub-clinical temporal lobe seizure.

2.5.6 Corrected Q-T prolongation exceeding 60 milliseconds

Four seizures resulting in the corrected Q-T exceeding 60 milliseconds, according to Fridericia's formula were derived from three patients (Table 15). The maximum increase in corrected Q-T during seizures was 74 milliseconds occurring during a left temporal lobe seizure and 84 milliseconds during a right sub-clinical temporal lobe seizure. However, none of the increases in corrected Q-T resulted in corrected Q-T prolongation according to Luo et al (2004).

Patient No. & Gender	Heart Rate During (msec)	QTc Before (msec)	QTc During (msec)	QTc Change (msec)	Seizure Type
19F	107.6	367	440	73	Left Temporal Lobe
44F	101.4	367	433	66	Left Temporal Lobe
44F	98.9	390	464	74	Left Temporal Lobe
9M paediatric	120	370	454	84	Right Sub-clinical Temporal

Table15. Summary of patients demonstrating an increase in corrected QT exceeding 60 milliseconds during a seizure according to Fridericia's Formula

2.5.7 Summary

Four patients (10%) from the total of 39 patients in the study were identified as prolonging the corrected Q-T during 6 seizures (3%) by applying Fridericia's formula. The 6 seizures were 1 sub-clinical right temporal lobe seizure, 1 generalised tonic clonic seizure, 1 left temporal lobe seizure and 3 right temporal lobe seizures. The three right temporal lobe seizures were from one patient.

Fridericia's formula shows a statistically significant difference ($p<0.001$) between the corrected Q-T value prior to the seizure and during the seizure for the total group. Fridericia's formula also agrees with Bazett's and Hodge's formulae in high statistical significance ($p<0.001$) during frontal lobe

seizures, temporal lobe seizures and right temporal lobe seizures. It disagrees with Bazett's and Hodge's formulae for generalised tonic clonic seizures of a high statistical significance (*p=0.002)* and instead calculates a lower statistical significance of *p=0.07.*

Four seizures resulting in the corrected Q-T exceeding 60 milliseconds according to Fridericia's formula were derived from three patients but all data remained within normal limits. Unlike Bazett's and Hodge's formulae, Fridericia identified more left temporal lobe seizures than right temporal lobe seizures increasing the corrected Q-T by more than 60 milliseconds. However, this formula does identify three right temporal lobe seizures resulting in corrected Q-T prolongation from one patient.

Chapter 14: Results: According to Framingham's Formula

Introduction: The 'Framingham Heart Study' (Sagie et al 1992) is a large epidemiological study of 5,018 patients analysed to test this correction formula and because of the large cohort could additionally sub-divide data for age and gender. Framingham's formula QTc=QT+154(1-R-R). Although this formula was derived from a large amount of data, the study limitations were that fast heart rates were not tested. Framingham is a neighbourhood in Massachusetts whose population was targeted in 1948 when the Framingham Heart Study was launched. This study is a landmark in history for linking high blood pressure and cholesterol levels with cardiovascular disease and revolutionised preventative medicine. The Framingham Heart Study continues today researching many cardiological conditions (Fitzgerald 2005).

2.6.1 Total seizure group

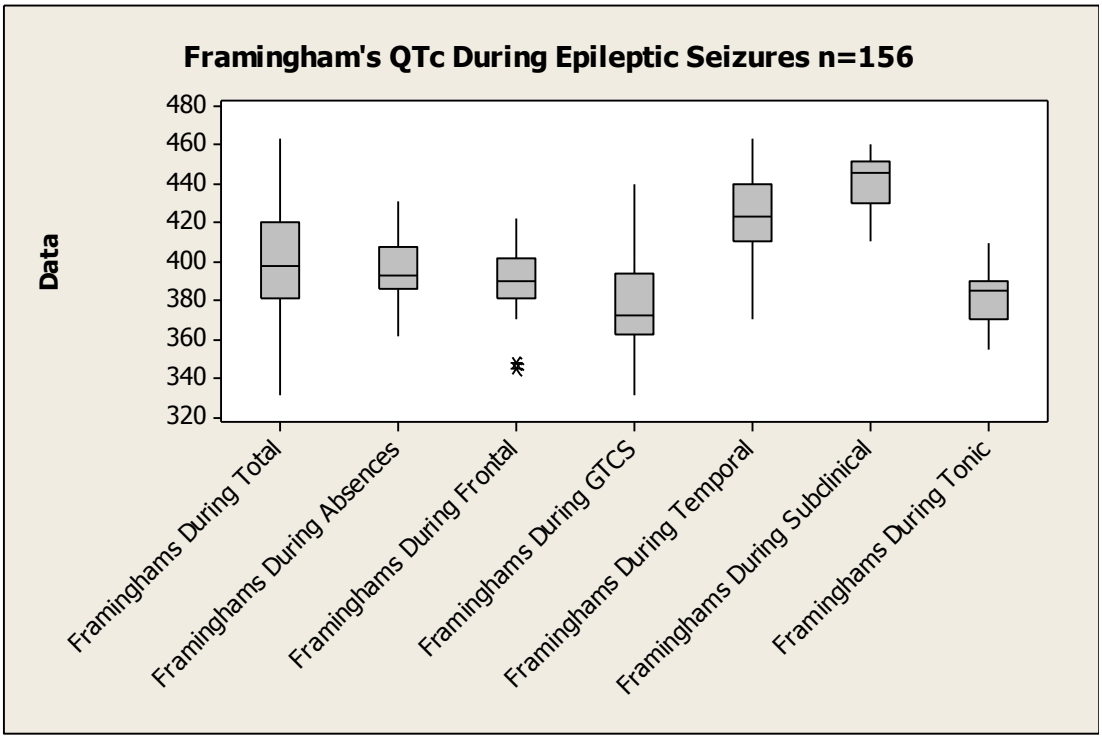


Figure 10 Boxplot of Framingham's corrected Q-T values during grouped seizures.

The subject gender mix was 25 males and 14 females (Table 2). The age range was 2 years 5 months to 60 years 3 months. The mean age was 17 years 2 months with a median age 11 years 5 months. A total of 156 seizures had corrected Q-T analysis performed (370 seizures had to be excluded from the study due to EMG artefact obscuring the ECG trace) The 156 analysed seizures were composed of: generalised tonic-clonic seizures (9), absences (34), tonic seizures (12), temporal lobe seizures (27), frontal lobe seizures (58) and 16 sub-clinical seizure events were clinically and electrographically identified.

From a total of 156 seizure events recorded and analysed, only 3 seizures were identified as demonstrating lengthening of the corrected Q-T during the seizure. The three identified seizures were

- 1 right sub-clinical temporal lobe seizure (paediatric).
- 1 left temporal lobe seizure
- 1 right temporal lobe seizure.

This result represents 2% (3/156) of total seizures from 8% patients (3/39) identified as having lengthened the corrected Q-T beyond normal limits during seizure events using Framingham's formula (Figure 11, Table 16).

Patient No &Gender	Heart Rate During Bpm	Framingham QTc Before (msec)	Framingham QTc During (msec)	Framingham QTc Change (msec)	Seizure Type
9M paediatric	88.8	371	451	80	Right Temporal Sub-clinical
17M	75	424	463	39	Left Temporal Lobe
20M	65.9	441	462	21	Right Temporal Lobe

Table 16 Summary of Framingham's corrected Q-T values for patients during seizures exceeding normal limits (according to Luo et al 2004).

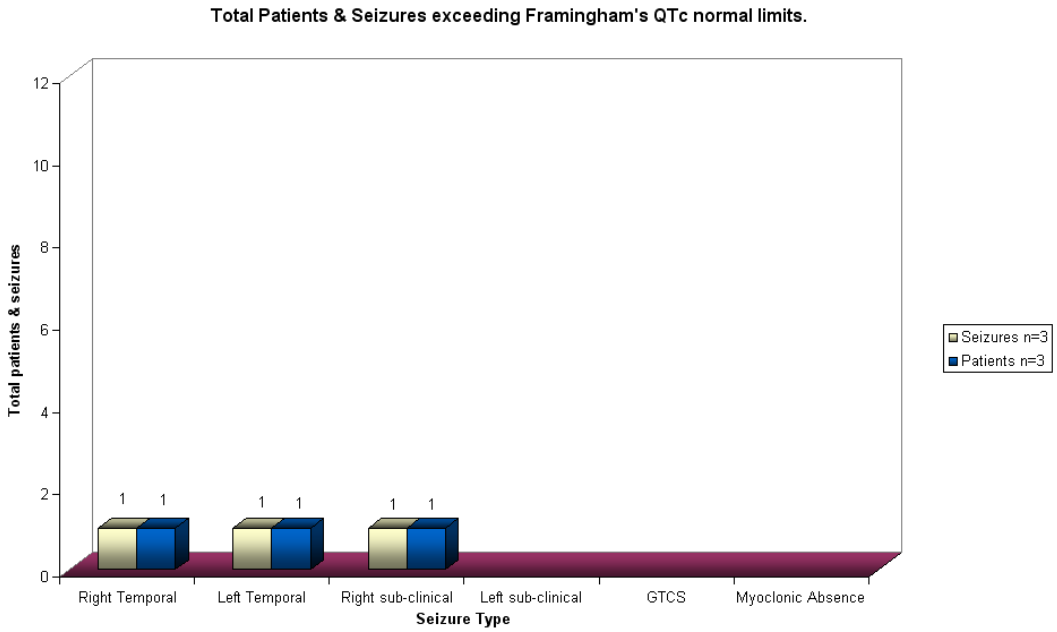


Figure 11 Bar chart of total patients & total seizures exceeding Framingham's corrected Q-T normal limits (according to Luo et al 2004).

Total Group Testing

Paired t-testing using minitab version 14 was performed on the total seizure group (n=156) data according to Framingham's formula and shows a statistically significant difference (*p>0.001)* between the corrected Q-T value prior to the seizure and during the seizure (Table 17). The mean corrected Q-T value for the group is within normal limits of 398 milliseconds. A mean average of 29 (427-398) milliseconds shorter than that presented using Bazett's formula, 11 (409-398) milliseconds shorter than Hodge's formula and is very similar to Fridericia's mean corrected Q-T for total group with very little difference of 1 (399-398) milliseconds.

Framingham's corrective formula agrees with all other formulae that the total seizure group shows a high statistical significance of *p<0.001*. It also agrees that frontal lobe seizures and total temporal lobe seizures show a high statistical significance (*p<0.001)* and that absence seizures do not demonstrate high statistical significance (*p=0.861)*. Framingham's formula agrees with Bazett's and Fridericia's formulae that left temporal lobe seizures (*p=0.009)* are not as statistically significant as the temporal lobe seizure group (*p<0.001)* as a whole. During generalised tonic clonic seizures Framingham (*p=0.284*) and Fridericia's (*p=0.07*) formulae do not reach the same degree of high statistical significance as that determined by Bazett's (*p=0.002*) and Hodge's (*p=0.002*) formulae. Tonic seizures show similar low statistical significance using Framingham's (*p=0.612*) and Fridericia's (*p=0.846*) formulae but disagree with Hodge's formula (*p=0.002*) of more statistically significant results for this group. Interestingly, Bazett's formula is more moderate in calculation of corrected Q-T change during tonic seizures (*p=0.06)*.

		Mean (msec)	St. Dev. (msec)	St.Error Mean (msec)	95% CI (msec)	*p value*
Framingham's Total Seizure Data n=156	During	398.3	26.9	2.1		
	Before	386.8	28.3	2.3		
	Difference	11.4	20.2	1.6	8.2,14.6	<0.001
Framingham's Absence Seizure Data n=34	During	391.8	15.8	2.7		
	Before	392.1	14.3	2.4		
	Difference	-0.3	9.7	1.7	-3.7,3.1	=0.861

Framingham's Frontal Lobe Seizure Data n=58	During	386.7	14.3	1.9		
	Before	370.7	21.9	2.9		
	Difference	16.0	16.8	2.2	11.6,20.5	<0.001
Framingham's GTCS Data n=9	During	375.5	30.9	10.9		
	Before	363.3	41.5	13.8		
	Difference	12.2	31.9	10.6	-12.3,36.7	=0.284
Framingham's Temporal Lobe Seizure Data n=27	During	424.9	23.9	4.6		
	Before	404.4	22.2	4.3		
	Difference	18.5	20.7	3.9	10.3,26.7	<0.001
Framingham's Right Temporal Lobe Data n=17	During	426.4	23.4	6.2		
	Before	413.6	23.7	6.3		
	Difference	12.8	12.0	3.2	5.9,19.8	=0.002
Framingham's Left Temporal Lobe Data n=10	During	421.8	26.3	7.9		
	Before	394.5	17.5	5.3		
	Difference	27.3	27.9	8.4	8.5,46.1	=0.009
Framingham's Tonic Seizures n=12	During	380.0	16.8	4.7		
	Before	383.8	21.8	6.0		
	Difference	-3.8	26.6	7.4	-19.9,12.2	=0.612
Framingham's Sub-clinical Seizures n=16	During	441.7	14.5	3.6		
	Before	423.2	23.9	5.9		
	Difference	18.5	19.4	4.9	8.14,28.9	=0.002

Table 17 Paired T-Testing Statistical Analysis for Framingham's QTc Formula Data.

2.6.2 Generalised seizures

Generalised Tonic-Clonic Seizures.

According to Framingham's corrective formula, changes in corrected Q-T during generalised tonic-clonic seizures are not statistically significant (*p=0.284)*. This contrasts with Bazett's and Hodge's formulae results for this group of high statistical significance (*p=0.002)*. Fridericia's result for this group (*p=0.07)* shows a statistical significance that comes somewhere in-between results of Bazett's or Hodges and those of Framingham's formulae calculations.

The mean corrected Q-T for this group is 375 milliseconds according to Framingham's formula compared to 417 milliseconds according to Bazett's formula, 422 milliseconds according to Hodge's formula and 378 milliseconds according to Fridericia's formula. The discrepancy of high statistical significance from Bazett's formula and Hodge's formula compared to lower statistical significance from Fridericia's formula and Framingham's formula probably lies with the well recognised fact that Bazett's and Hodge's formulae tend to over-estimate corrected Q-T at fast heart rates that occur during tonic-clonic seizures and that Fridericia and Framingham's formulae tend to under-estimate corrected Q-T at fast heart rates. The types of seizure groups most likely to be prone to these influencing factors are likely to be generalised tonic-clonic seizures and right temporal lobe seizures due to induced fast heart rates.

Another factor in this interpretation is the 95% confidence interval (-12.3, 36.8 milliseconds) with a difference of 49.1 milliseconds. This is the largest range

in confidence interval when using this formula however it also has the largest standard deviation of 31.9 milliseconds. The combination of these big changes with few seizures (n=9) brings in the probability of chance lowering the significance value.

Absence Seizures.

Framingham's corrective formula agrees generally Bazett's formula (p=0.329), Hodge's formula (p=0.191) and Fridericia's formula (p=0.856) that a lower statistical significance (*p=0.861)* in changes in corrected Q-T is calculated for absence seizures (n=34) and agrees very closely with Fridericia's statistical results for this group of seizures. Framingham's 95% confidence interval (-3.7, 3.1 milliseconds) is also similar to Fridericia's 95% confidence interval (-3.6, 2.9 milliseconds) with very small ranges of 6.5 milliseconds for Framingham's formula results and 6.5 milliseconds for Fridericia's formula.

Mean corrected Q-T from Framingham's formula is 391 milliseconds and is shorter than the mean for the total group of seizures (399 milliseconds). Fridericia has the same mean average during absence seizures of 391 milliseconds compared to Hodges (399 milliseconds) and Bazett's (414 milliseconds).

Tonic Seizures.

According to Framingham's formula tonic seizures do not show statistical significance (*p=0.612*). Similarly Fridericia has a low significance of p=0.846. Borderline significance is seen using Bazett's formula (*p=0.06)* during tonic seizures. Surprisingly Hodge's formula does show a high statistical

significance for this group of p=0.002. Framingham's formula 95% confidence interval results span zero (-19.9, 12.2) milliseconds. This compares to the 95% confidence interval of Hodge for this group (10.3, 36.2 milliseconds).

The mean corrected Q-T using Framingham's formula results during tonic seizures is 380 milliseconds which is much shorter than that seen using Bazett's (429 milliseconds), Hodge's (411 milliseconds) but similar to Fridericia's (383 milliseconds).

2.6.3 Complex Focal Seizures.

Frontal Lobe Seizures.

High statistical significance (*p<0.001)* is calculated in corrected Q-T changes during frontal lobe seizures (n=58) using Framingham's corrective formula (Table 15). The 95% confidence interval becomes increasingly narrower from Bazett's formula (27.1, 36.4 milliseconds), Hodge's formula (21.5, 29.7 milliseconds), Fridericia's formula (10.1, 19.5 milliseconds) and Framingham's formula (11.6, 20.5 milliseconds). Despite a shortening range, high statistical significance remains for frontal lobe seizures from all corrective formulae. This low probability of chance suggests that even though the measurements are small, consistent increases in corrected Q-T occur during frontal lobe seizures.

The mean corrected Q-T during frontal lobe seizures from Framingham's data is 386 milliseconds. This is almost identical to that seen using Fridericia's formula of 385 milliseconds. Hodge's mean value is longer at 397 milliseconds but Bazett's is the longest at 411 milliseconds.

Statistical significance however does not necessarily equate to clinical significance and although all formulae agree a high significance (*p<0.001*) in corrected Q-T change during frontal lobe seizures- no frontal lobe seizures demonstrated corrected Q-T prolongation during seizures in this group of patients.

Temporal lobe seizures

Framingham's formula agrees with all other corrective formulae that temporal lobe seizures (n=27) have a high statistical significant change in corrected Q-T during seizures (*p<0.001)*. However, when this group is sub-divided into right temporal lobe seizures (n=17) and left temporal lobe seizures (n=10), both groups lose some statistical significance of *p=0.002* and *p=0.009* respectively. Framingham's formula is the only formula which does not attach a value of *p<0.001* to right temporal lobe seizures, although *p=0.002* is still highly statistically significant (Table 17).

Framingham's mean corrected Q-T (422 milliseconds) for temporal lobe seizures is the second longest compared to other seizure groups. All other formulae give longer mean values with Bazett's (462 miliseconds), Hodge's (432 milliseconds) and Fridericia's (429 milliseconds).

95% confidence intervals are greatest for temporal lobe seizures according to Framingham's formula (10.3, 26.7 milliseconds) with a difference of 16.4 milliseconds. Left temporal lobe seizures give the largest 95% confidence interval of 8.5, 46.1 milliseconds with a difference of 37.6 milliseconds which is much wider than that seen from right temporal lobe seizures (5.9, 19.8 milliseconds) with a difference of 13.9 milliseconds. This may reflect that

Framingham's formula tends to under-correct at fast heart rates and over-corrects at slow heart rates. Right temporal lobe seizures generally tend to lead to increased fast heart rates compared to left temporal lobe seizures.

2.6.4 Sub-clinical seizures.

16 sub-clinical seizures recorded and analysed (*p=0.002),* (6 derived from the right hemisphere and 10 derived from the left hemisphere), one right temporal sub-clinical seizures showed an increase beyond normal QTc limits defined by Luo et al (2004) when Framingham's formula is applied with no left temporal sub-clinical seizures identified (Figure 11, Table 16).

High statistical significance is agreed by all corrective formulae for sub-clinical seizures with Bazett's (*p<0.001*), Hodge's (*p=0.006*), Fridericia's (*p=0.002*) and Framingham's (*p=0.002*).

Mean Q-T values for sub-clinical seizures when calculating from data derived from Framingham's formula give the longest values compared to any seizure group of 441 milliseconds compared to generalised tonic clonic seizures (375 milliseconds), temporal lobe seizures (426 milliseconds), frontal lobe seizures (386 milliseconds) and tonic seizures (380 milliseconds).

It is interesting that sub-clinical seizures demonstrate the longest mean value compared to other seizure types in that there is no physical exertion occurring to lengthen the corrected Q-T.

2.6.5 Right and Left Hemisphere Focal Seizure Comparison.

One right temporal lobe seizure and one right sub-clinical temporal lobe seizure were identified as prolonging the corrected Q-T according to Luo et al (2004) during seizures when Framingham's formula was applied, compared to one left temporal lobe seizure.

One right temporal lobe seizure and one left temporal lobe seizure are identified as increasing the corrected Q-T beyond 60 milliseconds (Table 18).

2.6.6 Corrected Q-T prolongation exceeding 60 milliseconds

Three seizures comprising 1 generalised tonic-clonic seizure, 1 left temporal lobe seizure and 1 right sub-clinical temporal lobe seizure, derived from three patients were identified as increasing the corrected Q-T by more than 60 milliseconds according to Framingham's formula but all remained within normal limits. The maximum increase of 82 milliseconds in corrected Q-T occurred during a generalised tonic-clonic seizure (Table 18).

Patient No. & Gender	Heart Rate During Bpm	QTc Before (msec)	QTc During (msec)	QTc Change (msec)	Seizure Type
43M	80.4	299	381	82	GTCS
44F	104.2	390	460	70	Left Temporal Lobe
9M paediatric	88.8	371	451	80	Right Sub-clinical Temp Lobe

Table18. Summary of patients demonstrating an increase in corrected QT exceeding 60 milliseconds during a seizure according to Framingham's Formula

2.6.7 Summary

Three seizures (2% total seizures) derived from three patients (8% total patients) were identified as prolonging the corrected Q-T according to Luo et al (2004) when Framingham's formula is applied to all data. The three seizures were 1 right sub-clinical temporal lobe seizure, 1 left temporal lobe seizure and 1 right temporal lobe seizure. Framingham's formula and shows a statistically significant difference ($p<0.001$) between the corrected Q-T value prior to the seizure and during the seizure for the total group. Frontal lobe seizures and total temporal lobe seizures show a high statistical significance ($p<0.001$).When the temporal lobe group is sub-divided into right temporal lobe seizures (n=17) and left temporal lobe seizures (n=10), both groups lose some statistical significance of $p=0.002$ and $p=0.009$ respectively. Framingham's formula is the only formula which does not attach a value of

p<0.001 to right temporal lobe seizures, although *p=0.002* is still highly statistically significant but is only slightly lower.

According to Framingham (*p=0.284*) and Fridericia's (*p=0.07*) formulae, generalised tonic-clonic seizures do not reach the same degree of high statistical significance as that determined by Bazett's (*p=0.002*) and Hodge's (*p=0.002*) formulae.

Three seizures (1 generalised tonic clonic seizure, 1 left temporal lobe seizure and 1 right sub-clinical temporal lobe seizure) from three patients were identified as increasing the corrected Q-T by more than 60 milliseconds during seizures but all remained within normal limits according to Luo et al (2004).

Chapter 15

2.7.1 Inter and Intra-observer Analyses

The inter and intra-observer analysis shows a maximum difference of 0.01 seconds which represents 0.02% of possible error in measuring 0.425 seconds. The numerical values of the cursors with a 500Hz sampling rate changes with increments of 0.005 seconds, which gives an error margin of 1 increment for inter observer analysis. When considering factors of observer judgement and precision of actually placing the cursors, the error margin is very small. This result is comparable to those accepted within guidelines agreed in drug trial regulations of inter and intra-observer variability of +/- 10 msec. (Pater 2005).

2.7.2 Kappa

The Kappa statistic was used to check the "precision" between two independent observers in the measurement of the corrected Q-T. The data measurements were compared to assess the level of agreement of prolonged Q-T results with normal Q-T results and the "expected agreement" because of the chance measurement agreement. "Accuracy" analysis for this type of data is not possible as there is not a "correct value" to compare the measured values to.

The Kappa calculation is based on the difference between how much agreement is actually present i.e the "observed agreement" compared to how much agreement would be expected by chance alone i.e the "expected agreement."

	Observer 1 Normal QTc	Observer 1 Prolonged QTc	Total
Observer 2 Normal QTc	15	1	16
Observer 2 Prolonged QTc	1	4	5
Total	16	5	21

Table 19 Number of observed agreement of normal QTc and prolonged QTc from two independent reviewers.

(a) Calculation of Observed Agreement.

Percentage of all agreement / total observations = 15+4 / 21=19/21=0.90 (90%)

(b) Difference of the observed agreement from the expected agreement

P e = (16/21) x (16/21) + (5/21) x (5/21)

= 0.579 + 0.056

= 0.635

(c) Kappa statistic

(Observed agreement minus expected agreement) / (1-expected agreement)

= (0.9 – 0.635) / (1-0.635)

= 0.265 / 0.365

Kappa = 0.726

A Kappa statistic of 0.726 constitutes a substantial agreement between the two observers even with the expected chance measurements. Perfect agreement of Kappa is "1" and chance agreement is "0" (Viera & Garrett 2005).

Chapter 16 Comparison of results according to Bazett's, Hodge's, Fridericia's and Framingham's Formulae.

2.8.1 Total Seizure Group.

The subject gender mix was 25 males and 14 females (Table 2). The age range was 2 years 5 months to 60 years 3 months. The mean age was 17 years 2 months with a median age 11 years 5 months. A total of 156 seizures had corrected Q-T analysis performed (370 seizures had to be excluded from the study due to EMG artefact obscuring the ECG trace) The 156 analysed seizures were composed of: generalised tonic-clonic seizures (9), absences (34), tonic seizures (12), temporal lobe seizures (27), frontal lobe seizures (58) and 16 sub-clinical seizure events were clinically and electrographically identified.

All formulae agreed a statistically significant increase in the corrected Q-T for the total group ($p<0.001$) when comparing values prior to the seizure with during the seizure (Table 17, Figure 12).

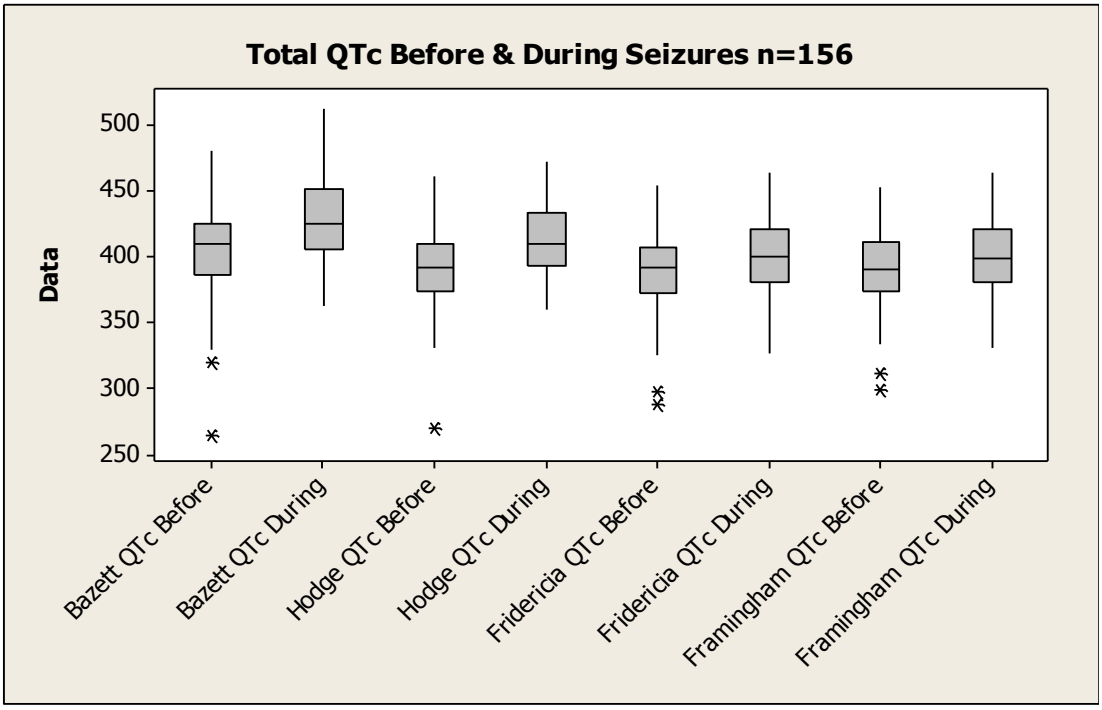


Figure 12 Box plot of corrected Q-T data derived from total seizures before and during seizure events calculated by Bazett's, Hodge's, Fridericia's and Framingham's formulae.

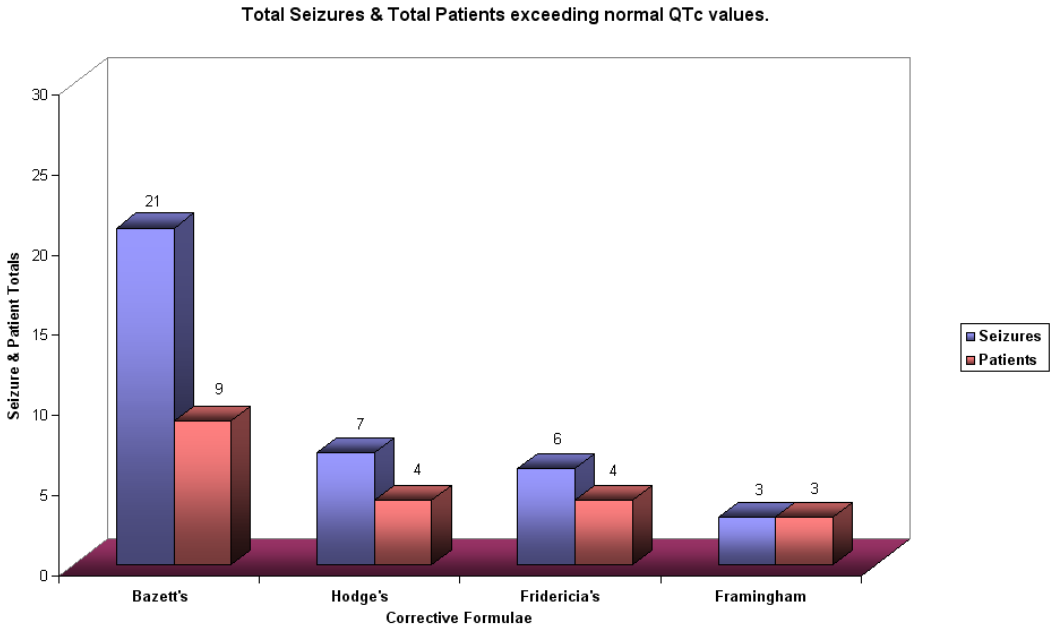


Figure 13 Total seizures and patients with corrected QT exceeding normal limits (Luo et al 2004) derived from Bazett's, Hodge's, Fridericia's & Framingham's applied Formulae.

Figure 13 shows a wide range of results seen using the same data for each formula. Bazett's identified 9 patients with prolonged Q-T occurring in 21 seizures, Hodge's identified 4 patients with prolonged corrected Q-T occurring in 7 seizures, Fridericia identified 4 patients with prolonged corrected Q-T occurring 6 seizures and Framingham identified 3 patients with prolonged corrected Q-T occurring in 3 seizures.

2.8.2 Formulae Identified Corrected Q-T Prolongation Seizure types and Patients

A general shortening trend in the mean corrected Q-T is seen for each formula when comparing the before and during seizure corrected Q-T values. Bazett's formula shows a difference for the grouped data at 27.7 milliseconds, Hodge's formula gives a difference of 21.5 milliseconds, Fridericia's formula then gives a difference for the group of 13.0 milliseconds and Framingham's give a difference for the grouped data at 11.4 milliseconds.

Bazett's 95% confidence interval is the largest with 95% of data measuring between 22.6, 32.8 milliseconds (difference of 10.2 milliseconds) compared to a fairly similar but shorter data window using Hodge's formula of 17.7, 25.4 milliseconds (difference of 7.7 milliseconds). Both Fridericia and Framingham's formula appear similar and squeeze data into narrower data windows with Fridericia's 95% confidence interval being 9.6, 16.4 milliseconds (difference of 6.8 milliseconds) and Framingham's 95% confidence interval being 8.2, 14.6 milliseconds (difference of 6.4 milliseconds).

Bazett's formula identified 21 seizures as prolonging the corrected Q-T. Of these 21 seizures there were 5 right sub-clinical temporal lobe seizures, 1 left sub-clinical temporal lobe seizure, 11 right temporal lobe seizures, 2 left temporal lobe seizures, 1 generalised tonic-clonic seizure and one myoclonic absence.

Hodge's formula identified 7 seizures prolonging the corrected Q-T beyond normal values, which were 3 right sub-clinical seizures, 1 right temporal lobe seizure, 1 generalised tonic-clonic seizure and 2 tonic seizures.

Fridericia's corrective formula identified 6 seizures resulting in a prolonged corrected Q-T of which there were 1 right sub-clinical seizure, 3 right temporal lobe seizures, 1 left temporal lobe seizure and 1 generalised tonic-clonic seizure.

Framingham's formula identified only 3 seizures that prolonged the corrected Q-T beyond normal limits of which there were 1 right sub-clinical temporal lobe seizure, 1 right temporal lobe seizure and 1 left temporal lobe seizure.

The only two seizure types consistently identified by all corrective formulae were right sub-clinical temporal lobe seizures and right temporal lobe seizures. Of the right sub-clinical temporal lobe seizures, Bazett's identified 5 of these sub-clinical seizures, Hodge's formula identified 3 seizures but Fridericia and Framingham equally only identified 1 sub-clinical seizure. Of the right temporal seizures identified as prolonging the corrected Q-T beyond normal limits, Bazett's identified 11 of these seizures, Hodge's formula identified 1 seizure, Fridericia's formula identified 3 of these

temporal lobe seizures and Framingham's formula identified only 1 right temporal lobe seizure.

Bazett's, Fridericia's and Framingham's formulae agreed that a left temporal lobe seizure prolonged the corrected Q-T beyond normal limits but Hodge's formula did not identify this seizure as prolonged. Three formulae identified a generalised tonic-clonic seizure as prolonging the corrected Q-T beyond normal limits but Framingham's formula did not identify this seizure. Only Hodge's corrective formula identified 2 tonic seizures as prolonging the corrected Q-T but this was not agreed with Bazett's, Fridericia's or Framingham's formula results. Bazett's formula identified 1 left sub-clinical temporal lobe seizure and 1 myoclonic absence but was not agreed by Hodge's, Fridericia's and Framingham's formulae.

There were only two patients who were identified by all four corrective formulae as having prolongation of the corrected Q-T during epileptic seizures. The corrected Q-T prolongation occurred as the seizure progressed and as the heart rate changed each formulae demonstrated prolongation during different epochs within the same seizure The first patient (9M) was a 2 years old male during a right sub-clinical seizure with prolonged QTc (Bazett's 492 milliseconds (heart rate 119.5/min), Hodge's 475 milliseconds (heart rate 127.3/min), Fridericia's 454 milliseconds (heart rate 92.8/min) and Framingham's 451 milliseconds (heart rate 88.8/min). The second patient (20M) was a 21 years old male during a right temporal lobe seizure with prolonged QTc (Bazett's 495 milliseconds (heart rate 66.7/min), Hodge's 479 milliseconds (heart rate 66.7/min), Fridericia's 463 milliseconds (heart rate 65.9/min) and Framingham's 462 milliseconds (heart rate 65.9/min).

Patient 20M had right temporal lobe seizures. Patient 9M proved to have drug resistant focal seizures and sub-clinical seizures. He later underwent neurosurgery in the attempt to control his intractable seizures and had an antero-temporal lobectomy. Since the surgery he has become seizure free and doing well. Patient 20M still has seizures although he is having fewer seizures than at the time of this study controlled therapeutically by anti-epileptic medication.

Comparison of Formulae Results QTc increasing by more than 60 milliseconds.

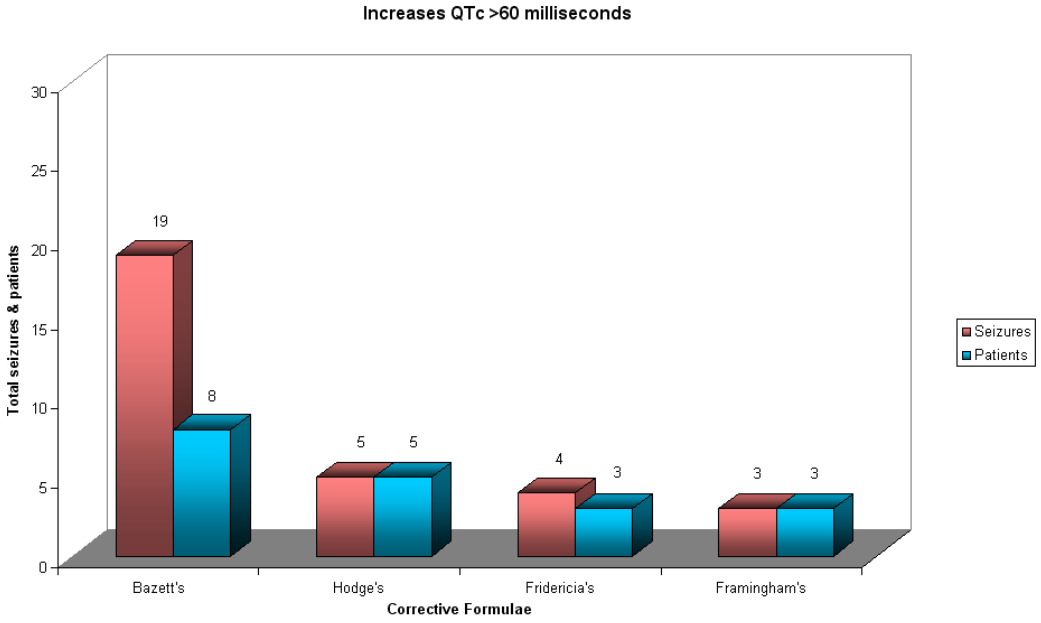


Figure 14 Total seizures and patients with corrected QT increasing >60 milliseconds derived from Bazett's, Hodge's, Fridericia's & Framingham's applied Formulae

Bazett's formula identified 19 seizures (8 patients) that increased the corrected Q-T by more than 60 milliseconds.

- 2 right temporal sub-clinical seizures (1 paediatric patient).
- 10 right temporal lobe seizures (3 patients).
- 4 left temporal lobe seizures (2 patients).
- 3 Generalised tonic-clonic seizures (1 adult, 1 paediatric patient).

Hodge's formula identified 5 seizures (5 patients) that increased the corrected Q-T by more than 60 milliseconds.

- 1 right temporal sub-clinical seizures (paediatric patient).
- 1 left temporal lobe seizure.
- 3 generalised tonic-clonic seizures (1 paediatric patient, 2 adult patients).

Fridericia's formula identified 4 seizures (3 patients) that increased the corrected Q-T by more than 60 milliseconds.

- 1 right temporal sub-clinical seizures (paediatric patient).
- 3 left temporal lobe seizures (2 patients).

Framingham's formula identified 3 seizures (3 patients) that increased the corrected Q-T by more than 60 milliseconds.

- 1 right temporal sub-clinical seizures (paediatric patient).

- 1 left temporal lobe seizure.

- 1 generalised tonic-clonic seizure.

All formula identified and agreed that 1 right temporal sub-clinical seizure and left temporal lobe seizure increased the corrected Q-T by more than 60 milliseconds. Three formulae identified a generalised tonic-clonic seizure that increased the corrected Q-T beyond 60 milliseconds but Fridericia did not agree.

Comparison of Results for Paediatric Patients, Exceeding Normal Values according to all Corrective Formulae.

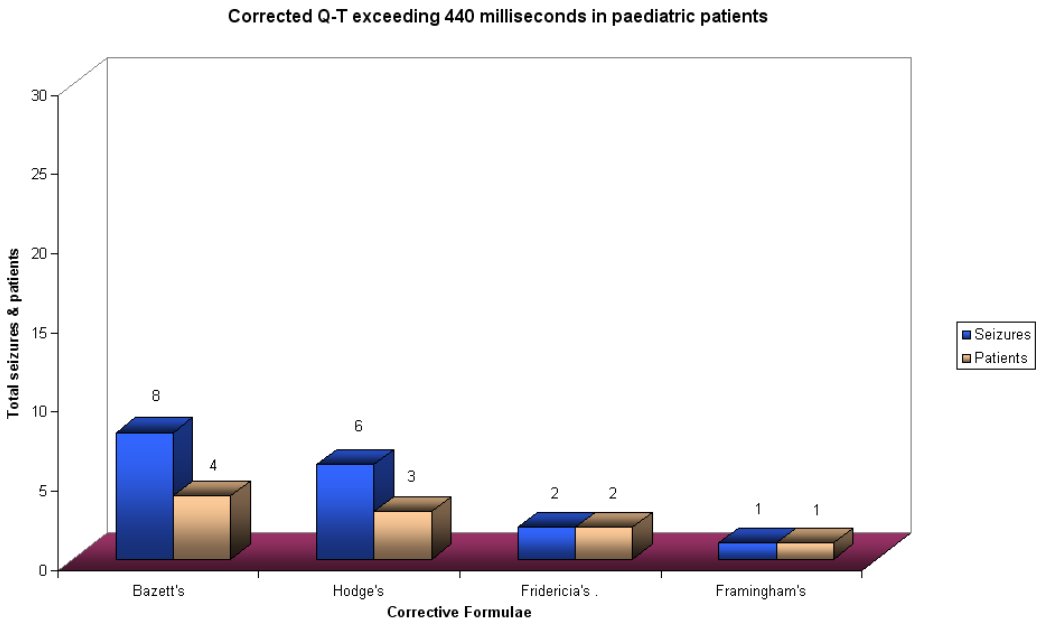


Figure 15 Total Paediatric seizures and patients with corrected QT exceeding normal limits according to Benetar et al, 2001 derived from Bazett's, Hodge's, Fridericia's & Framingham's applied Formulae.

Bazett's formula identified 8 seizures (4 paediatric patients) that lengthened the corrected Q-T beyond normal limits with QTc values up to 493 milliseconds.

- 5 right temporal sub-clinical seizures (1 patient).
- 1 left temporal lobe seizure
- 1 generalised tonic-clonic seizure.
- 1 myoclonic absence

Hodge's formula identified 6 seizures (3 paediatric patients) that lengthened the corrected Q-T beyond normal limits with QTc values up to 471 milliseconds.

- 3 right temporal sub-clinical seizures (1 patient).
- 1 generalised tonic-clonic seizure.
- 2 tonic seizures (1 patient).

Fridericia's formula identified 2 seizures (2 paediatric patients) that lengthened the corrected Q-T beyond normal limits with QTc values up to 464 milliseconds.

- 1 right temporal sub-clinical seizure.
- 1 generalised tonic-clonic seizure.

Framingham's formula identified 1 seizure (1 paediatric patient) that lengthened the corrected Q-T beyond normal limits with QTc value up to 451 milliseconds.

- 1 right temporal sub-clinical seizure.

All formulae agreed to the identification of 1 paediatric patient who had a right temporal sub-clinical seizure as lengthening the corrected Q-T beyond normal values. All formulae except Framingham's identified a paediatric patient having a generalised tonic-clonic seizure who lengthened the corrected Q-T beyond normal limits.

2.8.3 Characteristic Similarities and Differences in the Corrective Formulae Results.

Similarities of QTc results are found using Bazett's and Hodge's corrective formulae and also with Fridericia and Framingham's formulae. If we examine a scatterplot of total QTc data used for each formula there is a general emphasis of 'shortened' QTc to the left of the graph of data points belonging to Fridericia's and Framingham's corrective formula results in contrast to 'lengthened' QTc to the right of the graph of data points belonging to Bazett's and Hodge's corrective formulae.

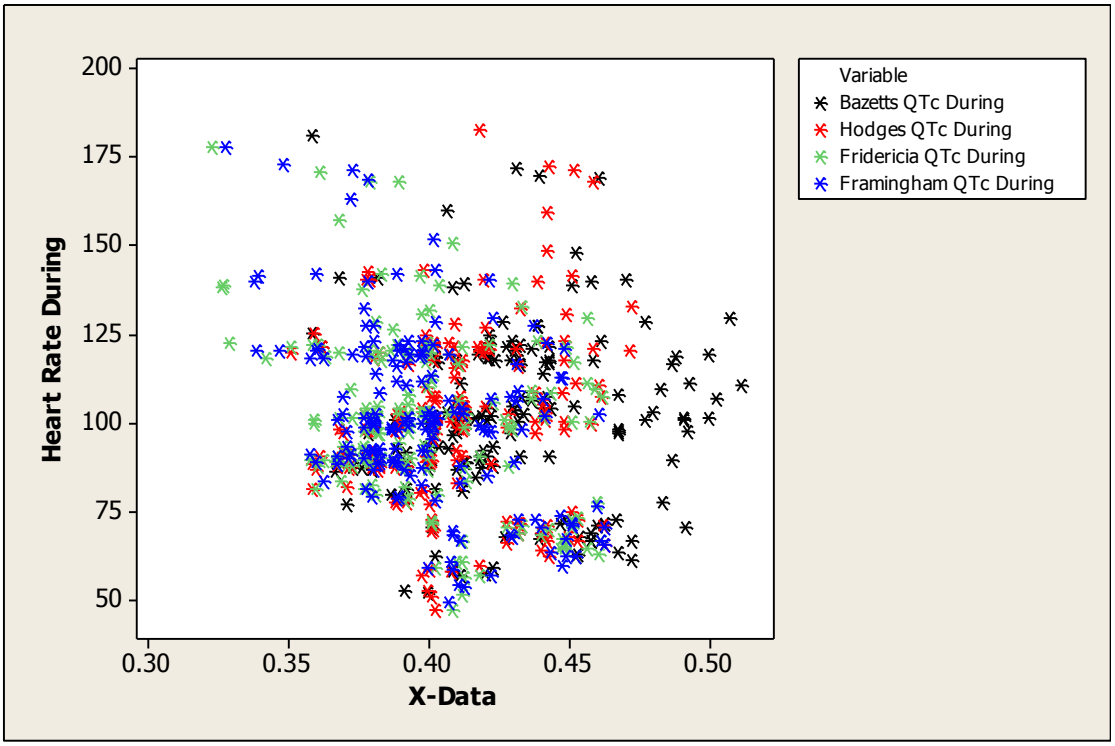


Figure 16 Scatterplot of corrected QT data and heart rate according to Bazett's, Hodge's, Fridericia's and Framingham's corrective formulae.

This similarity of formulae results is clarified further by separating data for each formula in adjacent scatterplots demonstrated in Figure 17. The distribution of Bazett's QTc data shows a similar pattern to that seen using Hodge's formula. The distribution of QTc data of Fridericia's formula appears to have a similar distribution as Framingham's data. Identical original R-R and Q-T data was used for each formula.

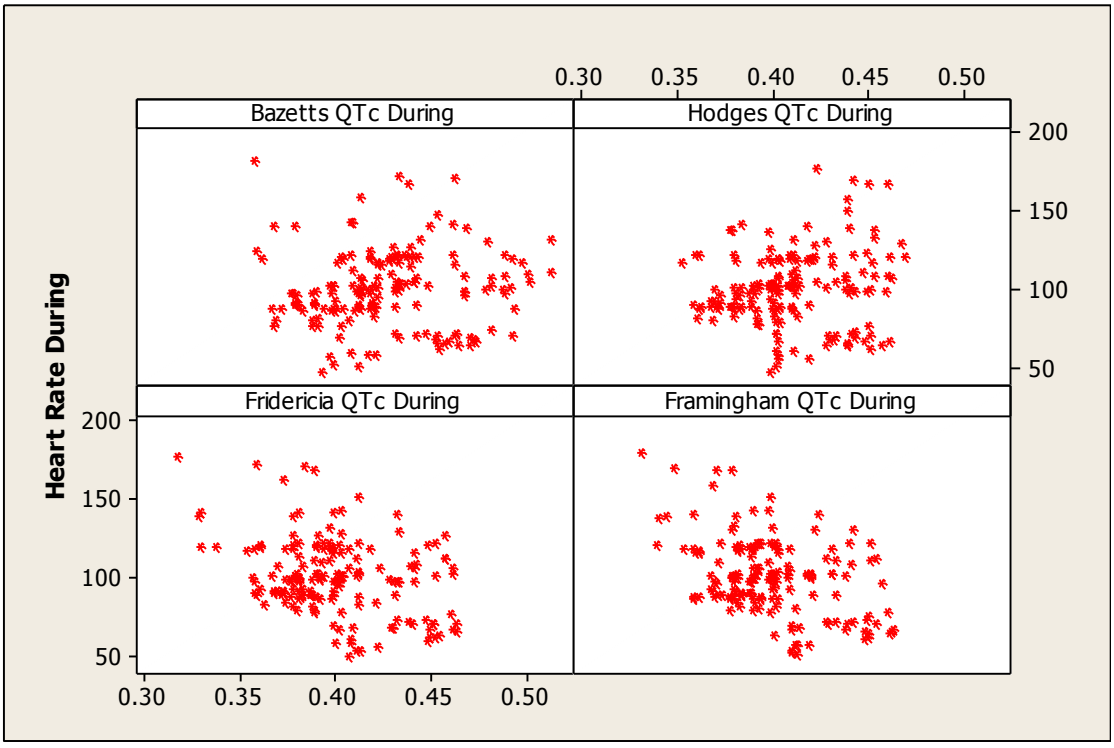


Figure 17 Scatterplots of QTc data calculated by Bazett's, Hodge's, Fridericia's and Framingham's corrective formulae.

Bazett's formula has been the most commonly used corrected formula for over 80 years and continues to be the formula used in clinical practice. Most cardiology equipment calculates the QTc using Bazett's formula in adult and paediatric services. Unfortunately, although Bazett's formula is the most commonly used corrective formula it is also the most criticised. This is

because Bazett's formula over-corrects and therefore over-estimates QTc at fast heart rates resulting in a tendency towards falsely prolonged corrected Q-T values and under-corrects and under-estimates QTc at slow heart rates resulting in a tendency towards falsely shortened corrected Q-T values (Sagie et al 1992, Hodges 1997, Pater 2005, Sredniawa et al 2005).

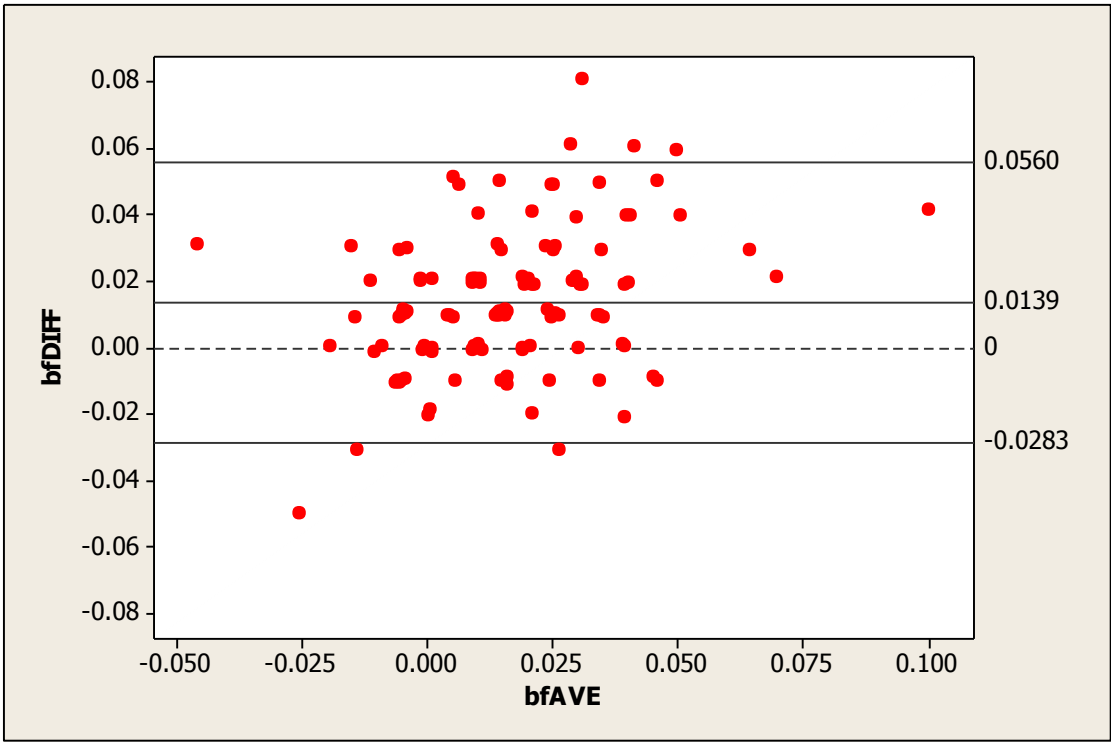


Figure 18 Scatterplot of corrected Q-T data according to Bazett's formula.

On further examination of the corrected Q-T data using Bazett's formula, the mean lies offset above the zero Figure 18. This indicates the tendency for Bazett's formula to over-emphasize the QTc values and lead to falsely prolonged corrected Q-T values.

2.8.4 Sensitivity and Specificity of Hodge's, Fridericia's and Framingham's formulae in comparison to Bazett's Formula

Cross tabulation was performed using Minitab 'version 14' to calculate the sensitivity and specificity of Hodges (Hodges 1997, 1983), Fridericia (Fridericia 1920) and Framingham's formulae (Sagie et al 1992) with Bazett's formula (Bazett 1920) used as the gold standard (Yu et al 1950). All formulae gave good specificity values with Framingham's giving the highest specificity of 100% of correlation with Bazett's formula in identifying normal values (Table 22) with Hodge's specificity slightly lower at 98.5% (Table 20).

Sensitivity of identifying positive events in agreement with Bazett's formula was poor from all comparative formulae with Hodge's (Table 20) and Fridericia's formula at 35.7% (Table 21) and Framingham's 21% (Table 22).

Cross Tabulation for sensitivity & specificity

Bazett's versus Hodge's Results.
Total Seizures

Formula	Bazett's Normal 0	Bazett's Abnormal 1	Total
Hodge's Normal 0	140	9	149
Hodge's Abnormal 1	2	5	7
Total	142	14	156

Sensitivity= proportion of +ve correctly identified QTc:-

Sensitivity=5/14
=35.7%
Specificity=proportion of -ve correctly identified QTc:-
Specificity= 141/142
=99.3%

Table 20 Sensitivity & Specificity of Hodge's Formula compared to Bazett's Formula

Bazett's versus Fridericia's Results
Total Seizures

Formula	Bazett's Normal 0	Bazett's Abnormal 1	Total
Fridericia's Normal 0	141	9	150
Fridericia's Abnormal 1	1	5	6
Total	142	14	156

Sensitivity =proportion of +ve correctly identified QTc:-

Sensitivity= 5/14
= 35.7%

Specificity=proportion of –ve correctly identified QTc:-

Specificity= 141/142
=99.3%

Table 21 Sensitivity & Specificity of Fridericia's Formula compared to Bazett's Formula

Bazett's versus Framingham's Results
Total Seizures

Formula	Bazett's Normal 0	Bazett's Abnormal 1	Total
Framingham's Normal 0	142	11	153
Framingham's Abnormal 1	0	3	3
Total	142	14	156

Sensitivity=proportion of +ve correctly identified QTc:-

Sensitivity=3/14
= 21%

Specificity= proportion of –ve correctly identified QTc:-
Specificity=142/142
= 100%

Table 22 Sensitivity & Specificity of Framingham's Formula compared to Bazett's Formula.

The results of identified cases of lengthening of the corrected Q-T are dependent on which formula is used. Data derived from Bazett's Formula is significantly different ($p<0.001$) from all comparative formula data

2.8.5 Summary

The results of identified cases of lengthening of the corrected Q-T are dependent on which formula is used. Bazett's formula identified a total of 21 seizures (9 patients), Hodge's formula identified 7 seizures (4 patients), Fridericia identified 6 seizures (4 patients) and Framingham's formula identified 3 seizures (3 patients). However, all formulae agreed on the identification of two patients as having a prolonged corrected Q-T during their seizures. The seizure types of these patients were a right sub-clinical seizure and a right temporal lobe seizure (Tables 23 & 24).

n=156	**Bazett's QTc**	**Hodge's QTc**	**Fridericia's QTc**	**Framingham' QTc**
Temporal Lobe Seizures n=27 Confidence interval (CI) *P*	CI.(39.5,68.7) *p<0.001*	CI.(24.0-37.9) *p<0.001*	CI.(16.7,36.9) *p<0.001*	CI.(10.3,26.7) *p<0.001*
Heart Rate (HR) Max. QTc msec	110 (HR) 512 (M)	66.7(HR) 479 (F)	103.2(HR) 464 (F)	65.9(HR) 462 (M)
Prolonged QTc seizures (patients)	13 (5)	1 (1)	4 (2)	2 (2)
No.seizuresQTc> 60 msec. (patients)	11 (4)	0 (0)	3 (2)	1 (1)
Sub-clinical seizures n=16 Confidence interval (CI) *P*	CI.(15.8,47.9) *p=0.001*	CI.(5.2,26.1) *p=0.006*	CI.(7.7,29.5) *p=0.002*	CI.(8.1,28.9) *p=0.002*
Heart Rate Max. QTc msec	120(HR) 493 (P)	127.3(HR) 475 (P)	92.8(HR) 454 (P)	88.8(HR) 451 (P)
Prolonged QTc seizures (patients)	6 (2)	3 (1)	1 (1)	1 (1)
No.seizuresQTc> 60 msec. (patients)	2 (1)	1 (1)	1 (1)	1 (1)
Frontal Lobe Seizures n=58 Confidence interval (CI) *P*	CI.(27.1,36.4) *p<0.001*	CI.(21.6,29.7) *p<0.001*	CI.(10.1,19.5) *p<0.001*	CI.(11.6,20.5) *p<0.001*
Heart Rate Max. QTc msec	117.9(HR) 462 (M)	117.9(HR) 437 (M)	117.9(HR) 423 (M)	117.9(HR) 422 (M)
Prolonged QTc seizures (patients)	0 (0)	0 (0)	0 (0)	0 (0)
No.seizuresQTc> 60 msec. (patients)	3 (1)	0 (0)	0 (0)	0 (0)
GTCS n=9 Confidence interval (CI) *P*	CI.(25.4,79.1) *p=0.002*	CI.(32.1,96.1) *p=0.002*	CI.(-2.3, 46.8) *p=0.07*	CI.(-12.3, 36.8) *p=0.284*
Heart Rate Max.QTc msec	148.1(HR) 490 (P)	148.1(HR) 466 (P)	131.8(HR) 464 (P)	131.8(HR) 440 (P)
Prolonged QTc seizures (patients)	1 (1)	1 (1)	1 (1)	0 (0)

No.seizuresQTc> 60 msec. (patients)	3 (2)	3 (3)	0 (0)	1 (1)
Tonic Seizures n=12 Confidence interval (CI) *P*	CI.(0.7,29.9) p=0.060	CI.(10.3, 36.2) *p=0.002*	CI.(-18.4, 15.3) *p=0.846*	CI.(-19.9, 12.2) *p=0.612*
Heart Rate Max. QTc msec	124.2(HR) 465 (M)	124.2(HR) 463 (M)	121.9(HR) 421 (M)	121.9(HR) 414 (M)
Prolonged QTc seizures (patients)	0 (0)	2 (1)	0 (0)	0 (0)
No.seizuresQTc> 60 msec. (patients)	0 (0)	0 (0)	0 (0)	0 (0)
Absence Seizures n=34 Confidence interval (CI) *P*	CI.(-10.2, 3.5) *p=0.329*	CI (-6.4,1.3) *p=0.191*	CI (-3.5, 2.9) *p=0.856*	CI.(-3.7, 3.1) *p=0.861*
Heart Rate Max. QTc msec	117.6(HR) 462 (P)	117.6(HR) 432 (P)	90.1(HR) 434 (F)	90.1(HR) 431 (F)
Prolonged QTc seizures (patients)	1 (1)	0 (0)	0 (0)	0 (0)
No.seizuresQTc> 60 msec. (patients)	0 (0)	0 (0)	0 (0)	0 (0)

(P)=Paediatric. (M)=Male. (F)=Female. HR=Heart Rate. CI=95% Confidence Interval.

Table 23 Summary of QTc Results During Epileptic Seizures according to Bazett's, Hodge's, Fridericia's and Framingham's Corrective Formulae

Patient	Bazett's QTc msec	Hodge's QTc msec	Fridericia's QTc msec	Framingham's QTc msec
9M	492	475	454	451
20M	495	479	463	462

Table 24 Corrected Q-T values for Patients 9M and 20M according to all Corrective formulae demonstrating QTc lengthening.

Chapter 17: Linear Regression Plots

Introduction

An alternative method for calculating Q-T interval rate correction that is less directly influenced by heart rate is described by Davey (1999). He obtained QT intervals from subjects at rest and during exercise. A Q-T / heart rate plot was created with each point on the graph representing the mean of eight measurements of the Q-T interval at that heart rate. A linear regression curve was then fitted to the rest and exercise Q-T intervals and the curve extrapolated back to obtain values of the Q-T interval at 60/min.

This method of calculating the Q-T interval for the standard heart rate of 60/min was tested on data derived from the two subjects whom all formulae agreed an increase in corrected Q-T in this study. A similar method was used in this analysis as Davey except that the mean of nine measurements of the Q-T interval is used for each data point instead of eight measurements. Minitab version 14 was used to create the scatterplot with linear regression and provided the QT value at 60/min.

2.9.1 Temporal Lobe Seizures

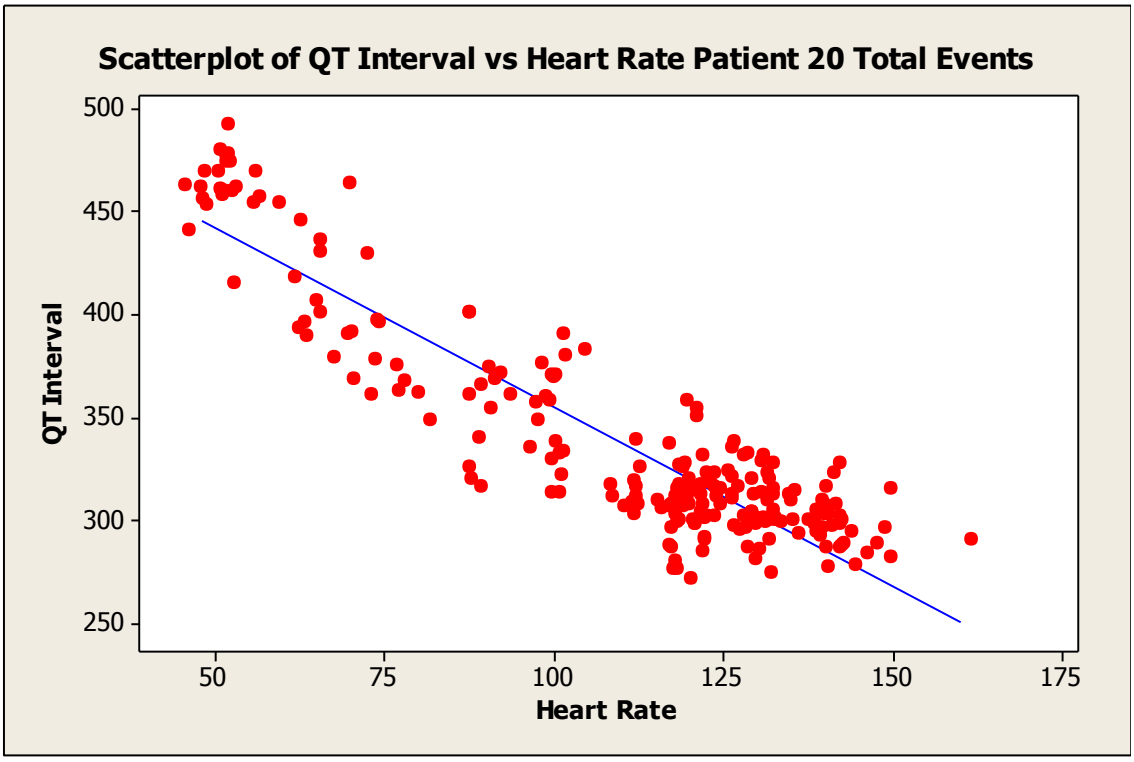


Figure 19 Scatterplot of QT Interval vs Heart Rate with Linear Regression Curve for Total Data during Right Temporal Lobe Seizures.

Regression Analysis: QT Interval versus Heart Rate
The regression equation is QT Interval = 529 - 1.74 Heart Rate QT Interval = 529 – 1.74 x 60 = 529 – 104.4 = 424.6 milliseconds
R-Sq = 83.8%

Table 25 Calculation of Q-T Interval for Linear Regression Curve during Total Right Temporal Lobe Seizures

The total QT and heart rate data was plotted with a linear regression curve fitted for total right temporal lobe seizures derived from patient 20 (Figure 19). Minitab version 14 shows a 'best fit' linear regression line through the data points and gives a Q-T value of 424.6 milliseconds at a heart rate of 60/min. A high square root value (R-Sq) of 83.8% indicates a high correlation of Q-T 'fit' with heart rate. The Q-T value derived using this method is normal at 424.6 milliseconds (Table 25). However, visual inspection of the linear regression line shows that the line is weighted evenly at fast heart rates but is not weighted evenly at slower heart rates with the majority of points found above the linear regression line in the region of prolonged Q-T values.

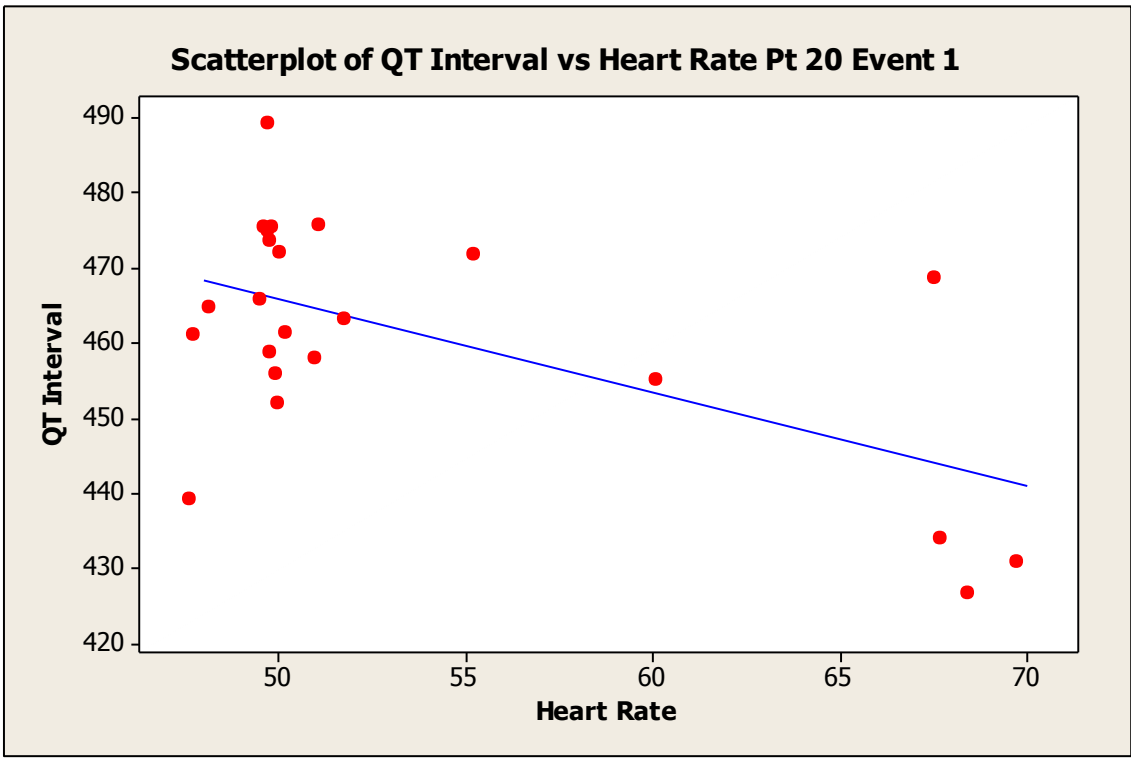


Figure 20 Scatterplot of QT Interval vs Heart Rate with Linear Regression Curve for Seizure 1

Regression Analysis: QT Interval versus Heart Rate
The regression equation is QT Interval = 528 - 1.25 Heart Rate QT Interval = 528 – 1.25 x 60 = 528 – 75 = 453 milliseconds
R-Sq = 34.2%

Table 26 Calculation of Q-T Interval for Linear Regression Curve during Right Temporal Lobe Seizure

The QT and heart rate data was plotted with a linear regression curve fitted for a single right temporal lobe seizure derived from patient 20 (Figure 20). The linear regression line through the data points calculated a Q-T value of 453 milliseconds at a heart rate of 60/min. A low square root value (R-Sq) of 34.2% indicates a poor correlation of Q-T 'fit' with heart rate (Table 26). This poor correlation may be a product of fewer data points or it may indicate that the Q-T values are not closely associated with heart rate and there is some other factor involved. The Q-T value derived when analysing a single seizure gives different results of a prolonged Q-T (453 milliseconds) compared to Q-T results when analysed in a larger group (424.6 milliseconds).

2.9.2 Sub-clinical Seizures

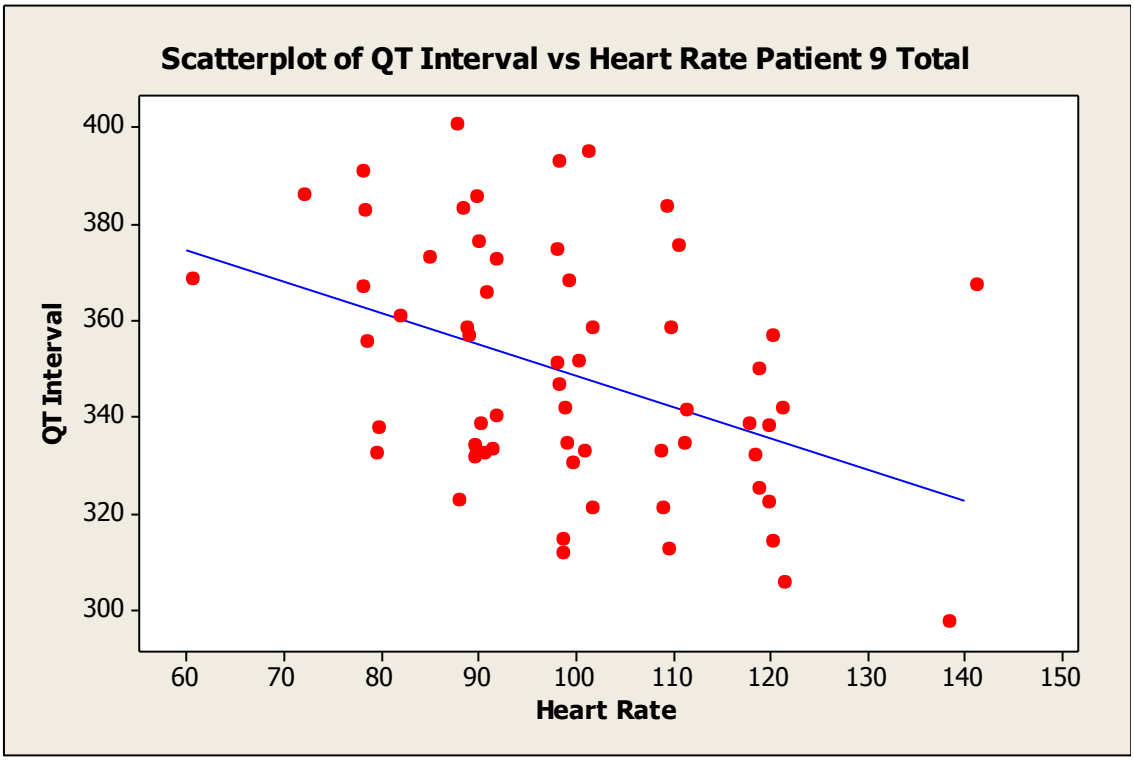


Figure 21 Scatterplot of QT Interval vs Heart Rate with Linear Regression Curve for Total Data (Patient 9) During Right Temporal Lobe Sub-Clinical Seizures.

Regression Analysis: QT Interval versus Heart Rate
The regression equation is QT Interval = 414 - 0.650 Heart Rate QT Interval = 414 – 0.650 x 60 = 414 – 39 = 375 msec.
R-Sq = 17.2%

Table 27 Calculation of Q-T Interval for Linear Regression Curve during Total Right Sub-clinical Temporal Lobe Seizures

The total QT and heart rate data was plotted with a linear regression curve fitted for total right temporal lobe sub clinical seizures derived from patient 9 (Figure 21). Minitab version 14 shows a 'best fit' linear regression line through the data points and gives a Q-T value of 375 milliseconds at a heart rate of 60/min. A high square root value (R-Sq) of 17.2% indicates a poor correlation of Q-T 'fit' with heart rate (Table 27). The Q-T value derived using this method is normal at 375 milliseconds. Patient 9 is a male aged 3 years and it could be argued that his resting heart rate is not likely to be 60/min. There is only one data point on the scatter plot at 60/min, which has been fundamental in the calculation for placing the linear regression line. If that one point did not exist, then the regression line could easily take a different position especially if the two points at around 140/min were not included. The wide distribution of points for any given heart rate in this patient highlights the degree of intra-subject Q-T variability.

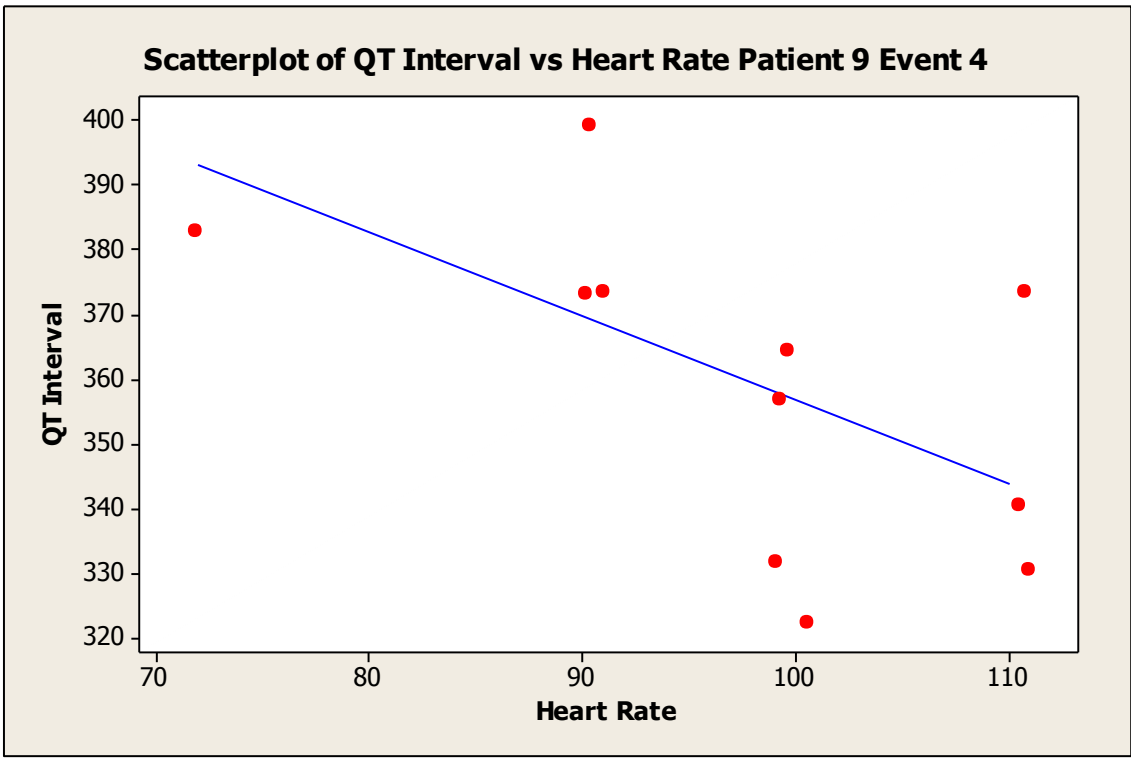


Figure 22 Scatterplot of QT Interval vs Heart Rate with Linear Regression Curve during a Right Temporal Lobe Sub-Clinical Seizure.

Regression Analysis: QT Interval versus Heart Rate
The regression equation is QT Interval = 487 - 1.30 Heart Rate QT Interval = 487 – 1.30 x 60 = 487 – 78 = 409
R-Sq=35.3%

Table 28 Calculation of Q-T Interval for Linear Regression Curve during a Right Sub-clinical Temporal Lobe Seizure

The QT and heart rate data was plotted with a linear regression curve fitted for a single right temporal lobe sub-clinical seizure derived from patient 9 (Figure 22). The linear regression line through the data points calculated a Q-T value of 409 milliseconds at a heart rate of 60/min. A low square root value (R-Sq) of 35.3% indicates a poor correlation of Q-T 'fit' with heart rate (Table 28). This poor correlation may be a product of fewer data points or it may indicate that the Q-T values are not closely associated with heart rate and there is some other factor involved. The Q-T value derived when analysing a single sub clinical seizure gives longer Q-T results (409 milliseconds) compared to Q-T results when analysed in a larger group (375 milliseconds).

2.9.3 Limitations

Scatter plots with few data points when analysing individual seizures and applying linear regression techniques are perhaps inappropriate as each point can dramatically change the course of the 'best fit' line. Conversely, lengthening of the corrected Q-T is sometimes not recognised if the data is weighted more at one end of the linear regression curve.

Chapter 18

Multivariate Analysis on Corrected Q-T and Anti-Epileptic Drugs in Relation to Age, Gender & Seizure Duration.

2.10.1 Results for Total Patients

Thirty-nine patients (25 males and 14 females), (Table 2) with an age range of 2 years 5 months to 60 years 3 months (mean age 17 years, 2 months) had a total of 156 epileptic seizures. Of the 156 seizures, there were 9 generalised tonic clonic seizures (5 patients), 34 absences (6 patients), 12 tonic seizures (6 patients), 27 temporal lobe seizures (14 patients), 58 frontal lobe seizures (4 patients) and 16 sub-clinical seizures (4 patients). Ten anti-epileptic drugs (AEDs) were included in this analysis; carbamazepine (7 patients), lamotrigine (8 patients), sodium valproate (14 patients), Phenytoin (3 patients), clobazam (5 patients), topiramate (6 patients), vigabatrin (1 patient), levetiracetam 3 patients), Nitrazepam (2 patients) and Phenobarbitone (3 patients). Nine patients in the QTc analysis were not being treated on any AEDs, 13 patients had montherapy treatment and 17 patients had polytherapy. Descriptive statistics of mean QTc (Table 29) demonstrate a normal range of mean QTc values for all patients regardless of anti-epileptic medication, monotherapy, polytherapy or nil AED medication.

Descriptive Statistics

Anti-Epileptic Drug	n	Mean QTc (msec)	Standard Deviation (msec)	Standard Error of Mean	Min. QTc (msec)	Median QTc (msec)	Max. QTc (msec)
Vigabatrin	1	471	28.9	4.63	353	475	511
Nitrazepam	2	380	27.1	4.34	330	380	430
Phenobarbitone	3	412	27.6	3.11	370	400	481
Levetiracetam	3	392	34.3	2.43	260	390	494
Topiramate	6	432	31.1	1.73	350	487	528
Carbamazepine	7	430	39.4	1.77	420	433	512
Clobazam	5	402	34.9	1.93	310	399	528
Phenytoin	3	382	23.1	2.51	330	390	440
Sodium Valproate	14	398	35.4	1.25	310	400	535
Lamotrigine	8	410	50.3	2.47	330	400	511

Table 29 Descriptive statistics of QTc for patients on anti-epileptic drugs

Analysis of QTc and AEDs

In this study group of patients, one patient receiving Vigabatrin demonstrated the longest mean QTc of 471 msec (still within normal limits for all heart rate according to Bazett's formula). However, patients treated on Sodium Valproate have the maximum QTc of 535 msec as monotherapy treatment and this is prolonged. Prolonged maximum QTc values are also present in patients receiving Vigabatrin, Levetiracetam, Topiramate,

Carbamazepine, Clobazam and Lamotrigine. However, patients receiving no anti-epileptic medication, although they have a normal mean QTc also demonstrate prolonged maximum QTc of 510 msec. This is slightly shorter compared to those patients on monotherapy of 535 msec and polytherapy of 528 msec. Pooled standard deviation for the group is 38.06 msec. The patients exhibiting the smallest standard deviation were being treated with Phenytoin (23.1 msec), Nitrazepam (27.1 msec), Phenobarbitone (27.6 msec) and Vigabatrin (28.9 msec). However, the number of QTc observations is smaller in these groups and the small standard deviation may simply be the result of less variability due to fewer observations.

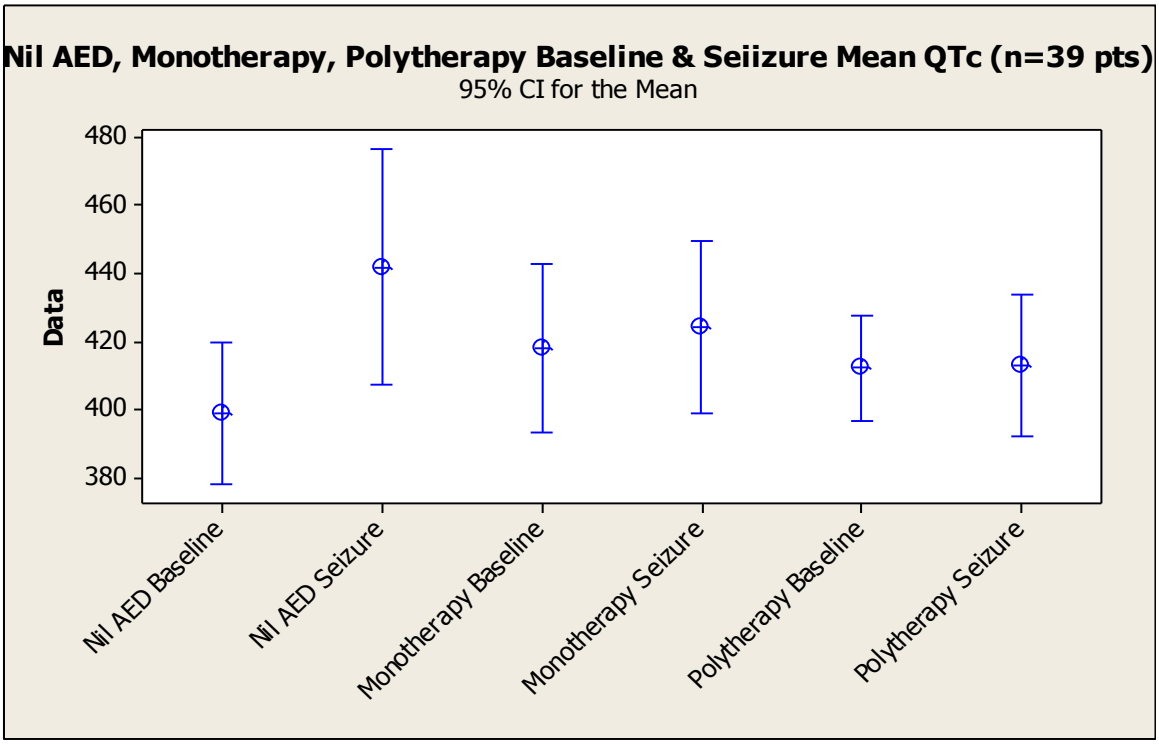


Figure 23 Mean Baseline and Seizure QTc for patients with nil, monotherapy and polytherapy AED.

One way Analysis of Variation (ANOVA), (Table 30) demonstrates that mean QTc increases the most from baseline QTc in patients who are not on any AEDs during the seizure (441 msec), (n=9)) compared to those patients on monotherapy (424 msec), (n=13) or polytherapy (412 msec), (n=17)

ANOVA	n	Baseline QTc	Standard Deviation	Seizure QTc	Standard Deviation
Nil AED	9	399.0	27.0	441.8	44.9
Monotherapy	13	417.8	40.9	424.2	41.9
Polytherapy	17	412.1	30.0	412.8	40.7
Age Monotherapy	13	470.0 (6 yrs)	77.1	505.0 (21 years)	28.3
Age Polytherapy	17	454.0 (7 yrs)	44.6	459.0 (7 to 49 years)	54.0
Gender Total	14(F)	420.8	38.4	432.8	37.6
	25(M)	405.5	29.6	417.9	44.9
Gender Nil AED	5 (F)	403.8	9.39	447.8	21.5
	4 (M)	393.0	41.7	434.2	68.1
Gender Monotherapy	5(F)	438.4	46.1	420.2	44.5
	8(M)	405.0	34.2	426.8	43.2
Gender Polytherapy	4(F)	420.0	49.3	429.8	47.1
	13(M)	409.7	23.8	407.5	39.1
Seizure Duration Nil AED	9	436.0	0.0	490.0 (45 seconds)	13.4
Seizure Duration Monotherapy	13	502.0	9.9	505.0 (190 seconds)	17.6

Seizure Duration Polytherapy	17	480.0	40.3	490.0 (120 seconds)	26.9

Table 30 ANOVA for QTc in patients with Nil, Monotherapy and Polytherapy Anti-Epileptic Drugs in relation to Age, Gender and Seizure Duration.

2.10.2 Monotherapy and Polytherapy and QTc

Anti-Epileptic Drug (AED) effect on QTc in relation to age shows that young adults (aged 21 years) have longer mean QTc (505 msec) compared to children and older adults for those patients receiving monotherapy. However, mean QTc increases in young children from 354 msec monotherapy and to 400 msec in patients receiving polytherapy AEDs.

2.10.3 Anti-Epileptic Drug Effect on QTc in relation to Seizure Duration.

ANOVA of QTc and seizure duration show that patients who are not on any AEDs have a shorter baseline QTc (420 msec), (n=9) than those patients on monotherapy (502 msec), (n=13) and polytherapy (480 msec), (n=17). For patients not on any AEDs, the longest mean QTc occurs at 490msec with seizure duration of 45 seconds. This compares to a longer QTc of 505msec occurring during a seizure lasting 190 seconds in patients receiving monotherapy and 490msec QTc at 120 seconds seizure duration in patients receiving polytherapy. A general uniform distribution of QTc is noted with all seizure durations with patients not on any AEDs. Patients on monotherapy tend to lengthen the mean QTc as the seizure duration increases.

2.10.4 Anti-Epileptic Drug on QTc in relation to Gender.

The effects of QTc and gender show that QTc is consistently longer in females (432 msec), (n=14) compared to males (417 msec), (n=25) during seizures. Baseline QTc is also longer in females (420 msec) compared to males (405 msec). This difference remains similar for patients on no AED, monotherapy and polytherapy. The largest difference in QTc in relation to gender is in those female patients on polytherapy with mean QTc 429 msec compared to males mean QTc 407 msec during seizures.

Chapter 19 Section Two Discussion and Future Studies

2.10.1 Discussion

Impulses from higher brain regions in the cerebral cortex, limbic system and hypothalamus affect the cardio-vascular centre (Torora and Grabowski 1992). During cases of SUDEP it has been hypothesized that an intrinsic 'channelopathy' may occur with sudden and intense impulses directed from cortical areas; driven by a seizure source, which over-stimulate either the cardio-inhibitory centre causing asystole or cause massive adrenergic effect on the sympathetic pathways resulting in tachycardia (Wannamaker 1985, Lathers et al 1987, Cheung and Hachinski 2000, Ansakorpi et al 2004) At autopsy, raised catecholamine detection has been identified on occasions, indicating massive Beta-adrenergic catecholamine effect (Nei et al 2004). It is considered that this physiological mechanism may not be amenable to intervention (Dashieff and Dickinson 1986). Soonhak et al (2003) comments that cardiac arrhythmia may be one of the major causes of sudden unexpected death in children with epilepsy. However, hypoxia is described

as the initial cause preceeding cardiac arrest in children (Carter 1993). Malfunction in ion channels resulting from mutations in the genes encoding channel proteins could be inter-related and part of the same disease spectrum.

Even though it has been recognised since the turn of the last century that seizure deaths could either be accidental or have intrinsic mechanisms (Nashef 2000), very little is really understood of what exactly these intrinsic mechanisms are, although several hypotheses have been postulated mainly concerning respiratory, cardiac and genetic involvement (Nashef et al 2007). Accidental death from suffocation or bodily injury during seizures can occur because of unfortunate body position if no one is alerted to the seizure, particularly during nocturnal seizures or if someone is living alone with epilepsy. 'Positioning of the patient or stimulation of respiration may prevent a fatal outcome in some cases. This raises the important issue of supervision' (Langan et al 2000). Accidental death during seizures may be prevented and hypoxic brain damage could be minimised by the administration of prescribed anti-epileptic medication in order to stop prolonged seizures. It is the true SUDEP cases which may not be preventable due to sudden physiological intrinsic mechanisms.

Channelopathies.

Over the last ten years increasing knowledge and interest has been gained in channelopathies and their pathophysiological basis in cardiac arrhythmias and epilepsy. The most understood type of channelopathy at this time is the voltage-gated sodium channelopathy group. Mutations of the voltage-gated sodium channel gene SCN4A affects peripheral neurones and causes 7

different disorders of muscle control including a myasthenic syndrome. In cardiac channelopathies, genetic mutations of the sodium channel SCN5A have been identified in 7 different syndromes including congenital long Q-T syndrome (Romano Ward), Idiopathic ventricular fibrillation (Brugada syndrome) and sudden infant death syndrome. In neuronal sodium channelopathies, genetic defects of sodium channels SCN1A, SCN2A and SCN1B have been identified in generalised epilepsy and febrile seizures, severe myoclonic epilepsy (Dravet syndrome), Intractable childhood epilepsy and benign familial neonatal infantile seizures. Sodium channel mutations are expressed in the mRNA of neurones found in the limbic regions and produce abnormal depolarisation and lower the seizure threshold.

A single channelopathy mutation that affects the myocardium causing a cardiac arrhythmia because of neuronal seizure activity has not been identified to date. However, highly homologous potassium channel mutation has been identified KCNQ2 and KCNQ3, which cause familial neonatal seizures and is homologous with KCNQ1 channelopathy causing mutations of two inherited cardiological conditions ie Long QT syndrome and Jervell and Lange-Nielson syndrome. In the neurone, including hippocampal pyramidal neurones, the potassium channel influences the M current (muscarinic current), which controls membrane excitability. Mutations that cause disruption of the M current of KCNQ2 and KCNQ3 result in a decrease in inhibitory electrical activity, resulting in seizures (Tripathi & Jain 2002).

Experts (George 1985, Kullmann 2002) suggest that many other channelopathies will be discovered in the near future. However, the

mechanisms of these channelopathies will take much longer before they are fully understood.

Cardiac-pacemaker Intervention?

Implantable loop recorders identified potentially fatal cardiac abnormalities in three out of nineteen patients with focal epilepsy over a period of 24 months monitoring in a study by Rugg-Gunn et al (2004). They suggested that the incidence of bradycardia and asystole have been under reported in patients with epilepsy. They believe that asystole underlies SUDEP and could be prevented by cardiac-pacemaker insertion. Four patients were identified as having bradycardia or periods of asystole had cardiac pacemaker insertion.

Identifying patients with epilepsy who have a cardiac abnormality that could potentially develop into the risk of sudden death and being offered protection by having an implanted pacemaker may prevent some fatalities.

The National Institute for Clinical Excellence (NICE) guidelines.

The requirement guidelines issued by the National Institute for Clinical Excellence (NICE) to medical staff is that "Individuals with epilepsy and their families/and or carers should be given and have access to information on SUDEP" (www.nice.org.uk, accessed 2009). The guidelines recommend to practitioners that all patients visiting a Neurology clinic who have the diagnosis of epilepsy are also to be told of the small risk of SUDEP. A national audit in 2006 by Morton et al highlighted the general reluctance of British Neurologists to implement these guidelines. Only 5% of UK

Neurologists discussed SUDEP with all patients because of the *expected* disproportionate amount of anxiety this knowledge would give to patients. The commonest reasons for SUDEP to actually be discussed were if the patients themselves asked about it and/or the Neurologist considered that the patients presented with considered risk factors for SUDEP.

Many clinical practitioners debate that imparting this knowledge to everyone is unjustifiable because of the level of anxiety caused to some individuals being so great that their lifestyle and outlook on life is devastated because of the worry to themselves and to their family of possible death during their habitual seizures. In a review by Beran et al (2004) of this legal obligation of informing the patient they ask the question "What will be gained by warning of that which cannot be prevented and knowledge of which may seriously deteriorate quality of life?" and consider the patient's right 'not to know.'

I view this approach as negligent and believe that all patients with epilepsy have the right to know about the *small* risk of SUDEP. If the risk is explained in the context of a comparative risk for example, deaths from road traffic accidents, people are then more able to understand the likelihood of the risk of SUDEP happening to them as being very small. The national statistics for road traffic fatalities was 3,201 in 2005 and this figure has remained similar over the last 10 years. In terms of road traffic fatalities per proportion of the general population it is estimated at 5.6/100,000 (www.statistics.gov.uk). If the number of deaths from seizures is compared proportionally to the number of deaths from road traffic accidents in the UK each year, less than 1/3 of people die from seizures at 1000 deaths per year which proportionally is 1.7/100,000 compared to 5.6/100,000 road traffic fatalities. In terms of the

relative proportion of SUDEP cases based on 600 deaths each year, to road traffic fatalities it calculates to be 1/100,000 of the general population, suggesting that someone could be *statistically nearly six times less likely to die from SUDEP than from a road traffic accident*. If people can relate the risk of SUDEP to the risk of a daily activity, I think this helps everyone put the level of risk into perspective. I believe that it is also extremely important however that patients and their families do have the knowledge that SUDEP *can* happen and this knowledge helps to minimise some of the anger in cases where SUDEP does occur because the families have had time to understand and acknowledge that there had been a risk from the start.

If some patients with epilepsy are identified as having a cardiac abnormality and are considered to have an increased risk of SUDEP because of this, then by offering an implanted cardiac pacemaker, intervention has been made possible on the basis of prevention and therefore a reduced risk of SUDEP would be anticipated. Therefore, the argument against the NICE guidelines of "What will be gained by warning of that which cannot be prevented and knowledge of which may seriously deteriorate quality of life?" is no longer quite true. However, some truth in this question does remain because the causes of all SUDEP cases are unknown at this time and until this evidence is found, the risk of SUDEP prevails.

Electro-cardiological Effects During Seizures and Possible Mechanisms.

In a study by Jeffrey (2006), 60% of patients who had severe epilepsy and learning disabilities had abnormalities on their electrocardiograms. Patients who have epilepsy with severe on-going symptoms accompanied by learning disabilities are considered to be in a high risk category of SUDEP and Jeffrey

raises the possibility of neuro-cardiac channelopathies as an underlying mechanism in this group.

The question however, still remains of what these intrinsic mechanisms are, what happens physiologically and what can be done to prevent this intrinsic mechanism from happening?

The data in this study has identified that transient lengthening of the corrected Q-T beyond normal limits according to Bazett's Formula occurs in a high proportion of right temporal lobe seizures (11/17) representing the most common seizure type to lengthen the corrected Q-T overall of (11/21) and right sub-clinical temporal lobe seizures with 5 events (5/21) compared to left temporal lobe seizures (2/21) and left temporal sub-clinical seizures (1/21) However, when data is analysed in terms of number of patients rather than the number of seizures, no statistical difference is seen.

It is considered that when the corrected Q-T lengthens by more than 60 milliseconds there is a small risk of a fatal arrhythmia (Nei et al 2000, Pater et al 2005, Morganroth 2001). In this study, right temporal lobe seizures (59%) right temporal sub-clinical seizures (33%) and generalised tonic clonic seizures (33%) demonstrated the highest proportions of increased corrected Q-T exceeding 60 milliseconds compared to other seizure types (Tables 7 & 8). Lengthening of the corrected Q-T during sub-clinical seizures from the right temporal lobe seen in this study, which have a cardiological effect of stimulating adrenergic pathways strengthens the possibility that Q-T lengthening could be involved in SUDEP where no evidence of a seizure has clinically taken place but an intrinsic cardiac effect may have resulted from sub-clinical seizure activity. Epileptic seizures are frequently associated with

alteration of cardiac activity causing tachycardia or bradycardia. Persson et al (2003) proposes the mechanism for these changes being the spread of seizure discharges to autonomic centres in the cortical, limbic and hypothalamic structures. Animal models of epilepsy suggest even inter-ictal epileptogenic activity may induce changes in the autonomic nervous system which could result in cardiac arrhythmia and risk of sudden death.

It is sometimes reported that generalised tonic clonic seizures are responsible for seizure-related deaths (Opherk et al 2002, Tavernor et al 1996). In this study, lengthening of the corrected Q-T beyond normal limits occurred during this type of seizure in one child. Two further generalised tonic clonic were found to cause a large increase of corrected Q-T of 130 milliseconds during one seizure in an adult male and 70 milliseconds during a seizure in a child but both remained within normal QTc limits during exercise according to Bazett's formula (Table 7). Even though values remain within normal limits, these increases in corrected Q-T may be a possible contributing factor in triggering cardiac arrhythmias in some individuals and additionally could be further compounded by cases of associated hypoxia.

Nocturnal Seizures and SUDEP

Sudden and extreme changes in heart rate can occur during nocturnal seizures. 'This increased instability during seizures arising from sleep may be a key factor in SUDEP' and 'seizures from sleep could cause sudden and extreme fluctuations in autonomic tone which might precipitate lethal cardiac arrhythmias' (Nei et al 2004). Nei et al reported 14/21 people died from SUDEP in sleep and studying seizure EEG/ECG data of these patients retrospectively discovered that much higher increases in heart rate occurred

during seizures arising from sleep than from wakefulness in the SUDEP group compared to the non-SUDEP group. Additionally, 'Ictal cardiac repolarization and rhythm abnormalities occurred in 56% of SUDEP.' Forced awakening occurs during nocturnal seizures and the effects of sudden waking with associated increase in heart rate is compounded by the seizure itself at a time of suspected autonomic instability and therefore could leave some individuals more vulnerable to an induced cardiac arrhythmia during early waking hours.

Marked changes in T-wave morphology, signalling an alteration in ventricular re-polarisation was demonstrated when subjects were unexpectedly woken from deep sleep (Dweck et al 2006) and 'sudden arousal has been associated with sudden cardiac death in individuals with ischaemic heart disease, cardiac arrhythmias and the congenital long Q-T syndrome' are described. Increased autonomic instability is described during early waking hours corresponding to a reported period of increased vulnerability to ventricular tachycardia and sudden death (Pater 2005). Cardiological effects during seizures can be the result of autonomic instability because of a nocturnal seizure presenting when vagal tone is high or an undiscovered channelopathy triggered by the seizure, directly affecting the heart (Lathers et al 1987, Wannamaker 1985, Cheung et al 2000, Ansakorpi et al 2004). Another consideration is that some susceptible individuals may develop an intracellular ionic flux disturbance in the myocyte because of changes in ionic environment due to the physiological demands of the seizure. This disturbance in ionic flux may deteriorate over time in cases of undetected prolonged nocturnal seizures and this could also be a contributing factor in some cases of SUDEP.

Myocardium Cellular Mechanisms and Physiological Effects during Seizures.

In the cardiac myocyte, release of Ca^{2+} from the sarcoplasmic reticulum is the key event linking membrane depolarisation and mechanical activity during excitation-contraction coupling. Intracellular calcium handling in ventricular cardiac myocytes may play an important role in the occurrence of cardiac arrhythmias in the failing heart. Diastolic calcium leak from the sarcoplasmic reticulum (SR) via ryanodine receptors (RyR2) may initiate delay in re-polarisation time that could lead to ventricular fibrillation or other arrhythmias (Wehrens et al 2005). Patients with inherited arrhythmia syndromes such as catecholaminergic polymorphic ventricular tachycardia (CPVT) demonstrate SR Ca^{2+} leak through mutant RyR2 triggered activity during exercise. During diastole, Ca^{+} is effluxed. If a cell did not have Ca^{+} extrusion mechanisms, Ca^{+} would rapidly load the cell. During rest, there is Ca^{+} leak from the SR lumen to the cytoplasm. Ca^{+} in the cytoplasm is then extruded from the cell via the Na/Ca exchanger or the sarcolemmal Ca-pump. This leak followed by Ca^{+} extrusion is called 'rest decay'. In CPVT patients, RyR2 are slow in Ca^{+} extrusion, thereby causing slow de-polarisation (Bers 2001).

The cardiac Na^{+} channel, skeletal muscle and brain neurone are highly homologous. Some agents e.g. quinidine (anti-arrhythmic agent) binds to the S6 region of domain 1V of the membrane. This produces cumulative block of Na current at high frequency; blocking Na current during tachycardia and in depolarised tissues can be pro-arrhythmic. Na channels characteristically snap open and shut very quickly to generate a large and brief inward Na current and cause the rapid upstroke of the action potential. Hypoxia often

occurs during seizures that could cause persistent Na channel openings even at very negative membrane potentials.

Human congenital mutation (deletion of the 3rd amino acid) in the cardiac Na channel in the region of III-IV loop, results in the long Q-T syndrome. This is characterised by long ventricular action potential depolarisations and may pre-dispose these individuals to arrhythmias. The mutation does not greatly alter the Na current but late openings occur at the single channel level, which cause the action potential depolarisation prolongation.

Sympathetic stimulation of the heart results in catecholamine release (isoprenaline) and produces inotropic (force) and chronotropic (rate) effect on cardiac-contraction coupling. Sympathetic nerve endings and Beta-adrenergic receptor agonists are found widely throughout the heart. Isoprotenolol, which is a B-adrenergic agonist, produces large increases in cardiac contraction. Although the intra-cellular Ca^{+} load increases, B-adrenergic agonists also increase cardiac K-conductance, which shortens the action potential. Another positive chronotropic effect of B-adrenergic agonists is that they alter the resting membrane potential of the pacemaker potential to a more de-polarised potential resulting in a faster depolarisation of the pacemaker. However, metabolic demands are high during sustained tachycardia and oxygen consumption increases dramatically. In the failing heart B-adrenergic receptors are ‘down-regulated’ during chronic activation.

This negative inotropic effect is then complicated further by hypoxia and ischaemia. Hypoxia is sometimes part of the physiological effect during seizures. Acidosis is an early consequence of hypoxia due to metabolism changing to glycolysis and lactic acid production. Acidosis decreases

myofilament Ca^+ sensitivity and reduces force. Respiratory acidosis produces an even faster decline in pH than metabolic acidosis, which adds to this negative inotropic effect because low pH inhibits the Na/Ca exchange pumps and the cell is unable to extrude Ca^+. In ischaemia, arrhythmias can occur after reperfusion when pH is restored. This is because a large outward H^+ gradient causes rapid Na^+ gain due to the Na/H exchanger, which in turn causes an inward flux of Ca^+ via the Na/Ca exchanger. Therefore this situation can also result in Ca^+ overload and potential arrhythmias. Re-oxygenation following hypoxia during a seizure may also result in Ca^+ overload of the cell due to oxygen free radical production. (Bers 2001)

Ionic flux in the heart is finely tuned and there are many situations that can affect the cardiac cell to produce arrhythmias. During seizures sudden changes in heart rate occur often when vagal tone is high during sleep. Sustained tachycardia could result in acidosis, acidosis results in decreased contractility and Ca^+ overload. Hypoxia exacerbates this negative inotropic effect and reperfusion ironically can result in arrhythmias.

Q-T Hysteresis

Another important aspect is cardiological physiological Q-T dynamics of Q-T hysteresis. In an ideal situation, when the heart rate increases and the R-R interval shortens, the Q-T interval should correspondingly also shorten. However, physiologically during a rapid onset of tachycardia when the R-R interval immediately shortens, there is a delay or 'lag effect' in the corresponding shortening of the Q-T interval. This effect has been described in studies (Lauer et al 2005) during exercise, which is similarly applicable during physical exertion during seizure activity. During nocturnal seizures

when vagal tone is high during sleep, sudden changes in heart rate could theoretically leave the heart vulnerable because of Q-T hysteresis. Q-T hysteresis is defined as the recovery Q-T peak interval subtracted from the exercise Q-T peak interval. (Chauhan et al 2002). Hysteresis loops demonstrating 'Q-T lag' associated with sudden changes in heart rate during epileptic seizures has not yet been studied and it is my intention to investigate the effects of Q-T hysteresis during different seizure types at some stage in the future. If there is a significant lag time relationship between the R-R interval and Q-T associated with a sudden tachycardia during a seizure then this phenomenon could theoretically lengthen the corrected Q-T and increase the risk of cardiac arrhythmia.

Suggested formula is available to 'correct' this cardiological 'lag effect' but the fact that hysteresis occurs during sudden heart rate increase is worth measuring in an uncorrected manner in order to ascertain what the actual ventricular re-polarisation time is during a seizure. If cardiac hysteresis contributes to a prolonged corrected Q-T then this may partially explain why the Q-T is prolonged. This may be the very key as to why sudden unexplained death in epilepsy occurs in some cases.

Proposed Imbalance of Autonomic Activity Resulting in SUDEP.

In recent years, researchers have tried to identify risk for sudden cardiac death and have mainly focussed on patients with poor left ventricular function. Although patients with poor left ventricular function have higher risks of sudden cardiac death, it does not explain why patients who do have good left ventricular function can also die from ventricular arrhythmias or fibrillation. Cain (2006) reports on findings of an imbalance of sympathetic

activity and vagal tone leads to increased vulnerability to ventricular arrhythmias in patients with ischaemic heart disease. Algra et al (1993) considers that in addition to an imbalance of sympathetic activity and vagal tone there is also an imbalance between the left and right sympathetic nervous systems and hypothesizes that this imbalance is related to sudden unexplained death. This finding hypothetically links with possible intrinsic mechanisms triggered during seizures that may suddenly induce cardiac arrhythmias because of an imbalance of autonomic activity resulting from seizure discharge activity leading to some SUDEP cases.

Hypertrophic Cardiomyopathy, Ischaemic Changes and Epilepsy.

Of course there are a group of patients with undiagnosed hypertrophic cardiomyopathy who experience episodes of exercise-induced ischaemia during intensive training that can result in myocardial cell death and fibrosis that over time can lead to triggered electrical instability and ventricular fibrillation (Gold 2006).The incidence of sudden cardiac death in apparently healthy young adults and athletes aged 12-35 years is reported to be 2.3/100,000 in the United States compared to 1/100,000 non-athletes. There may be some patients with epilepsy who have hypertrophic cardiomyopathy who with repeated seizures render their heart vulnerable to electrical instability and ventricular fibrillation because of increased myocardial cell death and fibrosis.

During a left temporal lobe seizure, of a 60 year-old female patient (patient 19F) in this study, evidence of ischaemic changes on the ECG with diminution of the T-wave occurred in the absence of physical exercise. The patient became apnoeic during this seizure resulting in clinically significant

hypoxia with oxygen saturations dropping to 75%. Her body position remained unchanged except for some subtle right hand automatisms and chewing movements of her mouth. On return of the T-wave, the corrected Q-T measurements according to Bazett's formula had increased from 396 milliseconds prior to the event to 494 milliseconds during the peak of the electroencephalographic seizure demonstrating marked spike wave activity over the left temporal lobe. This seizure occurred from sleep and at the onset of the seizure, the patient opened her eyes, her heart rate increased from 78/min to 90/min. Peak heart rate increased transiently to 120/min within the first 6 seconds of the seizure. T-wave diminution occurred for 18 seconds during an average heart rate of 110/min. Corrected Q-T prolongation did not occur until after 1 minute of the seizure onset and the T-wave morphology had been restored for some 30 seconds with an average heart rate of 100/min. At this time the electroencephalograph showed some spread of the spike wave activity to the left parietal region. At the end of the seizure, the patient simply closed her eyes and went back to sleep again with no memory of the event. Clearly, this patient is at risk of developing a serious cardiac arrhythmia given the ischaemic changes occurring electro-cardiologically, clinically significant hypoxia down to 75% with a hypoxic period of 78 seconds and with no obvious physical evidence of a seizure occurring to alert carers or a family member in case of need of resuscitation or rescue medication. Repeated seizures could result in myocardial cell death and increased fibrosis rendering the myocardium more electrically unstable.

QTc Prolongation

Although according to Bazett's formula, twenty-one seizure seizures in the study showed a transient increase in corrected Q-T, none of the nine patients had died of SUDEP at the time of this publication. The duration of QTc prolongation was typically brief with maximum seizure duration of 4 minutes 15 seconds and all seizures were self-resolving without the requirement of rescue medication. However, prolonged un-witnessed nocturnal seizures could lead to more marked and sustained cardiological effect of corrected Q-T lengthening and therefore place some individuals at risk of cardiac arrhythmia. Transient QTc prolongation (Kandler et al 2005) occurred in 7/30 paediatric patients during a post-convulsive period of two hours following generalised seizures.

Effects of Anti-epileptic Medication on Corrected Q-T.

The longest mean QTc was derived from one patient receiving Vigabatrin and from fewer observations than most other categories of AEDs. The QTc is still within normal range and may reflect more on the patient's own cardiological ability to re-polarise compared to others, regardless of medication. Vigabatrin inhibits the catabolism of gamma-aminobutyric acid (GABA) by irreversibly inhibiting GABA transaminase effectively preventing the breakdown to GABA after the neurone has depolarised and this results in increased amounts of GABA transmitter at the receptor sites maintaining the neurone in an inhibited state. However, GABA action is confined to brain neurotransmitters and is not a neurotransmitter in cardiac contraction and re-polarisation. Vigabatrin is not known to have any cardiological side

effects. It has restricted use in clinical practice because of cases of visual field loss.

Several different anti-epileptic medications were being used therapeutically in this study (Carbamazepine, Topiramate, Levetiracetam, Phenobarbitone, Sodium Valproate, Lamotrigine Clobazam and Vigabatrin) by patients that demonstrate transient maximal prolonged QTc. There were no correlations between the type of pharmacological action of the AED and transient prolonged QTc. Some AEDs like Carbamazepine act by stabilizing the inactivated state of the sodium channel once the neurone has depolarised, others like Topiramate and Sodium Valproate block voltage dependent sodium channels to increase GABA and Clobazam acts on the benzodiazepine receptors, enhacing binding of GABA and increasing the effectiveness of this neuroinhibitor, making the neurones less excitable.

In the study, two patients had prolonged QTc that was agreed by all corrective formulae (Bazett, Hodge, Fridericia and Framingham) during the seizure compared to baseline measurements. One patient was receiving carbamazepine and the other was not being treated by AEDs at that time. However, six other patients were also receiving carbamazepine in this study but did not indicate prolonged QTc according to all formulae.

Cardiac sodium channels play a key role in ventricular re-polarization. It is described by Waseem et al (2010) that the cardiovascular sodium channels were only “minimally effected” when therapeutic dosages of Carbamazepine were given. These authors describe that over dosage of Carbamazepine can produce sodium channel blockade and this can be pro-arrhythmic.

A case controlled study of 100 patients by Amin et al (2010) found that there was no association between carbamazepine as monotherapy and prolonged QTc interval. However, the authors do consider that carbamazepine may contribute to prolonged Q-T in situations of electrolyte disturbance and polytherapies. In this study, 17 patients were receiving polytherapy (4 patients with carbamazepine and other AED's). However, the mean baseline and seizure QTc is shorter (412 msec) in these patients than those patients receiving monotherapy (417 msec baseline, 424 msec seizure) and indeed shorter than the patients not on any AED's during a seizure (441msec).

If hypoxia occurs during a seizure, acidosis can result from metabolism altering glycolysis and lactic acid production. Low pH inhibits the Na/Ca exchange pumps and the myocyte is unable to extrude Ca^{+} leading to increased risk of cardiac arrhythmia. Characteristically, Na^{+} channels snap open and shut very quickly to generate a large brief inward current and cause the rapid upstroke of the action potential. Hypoxia causes persistent Na^{+} channel openings that can lead to cumulative block, especially during tachycardia where this combination can be pro-arrhythmic (Bers 2001).

In this study, four patients (one child, 3 adults) had hypoxia associated with their seizures. The level of hypoxia ranged between 67% and 75% with a duration between 33 seconds and 132 seconds (Table 5). The mean duration of seizure lasted 169.5 seconds with the longest seizure lasting 252 seconds. Rescue medication had not been required for any of these patients for their seizures as they were not prolonged i.e more than 5 minutes. However, there are many cases of patients having prolonged unwitnessed seizures where

hypoxia and tachycardia could theoretically result in cardiac arrhythmia due to cumulative block of sodium channels and Ca^{+} overload.

In this study, patients not receiving any AEDs lengthen to a maximum QTc quickly at a mean duration of 45 seconds. Patients receiving monotherapy and polytherapy take longer to reach the maximum QTc at 190msec and 120 msec respectively. This result may indicate that the types of seizures the patients have who are on AEDs have longer seizures, more difficult to control and there is always the compounding factors of hypoxia with longer seizures and the effects of these factors on cardiac repolarisation A previous study reported that there was no evidence of QTc prolongation detected in patients receiving anti-convulsant monotherapy or polytherapy in a paediatric group (Soonhak 2003).

The government Medicine & Healthcare Products Regulatory Agency (2008) Public Assessment Report includes several warnings of effects from carbamazepine. Plasma levels of concomitant agents can have reduced efficacy as carbamazepine increases liver metabolism and reduces the effectiveness of these medications. Phenytoin levels can be difficult to manage alongside carbamazepine. Warnings of neurotoxic reactions due to carbamazepine's structural relationship to tri-cyclic anti-depressants and the increased side effects of anti-depressants occasionally give rise to suicidal thoughts. Risk of Stevens-Johnson Syndrome in Asian patients. Teratogenecity of congenital abnormalities of spina bifida, craniofacial defects, cardiovascular malformations can be associated with carbamazepine if taken during the first trimester of pregnancy. In the long list of side effects of carbamazepine, cardiac conduction disturbances are stated as 'rare' and bradycardia and arrhythmias are described as 'very rare.' Carbamazepine

was the commonest drug used as a monotherapy in this study. The longest mean QTc occurred late into the mean seizure duration for the monotherapy group. Accumulative myocardiological changes are difficult to determine but there may be some association of carbamazepine, duration of seizure, hypoxia and lengthened QTc in some cases.

In cases of SUDEP, the cause is as yet unknown but believed to be multifactorial. Cardiac arrhythmia is one of the most suspected causes with the other being central apnoea. The contributing factors of what has led to cardiac arrhythmia in SUDEP cases are harder to assess. Increased circulating catecholamines are often found in the victim at autopsy, indicating sustained tachycardia during the seizure. Any factors of cumulative block of Na^+ channels, severe hypoxia and the effects of acidosis and what part a drug like carbamazepine would have had are difficult or impossible to find evidence. SUDEP is rare and people who are pre-disposed to the physiological demands of the seizure are relatively few compared to others with seizures, who are also taking anti-epileptic medication. The combined effects of all contributing factors may disguise how anti-epileptic medication may also be one of these contributing factors in a pre-disposed individual.

Rugg-Gunn et al (2004) report no clear correlation between cardiac events and specific epileptic drugs but use one of the risk criteria for SUDEP as the treatment of more than two antiepileptic drugs. This is expanded upon by Beran et al (2004) who explained that although there is no evidence that any particular anti-epileptic medication influences the risk of SUDEP, poly-therapy was found to be a significant risk factor, confirming the refractory nature of the epilepsy. Only anecdotal reports of brady-arrhythmia and

asystole have been associated with carbamazepine. However, carbamazepine is used to control simple focal and complex focal epilepsy and it is this type of epilepsy that has been reported in this study and in many others of causing marked changes in heart rate, respiration and autonomic control during seizures. At this time, there is no conclusive evidence of AEDs contributing to the risk of SUDEP and most researchers believe that cardiological changes occurring in focal or complex focal seizures are perhaps due to the nature of the seizure and not the medication.

Which Corrective Formula?

Bazett's formula is the commonest corrective formula and has been used widely for over 80 years (Bazett 1920, Yu et al 1950). For consistency of data collection in this study and to allow a comparison to other studies Bazett's has been the main formula used to compare other formulae results to. However, it is important to note that Bazett's formula over-corrects and therefore over-estimates QTc at fast heart rates resulting in a tendency towards falsely prolonged corrected Q-T values and under-corrects and under-estimates QTc at slow heart rates resulting in a tendency towards falsely shortened corrected Q-T values (Hodges 1997, Sagie 1992, Pater 2005, Sredniawa et al 2005).

Conversely, Framingham's formula can lead to falsely shortened corrected Q-T values at fast heart rates and falsely lengthened QTc values at slow heart rates (Sagie et al 1992). No single mathematical transformation can adjust for the rapidly changing non-linear dynamics of the QT/RR interval relationship (Fossa 2005).

Heart rate correction of the Q-T interval using scatterplots with linear regression curves (Davey 1999) were investigated in this study in the two subjects whom all corrective formulae had identified as showing an increase in corrected Q-T during seizures. Q-T values at 60/min were calculated by minitab version 14. Grouped data for each patient indicated normal values. However individual seizure data plots showed either a prolonged Q-T or a much longer Q-T than that calculated for each total group in both subjects. There are limitations in using this technique when there are only a few data points derived during a seizure as a single data point can dramatically influence the gradient of the linear regression curve. Conversely, important Q-T values can be lost in grouped scatter plot data if the linear regression curve is more strongly positioned in one area of the data points eg at fast heart rates compared to another area at slower heart rates.

Individual correction formulae have been proposed by Malik et al (2004). These authors describe the relationship between the Q-T interval and heart rate as highly individual and using a parabolic heart rate correction formula ($QTc= QT/RR^{\alpha}$) demonstrated a large variability of the $^{\alpha}$ exponent in healthy individuals and concluded that the correction of QT interval by heart rate may be misleading with any formula. However, creating individual correction formula in practice would be excessively time consuming. Luo et al 2004, Pater 2005, Fossa 2005 and Toivonen 2002 argues that there is no evidence that using an individual correction method would help to improve discrimination of diseases such as hereditary long Q-T syndrome. Walker et al (2005) accept that Bazett's formula may overcorrect at fast heart rates and can lose accuracy during sudden changes in heart rate but believe that

Bazett's formula is still the best predictor of Long Q-T syndrome carrier status.

All researchers and cardiologists in the field of corrected Q-T analysis describe the Q-T becoming 'over-corrected' leading to a falsely prolonged corrected Q-T and vice versa of an 'under-corrected' Q-T leading to a falsely shortened corrected Q-T value. I find the semantics of the use of the word 'corrects' to mean the opposite i.e if something is 'over-corrected' its value becomes shortened. However, the use of 'over-correction' in this field appears to apply 'numerically' to a prolonged value. Therefore, despite my reluctance of the use of the word 'corrects' to describe a numerical value instead of a description of function I recognise uniformity of describing results in this way for comparison with data to that researched by other authors.

Artificially Prolonged QTc due to Rapidly Accelerated Heart Rate?

Some authors warn of artificially prolonged QTc calculated from rapidly accelerating heart rate disproportionately affecting QTc measurements (Yu et al 1950, Malik 2004). This potential error was objectively assessed in this study and it was found that corrected Q-T lengthening occurred during some seizures whether heart rate increased or decreased. Also during some sub-clinical seizures where there is no element of physical exertion, again measurements of Q-T prolongation occurred whether heart rate increased or decreased. During a left temporal sub-clinical seizure heart rate decreased from 80-70/min and the corrected Q-T increased from 425-454 milliseconds. Therefore, although there is a strong heart rate correlation with corrected Q-T calculations when using a linear formula like Bazett's, we have found that

during seizures corrected Q-T prolongation is not simply the result of the previous R-R history. Magnano et al (2002) demonstrated that autonomic conditions effect the ventricular myocardium and cause differences in Q-T that are independent of heart rate.

Measuring corrected Q-T during exercise is used as a clinical method for distinguishing and identifying patients with latent long Q-T syndrome from healthy subjects who all have normal Q-T at rest. Bazett's formula is used widely in clinical practice as remains the best predictor of carrier status compared to other formulae (Walker 2005). Catecholaminergic polymorphic ventricular tachycardia is rare but can occur in apparently healthy children. Exercise testing of the ECG dynamics is necessary in this group as the corrected Q-T is normal at rest. Delayed after de-polarisation potentials are considered to be the probable electrophysiological mechanism responsible for this cardiac arrhythmia induced by exercise or sudden emotion that can then result in syncope and sudden cardiac death (Leite et al 2001).

Some epileptic seizures cause more rapid acceleration or deceleration than others and this is highly variable both between individuals and within the same individual. Nocturnal seizures causing forced arousal compounds heart rate acceleration than simple arousal itself. There may be an element of 'artificial prolongation' effect in some cases where heart rate increases dramatically and short epochs are used. Many researchers only average 3 beats and apply these values to corrective formulae. In fact a minimum of 3 or 4 beats is recommended in drug trials. However, since 'artificial prolongation' of the corrected Q-T is possible in accelerated heart rates when

analysing the effects during seizures, I used a longer epoch of 9 seconds to average out this effect.

Formula Comparison of Identified Patients and Seizure types with Prolonged QTc.

Twenty three percent (9 patients) were identified as having transiently lengthened the corrected Q-T during epileptic seizures using Bazett's Formula compared to 10 percent (4 patients) identified by Hodges and Fridericia's and only eight percent (3 patients) identified by Framingham's formula. Only two patients (2/39) were identified consistently by all four formulae as having QTc prolongation during epileptic seizures. This represents 5% of the total patients in the study. Only two types of seizures were consistently agreed by all four formulae as having a prolonged corrected Q-T during the seizure and those were right sub-clinical temporal lobe seizures and right temporal lobe seizures. One generalised tonic-clonic seizure was identified by three corrective formulae as prolonging the corrected Q-T beyond normal limits but this was not agreed with Framingham's formulae. Three formulae identified a left temporal lobe seizure as having a prolonged corrected Q-T but Hodge's formula did not identify this seizure.

A large study by Luo et al (2004) analysing 10,303 normal ECG's testing the effect of heart rate using all four formulae concluded that Hodge's formula fitted the database globally better than the other formulae. They also comment on the results from using Bazett's formula suggested that 30% of apparently normal ECGs had abnormal intervals compared to 2% identified by other formulae.

In a study by Benatar et al (2001), at peak exercise in healthy children, Hodge's and Bazett's correction formulae resulted in prolongation of the corrected Q-T whereas Fridericia's and Framingham's formulae resulted in a shortening of the corrected Q-T. They concluded that none of the four formulae provided an optimum QT interval correction.

A previous study analysed corrected Q-T during epileptic seizures and reported that all mean QTc values using Bazett's formula, were normal for total grouped data (Nei et al 2000). Unfortunately transient QTc increases or individual patients demonstrating an increase in corrected Q-T are lost if calculated as a mean average of total patient grouped 'pre-seizure' and 'during seizure' event data. Differing epoch lengths were used to calculate the pre seizure data with the seizure data, lead I was measured instead of lead II and there was no explanation as to whether different normal limits were applied to gender and age differences by these authors. By comparison, this study used a standard epoch length of 9 seconds to measure 9 consecutive beats in order to calculate the corrected Q-T prior to the seizure and throughout the seizure as described in the methodology. Lead II is also generally recommended instead of lead 1 so that the U wave is not included in the Q-T measurement.

The 'Lockstep Phenomenon' and SUDEP.

In this study, sub-clinical seizures demonstrated marked corrected Q-T lengthening particularly with seizures arising from the right hemisphere. A mechanism called the 'lockstep phenomenon' is described in a study by Lathers et al (1987) of anaesthetised cats where 'the sympathetic discharge was synchronised with epileptogenic activity and associated with changes in

the electrocardiogram.' The changes during an epileptiform discharge were shown to alter the sympathetic activity and caused an alteration of peripheral efferent discharge to the heart. Lathers postulated that the lockstep phenomenon maybe a factor of SUDEP where there has been no evidence of a clinical seizure around the time of death. Increases in corrected Q-T during sub-clinical seizures are not related to exercise as no physical exertion takes place and therefore must have an intrinsic basis. Hypothetically, a sudden and intense electrical discharge caused by a sub-clinical seizure could directly alter the peripheral efferent discharge to the heart causing lengthening of the corrected Q-T and lead to a cardiac arrhythmia.

The Effects of Hemisphere Laterality of Seizure Activity.

The results of corrected Q-T differences relating to hemisphere laterality may be due to physiological differences of innervation pathways. Cheung (2000) describes 'There is clinical evidence of lateralization in neurocardiac control.' Intra-operative stimulation of the insula and amygdala has demonstrated that the right cerebral hemisphere mainly modulates sympathetic activity. Nouri supports this finding ' stimulation of the left anterior insula cause a bradycardia whereas stimulation of the right insular cortex induces tachycardia' Rugg-Gunn et al (2004), reported that there was no effect of seizure lateralisation on heart rate but continue to explain that their study was not large enough to allow detailed analysis of this.

Study Limitations

Studies of larger sample sizes with controlled drug monotherapy and polytherapy analyses may be useful in the investigation of any contributing

effect on lengthening of the corrected Q-T. However, a previous study reported that there was no evidence of QTc prolongation detected in patients receiving anti-epileptic drug monotherapy or polytherapy in a paediatric group (Soonhak et al 2003).

Effects of diurnal variation, effects of winter months on adult male subjects and stages of sleep were not quantified in this study.

2.10.2 Future Studies

Continued research analysing corrected Q-T in larger populations of people with epilepsy may provide risk stratification of SUDEP for different seizure types.

2.10.3 Conclusion

One of the main aims of this study was to determine if there was any lengthening of the corrected Q-T during epileptic seizures. This study has indicated that significant lengthening of the corrected Q-T beyond normal limits in children and adults transiently occurs during some epileptic seizures. Prolonged corrected Q-T is associated with an increased risk of cardiac arrhythmia and this study supports the possibility that this cardiological mechanism may be involved in SUDEP.

Section Three

Cardiac Vagal Tone and Heart Rate Variability during sub-clinical Seizures

Section Three List of Figures Page

Section Three List of Figures Page

Section Three List of Figures Page

Section Three List of Figures Page

Section Three List of Figures Page

Section Three List of Figures Page

Section Three List of Figures Page

Section Three List of Figures Page

Section Three List of Figures Page

Section Three List of Figures Page

Section Three List of Figures Page

Section Three List of Tables Page

Section Three List of Tables Page

Section Three List of Tables Page

Section Three List of Tables Page

Section Three

ABSTRACT

Introduction. To measure reflex and tonic vagal activity using the NeuroScope and BioSignal software during sub-clinical seizures. ***Methods*** Video-EEG/ECG/SAO2 telemetry patients were included in the prospective study. Sub-clinical seizures were identified electrographically during stage 3 or 4 sleep. R-R intervals were measured one minute prior to the onset of the sub-clinical seizure and until the sub-clinical seizure had ended. A matched R-R baseline was selected from non-sub-clinical seizure trace during stage 3 or 4 sleep. R-R interval data were analysed by the NeuroScope for cardiac index of parasympathetic activity (CIPA). Short-term Heart Rate Variability (HRV) was then analysed with the selected section of R-R intervals embedded within 5minute period of baseline data and sub-clinical seizure data. ***Results*** A total of 33 sub-clinical seizures from eleven patients were analysed. 19 generalised sub-clinical seizures (two patients), 9 right temporal lobe sub-clinical seizures (five patients) and 5 left temporal lobe sub-clinical seizures (four patients) were compared to matched baseline studies. Clear altered parasympathetic activity occurs during total sub-clinical seizures in both CIPA ($p<0.001$) and 5minute HRV HF% ($p=0.026$) compared to matched baseline data. Generalised sub-clinical seizures resulted in increased cardiac parasympathetic activity and low coefficient of variation of R-R intervals compared to a decrease in cardiac parasympathetic activity and high coefficient of variation of R-R intervals during temporal lobe seizures. ***Conclusion*** This study favours the view that generalised seizures could result in autonomic instability and may be one of the contributing factors in Sudden Unexplained Death in Epilepsy (SUDEP) in predisposed individuals.

Section Three

Chapter 19

Cardiac Vagal Tone and Heart Rate Variability during Sub-clinical Seizures

3.1.1 Introduction

The evidence of mechanisms involved in Sudden Unexpected Death in Epilepsy is yet to be proven (SUDEP). A proposed definition by Nashef & Shorvon (1997) is a "sudden, unexpected, witnessed or un-witnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, where post-mortem examination does not reveal any toxicological or anatomical cause of death" Alterations in autonomic control during seizures are well documented e.g. alterations in heart rate and respiration, cardiac dysrhythmias and respiratory arrest, sweating, pallor, urinary and bowel incontinence.

A measure of autonomic changes during different types of seizures may give some insight as to a possible mechanism involved during sudden unexpected death in epilepsy. A study by Al-Aweel et al (1999) investigated post-ictal heart rate oscillations in partial/ focal epilepsy. They reported a type of 'ringing' oscillation pattern following focal seizures distinct from the increase in sympathetic activity and vagal withdrawal. Their conclusions were that this type of activity maybe associated with unstable cardiopulmonary dynamics.

Beat to beat variation of heart rate is partly due to influences of the autonomic nervous system innervating the sinus node. Loss of this variation is widely considered to be a measure of risk for sudden death in myocardial infarction patients (Bigger et al 1984, Kleiger et al 1987, Malpas 2002, Miller et al 2004). Cardiac vagal tone is a measurement of parasympathetic activity and is analysed in this study using the NeuroScope measuring baroreflex cardiac vagal tone and BioSignal HRV measuring tonic vagal activity.

Measurements of cardiac index of parasympathetic activity (CIPA) and heart rate variability analyses during clinical seizures are impossible to interpret due to influencing factors including alteration in body position and physical movement and increased cardiologic demand, changes in conscious level, alteration in temperature etc. However, it is possible to measure cardiac vagal tone during sub-clinical seizures where no perceived alteration occurs in conscious level during non-REM sleep where there is no physical activity or change in body position to alter blood pressure and heart rate. Sub-clinical seizures have been defined as "electroencephalographic ictal-like patterns without any disturbance of motor, sensory and conscious functions in the wake patient and without any movement or arousal during sleep" (Zangaladze et al 2008).

Sometimes in cases of sudden unexpected death in epilepsy (SUDEP) there is no evidence of the victim having had a seizure and no evidence of any anatomical or toxicological cause of death (Nashef 1997). Many researchers believe that death must be the result from a fatal cardiac arrhythmia or respiratory arrest mediated by a seizure source (Ansakorpi 2000, Healy et al 1995, Novak et al 1999). Alteration of autonomic activity driven by seizures

and sub-clinical seizures may lead to cardiac or respiratory instability and may be the underlying cause of SUDEP in some cases.

Autonomic manifestations during seizures are common. The aim of this study is to measure cardiac vagal tone and heart rate variability during sub-clinical seizures where there is no perceived alteration in body position (orthostatic stress), conscious level and where sleep state remains unchanged and no physical activity occurs. The data will be collected from the same cohort of patients from the original study group of whom some have been included in corrected Q-T analysis in the previous thesis section.

3.1.2 The NeuroScope.

A method for physiological measurement of neuro-cardiological control.

Cardiac vagal tone is a measure of medullary cardio-inhibition. Medullary cardio-inhibition has its motor nucleus in the Nucleus Ambiguus (NA) of the medulla oblongata, its efferent pathway is entirely in the vagus. It is the only parasympathetic activity of the heart. During ventricular systole, brief elevation of blood pressure stretches arterial smooth muscle and stimulates baroreceptors in the vessel lining. This causes a reflex response (240msec in humans) of the baroreceptor to sino-atrial node via the vagal nerve, directly modulating the firing rate of the sino-atrial node, gradually slowing the heart and increasing the R-R intervals on a beat-by-beat basis (Little et al 1999, Murray et al 2001). This increase in R-R interval slowing the heart is proportional to the concentration of acetylcholine at the sino-atrial node accumulated by the release from vagal stimulation of synaptic vesicles but also remaining acetylcholine neurotransmitter from the previous beat that

has not been degraded by acetylcholinesterase. Sympathetic control of the heart is slower in effect and is activated by peripheral resistance.

The NeuroScope is described as the first brainstem monitor to be produced commercially, invented by Dr Peter Julu (Pontoppidan, Copenhagen, Denmark) and is based on a theoretical model by Katona (1970). The NeuroScope measures cardiac vagal tone by predicting R-R interval measurements based on incoming QRS signal compared to a previously acquired QRS template generated at the initial stage of the recording. The NeuroScope measures the delay in the next cardiac cycle induced by baroreceptor stimulation, which is proportional to baroreceptor strength and duration (Little et al 1999). The physiological ECG signal is sampled at a very high sampling rate of 5KHz to ensure precise identification of the peak of the 'R' wave and accurate R-R intervals. Ectoptic beats and electromyographic artefact must not be included in data for analysis.

The NeuroScope generates a QRS template and compares this to incoming QRS signals. Using high pass and low pass filters and integrators the High Frequency oscillation signal amplitude is extracted, so that the vagal signal is isolated and changes in heart beat variation are converted to a linear scale called the Cardiac Index of Parasympathetic Activity (CIPA) and has been shown to be a sensitive and specific measure of vagal activity (Julu 1992, Little et al 1999). The NeuroScope detects pulse-synchronised delays in the onset of successive cardiac cycles as phase-shifts and quantifies these delays in milliseconds independently from respiration and heart rate (Julu 1992, Little et al 1999). CIPA is defined as "the increase in pulse interval per unit increase in systolic pressure" (Smeets et al 2006) and measured on an arbitrary scale of 1-10 based on studies of supine resting healthy volunteers

in response to atropine and uses a zero reference point. An output measurement 1-4 units represents low cardiac vagal tone and 5-10 units represents the normal range of Cardiac Index of Parasympathetic Activity (CIPA), (Murray et al 2001). However, in a review article by McKechnie et al (2002) they suggested that the upper limit of normal should be extended.

Since the NeuroScope quantifies the effects of the baroreflex on the pulse intervals on a beat-by-beat basis, it can output the CIPA results on this basis and can therefore give real-time measurements of cardiac vagal tone.

3.1.3 BioSignal Heart Rate Variability

The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) produced standards of measurements, physiological interpretation and clinical use made the following statement:-

'The last two decades have witnessed the recognition of a significant relationship between the autonomic nervous system and cardiovascular mortality, including sudden cardiac death. Experimental evidence for an association between the propensity for lethal arrhythmias and signs of either increased sympathetic or reduced vagal activity has spurred efforts for the development of quantitative markers of autonomic activity. Heart Rate Variability represents one of the most promising such markers.'

Many factors have to be considered when using this type of measurement. Body position should be recumbent or semi-recumbent with no physical movement to produce any visceral changes to the passive autonomic balance of the sympathetic and parasympathetic nervous system at rest. Regular

respiration, normal resting body temperature and consistency in recordings should all be made either nocturnally or in daylight hours due to circadian cycle influences on vagal tone.

BioSignal Heart Rate Variability Software.

Heart Rate Variability is the comparison of sequential R-R intervals from ECG recordings. The changes in time domain R-R interval can be plotted on a Tachogram and ranges of heart rate for a selected period can be quantified. Several measurements can be made from the time domain R-R interval including the mean and the standard deviation (SDNN). The standard deviation measures the overall variation in the R-R interval (or Normal to Normal beat interval). The root mean square of the differences of consecutive R-R intervals is known as RMSSD. The NN50 gives the number of consecutive intervals that increase by more than 50 milliseconds and the pNN50 is the percentage value of NN50 intervals.

The Time Domain R-R interval tachogram is interpolated using a cubic interpolation at a default ratio of 4Hz prior to spectrum estimation. Frequency Domain is displayed separately for Welch's Periodogram Fast Fourier Transform (FFT) and an autoregressive modelling based spectrum (AR). Frequency oscillations are quantified and displayed as a power spectral density once any leakage current frequencies are removed using a Hamming window filter. The power spectral density is calculated by BioSignal software producing powers and peak frequencies for different frequency bands. The frequency bands are very low frequency (VLF, 0-0.04Hz), low frequency (LF, 0.04-0.15Hz) and high frequency (HF, 0.15-0.4Hz). In this study, only HF will be considered, as it is believed to be a measure confined to parasympathetic vagal activity. Heart Rate Variability functional indices are based on

generalisations of cardiac sympathetic and parasympathetic activity. Low frequency (LF) HRV is believed to be a mixture of both sympathetic and parasympathetic activity and Very Low Frequency (VLF) signal reflects rennin-angiotensin-aldosterone hormonal interplay of the autonomic nervous system.

The use of HRV in the clinical setting has not been evaluated in each disease to know what the expected measurement should be in different disease processes. Shifts in spectral density of LF and HF signal can be quantified during events but there are no pre-determined normal values and only general description of the changes can be described at this stage until comparisons to other disease processes are made in the future. In this study, HRV will be analysed using advanced HRV BioSignal software which was developed by Juha-Pekka Niskanen, Mika P. Tarvainen, Perttu O. Ranta-aho and Pasi A. Karjalainen, University of Kuopio, Department of Applied Physics, Finland in conjunction with the Kuopio university Hospital and the Brain@Work –Laboratory of the Finnish Institute of Occupational Health using a Matlab platform for event-related BioSignal analysis (2002).

3.1.4 Aims and Limitations

- To measure and analyse counted R-R intervals during electroencephalographic sub-clinical seizures from the original study group of patients and compare this to non sub-clinical seizure baseline counted R-R intervals taken from the same stage of sleep from the same patients' recordings using the NeuroScope to determine cardiac index of parasympathetic activity (CIPA). In effect, the patients act as their own controls.

- To analyse the same counted R-R interval data collected for the NeuroScope (CIPA) and directly compare results with BioSignal software.

- To measure and analyse R-R intervals using traditional 5 minute epochs encapsulating the electroencephalographic sub-clinical seizure and compare this to a baseline 5 minute epoch taken from the same stage of sleep and processed using BioSignal Heart Rate Variability.

- To quantify and compare the high frequency (HF) component produced by the BioSignal Heart Rate Variability software between counted epochs and 5 minute epochs.

- To assess sub-clinical seizure laterality for CIPA and HF Heart Rate Variability.

- To group data and compare differences for adult and paediatric CIPA and HF Heart Rate Variability.

- To compare results from NeuroScope CIPA and BioSignal HRV software using R-R intervals, CIPA and High Frequency (HF) data.

- To assess effects of anti-epileptic medication monotherapy and polytherapy on CIPA in relation to age, gender and sub-clinical seizure duration

- It is recognised that it is inappropriate to compare different lengths of time domain data and "counted" BioSignal Heart Rate Variability should not be directly compared with the 5 minute BioSignal Heart Rate Variability analysis. However, for the purposes of this study, deliberate comparisons will be made of NeuroScope, "counted" and 5 minute HRV HF to determine whether shorter epochs can provide similar results when investigating changes in parasympathetic control during brief sub-clinical seizures which may be lost over longer epochs.

- Clinical seizures cannot be investigated for changes in vagal tone due to alterations in autonomic control related to changes in conscious levels e.g. from sleep to wakefulness, body position, voluntary muscle activity and catecholamine release and temperature change. These all alter autonomic balance and would therefore make interpretation of CIPA or Heart Rate Variability impossible.

- Limitations of number of original study patients with sub-clinical seizures arising from the same stage of sleep meant that only a few could be included in the analysis of cardiac vagal tone. Ideally, many more patients would have to be included for this study to be age and sex matched if the study had been designed to analyse sub-clinical seizures from the outset. In this study it was only possible to group adults and paediatric data instead of age-matched data.

- Manual measurements are extremely time consuming but are necessary for importing R-R intervals via Excel and then transformed to MSDOS for BioSignal analysis. In this study, a total of twenty-seven thousand, one hundred and fifty one R-R interval measurements were manually measured for 5 minutes data analysis. Clearly, this is a time-limiting factor and a larger study would require a reliable method of automated peak detection software. Automated peak detection software other than the NeuroScope was investigated but the software was very inaccurate. Manual measurement of the R-R interval was preferred to ensure reliable data.

3.1.5 Null Hypotheses

- There are no differences in CIPA or Heart Rate Variability parameters when comparing baseline measurements with sub-clinical seizure measurements whether "counted" or during 5 minutes epochs.

- There are no differences when comparing CIPA or Heart Rate Variability parameters for laterality of sub-clinical seizures or generalised sub-clinical seizures.

- There is no difference when comparing paediatric and adult CIPA or Heart Rate Variability HF%

- There is no difference in "scatter" or co-efficient of variation comparing baseline data with sub-clinical data for total, lateralised or generalised sub-clinical seizures.

Chapter 20

Methodology

3.2.1 Video-EEG/ECG/SAO2 telemetry.

Sub-clinical electroencephalographic seizures were captured and identified on XLTEK videotelemetry equipment from the original study group data (Ethical approval LREC/2003/6/22). Video enhancement was used to ensure that there were no clinical manifestations accompanying the sub-clinical seizures and all patients were lying in a recumbent position. Twenty-three silver silver-chloride electrodes including surface sphenoidal were applied to the patient's scalp in accordance to the international 10:20 electrode placement system. Conductive gel filled each electrode with skin impedance below 10 kilo-ohms. Modified lead II ECG, oxygen saturation and integrated video were recorded simultaneously with the electrographic signals. XLTEK sampling rate for ECG signal was 500Hz with a digital chart speed of 30mm/sec. High frequency filter (low pass) was 150Hz and low frequency filter (high pass/time constant) was 0.5Hz. This bandwidth exceeds the minimum requirements set out by the American Heart Association's recommendations for recording physiological electrocardiographic data (Bailey et al 1990).

3.2.2 NeuroScope and "Counted" BioSignal HRV analysis.

The start of the sample was taken 1 minute prior to the sub-clinical electrographic change to ensure that any cardiac vagal tone changes just prior to sub-clinical seizure onset were not omitted. The end of the sample

was where the sub-clinical seizure ended electrographically and the resting trace was resumed. R-R intervals were counted manually for each sub-clinical seizure duration and a matched baseline count was selected from the same stage 3 or 4 slow wave sleep (Rechtschaffen & Kales 1968, Carskadon & Rechtschaffen 1994) or "N3 or N4" stage as defined by the American Academy of Sleep Medicine (2007) in which the sub-clinical seizure had occurred, for baseline measurements. The baseline matched R-R intervals were compared to data derived to R-R intervals during the sub-clinical seizures. Manual selection of R-R interval sections ensured that the trace was artefact free, void of waking or movement or change in sleep stage and any ectoptic beats could be excluded. All patients were in sinus rhythm throughout. No patients were known to have diabetes or coronary heart disease.

HRV measurements cannot be compared to files of different lengths and therefore individual patients cannot be compared to another. However, the baseline and sub-clinical files per patient can be compared to each other as they are heartbeat matched and act as their own control. Total patient baseline and sub-clinical files can also be compared, as they are summated matched data for baseline compared to sub-clinical data.

The data used for the CIPA analysis was then converted from Excel spreadsheets into Text (MSDOS) files and then imported into BioSignal Analysis software. Identical R-R data used in the CIPA analysis was therefore used in the counted HRV analysis. Categories of High Frequency (HF, representing the parasympathetic component of heart rate variability analysis) and R-R interval analysis compared total sub-clinical data with total baseline data using Minitab version 14. Skewed distribution of total data

meant that nonparametric analysis was required using Wilcoxon two sample testing. Comparisons of baseline and sub-clinical data were also analysed in terms of hemisphere laterality and generalised sub-clinical seizures.

Coefficient of variation was calculated for grouped data to determine scatter of HF data. HF% data was interpreted from the BioSignal software and displayed with limits of agreement calculated using Bland & Altman plots (Bland & Altman 1983, 1986).

The High Frequency (HF%) band of heart rate variability frequency domain analysis is considered to represent cardiac vagal tone. This is the closest equivalent to CIPA in measuring vagal tone. Like CIPA, a decrease in HF% indicates a reduction of cardiac vagal tone resulting in an increase in heart rate and vice versa.

3.2.3 BioSignal 5 minute HRV Analysis

R-R intervals of sub-clinical seizures analysed for 'counted' HRV and CIPA analysis were embedded within a 5 minute epoch of R-R intervals for BioSignal analysis. Matched 5 minute R-R interval baseline studies for each patient were again selected within the same stage of sleep as the sub-clinical seizure for each patient and imported into BioSignal software for comparison to sub-clinical R-R intervals. R-R intervals were manually measured for all 5 minute sub-clinical and baseline studies and entered onto Excel spreadsheets. The spreadsheets were then converted to Text (MSDOS) files and imported into Bio-Signal analysis software.

R-R interval, High Frequency (HF, parasympathetic component) data were analysed for individual and grouped data. Wilcoxon two sample testing was

performed on data with a tailed distribution. Data is displayed and limits of agreement calculated using Bland & Altman plots (Bland & Altman 1983, 1986). Coefficient of Variation was performed to indicate scatter on grouped data. Data is displayed at ± 2 standard deviations.

3.2.4 Multivariate analysis on the effects of Anti-Epileptic Drugs on CIPA

Multivariant analysis on the effects of Anti-Epileptic Drugs was performed on CIPA data derived from patients and analysed in terms of monotherapy, polytherapy and those patients not receiving any anti-epileptic drug (AED). Analysis was performed using One-way ANOVA for comparisons of means in each category, Minitab version 14

3.2.5 Inter & Intra-observer analysis.

Consecutive R-R intervals (n=369) over a selected 5 minutes period were manually measured in a blind controlled trial by a qualified cardiographer (Observer 1) and compared to values measured by myself (Observer 2) from the same selected 5 minutes period. Low Frequency Filter (1.0Hz) and High Frequency Filter (70Hz) settings were the same and the gain sensitivity was 50uv/mm and the Notch Filter was off on the XLTEK electroencephalographic / electrocardiographic display.

The R-R intervals were listed onto an Excel spreadsheet and matched and unmatched R-R intervals identified and counted. The data was imported into Minitab version 14 and descriptive statistics were performed. The data was also imported into BioSignal software and HRV was analysed from each observer sample and statistical analysis compared.

Bland Altman plots (Bland & Altman 1983, 1986) are plotted to show distribution of differences in observer analysis. Histograms were created to show distribution curves and differences between observer measurements. Boxplots were used to demonstrate distribution of R-R interval measurements for each observer with whisker outlier limits. Paired t testing was appropriate for this data with normal distribution. A Kappa statistic could not be used in this analysis as R-R intervals are continuous data and there is no 'normal' value to test against for observer agreement.

3.2.6 Statistical analysis.

Statistical analyses compared total sub-clinical CIPA with total baseline CIPA data using Minitab version 14. Tailed distribution of total data meant that nonparametric analysis was required using Wilcoxon paired sample testing. Comparisons of data were also analysed in terms of hemisphere laterality of sub-clinical seizures and generalised sub-clinical seizures. Mean CIPA were calculated for each group to allow for data comparison with BioSignal HF% HRV. Bland & Altman plots (Bland & Altman 1983, 1986) are used to display limits of agreement to give a range of results in each area of analysis. Data is described to ± 2 standard deviations. One-way ANOVA is applied to test variance of data within individuals and between individuals. Bonferroni correction is applied for multiple measurements of repeated sub-clinical seizures in the same patient.

Chapter 21: Results

3.3.1 Patient Demographics

Patient ID	Gender	Age	Epilepsy Classification	Etiology	Anti-epileptic Medication
Patient 1 (study pt 48)	Male	34 years 11 mos	Right Temporal Complex Focal seizures	Nil	Carbamazepine
Patient 2 (study pt 7)	Male	14 years 5 mos	Right Focal seizures	Rassmussen's encephalitis	Sodium valproate, carbamazepine, clobazam
Patient 3 (study pt 24)	Female	27 years 9 mos	Right Temporal Focal seizures	Nil	Nil. New diagnosis. Commenced on AED after videotelemetry
Patient 4 (study pt 20)	Male	20 years 9 mos	Right Temporal lobe Complex focal seizures	Extensive polymicrogyria medial & inferior temporal lobe.	Sodium valproate, Carbamazepine
Patient 5 (study pt 9)	Male	3 years 1 mos	Right Temporal lobe Complex focal seizures	Autistic spectrum disorder	Nil. Commenced on AED after videotelemetry
Patient 6 (study pt 44)	Female	22 years 8 mos	Left Temporal lobe Complex focal seizures	Nil	Nil. Commenced on AED after videotelemetry.
Patient 7 (study pt 22)	Female	11 years 3 mos	Left Temporal lobe Complex focal seizures	Nil.	Carbamazepine
Patient 8 (study pt 17)	Male	49 years 7 mos	Left Temporal lobe Complex focal seizures	Nil	Carbamazepine
Patient 9 (study pt 19)	Female	60 years 3 mos	Left Temporal lobe Complex focal sezures	Nil	Nil. Commenced after videotelemetry
Patient 10 (study pt 38)	Male	5 years 11 mos	Absences, atonic, myoclonic, tonic, GTCS & NCSE	Myoclonic Astatic Epilepsy	PhenobarbitoneTopiramate.
Patient 11 (study pt 18)	Male	5 years 9 mos	Absences, atonic, nocturnal GTCS	Myoclonic Astatic Epilepsy	Sodium valproate, clobazam

Table 1 Section 3 Patient Demographics

3.3.2 Results: R-R interval Analysis prior to NeuroScope Conversion

Thirty-three R-R counted (R-R n=8583) sub-clinical seizures and matched R-R counted (R-R n=8583) baseline measurements were analysed from 11 original study group patients (Table 1) with an age range of 3 years 1 month to 60 years 3 months (mean age 23.1 ± 18.7 years). Six patients were adults (3 male and 3 female, mean age of 35.8 ± 16.0 years) and 5 patients were paediatric (4 male and 1 female, mean age of 7.8 ± 4.8 years). Nine sub-clinical seizures (Sub-clinical R-R intervals n=2688 & Baseline R-R intervals n=2688) were derived from the right temporal lobe (5 patients: 3 adults; 3 seizures & 2 paediatrics; 6 seizures) and five sub-clinical seizures (Sub-clinical R-R intervals n=1307 & Baseline R-R intervals n=1307) were derived from the left temporal lobe (4 patients: 3 adults; 3 seizures & 1 paediatric; 2 seizures). Nineteen generalised sub-clinical seizures (Sub-clinical R-R intervals n=4588 & Baseline R-R intervals n=4588) were analysed from two paediatric patients. No changes in oxygen saturation during sub-clinical seizures occurred.

R-R interval analysis of raw input data prior to analysis using the NeuroScope or BioSignal software.

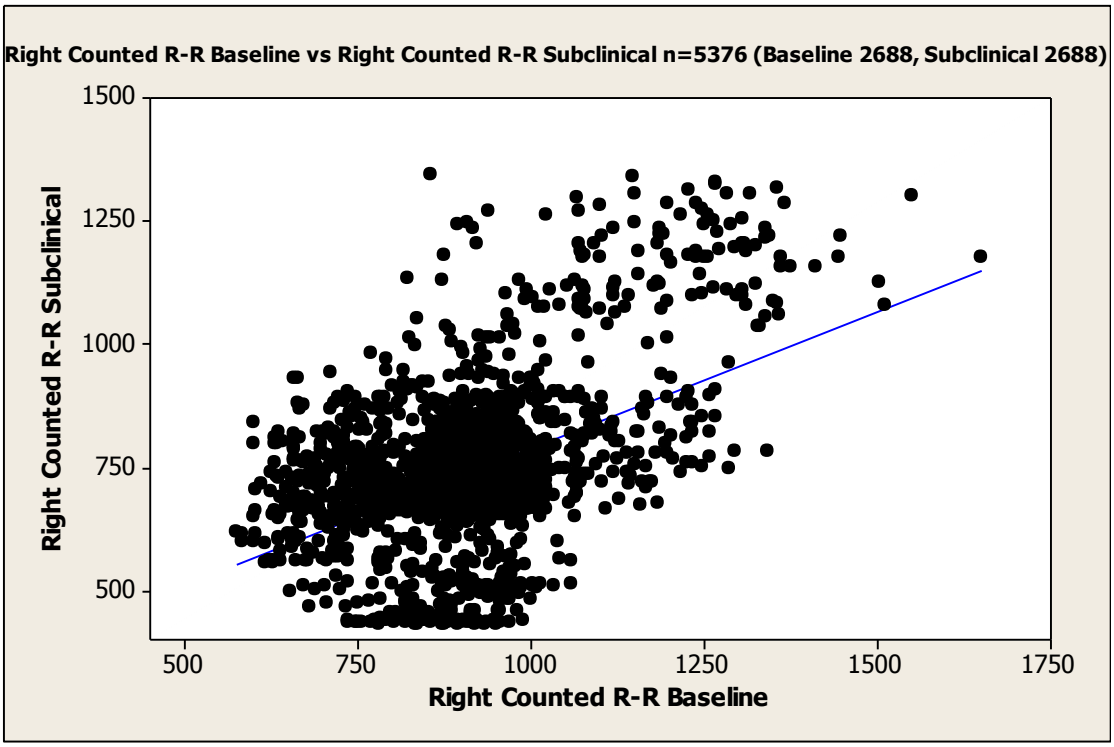


Figure 1 Scatterplot of R-R intervals during right temporal lobe sub-clinical seizures versus matched baseline R-R intervals

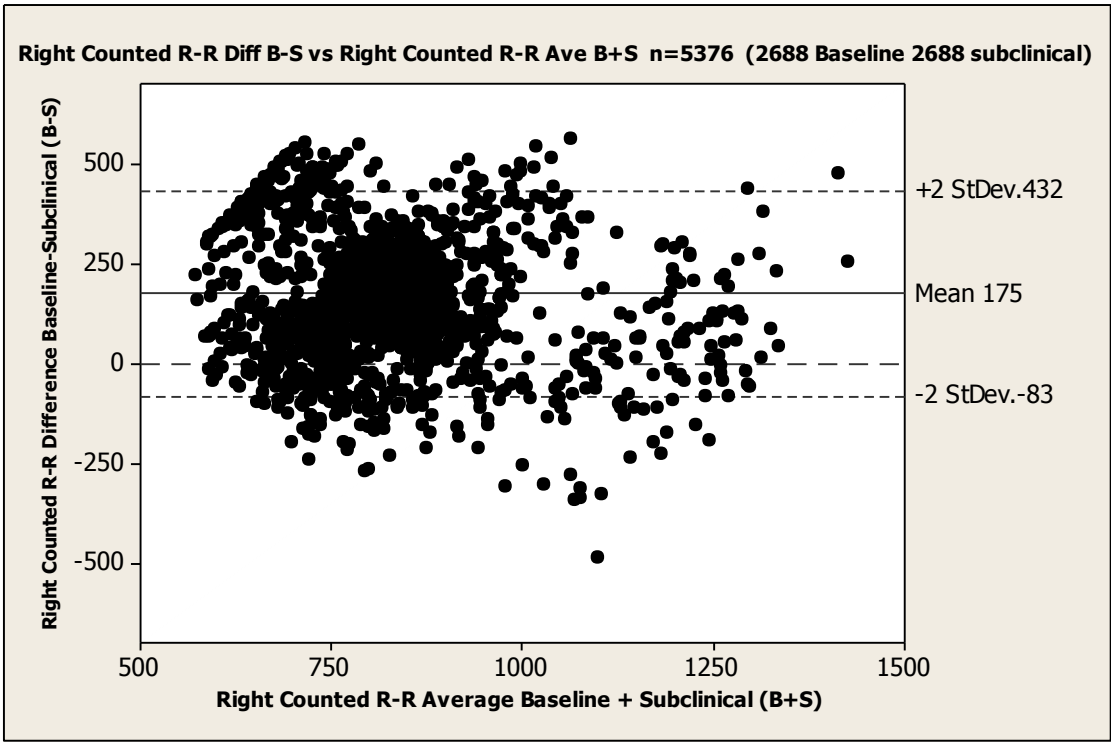


Figure 2 Bland & Altman scatterplot of the difference (Baseline minus sub-clinical) versus average of R-R intervals during right temporal sub-clinical

seizures. Limits of agreement are (–83) and 432.

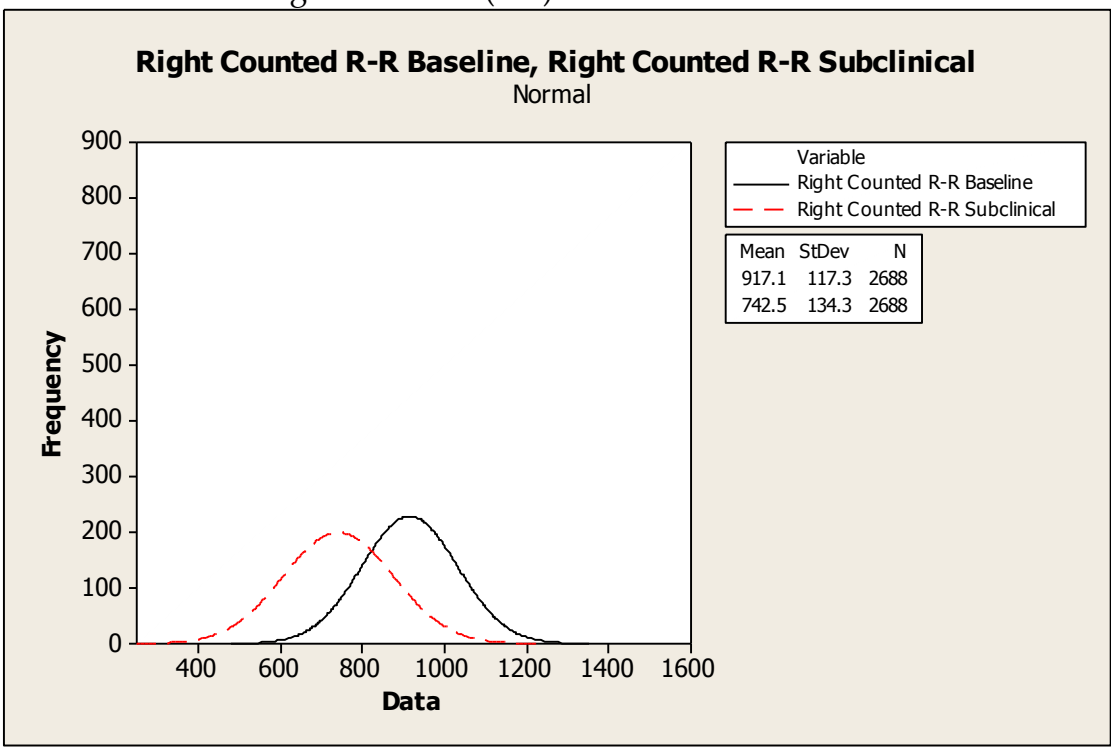


Figure 3 Histogram of Baseline R-R intervals & Sub-clinical R-R intervals during right temporal lobe sub-clinical seizures.

Analysis of R-R intervals during right temporal seizures compared to baseline show a decrease in interval (Figure 3) and therefore indicates an overall increase in heart rate (*p<0.001).* The limits of agreement (–83 and 432) give a range of 515 milliseconds (95% confidence interval), (Figure 2*).*

Patient ID	n	Right Temporal Counted R-R				Difference Median R-R	Wilcoxon Two Sample Test P</=
		Baseline		Sub-clinical			
		R-R	Coef. Variance%	R-R	Coef Variance%		
Patient 1	132	1084	7.8	840	17.4	247	0.158
Patient 2	257	920	5.2	750	6.6	159	0.449
Patient 2	327	925	5.1	758	6.3	164	0.293
Patient 2	408	924	5.2	724	6.4	196	0.308
Patient 2	363	927	5.2	729	5.9	184	0.652
Patient 2	373	923	5.2	696	3.8	224	0.601
Total Patient 2	1728	923	5.2	764	6.7	231	0.109
Patient 3	359	904	8.4	578	29.2	300	0.003
Patient 4	123	1236	11.6	1140	14.5	106	0.705
Patient 5	346	740	12.6	700	12.8	41	0.420
Total Right Temporal	2688	918	12.8	726	18.1	184	0.018

Table 2 Baseline & sub-clinical R-R intervals for patients with right temporal lobe sub-clinical seizures.

During right temporal sub-clinical seizures, R-R intervals show an average shortening from 917.1 to 742.5 milliseconds ($p<0.001$) indicating an increase in heart rate (65.4/min to 80.8/min). A mean difference of 175 ± 257 milliseconds increase with limits of agreement (-83) and 432 milliseconds occurred during right temporal sub-clinical seizures (Figure 2, Table 2).

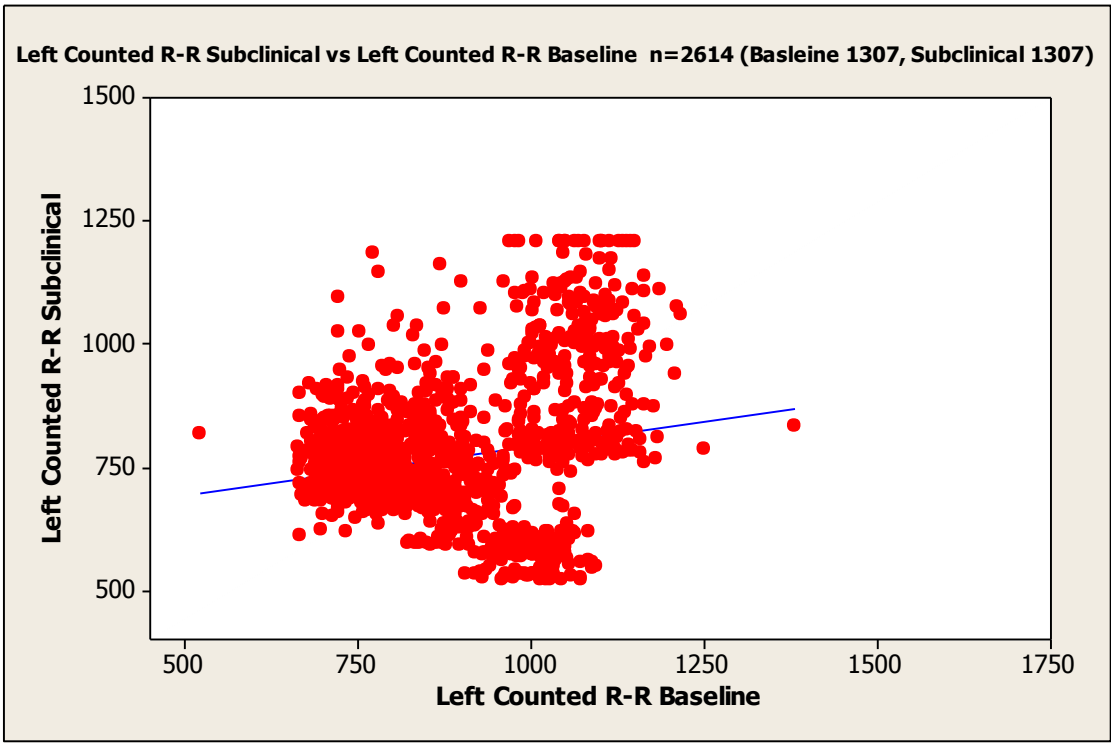


Figure 4 Scatterplot of R-R intervals during left temporal lobe sub-clinical seizures versus matched baseline R-R intervals

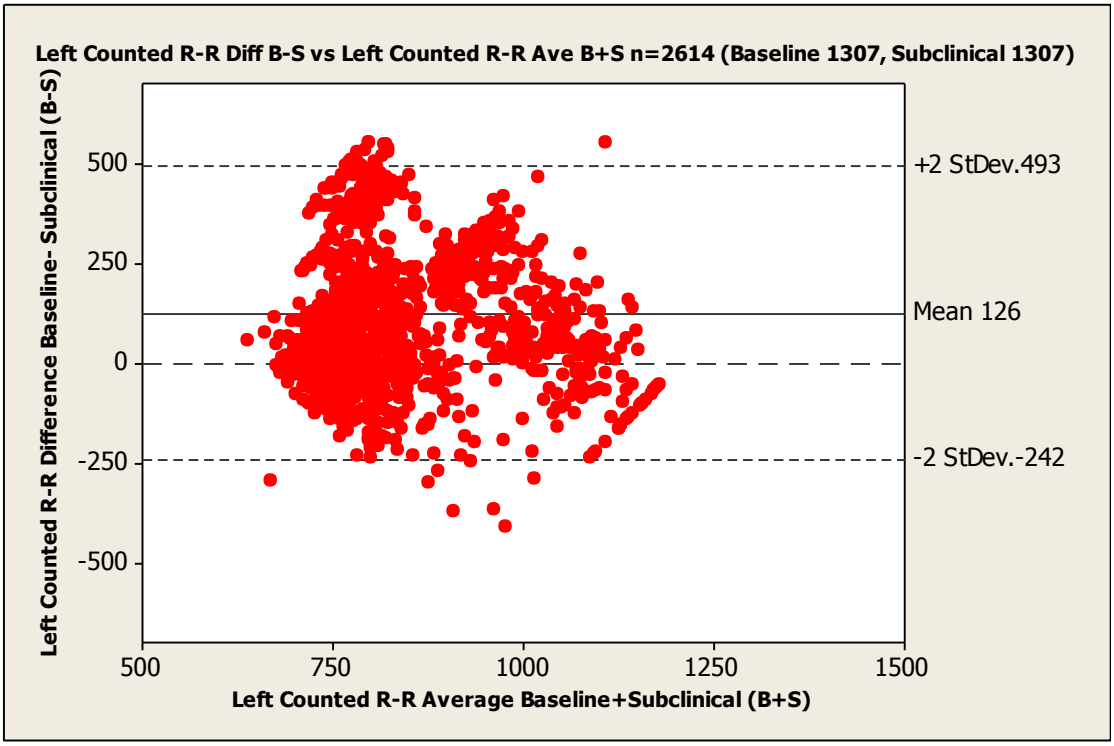


Figure 5 Bland & Altman scatterplot of the difference (Baseline minus sub-clinical) versus average of R-R intervals during right temporal sub-clinical seizures. Limits of agreement are (–242) and 493.

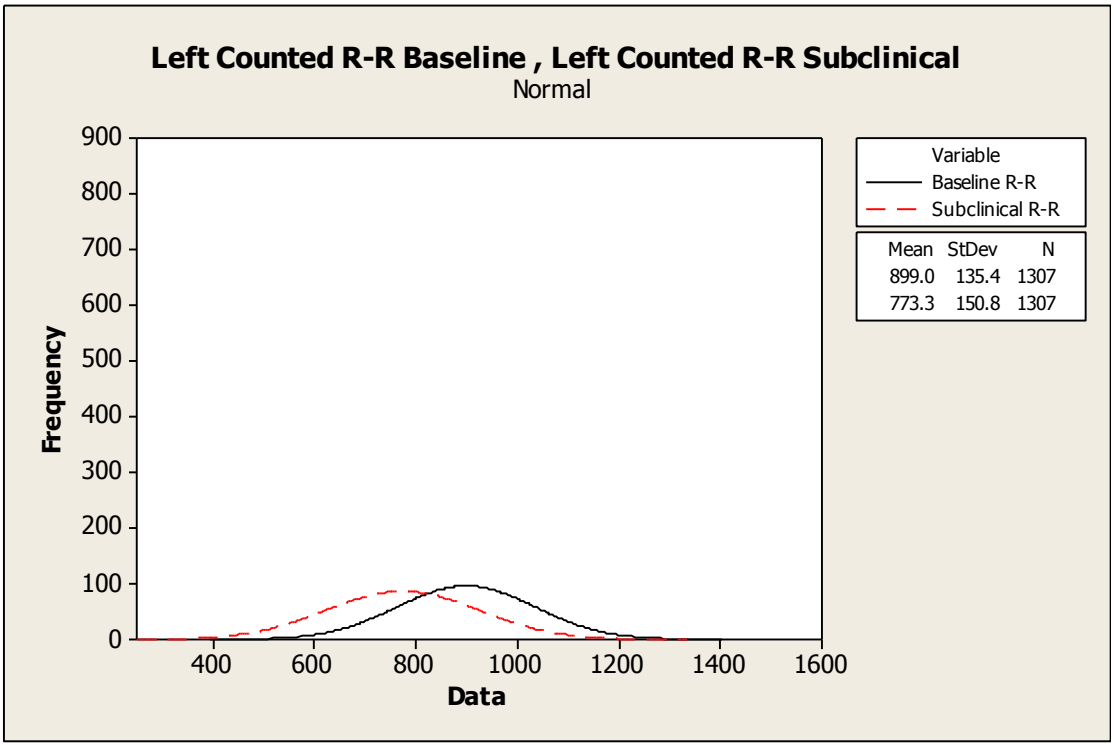


Figure 6 Histogram of Baseline R-R intervals & Sub-clinical R-R intervals during left temporal lobe sub-clinical seizures

The analysis of R-R interval data during left temporal lobe data compared to baseline shows an overall shortening of R-R intervals (Figure 6), (*p<0.001).* The limits of agreement (–242 and 493) give a range of 735 milliseconds (95% confidence interval), (Figure 5).

Patient ID	n	Left Temporal Counted R-R				Diff. Med. R-R	Wilcoxon Two Sample Test P</=
		Baseline		Sub-clinical			
		R-R	Coef. Variance %	R-R	Coef. Variance %		
Patient 6	52	1094	8.7	976	10.4	102	0.852
Patient 7	404	792	9.3	744	8.7	38	0.790
Patient 7	306	780	9.4	776	11.6	3.0	0.908
Total Patient 7	710	786	9.4	759	10.3	23.0	0.732
Patient 8	211	1068	6.7	984	13.8	77.0	0.165
Patient 9	334	992	6.2	586	12.2	399	0.000
Total Left Temporal	1307	899	15.1	773	19.5	87.5	0.000

Table 3 Baseline & sub-clinical R-R intervals for patients with left temporal lobe sub-clinical seizures.

A shortening occurs on average during left temporal sub-clinical seizures from 899.0 to 773.3 milliseconds ($p<0.001$) again indicating an increase in heart rate (66.7/min to 77.6/min). A mean difference of 126 ± 367 milliseconds with limits of agreement (-242) and 493 milliseconds occur during left temporal lobe sub-clinical seizures (Figure 5, Table 2).

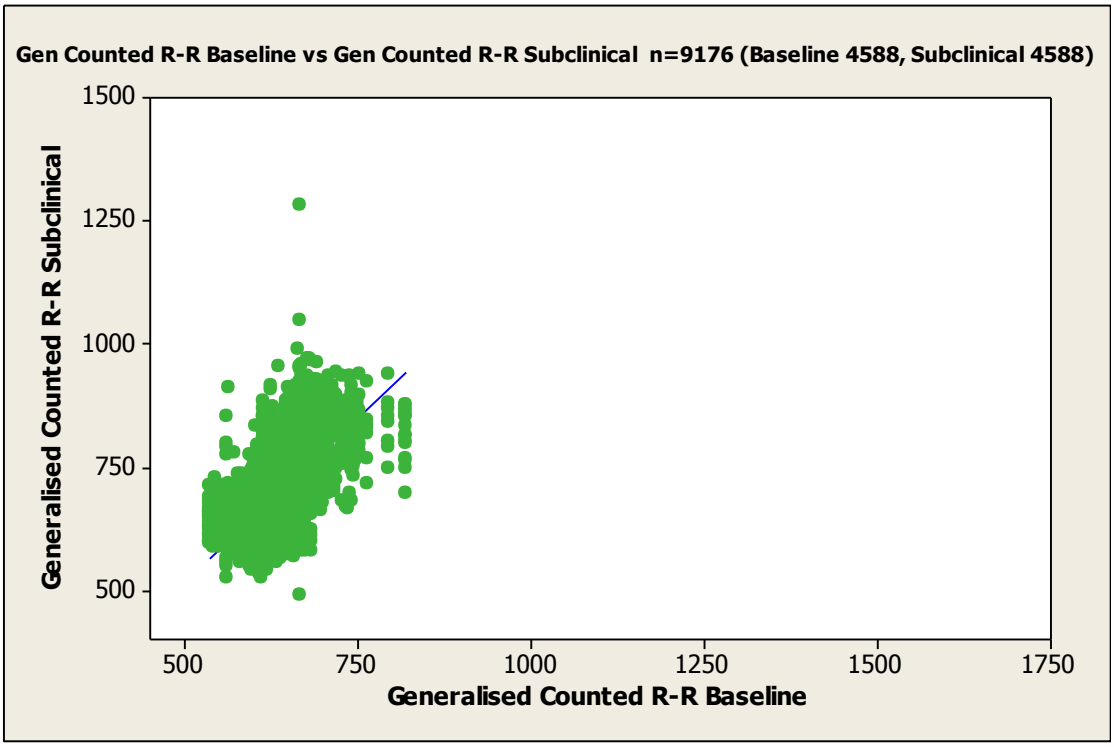


Figure 7 Scatterplot of R-R intervals during generalised sub-clinical seizures versus matched baseline R-R intervals

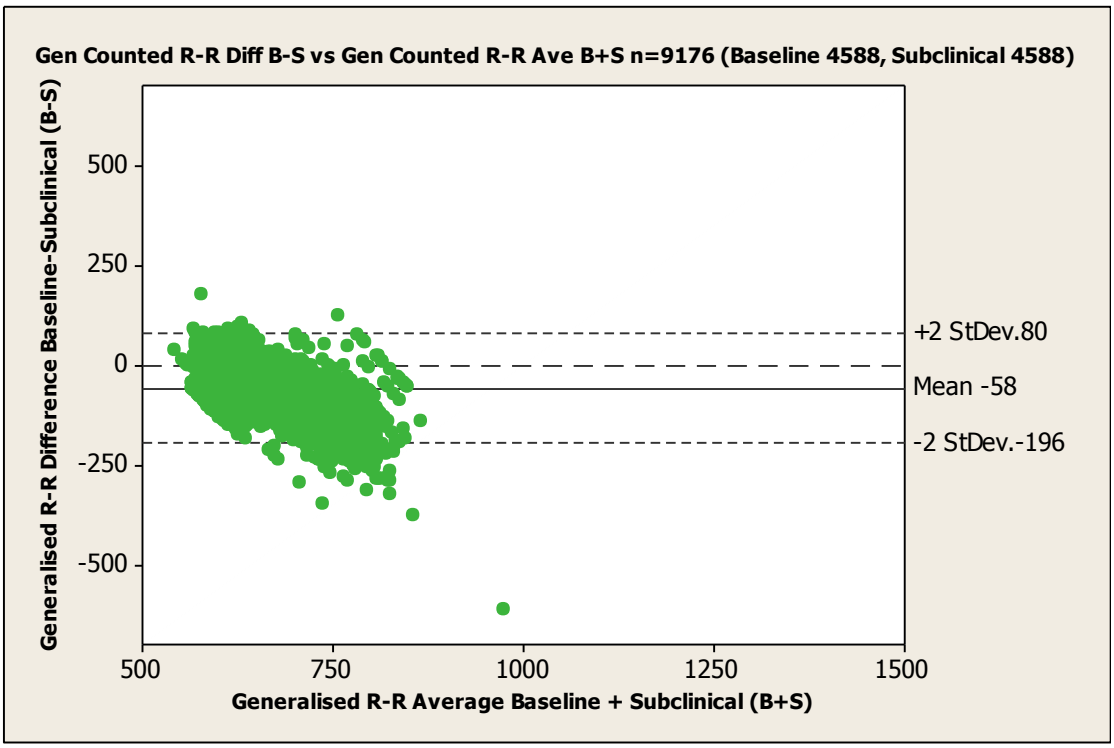


Figure 8 Bland & Altman scatterplot of the difference (Baseline minus sub-clinical) versus average of R-R intervals during generalised sub-clinical seizures. Limits of agreement are (–196) and 80.

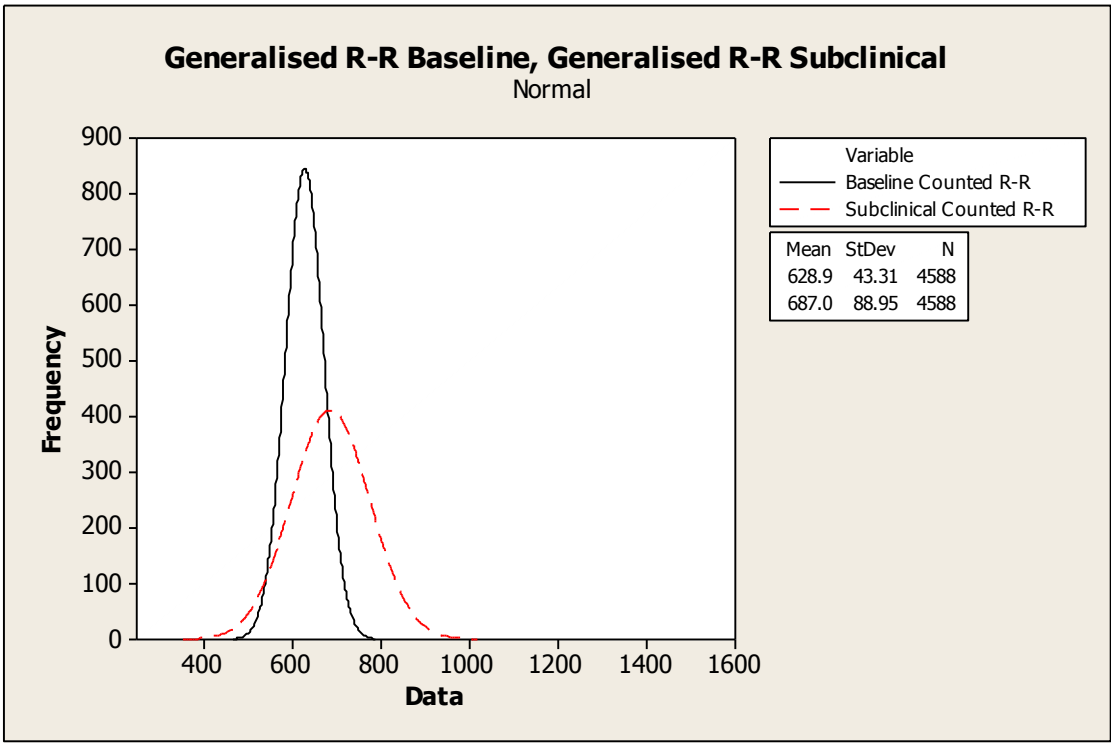


Figure 9 Histogram of Baseline R-R intervals & Sub-clinical R-R intervals during generalised sub-clinical seizures

The analysis of R-R interval data of generalised sub-clinical data compared to baseline shows an overall increase in R-R interval data (Figure 9), ($p<0.001$). The limits of agreement (–196 and 80) give a range of 276 milliseconds (95% confidence interval) during generalised sub-clinical seizures (Figure 8).

Patient ID	n	Generalised Counted R-R				Diff. Median R-R	Wilcoxon Two Sample Test P</=
		Baseline		Subclinical			
		R-R	Coef. Variance%	R-R	Coef. Variance%		
Patient 10	322	616	4.3	614	5.3	0.0	0.332
Patient 10	264	610	4.4	624	4.9	-16.5	0.662
Patient 10	272	610	4.5	615.5	5.5	-8.0	0.355
Patient 10	241	608	4.5	621	6.3	-17.0	0.056
Patient 10	347	615	4.6	637	3.6	-27.0	0.674
Patient 10	340	615	4.6	653	4.8	-41.0	0.839
Patient 10	345	615	4.6	650	6.3	-31.0	0.467
Patient 10	431	618	4.5	655	3.4	-39.0	0.380
Patient 10	270	610	4.4	658	5.0	-47.5	0.069
Patient 10	374	616	4.5	648	4.8	-32.0	0.365
Patient 10	317	613	4.4	651	4.8	-46.0	0.618
Total Patient 10	3523	613	4.5	643	5.5	-29.0	0.020
Patient 11	189	676	4.5	808	5.6	-134	0.377
Patient 11	136	680	4.8	815	8.5	-135	0.093
Patient 11	131	681	4.9	832	6.3	-148	0.728
Patient 11	120	683	5.0	828	7.4	-138.5	0.685
Patient 11	123	682	4.9	844	3.5	-160	0.422
Patient 11	111	686	5.2	843	5.4	-157	0.722
Patient 11	133	680	4.9	860	7.3	-174	0.048
Patient 11	122	681.5	5.0	861	4.9	-171	0.896
Total Patient 11	1065	680	4.9	834	6.6	-150	0.167
Generalised Total	4588	622	6.9	654	12.9	-44	0.000

Table 4 (above) Baseline & sub-clinical R-R intervals for patients with generalised sub-clinical seizures

In contrast with R-R intervals derived during right and left temporal sub-clinical seizures, generalised sub-clinical seizures show a mean increase in R-R interval 628.9 to 687.0 milliseconds ($p<0.001$), indicating a decrease in heart rate (95.4/min to 87.3/min). A mean difference of (–58) ± 138 milliseconds with limits of agreement (-196) and 80msec occurred during generalised sub-clinical seizures (Figure 8, Table 2).

Counted R-R Interval Descriptive Data	n	Baseline R-R	n	Sub-clinical R-R
Right Temporal Mean R-R	2688	917.1	2688	742.5
Left Temporal Mean R-R	1307	899.0	1307	773.3
Generalised Mean R-R	4588	628.9	4588	686.9
Right Temporal Standard Deviation R-R	2688	117.3	2688	134.3
Left Temporal Standard Deviation R-R	1307	135.4	1307	150.8
Generalised Standard Deviation R-R	4588	43.3	4588	88.9
Right Temporal Coefficient of Variation%	2688	12.8	2688	18.1
Left Temporal Coefficient of Variation%	1307	15.1	1307	19.5
Generalised Coefficient of Variation%	4588	6.89	4588	12.95

Table 5 Descriptive statistics for Baseline and Sub-clinical R-R during right temporal, left temporal lobe and generalised sub-clinical seizures

R-R interval analysis shows a statistically significant difference between baseline and sub-clinical data ($p<0.001$), (Figures 3, 6 & 9). Generalised sub-clinical seizures demonstrate a much tighter co-efficient of variation of R-R interval data despite having a much larger pool of data (n=9176) compared to right temporal data (n=5376) and left temporal data (n=2614), (Table 2). The co-efficient of data reflects the amount of "scatter" of data and generalised baseline data has coefficient of data (6.9) which is half or less than half of that seen during right temporal baseline data (12.8) and left temporal baseline data (15.1). All data shows an overall increase in coefficient of variation during sub-clinical seizures compared to baseline measurement but generalised data still remains much tighter with an average value of 12.9 compared to right temporal sub-clinical seizures (18.1) and left temporal sub-clinical seizures (19.5).

3.3.3 NeuroScope Results: Total Sub-clinical Seizures

Patient ID	Baseline CIPA				Sub-clinical CIPA				Event (sec)	Wilcoxon $p</=$
	n	Mean CIPA	Median CIPA	Mean HR	n	Mean CIPA	Median CIPA	Mean HR		
Pt 1	132	14.6	14.6	55.7	132	7.8	8.0	71.2	146	0.032
Pt 2	257	10.4	10.4	65.8	257	8.5	8.6	80.2	259	0.074
Pt 2	327	10.7	10.9	65.3	327	9.7	9.2	79.0	232	0.094
Pt 2	408	10.8	10.8	65.2	408	8.7	8.5	82.1	202	0.001
Pt 2	363	10.9	10.9	65.2	363	9.0	8.9	81.4	253	0.926
Pt 2	373	10.7	10.7	65.1	373	4.7	4.6	86.3	317	0.017
Pt 3	359	12.0	12.0	67.4	359	4.4	2.3	100.5	269	0.019
Pt 4	123	28.3	24.6	50.0	123	21.2	22.4	55.4	261	0.949
Pt 5	346	17.1	15.8	80.8	346	15.2	16.6	86.8	139	0.002
Pt 6	52	17.7	17.6	56.6	52	15.1	15.9	62.7	313	0.420
Pt7	404	17.8	17.6	75.6	404	12.9	13.2	79.7	159	0.604
Pt 7	306	18.0	17.8	76.0	306	16.9	17.0	76.4	149	0.296
Pt 8	211	16.4	14.8	56.3	211	6.7	6.1	62.6	161	0.152
Pt 9	334	4.9	4.6	61.6	334	1.3	0.9	98.6	218	0.485
Pt 10	322	3.5	3.6	97.7	322	4.0	3.4	97.0	154	0.008
Pt 10	264	3.3	3.5	99.1	264	4.1	3.8	96.0	109	0.235
Pt 10	272	3.3	3.5	98.9	272	4.0	3.7	97.1	108	0.280
Pt 10	241	3.3	3.5	99.3	241	4.9	4.3	95.4	98	0.004
Pt 10	347	3.4	3.6	98.0	347	3.3	2.7	93.8	104	0.000
Pt 10	340	3.4	3.6	98.1	340	4.3	3.4	91.6	93	0.013
Pt 10	345	3.4	3.6	98.0	345	4.1	4.0	93.0	114	0.190
Pt 10	431	3.6	3.7	97.4	431	3.0	2.2	91.1	103	0.000
Pt 10	270	3.3	3.5	99.0	270	4.0	3.4	90.8	199	0.629
Pt 10	374	3.5	3.6	97.8	374	3.2	2.6	92.5	234	0.000
Pt 10	317	3.4	3.6	98.4	317	3.9	3.4	91.2	168	0.256
Pt 11	189	4.5	3.7	88.1	189	8.1	7.7	74.2	157	0.482
Pt 11	136	4.7	3.6	87.4	136	9.0	8.9	75.1	225	0.971
Pt 11	131	4.8	3.7	87.3	131	8.8	7.9	72.8	223	0.424
Pt 11	120	4.9	4.0	87.2	120	7.8	6.5	72.4	224	0.721
Pt 11	123	4.9	3.9	87.2	123	6.4	6.5	71.1	340	0.052
Pt 11	111	5.1	4.1	87.1	111	8.8	7.8	71.5	179	0.660
Pt 11	133	4.8	3.7	87.3	133	9.5	9.6	71.2	243	0.376
Pt 11	122	5.0	3.9	87.2	122	7.2	6.3	70.1	209	0.548
Total Pts (mean)	260	8.2	8.0	81.4	260.1	6.9	7.3	82.2	193	0.001

Table 6 Total Baseline & sub-clinical Cardiac index parasympathetic activity (CIPA) (Wilcoxon Two Sample Test) for all patients.

A decrease in CIPA indicates reduced vagal tone and tends to result in an increase in heart rate and vice versa. CIPA alters during sub-clinical seizures compared to baseline data (*p<0.001*) with baseline (n=8583) CIPA 8.2 ± 6.3 decreasing to 6.9 ± 5.1 for total sub-clinical data (n=8583), (Table 6).

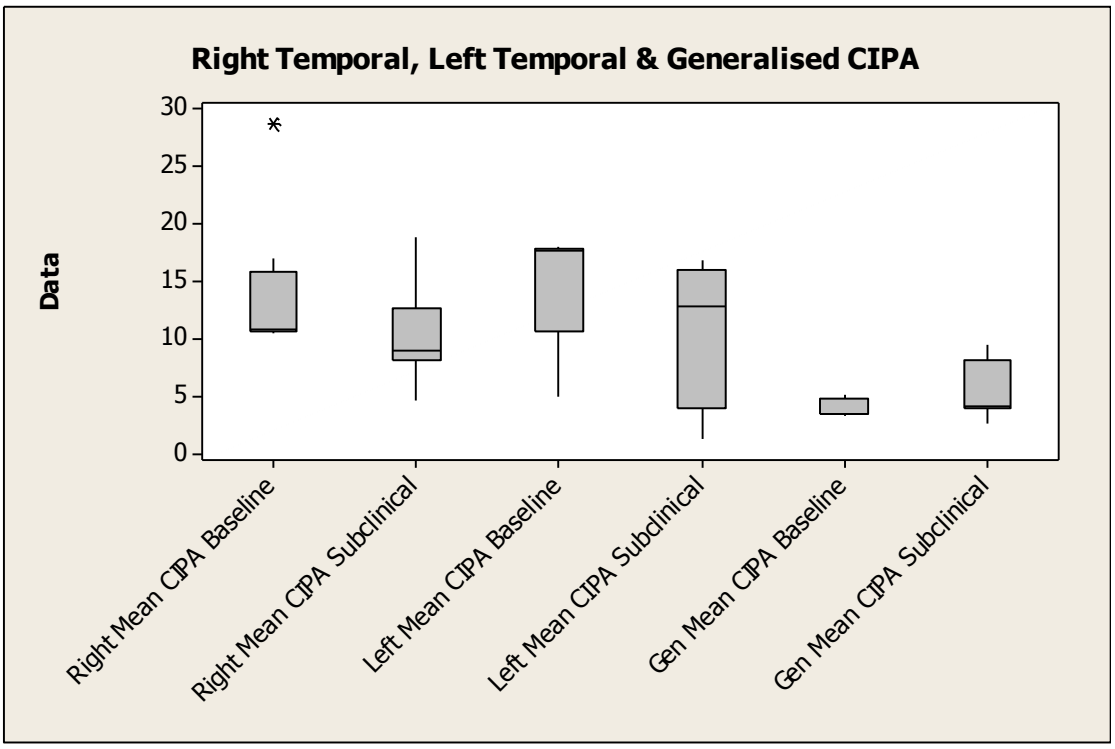


Figure 10 Boxplot of Mean CIPA baseline & sub-clinical for right temporal, left temporal and generalised sub-clinical seizures.

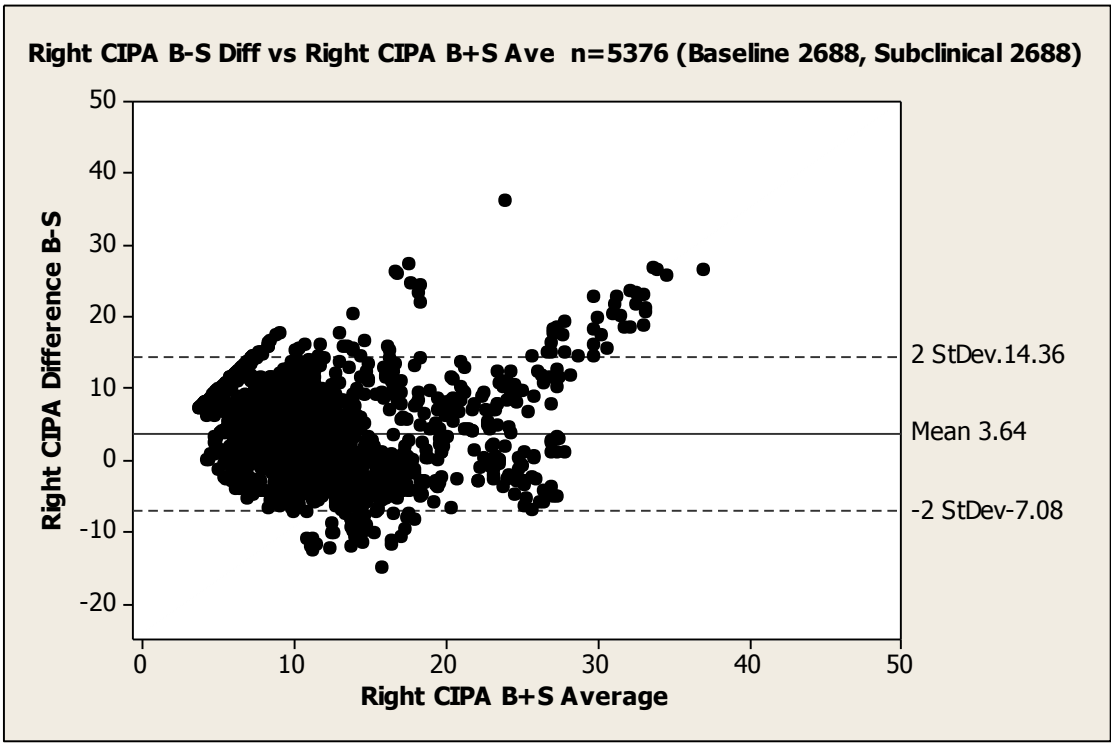


Figure 11 Bland & Altman scatterplot of the difference (Baseline minus sub-clinical) versus average of CIPA during right temporal sub-clinical seizures.
Limits of Agreement are (–7.00) and 14.3

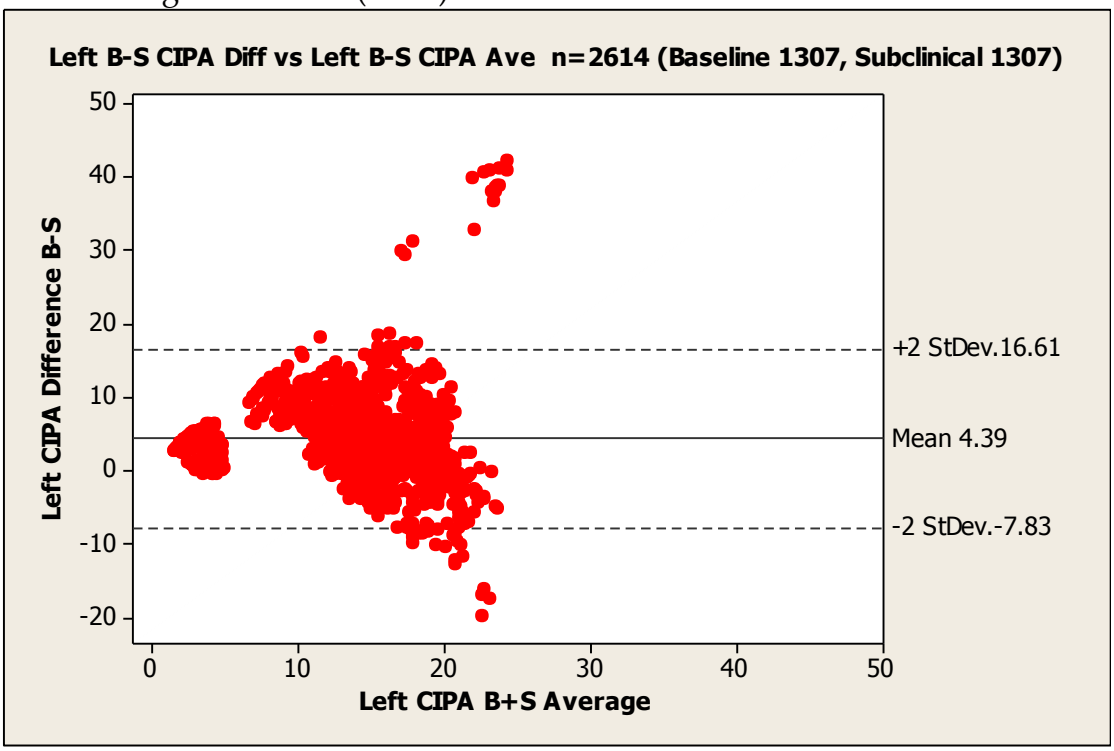


Figure 12 Bland & Altman scatterplot of the difference (Baseline minus sub-clinical) versus average of CIPA during left temporal sub-clinical seizures. Limits of Agreement are (–7.8) and 16.6.

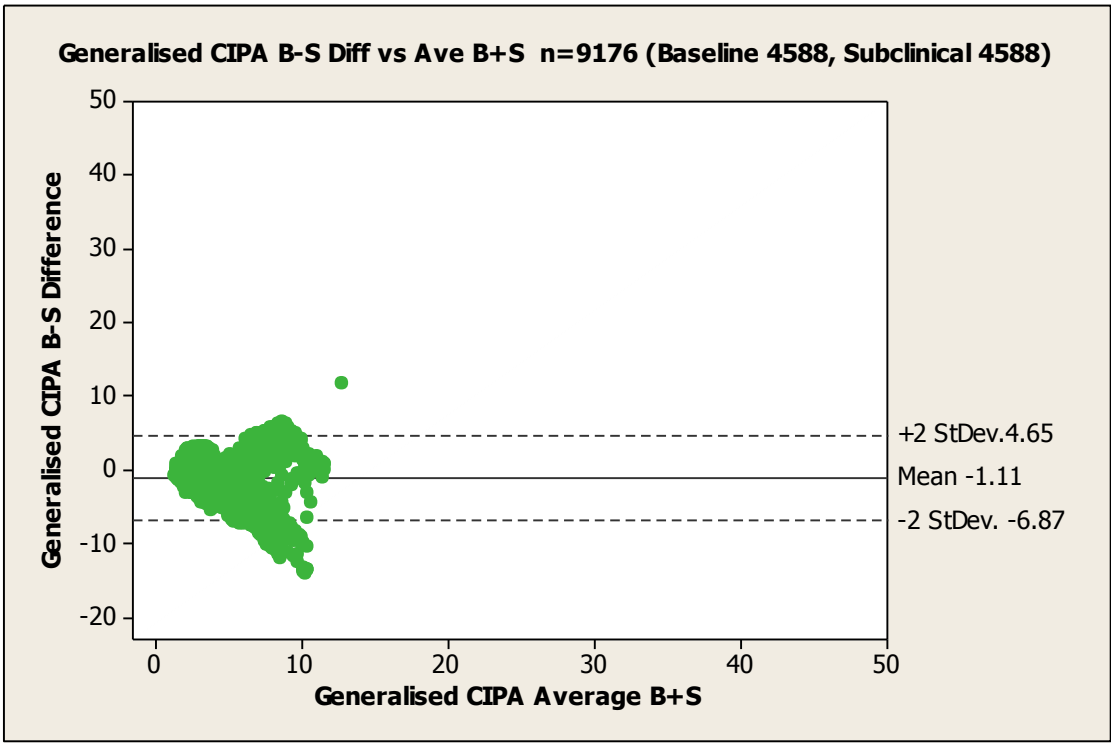


Figure 13 Bland & Altman scatterplot of the difference (Baseline minus sub-clinical) versus average of CIPA during generalised sub-clinical seizures Limits of Agreement are (–6.8) and 4.6.

Sub-clinical seizures arising from the right temporal lobe have a mean difference of 3.64 ± 10.72 with limits of agreement (-7), 14.3 (range of 21.3). (Figure 11*)*.This is fairly similar to left temporal lobe data mean difference 4.39 ± 12.22 with limits of agreement (-7.8), 16.6 (range 24.4), (Figure 12). Generalised data shows a mean difference of (-1.11) ± 5.76 with limits of agreement (-6.8), 4.6 (range 11.4), (Figure 13).

(Total CIPA for Right, Left and Generalised data exceeds Minitab limit and cannot be graphed).

Patient ID	n	Mean Baseline CIPA			Mean Sub-clinical CIPA		
		Mean	St. Dev	Coef Var%	Mean	St Dev	Coef Var%
Pt 1	132	14.7	2.2	15.0	7.8	2.7	33.8
Pt 2	257	10.4	2.1	20.6	8.5	1.8	20.7
Pt 2	327	10.8	2.1	19.4	9.7	2.7	27.9
Pt 2	408	10.8	2.1	19.0	8.7	2.8	31.7
Pt 2	363	10.9	2.3	20.7	9.0	2.3	25.5
Pt 2	373	10.7	2.2	20.5	4.7	1.2	26.1
Pt 3	359	12.0	2.7	22.7	4.4	5.1	115.6
Pt 4	123	28.3	8.8	31.0	21.2	5.7	27.1
Pt 5	346	17.1	6.0	34.9	15.2	4.8	31.7
Pt 6	52	17.7	2.5	14.2	15.2	4.7	31.3
Pt7	404	17.8	3.2	18.2	12.9	2.9	22.9
Pt 7	306	18.0	3.0	16.9	16.9	5.4	32.0
Pt 8	211	16.4	7.2	44.0	6.7	3.5	51.2
Pt 9	334	4.9	2.5	51.8	1.3	1.1	86.6
Pt 10	322	3.5	0.8	23.3	4.0	2.2	55.8
Pt 10	264	3.3	1.0	29.0	4.2	1.5	35.4
Pt 10	272	3.3	0.9	28.6	4.0	1.3	32.7
Pt 10	241	3.3	1.0	30.0	4.9	2.1	43.4
Pt 10	347	3.4	0.9	25.6	3.3	1.6	47.5
Pt 10	340	3.4	0.9	25.8	4.3	2.5	57.9
Pt 10	345	3.4	0.9	25.6	4.1	1.7	40.6
Pt 10	431	3.6	0.9	24.9	3.0	2.1	69.3
Pt 10	270	3.3	1.0	28.7	4.0	2.4	59.6
Pt 10	374	3.5	0.9	25.2	3.2	1.6	51.0
Pt 10	317	3.4	0.9	26.6	4.0	2.2	55.4
Pt 11	169	4.5	2.1	47.7	8.1	2.4	29.8
Pt 11	136	4.7	2.5	52.2	9.0	2.0	21.8
Pt 11	131	4.8	2.5	51.9	8.8	2.5	28.9
Pt 11	120	4.9	2.5	51.1	7.8	2.6	33.9
Pt 11	123	4.9	2.5	51.4	6.4	0.9	14.6
Pt 11	111	5.1	2.6	50.4	8.8	3.1	35.4
Pt 11	133	4.8	2.5	52.0	9.5	1.5	15.6
Pt 11	122	5.0	2.8	56.0	7.2	2.7	37.5
Total pts (mean)	259.5	8.4	2.4	32.0	7.6	2.6	40.3

Table 7 Descriptive statistics for baseline & sub-clinical mean CIPA for total sub-clinical seizures and patients.

Mean differences in data are analysed using Bland & Altman plots The Y-axis determines the mean difference, limits of agreement within ± 2 standard deviations (95% confidence intervals) of baseline minus sub-clinical data.

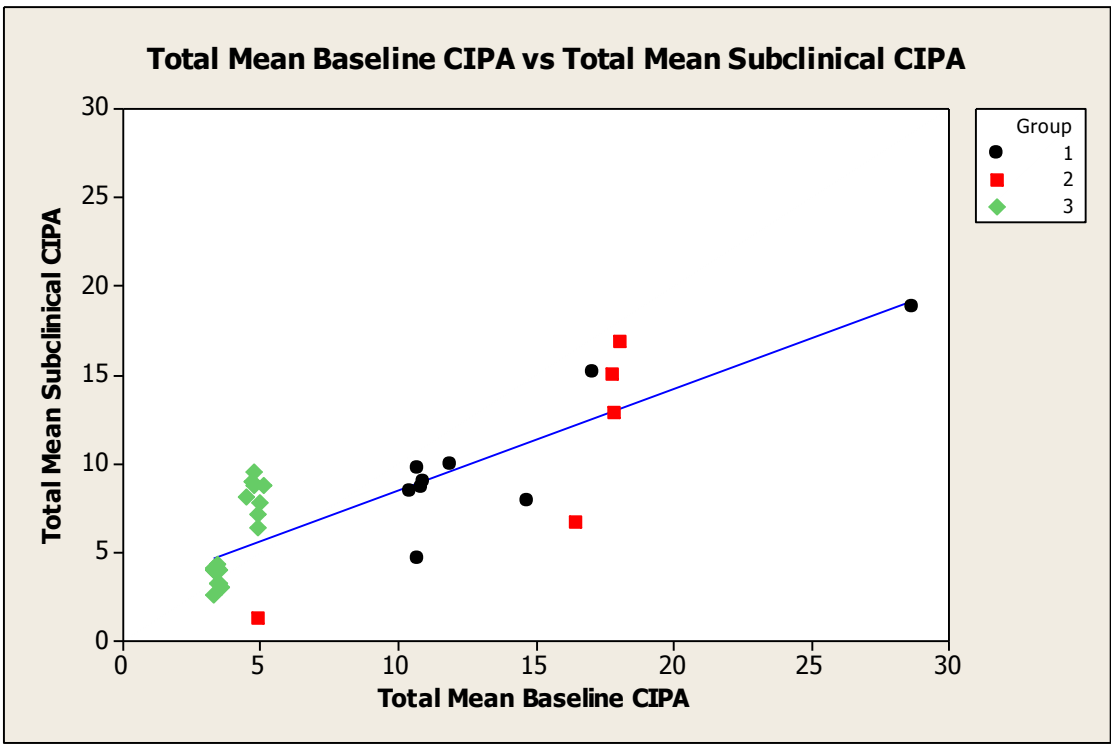


Figure 14 Scatterplot of total mean baseline CIPA versus total mean sub-clinical CIPA

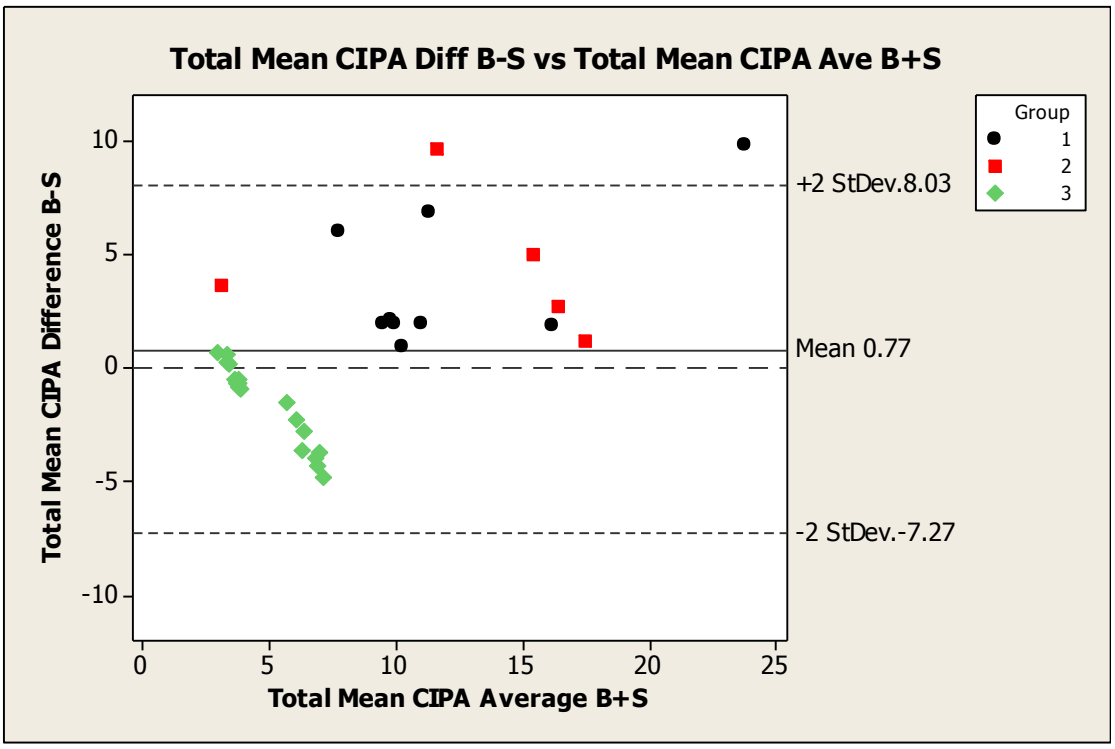


Figure 15 Bland & Altman scatterplot of the difference (Baseline minus

sub-clinical) versus average of Mean CIPA during right temporal[1], left temporal[2] and generalised sub-clinical seizures[3].
Limits of agreement are (–4.78) and 6.82.

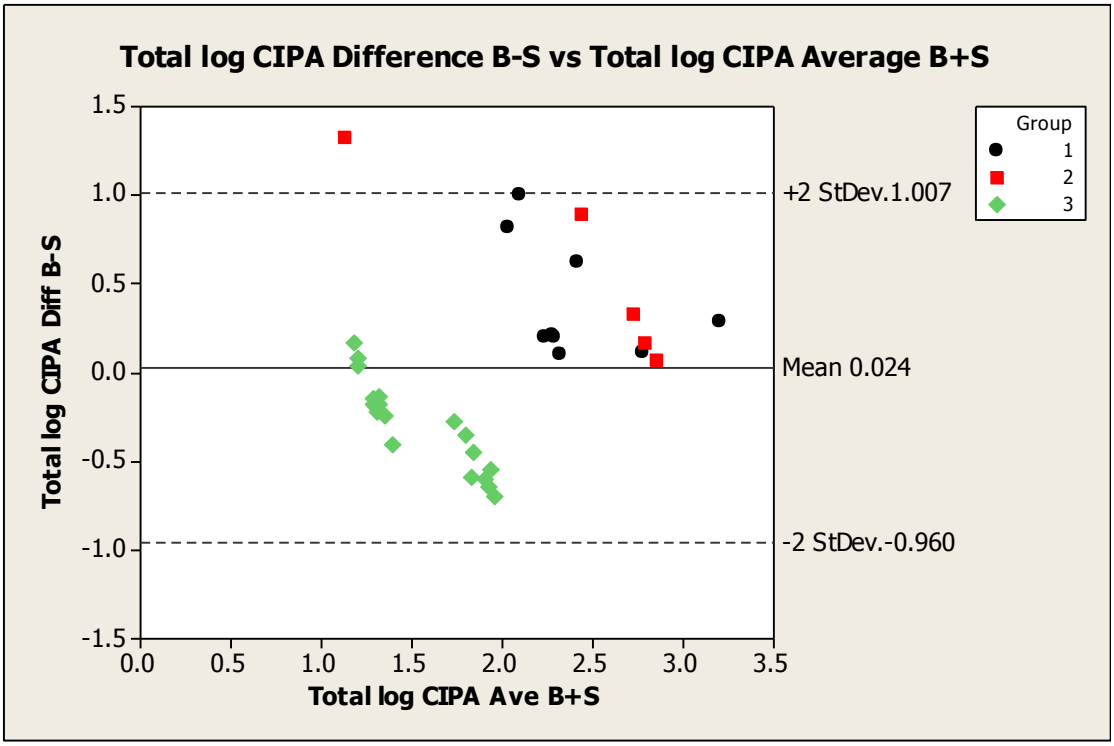


Figure 16 Bland & Altman scatterplot of the difference (Baseline minus sub-clinical) versus average of Mean log CIPA during right temporal, left temporal and generalised sub-clinical seizures.

Limits of agreement of log values are (-0.7) and 1.0 from this Bland & Altman plot. The antilog of these values are 0.5 and 2.7 which indicates that the limits of agreement for 95% data are between 0.5 and 2.7 change in CIPA from mean baseline to mean sub-clinical data for the total group.

Looking at the mean difference for right temporal sub-clinical seizures CIPA difference is 3.7 ± 6.1 with limits of agreement 1.0 and 9.8 (p=0.032). Figure 19 is similar to left temporal sub-clinical seizures CIPA difference 4.4 ± 6.5 with limits of agreement 1.1 and 9.7 (*p=0.855*), (Figure 23, Table 8).

Bland & Altman analysis of differences between baseline CIPA measurements and CIPA derived during right temporal sub-clinical seizures show the limits of agreement of log values 0.1 and 1.0 (Figure 16). The antilog of these values are 1.1 and 2.7 indicating that the limits of agreement for 95% data are between 1.1 and 2.7 change in CIPA from mean baseline to mean sub-clinical data for right temporal sub-clinical seizures. The scatter relationship shows all values are above zero and show a general change in CIPA from baseline to sub-clinical. Generally there is a marked increase in heart rate and a resultant decrease in CIPA as vagal tone withdraws during right temporal sub-clinical seizures.

Bland & Altman analysis of differences between baseline CIPA measurements and CIPA derived during left temporal sub-clinical seizures show the limits of agreement of log values 0.1 and 1.3 (Figure 16).The antilog of these values are 1.1 and 3.8 indicating that the limits of agreement for 95% data are between 1.1 and 3.8 change in CIPA from mean baseline to mean sub-clinical data for left temporal sub-clinical seizures. The distribution of values on the plot shows a general change in CIPA from baseline to sub-clinical. Generally there is an increase in heart rate and a correlated decrease in CIPA as vagal tone decreases during some left temporal sub-clinical seizures.

Bland & Altman analysis of differences between baseline CIPA measurements and CIPA derived during generalised sub-clinical seizures show the limits of agreement of log values (-0.7) and 0.2 (Figure 16). The antilog of these values are 0.5 and 1.2 indicating that the limits of agreement for 95% data are between 0.5 and 1.2 change in CIPA from mean baseline to mean sub-clinical data for generalised sub-clinical data. The plot distribution

shows two distinct areas relating to each of the two patients. Both clusters are mainly below zero indicating that there is a consistent change in CIPA related to generalised sub-clinical seizures. Generally there is a small decrease in heart rate and a relative increase in CIPA as vagal tone increases during generalised sub-clinical seizures.

Statistically, the left temporal sub-clinical data mean difference is not significant because of small data volume but the range of limits of agreement are similar to that of the right temporal sub-clinical data. Generalised mean data has a mean difference of (-1.6) ± 3.5 with limits of agreement are (-7.8) and 0.6 with a smaller range (Figure 27*)* but statistically significant (*p=0.024)*, (Table 8).

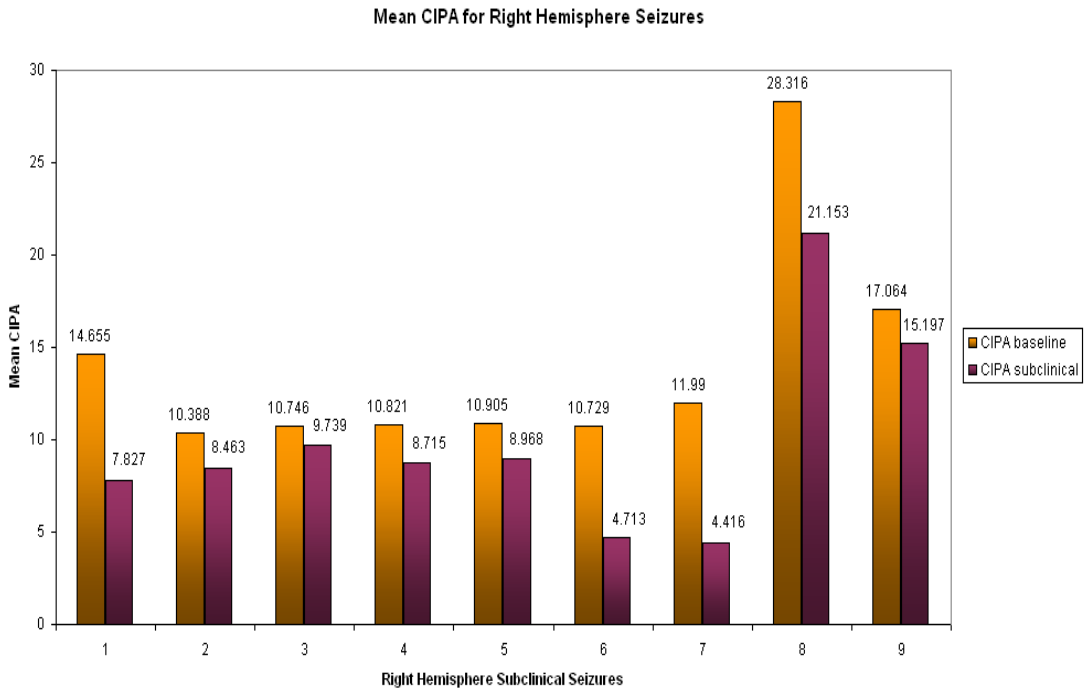


Figure 17 Bar chart of baseline & sub-clinical CIPA for right temporal sub-clinical seizures.

All nine sub-clinical seizures arising from the right temporal lobe indicate a decrease in cardiac vagal tone compared to matched baseline measurements.

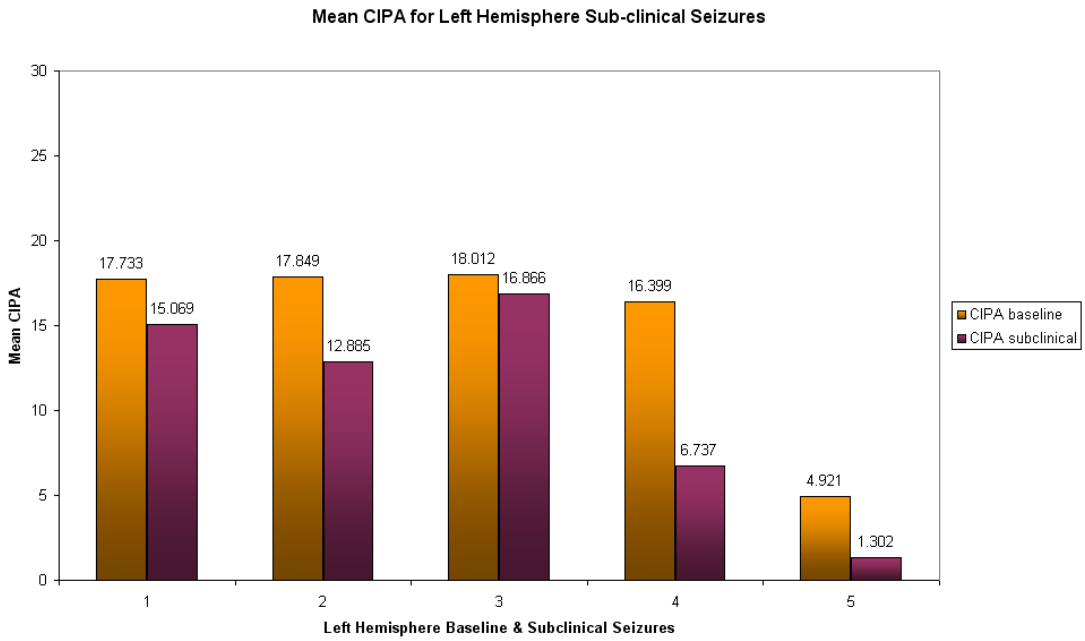


Figure 18 Bar chart of baseline & sub-clinical CIPA for left temporal sub-clinical seizures.

All five sub-clinical seizures arising from the left temporal lobe indicate a decrease in cardiac vagal tone compared to matched baseline measurements.

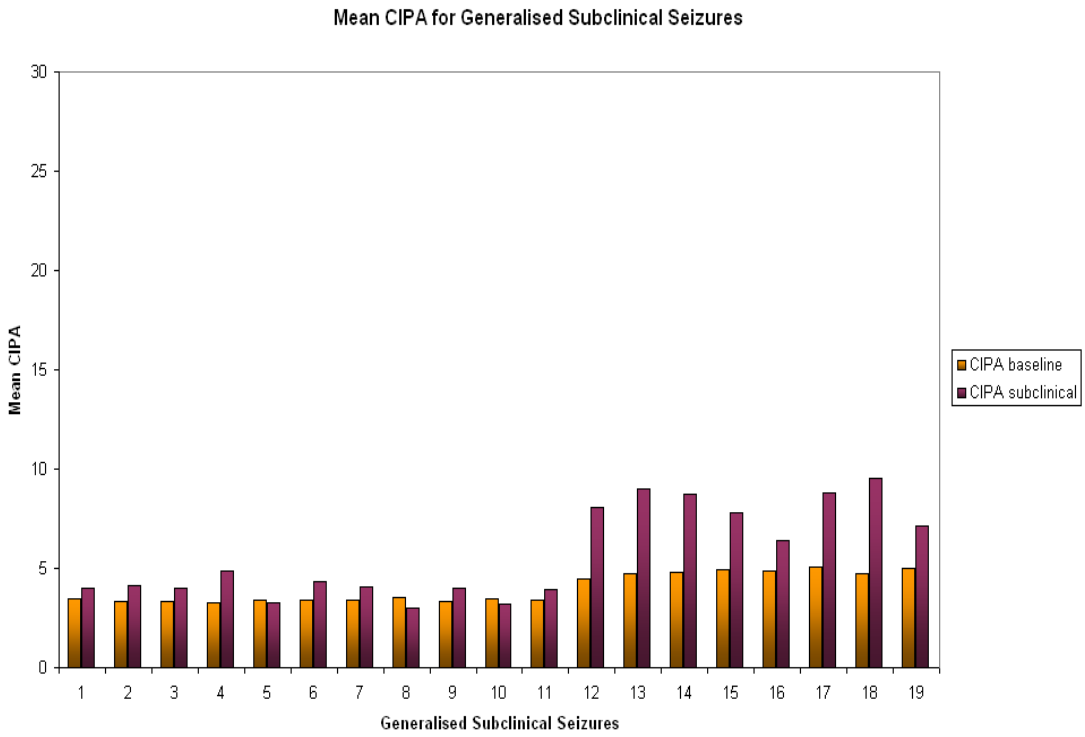


Figure 19 Bar chart of baseline & sub-clinical CIPA for generalised sub-clinical seizures.

Eighty-four percent (16/19) of generalised sub-clinical seizures indicate an increase in cardiac vagal tone compared to matched baseline measurements.

Section Three

Total & Mean CIPA Difference (Baseline minus Sub-clinical)	CIPA n	Mean CIPA Difference Bland & Altman B-S	Lower limit of Agree-ment Bland & Altman B-S	Upper limit of Agree-ment Bland & Altman B-S	Difference from lower to upper B-S of Bland & Altman	Wilcoxon p</=
Total Counted CIPA	8583	Minitab exceeded	Minitab exceeded	Minitab exceeded	Minitab exceeded	Minitab exceeded
Total Mean Counted CIPA	33	0.8	- 4.8	6.8	11.6	0.233
Total Mean Counted log CIPA	33	0.02	0.5	2.7	2.2	0.784
Total Right Counted CIPA	2688	3.6	-7.0	14.3	21.3	0.001
Right Mean Counted CIPA	9	3.7	1.0	9.8	8.8	0.032
Right Mean Counted log CIPA	9	0.4	1.1	2.7	1.6	0.007
Total Left Counted CIPA	1307	4.4	-7.8	16.6	24.4	0.001
Left Mean Counted CIPA	5	4.4	1.2	9.7	8.52	0.855
Left Mean Counted log CIPA	5	0.6	1.1	3.8	2.3	0.082

Total Gen. Counted CIPA	4588	-1.1	-6.8	4.6	11.4	0.001
Gen. Mean Counted CIPA	19	-1.6	-7.8	0.6	8.4	0.024
Gen. Mean Counted log CIPA	19	-0.3	0.5	1.2	0.7	0.001

Table 8 Bland & Altman lower and upper limits of agreement for Total and Mean CIPA & Mean log CIPA for right temporal, left temporal and generalised sub-clinical seizures.

	Baseline CIPA				Sub-clinical CIPA				
	n	Mean CIPA	Median CIPA	Mean *HR*	n	Mean CIPA	Median CIPA	Mean HR	Wilcoxon p</=
Right Temporal CIPA	2688	12.7	11.5	66.4	2688	9.1	8.4	83.3	0.001
Left Temporal CIPA	1307	14.3	15.5	68.2	1307	9.9	10.1	80.3	0.001
Generalised CIPA	4588	3.7	3.6	95.7	4588	4.8	4.0	88.5	0.001
Total CIPA	8583	8.16	4.7	82.3	8583	6.94	5.7	85.6	0.001

Table 9 Total & sub-total baseline CIPA & total & sub-total sub-clinical CIPA (Wilcoxon Paired Sample Test- CIPA Difference).

Sub-clinical seizures arising from the right temporal lobe show a decrease in CIPA (*p<0.001*) from 12.7 ± 5.3 baseline (n=2688) to 9.1 ± 5.4 sub-clinical (n=2688). Similarly, sub-clinical seizures arising from the left temporal lobe also decreased CIPA (*p<0.001*) from baseline 14.3 ± 6.8 (n=1307) to sub-clinical 10.0 ± 6.9 (n=1307). Conversely, generalised sub-clinical seizures indicate increased CIPA (*p<0.001*) from 3.7 ± 1.5 baseline (n=4588) to 4.8 ± 2.8 sub-clinical (n=4588), (Table 9). An increase in CIPA reflects increased vagal tone during generalised sub-clinical seizure electroencephalographic activity and results in decreased heart rate. This result is consistent with that shown in the R-R analysis (Tables 2, 3 & 4).

3.3.4 Standard Deviation of CIPA

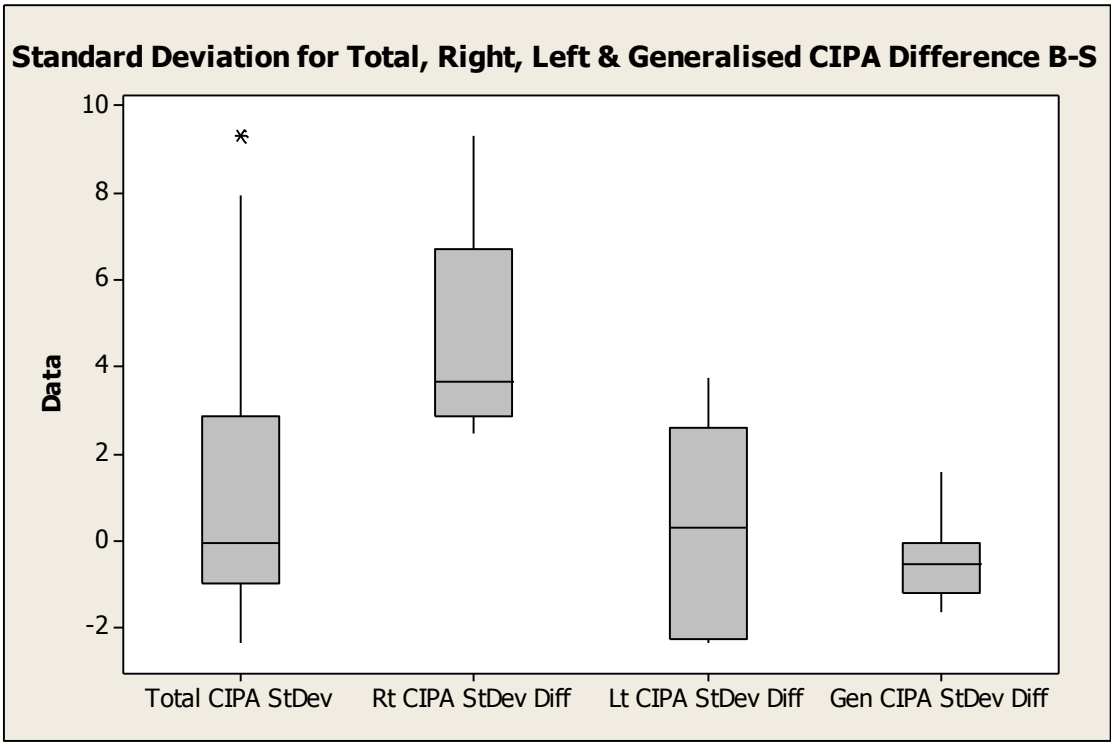


Figure 20 Boxplot of standard deviation of CIPA for total, right temporal, left temporal and generalised sub-clinical seizures.

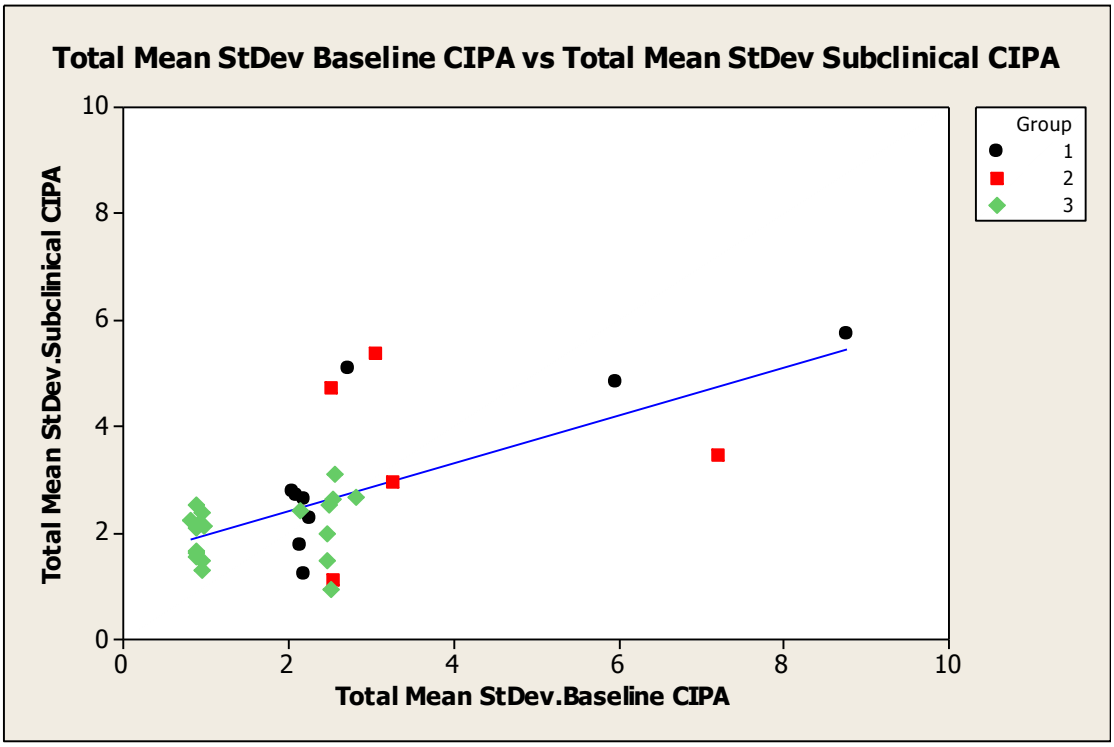


Figure 21 Scatterplot of baseline mean CIPA standard deviation versus mean sub-clinical CIPA standard deviation for right temporal, left temporal and generalised sub-clinical seizures.

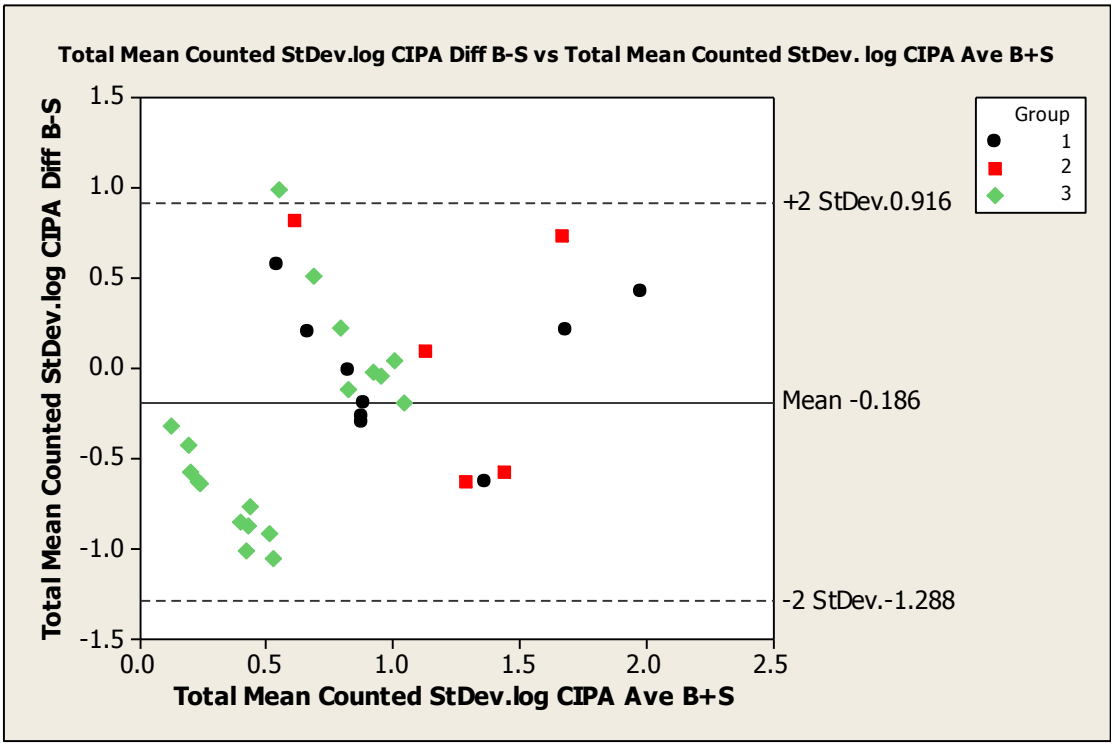


Figure 22 Bland & Altman scatterplot of mean CIPA standard deviation difference (baseline minus sub-clinical) versus average for right temporal, left temporal and generalised sub-clinical seizures.

Limits of agreement of log values for total data are 0.8 and 1.0 from the Bland & Altman plot. The antilog of these values are 0.4 and 2.3 indicating that the limits of agreement for 95% data are between 0.4 and 2.3 change in CIPA standard deviation from mean baseline to mean sub-clinical data for total seizures. Limits of agreement of log values are (-0.6) and 0.6 from CIPA data derived during right temporal sub-clinical seizures. The antilog is 0.5 and 1.8 (range 1.3). Limits of agreement of log values are (-0.6) and 0.8 from CIPA derived during left temporal sub-clinical seizures. The antilog of these values are 0.5 and 2 (range is 1.5) Limits of agreement of log values are (–1.048) and 0.507 from CIPA derived during generalised sub-clinical seizures. The antilogs of these values are 0.4 and 1.7 (range 1.3).

The largest standard deviation difference between baseline and sub-clinical seizures is found in left temporal sub-clinical seizures of 1.726 compared to right temporal sub-clinical seizures standard deviation of 1.261 and generalised sub-clinical seizures standard deviation of 1.31. A possible reason for this could be that standard deviation generally decreases or lessens as the quantity of data increases (Figure 22).

3.3.5 Right Temporal Sub-clinical Seizures

Patient ID	n	Right Temporal Median CIPA		Difference Median CIPA	Wilcoxon Paired Sample Test *p*</=
		Baseline CIPA	Sub-clinical CIPA		
Patient 1	132	14.5	8.0	5.9	0.032
Patient 2	257	10.4	8.6	1.5	0.074
Patient 2	327	10.9	9.2	1.5	0.094
Patient 2	408	10.8	8.5	2.8	0.001
Patient 2	363	10.9	8.9	1.9	0.926
Patient 2	373	10.7	4.6	5.7	0.017
Total Patient 2	1728	10.7	8.0	2.9	0.036
Patient 3	359	12.0	2.3	8.8	0.019
Patient 4	123	24.6	22.4	7.1	0.949
Patient 5	346	15.8	16.6	0.1	0.002
Total Right Temporal	2688	11.5	8.4	3.4	0.001

Table 10 Total & sub-total median baseline minus sub-clinical CIPA for right temporal sub-clinical seizures.

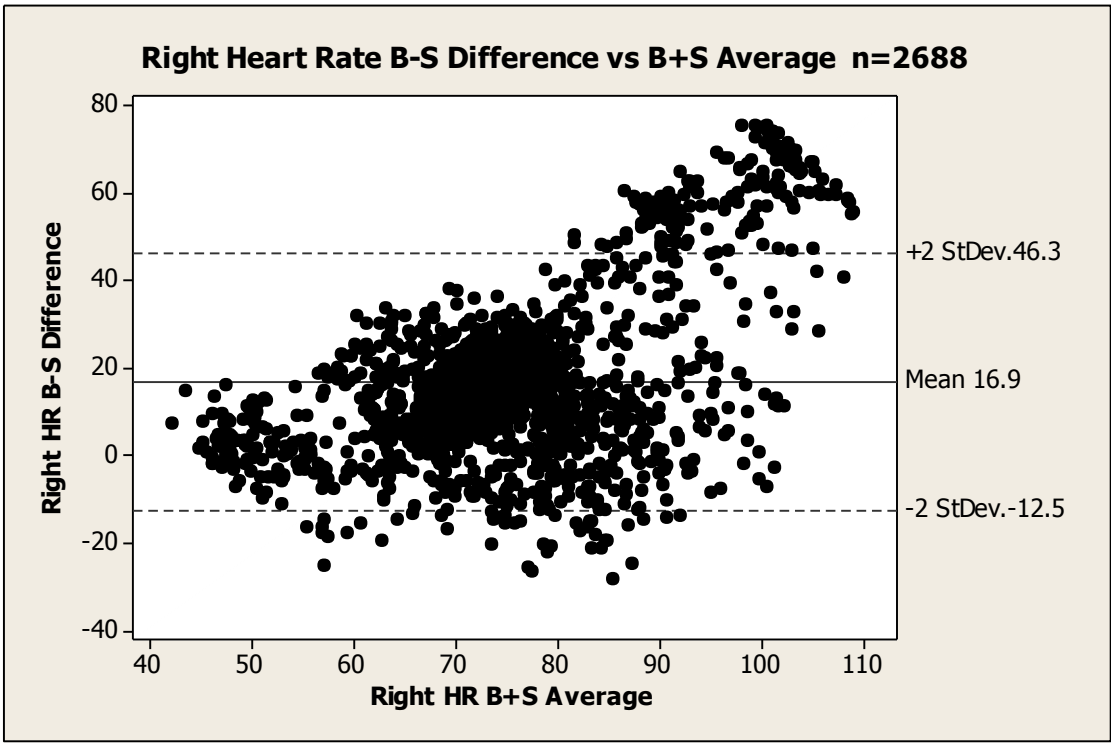


Figure 23 Bland & Altman scatterplot for heart rate difference (baseline minus sub-clinical) versus average for right temporal lobe seizures.
Limits of agreement are 12.4 and 46.1

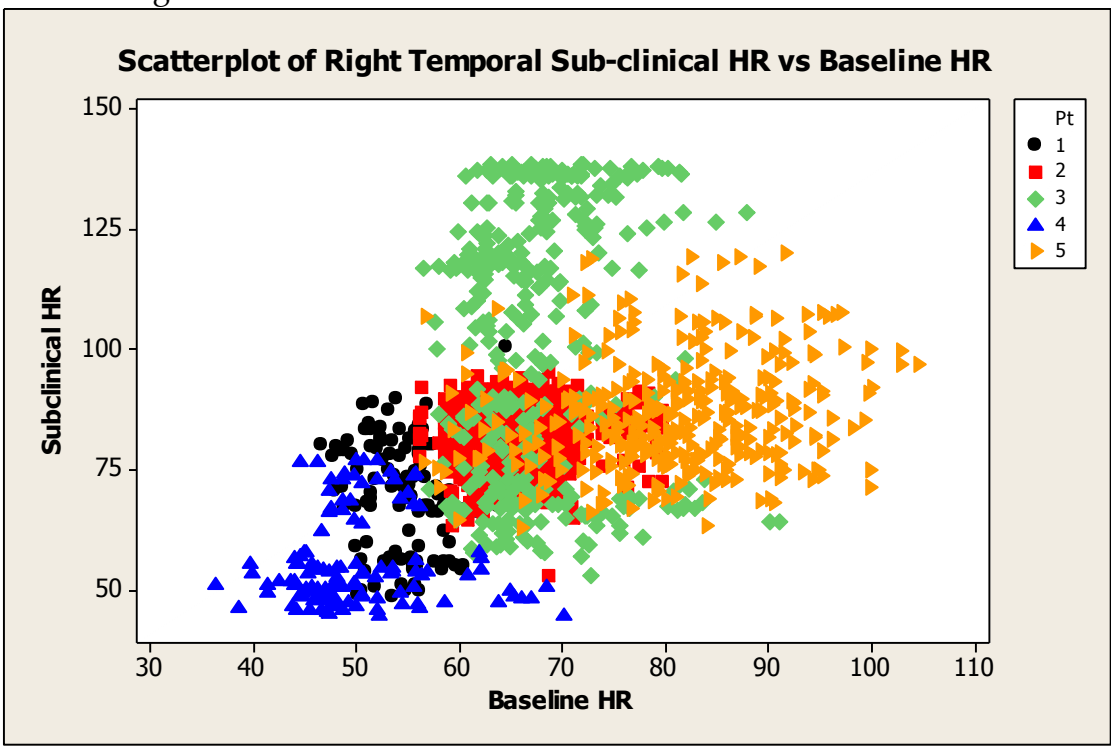


Figure 24 Scatterplot of baseline heart rate versus sub-clinical heart rate during right temporal lobe sub-clinical seizures (patient defined).

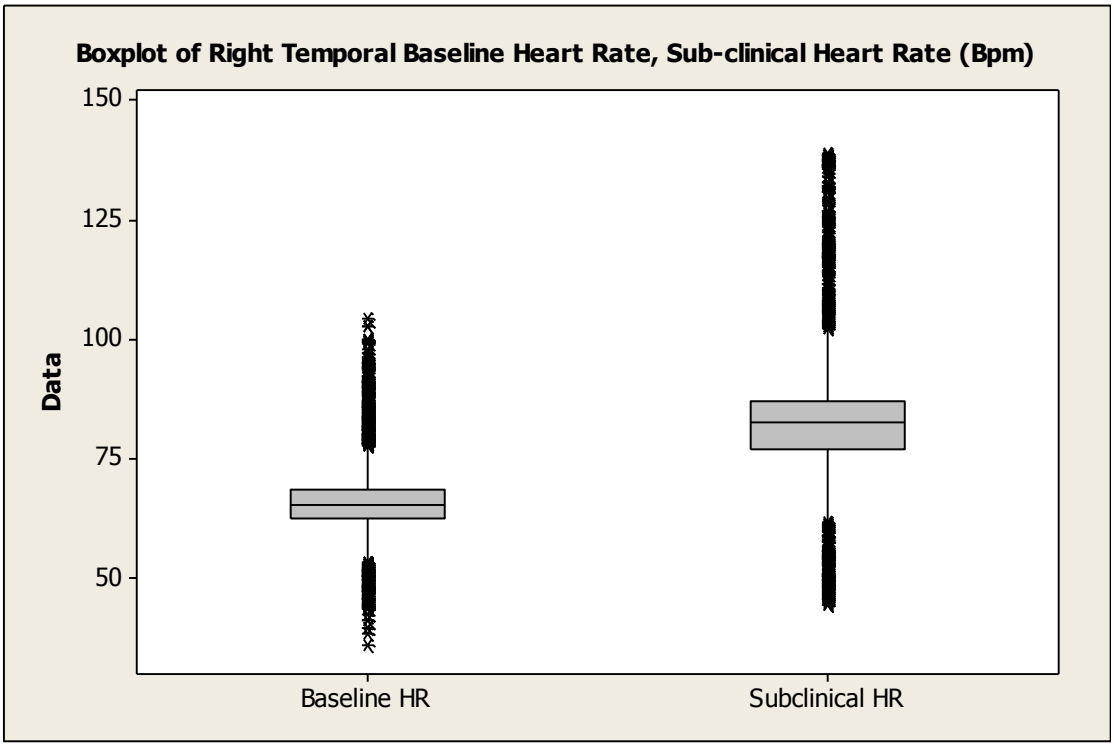


Figure 25 Boxplot of baseline heart rate and sub-clinical heart rate for right sub-clinical seizures.

An overall increase in heart rate is seen during sub-clinical seizures arising from the right temporal lobe compared to matched baseline studies (Figure 25). A mean difference in heart rate of 16.9/minute is found using Bland & Altman scatterplot (Figure 23).

	Baseline CIPA		Sub-clinical CIPA	
	Total Count	Pt Studies	Total Count	Pt Studies
n	2688	9	2688	9
Mean	12.7	14.0	9.1	10.3
SE Mean	0.1	1.9	0.1	1.4
StDev	5.4	5.9	5.4	4.2
Variance	28.6	35.4	28.8	17.8
CoefVariance	42.0	42.5	59.1	41.0
Minimum	4.2	10.4	0.2	4.7
Q1	9.8	10.7	5.5	8.2
Median	11.5	10.9	8.4	9.0
Q3	13.6	15.9	11.5	12.6
Maximum	50.3	28.6	30.0	18.8
Range	46.1	18.2	29.8	14.1
IQR	3.8	5.2	5.9	4.4
MSSD	0.8	22.2	0.4	19.0

Table 11 Descriptive statistics for right temporal CIPA baseline & right temporal CIPA sub-clinical seizures

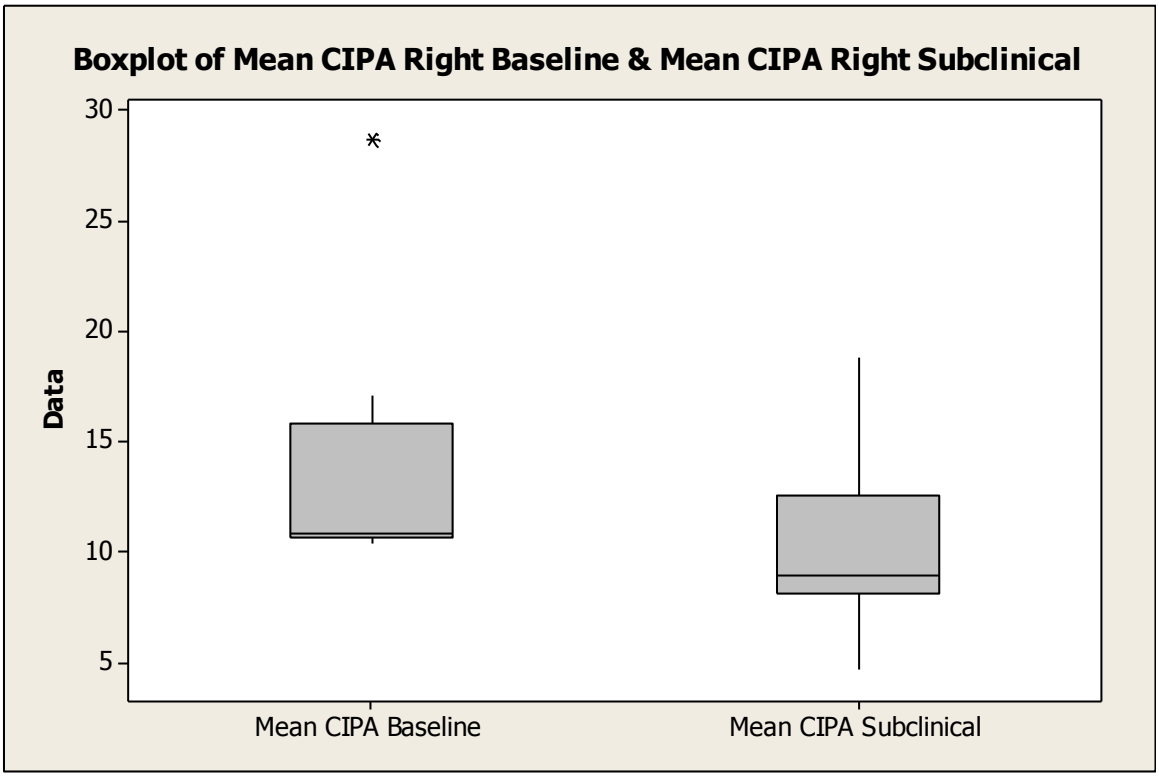


Figure 26 Boxplot of mean CIPA right temporal baseline, mean CIPA right temporal sub-clinical

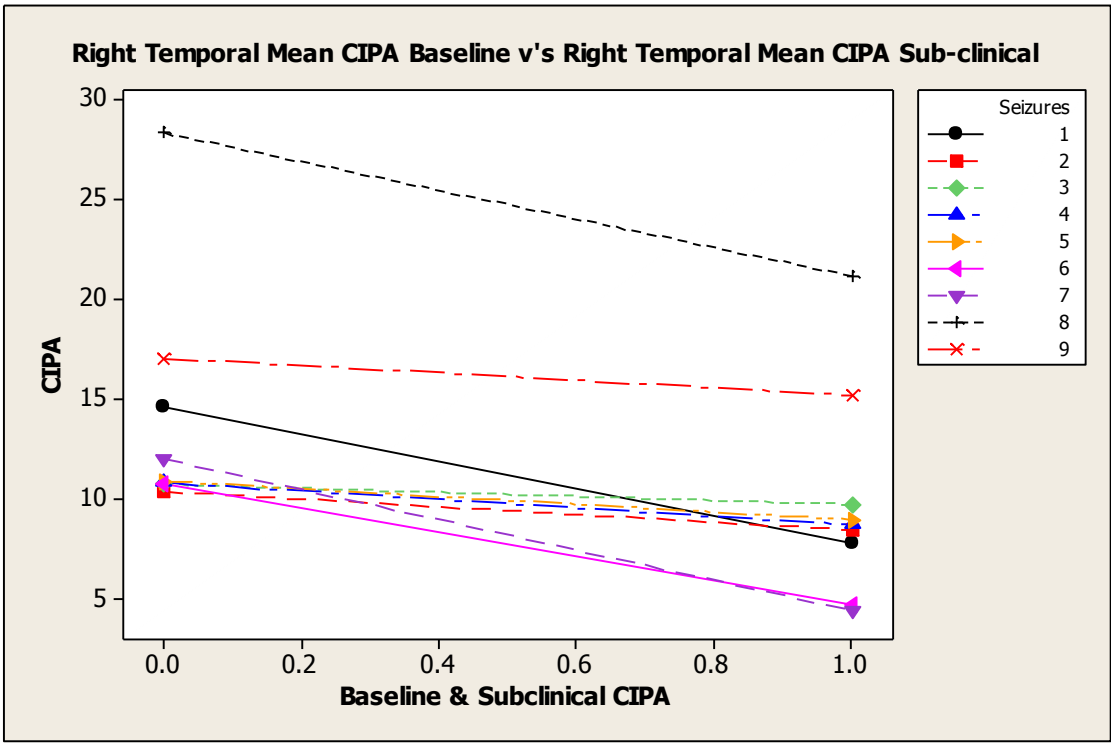


Figure 27 Scatterplot with connect lines from baseline to sub-clinical data for right temporal lobe seizures

Mean CIPA (B-S) Difference	Right Temporal Mean CIPA (B-S) Difference	Left Temporal Mean CIPA (B-S) Difference	Generalised Mean CIPA (B-S) Difference	Total Mean CIPA (B-S) Difference
n	9	5	19	33
Mean	3.7	4.4	-1.6	0.8
SE Mean	1.0	1.4	0.4	0.6
St. Deviation	3.1	3.3	1.8	3.6
Minimum	1.0	1.2	-4.8	-4.8
Q1	1.9	1.2	-3.6	-1.2
Median	2.0	3.6	-0.8	0.3
Q3	6.4	7.3	-0.5	2.0
Maximum	9.8	9.7	0.6	9.8
Wilcoxon Two Sample Test *p</=*	0.032	0.855	0.024	0.743

Table 12 Descriptive statistics for mean CIPA differences for right temporal, left temporal and generalised sub-clinical seizures.

Data is then analysed as mean values for total events to be able to compare CIPA results with BioSignal results. When mean data is analysed, statistical significance is lost for total data (*p=0.743*), (Table 19) but statistical significant changes in CIPA are still seen for right temporal (*p=0.032*) and generalised data (*p=0.024*) but not for left temporal (*p=0.855*), (Tables 12 & 19, Figures 17, 18 & 19). For right temporal lobe sub-clinical seizures (n=9), (*p=0.032)*, left temporal lobe sub-clinical seizures (n=5), (*p=0.855)* and generalised sub-clinical seizures (n=19), (*p=0.024)* when comparing baseline data with sub-clinical data (Table 8).

3.3.6 Left Temporal Lobe Sub-clinical Seizures

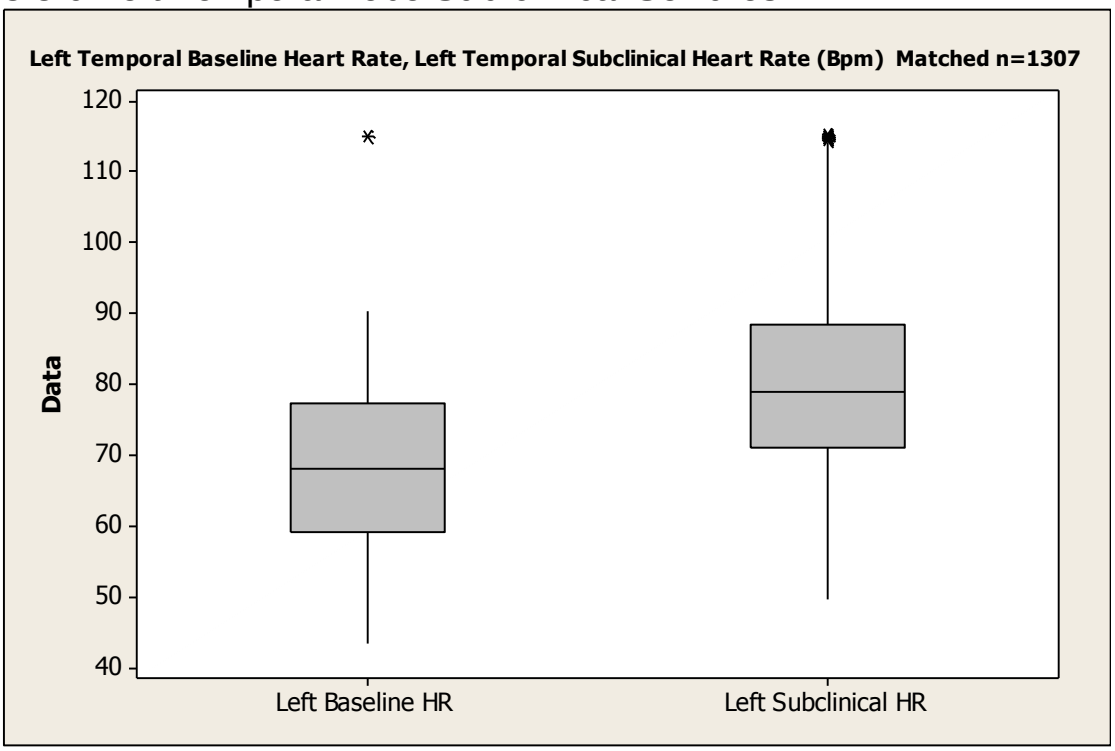


Figure 28 Boxplot left baseline heart rate, left sub-clinical heart rate.

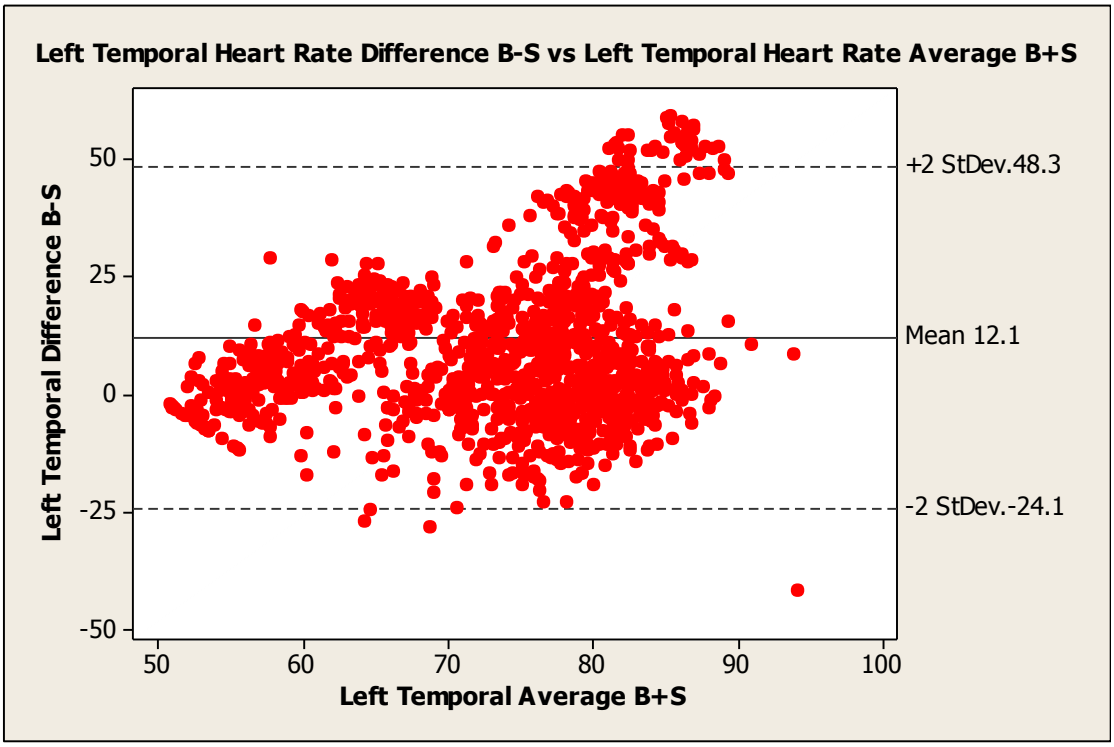


Figure 29 Bland & Altman plot scatterplot for heart rate difference (baseline minus sub-clinical) versus average for left temporal lobe seizures.
Limits of agreement of Difference are (-23.2) and 48.1

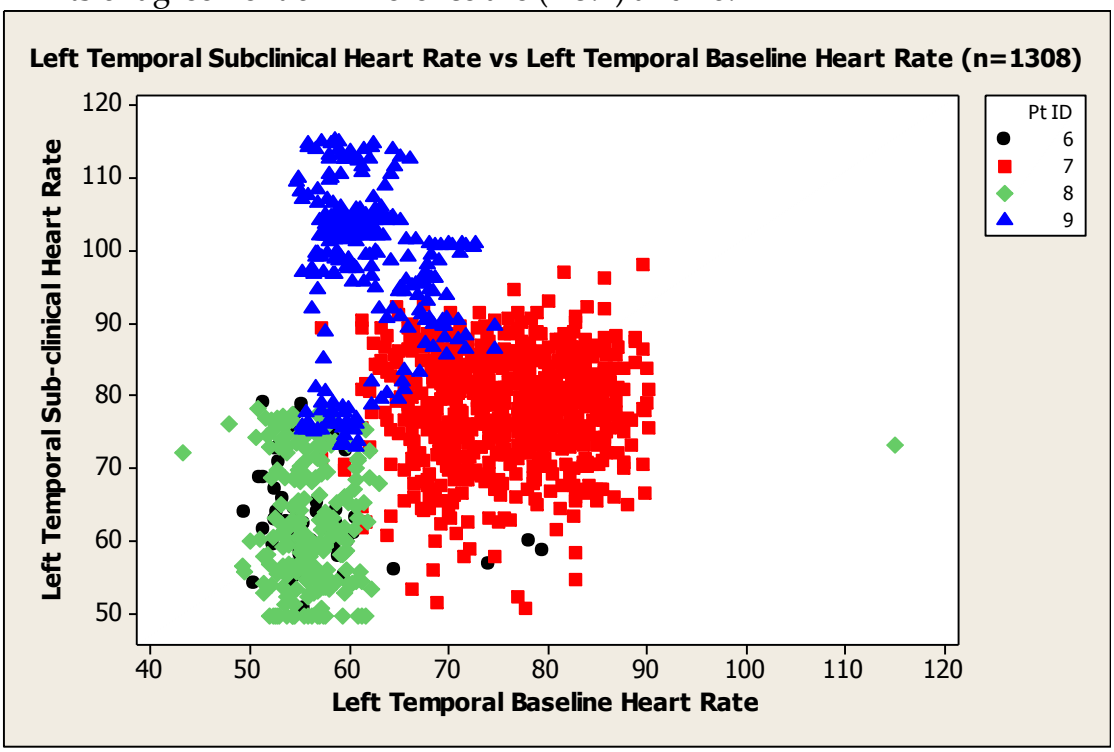


Figure 30 Scatterplot of baseline heart rate versus sub-clinical heart rate during left temporal lobe sub-clinical seizures (patient defined).

An overall increase in heart rate is seen during sub-clinical seizures arising from the left temporal lobe (Figure 28). A mean difference in heart rate is 12.1/minute derived by using Bland & Altman scatterplot (Figure 29).

Patient ID	n	Left Temporal Median CIPA		Difference Median CIPA	Wilcoxon Two Sample Test *p</=*
		Baseline CIPA	Sub-clinical CIPA		
Patient 6	52	17.6	15.9	1.8	0.420
Patient 7	404	17.6	13.2	5.0	0.604
Patient 7	306	17.8	17.0	1.6	0.296
Total Patient 7	710	17.7	14.2	3.5	0.682
Patient 8	211	14.8	6.1	7.8	0.152
Patient 9	334	4.6	0.9	3.5	0.485
Total Left Temporal	1307	15.5	10.1	4.0	0.249

Table 13 Total & sub-total median baseline minus sub-clinical CIPA for left temporal sub-clinical seizures

Median CIPA gives poorer statistical significance for left temporal sub-clinical data (*p=0.249),* (Table 13) compared to right temporal sub-clinical data (*p<0.001),* (Table 10). The median differences in CIPA overall are similar for both right temporal (3.4) compared to left temporal (4.0). However the standard deviation of data (6.9) is wider from data derived the left temporal (*Table 14)* with fewer observations (n=1307) compared to the standard deviation (5.3) derived from the right temporal n=2688 (Table 11).

	Baseline CIPA		Sub-clinical CIPA	
	Total Count	Pt Studies	Total Count	Pt Studies
n	1307	5	1307	5
Mean	14.3	15.0	9.9	10.6
SE Mean	0.2	2.5	0.2	2.9
StDev	6.8	5.7	6.9	6.4
Variance	46.5	32.0	48.3	41.4
CoefVariance	47.5	37.8	69.8	60.9
Minimum	2.8	4.9	0.2	1.30
Q1	6.9	10.7	2.8	4.0
Median	15.5	17.7	10.1	12.9
Q3	18.6	17.9	15.0	16.0
Maximum	45.4	18.0	32.5	17.0
Range	42.6	13.1	32.3	15.6
IQR	11.7	7.3	12.2	12.0
MSSD	1.7	16.8	0.5	19.1

Table 14 Descriptive statistics for CIPA baseline & CIPA sub-clinical for left temporal lobe.

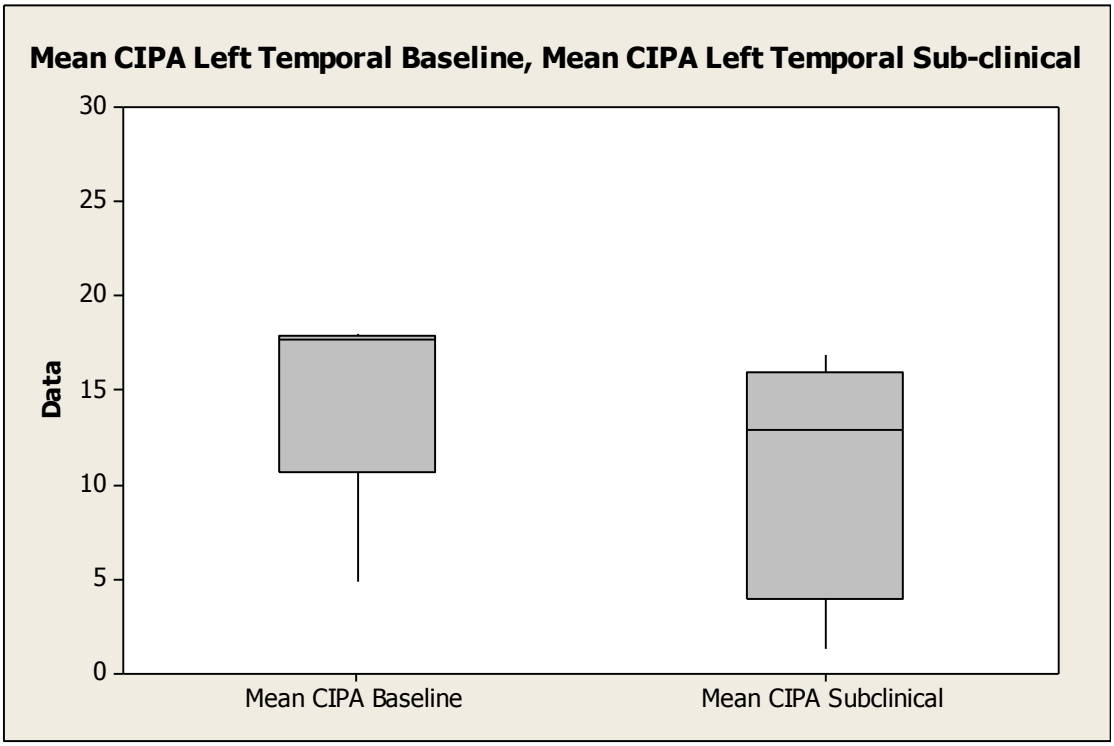


Figure 31 Boxplot of mean CIPA left temporal baseline, mean CIPA left temporal sub-clinical seizures.

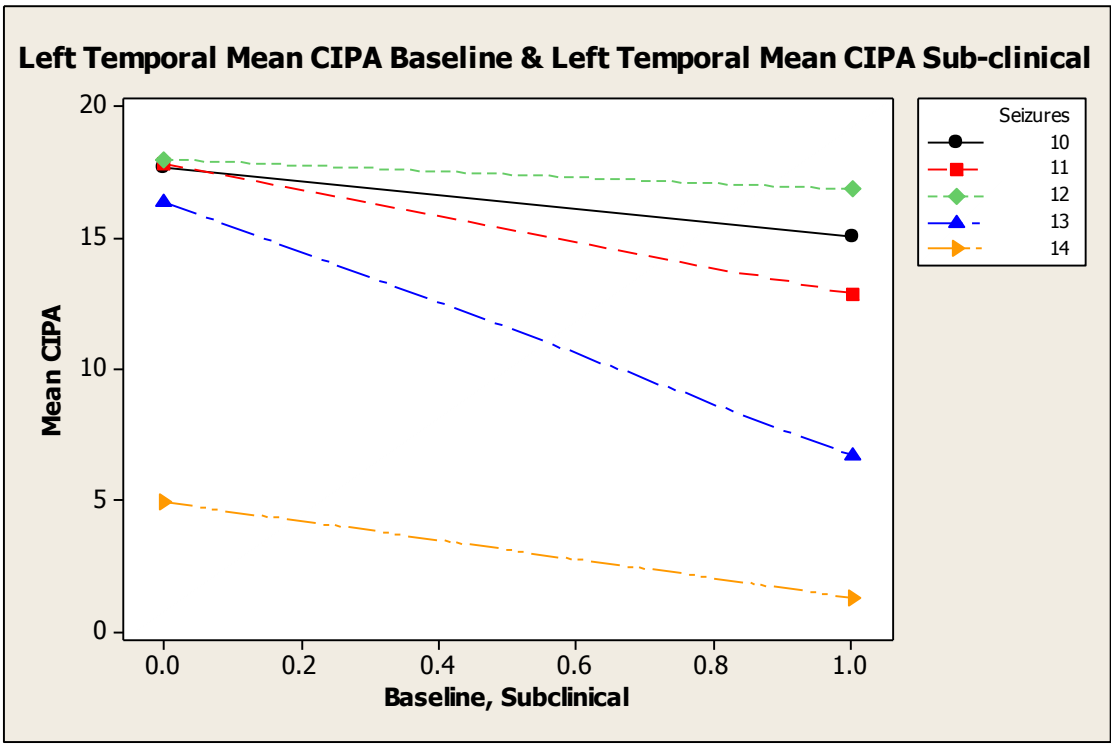


Figure 32 Scatterplot with connect lines from baseline to sub-clinical data for left temporal lobe seizures

Figure 32 scatterplot shows an individual plot of each seizure for CIPA during baseline measurements and left temporal lobe sub-clinical seizures data. CIPA shows a mean decrease from baseline for all left sub-clinical seizures.

3.3.7 Generalised Sub-clinical Seizures

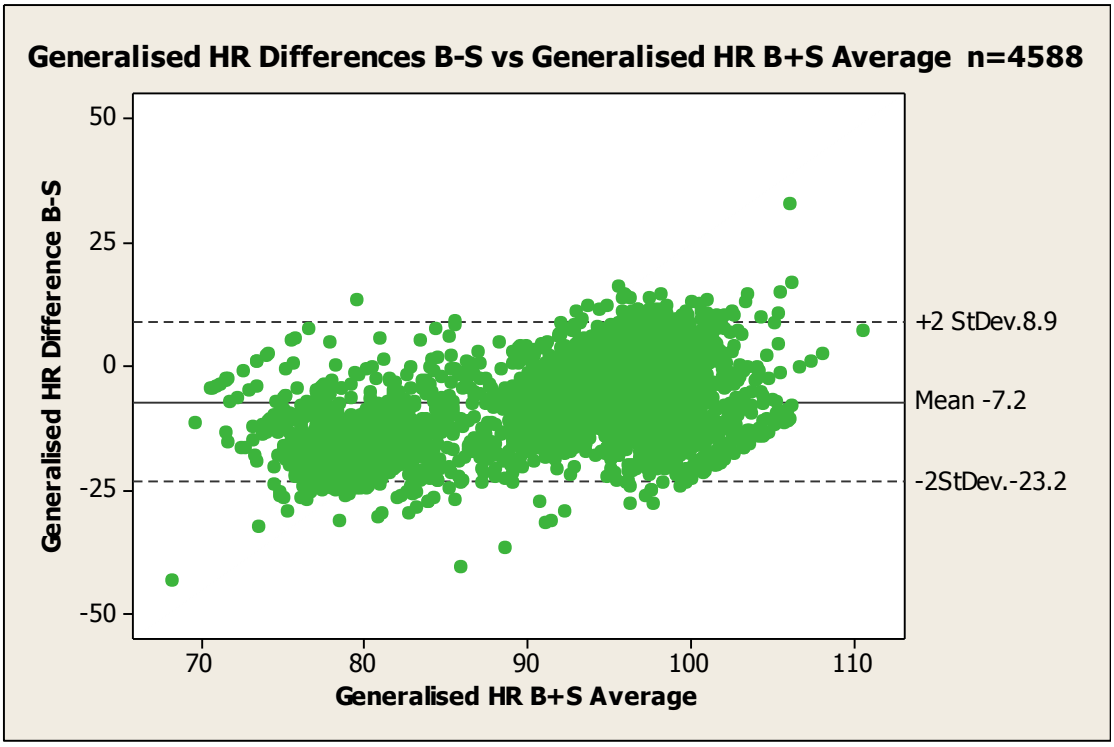


Figure 33 Bland & Altman plot scatterplot for heart rate difference (baseline minus sub-clinical) versus average for generalised sub-clinical seizures Limits of agreement for Difference are (-23.2) and 8.9.

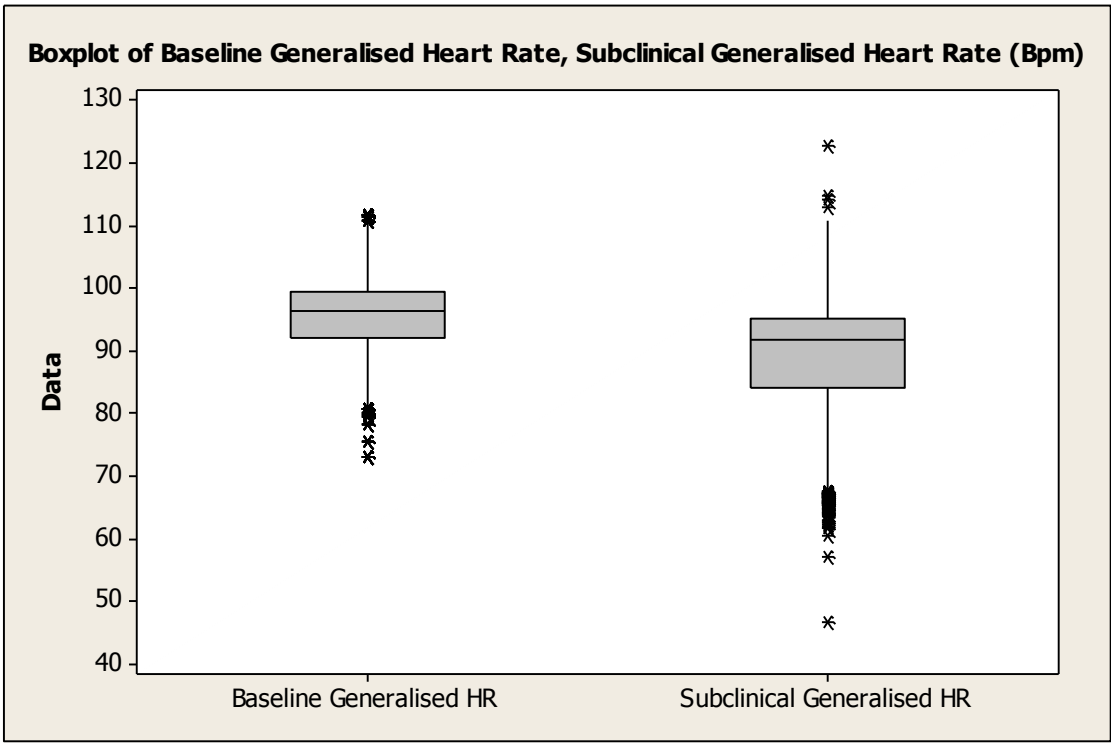


Figure 34 Boxplot generalised baseline heart rate, generalised sub-clinical heart rate.

Figure 34 boxplots indicate that there is a general decrease in heart rate during sub-clinical seizures compared to matched baseline studies. The mean decrease in heart rate calculated from Bland & Altman scatterplot is (–7.2) /minute.

The difference of mean heart rate from baseline to sub-clinical for right temporal sub-clinical data is 16.9 ± 29.4 with limits of agreement 12.4 and 46.1 (n=2688), (Figure 23). Left temporal sub-clinical seizures have a mean heart rate difference of 12.1 ± 36.2 with a wider range in limits of agreement of (-23.2) and 48.1 (Figure 29). Generalised sub-clinical seizures have a mean heart rate difference of (-7.2) ± 16.1, limits of agreement (-23.2) and 8.9 (Figure 33). This indicates that there is mean increase in heart rate for right and left temporal sub-clinical seizures but a mean decrease in heart rate

difference from generalised baseline to sub-clinical data. Patient defined heart rate scatterplots for right and left temporal lobe baseline data versus matched sub-clinical data are presented in Figures 24 & 30. A scatterplot for generalised data could not be created due to the quantity of data exceeding Minitab limits of 10,000 values. However, the patients' defined heart rate graphs, show that individual data clusters with a little overlap but are generally distinct. Therefore a much larger study would be required to overcome the effect of individual data on heart rate over a wide age range.

Section Three

Patient ID	n	Generalised Median CIPA		Median CIPA Difference	Wilcoxon Two Sample Test *p*</=
		Baseline CIPA	Sub-clinical CIPA		
Patient 10	322	3.6	3.4	0.2	0.008
Patient 10	264	3.5	3.8	-0.5	0.235
Patient 10	272	3.5	3.7	-0.2	0.280
Patient 10	241	3.5	4.3	-0.8	0.004
Patient 10	347	3.6	2.7	0.9	0.000
Patient 10	340	3.6	3.4	0.2	0.013
Patient 10	345	3.6	4.0	-0.4	0.190
Patient 10	431	3.7	2.2	1.5	0.000
Patient 10	270	3.5	3.4	0.1	0.629
Patient 10	374	3.6	2.6	1.0	0.000
Patient 10	317	3.6	3.4	0.2	0.256
Total Patient 10	3523	3.6	3.3	0.3	0.000
Patient 11	189	3.7	7.7	-4.0	0.482
Patient 11	136	3.6	8.9	-5.3	0.971
Patient 11	131	3.7	7.9	-4.2	0.424
Patient 11	120	3.9	6.5	-2.6	0.721
Patient 11	123	3.9	6.5	-2.6	0.052
Patient 11	111	4.1	7.8	-3.7	0.660
Patient 11	133	3.7	9.6	-5.9	0.376
Patient 11	122	3.9	6.3	-2.4	0.548
Total Patient 11	1065	3.8	7.6	-3.8	0.454
Generalised Total	4588	3.6	4.0	-0.4	0.000

Table 15 (above) Total & sub-total median baseline minus sub-clinical CIPA for generalised sub-clinical seizures

	Baseline CIPA		Sub-clinical CIPA	
	Total Count	Pt Studies	Total Count	Pt Studies
n	4588	19	4588	19
Mean	3.7	4.0	4.8	5.6
SE Mean	0.0	0.2	0.0	0.6
StDev	1.6	0.7	2.8	2.4
Variance	2.4	0.5	8.0	5.8
CoefVariance	41.5	18.4	58.4	43.2
Minimum	0.5	3.3	0.9	2.6
Q1	3.2	3.4	2.7	3.9
Median	3.6	3.5	4.0	4.2
Q3	4.1	4.8	6.4	8.1
Maximum	18.6	5.1	17.3	9.5
Range	18.1	1.8	16.4	6.9
IQR	0.9	1.4	3.7	4.2
MSSD	0.1	0.1	0.1	0.9

Table 16 Descriptive statistics for generalised baseline CIPA & sub-clinical CIPA

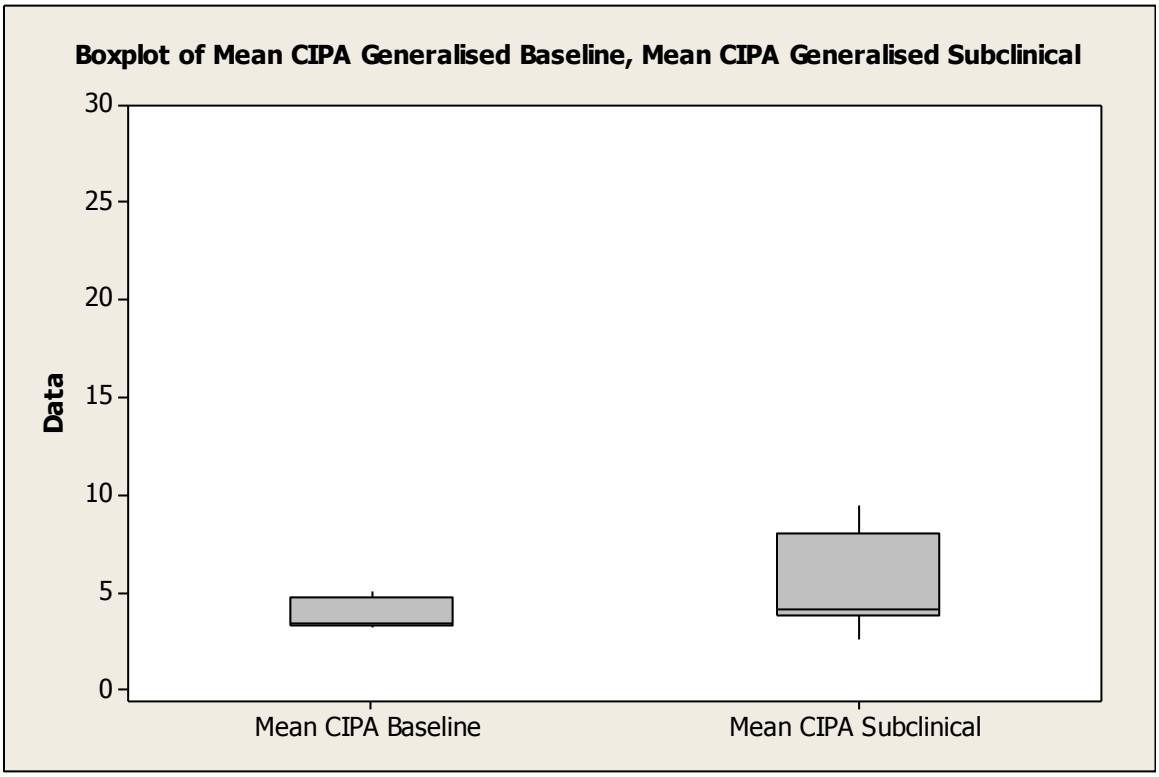


Figure 35 Boxplot generalised baseline mean CIPA, generalised sub-clinical mean CIPA.

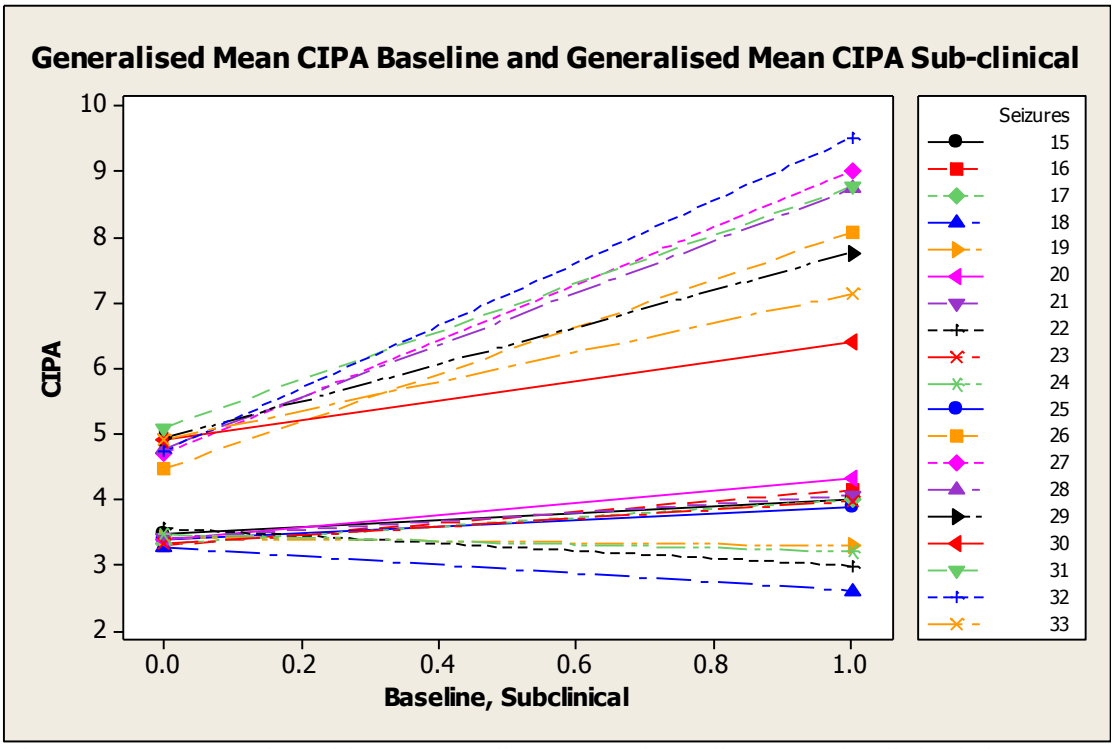


Figure 36 Scatterplot with connect lines from baseline to sub-clinical data for generalised sub-clinical seizures

3.3.8 Total Sub-clinical Seizures and Results Interpretation of CIPA

	Baseline CIPA		Sub-clinical CIPA	
	Total Count	Pt Studies	Total Count	Pt Studies
n	8583	33	8583	33
Mean	8.2	8.4	6.9	7.6
SE Mean	0.1	1.1	0.1	0.8
StDev	6.3	6.3	5.1	4.3
Variance	40.1	40.2	25.8	18.7
CoefVariance	77.6	75.6	73.1	56.8
Minimum	0.5	3.3	0.2	1.3
Q1	3.5	3.5	3.1	4.0
Median	4.7	4.9	5.7	7.8
Q3	11.9	11.4	9.5	9.3
Maximum	50.3	28.6	32.5	18.8
Range	49.8	25.4	32.3	17.6
IQR	8.4	8.0	6.4	5.3
MSSD	0.6	8.9	0.3	5.3

Table 17 Descriptive statistics for total baseline & total sub-clinical seizures

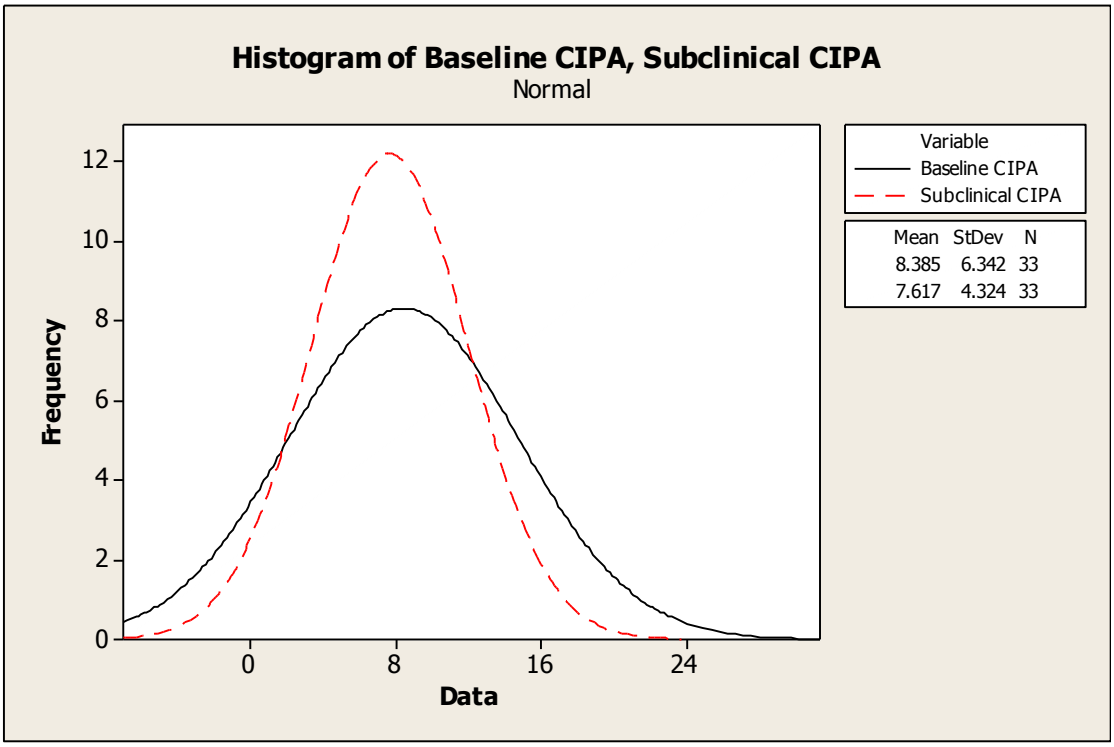


Figure 37 Histogram of total baseline CIPA, total sub-clinical CIPA

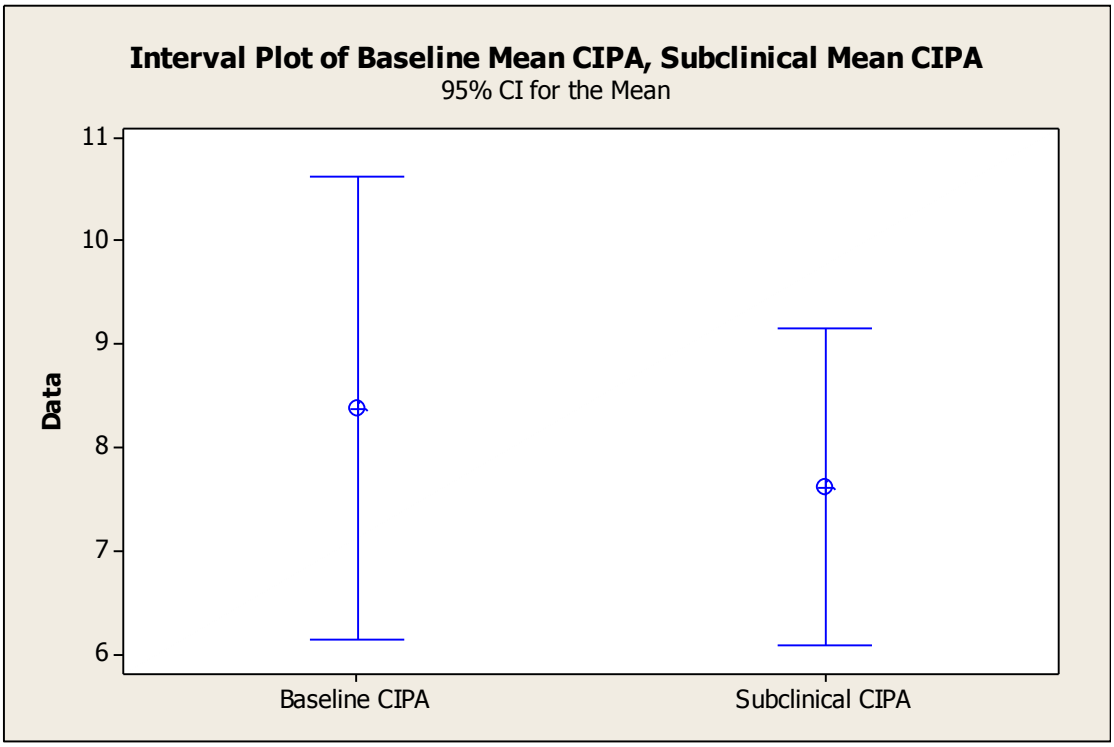


Figure 38 Interval plot of total mean baseline CIPA, total mean sub-clinical CIPA

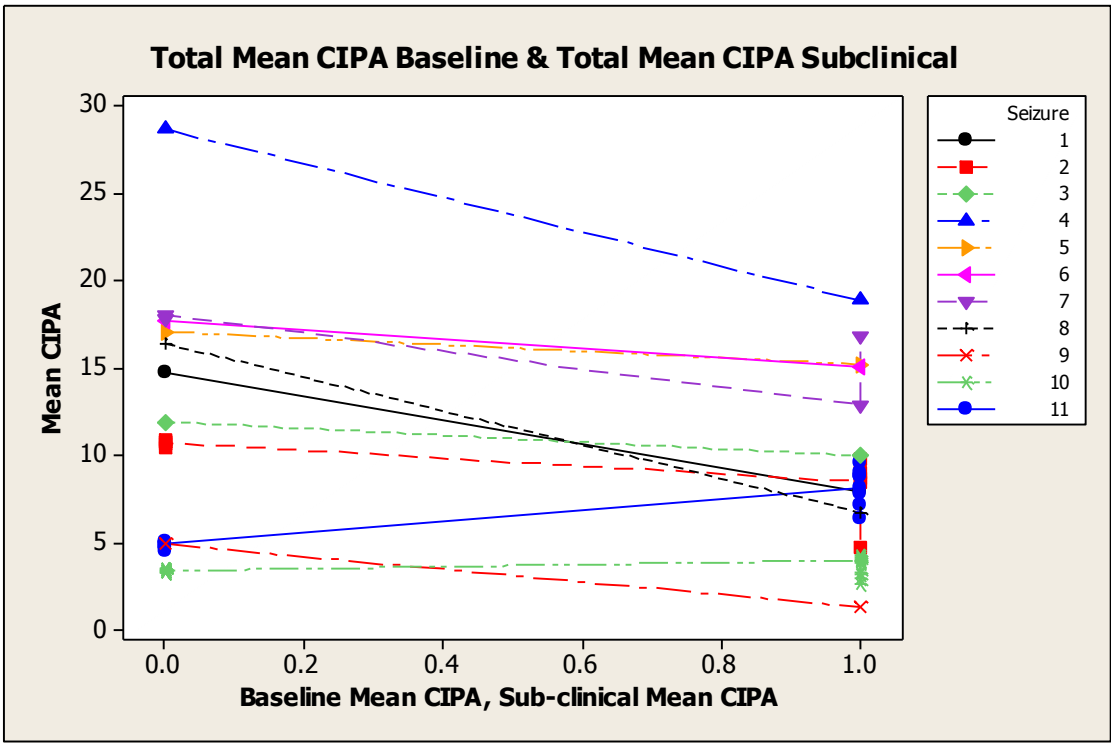


Figure 39 Scatterplot baseline mean CIPA and sub-clinical mean CIPA with connect lines for total patients

An overall decrease in CIPA occurs during total sub-clinical seizures (Figures 38 & 39). Baseline mean CIPA reduces from 8.3 to 7.6 (Figure 37) with statistical significant change (*p<0.001),* (Table 19).

3.3.9 CIPA Co-efficient of variation

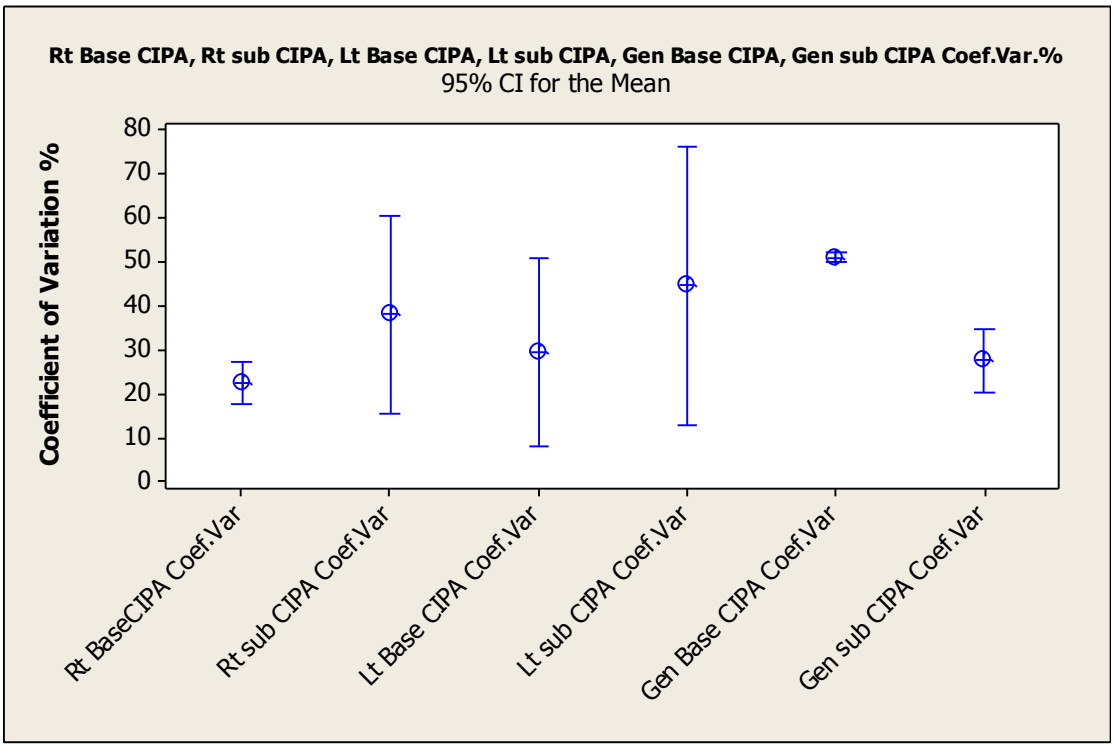


Figure 40 Interval plot of coefficient of variation for CIPA in Right baseline, subclinical (n=2688) Left baseline , Left sub-clinical n=1307) and Generalised baseline ,sub-clinical n=4588).

The co-efficient of variation is a normalised measure of dispersion or scatter of data. The co-efficient of variation of CIPA data show an average increase in scatter of total data from baseline 32 to sub-clinical 40.3 (Table 7).

Sub-clinical seizures arising from the right temporal lobe have a co-efficient of variation of 37.8% (C.I 15.4, 60.3) increasing from baseline measurements 22.1% (C.I 17.2, 26.9), (Figure 40). An increase in coefficient of variation is also seen from sub-clinical seizures arising from the left temporal lobe of 44.4% (C.I 12.7, 76.0) increasing from baseline measurements 29.4% (C.I 7.8, 50.9) Figure 4 Conversely, the co-efficient of variation difference from

generalised sub-clinical seizures decreases during sub-clinical seizures 27.3% (C.I 20.0, 34.6) from baseline measurements 50.8% (C.I 49.7, 52.0)

Mean CIPA Difference (B-S)	Right Temporal Mean CIPA Difference	Left Temporal Mean CIPA Difference	Generalised Mean CIPA Difference	Total Mean CIPA Difference
n	9	5	19	33
Mean	3.7	4.4	-1.6	0.8
SE Mean	1.0	1.4	0.4	0.6
Standard Deviation	3.1	3.2	1.8	3.6
Minimum	1.0	1.1	-4.8	-4.8
Q1	1.9	1.9	-3.6	-1.2
Median	1.9	3.6	-0.8	0.3
Q3	6.4	7.3	-0.5	2.0
Maximum	9.8	9.7	0.6	9.8
Wilcoxon One Sample Test *p</=*	0.032	0.855	0.024	0.743

Table 18 Descriptive statistics for total mean CIPA difference (Baseline minus sub-clinical) for total, right temporal, left temporal and generalised data.

	n (Total CIPA)	Wilcoxon Two Sample Test *p</=*	n (mean CIPA per patient)	Wilcoxon Two Sample Test *p</=*
Right Temporal CIPA Difference (B-S)	2688	0.001	9	0.032
Left Temporal CIPA Difference (B-S)	1307	0.001	5	0.855
Generalised CIPA Difference (B-S)	4588	0.001	19	0.024
Total CIPA Difference (B-S)	8583	0.001	33	0.743

Table 19 CIPA difference (baseline minus sub-clinical) for total & mean CIPA for total, right temporal, left temporal and generalised data.

N.B When CIPA is analysed using total CIPA data per patient, significant differences are seen comparing baseline CIPA with Sub-clinical CIPA. If mean CIPA data is used to compare baseline CIPA with Sub-clinical CIPA, then significance is reduced when using limited data.

3.3.10 Comparison of Adult CIPA and Paediatric CIPA

This pilot study included 5 paediatric patients (2 patients with generalised sub-clinical seizures, 2 patients with right temporal and 1 patient with left temporal lobe sub-clinical seizures) and 6 adult patients (3 patients with right temporal lobe and 3 patients with left temporal lobe sub-clinical seizures). No generalised sub-clinical seizures were recorded from the adult patients to compare to the CIPA results from two paediatric patients who had a total of 19 generalised sub-clinical seizures with mean CIPA increasing from 3.7 to 4.8, ($p<0.001$).

Paediatric CIPA

Total CIPA measurements for paediatric baseline and sub-clinical is 14,744 and therefore exceeds the maximum of 10,000 values for Minitab to produce a graph and statistics. Therefore patient profiles for generalised CIPA are produced separately.

	n	Baseline CIPA	Subclinical CIPA	Difference CIPA	Limits of Agreement	Wilcoxon *p*</=
Pt 10 Generalised	3523	3.4	3.8	-0.4	-4.7, 3.9	<0.001
Pt 11 Generalised	1065	4.8	8.2	-3.4	-10.7,3.9	0.454
Total Generalised	4588	3.7	4.8	-1.1	-6.9,4.7	<0.001
Pt 2 Right Temporal	1728	10.7	8.1	2.6	-4.28, 9.6	0.036
Pt 5 Right Temporal	346	17.1	15.2	1.9	-12.7, 17.7	0.002
Total Right Temporal	2074	11.8	9.3	2.5	-6.5, 11.4	0.006
Pt 7 Total Left Temporal	710	17.9	14.6	3.3	-8, 14.6	0.682
Total Paediatric	7372	7.4	7.0	0.4	Data beyond Minitab limit	0.203

Table 20 Total paediatric baseline, sub-clinical & difference in CIPA

A decrease in CIPA occurred in three paediatric patients having focal sub-clinical seizures. For two patients with right temporal lobe sub-clinical seizures mean CIPA decreased from 11.8 to 9.2, (p=0.006). In the patient with left temporal lobe sub-clinical seizures mean CIPA decreased from 17.9 to 14.6 *(p=0.682).*

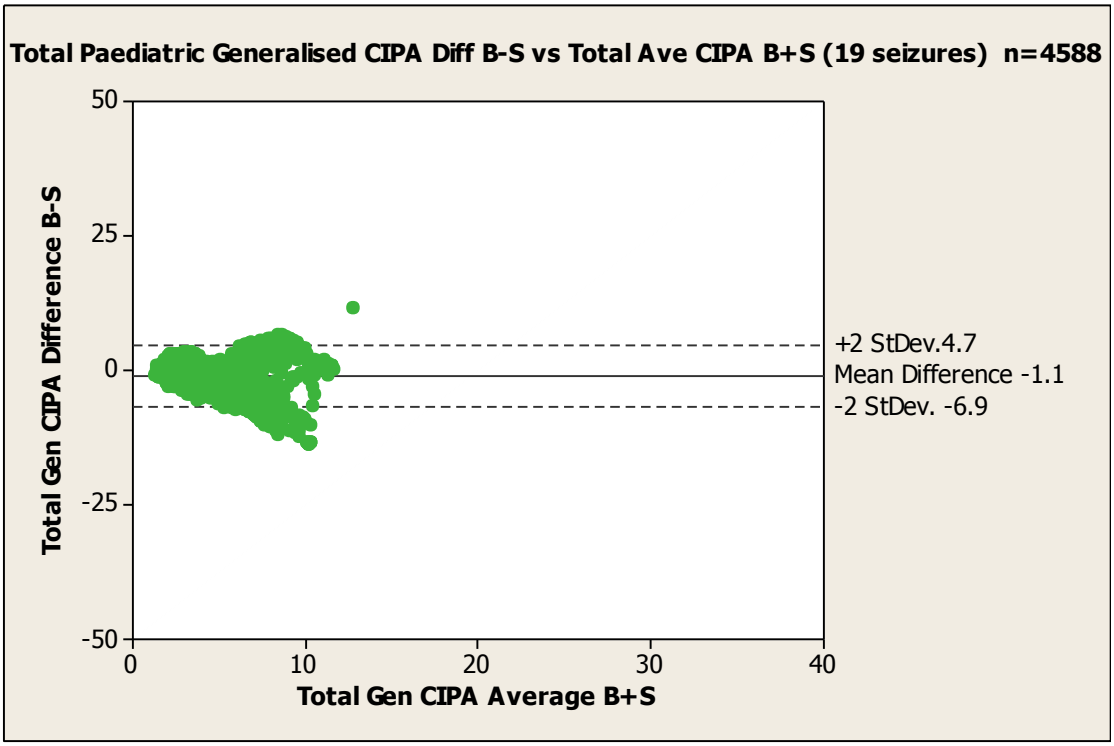


Figure 41 Bland & Altman scatterplot for total (paediatric) CIPA difference (baseline minus sub-clinical) versus average for generalised data
Limits of agreement are 4.7 and (–6.9). Mean CIPA *p<0.001*

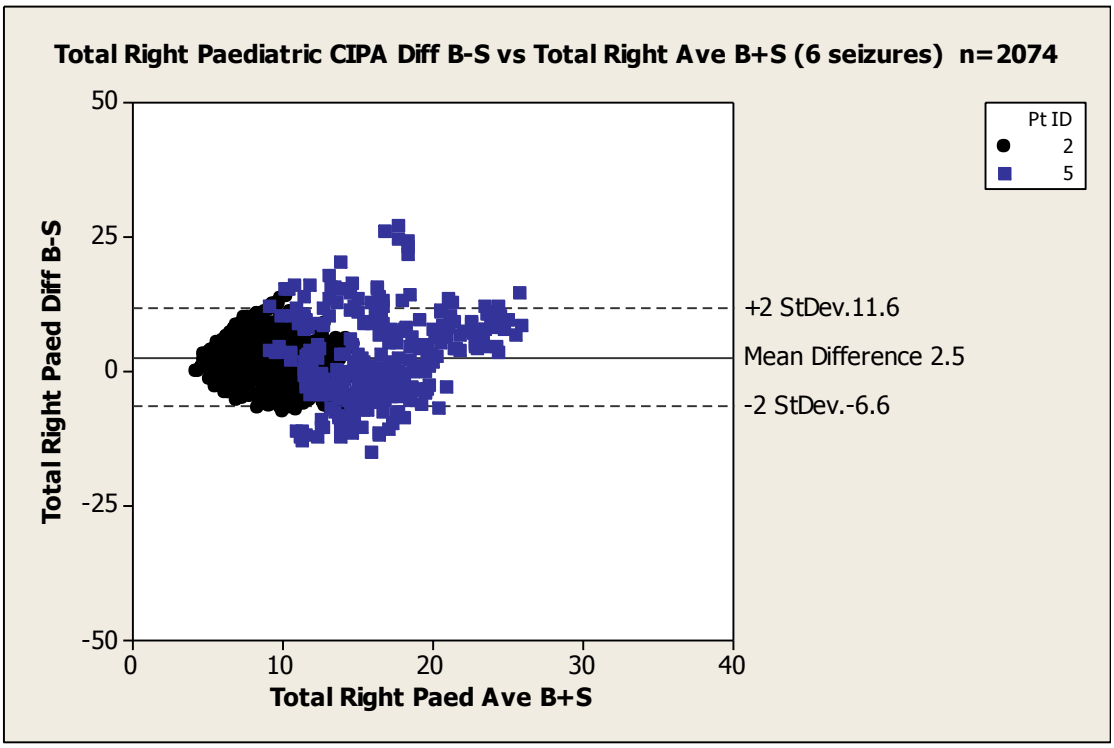


Figure 42 Bland & Altman scatterplot for total CIPA difference (baseline minus sub-clinical) versus average for paediatric right temporal lobe data.
Limits of agreement are 11.4 and (–6.5). *p=0.006*

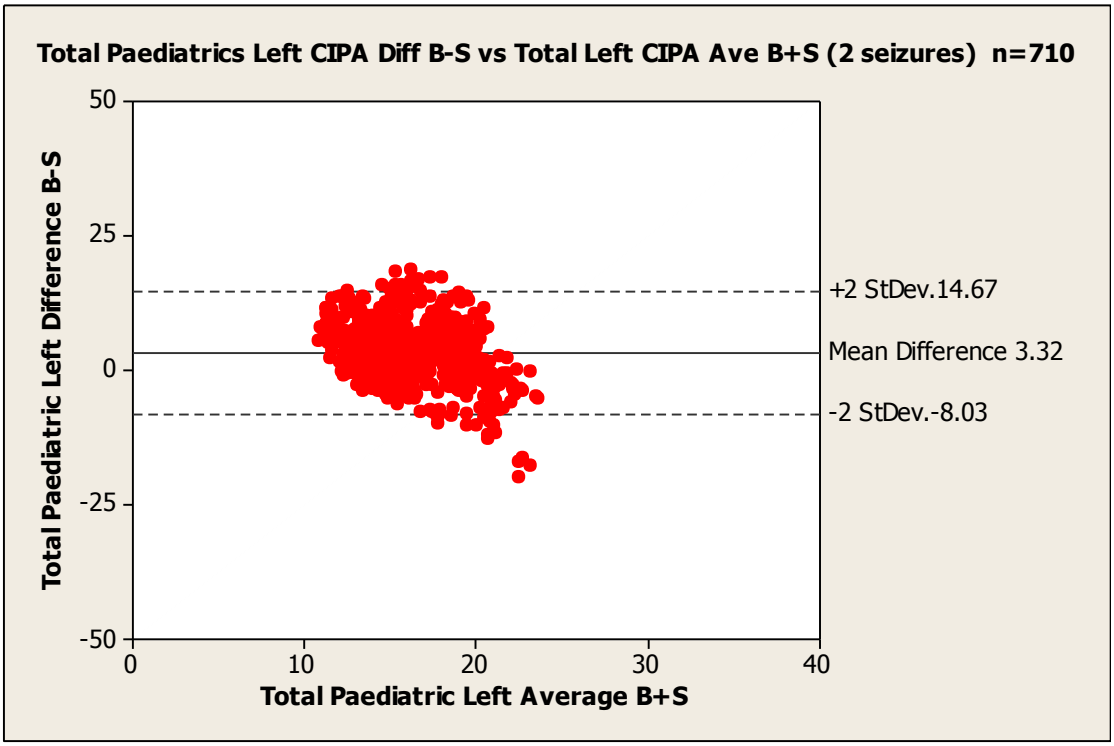


Figure 43 Bland & Altman scatterplot for total CIPA difference (baseline minus sub-clinical) versus average for paediatric left temporal lobe data. Limits of agreement are 14.6 and (–8). *p=0.682*

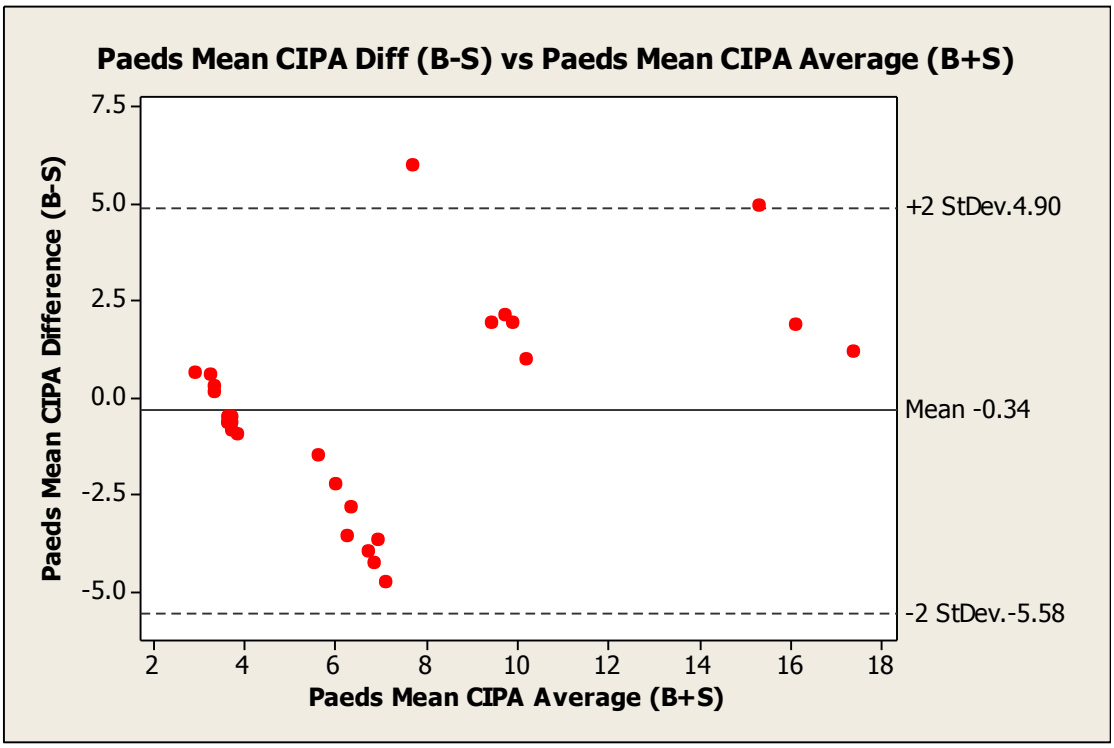


Figure 44 Bland & Altman scatterplot for total CIPA difference (baseline minus sub-clinical) versus average for paediatric data. Limits of agreement are (-4.78) and 2.11) *p=0.772*.

Adult CIPA

	n	Baseline CIPA	Subclinical CIPA	Difference CIPA	Limits of Agreement	Wilcoxon *p</=*
Pt 1 Right Temporal	132	14.6	7.8	6.8	(-0.9),14.3	0.032
Pt 3 Right Temporal	359	12.0	4.4	7.6	(-3.3), 17.5	0.019
Pt 4 Right Temporal	123	28.3	21.2	7.1	(-7), 25.7	0.949
Total Right Temporal	614	15.8	8.5	7.3	(-5), 19.6	0.010
Pt 6 Left Temporal	52	17.7	15.1	2.6	(-8.7), 12.9	0.420
Pt 8 Left Temporal	211	16.4	6.7	9.7	(-1.3), 18.1	0.152
Pt 9 Left Temporal	334	4.9	1.3	3.6	(-0.6), 6.3	0.485
Total Left Temporal	597	10.1	4.4	5.7	(-5.6), 18.1	0.014
Total Adults	1211	13.0	6.5	6.5	(-6), 19.1	0.001

Table 21 Total adult baseline, sub-clinical & difference in CIPA.

Similar to the paediatric group, a decrease in CIPA occurred in all focal seizures in the adult group. Mean CIPA decreased from 15.8 to 8.5 in three adult patients with right temporal lobe sub-clinical seizures (*p=0.010)*. Similarly mean CIPA decreased from 10.1 to 4.4 in three adult patients with left temporal sub-clinical seizures, (*p=0.014)*.

Changes in baseline CIPA to sub-clinical CIPA are more statistically marked in adults (n=1211), (*p<0.001),* (Table 21) than in paediatrics (n=7372), (*p=0.203)* (Table 20). This statistical difference between paediatrics and adults is possibly due to the combined effect of generalised data with lateralised data for paediatrics that is not comparable for adults. Generalised sub-clinical seizures tend to result in an increase in CIPA from baseline to sub-clinical (baseline minus sub-clinical calculates as a negative value, Table 20). This contrasts generally for CIPA changes from baseline to sub-clinical for right and left temporal lobe sub-clinical seizures which tend to show a decrease in CIPA from baseline to sub-clinical (baseline minus sub-clinical calculates as a positive, Tables 20 & 21). In the case of paediatrics, combining generalised and lateralised data gives a poor overall statistical result because of this combination.

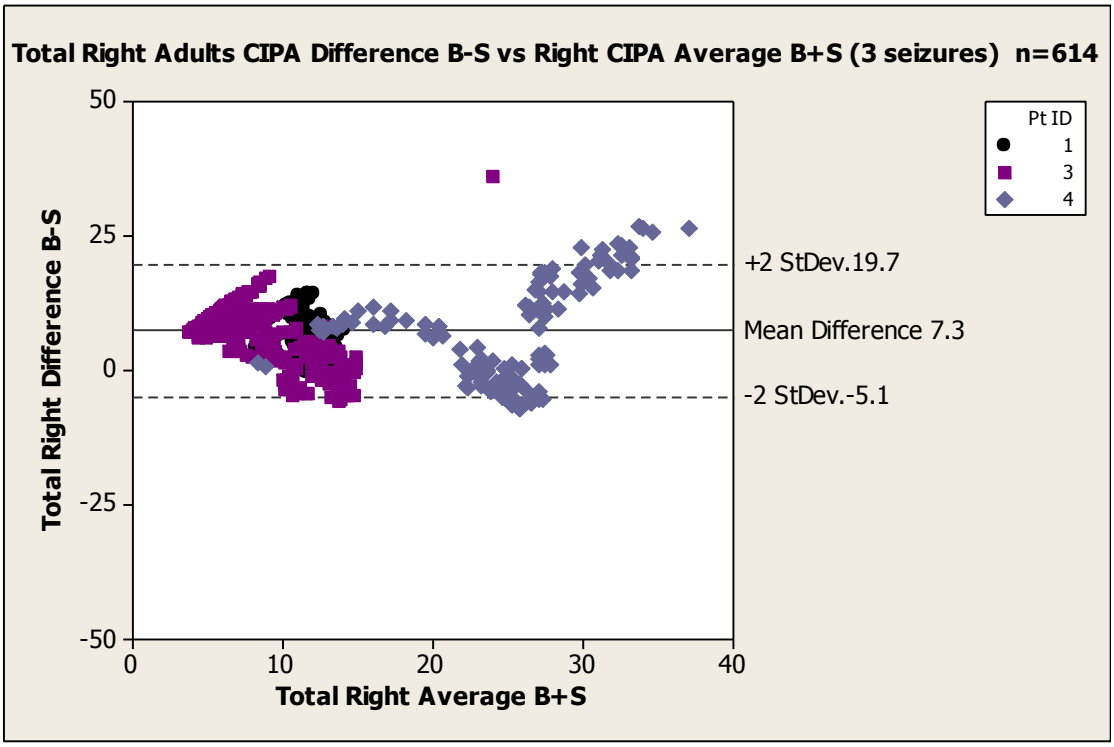


Figure 45 Bland & Altman scatterplot for CIPA difference (baseline minus sub-clinical) versus average for adult total right temporal lobe data
Limits of agreement are 19.6 and (–5). *p=0.01*

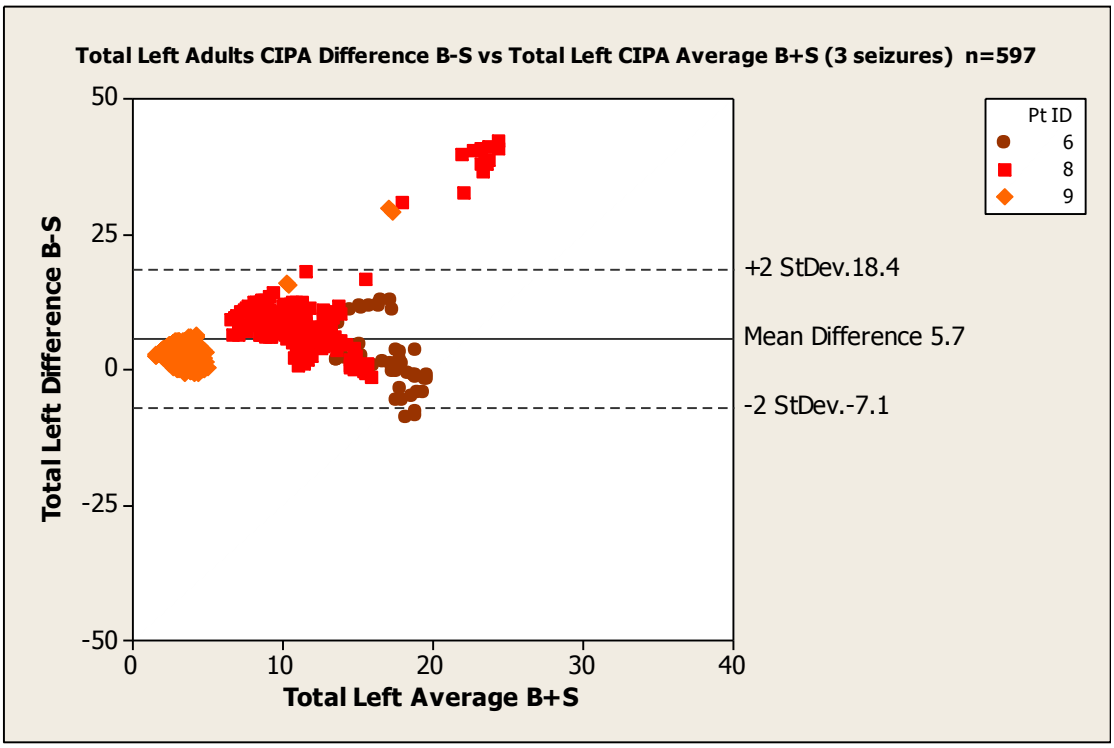


Figure 46 Bland & Altman scatterplot for CIPA difference (baseline minus sub-clinical) versus average for adult total left temporal lobe data
Limits of agreement are 18.1 and (–5.6). *p=0.014*.

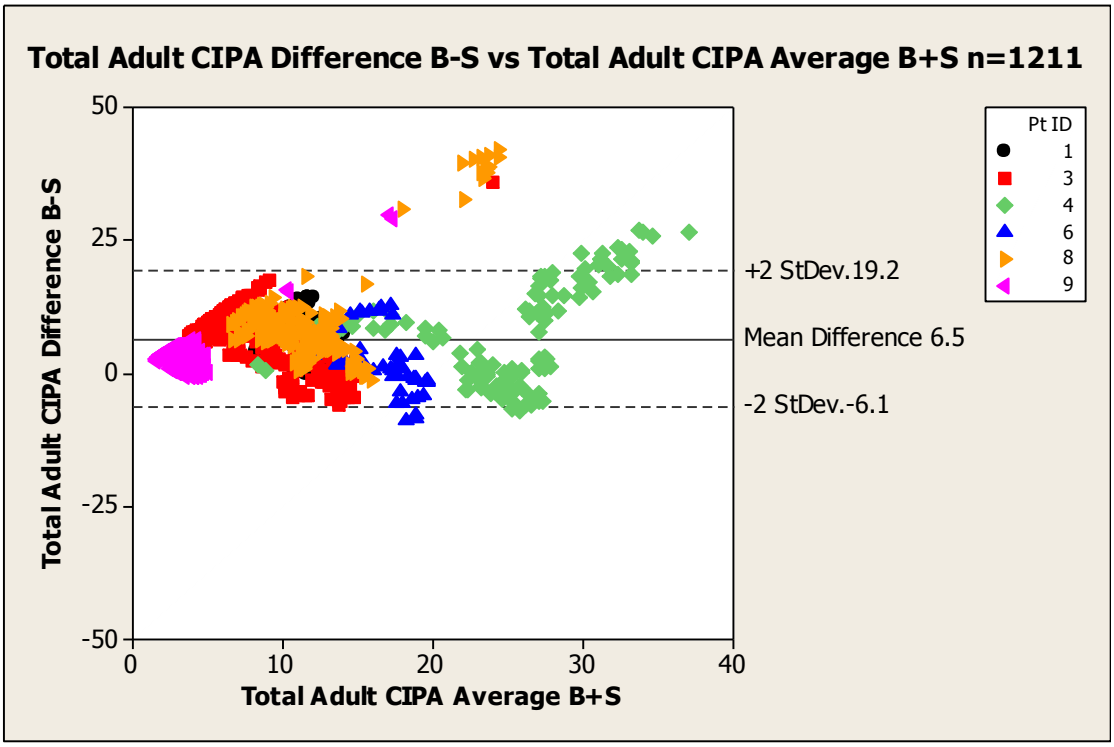


Figure 47 Bland & Altman scatterplot for CIPA difference (baseline minus sub-clinical) versus average for total adult data
Limits of agreement are 19.1 and (–6.0). *p<0.001*

CIPA differences in right temporal lobe data in adults (n=614) is 7.3 ± 12.4 with limits of agreement (-5) and 19.6 (*p=0.01*), (Figure 45) compared to paediatrics (n=2074) of CIPA difference 2.5 ± 9.1.with limits of agreement (-6.5) and 11.4 (*p=0.006*), (Figure 42*)*. In left temporal sub-clinical seizures a CIPA difference of 5.7 ± 12.7 is seen in adults (n=597) with limits of agreement (-5.6) and 18.1 (*p=0.014*), (Figure 46*)* compared to a CIPA difference of 3.3 ± 11.3 in paediatrics (n=710) with limits of agreement (-8) and 14.6 (*p=0.682*), (Figure 43). No generalised sub-clinical seizures were recorded in adults and therefore a comparison cannot be made between paediatrics and adults.

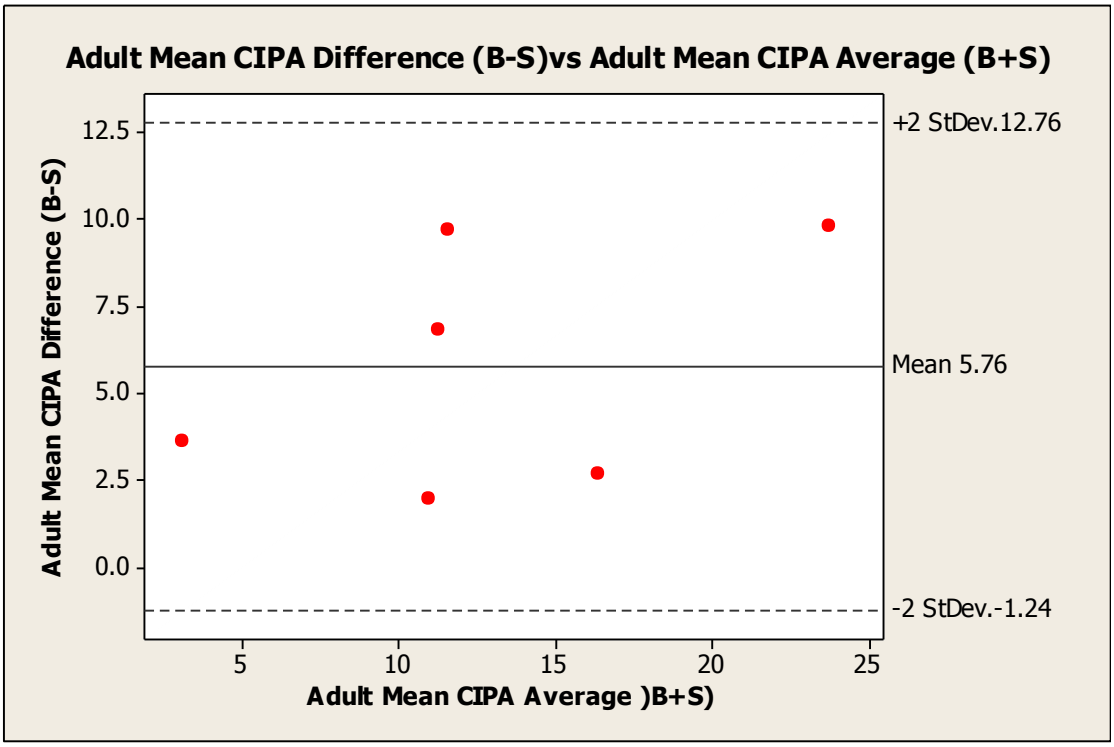


Figure 48 Bland & Altman scatterplot for mean CIPA difference (baseline minus sub-clinical) versus average for total adult data
Limits of agreement are 1.95 and 9.67. *p=0.191*

For mean data (n=33), a lower statistical significance is seen compared to total CIPA values with adults mean CIPA (n=7) difference 5.8 ± 7 (limits of agreement 1.9 and 9.7) range 7.8, (*p=0.191),* (Figure 48). Paediatric mean values (n=26) have a mean CIPA difference of (-0.3) ± 5.2 (limits of agreement (-4.8) and 2.1) range 6.9, (*p=0.772),* (Figure 44). Again, poorer statistical significance in the paediatric group occurs compared to the adult group as the same influence of the inclusion of generalised data is again reflected in the mean CIPA results.

One-way ANOVA: CIPA Difference versus Patient ID Co-efficient of variation

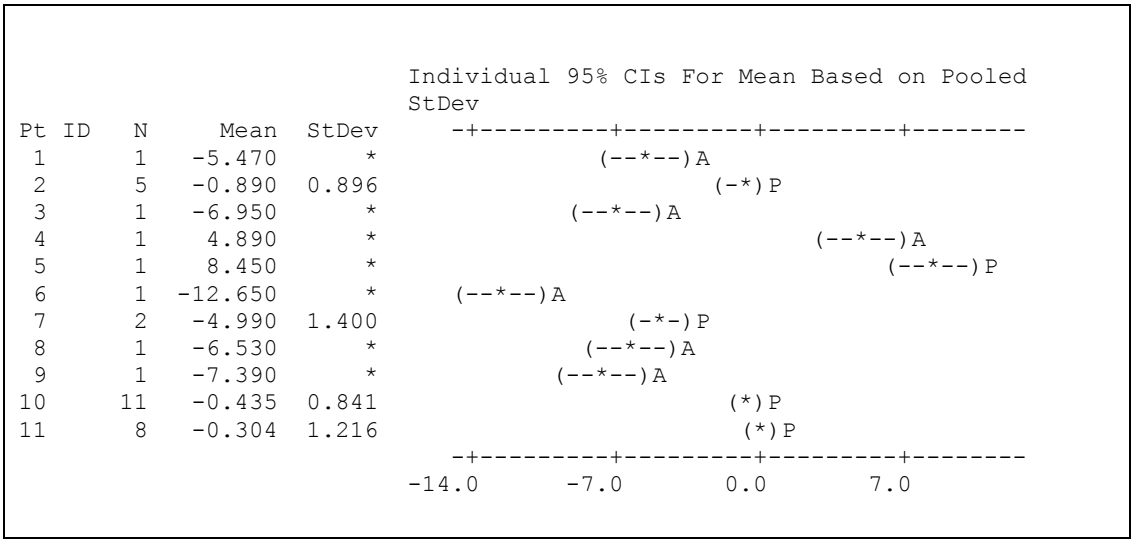


Figure 49 One-way ANOVA CIPA difference versus patient ID co-efficient of variation. (Key A=Adult, P=Paediatric).

One-way analysis of variation (ANOVA) was used to identify if there were any systematic differences between paediatric and adult CIPA co-efficient of variation. ANOVA compares variation in data within each patient and also between each patient. Figure 49 shows a scattered distribution for both adult (A) and paediatrics (P) data. This would suggest that any differences in coefficient of variation in CIPA are not due to any inherent differences between adults and paediatrics.

3.3.11 Multivariate Anaysis of Anti-epileptic Drugs and Cardiac Vagal Tone

Cardiac vagal tone was measured by the NeuroScope device producing an output of Cardiac Index of Paraympathetic Activity (CIPA) from eleven patients who took part in the study previously described. The CIPA data for matched baseline 'counted' vagal tone (but not the sub-clinical data), selected

from the same stage of sleep, was then analysed in terms of CIPA derived from patients receiving anti-epileptic medication and further categorised as monotherapy, polytherapy and those patients not receiving any anti-epileptic drug (AED). Analysis was performed using One-way ANOVA for comparisons of means in each category, Minitab version 14

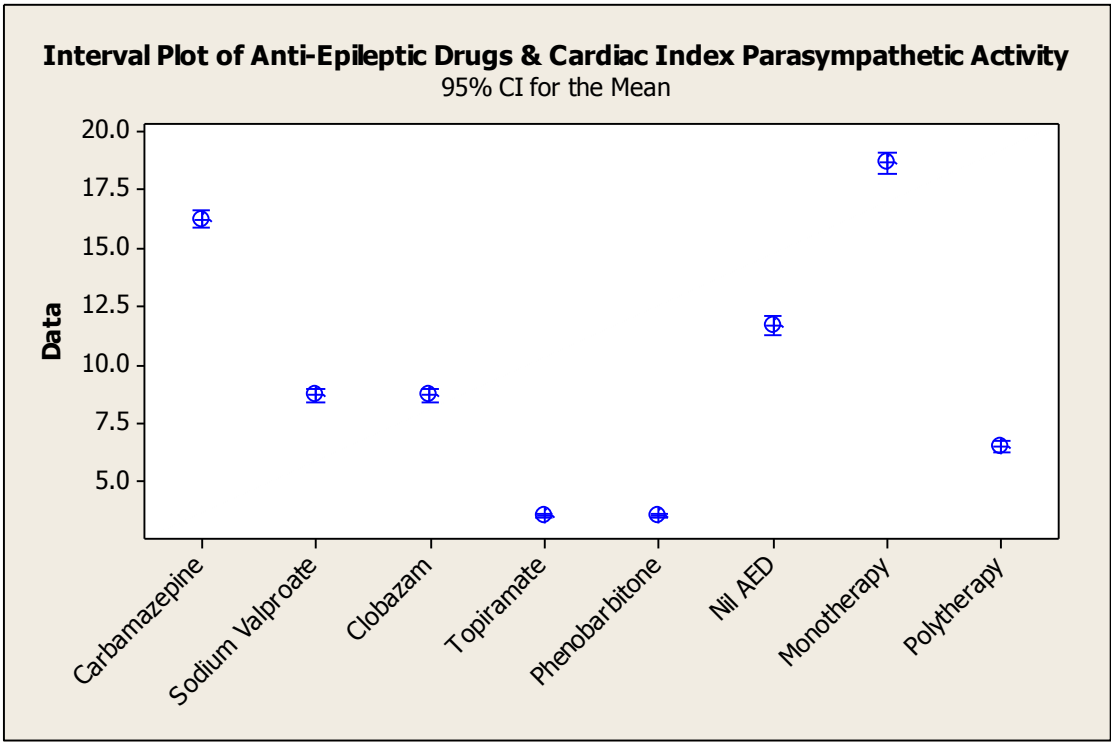


Figure 50 Interval plot of Cardiac Index of Parasympathetic Activity (CIPA) from baseline measurements for anti-epileptic drugs.

In this pilot study, eleven patients (mean age 23.09 ± 18.73 years) were 7 males and 4 females. Six patients were adults (3 male and 3 female, mean age of 35.8 ± 16.0 years) and 5 patients were children (4 male and 1 female, mean age of 7.8 ± 4.8 years). Thirty-three sub-clinical seizures (mean duration 191.1 ± 136.4 seconds of which 9 were derived and confined to the right temporal lobe, 5 were derived from and confined to the left temporal lobe and 19 sub-

clinical attacks were generalized. Matched 'counted' baseline measurements selected from the same stage of sleep were analysed in terms of AED's. Five anti-epileptic drugs (AEDs) were included in this analysis; carbamazepine (5 patients), sodium valproate (2 patients), clobazam (2 patients), topiramate (1 patient), phenobarbitone (1 patient). Four patients were not receiving any anti-epileptic medication, four patients were being treated with monotherapy and three patients were receiving polytherapy. Figure 50 shows that CIPA analysed from the patient receiving topiramate and phenobarbitone is very low. All other results would be considered to be in the normal range for CIPA with someone at rest and in particular, asleep.

Descriptive Statistics

Anti-Epileptic Drug	n	Mean CIPA	Standard Error of Mean CIPA	Standard Deviation CIPA	Minimum CIPA	Maximum CIPA
Carbamazepine	5	16.2	0.2	6.8	4.2	50.3
Sodium Valproate	2	8.6	0.1	3.6	2.5	17.2
Clobazam	2	8.6	0.1	3.6	2.5	17.2
Topiramate	1	3.5	0.0	0.9	0.9	5.2
Phenobarbitone	1	3.5	0.0	0.9	0.9	5.2

Table 22 Descriptive statistics of Cardiac Index of Parasympathetic Activity (CIPA) for patients on anti-epileptic medication.

The NeuroScope uses an arbitrary scale of 1-4 is considered to be low cardiac vagal tone. The lowest mean CIPA (3.5) is from one patient receiving polytherapy of topiramate and phenobarbitone. All other mean CIPA data is in normal range. However, patients receiving carbamazepine have the highest resting CIPA (16.2) indicating a slow heart rate. The maximum CIPA form patients receiving carbamazepine is much higher than any other group of 50.3. Low minimum CIPA are observed in all categories of AED's except those patients on carbamazepine.

Analysis of one-way ANOVA, where the pooled standard deviation (5.255) is compared to data for each AED category, is in normal range. Low CIPA is found in data derived from a patient being treated by topiramate and phenobarbitone. High CIPA is distinct in data derived from patients receiving carbamazepine.

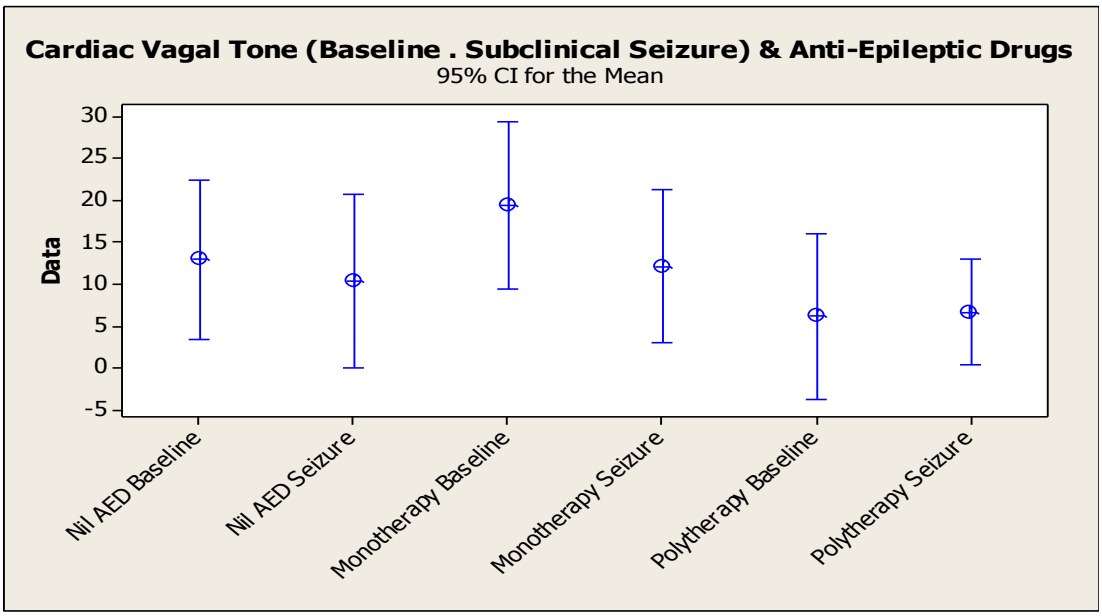


Figure 51 Baseline & Subclinical CIPA for patients with nil Anti-Epiletic Drugs, Monotherapy & Polytherapy.

Patients receiving polytherapy AEDs have the lowest baseline CIPA compared to those patients on monotherapy or nil AED (Table 23). Mean CIPA is within normal range but minimum values for patients in the nil AED group during the sub-clinical seizure and for the polytherapy group are low, indicating high heart rates.

Cardiac Vagal Tone (Cardiac Index of Parasympathetic Activity CIPA)	n	Baseline Mean CIPA	Standard Deviation	Subclinical Mean CIPA	Standard Deviation
Nil AED	4	11.6	6.3	10.9	6.5
Monotherapy	4	18.6	6.8	12.0	5.7
Polytherapy	3	6.1	3.8	6.6	2.5
Gender	4(F)	13.1	6.2	10.3	6.4
Total	7(M)	13.6	8.6	9.8	5.2
Gender	3(F)	11.5	6.4	8.8	6.9
Nil AED	1(M)	17.1	0.0	15.1	0.0
Gender	1(F)	18.0	0.0	14.8	0.0
Monotherapy	3(M)	19.9	7.5	11.1	6.7

Table 23 Cardiac Vagal Tone in relation to Nil Anti-Epileptic Drugs, Monotherapy, Polytherapy and Gender.

N.B. Too few observations are available to perform ANOVA for polytherapy and gender. Also, ANOVA was not possible to investigate any relationship between CIPA and seizure duration.

CIPA is within normal ranges for all patients whether receiving nil AED, monotherapy or polytherapy. The standard deviation indicates that CIPA

can be low for polytherapy patients during sub-clinical seizures. This however is due to one patient with intractable generalised epilepsy.

CIPA in relation to gender is similar for total comparison for the group but also for those receiving monotherapy. One male had a higher CIPA compared to three females who were not being treated with any AEDs.

Chapter 22 BioSignal Heart Rate Variability

3.4.1 Inter and Intra Observer Analysis

Statistical Test	Observer 1 (Thea)	Observer 2 (Ruth)	Difference	Average
Total count (R-R intervals)	369	369	0.0	369
Mean	817.57	817.63	0.06	817.6
Standard Error of Mean	0.734	0.737	0.003	0.727
Standard Deviation	14.09	14.15	0.06	13.96
Variance	198.59	200.20	1.61	194.78
Coefficient of Variance	1.72	1.73	0.01	1.71
Minimum	784	784	0.0	784
Median	816	816	0.0	816
Maximum	848	848	0.0	848.0
Range	64	64	0.0	64.0
MSSD	92.54	87.41	5.13	83.91
Q1	808.00	808.00	0.0	808.0
Q3	824.00	830.00	0.0	826.5

Table 24 Descriptive statistics for R-R Inter-observer analysis

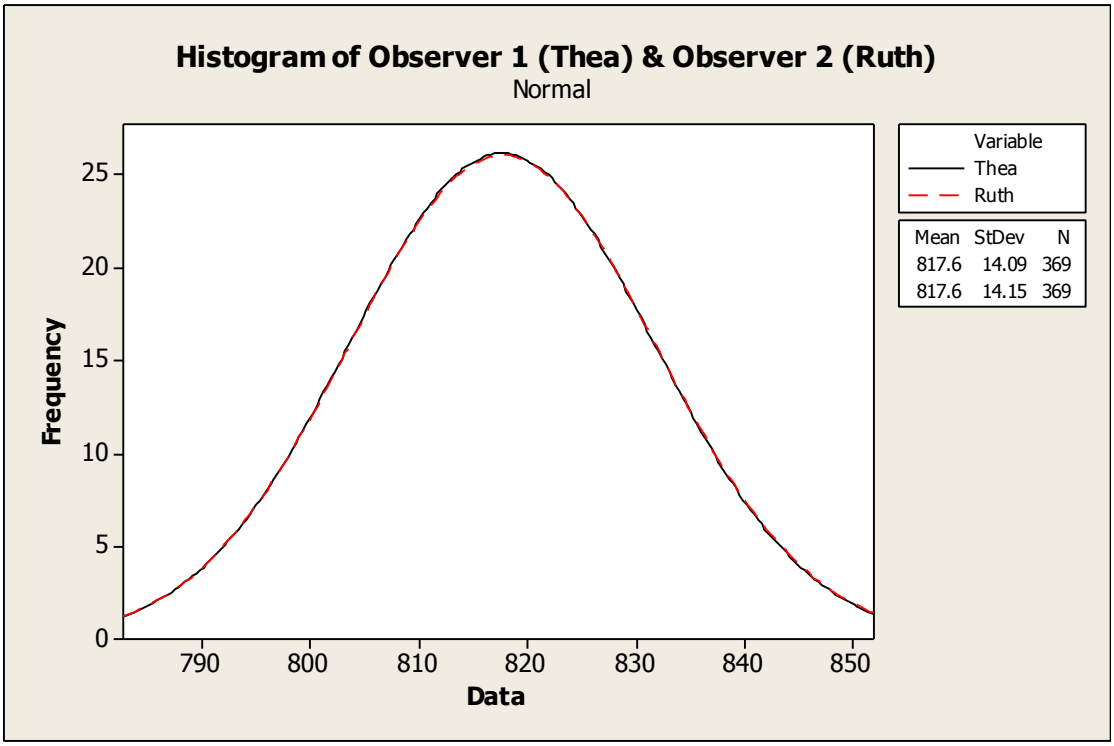


Figure 52 Histogram of Inter-observer analyses

With normal distribution, a paired t test was performed comparing observer 1 and observer 2 data. No significant difference was determined p=0.809

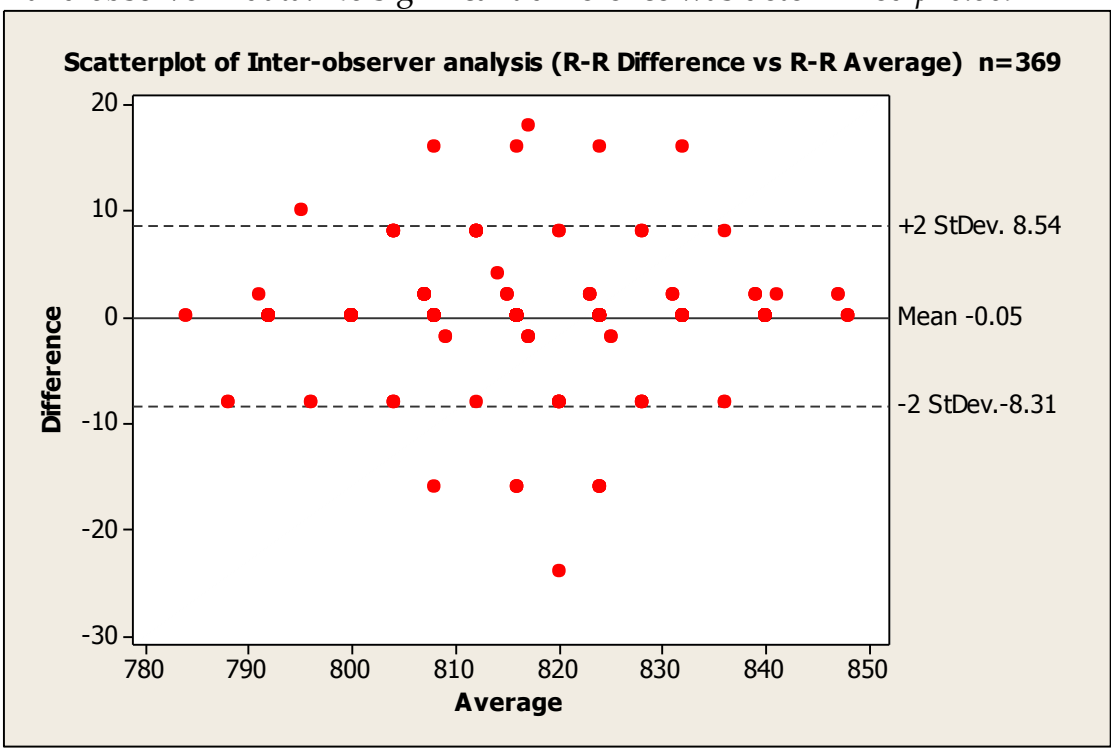


Figure 53 Bland & Altman scatterplot of Inter-observer difference (baseline minus sub-clinical) versus average in R-R

Mean Difference is (-0.05) ± 8.59. Limits of agreement are (-8) and 8

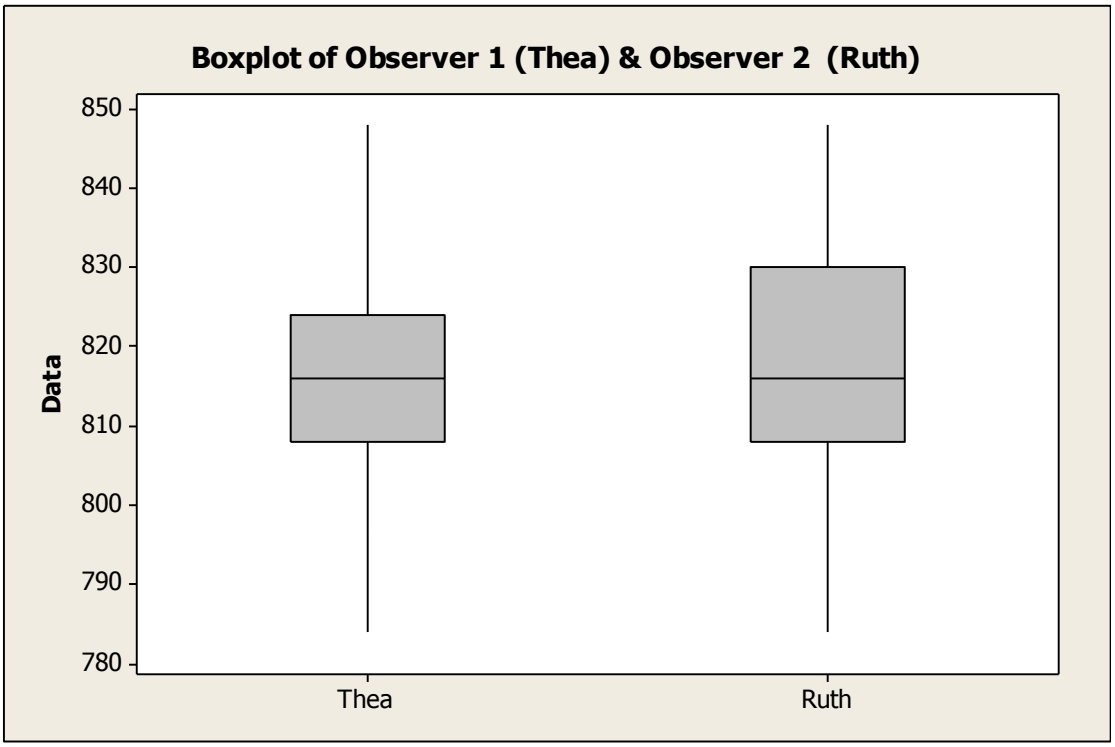


Figure 54 Boxplot R-R intervals for observer 1, observer 2

Observer 1 has a mean R-R measurement of 817.57 compared to observer 2 mean measurement of 817.63 with a difference of (0.06 milliseconds). Both observers measured identical minimum and maximum measurements but the standard deviation and variance are slightly different at 0.06 and 1.61 milliseconds respectively

Observer 1

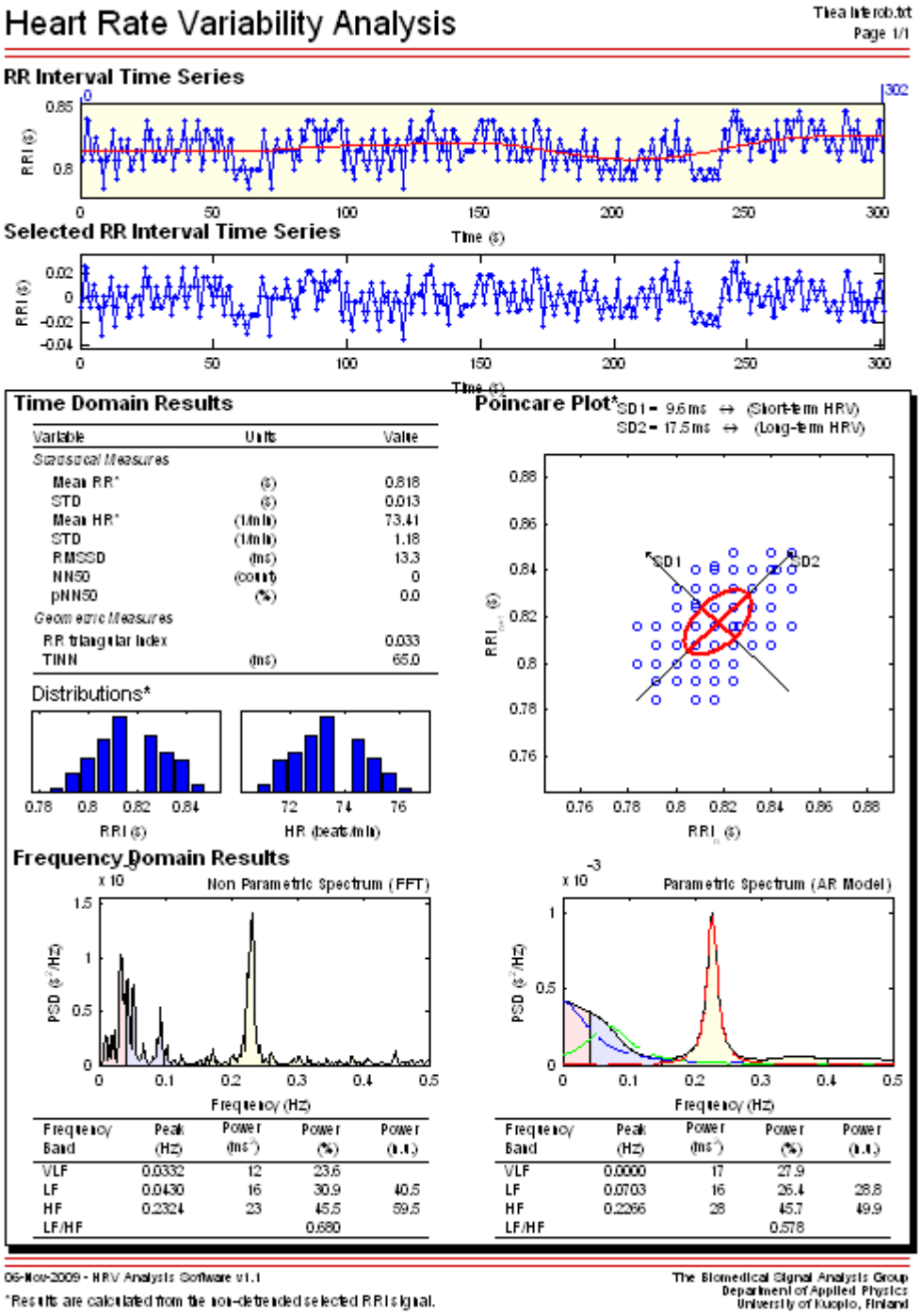


Figure 55 BioSignal HRV Observer 1 R-R analyses.

Observer 2

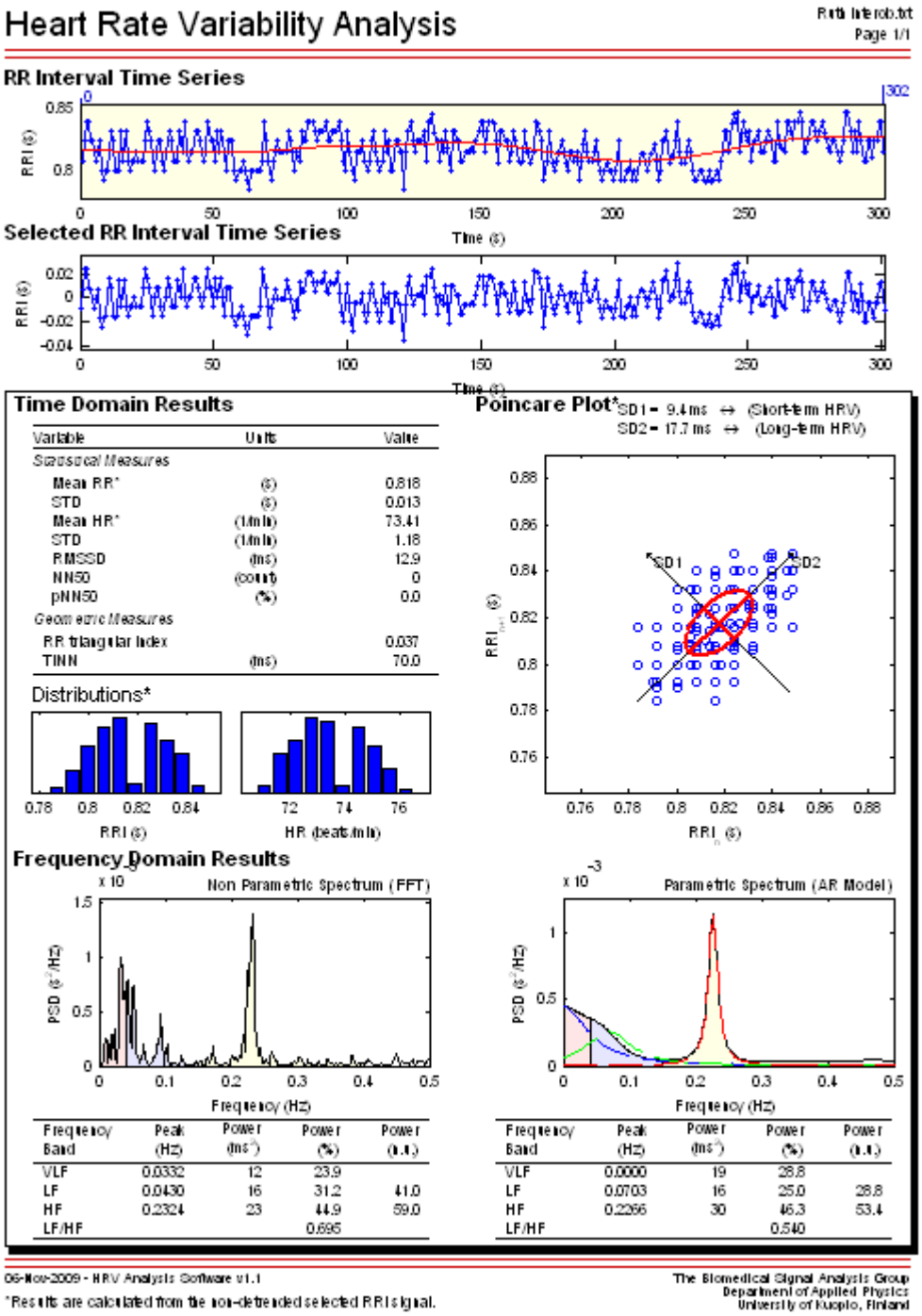


Figure 56 BioSignal HRV Observer 2 R-R analyses.

Vagal tone is represented by the High Frequency (HF) band and is calculated and displayed by BioSignal software. Only slight differences in HF power % are produced by the Inter-observer measurements of Observer 1 (45.7%), (Figure 55) and Observer 2 (46.3%), (Figure 56).

Inter-observer agreement of identical R-R measurements was 280/369=75.9%. Unmatched R-R intervals are still close in measurement with mean (817.6) and Median (816) values being identical (Table 24). This is also represented by a very tight standard deviation of 14.09 (observer 1) and 14.15 (observer 2) with no statistically significant difference between observers (p=0.809), (Figure 52). Mean difference between observers is (-0.05) ± 8.59 with limits of agreement (-8) and 8 (Figure 53).

3.4.3 Intra-observer Analysis

The same methods were employed as for the inter-observer analysis except that the same 5 minutes sample of data (n=369) was re-measured by Observer 2 (blind to the first run measurements) and then entered the data onto an Excel spreadsheet.

	Intra-observer Run 1	Intra-observer Run 2	Difference	Average
Total count (R-R intervals)	369	369	0.0	369
Mean	817.63	817.63	0.0	817.63
Standard Error of Mean	0.735	0.733	0.002	0.729
Standard Deviation	14.13	14.09	0.04	14.0
Variance	199.58	198.41	1.17	195.96
Coefficient of Variance	1.73	1.72	0.01	1.72
Minimum	784	784	0.0	784.0
Median	816	816	0.0	828
Maximum	848	848	0.0	848
Range	64.00	64.00	0.0	64.0
MSSD	85.73	90.80	5.07	84.99
Q1	808.00	808.00	0.0	808
Q3	830.00	829.00	0.0	828

Table 25 Descriptive statistics for R-R Intra-observer 2 analysis

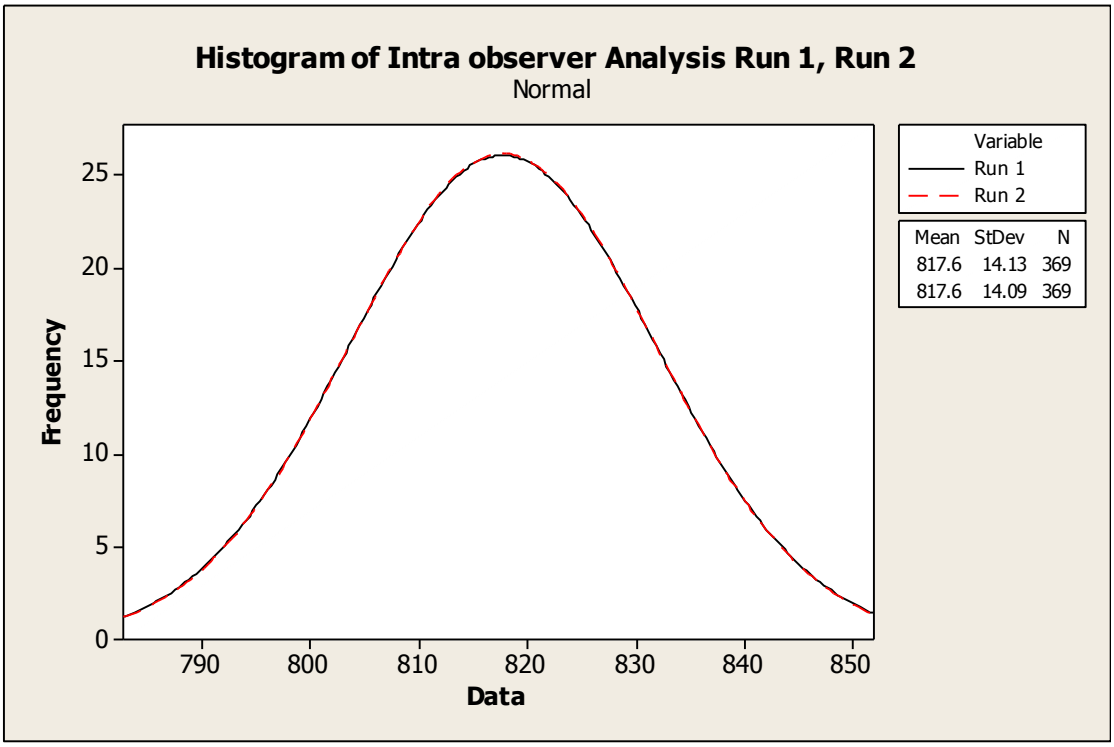


Figure 57 Histogram of Intra-observer 2 analyses.

With normal distribution, a paired t test was performed comparing Run 1 and Run 2 data. No significant difference was determined *p=0.976*

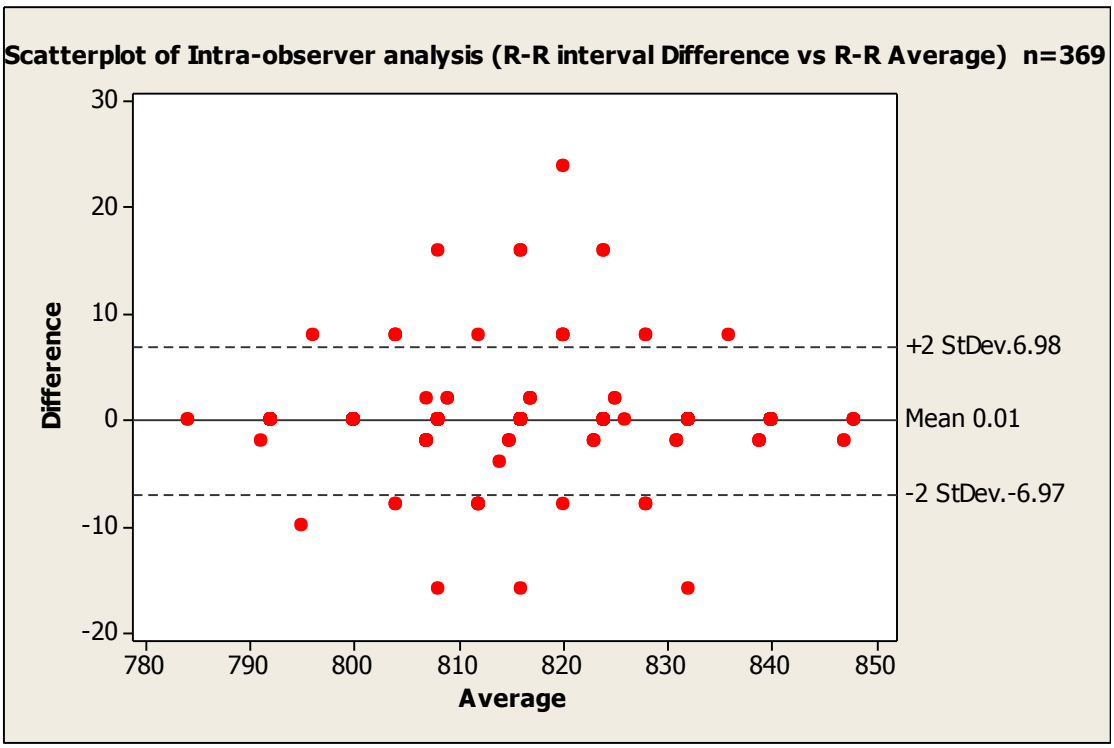


Figure 58 Bland & Altman scatterplot of Intra-observer 2 difference (baseline minus sub-clinical) versus average in R-R.

Mean Difference is 0.01 ± 6.97. Limits of agreement are (-4) and 2.

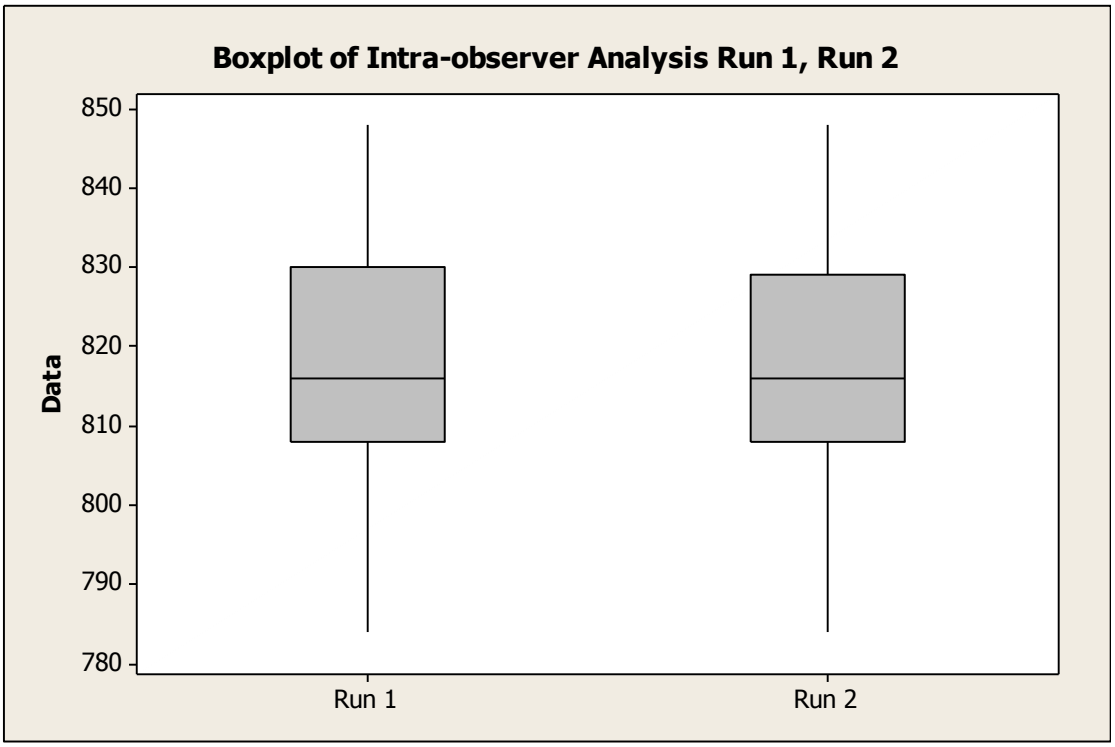


Figure 59 Boxplot Intra-observer 2 Run 1, Run 2

Observer 2 made two measurement studies of the same data. Mean R-R measurement of 817.63 with no difference between Run 1 and Run 2. Both Run 1 and Run 2 measured identical minimum and maximum measurements but the standard deviation and variance are slightly different at 0.04 and 1.17 milliseconds respectively. Run 1 and Run 2 measurements are closer for intra-observer measurement than that of inter-observer measurements.

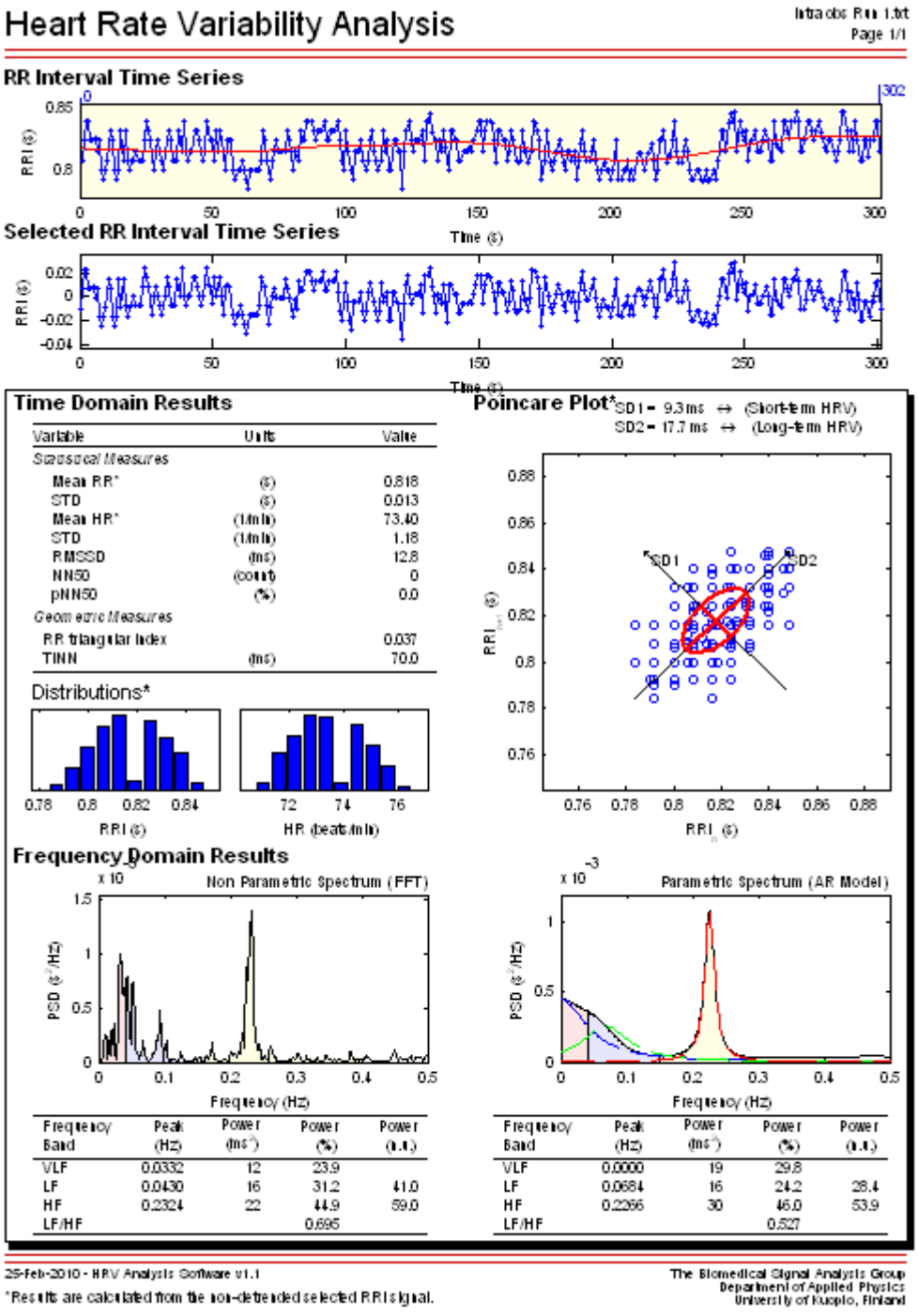


Figure 60 BioSignal HRV Intra-observer 2 Run 1 R-R analyses

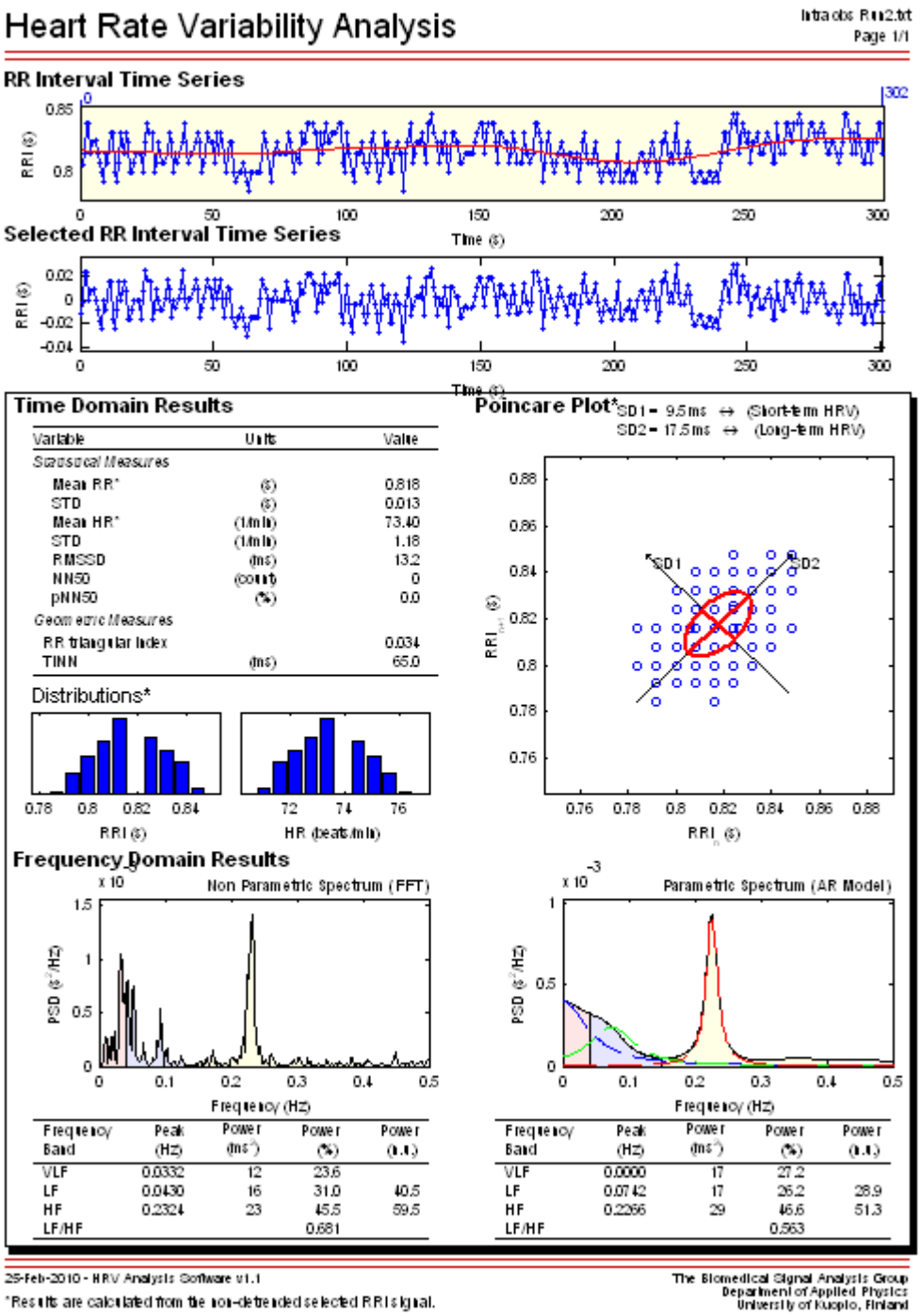


Figure 61 BioSignal HRV Intra-observer 2 Run 2 R-R analyses

Vagal tone is represented by the High Frequency (HF) band and is calculated and displayed by the BioSignal software. HF% is closely matched comparing Intra-observer Run 1 (46%), (Figure 60) and Run 2 (46.6%), (Figure 61).

3.4.5 Conclusion

Intra-observer agreement of identical R-R measurements was 300/369=81.3%. Unmatched R-R intervals are close in measurement with mean (817.6) and median (816) values being identical (Table 25). This is again represented by a very tight standard deviation of 14.13 (Run 1) and 14.09 (Run 2), with no statistically significant difference between runs of observations (p=0.976), (Figure 57). Mean difference between run 1 and run 2 is (-0.01) ± 6.97 with limits of agreement (-4) and 2 (Figure 58).

Inter-observer analysis shows a close measurement outcome of R-R intervals comparing observer 1 and observer 2. Intra-observer analysis shows an even closer match of R-R intervals comparing Run 1 and Run 2.

Chapter 23 BioSignal Heart Rate Variability: Counted Data.

3.5.1 BioSignal Analysis of Counted beats and Matched Baselines for Total Sub-clinical Seizures

Thirty-three sub-clinical seizures (R-R intervals n=8583) and matched R-R counted baseline studies (n=8583) were analysed from 11 patients, mean age 23.1 ± 18.7 years. Nine sub-clinical seizures (R-R interval n=2688) were derived from the right temporal lobe (5 patients) and five sub-clinical seizures (R-R intervals n=1307) were derived from the left temporal lobe (4 patients). Nineteen generalised sub-clinical seizures (R-R intervals n=4588) were analysed from two patients.

Only one mean value is produced to represent the entire baseline or sub-clinical epoch using the BioSignal HRV software. Thus although total data for right temporal lobe derived data was imported (from identical data used for CIPA) n=2688 baseline and n=2688 sub-clinical, 9 mean data values are given for both baseline and sub-clinical HF%. Left temporal lobe derived data was imported into BioSignal software n=1307 baseline and n= 1307 sub-clinical, 5 mean data values are produced for both baseline and sub-clinical HF%. Generalised data n=4588 was imported into BioSignal and 19 mean data values were produced for baseline and sub-clinical data.

Pt. ID	Baseline HRV (counted beats)				Sub-clinical HRV (counted beats)				Event (sec)
	RMSSD (ms)	SDNN (sec)	NN50 (count)	pNN50 (%)	RMSSD (ms)	SDNN (sec)	NN50 (count)	pNN50 (%)	
Pt 1	69.2	0.080	73	55.7	47.2	0.108	20	15.3	146
Pt 2	48.2	0.045	77	30.1	40.3	0.037	49	19.1	259
Pt 2	48.8	0.044	107	32.8	48.9	0.045	89	27.3	232
Pt 2	49.8	0.045	138	33.9	48.0	0.043	89	21.9	202
Pt 2	50.0	0.045	124	34.3	44.5	0.039	93	25.7	253
Pt 2	50.0	0.045	127	34.2	22.1	0.023	11	3.0	317
Pt 3	57.4	0.067	148	41.5	86.5	0.093	48	13.4	269
Pt 4	146.3	0.139	85	69.7	112.4	0.103	70	57.4	261
Pt 5	89.7	0.090	170	49.3	76.2	0.073	153	44.3	139
Pt 6	80.4	0.078	31	60.8	88.1	0.099	22	43.1	313
Pt 7	81.7	0.072	256	63.5	64.2	0.064	145	36.0	159
Pt 7	82.5	0.073	196	64.3	88.8	0.087	152	49.8	149
Pt 8	95.6	0.067	117	55.7	36.3	0.078	32	15.3	161
Pt 9	23.2	0.045	13	3.9	8.1	0.039	0	0.0	218
Pt 10	16.2	0.017	0	0.0	26.9	0.029	10	3.1	154
Pt 10	15.3	0.016	0	0.0	21.8	0.025	6	2.3	109
Pt 10	15.4	0.017	0	0.0	21.2	0.032	9	3.3	108
Pt 10	15.3	0.016	0	0.0	27.4	0.032	17	7.1	98
Pt 10	15.9	0.017	0	0.0	18.0	0.021	5	1.4	104
Pt 10	15.9	0.017	0	0.0	26.4	0.029	17	5.0	93
Pt 10	15.8	0.017	0	0.0	22.0	0.027	14	4.1	114
Pt 10	16.6	0.017	0	0.0	18.3	0.020	9	2.1	103
Pt 10	15.4	0.016	0	0.0	24.2	0.027	9	3.3	199
Pt 10	16.3	0.017	0	0.0	17.7	0.024	8	2.1	234
Pt 10	15.6	0.017	0	0.0	22.8	0.028	13	4.1	168
Pt 11	22.1	0.028	7	3.7	38.6	0.040	33	17.6	157
Pt 11	23.5	0.031	7	5.2	52.1	0.065	31	23.0	225
Pt 11	23.8	0.031	7	5.4	46.4	0.052	26	20	223
Pt 11	24.5	0.032	7	5.9	56.5	0.060	19	16	224
Pt 11	24.3	0.032	7	5.7	31.4	0.029	11	9.0	340
Pt 11	25.2	0.033	7	6.4	48.1	0.044	17	15.5	179
Pt 11	23.7	0.031	7	5.3	51.9	0.061	36	27.3	243
Pt 11	24.3	0.032	7	5.8	43.1	0.041	12	9.9	209
Total Rt	66.3	0.069	1049	39.7	60.1	0.064	622	23.3	230.9

Total Lt	75.7	0.069	613	47.2	60.7	0.072	351	27.3	200
Total Gen	18.5	0.024	56	1.4	31.0	0.034	302	6.9	172.8
Mean Total	40.54	0.041	52.1	20.4	43.22	0.049	38.64	16.6	192.8

Table 26 (above) Total patient & group data for baseline & sub-clinical Heart Rate Variability (HRV) RMSSD, SDNN, SDNN50 count, pNN50 for counted data.

3.5.2 NN50 and pNN50 for Counted HRV

NN50 and pNN50 data approximately halve during right temporal sub-clinical (NN50 1064 to 626, pNN50 39.7 to 23.3) and left temporal sub-clinical (NN50 615 to 356, pNN50 47.2 to 27.3) but generalised sub-clinical seizures increase (NN50 64 to 315, pNN50 1.4 to 6.9), (Table 26). The NN50 is the number of intervals of successive NN intervals increased more than 50msec. pNN50 is the proportion derived by dividing NN50 by the total NN intervals. Generalised sub-clinical seizures again are characteristically different compared to sub-clinical seizures derived from either the right or left temporal lobes. NN50 and pNN50 data approximately halve during right temporal sub-clinical (NN50 1064 to 626, pNN50 39.7 to 23.3) and left temporal sub-clinical (NN50 615 to 356, pNN50 47.2 to 27.3) but generalised sub-clinical seizures have a low baseline and show an increase NN50 during sub-clinical seizures (NN50 64 to 315, pNN50 1.4 to 6.9), (Table 26). Bland & Altman plots show that SDNN derived from data during right temporal lobe activity has the largest limits of agreement and range (0.7 to 2.0, range 1.2) compared to SDNN derived from data during left temporal lobe activity (0.5 and 1.2, range 0.7), and then generalised data for SDNN (0.5 to 0.8, range 0.4), (Figure 67, Table 30). This result would indicate that during generalised sub-clinical seizures, heart rate variability reduces compared to baseline.

3.5.3 High Frequency HRV: Total Sub-clinical Seizures

Pt. ID	Baseline HRV HF (counted beats)			Sub-clinical HRV HF(counted beats)			Difference HRV HF B-S (counted beats)		
	HF power %	HF power ms^2	HF power nu	HF power %	HF power ms^2	HF power nu	HF power %	HF power ms^2	HF power nu
Pt 1	45.5	1692	50.1	1.5	87	12.0	<44	<1605	<38.1
Pt 2	53.1	393	42.2	58.6	287	62.6	>5.5	<106	>20.4
Pt 2	60.5	465	50.3	44.8	307	54.5	<15.7	<158	>4.2
Pt 2	63.3	512	53.1	60.5	652	66.3	<2.8	>140	>13.2
Pt 2	61.7	488	50.7	56.9	380	58.5	<4.8	<108	>7.8
Pt 2	61.9	503	52.6	42.0	99	39.8	<19.9	<404	<12.8
Pt 3	45.5	657	31.3	27.5	1187	29.3	<18.0	>530	>2
Pt 4	36.8	2654	30.4	57.8	3973	59.1	>21.0	>1319	>28.7
Pt 5	40.8	1170	28.9	33.0	645	25.8	<7.8	<525	<3.1
Pt 6	27.8	1203	91.7	23.0	888	21.8	<4.8	<315	<69.9
Pt 7	81.1	1843	73.8	53.5	1039	47.5	<27.6	<804	<26.3
Pt 7	79.5	1882	73.0	52.5	2042	60.8	<27	>160	<12.2
Pt 8	59.8	906	45.3	1.5	59	77.8	<58.3	<847	>32.5
Pt 9	6.0	54	98.9	0.3	2	2.4	<5.7	<52	<96.5
Pt 10	58.2	69	56.3	57.8	235	59.8	<0.4	>166	>3.5
Pt 10	52.5	57	54.6	45.3	133	48.5	<7.2	>76	<6.1
Pt 10	50.6	59	54.0	22.3	109	21.3	<28.3	>50	<32.7
Pt 10	51.7	58	54.1	53.8	270	48.7	>2.1	>212	<5.4
Pt 10	54.7	68	55.6	37.7	73	34.8	<17	>5	<20.8
Pt 10	53.3	65	54.8	46.2	207	43.1	<7.1	>142	<11.7
Pt 10	54.2	66	55.4	43.8	145	78.2	<10.4	>79	>22.8
Pt 10	58.6	77	59.3	40.4	78	40.2	<18.2	>1	<19.1
Pt 10	52.7	59	55.6	39.0	134	36.7	<13.7	>75	<18.9
Pt 10	57.0	74	58.4	21.3	55	58.3	<35.7	<19	<0.1
Pt 10	52.6	64	56.3	32.7	116	60.2	<19.9	>52	>3.9
Pt 11	27.8	89	36.9	38.3	267	73.6	>10.5	>178	>36.7
Pt 11	22.5	88	29.8	21.4	565	19.2	<1.1	>477	<10.6
Pt 11	22.7	90	28.7	25.5	254	20.6	>2.8	>164	<8.1
Pt 11	21.7	92	26.8	26.9	757	21.5	>5.2	>665	<5.3
Pt 11	22.7	95	28.2	56.3	230	51.1	>33.6	>135	>22.9
Pt 11	21.6	98	26.8	36.6	240	28.8	>15	>142	>2

Pt 11	22.3	88	29.0	19.5	248	15.3	<2.8	>160	<13.7
Pt 11	22.3	94	27.7	36.8	257	32.1	>14.5	>163	>4.4
Total Rt	37.5	810	33.7	26.5	454	49.6	<11	<356	>15.9
Total Lt	51.1	1200	93.5	30.3	804	50.0	<20.8	<396	<43.5
Total Gen	28.5	78	43.9	33.8	165	27.4	>5.3	>87	<16.5
Mean Total	45.55	481	49.11	36.82	485	42.73	<8.73	<4	<6.38

Table 27 (above).Total patient & group data for baseline, sub-clinical & Difference in Heart Rate Variability (HRV) for High Frequency (HF) counted data.

Statistically significant changes in HF% occurred comparing baseline and sub-clinical values. Baseline HF% 45.6 ± 18.3 for total sub-clinical seizures alters to sub-clinical HF% 36.8 ± 16.9 (Table 27) showing a definite alteration in HF% (*p=0.049),* (n=33). Right baseline HF% 52.1 ± 10.2 alters to sub-clinical HF% 42.5 ± 19.4, (*p=0.151),* (n=9). Left baseline HF% 50.8 ± 33.0 alters more dramatically to sub-clinical HF% 26.2 ± 26.1 (*p=0.065),* (n=5). Generalised baseline HF% 41.0 ± 16.0 alters to sub-clinical HF% 36.9 ± 12.0, (*p=0.291),* (n=19), (Table 27).

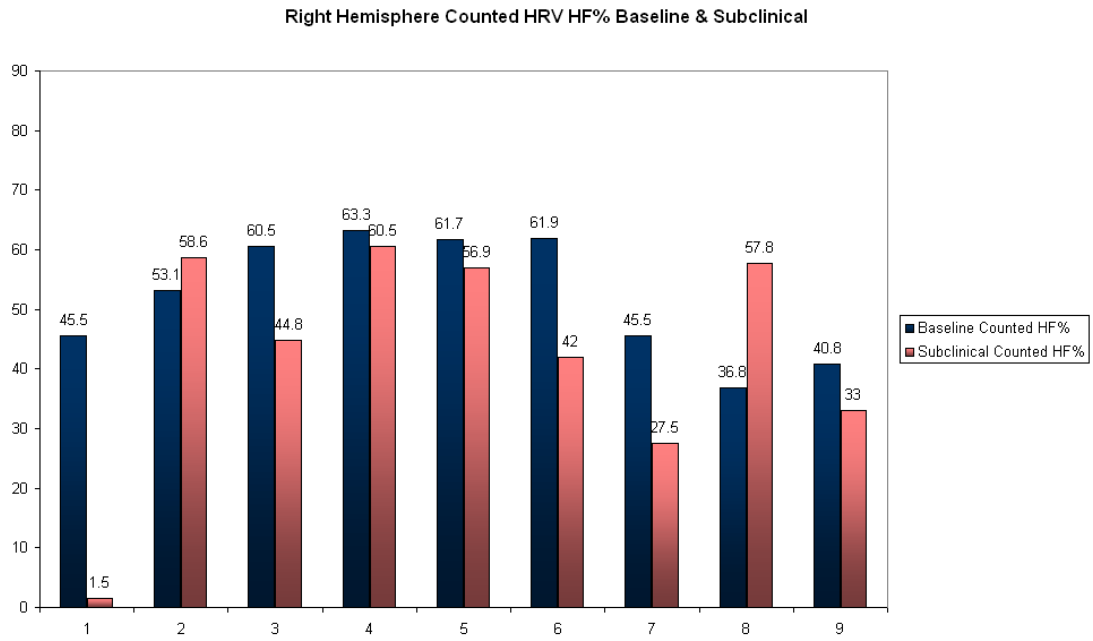


Figure 62 Bar chart baseline & sub-clinical HF% HRV for right hemisphere counted data.

Figure 62 shows counted HF% derived from sub-clinical seizure from the right temporal lobe. 7/9 seizures resulted in a decrease in HF% (77%) compared to baseline measurements, indicating that most sub-clinical seizures derived from the right temporal lobe results in a decrease in parasympathetic activity and increased heart rate.

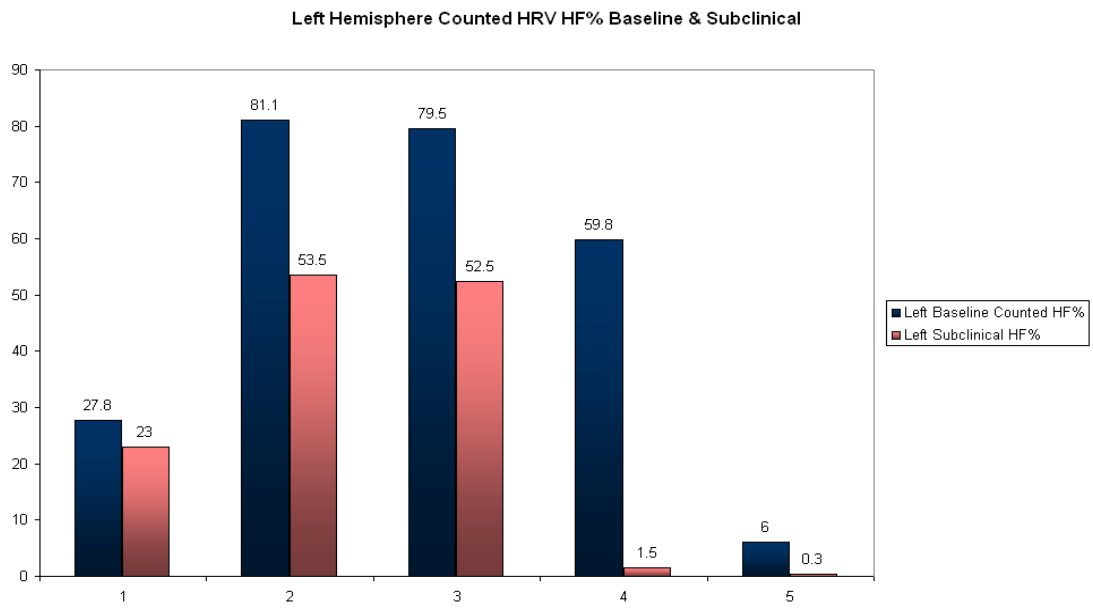


Figure 63 Bar chart baseline & sub-clinical HF% HRV for left hemisphere counted data.

Figure 63 presents counted HF% derived from sub-clinical seizures from the left temporal lobe. All sub-clinical seizures from the left temporal lobe resulted in a decrease in HF% suggesting an increase in heart rate.

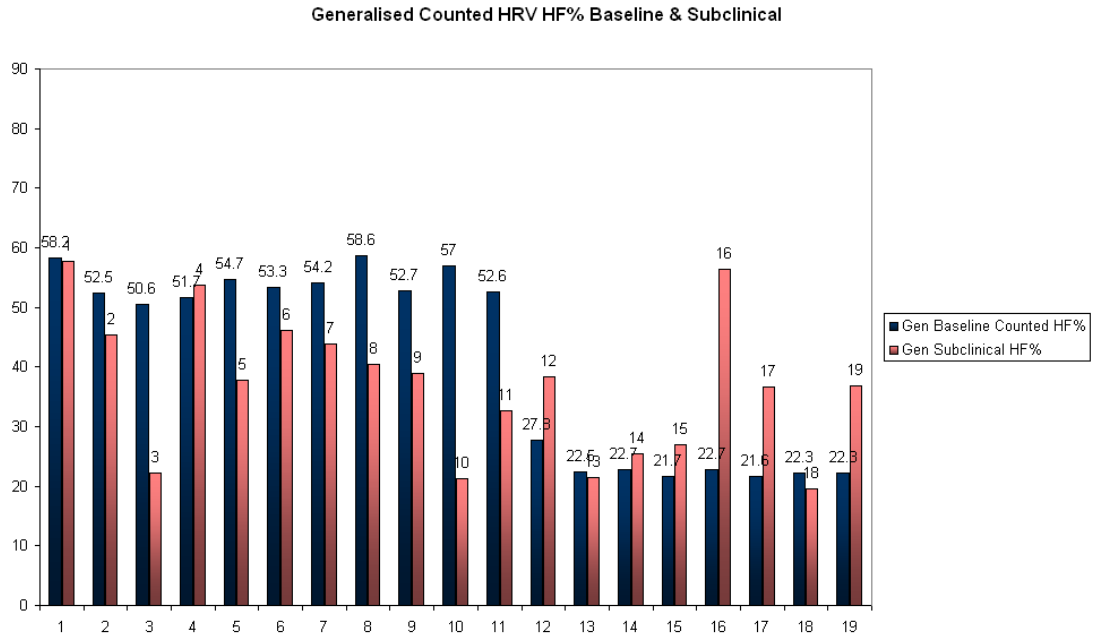


Figure 64 Bar chart baseline & sub-clinical HF% HRV for generalised counted data.

Figure 64 presents HF% from two patients who had generalised sub-clinical seizures. There is a general split in results with one patient (sub-clinical seizures 1 to 11) having 10/11 decreased HF% during sub-clinical seizures compared to baseline. The second patient (sub-clinical seizures 12 to 19) having 6/8 increased HF% during sub-clinical seizures.

Estimation of Short term HRV components
Root Mean Square of Successive Differences (RMSSD)
Counted beats: matched baseline & sub-clinical

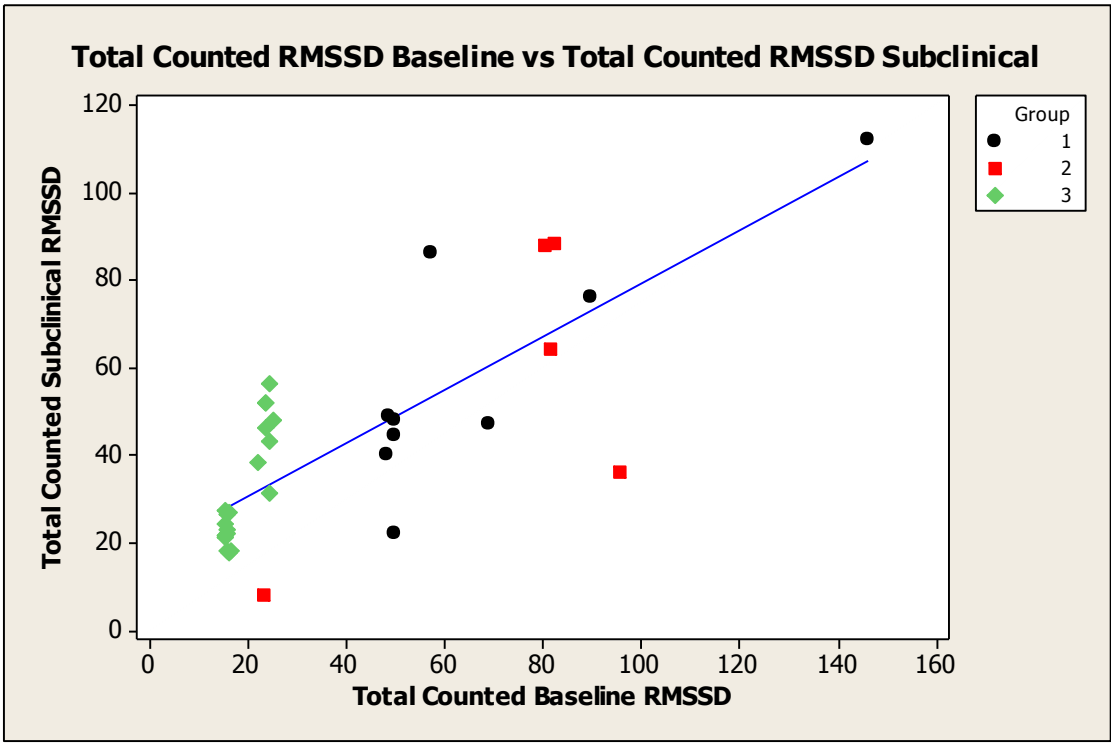


Figure 65 Scatterplot baselines RMSSD versus sub-clinical RMSSD for total mean counted HRV data.

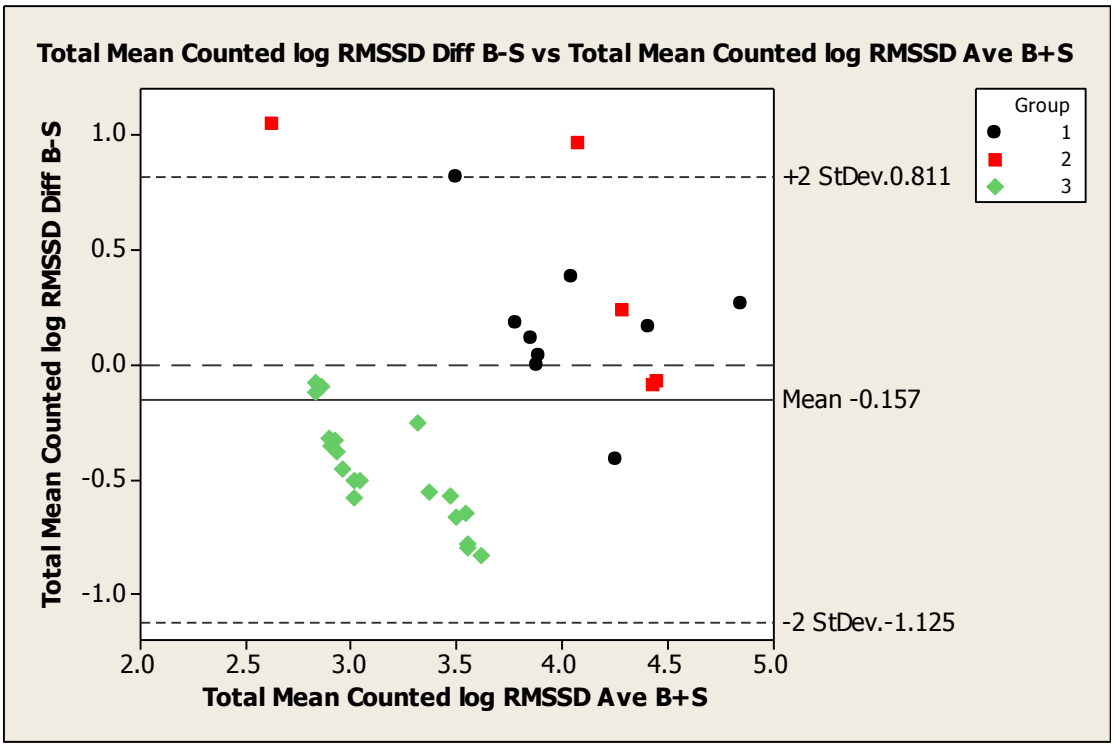


Figure 66 Bland & Altman scatterplot log RMSSD difference (baseline minus sub-clinical) versus average for total mean counted HRV data.

RMSSD is the square root of the mean squared differences of successive NN intervals and is an estimate of short term HRV. Generalised total baseline RMSSD (18.5) is much lower than right RMSSD (66.3) and left RMSSD (75.7) baseline studies (Table 26). During generalised sub-clinical seizures, RMSSD increases (31.0) whereas, right temporal sub-clinical RMSSD (60.1) and left temporal sub-clinical RMSSD ((60.7) show reduced short term HRV compared to baseline. Generalised sub-clinical seizures again are characteristically different compared to sub-clinical seizures derived from either the right or left temporal lobes.

Bland & Altman analysis of log RMSSD difference between HRV derived during total baseline and total sub-clinical seizures show limits of agreement of log values are (-0.8) and 0.8 with antilog values of 0.4 and 2.3. Limits of agreement of log RMSSD derived during baseline and right temporal sub-clinical seizures are -0.4 and 0.8 with antilog values of 0.7 and 2.3 (Range of 1.6 seconds). Limits of agreement of log RMSSD derived during baseline and left sub-clinical seizures are (-0.1) and 1.1 with antilog values of 0.9 and 3.0 (Range of 2 seconds). Limits of agreement of log RMSSD derived during baseline and generalised sub-clinical seizures are (-0.8 and –0.1) with antilog values of 0.4 and 0.9 (Range of 0.5 seconds), (Figure 66, Table 30). Results indicate that there is less short term variability during generalised sub-clinical seizures and baseline measurements compared to HRV data derived during right or left temporal lobe sub-clinical seizures.

Standard Deviation of Normal-to-Normal Beat variation (SDNN)

The **SDNN** is the standard deviation of the NN intervals, which is the square root of variance and is an overall estimate of HRV. It is possible to compare counted baseline studies and matched counted sub-clinical studies as they are of equal number of NN intervals. It is inappropriate to compare individual patient studies as each event is of a different duration.

Using Bland & Altman plots to analyse the difference versus the average for matched counted baseline R-R studies and counted sub-clinical R-R studies, the smallest range in limits of agreement for SDNN is seen with generalised sub-clinical seizures (0.5 and 0.8), (Figure 68) indicating the smallest heart rate variability compared to right (0.7, 2.0) and left (0.5, 1.2) temporal sub-clinical seizure manifestations in HRV.

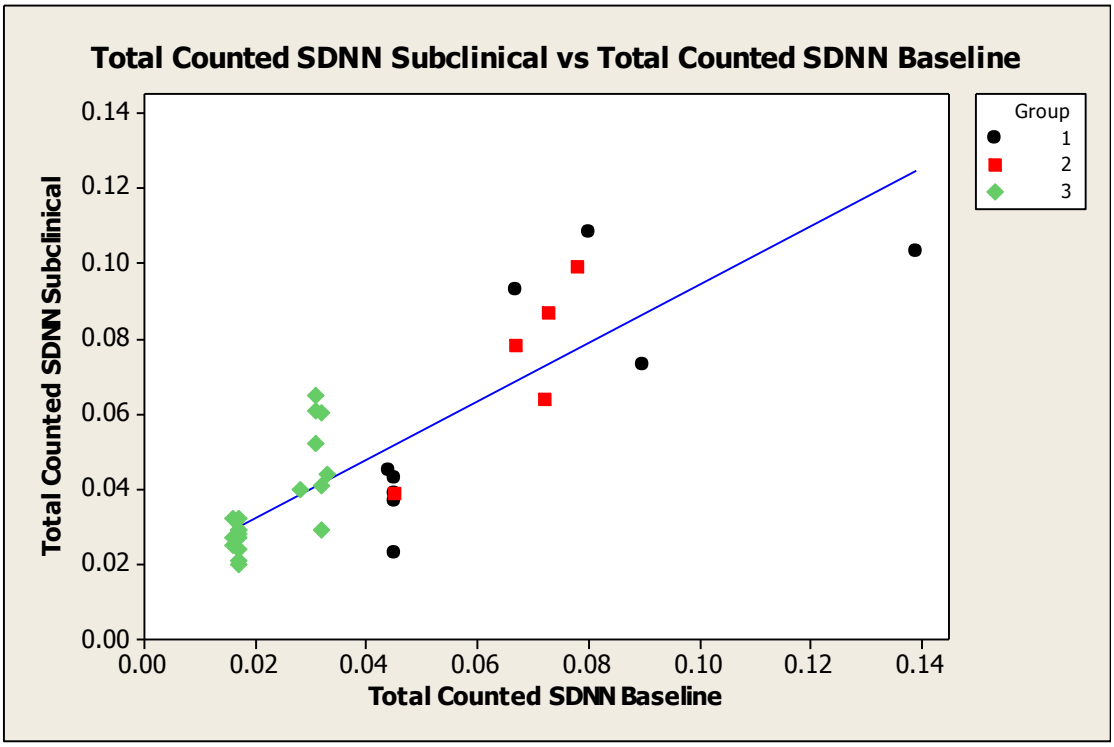


Figure 67 Scatterplot baselines SDNN versus sub-clinical SDNN for total mean counted HRV data.

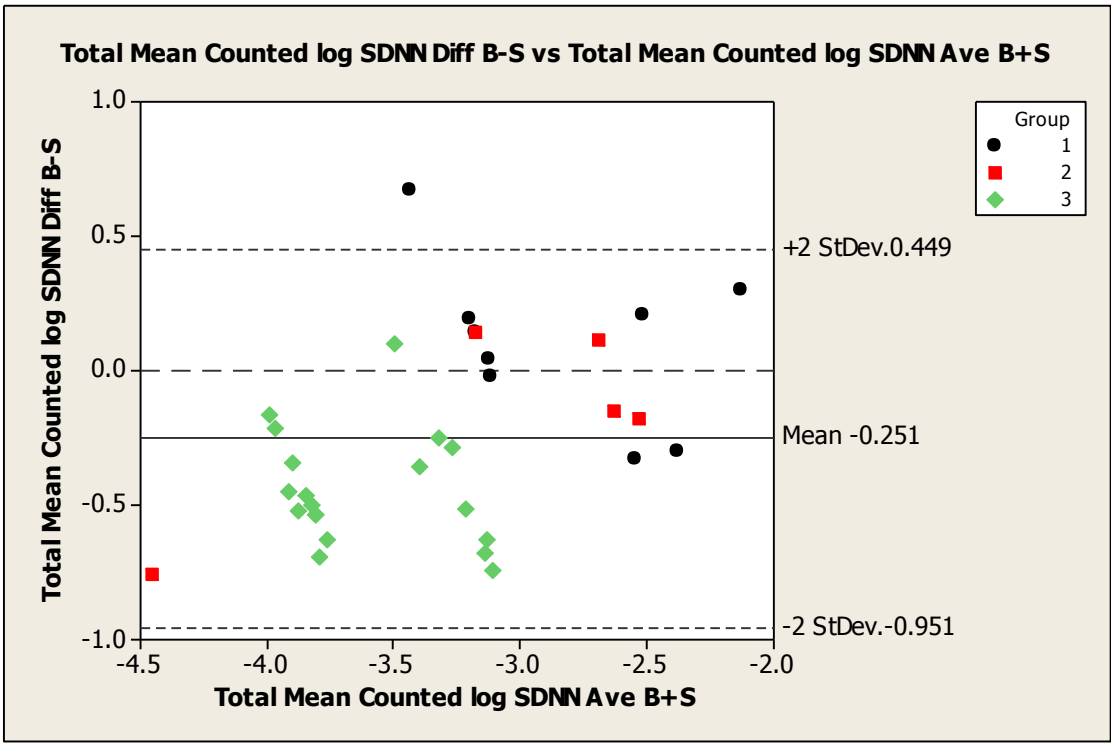


Figure 68 Bland & Altman scatterplot log SDNN difference (baseline minus sub-clinical) versus average for total mean counted HRV data.

Limits of agreement of log values for total sub-clinical seizures are (–0.8) and 0.3 from the Bland & Altman plot with antilog values of 0.5 and 1.3. Limits of agreement of log values for SDNN derived during right sub-clinical seizures compared to baseline measurements are (–0.3) and 0.7 with antilog values are 0.7 and 2.0 (Range of 1.2 seconds). Limits of agreement of log values for SDNN derived during left temporal sub-clinical seizures compared to baseline measurements are (–0.8) and 0.1 with antilog values of 0.5 and 1.2 (Range of 0.7 seconds). Limits of agreement of log values for SDNN derived during generalised sub-clinical seizures compared to baseline measurements are (–0.740 and –0.162) with antilog values of 0.5 and 0.8 (Range of 0.4 seconds). This result indicates that overall estimation of HRV is smallest during generalised sub-clinical seizures compared to HRV derived during right or left sub-clinical seizures (Figure 68, Table 30).

Standard Deviation of Heart Rate

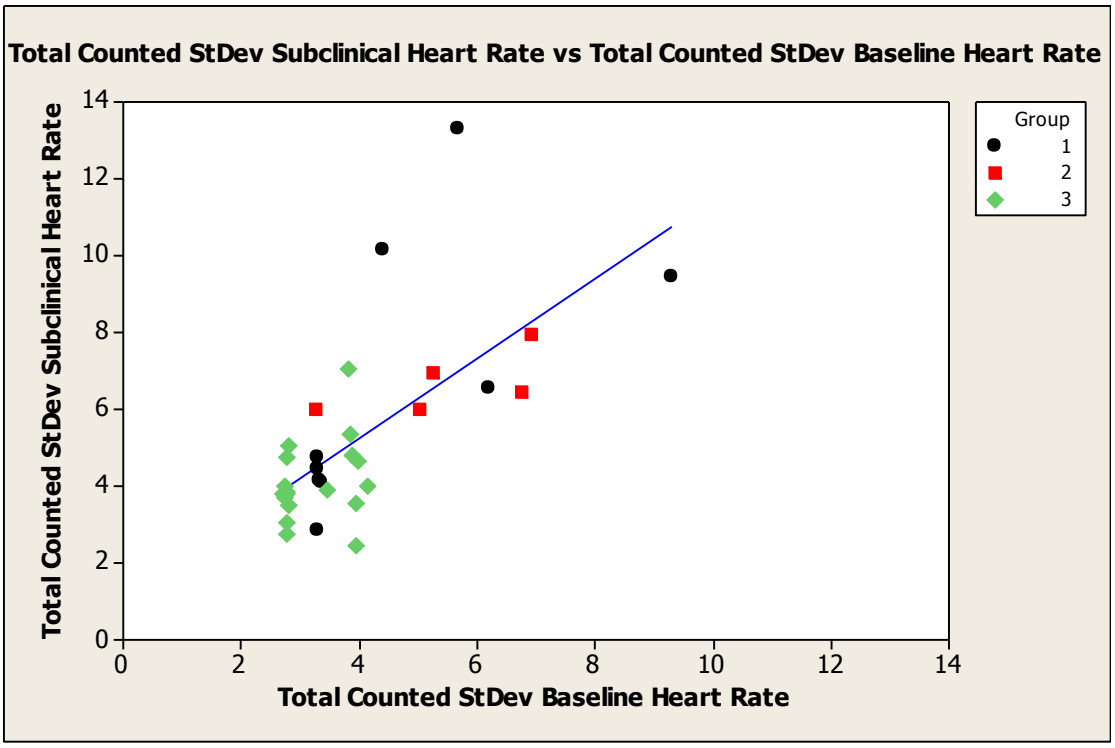


Figure 69 Scatterplot baselines standard deviation of heart rate versus sub-clinical standard deviation of heart rate for total mean counted HRV data.

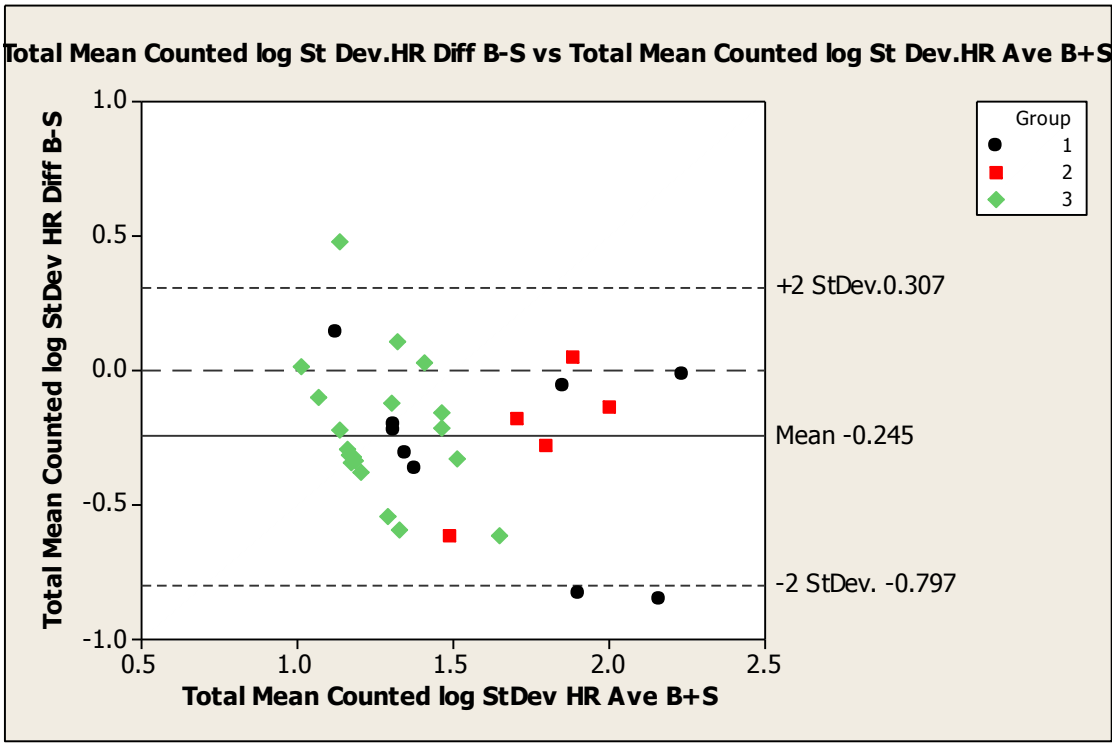


Figure 70 Bland & Altman scatterplot log standard deviation of heart rate difference (B-S) versus average for total mean counted HRV data.

Limits of agreement of log values for total standard deviation of heart rate during total sub-clinical seizures are (-0.6) and 0.2 with antilog values 0.5 and 1.2. Limits of agreement of log values for standard deviation of Heart Rate during right temporal lobe seizures are (-0.8) and 0.2 with antilog values of 0.4 and 1.2 (Range of 0.7 beats per minute). Limits of agreement of log values for standard deviation of heart rate during left temporal lobe seizures are (-0.6) and 0.1 with antilog values are 0.5 and 1.0. (Range of 0.5 beats per minute). Limits of agreement of log values for standard deviation of heart rate during generalised sub-clinical seizures are (-0.6) and 0.1 with antilog values of 0.5 and 1.1 (Range of 0.7/min). This result shows that changes in mean heart rate are small during sub-clinical seizures compared to baseline measurements.

HF Power ms^2 HRV Counted Beats

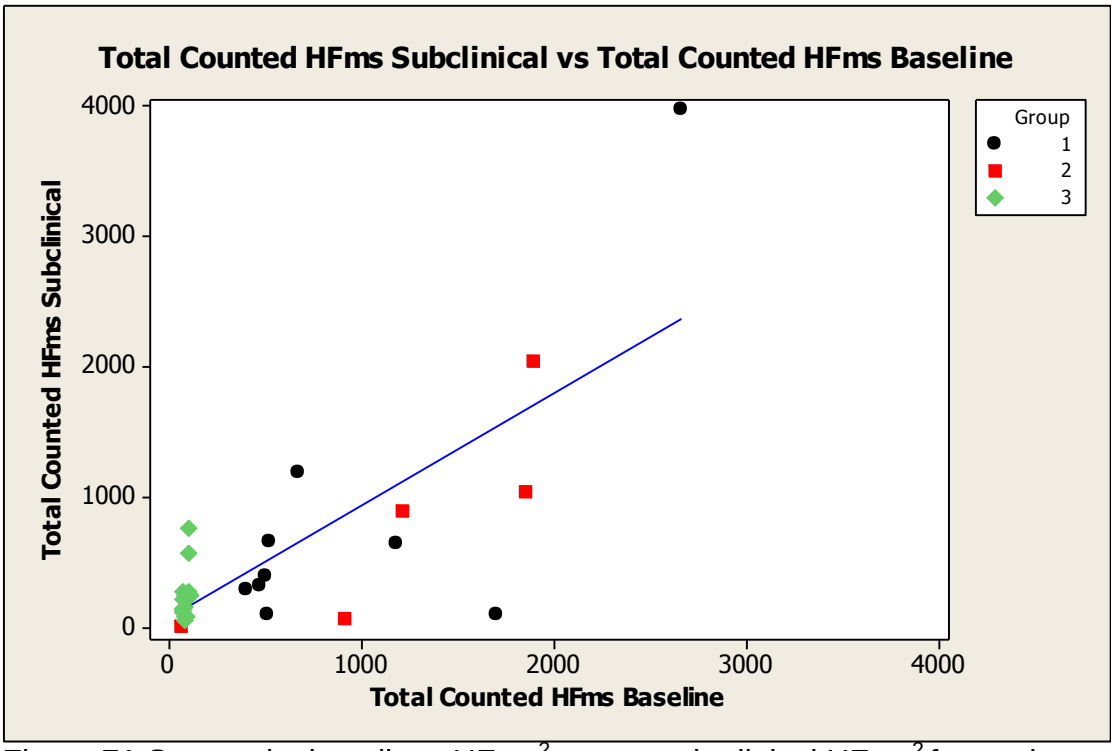


Figure 71 Scatterplot baselines HFms^2 versus sub-clinical HFms^2 for total mean counted HRV data.

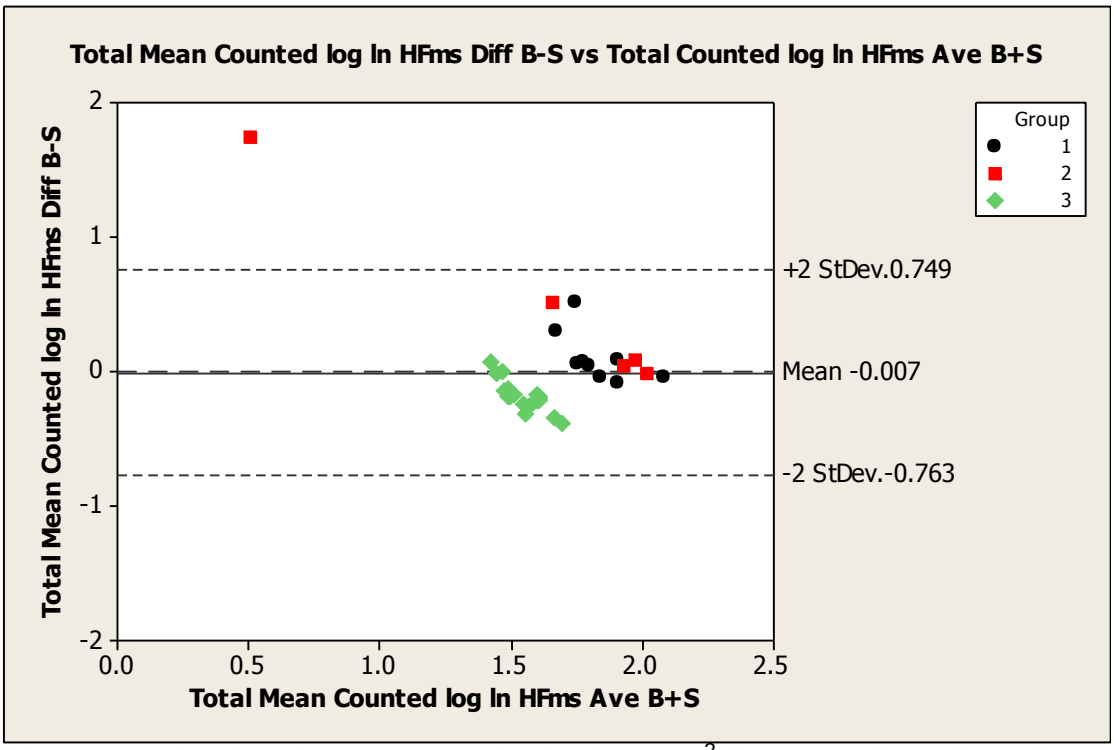


Figure 72. Bland & Altman scatterplot log lnHFms^2 difference (baseline minus sub-clinical) versus log lnHFms^2 average for total mean counted HRV data.

Limits of agreement of log ln values for HRV HFms^2 for total sub-clinical seizures are (–0.4) and 0.5 with ln (natural log) of 0.7 and 1.7 power. Limits of agreement of log ln for HRV HFms^2 for right temporal sub-clinical seizures are (–0.1) and 0.3 with ln (natural log) of 0.9 and 1.4. (Range of 0.4 mean counted HRV HFms^2 power). Limits of agreement of log ln for HRV HFms^2 for left temporal sub-clinical seizures are (–0.1) and 1.8 with ln (natural log) of 1.0 and 2.8. (Range of 1.8 mean 'counted' HRV HFms^2 power). Limits of agreement of log ln for HRV HFms^2 for generalised sub-clinical seizures are (–0.383) and 0.017 with ln (natural log) of 0.7 and 1.0. (Range of 0.3 mean 'counted' HRV HFms^2 power), (Figure 72).

HF% HRV (Counted Beats)

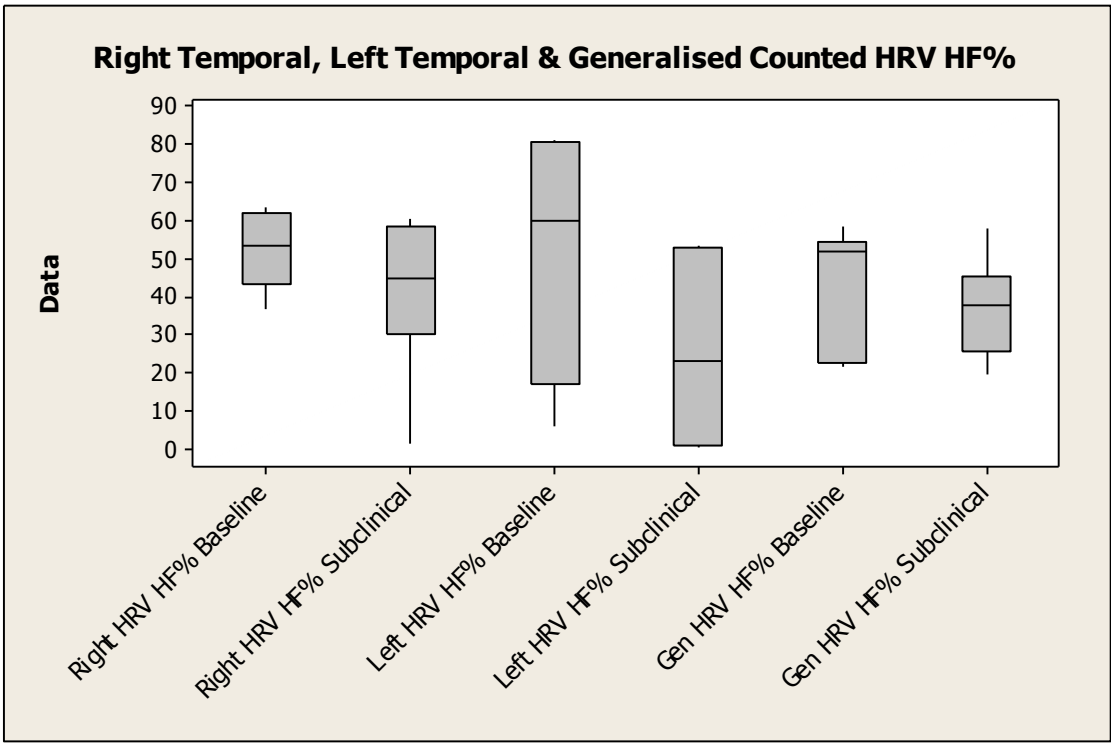


Figure 73 Boxplot right, left & generalised baseline & sub-clinical mean counted HRV HF%

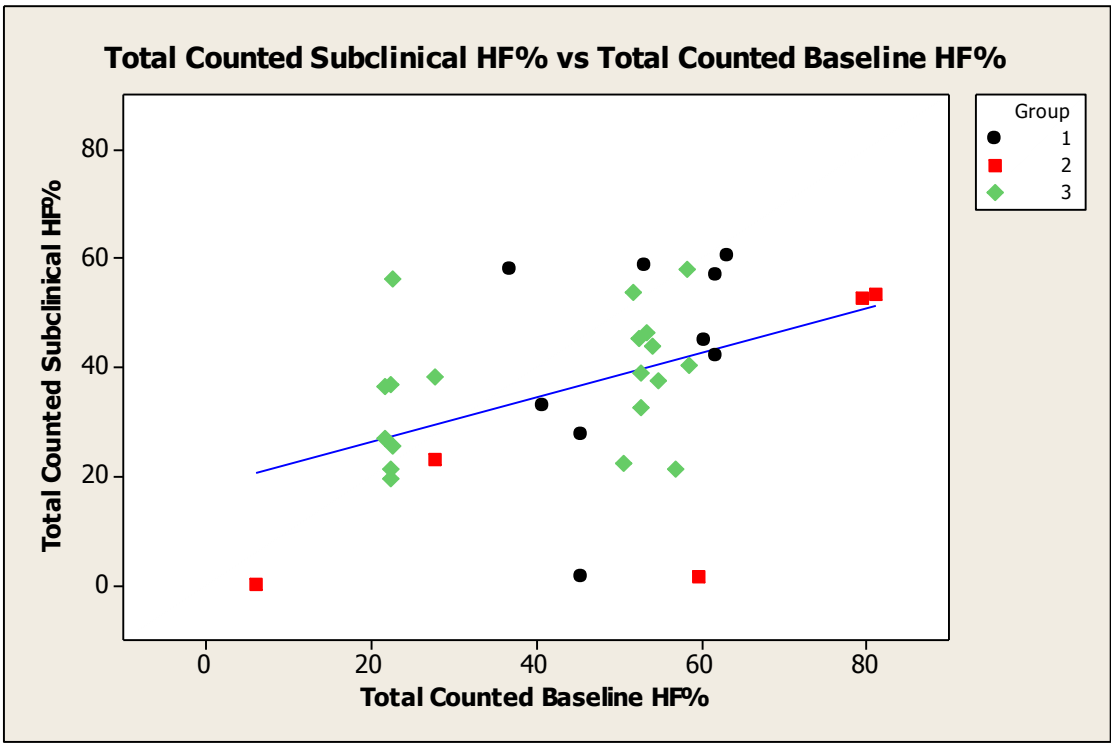


Figure 74 Scatterplot baselines HF% versus sub-clinical HF% for total counted HRV data.

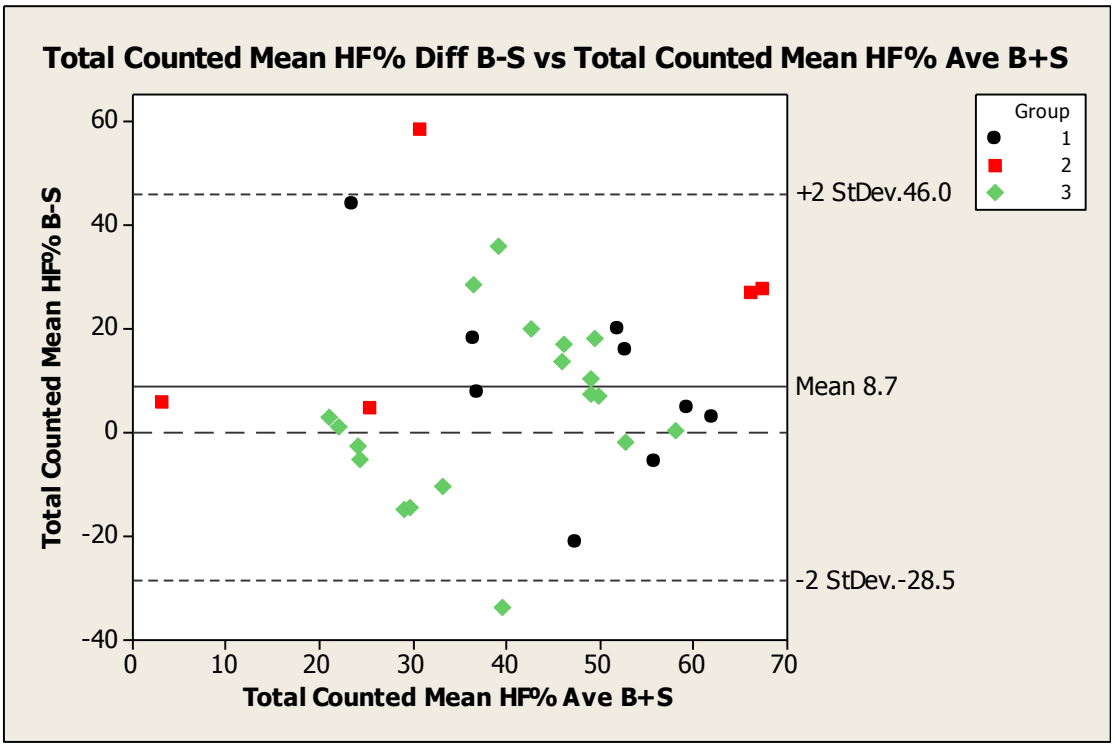


Figure 75 Bland & Altman scatterplot of HF% difference (baseline minus sub-clinical) versus HF% average for total mean counted data.
Group key 1=right 2=left 3=generalised HF%

Limits of agreement are 44.0 and (–21) for counted HF% during total sub-clinical seizures compared to baseline measurements. Limits of agreement are 44 and (–21) for counted HF% derived during right temporal lobe sub-clinical seizures. (Range of 65%) Limits of agreement are 58.3 and 4.8 for counted HF% derived during left temporal lobe sub-clinical seizures. (Range of 53.5%) Limits of agreement are 35.7 and (–15) for counted HF% derived during generalised sub-clinical seizures (range of 50.7%). This result shows a fairly similar spread of HRV HF% for all groups. The smallest HRV HF% is found marginally in generalised sub-clinical seizures compared to baseline measurements (Figure 75, Table 30).

Many researchers measure $HFms^2$ as the main parasympathetic component of HRV. ln $HFms^2$ gives the widest limits of agreement and range during left temporal lobe activity (1.0 to 5.8, range 4.8). The ln $HFms^2$ is much less (0.9 to 1.4, range 0.5). The smallest limits of agreement and range are from generalised data (0.7 to 1.0, range 0.3). When all baseline ln $HFms^2$ data is compared to sub-clinical ln $HFms^2$ data, poor statistical significance (*p=0.980*) is found (Figure 77). Poor correlations are found between $HFms^2$ and CIPA and are investigated in the final chapter.

	Baseline Counted HF%				Sub-clinical Counted HF%				
	n	Mean HF% ±2StDev.	Median HF%	Mean HR	n	Mean HF% ±2StDev.	Median HF%	Mean HR	*p</=*
Right Temporal HF%	9 (2688)	52.1 ±10.2	53.1	66.4	9 (2688)	42.5 ±19.4	44.8	83.3	0.151
Left Temporal HF%	5 (1307)	50.8 ±33.0	59.8	68.2	5 (1307)	26.2 ±26.1	23.0	80.3	0.065
Generalised HF%	19 (4588)	41.0 ±16.0	51.7	95.7	19 (4588)	36.9 ±12.0	37.7	88.5	0.291
Total HF%	33 (8583)	45.6 ±18.3	52.5	82.3	33 (8583)	36.8 ±16.9	38.3	85.6	0.049

Table 28 Total & Sub-Total Baseline HRV HF%, Total & Sub-Total Sub-clinical HRV HF% for counted data (Wilcoxon Two Sample Test).

Sub-clinical seizures derived from the right or left temporal lobes demonstrate a decrease in HF% indicating a decrease in vagal tone and resulting in an increase in heart rate, similar to CIPA results. Generalised data shows a mixture of an increase and decrease in HF% but overall shows an increase in HF% indicating an increase in vagal tone resulting in a decrease in heart rate, again similar to CIPA results.

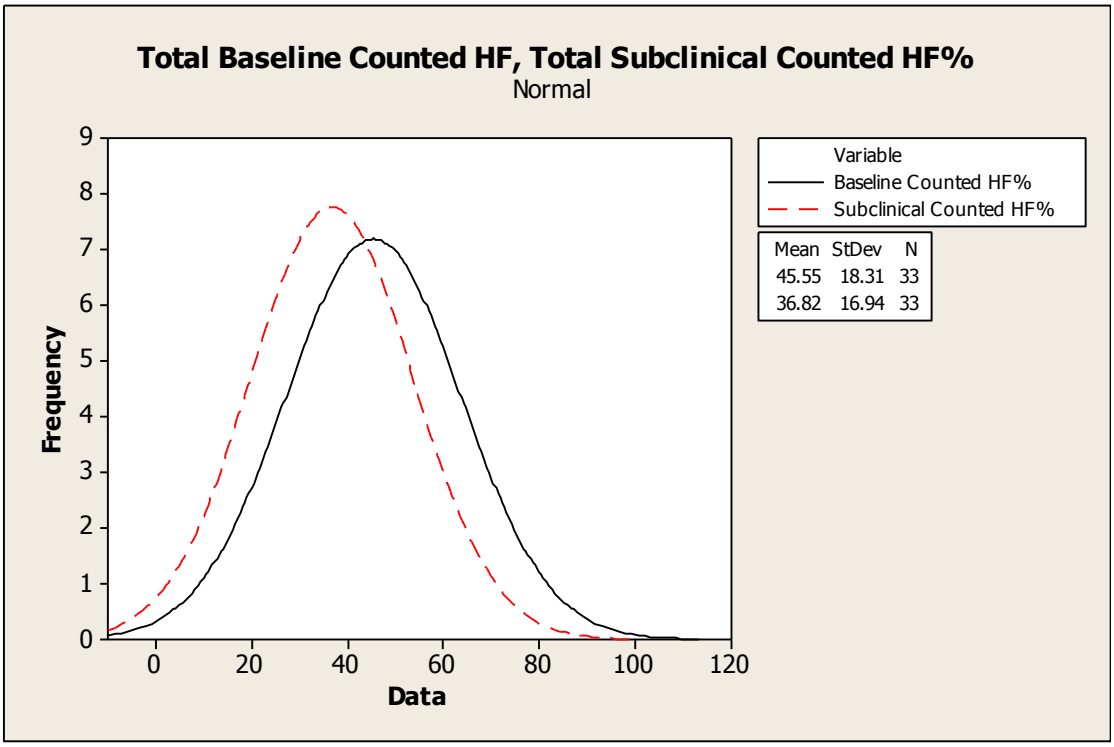


Figure 76 Histogram of HF% baseline, HF% sub-clinical total counted HRV data. Total HRV HF% counted beats (*p=0.049*).

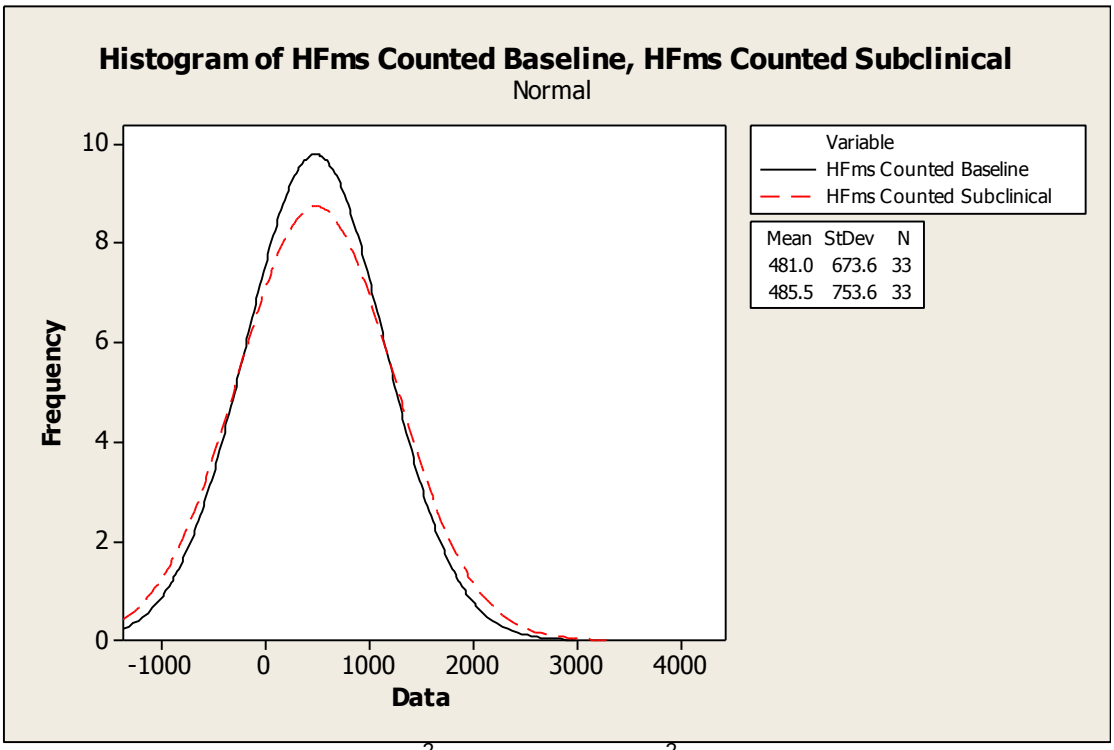


Figure 77 Histogram of $HFms^2$ baseline, $HFms^2$ sub-clinical total counted HRV data. Total HRV $HFms^2$ counted beats (*p=0.980*)

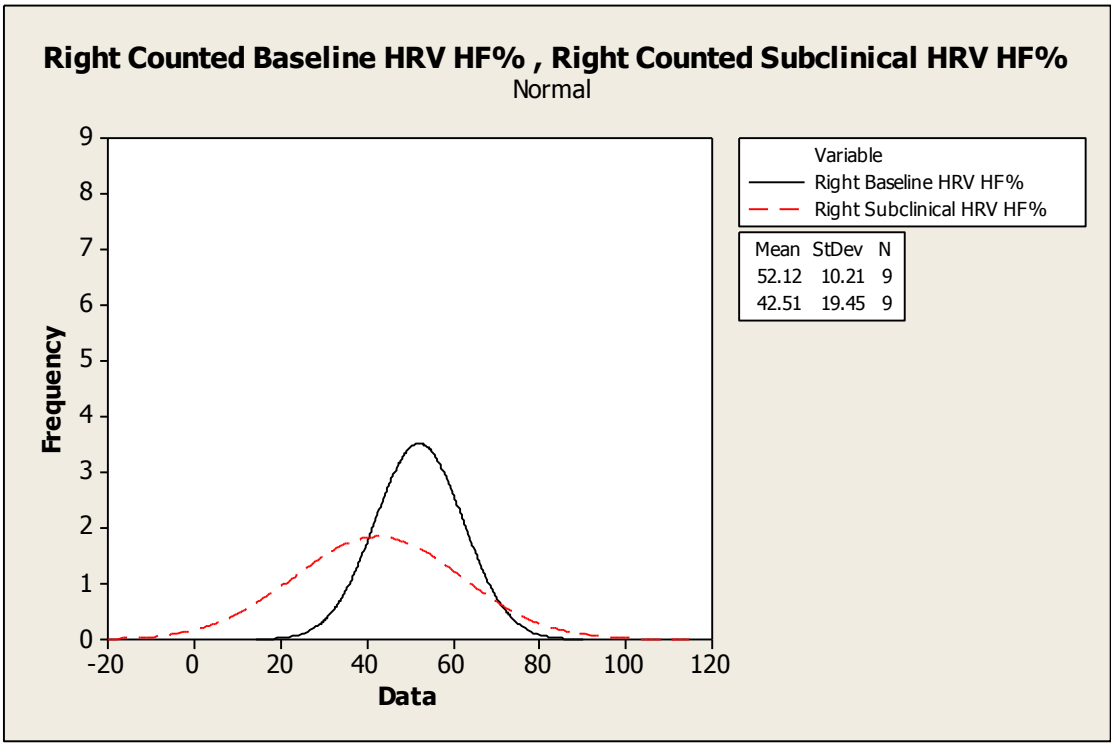


Figure 78 Histogram of right counted HRV HF%, right counted sub-clinical HRV HF%

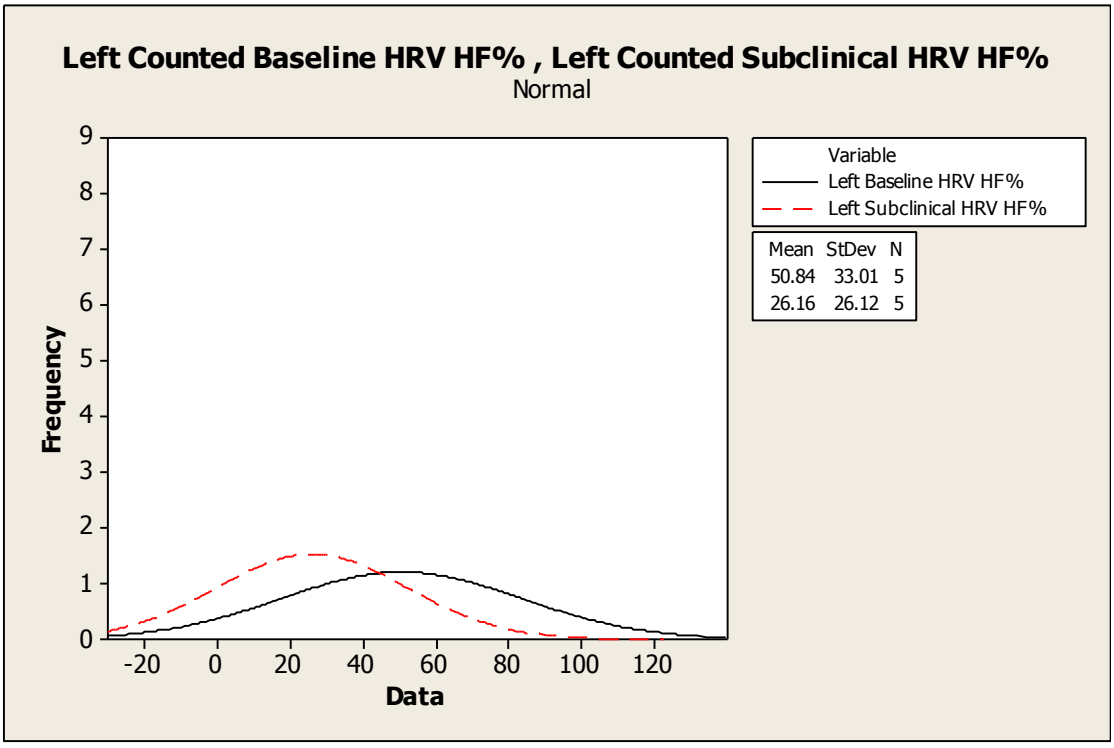


Figure 79 Histogram of left counted HRV HF%, left counted sub-clinical HRV HF%

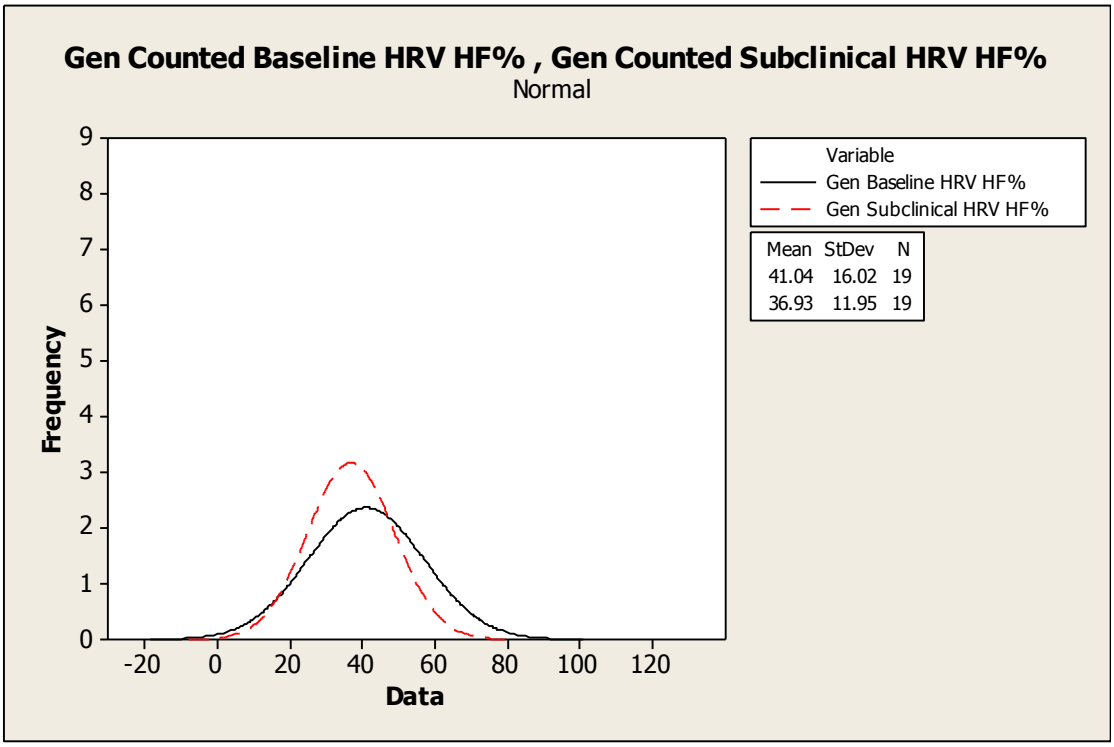


Figure 80 Histogram of generalised counted HRV HF%, generalised counted sub-clinical HRV HF%

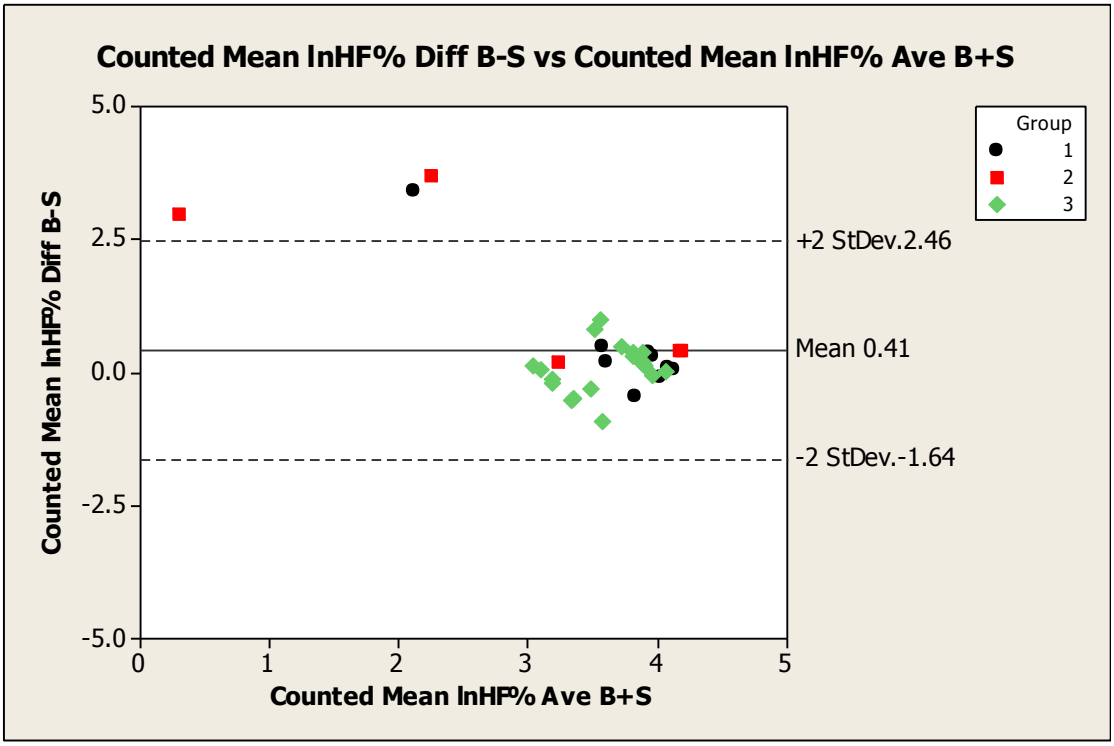


Figure 81 Bland & Altman scatterplot lnHF% difference (baseline minus sub-clinical) versus lnHF% average for total mean counted HRV data.

Limits of agreement from Bland & Altman analysis of Counted lnHF% derived during total sub-clinical seizures compared to baseline are (-0.9) and 1.0 with anti-log values of 0.4 and 2.7. Limits of agreement for Counted HRV lnHF% derived during right temporal sub-clinical seizures are (-0.4) and 2.5 with anti-log values of 0.6 and 32.0. Range in lnHF% of 32.6 % HF power). Limits of agreement for Counted HRV lnHF% derived during left temporal sub-clinical seizures are 0.2 and 3.7 with anti-log values of 1.2 and 39.9. (Range in lnHF% of 38.7 % HF power). Limits of agreement for Counted HRV lnHF% derived from generalised sub-clinical seizures are (-0.5) and 1.0 with antilog values of 0.6 and 2.7. (Range in lnHF% of 2.1%). This indicates that lower parasympathetic activity is present during generalised sub-clinical seizures compared to right and left temporal sub-clinical seizures (Figure 81, Table 30).

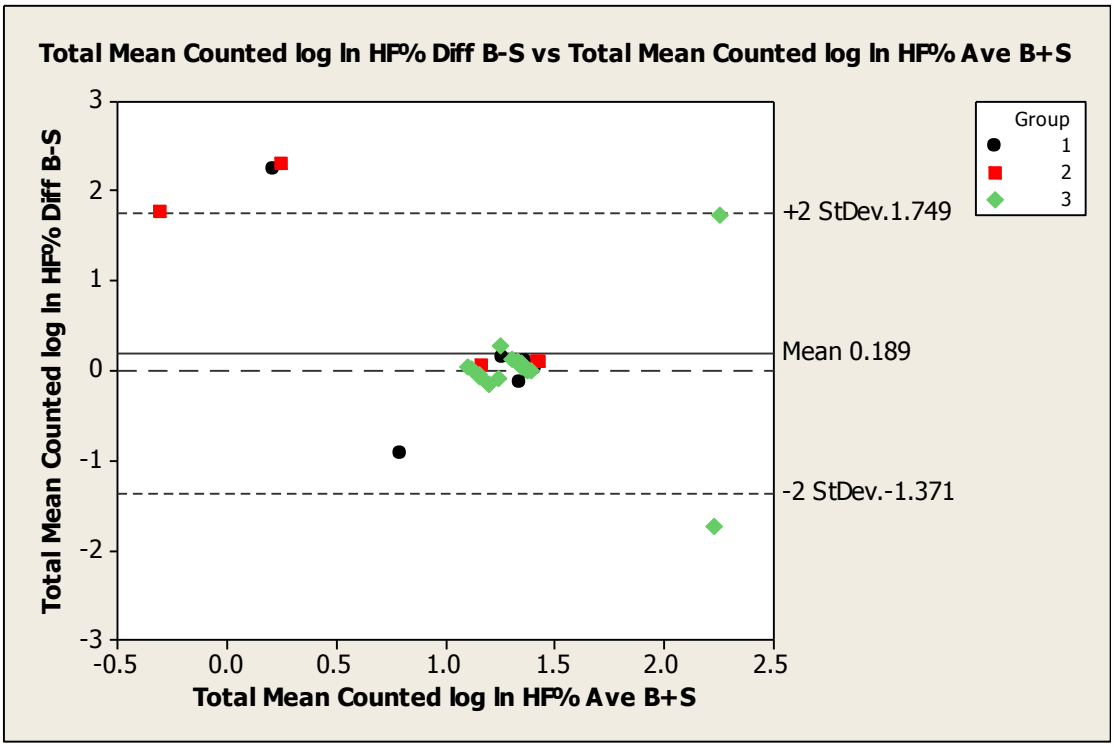


Figure 82 Bland & Altman scatterplot log lnHF% difference (baseline minus sub-clinical) versus log lnHF% average for total mean counted HRV data.

Limits of agreement of Bland & Altman analysis for Counted HRV log lnHF% for total sub-clinical seizures compared to baseline are (–0.9) and 1.7 with antilog 0.4 and 5.6. Limits of agreement analysis for HRV log ln HF% for right sub-clinical seizures compared to baeline are (–0.9) and 0.2 with antilog 0.4 and 1.2. (Range 0.8 log ln HF% power). Limits of agreement analysis for HRV log In HF% for left sub-clinical seizures compared to baseline are 0.1 and 2.3 with antilog 1.1 and 10.1. (Range of 9.0 log ln HF% power). Limits of agreement analysis for HRV log ln HF% for generalised sub-clinical seizures are (–0.2) and 0.3 with antilog 0.9 and 1.3 (range of 0.5 log lnHF% power), (Figure 82, Table 30).

Descriptive Statistics: Total CIPA & HF Difference (Counted R-R)

	Total mean CIPA Difference (CIPA Baseline minus CIPA Sub-clinical)	Total Mean log CIPA Difference (CIPA Baseline minus CIPA Sub-clinical)	Total mean Counted HF %Difference (HF% Baseline minus HF% Sub-clinical	Total mean Counted ln HF% Difference (ln HF% Baseline minus ln HF% Sub-clinical)	Total mean Counted log ln HF% Difference (log ln HF% Baseline minus log ln HF% Sub-clinical)
n	33	33	33	33	33
Mean	0.8	0.02	8.7	0.4	0.2
SE Mean	0.6	0.1	3.2	0.2	0.1
St. Deviation	3.6	0.5	18.6	1.0	0.8
Minimum	-4.8	-0.7	-33.6	-0.9	-1.7
Q1	-1.2	-0.3	-2.4	-0.1	0.0
Median	0.3	0.0	7.1	0.2	0.0
Q3	2.0	0.2	19.0	0.4	0.1
Maximum	9.8	1.3	58.3	3.7	2.3
Wilcoxon two sample test *p</=*	0.568	0.472	0.049	0.076	0.174

Table 29 Descriptive statistics of CIPA, log CIPA, HF%, lnHF% & log lnHF% difference (baseline minus sub-clinical) in total counted data

Counted HRV Mean Difference (baseline minus sub-clinical)		Mean Diff-erence	Lower limit of Agree-ment Bland & Altman Antilog values	Upper limit of Agree-ment Bland & Altman Antilog values	Range of Limit of Agree-ment Bland & Altman	Wilcoxon *p*</=
Total Subclinical Seizures N=33	log RMSSD	-0.2	0.4	2.3	1.8	0.337
	log SDNN	-0.3	0.5	1.3	0.9	0.096
	HF%	8.7	-21.0	44.0	65.0	0.049
	lnHF%	0.4	0.4	2.7	2.3	0.076
	log ln HF%	0.2	0.4	5.6	5.2	0.214
Right Temporal Subclinical Seizures N=9	log RMSSD	0.2	0.7	2.3	1.6	0.412
	log SDNN	0.1	0.7	2.0	1.2	0.662
	HF%	9.6	-21.0	44.0	65.0	0.214
	lnHF%	0.5	0.6	32.0	32.6	0.254
	log ln HF%	0.2	0.4	1.2	0.8	0.549

Left Temporal Subclinical Seizures N=5	log RMSSD	0.4	0.9	3.0	2.0	0.597
	log SDNN	-0.2	0.5	1.2	0.7	0.758
	HF%	24.7	4.8	58.3	53.5	0.231
	lnHF%	1.5	1.2	39.9	38.7	0.240
	log ln HF%	0.9	1.1	10.1	9.0	0.223
Generalised Subclinical Seizures N=19	log RMSSD	-0.5	0.4	0.9	0.5	0.001
	log SDNN	-0.4	0.5	0.8	0.4	0.001
	HF%	4.1	-15.0	35.7	50.7	0.376
	lnHF%	0.1	0.6	2.7	2.1	0.572
	log ln HF%	0.0	0.9	1.3	0.5	0.898

Table 30 Bland & Altman limits of agreement for log RMSSD, log SDNN, HF%, lnHF% & log lnHF% in total, right, left and generalised difference (baseline minus sub-clinical) for mean counted HRV data.

3.5.4 Results: Coefficient of Variation of HF% for Counted HRV

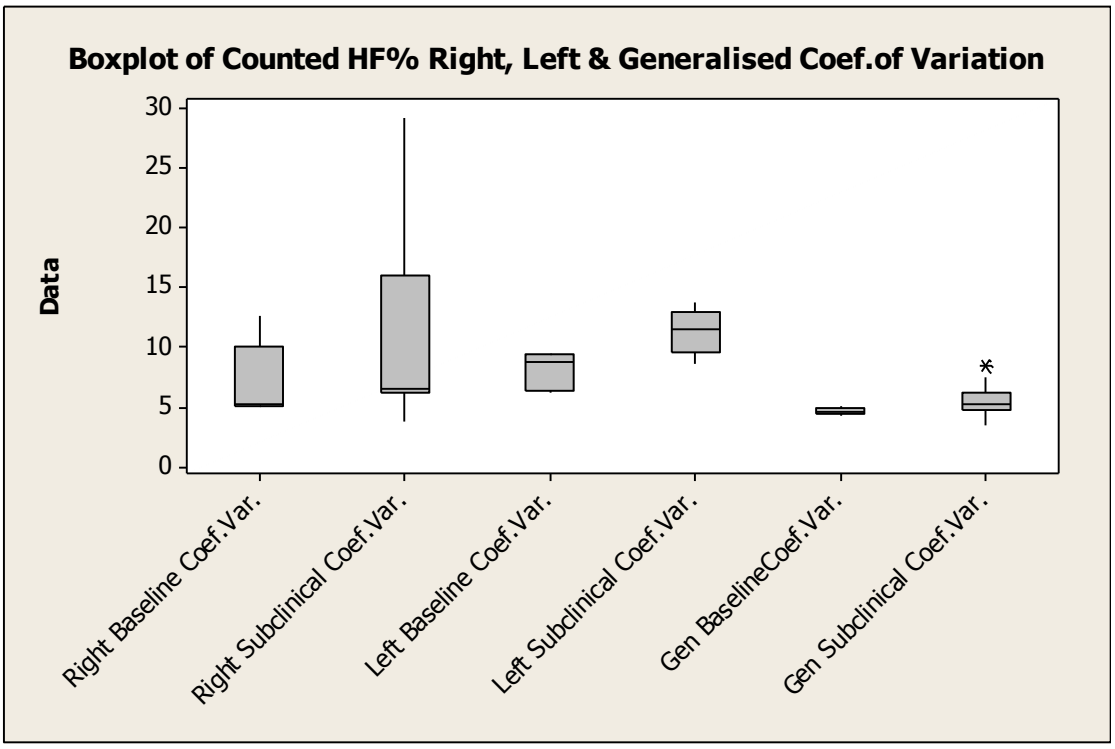


Figure 83 Boxplot of co-efficient of variation for right, left and generalised baseline & sub-clinical data.

Coefficient of variation for counted HF% shows an increase for all sub-clinical seizures although generalised sub-clinical seizures has lower mean coefficient of variation (Baseline 4.7%, Sub-clinical 5.5%) compared to mean coefficient of variation for right subclinical seizures Baseline (7.4%, Sub-clinical 11.4%) and left sub-clinical seizures (Baseline 8.1%, Sub-clinical 11.3%), (Figure 83).

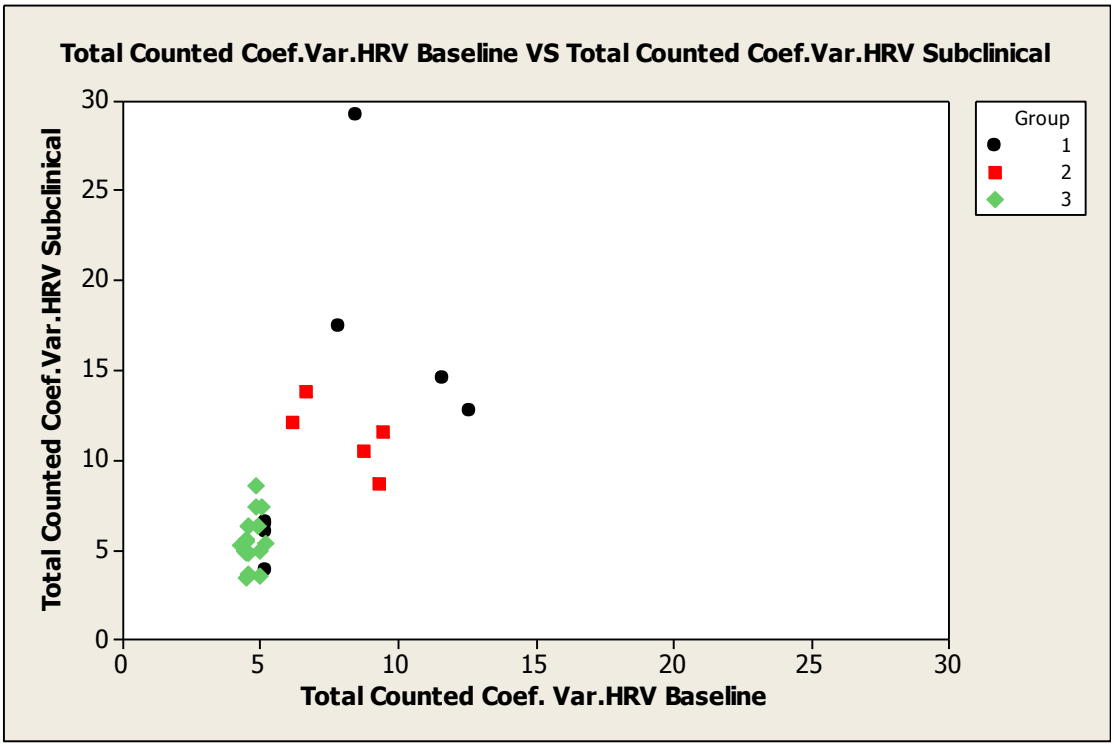


Figure 84 Scatterplot of coefficient of variation baseline versus sub-clinical HRV for total mean counted data.

Bland & Altman plot of coefficient of variation for counted HF% HRV shows data derived during generalised sub-clinical seizures has the least variation compared to data derived from right and left sub-clinical seizures (Figure 84).

3.5.5 Comparison of Adult HF% and Paediatric HF% (Counted).

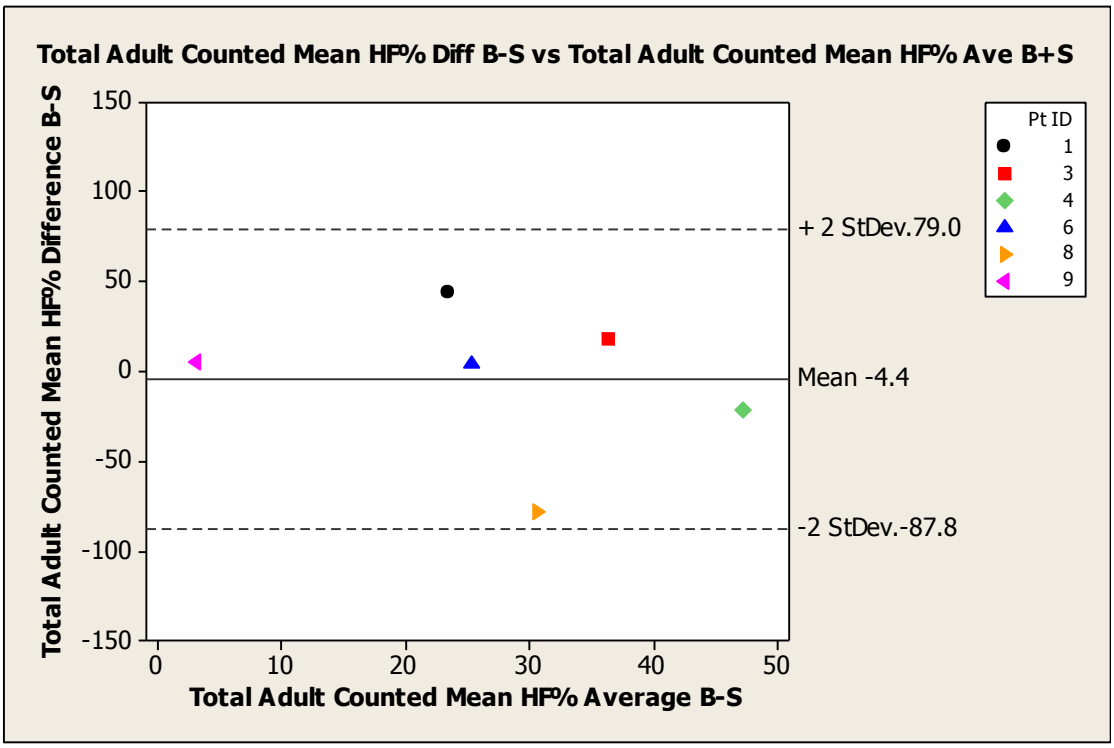


Figure 85 Bland & Altman scatterplot HF% difference (baseline minus sub-clinical) versus average HF% for total mean counted adult HRV data
Limits of agreement are 44 and (–77.8). Wilcoxon *p=0.917*

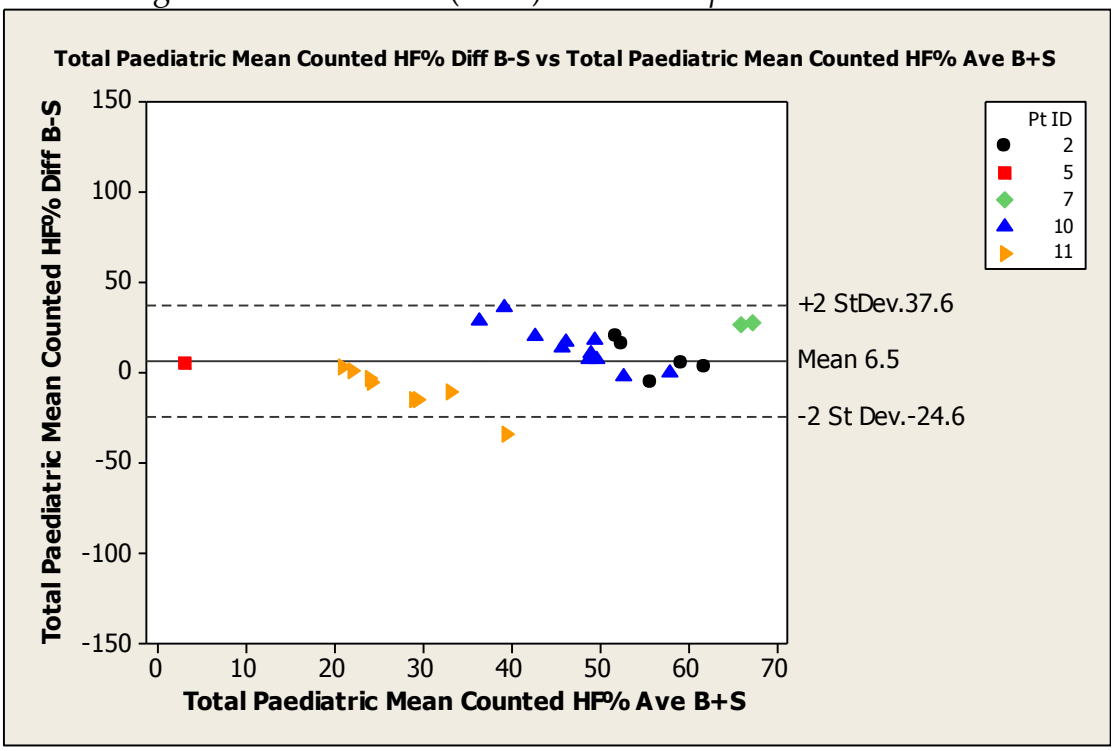


Figure 86 Bland & Altman scatterplot HF% difference (baseline minus sub-clinical) versus average HF% for total mean counted paediatric HRV data
Limits of agreement are 35.7 and (–15) Wilcoxon *p=0.648*

3.5.6 Adult HF% and Paediatric HF%:Counted.HRV

Mean HF% differences are calculated for total paediatric (*p=0.648*) and total adult (*p=0.917*) data. Mean HF% Bland & Altman difference for paediatric data (n=27) is 6.5 ± 31.1 with limits of agreement (-15) and 35.7 (Figure 86). Mean HF% Bland & Altman difference for adult data (n=6) is (-4.4) ± 83.4 with limits of agreement (-77.8) and 44 (Figure 85). Neither group reach statistical significance. Standard deviations are larger for the adult group with the total being much smaller with a range of 121.80 compared to paediatrics range of 50.7.

Chapter 24 Relationship of NeuroScope CIPA data and BioSignal HF% from Matched Counted R-R

3.6.1 Total Sub-clinical Seizures

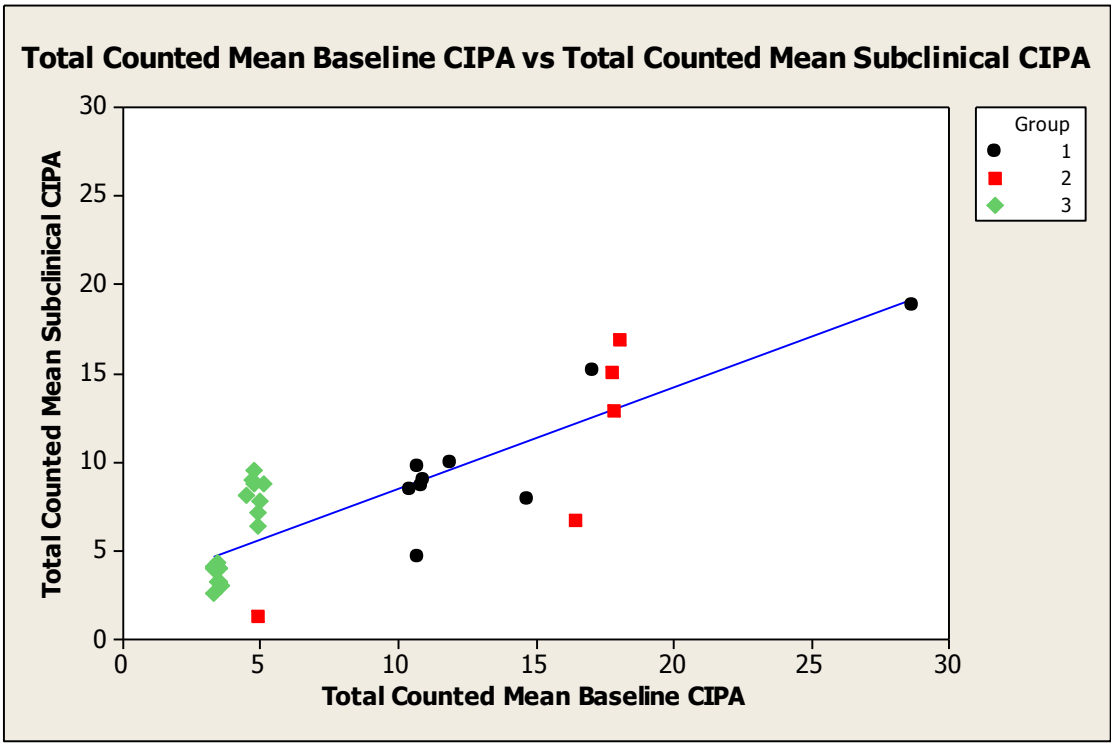


Figure 87 Scatterplot of baseline CIPA versus sub-clinical CIPA for total mean counted data

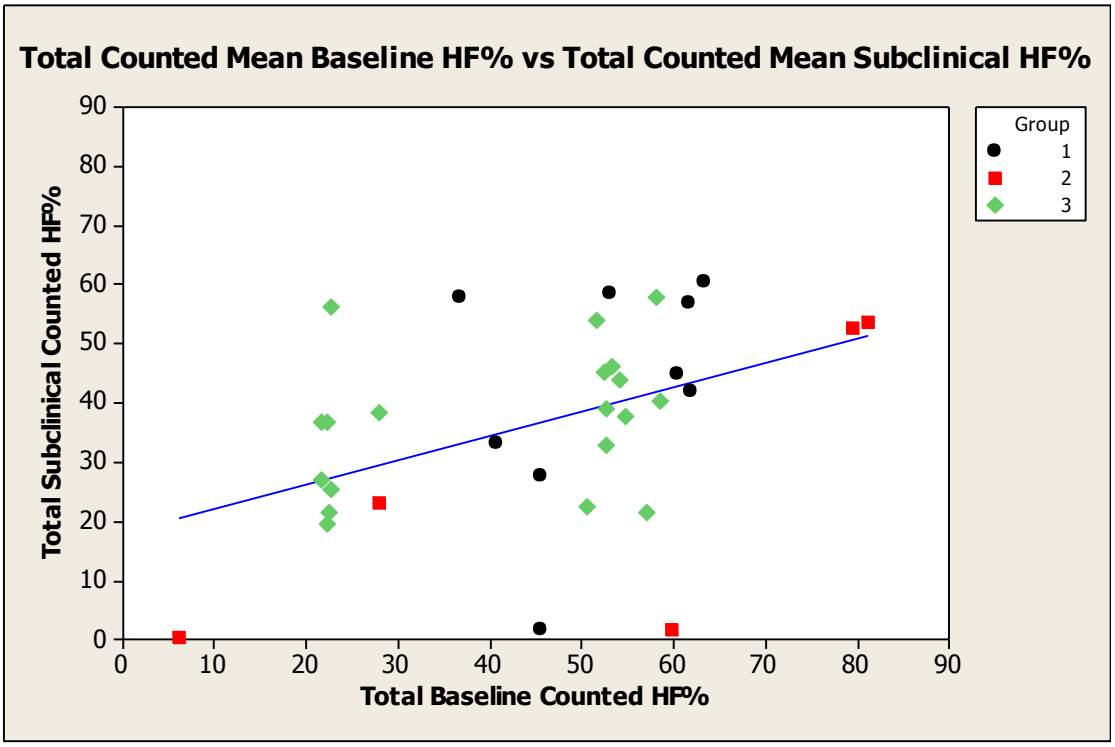


Figure 88 Scatterplot of baseline HF% versus sub-clinical HF% for total mean counted data

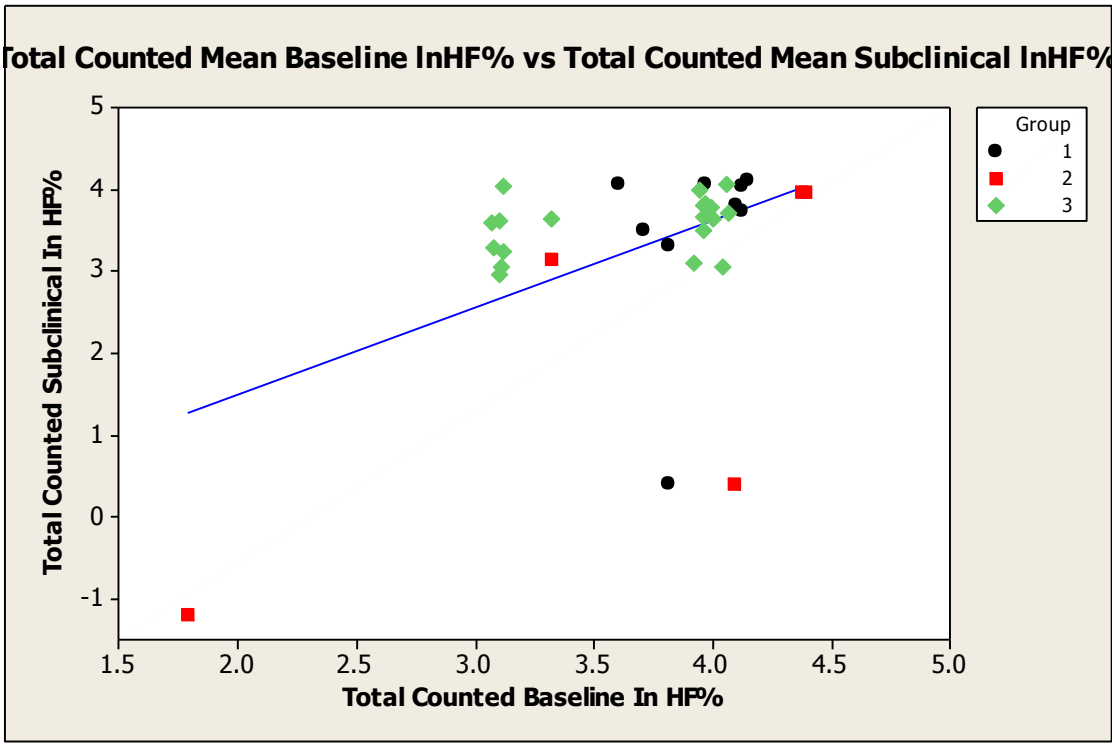


Figure 89 Scatterplot of baseline lnHF% versus sub-clinical lnHF% for total mean counted data.

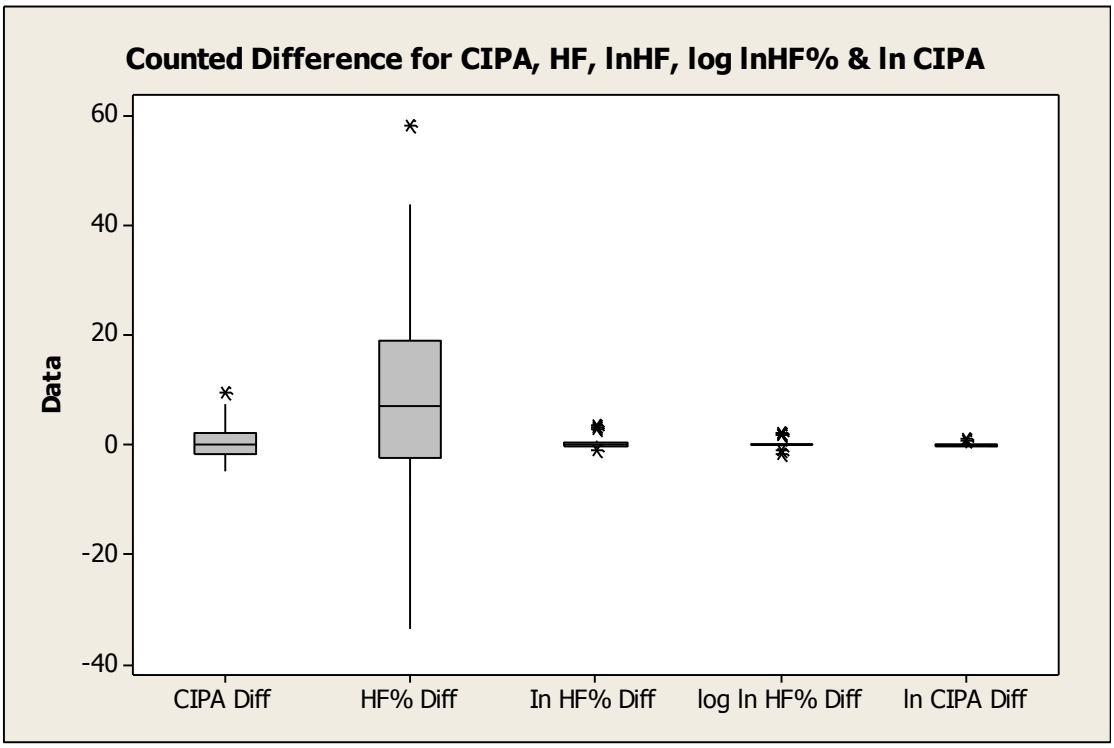


Figure 90 Boxplot of differences (baseline minus sub-clinical) in CIPA, HF%, lnHF%, log lnHF% & ln CIPA.

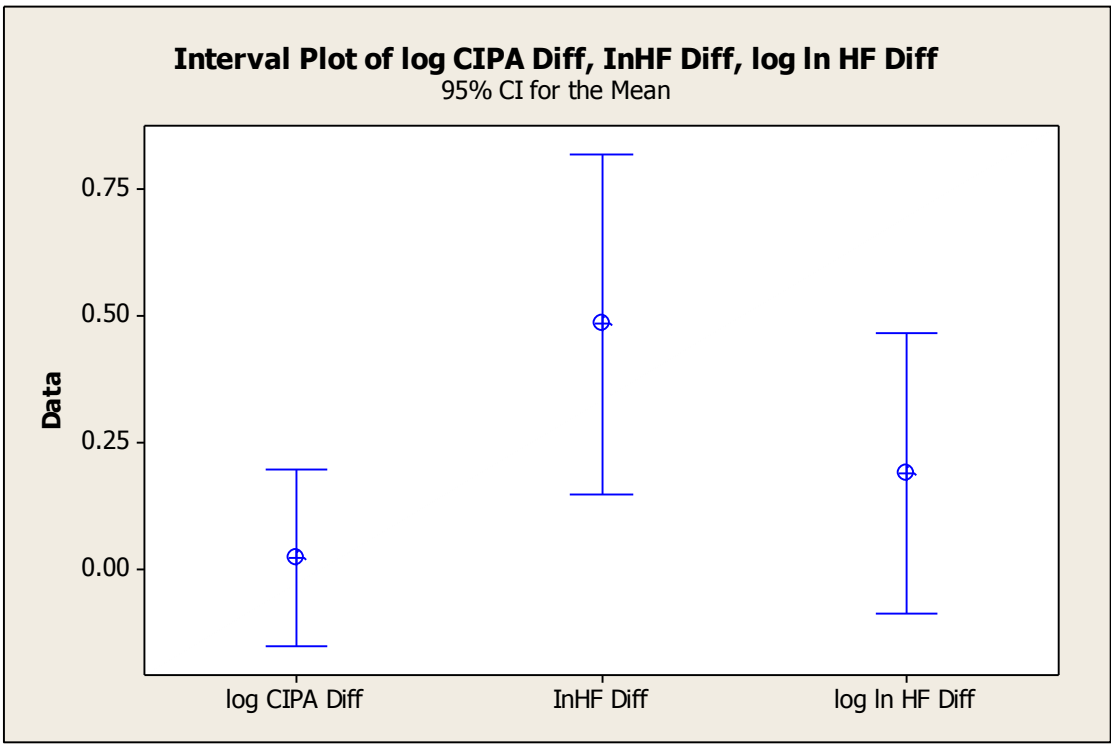


Figure 91 Interval plot of differences (baseline minus sub-clinical) in lnCIPA, lnHF% & log lnHF%

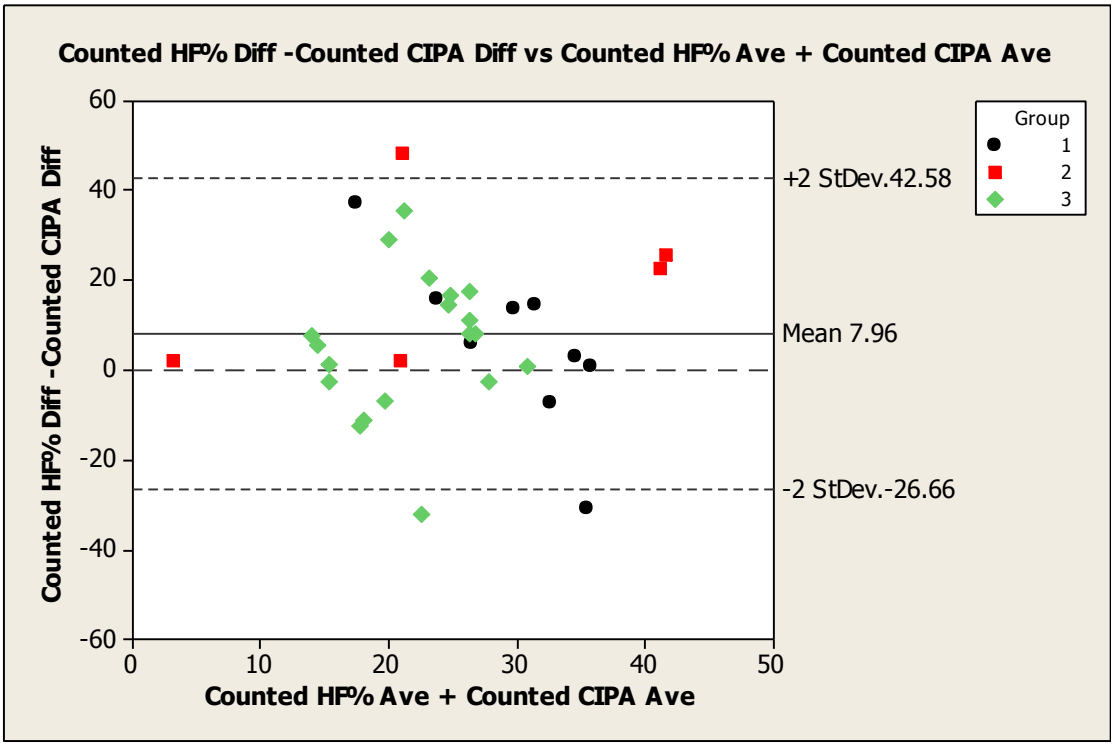


Figure 92 Bland & Altman scatterplot of difference (HF% difference minus CIPA difference) versus CIPA & HF% average for total mean counted data. Limits of agreement are (–12.26) and 37.18. Range is 49.44.

HF% difference (baseline minus sub-clinical) minus CIPA difference (baseline minus sub-clinical) versus HF% & CIPA average lets us look at what the difference is between the data represented by BioSignal and the NeuroScope. The mean difference is 8.0 ± 34.6 with limits of agreement (-12.3) and 37.2 (range 49.4), (Figure 92). Clinically, this is difficult to interpret, as it is the wrong scale for HF%. In order to look at the scale closer to CIPA, the natural log of HF% is analysed.

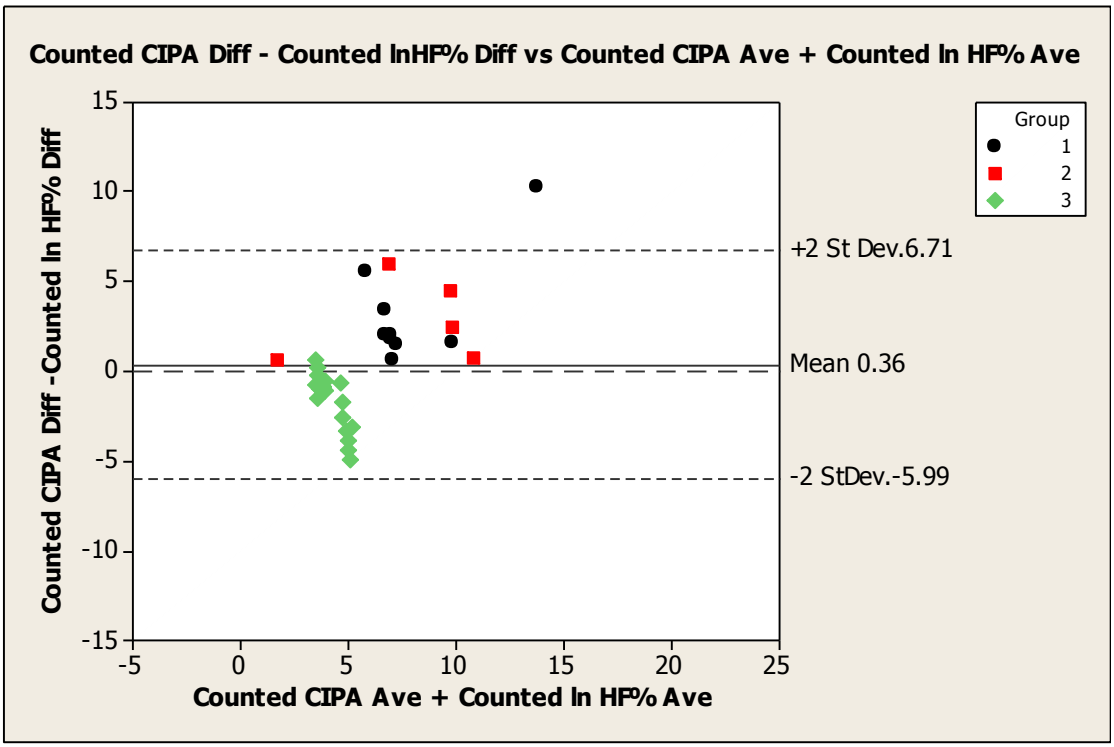


Figure 93 Bland & Altman scatterplot of difference (CIPA difference minus lnHF% difference versus CIPA & lnHF% average for total mean counted data. Limits of agreement are (–4.914) and 5.984. Range is10.89.

CIPA difference (baseline minus sub-clinical) minus lnHF% difference (baseline minus sub-clinical) versus CIPA & lnHF% average again let us look at the difference between data represented by the NeuroScope and BioSignal

but on a more comparable scale. The mean difference between data from the NeuroScope and BioSignal for CIPA and lnHF% is 0.4 ± 6.4 with limits of agreement (-4.9) and 6.0 (range 10.9), (Figure 93).

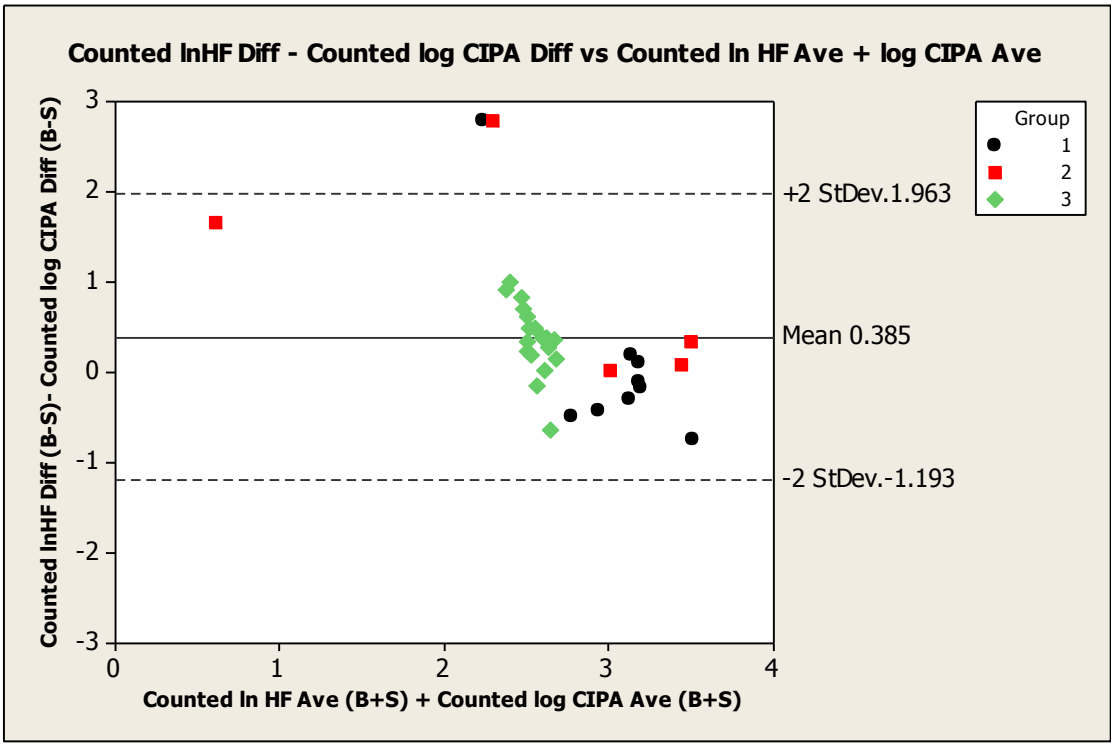


Figure 94 Bland & Altman scatterplot of difference (lnHF% difference minus lnCIPA difference versus lnHF% & lnCIPA average for total mean counted data. Limits of agreement are (–0.743) and 1.664. Antilog of these values are 0.475 and 5.280. Range is 4.805.

The mean difference between lnHF% and log CIPA is 0.4 ± 1.6 with antilog limits of agreement 0.5 and 5.3 (range 4.8), (Figure 94).

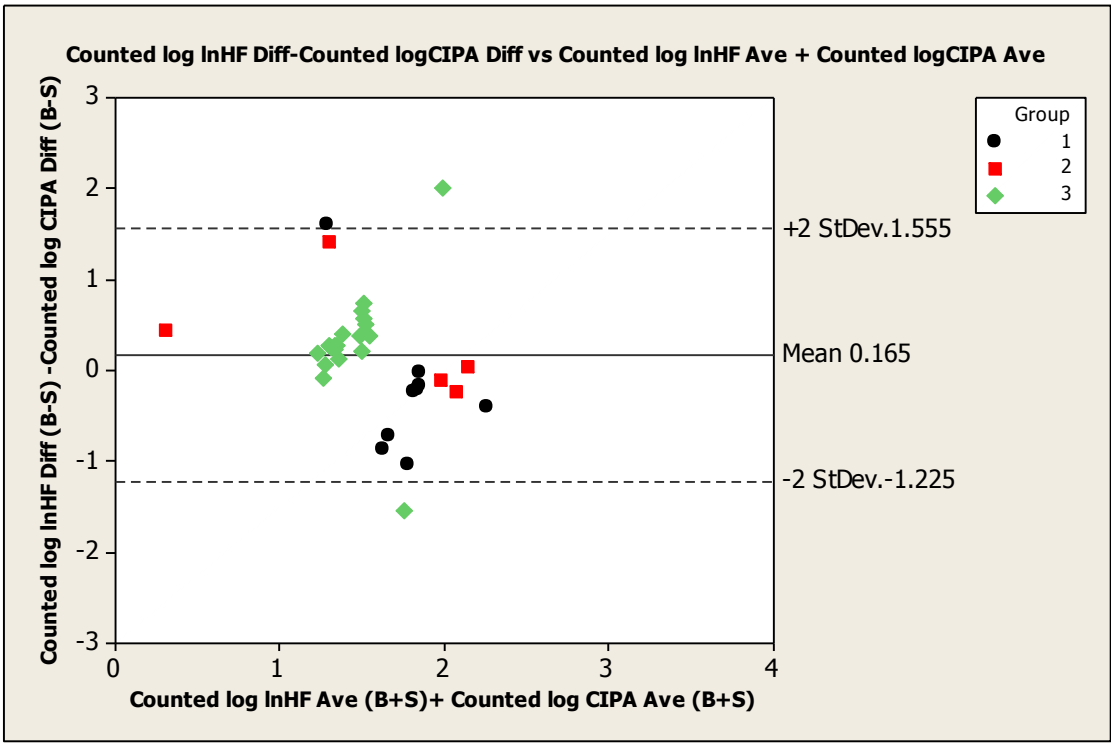


Figure 95. Bland & Altman scatterplot of difference (log lnHF% difference minus lnCIPA difference versus log lnHF% & lnCIPA average for total mean counted data. Limits of agreement are (-1.026) and 1.420. Antilog values are 0.358 and 4.137. Range is 3.779.

A further reduction between the difference between the NeuroScope and BioSignal is seen using log lnHF and log CIPA with a mean difference of 0.02 ± 1.0 with antilog limits of agreement 0.4 and 4.1 (range 3.8), (Figure 95, Table 31).

Counted Mean Data Comparing BioSignal & NeuroScope Bland & Altman plot n=33	HF% Diff(B-S) minus CIPA Diff (B-S) vs HF% Ave +CIPA Ave	CIPA Diff (B-S) minus lnHF%Diff (B-S) vs CIPA Ave +lnHF% Ave	lnHF% Diff (B-S) minus logCIPA Diff (B-S) vs lnHF% Ave + logCIPA Ave	Log lnHF% Diff(B-S) minus logCIPA Diff (B-S) vs log lnHF% Ave + logCIPA Ave
Mean	8.0	0.4	0.4	0.02
Standard Deviation	34.6	6.4	1.6	1.0
Lower limit of agreement	-12.3	-4.9	0.5	0.4
Upper limit of agreement	37.2	6.0	5.3	4.1
Range	49.4	10.9	4.8	3.8

Table 31 Bland & Altman limits of agreement between NeuroScope & BioSignal data

3.6.2 Scale Relationship of HF% & CIPA for Counted Data

In clinical practice, a new device should be compared to an accepted technology before it can be used confidently. BioSignal is a traditionally accepted method for quatifying HRV. The NeuroScope is a novel device and is compared to BioSignal results in this pilot study for a limited comparison.

HF% mean difference of baseline minus sub-clinical (n=33) is 8.7 (with limits of agreement (-21) to 44, range 65), (Figure 75, Table 30), (*p=0.049*) is on a larger scale compared to CIPA. Mean CIPA difference (n=33) is 0.8 ± 3.6 (with limits of agreement (–4.8) to 6.8, range 11.6), (Figure 15, Table 8), (*p=0.233*). By using natural log HF%, the HF% data is scaled down to a closer relationship to CIPA but is smaller with a mean difference (n=33) of 0.4 ± 1.0 (limits of agreement 0.4 to 2.7, range 2.3), (Figure 81, Table 29), *(p=0.076*).

The closest scale difference between NeuroScope CIPA and BioSignal HF% is log CIPA and log lnHF% mean difference 0.02 ± 1.0 (limits of agreement are 0.5 to 2.7, range 2.2), (Figure 16, Table 29). This would indicate that at this scale comparison, there would be a 2% difference in the results between the systems for shorter 'counted' epochs, less than 5 minutes HRV.

Mean data per epoch of data is limiting and can only be useful for trend interpretation for CIPA and HF. There are obvious scale differences between CIPA, log CIPA, HF%, lnHF% and log lnHF% data and direct comparisons are limited. However, similar representation of vagal measurements are found in data distribution for baseline, sub-clinical and visually proportional differences are present between baseline and sub-clinical values for NeuroScope CIPA and BioSignal HF% data.

In summary, counted data comparison of CIPA and lnHF% shows similar results on a different scale with lnHF% approximately half that of CIPA. The closest scale comparisons for mean values are log CIPA and log lnHF% for counted data. With limited mean data to test this comparison only very general observations can be made.

Chapter 25. Heart Rate Variability (5 minutes)

3.7.1 Results of R-R Interval Analysis prior to 5 minute BioSignal Analysis.

From data derived from the original study group of patients, twenty-seven thousand, one hundred and fifty-one (27,151) R-R intervals were manually measured from thirty-three (33) sub-clinical seizures and time matched baseline studies. The sub-clinical seizures were encapsulated within 5minute epochs and R-R intervals (n= 13,229) measured and analysed. Matched 5 minute baseline studies were manually measured (n= 13,922) and analysed from 11 patients mean age 23.1 ± 18.7 years. Nine sub-clinical seizures were derived from the right temporal lobe (5 patients) (R-R intervals n= 3330 sub-clinical, n=3110 baseline) and five sub-clinical seizures were derived from the left temporal lobe (4 patients), (R-R intervals n=1780 sub-clinical, n=1757 baseline). Nineteen generalised sub-clinical seizures (R-R intervals n=8119 sub-clinical, 9055 baseline) were analysed from two patients.

Twenty-seven thousand, one hundred and fifty-one (27,151) R-R intervals were manually measured.

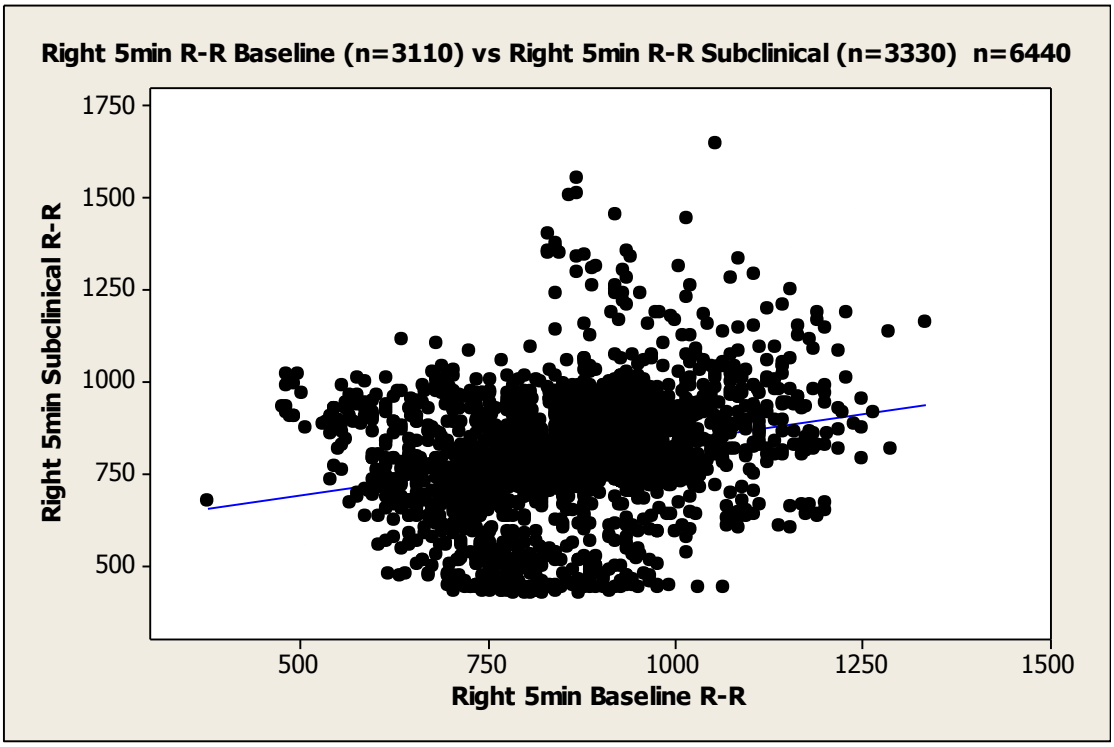


Figure 96 Scatterplot of R-R intervals during right temporal lobe sub-clinical seizures versus matched 5minute baseline R-R intervals

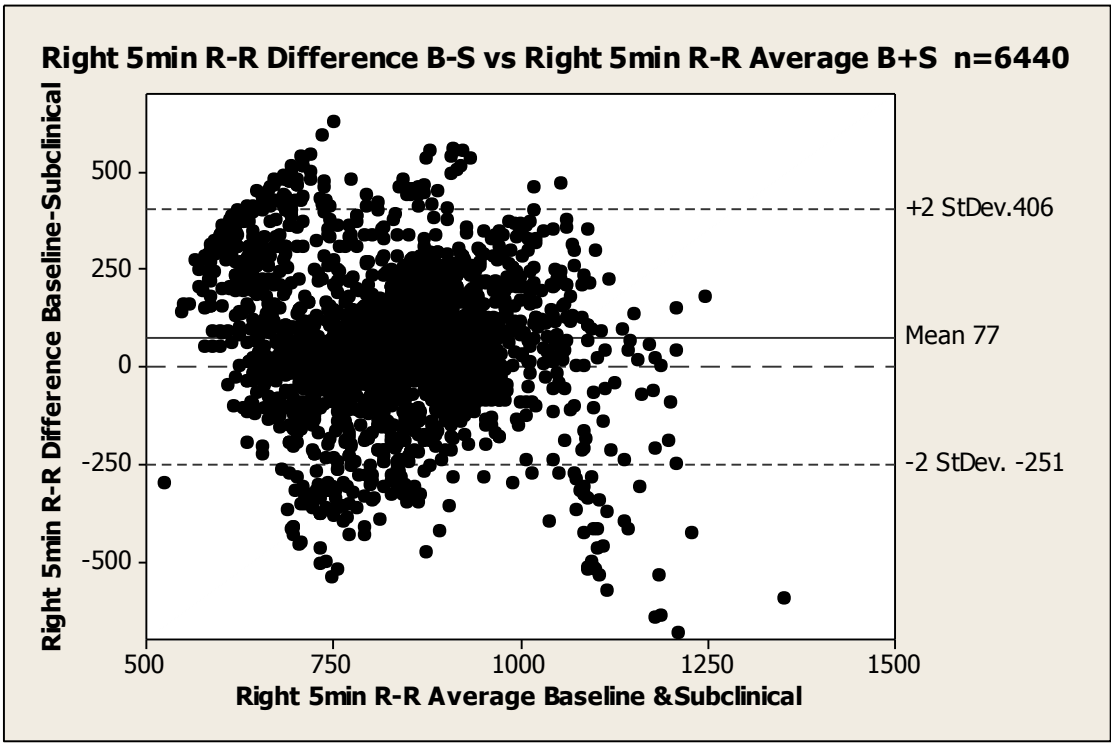


Figure 97 Bland & Altman scatterplot difference (baseline minus sub-clinical) R-R interval versus average (B-S) for right hemisphere 5minute data Limits of agreement are –250 and 405.87. Range is 655.87

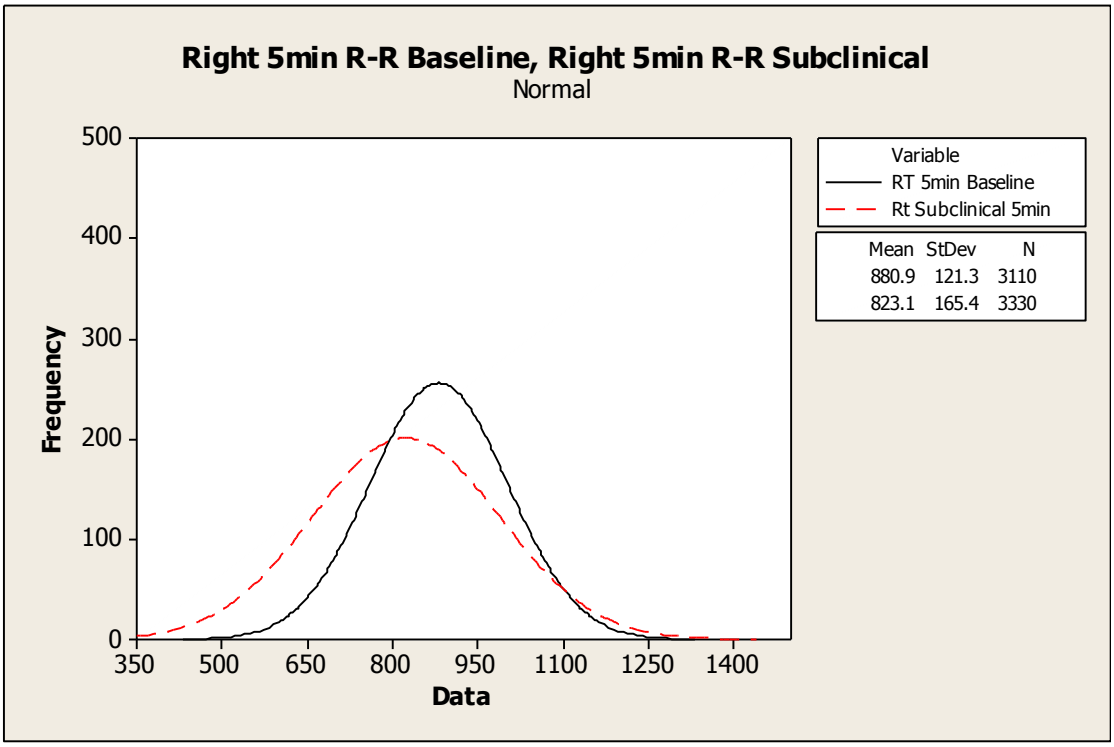


Figure 98 Histogram of 5minute R-R baseline, 5minute R-R sub-clinical during right temporal lobe data. Wilcoxon Two Sample $p<0.001$. Mean baseline heart rate is 68.11/min, mean sub-clinical heart rate is 72.89/min,

Similar to 'counted' R-R interval analysis, 5 minute R-R interval also shows a difference when comparing baseline R-R with sub-clinical R-R interval data but to a lesser extent. R-R intervals shorten from right temporal baseline (n=3,110) 880.9 ± 121.3 milliseconds to right temporal sub-clinical (n=3,330) 823.1 (72.89/min) ± 165.4 milliseconds ($p<0.001$), (Figure 98, Table 32). This indicates an overall increase in heart rate and has a mean difference of 77 ± 329 milliseconds and limits of agreement (-250) and 405.9 milliseconds (Figure 97). A smaller increase in mean heart rate (4.62/min) is seen comparing 5 minute epochs to 'counted' epochs of mean heart rate increase (10.5/min) due to the longer epoch diminishing the sub-clinical data with non critical data.

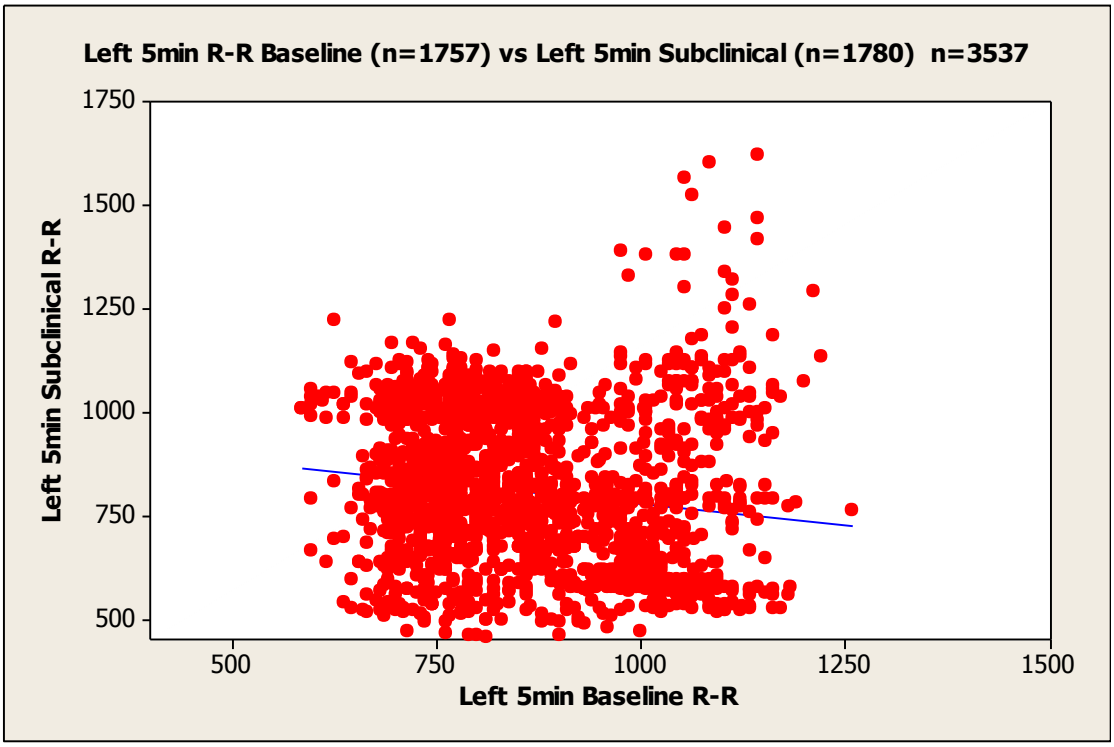


Figure 99 Scatterplot of R-R intervals during left temporal lobe sub-clinical seizures versus matched 5minute baseline R-R intervals

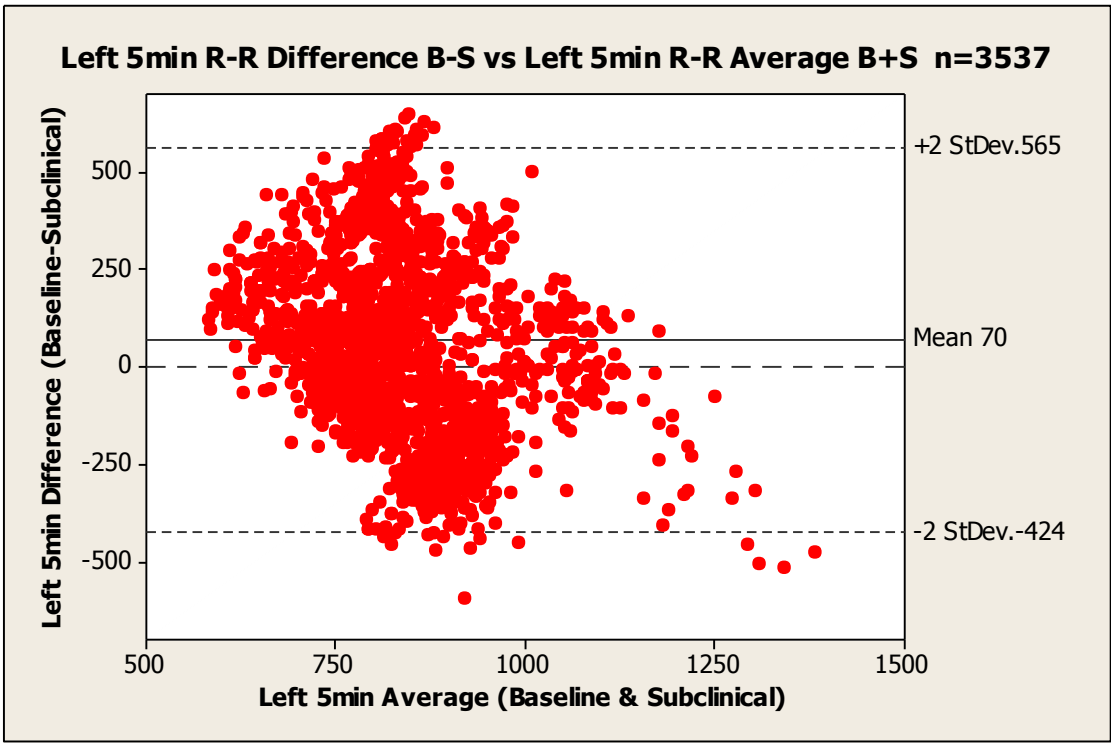


Figure 100 Bland & Altman scatterplot difference (baseline minus sub-clinical) R-R interval versus average (baseline & sub-clinical) for left hemisphere 5minute data. Limits of agreement are (–424) and 565.

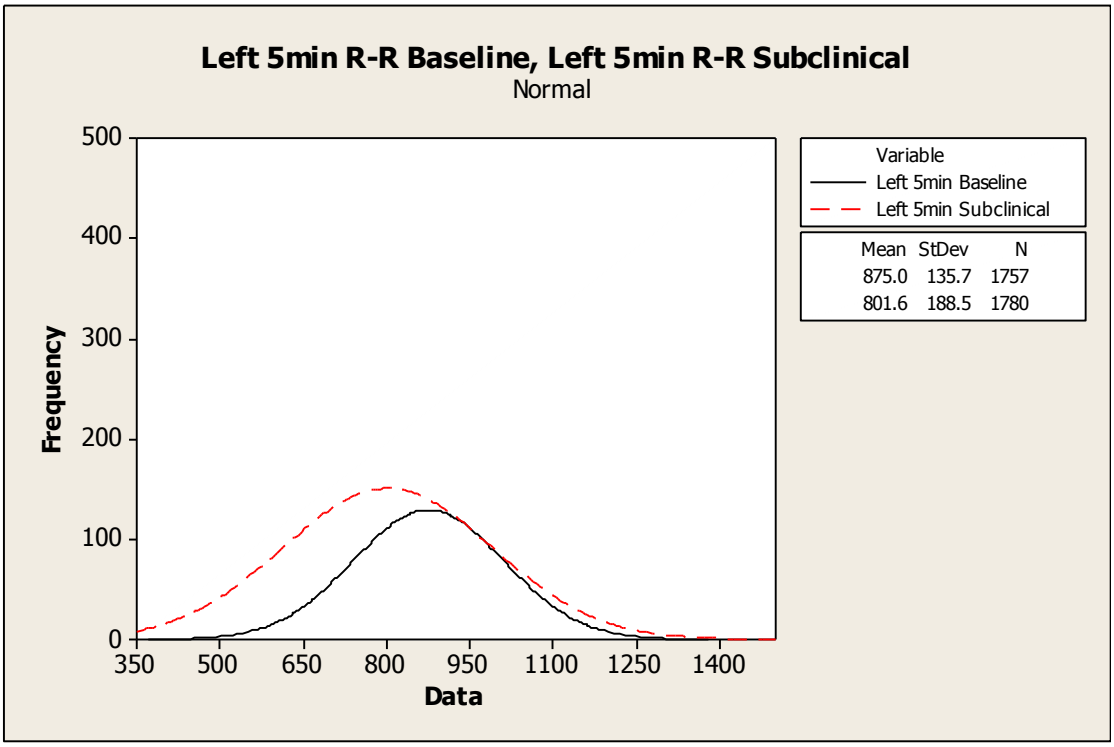


Figure 101 Histogram of 5minute R-R baseline, 5minute R-R sub-clinical during left temporal lobe data. Wilcoxon Two Sample *p<0.001* Mean baseline heart rate is 68.57/minute mean sub-clinical heart rate is 74.85/min.

The results for left temporal and generalised data give a similar trend as seen with counted R-R interval epochs but again are less marked for the same reason of diminution. Left baseline (n=1757) 875.0 (68.6) ± 135.7milliseconds shortens during left temporal sub-clinical (n=1780) 801.6 (74.8/min) ± 188.5msec (*p<0.001*). This again indicates an overall increase in heart rate and has a mean difference of 70 ± 495msec and limits of agreement (-424) and 565 milliseconds (Figures 100 & 101). The mean difference 70 ± 495milliseconds is only slightly less than that seen from counted data 126 ± 367msec

Generalised 5min limits of agreement are (–231) and 112. Unable to combine on a single graph as generalised data n=17,174 (exceeds Minitab limit).

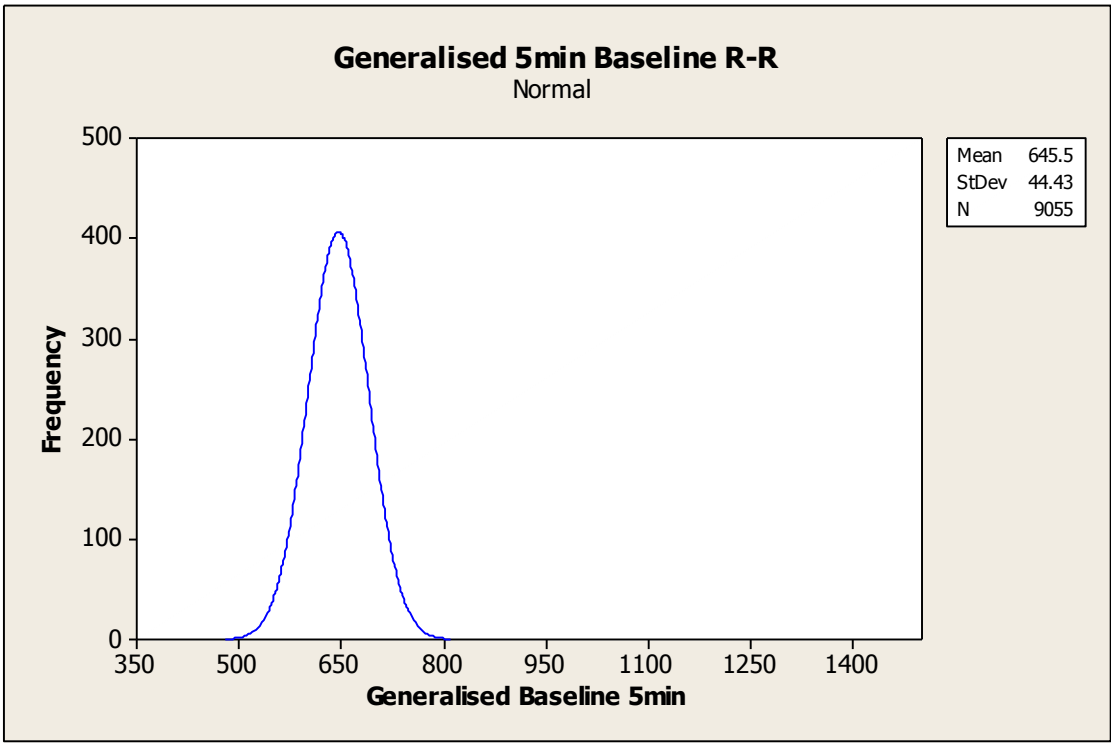


Figure 102 Histogram 5minute R-R interval generalised baseline data.

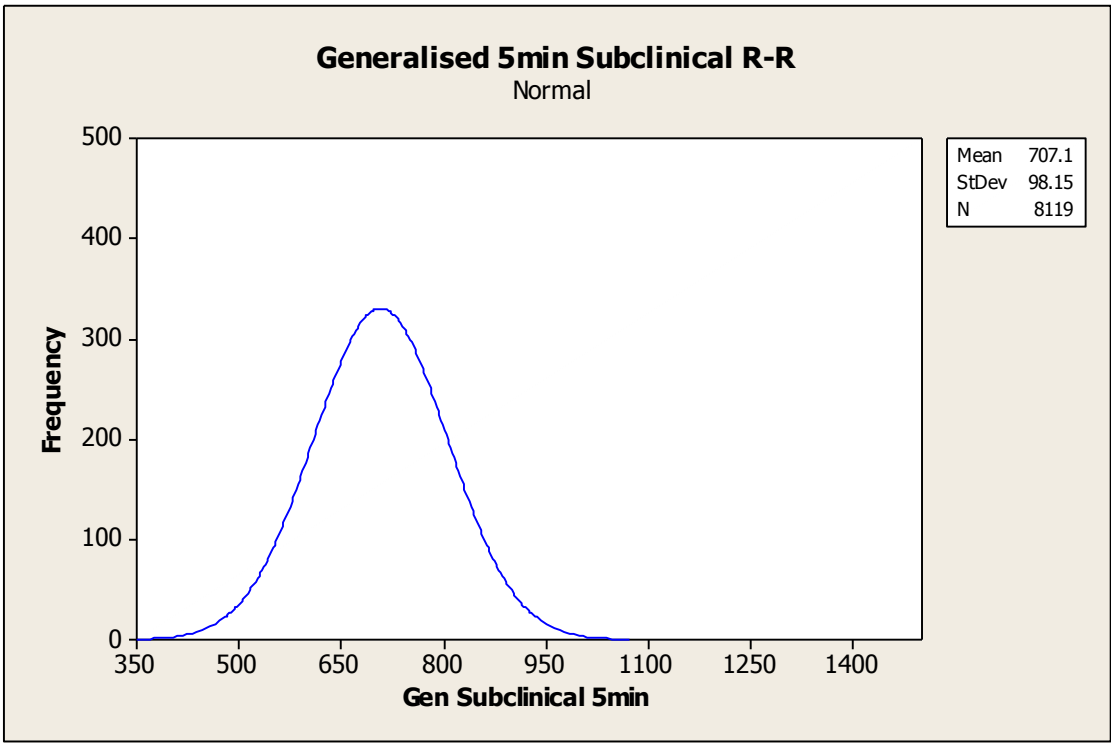


Figure 103 Histogram 5minute R-R interval for generalised sub-clinical data. Baseline heart rate is 92.9/min and the sub-clinical heart rate is 84.85/min.

Generalised data indicates a lengthening of R-R interval from baseline (n=9055) 645.5 (92.95/min) ± 44.4 milliseconds to sub-clinical (n=8119) 707.1

(84.84/min) ± 98.1 milliseconds as seen with counted data (Figures 102 & 103). A mean difference between baseline and sub-clinical R-R data is (-61.6) and limits of agreement (-231) and 112 milliseconds. The mean difference of R-R intervals baseline minus sub-clinical are similar to that seen for 5 minute (-61.6 milliseconds) counted R-R interval difference (-58 milliseconds)

5min R-R Interval Descriptive Data	n	Baseline R-R	n	Sub-clinical R-R
Right Temporal Mean	3110	880.9	3330	823.1
Left Temporal Mean	1757	875.0	1780	801.6
Generalised Mean	9055	645.5	8119	707.1
Right Temporal Standard Deviation	3110	121.3	3330	165.4
Left Temporal Standard Deviation	1757	135.7	1780	188.5
Generalised Standard Deviation	9055	44.4	8119	98.1
Right Temporal Coefficient of Variation%	3110	7.3	3330	10.7
Left Temporal Coefficient of Variation%	1757	8.6	1780	15.8
Generalised Coefficient of Variation%	9055	5	8119	4.3

Table 32 Descriptive data for 5minute R-R interval data

Co-efficient of variation of R-R intervals from 5 minute epochs show the same trends as seen with counted data for right, left and generalised baseline and sub-clinical data but have a slightly wider scatter. Generalised data again has the tightest coefficient of variation baseline 5% and sub-clinical 4.3% (Table 32). R-R interval data for right temporal lobe baseline data is 7.3% and right temporal lobe sub-clinical data 10.66% (Table 32). The left temporal baseline data is 8.6% and left temporal sub-clinical data 15.8% (Table 32). There is an expected wider scatter because of a greater number of R-R intervals analysed and the inherent increased chance of variation captured. However, despite generalised data having the greatest number of R-R intervals, generalised sub-clinical seizures have the smallest co-efficient of variation compared to lateralised data.

Standard Deviation Heart Rate 5minutes HRV

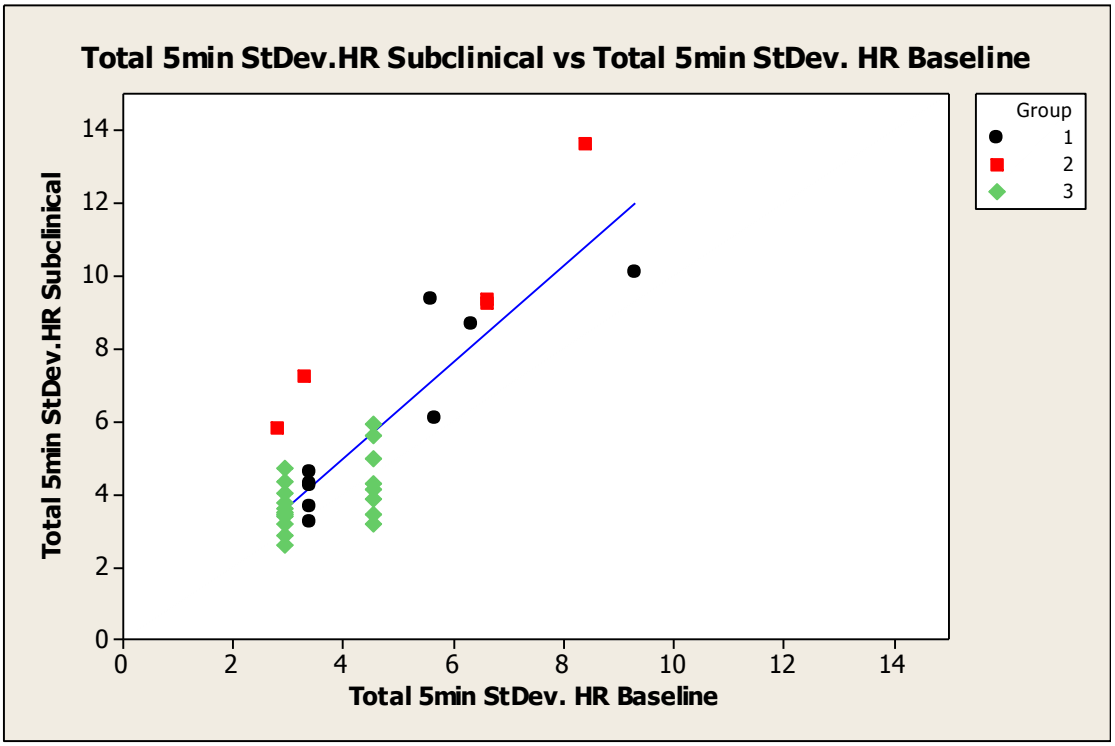


Figure 104 Scatterplot baseline heart rate standard deviation versus sub-clinical heart rate standard deviation for total mean 5minute data

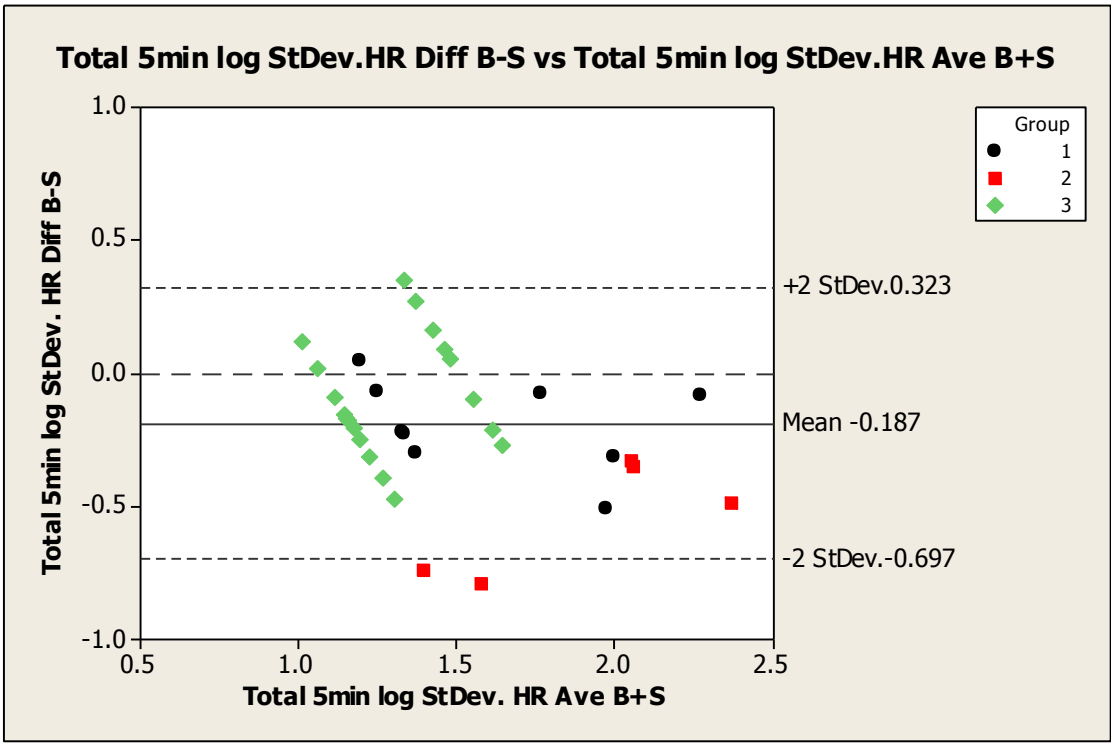


Figure 105 Bland & Altman scatterplot of difference (B-S) log heart rate standard deviation versus average log heart rate standard deviation for total mean 5minute data.

Limits of agreement for 5 min HRV standard deviation of heart rate during total sub-clinical seizures compared to baseline data (Figure 105) are (–0.5) and 0.3 with antilog of 0.6 and 1.3. Limits of agreement for 5 min HRV standard deviation of heart rate derived during right temporal sub-clinical seizures are (–0.5 and -0.0) with antilog of 0.6 and 1.0 (range 0.4). Limits of agreement for 5 min HRV standard deviation of heart rate derived during left temporal sub-clinical seizures are (–0.8 and –0.3) with antilog of 0.4 and 0.7 (range 0.3). Limits of agreement for 5 min HRV standard deviation of heart rate derived during generalised sub-clinical seizures are (–0.5) and 0.4 with antilog of 0.6 and 1.4 (range 0.8).

3.7.2 BioSignal Analysis of 5 minutes HRV for Total Sub-clinical Seizures & Baseline Data.

As with imported counted R-R data, only mean values can be measured per event with the BioSignal HRV software. 5 minute R-R interval epochs of baseline and sub-clinical data for each event were imported into the BioSignal software for analysis. A total of 27,151 R-R intervals (13,922 baseline & 13,229 sub-clinical) were imported comprising of 6,440 R-R intervals for the right temporal lobe (3,110 baseline, 3,330 sub-clinical), 3,537 R-R intervals for the left temporal lobe (1,757 baseline, 1,780 sub-clinical) and 17,174 R-R intervals for generalised data (9,055 baseline, 8,119 sub-clinical). After software conversion of this data, mean values were produced resulting in one mean total per baseline study and one mean total per sub-clinical seizure study. A total mean of 33 baseline studies and matched sub-clinical comprising of right temporal lobe (9 baseline, 9 sub-clinical) left temporal lobe (5 baseline, 5 sub-clinical) and generalised (19 baseline, 19 sub-clinical). This data encapsulated the same data analysed for counted R-R data but extended to 5 minutes epochs for baseline and sub-clinical data.

Pt. ID	Baseline HRV (5 minutes)				Sub-clinical HRV (5 minutes)			
	RMSSD (ms)	SDNN (sec)	NN50 (count)	pNN50 (%)	RMSSD (ms)	SDNN (sec)	NN50 (count)	pNN50 (%)
Pt 1	74.6	0.091	145	51.4	66.5	0.111	116	33.2
Pt 2	50.1	0.046	106	32.1	50.8	0.044	110	33.2
Pt 2	50.1	0.046	106	32.1	16.2	0.037	56	0.4
Pt 2	50.1	0.046	106	32.1	35.6	0.051	66	15.2
Pt 2	50.1	0.046	106	32.1	41.7	0.046	90	17.9
Pt 2	50.1	0.046	106	32.1	44.3	0.044	64	24.2
Pt 3	57.5	0.067	149	41.6	46.1	0.055	78	17.3
Pt 4	77.8	0.078	175	51.3	142.6	0.138	171	62.6
Pt 5	78.6	0.075	200	45.0	98.3	0.087	207	49.1
Pt 6	78.3	0.079	165	43.0	88.6	0.109	124	31.3
Pt 7	79.9	0.070	235	60.7	111.4	0.104	213	63.8
Pt 7	79.9	0.070	235	60.7	105.8	0.104	151	51.0
Pt 8	65.3	0.052	139	50.0	49.3	0.098	78	27.6
Pt 9	23.8	0.046	12	3.8	11.1	0.046	1	0.2
Pt 10	19.2	0.018	7	1.4	16.2	0.019	2	0.4
Pt 10	19.2	0.018	7	1.4	21.5	0.025	7	1.5
Pt 10	19.2	0.018	7	1.4	21.0	0.030	13	2.7
Pt 10	19.2	0.018	7	1.4	24.8	0.029	20	5.3
Pt 10	19.2	0.018	7	1.4	18.3	0.019	7	1.4
Pt 10	19.2	0.018	7	1.4	23.0	0.025	20	4.4
Pt 10	19.2	0.018	7	1.4	22.2	0.025	17	3.7
Pt 10	19.2	0.018	7	1.4	17.2	0.019	9	2.0
Pt 10	19.2	0.018	7	1.4	23.4	0.026	18	4.0
Pt 10	19.2	0.018	7	1.4	18.7	0.025	12	2.6
Pt 10	19.2	0.018	7	1.4	24.5	0.027	15	3.3
Pt 11	24.3	0.035	14	3.1	41.4	0.040	45	16.6
Pt 11	24.3	0.035	14	3.1	37.0	0.035	43	11.5
Pt 11	24.3	0.035	14	3.1	55.4	0.059	79	21.5
Pt 11	24.3	0.035	14	3.1	44.9	0.051	61	16.4
Pt 11	24.3	0.035	14	3.1	39.9	0.045	46	12.8
Pt 11	24.3	0.035	14	3.1	69.8	0.069	104	29.4
Pt 11	24.3	0.035	14	3.1	38.9	0.044	37	10.0
Pt 11	24.3	0.035	14	3.1	42.7	0.037	47	13.5
Total Rt	60.8	0.067	1199	36.6	68.7	0.075	958	29.1

Total Lt	70.6	0.068	786	44.9	79.8	0.094	567	31.9
Total Rt & Lt	64.6	0.068	1985	39.6	73	0.084	1525	30.2
Generalised	21.5	0.028	189	2.0	33.2	0.036	602	7.5
Mean Total	38.5	0.040	65.9	18.4	45.7	0.052	64.5	17.9

Table 33 BioSignal analysis RMSSD, SDNN, NN50 count, & pNN50 for baseline and sub-clinical 5minute data

Pt. ID	Baseline HRV (5 minutes)			Sub-clinical HRV (5 minutes)			Difference HRV (5 minutes)		
	HF power ms^2	HF power %	HF power nu	HF power ms^2	HF power %	HF power nu	HF power ms^2	HF power %	HF power nu
Pt 1	1352	37.1	47.7	792	13	60.0	<560	<24.1	>12.3
Pt 2	464	57.2	46.6	692	75.4	73.4	>228	>18.2	>26.8
Pt 2	464	57.2	46.6	253	41.3	71.4	<211	<15.9	>24.8
Pt 2	464	57.2	46.6	285	24.7	60.1	<179	<32.5	>13.5
Pt 2	464	57.2	46.6	466	43.7	132.2	>2	<13.5	>85.6
Pt 2	464	57.2	46.6	280	33.3	65.2	<184	>23.9	>18.6
Pt 3	653	45.5	31.3	417	32.3	24.7	<236	<13.2	<6.6
Pt 4	1152	53.8	39.7	2861	36.2	33.0	>1709	<17.6	<6.7
Pt 5	981	41.6	34.1	1249	48.7	32.6	>268	>7.1	>1.5
Pt 6	428	16.7	19.3	843	15.9	22.3	>415	<0.8	>3
Pt 7	1769	79.6	73.1	1330	35.5	32.2	<439	<44.1	<40.9
Pt 7	1769	79.6	73.1	2789	55.7	57.2	>1020	<23.9	<15.9
Pt 8	617	52.9	47.6	197	8.0	8.1	<420	<44.9	<39.5
Pt 9	56	6.1	74.2	6	0.7	6.2	<50	<5.4	<68
Pt 10	83	63.2	56.6	66	41.3	53.3	<17	<21.9	<3.3
Pt 10	83	63.2	56.6	155	56.1	62.2	>72	<7.1	>5.6
Pt 10	83	63.2	56.6	108	24.7	24.1	>25	<38.5	<32.5
Pt 10	83	63.2	56.6	209	51.1	47.4	>126	<12.1	<9.2
Pt 10	83	63.2	56.6	72	46.0	39.2	<11	<17.2	<17.4
Pt 10	83	63.2	56.6	137	48.7	51.6	>54	<14.5	<5

Pt 10	83	63.2	56.6	125	43.8	78.1	>42	<19.4	>21.5
Pt 10	83	63.2	56.6	59	38.9	38.6	<24	<24.3	<18
Pt 10	83	63.2	56.6	135	42.9	47.8	>52	<20.3	<8.8
Pt 10	83	63.2	56.6	58	21.5	19.0	<25	<41.7	<37.6
Pt 10	83	63.2	56.6	91	30.9	37.4	>8	<32.3	<19.2
Pt 11	79	14	30.3	270	41.2	36.6	>191	>27.2	>6.3
Pt 11	79	14	30.3	289	51.7	50.1	>210	>37.7	>19.8
Pt 11	79	14	30.3	372	30.0	22.8	>293	>16	<7.5
Pt 11	79	14	30.3	235	24.6	20.1	>156	>10.6	<10.2
Pt 11	79	14	30.3	212	26.1	23.0	>133	>12.1	<7.3
Pt 11	79	14	30.3	600	37.8	28.3	>521	>23.8	<2
Pt 11	79	14	30.3	233	28.8	28.4	>154	>14.8	<1.9
Pt 11	79	14	30.3	254	48.4	40.9	>175	>34.4	>10.6
Total Rt	740	37.8	35.4	757	28.0	24.4	>17	<9.8	<11
Total Lt	950	47.2	58.3	1064	25.4	40.5	>114	<21.8	<17.8
Total Rt & Lt	790	38.5	65.5	872	26.1	57	>82	<12.4	<8.5
Generalised	89	24.3	44.8	185	32.8	26.9	>96	>8.5	<17.9
Mean Total	383.1	45.6	46.6	489	36.3	43.3	>105.9	<9.3	<3.35

Table 34 BioSignal analysis HFms^2, HF% & HFnu for baseline and sub-clinical 5minute data

LF% & VLF% HRV Spectral Frequencies

LF% HRV is considered to represent sympathetic and to some extent includes parasympathetic activity. VLF% HRV physiological representation is largely unexplained but considered to be indicative of rennin-angiotensin-aldosterone hormonal interplay on the autonomic nervous system. Data for LF% and VLF% are not presented briefly in this study. An increase in LF% HRV occurs during generalised sub-clinical seizures 51.4 ± 14.8 compared to

baseline measurements 26.1 ± 0.56. In contrast, decreases in LF% are noted during right sub-clinical seizures 38.4 ± 31.45 compared to baseline 48.14 ± 8.14 and left sub-clinical seizures 22.17 ± 26.16 compared to baseline 31.32 ± 25.6. Statistical significance is not demonstrated for LF% in any group (Table 42). VLF% data demonstrates no statistically significant results

3.7.3 RMSSD, SDNN

RMSSD is the square root of the mean squared differences of successive NN intervals and is an estimate of short term HRV. All groups show an increase in RMSSD short term HRV when analysed using 5minute epochs.

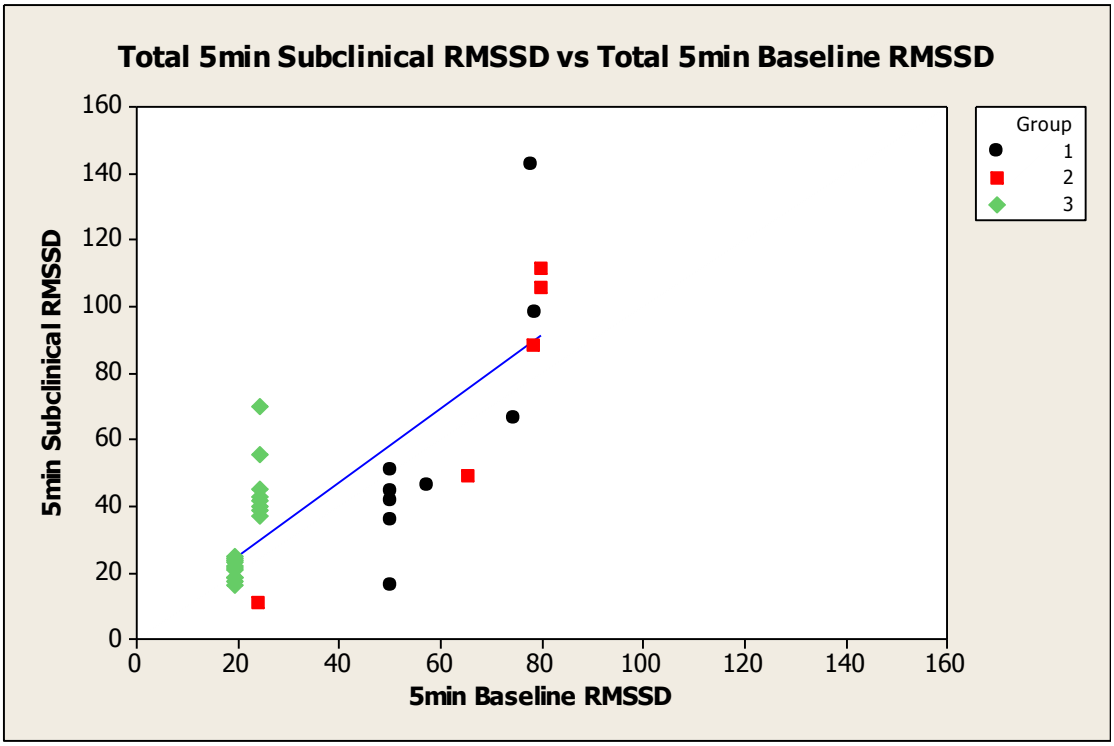


Figure 106 Scatterplot of baseline RMSSD versus sub-clinical RMSSD for total mean 5minute data.

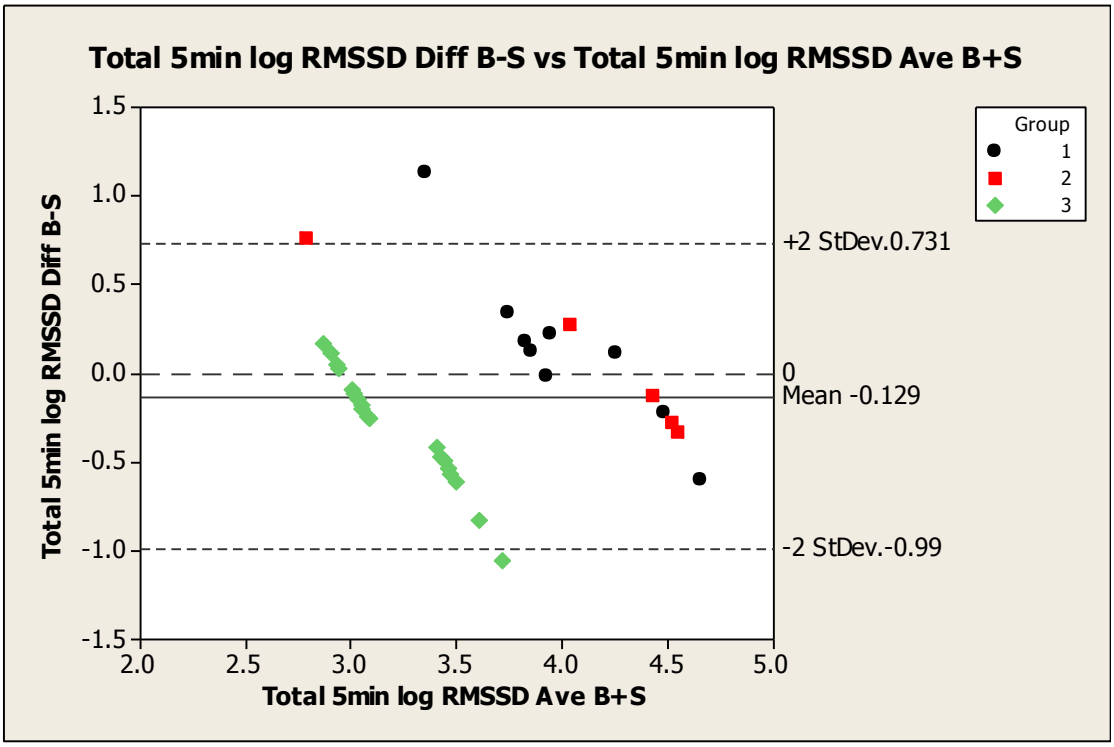


Figure 107 Bland & Altman scatterplot of difference (baseline minus sub-clinical) RMSSD versus average RMSSD for total mean 5minute data

Limits of agreement from Bland & Altman analysis for 5 min HRV RMSSD derived during total sub-clinical seizures (Figure 107) are (–0.8) and 0.3 with antilog of 0.4 and 1.4. Limits of agreement of 5 min HRV RMSSD derived during right temporal lobe sub-clinical seizures (–0.6) and 0.3 with antilog of 0.5 and 1.4 (range 0.9). Limits of agreement of 5 mn HRV RMSSD derived during left temporal lobe sub-clinical seizures are (–0.3) and 0.3 with antilog of 0.7 and 1.3 (range 0.6). Limits of agreement of 5 min HRV RMSSD derived during generalised sub-clinical seizures are (–0.8) and 0.2 with antilog of 0.4 and 1.2 (range 0.8). This result indicates similar short term variability for all categories of sub-clinical seizures compared to baseline data.

Generalised baseline RMSSD increases from 21.5 to sub-clinical 33.2msec, right baseline RMSSD increases from 60.8 to sub-clinical 68.7msec and left

baseline RMSSD increases from 70.6 to sub-clinical 79.8msec (Table 33). Differences between baseline and sub-clinical RMSSD limits of agreement again have the smallest range from generalised data of 0.7 (limits of agreement are 0.4 and 1.2), (Figure 107) compared to right temporal 0.9 (limits of agreement are 0.5 and 1.4) and left temporal 0.6 (limits of agreement are 0.7 and 1.3) similar to counted data (Table 8). However, the ranges are reduced for all data when using 5minute epoch compared to counted data and are considered to be more accurate over 5minute epochs.

Standard Deviation of Normal-to-Normal beat variation (SDNN) 5minutes HRV

SDNN is the square root of variance and is mathematically equal to the total power of spectral analysis and represents all the cyclic components contributing to HRV. It is appropriate to compare 5minute baseline studies and matched 5minute sub-clinical studies as they are of equal duration.

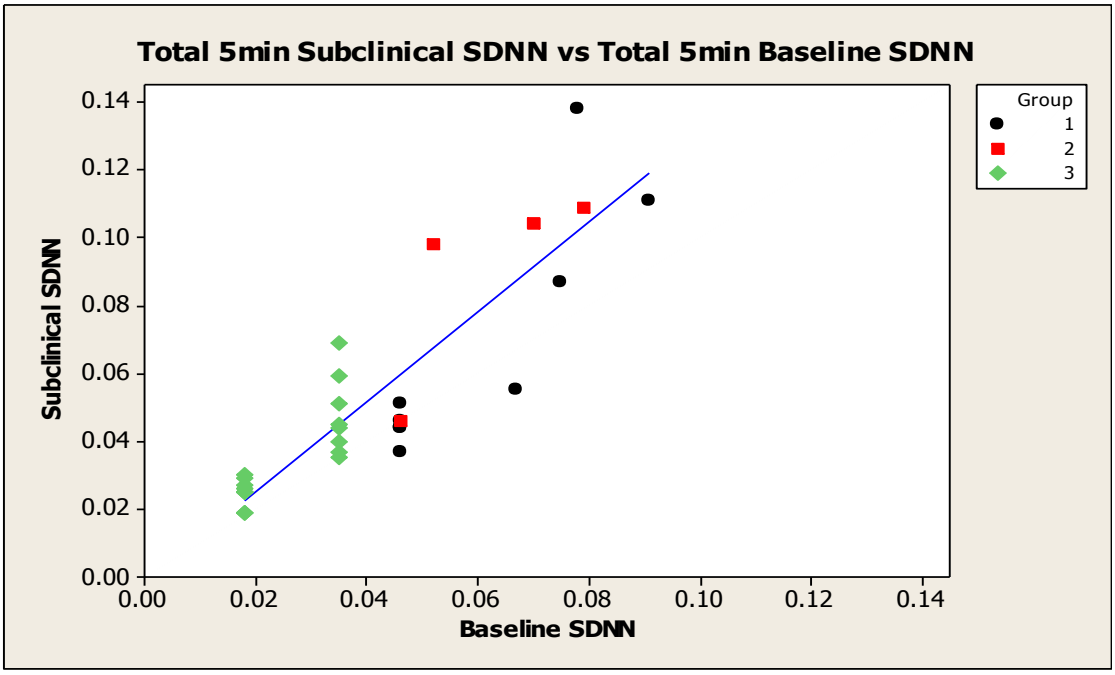


Figure 108 Scatterplot of baseline SDNN versus sub-clinical SDNN for total mean 5minute data.

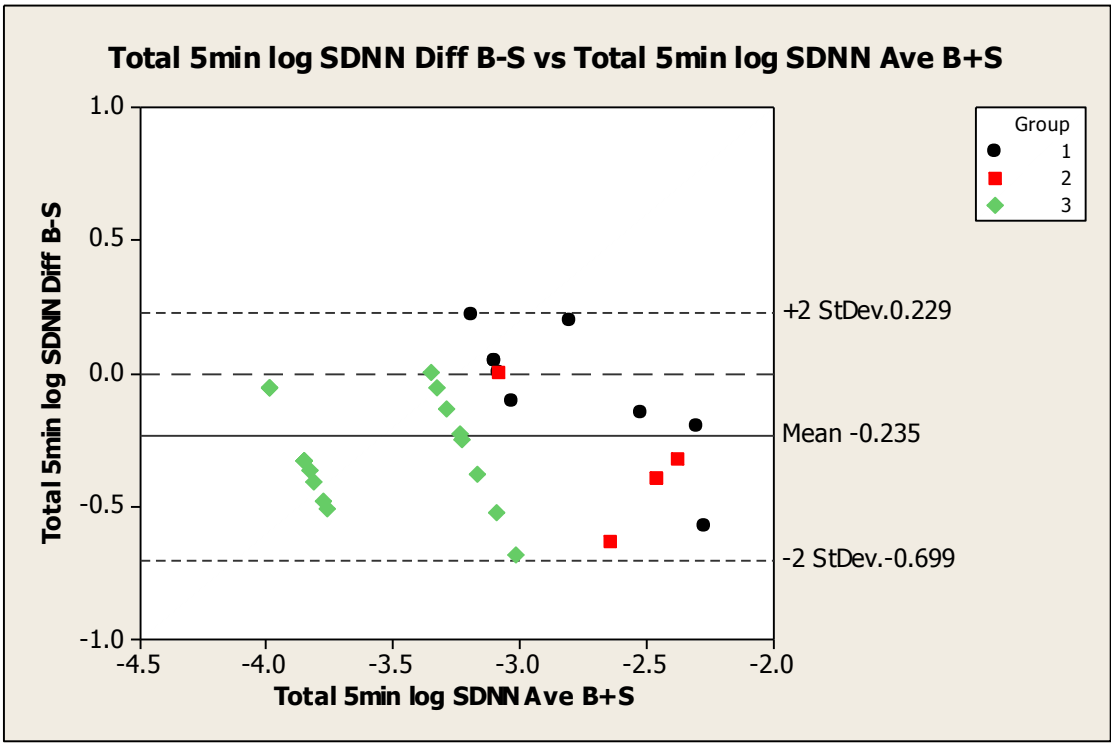


Figure 109 Bland & Altman scatterplot of difference (baseline minus sub-clinical) log SDNN versus average log SDNN for total mean 5minute data

Limits of agreement from Bland & Altman analysis of 5 min HRV SDNN derived for total sub-clinical seizures (Figure 109) are (–0.7) and 0.2 with antilog 0.5 and 1.2. Limits of agreement of 5 min HRV SDNN derived during right temporal sub-clinical seizures are (–0.2) and 0.2 with antilog of 0.8 and 1.2 (range 0.4). Limits of agreement of 5 min HRV SDNN derived during left temporal sub-clinical seizures are (–0.6) and 0.0 with antilog of 0.5 and 1.0 (range 0.5). Limits of agreement of 5 min HRV SDNN derived during generalised sub-clinical seizures are (–0.5) and 0.0 with antilog of these values are 0.6 and 1.0 (range 0.4).

Overall variability during 5 min HRV is seen for right and left temporal sub-clinical seizures and generalised sub-clinical seizure data compared to baseline data.

3.7.4 HFms^2 Power & HF% 5 minutes HRV

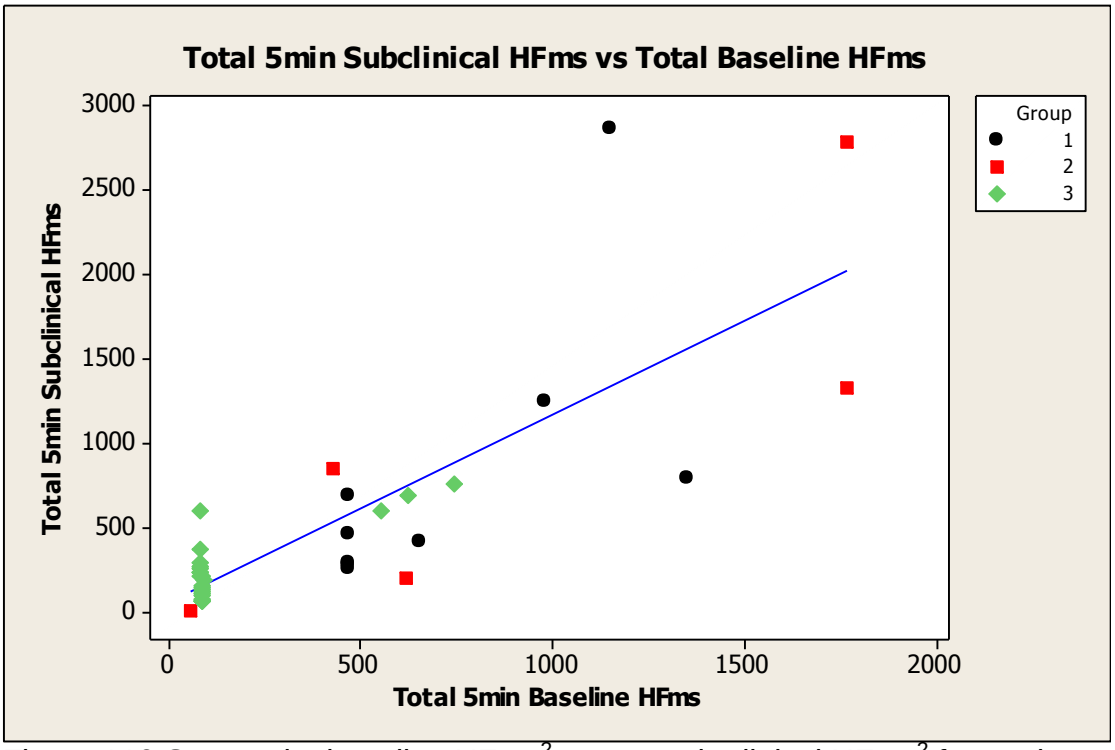


Figure 110 Scatterplot baseline HFms^2 versus sub-clinical HFms^2 for total mean 5minute data.

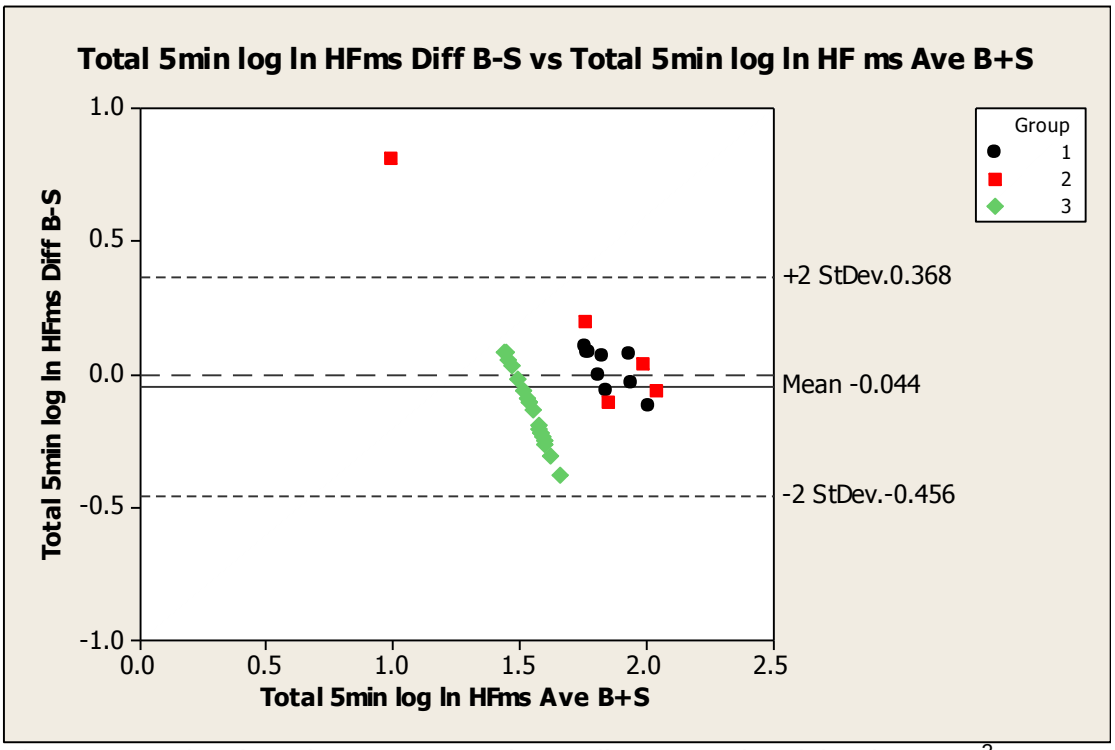


Figure 111 Bland & Altman scatterplot of difference (B-S) log lnHFms^2 versus average log lnHFms^2 for total mean 5minute data.

Limits of agreement of 5 min HRV log ln HFms derived from total sub-clinical seizures (Figure 111) are (–0.4) and 0.2. The ln (natural log) of these values are 0.7 and 1.2 (*p=0.144).* Limits of agreement of 5 min HRV log ln HFms derived during right temporal sub-clinical seizures are (–0.1) and 0.1. The ln (natural log) of these values are 0.9 and 1.1 (*p=0.363), (*range is 0.2) Limits of agreement of 5 min HRV log ln HFms derived during left temporal sub-clinical seizures are (–0.1) and 0.8. The ln (natural log) of these values are 0.9 and 2.2 (*p=0.584),* (range is 1.3). Limits of agreement of 5 min HRV log ln HFms derived during generalised sub-clinical seizures are (–0.4) and 0.1. The ln (natural log) of these values are 0.7 and 1.1 (*p=0.317)*, (range 0.4).

HF% 5min HRV

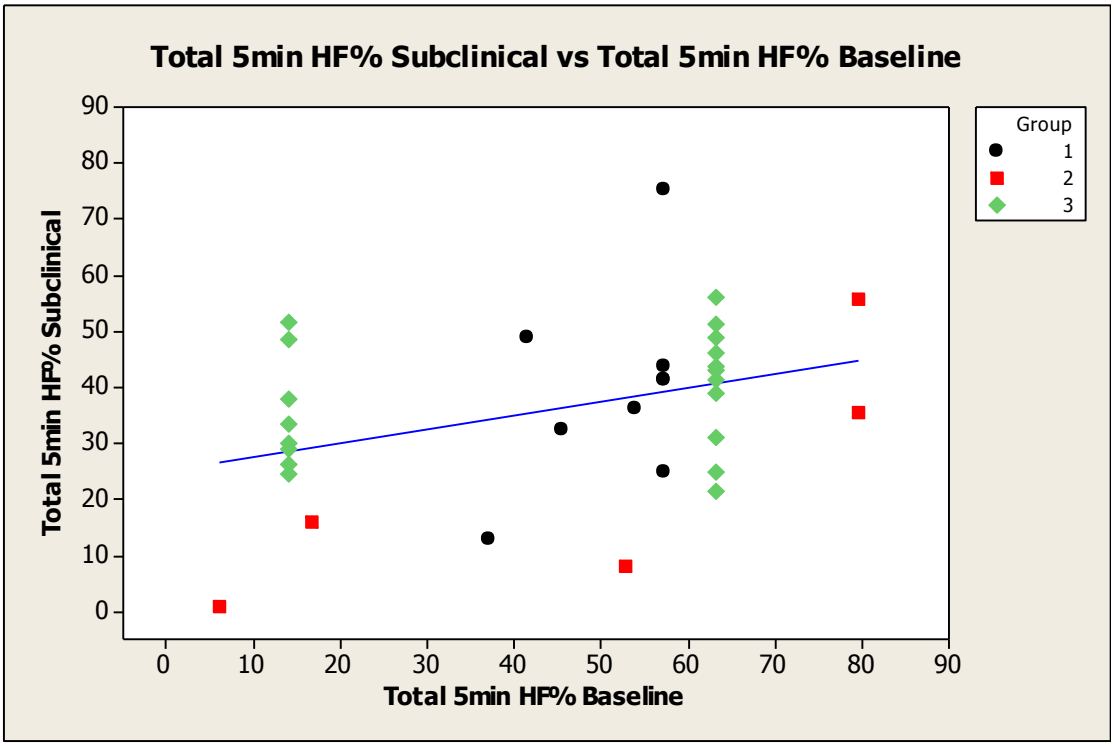


Figure 112 Scatterplot baseline HF% versus sub-clinical HF% for total mean 5minute data

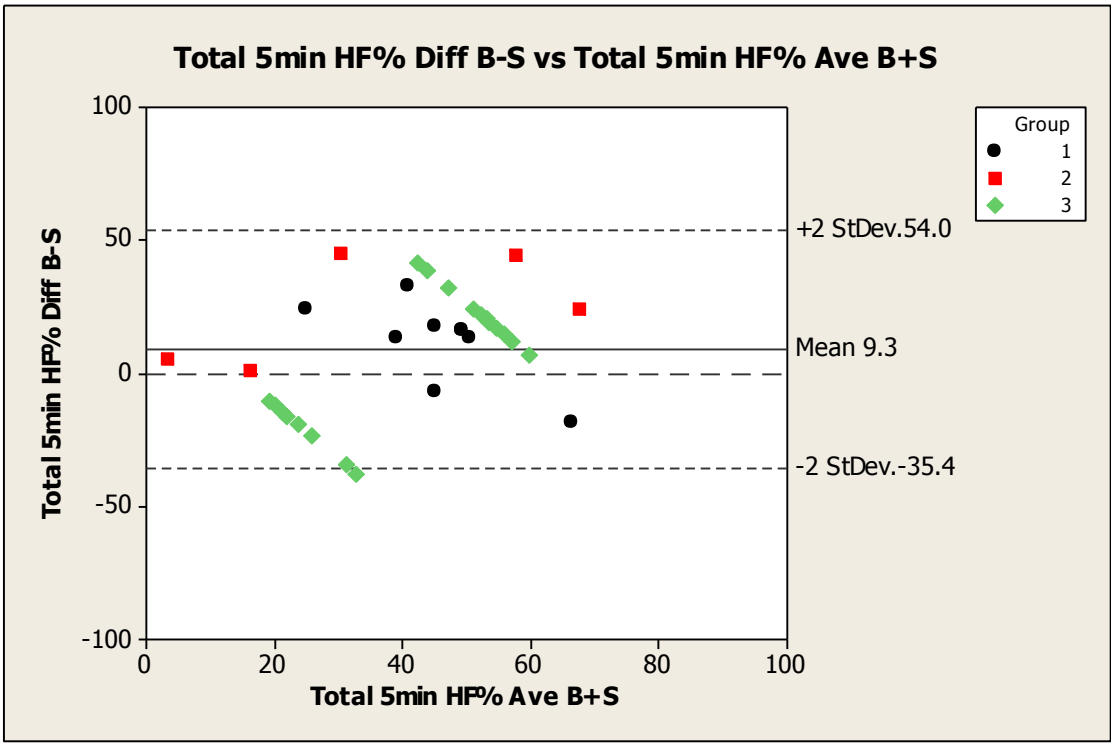


Figure 113 Bland & Altman scatterplot of difference (B-S) HF% versus average HF% for total mean 5minute data.

Bland & Altman analysis of limits of agreement for 5 min HF% HRV derived during total sub-clinical seizures (Figure 113) are (-34.4) and 44.9. Limits of agreement for 5 minHF% HRV derived during right temporal sub-clinical seizures are (–18.2) and 32.5 (range 50.7%). Limits of agreement for 5 min HF% HRV derived during left temporal sub-clinical seizures are 0.8 and 44.9 (range 44.1%). Limits of agreement for 5 min HF% HRV derived during generalised sub-clinical seizures are (–37.7) and 41.7 (range 79.4%).

5 minute HF%HRV shows that there is more parasympathetic activity during generalised sub-clinical seizures indicating reduced heart rate during generalised sub-clinical seizures compared to baseline data than during right or left temporal lobe sub-clinical seizures

Bland & Altman plots analysing the 5minute epoch differences in baseline minus sub-clinical data for each group show impressively similar mean differences to counted data. Caution is used in comparing different epochs for HF% but is investigated in this instance to investigate further reasons why the results have changed for generalised data when using a longer epoch. Right mean HF% difference is 11.9 ± 30.9 (counted mean difference 9.6 ± 36.3) with limits of agreement (-18.2) and 32.5 (Figure 113). Left mean HF% difference is 23.8 ± 41.6, (counted mean difference 24.7 ± 43.6) with limits of agreement 0.8 and 44.9. Generalised mean difference is 4.2 ± 48.9 (counted mean difference 4.1 ± 33) with limits of agreement (-37.7) and 41.7. Even though the mean difference for generalised data is practically identical, the limits of agreement are wider using 5 minute epochs (-37.7 and 41.7) compared to counted HF% limits of agreement (-15 and 35.7).

	Baseline HRV5 HF%				Sub-clinical HRV5 HF%				Wilcoxon
	n	Mean HF	Median HF	Mean HR/min	n	Mean HF	Median HF	Mean HR/min	*p*</=
Right Temporal HF%	9 (3110)	51.6± 8.0	57.2	68.1	9 (3330)	39.6 ±17.2	41.3	73.0	0.042
Left Temporal HF%	5 (1757)	47.0 ±34.5	52.9	52.5	5 (1780)	23.2 ±22.4	15.9	48.1	0.062
Generalised HF%	19 (9055)	42.5 ±25.0	63.2	93.0	19 (8119)	38.2 ±10.6	38.9	84.7	0.512
Total HF%	33 (13922)	45.6 ±23.0	57.2	71.2	33 (13229)	36.3 ±15.2	37.8	68.6	0.026

Table 35 Baseline & sub-clinical HF% 5minute data.

HF% HRV is believed to represent parasympathetic activity. Statistical significance is seen from 5 minutes HF% data when comparing mean baseline with mean sub-clinical studies for total data There is a reduction of parasympathetic activity from total baseline HF% measurements 45.6 ± 23.0 compared to total sub-clinical seizures 36.3 ± 15.2, (*p=0.026).* For right temporal lobe sub-clinical seizure data there is a decrease in baseline HF% 51.6 ± 8 reducing to sub-clinical HF% 39.6 ± 17.2, *(p=0.042).* Left temporal lobe sub-clinical seizure data similarly reduces from baseline HF% 47.0 ± 34.5 to sub-clinical HF% 23.2 ± 22.4, (*p=0.062*). However, generalised data shows an increase in parasympathetic activity from baseline HF% 42.5 ± 25.0 to sub-clinical HF% 38.2 ± 10.6 but does not reach statistical significance (*p=0.512),* (*Table 35).*

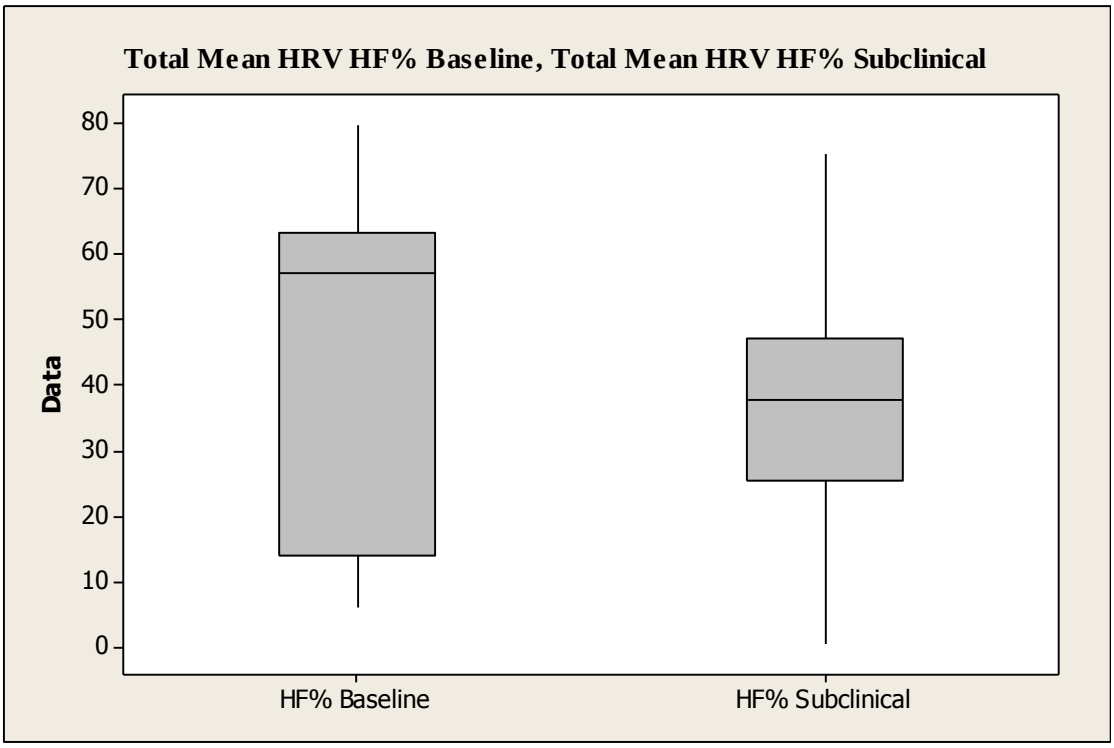


Figure 114 Boxplot of HF% baseline, HF% sub-clinical 5minute HRV total mean data.

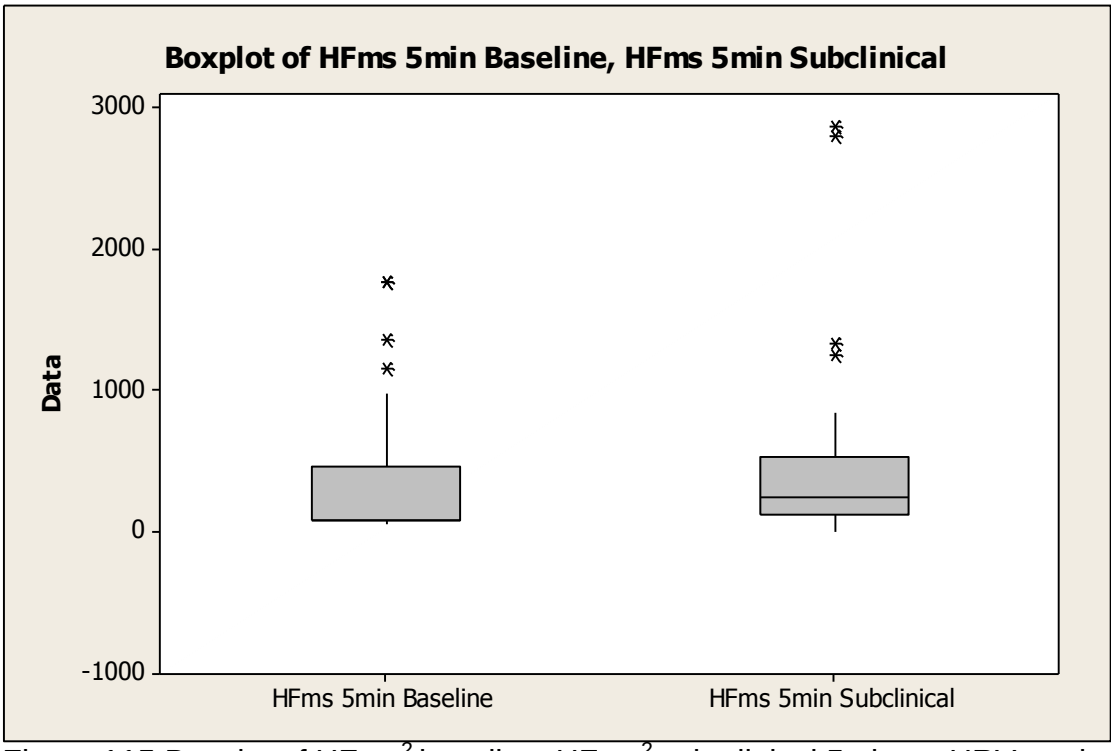


Figure 115 Boxplot of $HFms^2$ baseline, $HFms^2$ sub-clinical 5minute HRV total mean data.

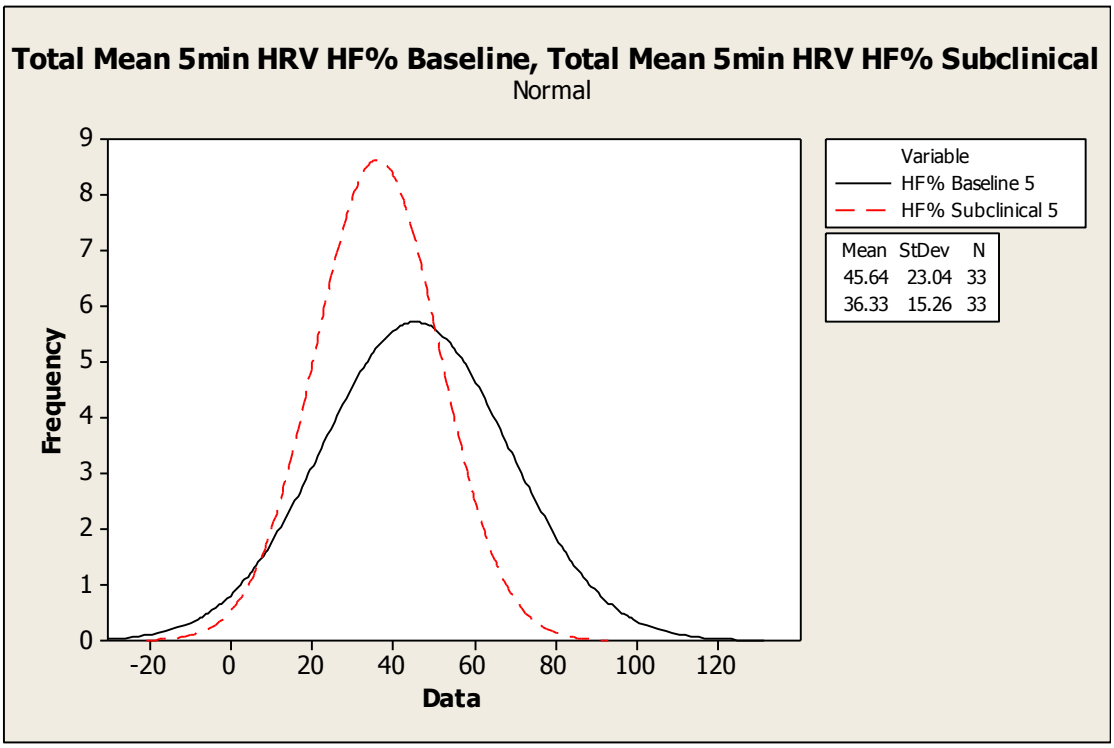


Figure 116 Histogram of HF% baseline, HF% sub-clinical 5minute HRV total mean data. Wilcoxon *p=0.026*. This histogram is very similar to CIPA & shows a decrease in HF% from baseline (45.64) to sub-clinical (36.33).

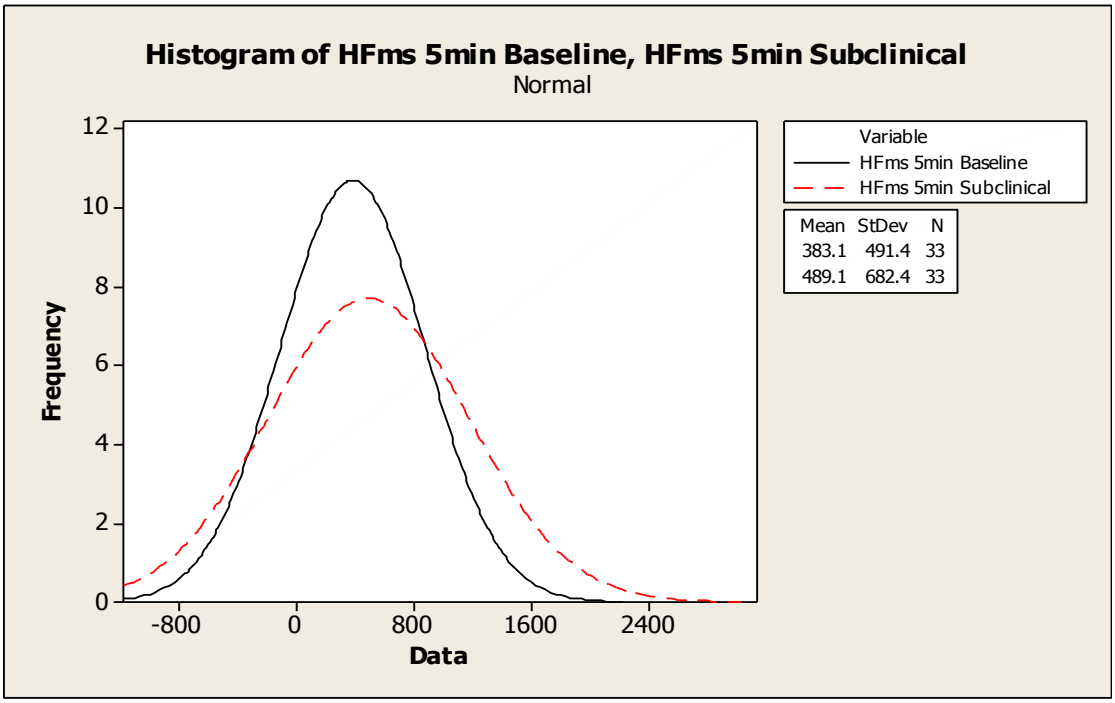


Figure 117 Histogram of HFms^2 baseline, HFms^2 sub-clinical 5minute HRV total mean data. Wilcoxon *p= 0.472*. This histogram is not concordant with CIPA or HF% and conversely shows an increase in HFms^2 baseline (383.1) to sub-clinical (489.1).

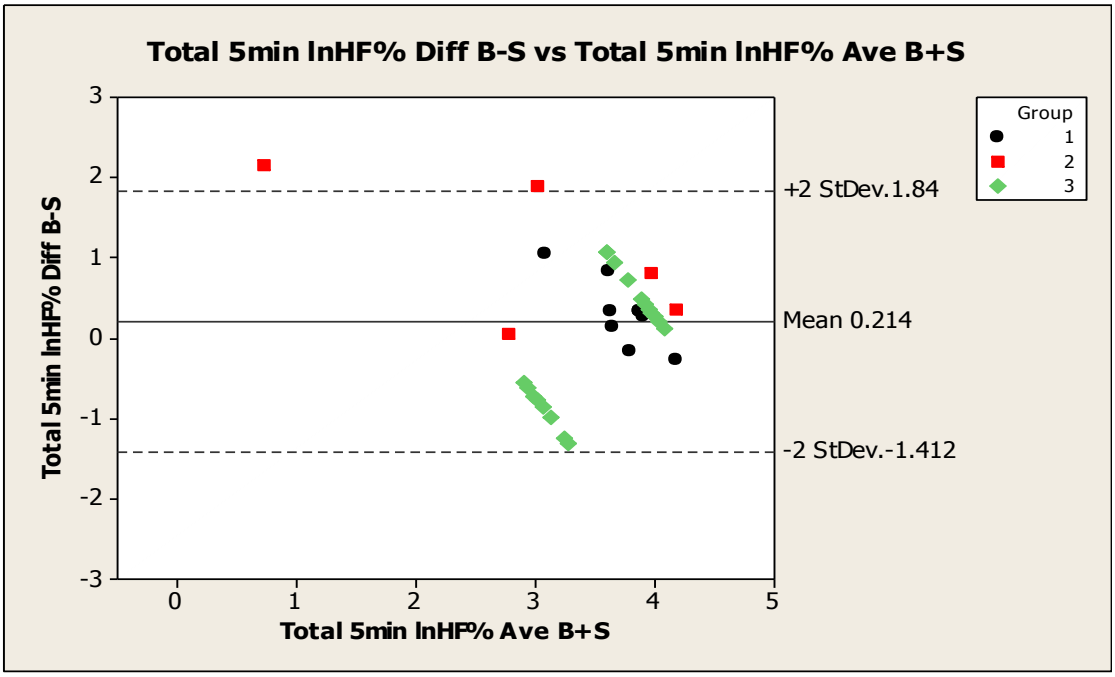


Figure 118 Bland & Altman scatterplot of difference (B-Sl) lnHF% versus average lnHF% for total mean 5minute data.

Bland & Altman plot analysis of 5 min lnHF% HRV derived from total sub-clinical seizures compared to baseline data (Figure 118) with limits of agreement (-1.3) and 1.0 and antilog of 0.3 and 2.8. Limits of agreement of 5 min lnHF% HRV derived from right temporal sub-clinical seizures are (-0.3) and 1.1 with antilog 0.8 and 2.8 (range 2.0). Limits of agreement of 5 min lnHF% HRV derived from left temporal sub-clinical seizures are 0.1 and 2.2 with antilog 1.0 and 8.7 (range 7.7). Limits of agreement of 5 min lnHF% HRV derived from generalised sub-clinical seizures are (-1.3) and 1.1 with antilog of 0.3 and 3.0 (range 2.7).

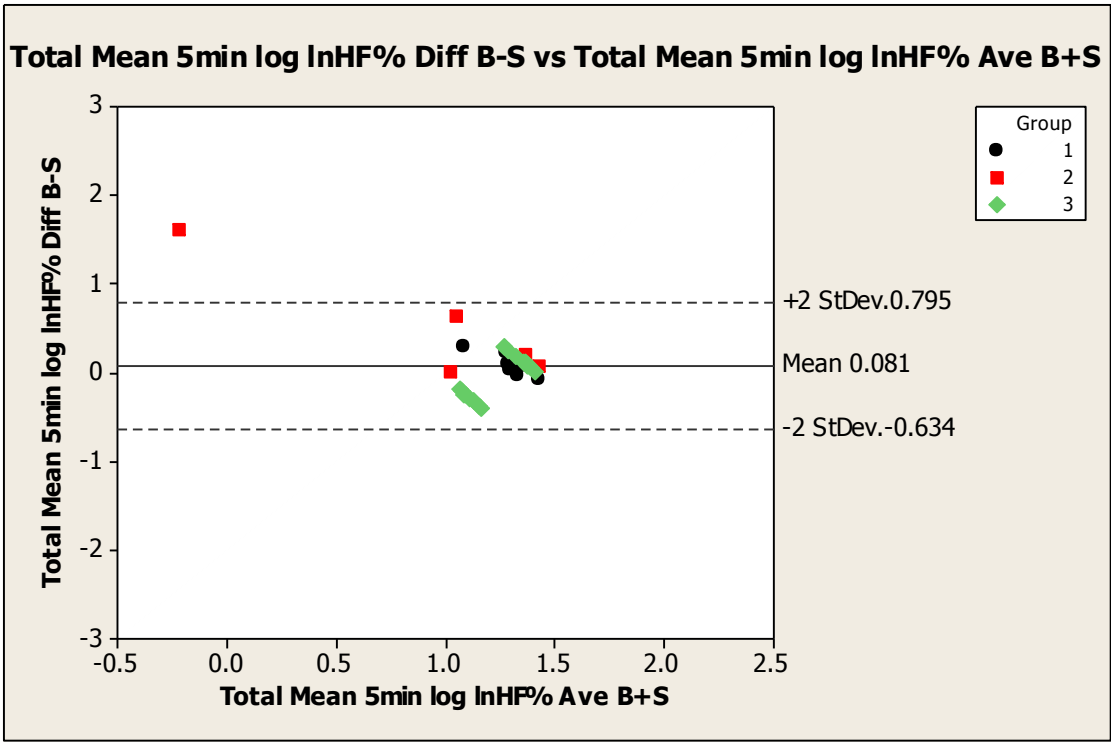


Figure 119 Bland & Altman scatterplot of difference (B-S) log lnHF% versus average log lnHF% for total mean 5minute data.

Bland & Altman plot analysis of 5 min log lnHF% HRV derived during total sub-clinical seizures compared to baseline data (Figure 119) has limits of agreement of (–0.4) and 0.6 with (natural log) of 0.7 and 2.0. Limits of agreement of 5 min log lnHF%HRV derived during right temporal sub-clinical seizures are (-0.1) and 0.3 with ln (natural log) of 0.9 and 1.3 (range 0.4%). Limits of agreement of 5 min log lnHF%HRV derived during left temporal sub-clinical seizures are 0.0 and 0.2 with ln (natural log) of 1.0 and 1.2 (range 0.2%). Limits of agreement of 5 min log lnHF%HRV derived during generalised sub-clinical seizures are (–0.4) and 0.3 with ln (natural log) of 0.7 and 1.4 (range 0.7%).

	Total mean CIPA Difference (CIPA Baseline minus CIPA Sub-clinical)	Total mean log CIPA Difference (CIPA Baseline minus CIPA Sub-clinical	Total mean 5min HF %Difference (HF% Baseline minus HF% Sub-clinical).	Total mean 5min ln HF% Difference (ln HF% Baseline minus ln HF% Sub-clinical)	Total mean 5min log ln HF% Difference (log ln HF% Baseline minus log ln HF% Sub-clinical)
n	33	33	33	33	33
Mean	0.8	0.02	9.3	0.2	0.1
SE Mean	0.6	0.1	3.9	0.0	0.1
St. Deviation	3.6	0.5	22.4	0.3	0.4
Minimum	-4.8	-0.7	-37.7	-0.4	-0.4
Q1	-1.2	-0.3	-11.4	-0.1	-0.1
Median	0.3	0.0	14.5	0.1	0.1
Q3	2.0	0.2	24.0	0.2	0.2
Maximum	9.8	1.3	44.9	1.0	1.6
Wilcoxon two sample test *p</=*	0.743	0.472	0.026	0.235	0.204

Table 36 Descriptive statistics for differences (baseline minus sub-clinical) in CIPA, log CIPA, HF%, lnHF% & log lnHF% in 5minute data.

5 min HRV Mean Difference (baseline minus sub-clinical)		Mean Differ-ence	Lower limit of Agree-ment Bland & Altman Antilog values	Upper limit of Agree-ment Bland & Altman Antilog values	Range of limits of agree-ment Bland & Altman	Wilcoxon *p*</=
Total **Sub-clinical Seizures** n=33	log RMSSD	-0.1	0.4	1.4	1.0	0.387
	log SDNN	-0.2	0.5	1.2	0.7	0.092
	HF%	9.3	-34.4	44.9	79.3	0.026
	lnHF%	0.2	0.3	2.9	2.6	0.235
	log ln HF%	0.1	0.7	1.9	1.2	0.204
Right **Temporal Sub-clinical Seizures** n=9	log RMSSD	0.1	0.5	1.4	0.9	0.533
	log SDNN	-0.1	0.8	1.2	0.4	0.756
	HF%	11.9	-18.2	32.5	50.7	0.042
	lnHF%	0.3	0.8	2.9	2.1	0.097
	log ln HF%	0.1	0.9	1.3	0.4	0.127
Left **Temporal Sub-clinical Seizures** n=5	log RMSSD	0.1	0.7	1.3	0.6	0.905
	log SDNN	-0.4	0.5	1.0	0.5	0.120
	HF%	23.8	0.8	44.9	44.1	0.062

	lnHF%	1.1	1.0	8.7	7.7	0.295
	log ln HF%	0.1	1.0	1.2	0.2	0.326
Generalised **Sub-clinical Seizures** n=19	log RMSSD	-0.3	0.4	1.2	0.7	0.007
	log SDNN	-0.3	0.6	1.0	0.4	0.018
	HF%	4.2	-37.7	41.7	79.4	0.512
	lnHF%	-0.1	0.3	2.9	2.7	0.769
	log ln HF%	-0.1	0.7	1.3	0.7	0.522

Table 37 Bland & Altman limits of agreement for log RMSSD, log SDNN, HF%, lnHF% & log lnHF% in total, right, left and generalised 5minute data

3.7.5 Relationship between NeuroScope data and BioSignal HF% & HFms^2

The High Frequency (HF) band of heart rate variability frequency domain analysis is considered to represent cardiac vagal activity. This is the closest equivalent to CIPA in measuring vagal tone. Like mean CIPA (*p=0.233).* (Table 8) & Counted HF% (*p=0.049),* (Table 30) a decrease in 5minute HF% (*p=0.026),* (Table 37) indicates a reduction of cardiac vagal tone and tends to result in an increase in heart rate and vice versa. This is not concordant with HFms^2 indicating a slight increase in vagal activity for total HFms^2 baseline (383.1) to sub-clinical HFms^2 (489.1) *(p= 0.472),* (Figure 117)

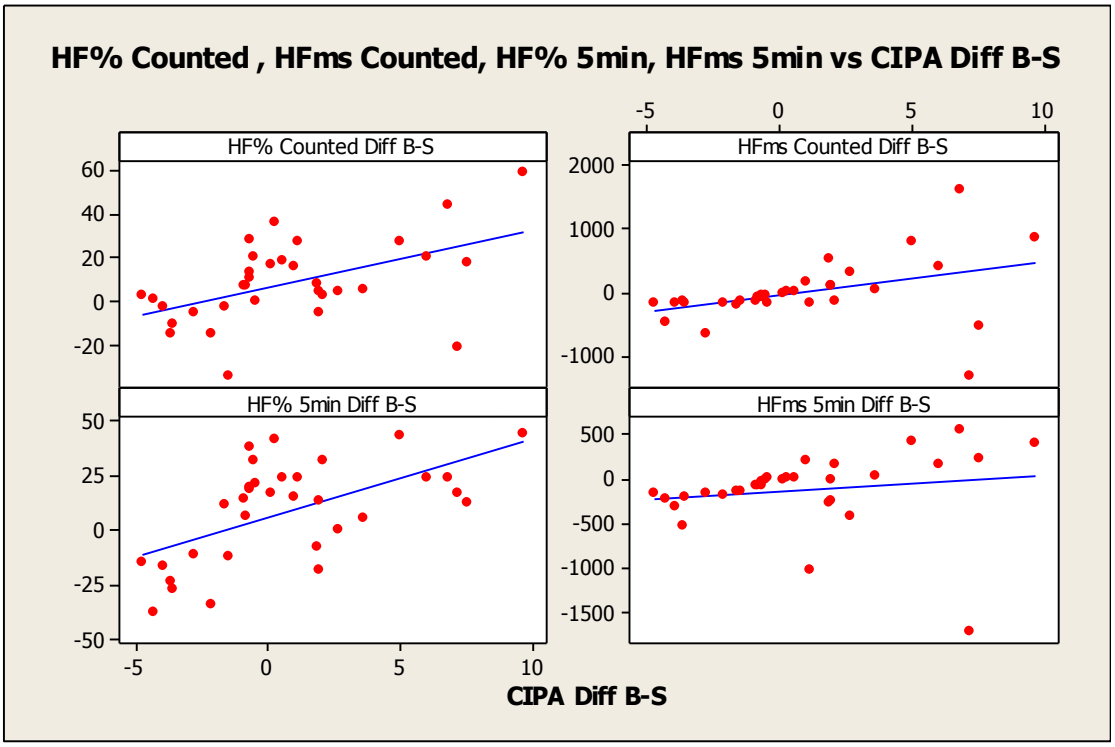


Figure 120 Pearson correlation analysis of counted HF% & 5minute HF% (BioSignal) data with CIPA (NeuroScope) data.

The closest Pearson correlation is CIPA versus 5min HRV HF% of $p<0.001$, followed by CIPA versus Counted HF% ($p=0.002$). CIPA is least correlated to 5minute HRV HFms^2 ($p=0.359$), followed by Counted HFms^2 ($p=0.025$).

Due to closest data correlation found between CIPA and HF%, more detailed analysis was performed examining seizure type using HF% rather than HFms^2 (Figure 120). Additionally, HFms^2 could not be used for the purposes of this study due to the huge standard deviation compared to the mean baseline 383.1 ± 982.8 and mean sub-clinical 489 ± 1364 (derived from Table 34) With a study of 33 mean totals a disproportionate standard deviation would make results difficult to interpret.

3.7.6 BioSignal Heart Rate Variability Coefficient of Variation (5minutes)

Patient ID	Right Temporal HRV 5min R-R						Wilcoxon Two sample Test *p*</=
	Baseline			Sub-clinical			
	n	R-R	Coef. Variation %	n	R-R	Coef. Variation %	
Patient 1	283	1075	9.5	350	905	14.9	0.001
Patient 2	331	982	5.4	332	920	5.2	0.866
Patient 2	331	928	5.4	369	808	5.5	0.001
Patient 2	331	928	5.4	370	792	7.4	0.001
Patient 2	331	928	5.4	373	792	6.6	0.001
Patient 2	331	928	5.4	387	768	6.6	0.001
Total Patient 2	1655	928	5.4	1831	800	8.5	0.001
Patient 3	385	784	8.0	452	652	14.9	0.001
Patient 4	342	870	10.1	274	1172	5.2	0.001
Patient 5	445	705	14.0	423	715	5.5	0.022
Total Right Temporal	3110	895	13.8	3330	800	20.1	0.001

Table 38 Baseline & sub-clinical 5minute R-R interval & coefficient of variation in patients with right temporal lobe sub-clinical seizures.

Patient ID	Left Temporal HRV 5min R-R						Wilcoxon Two Sample Test *p*</=
	Baseline			Sub-clinical			
	n	R-R	Coef. Variation %	n	R-R	Coef. Variation %	
Patient 6	385	780	13.5	397	765	26.2	0.229
Patient 7	388	790	9.0	335	825	15.0	0.001
Patient 7	388	790	9.0	297	800	13.0	0.048
Total Patient 7	776	790	9.0	632	812.5	14.3	0.001
Patient 8	279	1074	5.2	284	1025	11.7	0.001
Patient 9	317	995	5.6	467	605	13.0	0.001
Total Left Temporal	1757	875	15.5	1780	801	23.5	0.001

Table 39 Baseline & sub-clinical 5minute R-R interval & coefficient of variation in patients with left temporal lobe sub-clinical seizures

Patient ID	Generalised 5min R-R						Wilcoxon Two Sample Test *p*</=
	Baseline R-R			Sub-clinical R-R			
	n	R-R msec	Coef.Variation%	n	R-R msec	Coef.Variation%	
Patient 10	493	625	4.1	514	605	4.1	0.001
Patient 10	493	625	4.1	481	625	4.7	0.038
Patient 10	493	625	4.1	514	615	5.3	0.052
Patient 10	493	625	4.1	381	635	5.7	0.001
Patient 10	493	625	4.1	495	635	3.3	0.001
Patient 10	493	625	4.1	458	650	4.1	0.001
Patient 10	493	625	4.1	461	645	5.8	0.001
Patient 10	493	625	4.1	456	655	3.2	0.001
Patient 10	493	625	4.1	453	660	4.8	0.001
Patient 10	493	625	4.1	514	655	4.8	0.001
Patient 10	493	625	4.1	457	655	4.6	0.001
Total Patient 10	5423	625	4.1	5184	640	5.5	0.365
Patient 11	454	675	5.8	383	805	5.3	0.001
Patient 11	454	675	5.8	376	800	5.0	0.001
Patient 11	454	675	5.8	368	820	7.4	0.001
Patient 11	454	675	5.8	373	830	6.6	0.001
Patient 11	454	675	5.8	360	840	5.6	0.001
Patient 11	454	675	5.8	355	850	8.3	0.001
Patient 11	454	675	5.8	370	810	6.1	0.001
Patient 11	454	675	5.8	350	860	4.8	0.001
Total Patient 11	3632	675	5.8	2935	830	6.6	0.001

Table 40 (above) Baseline & sub-clinical 5minute R-R interval & coefficient of variation in patients with generalised sub-clinical seizures

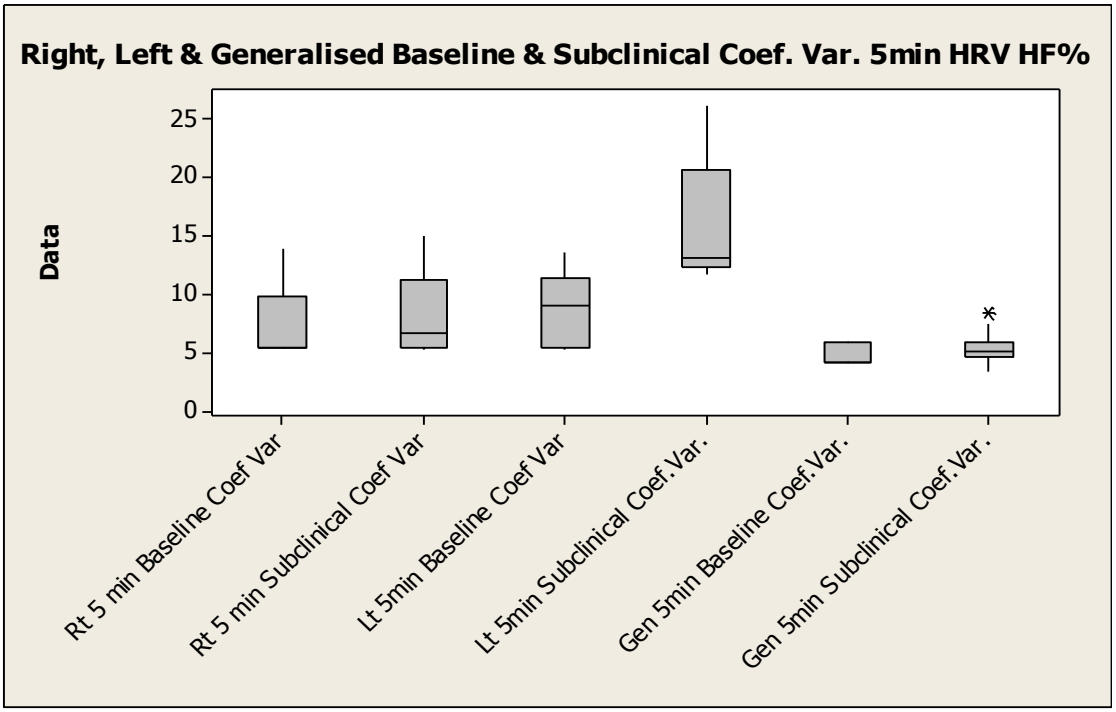


Figure 121 Boxplot of baseline & sub-clinical coefficient of variation for right, left & generalised 5minute data

Bland & Altman Summary	Right Temporal n=9	Left Temporal n=5	Generalised n=19
CIPA Mean Difference (Baseline minus sub-clinical)	3.7	4.4	-1.6
CIPA Average	12.1	12.8	4.8
HF% (Counted) Difference (Baseline minus sub-clinical)	9.6	24.7	4.1
HF% (Counted) Average	47.3	38.5	39.0
HF% (5min) Difference (Baseline minus sub-clinical)	11.9	23.8	4.24
HF% (5min) Average	45.6	35.1	40.36

Table 41 Difference (baseline minus sub-clinical) in mean CIPA, HF% in right, left & generalised 5minute data

Biomarker	Baseline	Sub-clinical	Wilcoxon *P*=/<	Bonferroni
CIPA during Total data.	8.2 ± 6.3	6.9 ± 5.0	0.001	0.001
CIPA during Right temporal lobe data.	12.7 ± 5.3	9.1 ± 5.4	0.001	0.005
CIPA during Left temporal lobe data.	14.3 ± 6.8	9.9 ± 6.9	0.001	0.01
CIPA during Generalised data.	3.7 ± 1.5	4.8 ± 2.8	0.001	0.002
HRV %HF (& %LF) during Total baseline & sub-clinical data	45.6 ± 23.0 (38.0±17.9)	36.3 ± 15.2 (34.9±27.4)	0.04 (0.699)	0.001
HRV %HF% (& %LF) during Right temporal lobe activity	37.8 ± 8.0 (48.1 ± 8.1)	28.0 ± 17.4 (38.4 ± 31.4)	0.079 (0.449)	0.005
HRV %HF (& %LF) during Left temporal lobe activity	47.2 ± 34.5 (31.32 ± 25.6)	25.4 ± 22.4 (22.17±26.16)	0.143 (0.53)	0.01
HRV %HF (& %LF) during Generalised activity	24.3 ± 25.0 (26.1 ± 0.6)	32.8 ± 10.6 (51.4 ± 14.8)	0.991 (0.242)	0.002
SDNN (& RMSSD) during Total data	0.04 ± 0.02 (38.5 ± 23.1)	0.05 ± 0.03 (45.7 ± 31.7)	0.001 (0.037)	0.001
SDNN (& RMSSD) during Right temporal lobe activity	0.06 ± 0.017 (59.8 ± 13.09)	0.068 ± 0.03 (60.2 ± 38.2)	0.304 (0.97)	0.005
SDNN (& RMSSD) during Left temporal lobe activity	0.1 ± 0.01 (65.4 ± 24.07)	0.09 ± 0.02 (73.2 ± 42.3)	0.02 (0.466)	0.01
SDNN (& RMSSD) during Generalised activity	0.03 ± 0.02 (30.53 ± 20.9)	0.05 ± 0.03 (40.29 ± 27.9)	0.001 (0.003)	0.002

SDNN50 count during total data	65.9 ± 76.3	64.5 ± 58.2	0.932	0.001
SDNN50 count during Right temporal lobe activity	133.2 ± 35.9	106.4 ± 51.8	0.016	0.005
SDNN50 count during Left temporal lobe activity	157.2 ± 91.6	113.4 ± 79.6	0.029	0.01
SDNN50 during Generalised activity	9.94 ± 0.815	31.68 ± 27.29	0.001	0.002

Table 42 Comparison of CIPA, HRV HF%, LF%, SDNN, RMSSD & SDNN50 derived during 33 subclinical seizures and 33 matched baseline studies.

Statistically significant differences are seen for total sub-clinical seizures 0.05 ± 0.03 compared to baseline measurements 0.04 ± 0.02 ($p<0.001$) and Generalised sub-clinical seizures 0.046 ± 0.029 ($p<0.001$) compared to baseline measurements 0.03 ± 0.018 after Bonferroni correction. SDNN for right ($p=0.304$) and left ($p=0.02$) temporal lobe seizures are not considered statistically significant after correction for multiple measurements (Table 42).

When SDNN50 mean counts are considered for all patients there is no significant difference between total baseline counts (65.9 ± 76.3) and sub-clinical seizure (64.5 ± 58.2) data (*p=0.932)*. However, differences are detected when sub-clinical seizure types are analysed separately. There are generally smaller counts during baseline and sub-clinical seizure counts for patients with refractory generalised epilepsy compared to analysis of counts for patients with temporal lobe seizures. Baseline mean counts of SDNN50 for right temporal sub-clinical seizures for baseline measurements (133.2 ± 35.9) reduce to sub-clinical (106.4 ± 51.8), (*p=0.016)*. Left temporal lobe sub-clinical seizures SDNN50 shows a similar reduction from baseline (157.2 ± 91.6) to

sub-clinical (113.4 ± 79.6), (*p=0.029)*. Generalised sub-clinical seizures are comparatively much lower SDNN50 counts compared to temporal lobe counts with baseline SDNN50 (9.947 ± 0.815) to sub-clinical (31.68 ± 27.29), (*p<0.001)* and this would indicate that there is generally less beat-beat variability in this group (Table 42).

Following Bonferroni correction, the only statistically significant change *(p=0.003*) is attributed to generalised sub-clinical seizures 40.3 ± 30.5 compared to baseline measurements 30.5 ± 20.9. Right temporal lobe sub-clinical seizures 60.2 ± 38.2 compared to baseline 59.8 ± 13.1 *(p=0.97)* and left temporal lobe sub-clinical seizures 73.2 ± 42.3 compared to baseline measurements 65.4 ± 24.07 *(p=0.466)* are not statistically significant.

3.7.7 Comparison of Adult HF% and Paediatric HF% (5min)

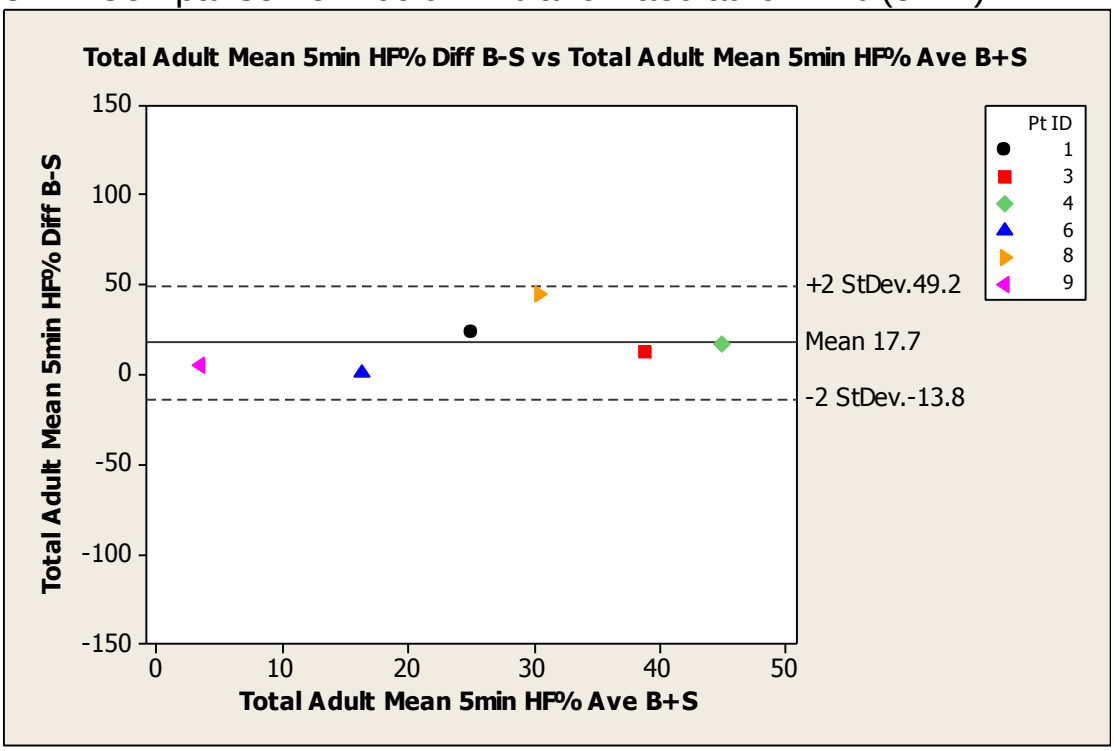


Figure 122 Bland & Altman scatterplot difference (baseline minus sub-clinical) HF% versus HF% average in adult 5 minutes HRV data. Limits of agreement are 44.9 and 0.8. Wilcoxon *p=1.0*

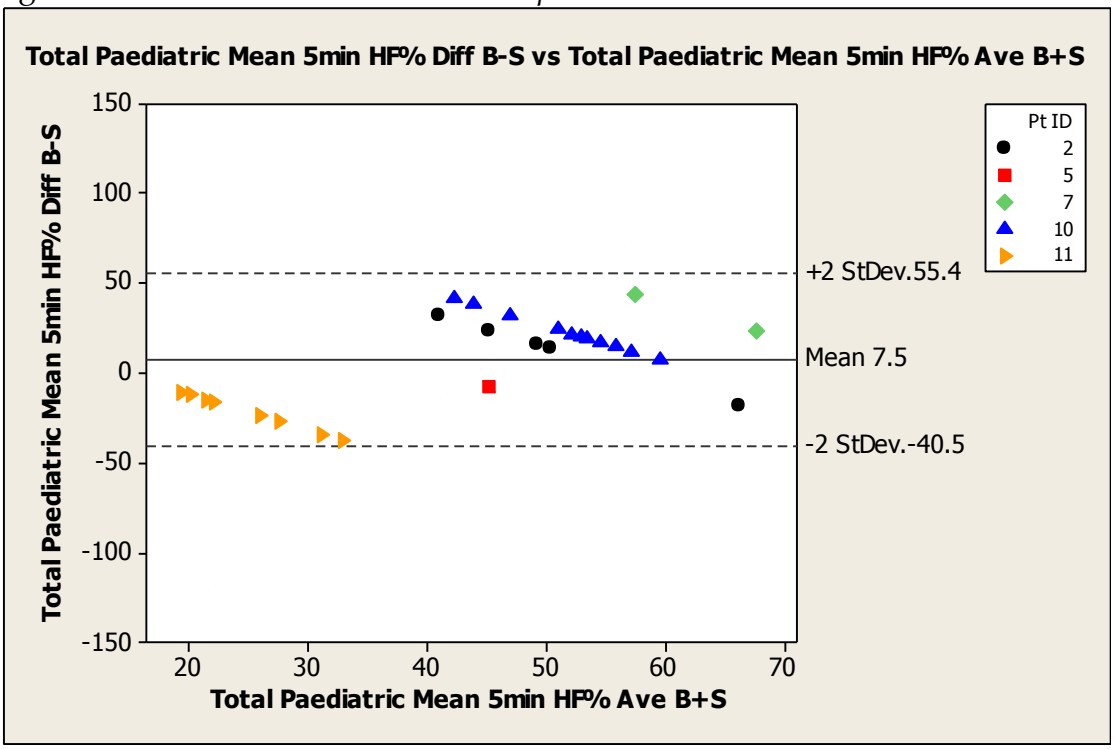


Figure 123 Bland & Altman scatterplot difference (baseline minus sub-clinical) HF% versus HF% average in paediatric 5 minutes HRV data. Limits of agreement are 44.1 and –37.7. Wilcoxon *p=0.28*

Adult HF% and Paediatric HF% (5min)

Mean difference in HF% baseline minus sub-clinical was calculated for paediatrics (n=5) and adults (n=6) for 5 minute epochs HRV. The mean difference for paediatrics data was 7.5 ± 47.9 (*p=0.28*) with limits of agreement (-37.7) and 44.1 (range 81.8), (Figure 123). Adult mean difference is 17.7 ± 31.5 (*p=1.0*) with limits of agreement 0.8 and 44.9 (range 44.1), (Figure 122). Standard deviation is smaller for adult data (6 patients and 6 sub-clinical seizures) compared to paediatrics (5 patients, 27 sub-clinical seizures).

Poor statistically significant differences in HF% are demonstrated when total adults and total paediatric mean HF% data are analysed separately for either counted or for 5minute HF%. Total adult mean counted HF% difference is (-4.4) ± 83.4 (limits of agreement -77.8 and 44) range 121.8, p=0.917 (*Figure 160)*. Total paediatric mean counted HF% difference is 6.5 ± 31.1 (limits of agreement -15 and 35.7) range 50.7, (*p=0.648),* (Figure 85). Total adult mean 5minute HF% difference is 17.7 ± 31.5 (limits of agreement 0.8 and 44.9) range 44.1, (*p=1.0),* (Figure 122). Total paediatric mean 5minute HF% difference is 7.5 ± 47.9 (limits of agreement -37.7 and 44.1) range 81.8, (*p=0.28),* (Figure 123).

When data is grouped into paediatric and adult data, poor significance is demonstrated for differences in HF% from baseline to sub-clinical. Results are clearly different when the data is analysed in terms of type of sub-clinical seizure. In this study, age effect on results of HF% would appear to be non-contributory to overall results when data is analysed in terms of sub-clinical seizure type.

Chapter 26

Relationship of NeuroScope CIPA and BioSignal HF% (5minutes)

3.8.1 Total Sub-clinical Seizures

Mean data per event is limiting and can only be useful for trend interpretation for CIPA and HF. There are obvious scale differences between CIPA, log CIPA, HF%, lnHF% and log lnHF% data and direct comparisons are limited. However, similar representation of parasympathetic measurements are found in data distribution for baseline, sub-clinical and visually proportional differences are present between baseline and sub-clinical values for NeuroScope CIPA and BioSignal HF% data. Comparisons are made between the two systems to determine whether it might be possible to find a relationship in the output of results that could be useful in future studies.

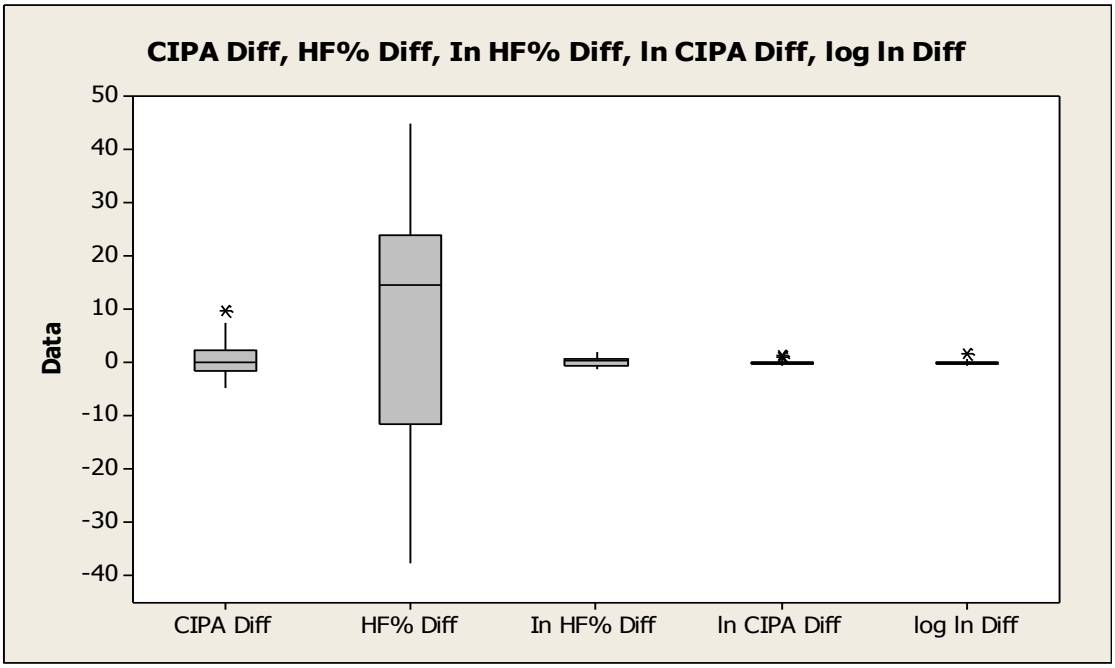


Figure 124 Boxplot of difference (baseline minus sub-clinical) in CIPA, HF%, lnHF%, log CIPA & log lnHF%.

HF% mean difference of baseline minus sub-clinical (n=33) for 5 min data is 9.3 ± 22.4, (*p=0.026),* (Figure 113.Table 35) but is on a larger scale compared to mean CIPA. CIPA mean difference (n=33) is 0.8 ± 3.6, (*p=0.233)*, (Figure 15, Table 8). By using log lnHF%, the HF% data is scaled down to a mean difference 0.1 ± 1.0, (*p=204),* (Figure 119, Table 36) with a closer relationship to log CIPA with a mean difference (n=33) of 0.02 ± 1.0, (*p=0.784),* (Figure 16, Table 8).

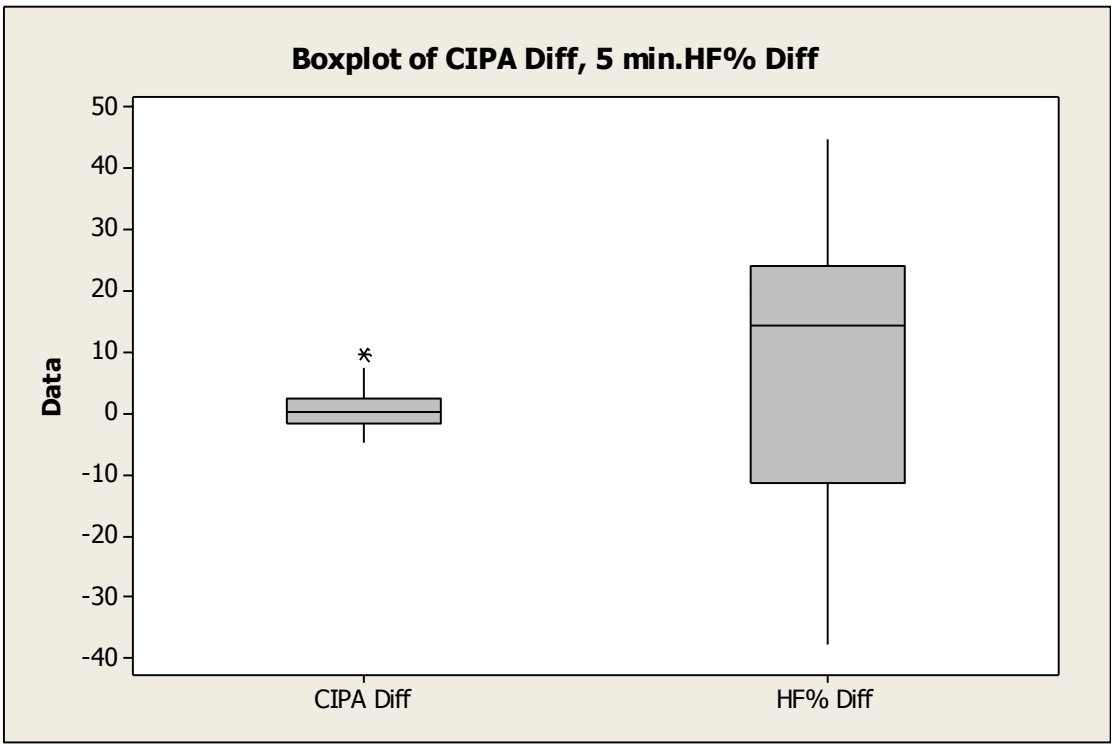


Figure 125 Boxplot of difference (baseline minus sub-clinical) in CIPA & 5minute HF%

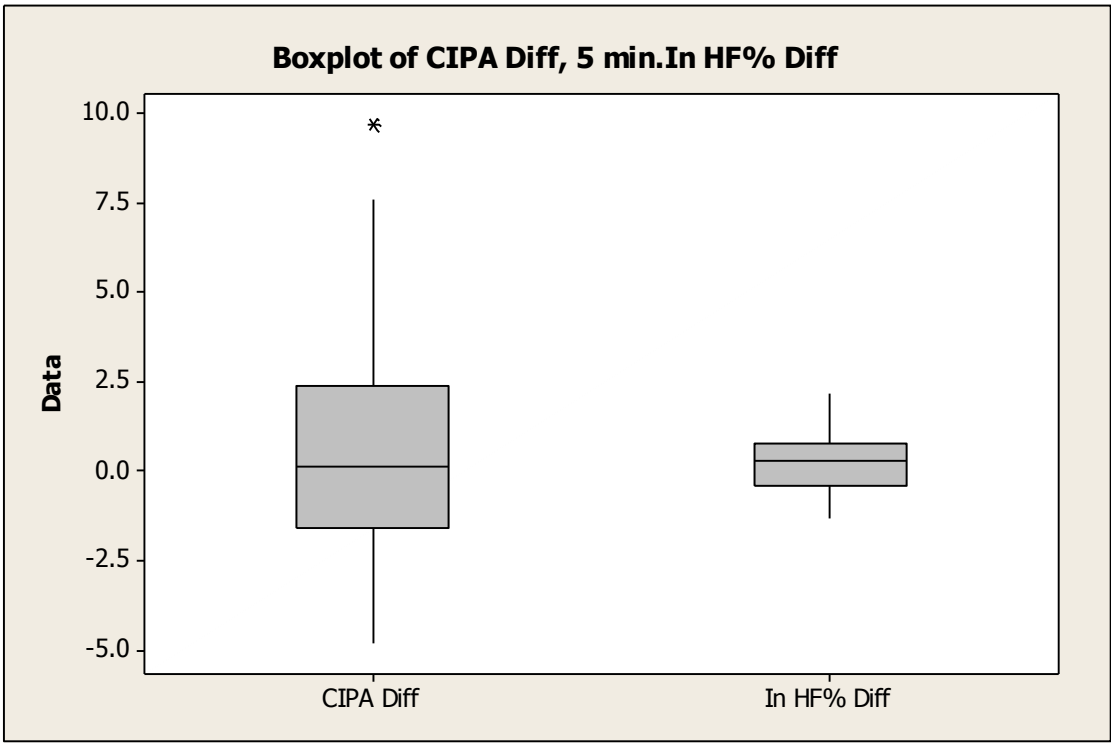


Figure 126 Boxplot of difference (baseline minus sub-clinical) CIPA & lnHF% 5minute HRV

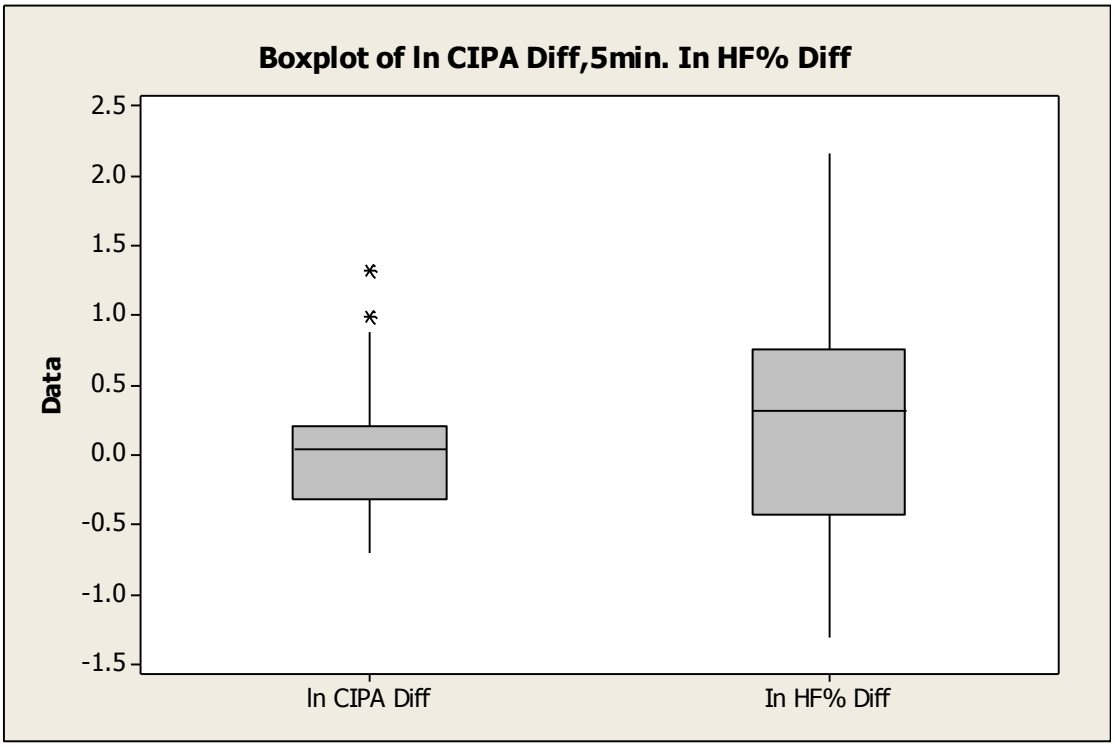
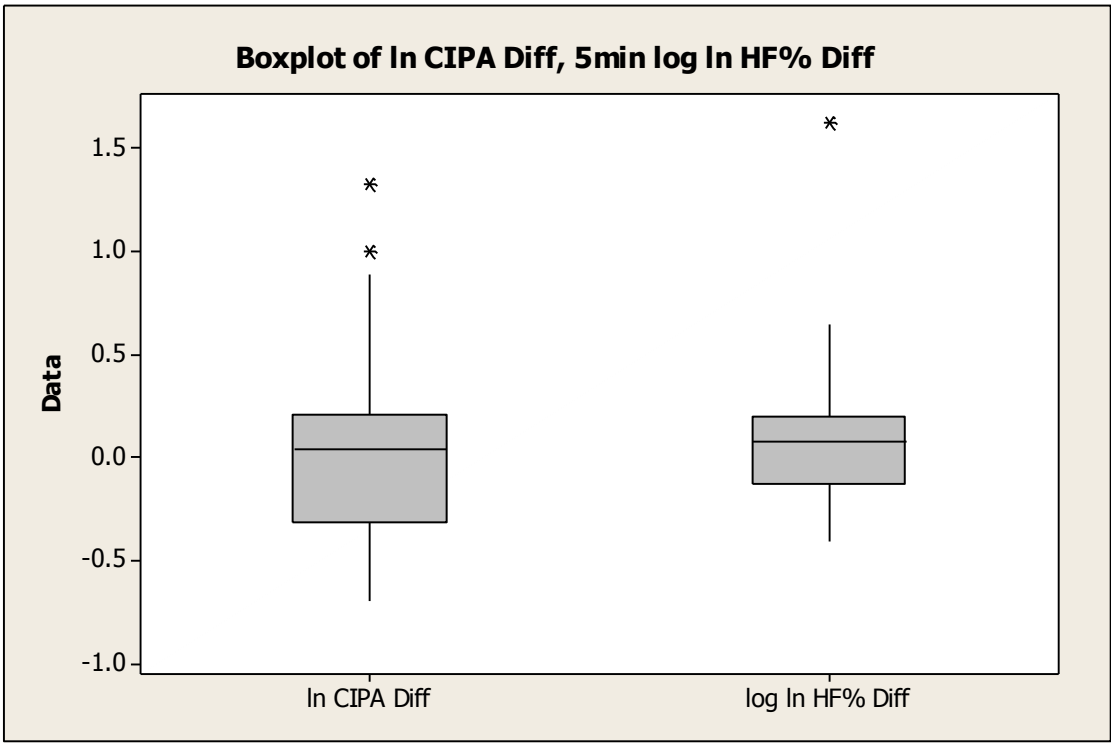


Figure 127 Boxplot of differences in log CIPA & lnHF% 5minute total HRV data

.



Closest to scale comparison.
Figure 128 Boxplot of difference (baseline minus sub-clinical) log CIPA & log lnHF% 5minute HRV total data.

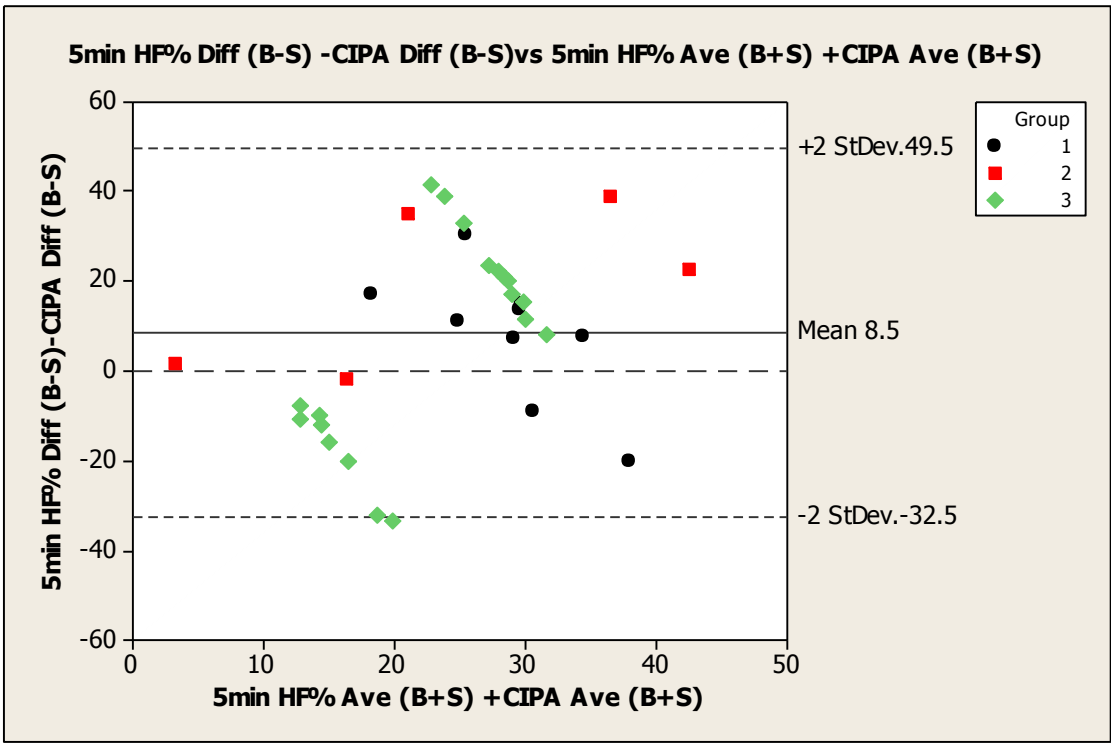


Figure 129 Bland & Altman scatterplot of difference (HF% difference minus CIPA difference) versus average for total 5minute data
Limits of agreement are (–32.2) and 41.44. Range is 73.6

Bland & Altman plots HF% difference (baseline minus sub-clinical) minus CIPA difference (baseline minus sub-clinical) versus HF% & CIPA average allows us to look at what the difference is between the data represented by BioSignal and the NeuroScope. The mean difference is 8.5 ± 41 with limits of agreement (-32.2) and 41.4 (range 73.6), (Figure 129). Clinically, this is difficult to interpret, as it is the wrong scale for HF%. In order to look at the scale closer to CIPA, the natural log of HF% is analysed.

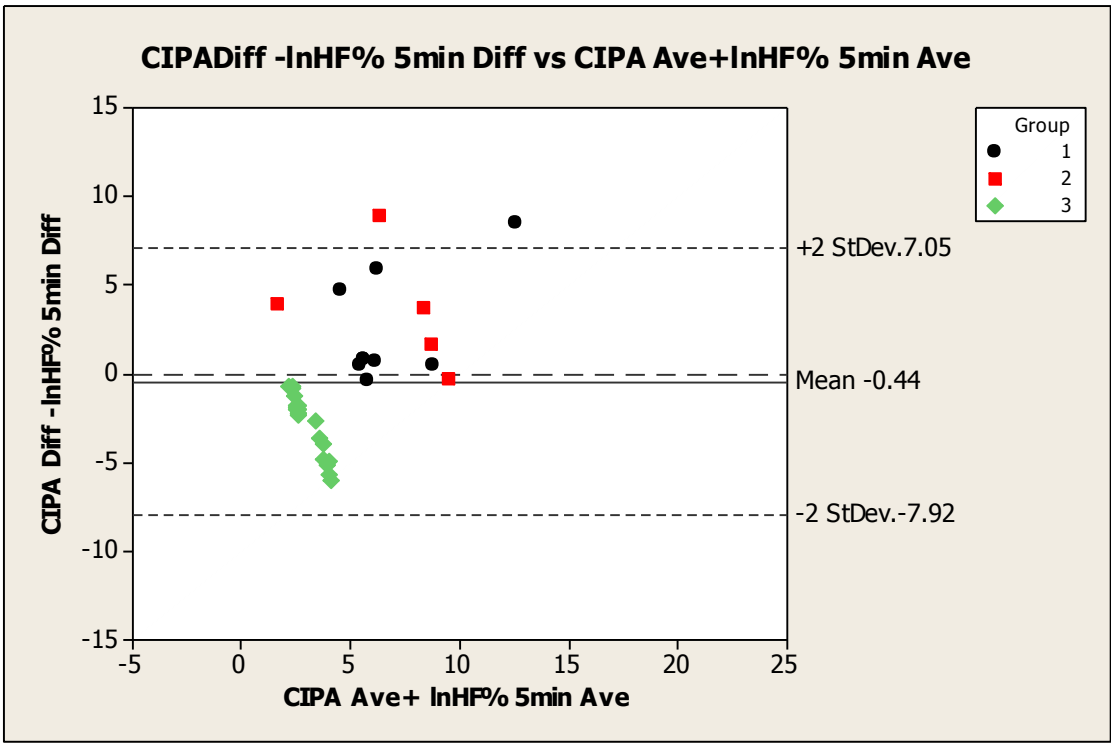


Figure 130 Bland & Altman scatterplot of difference (CIPA difference minus lnHF% difference) versus average for total 5minute data
Limits of agreement are (–5.992) and 5.879. Range is 11.871

CIPA difference (baseline minus sub-clinical) minus lnHF% difference (baseline minus sub-clinical) versus CIPA & lnHF% average again allows us to look at the difference between data represented by the NeuroScope and BioSignal but on a more comparable scale. The mean difference between data

from the NeuroScope CIPA and BioSignal lnHF% is (-0.4) ± 7.5 with limits of agreement (-6.0) and 5.9 (range 11.9), (Figure 130).

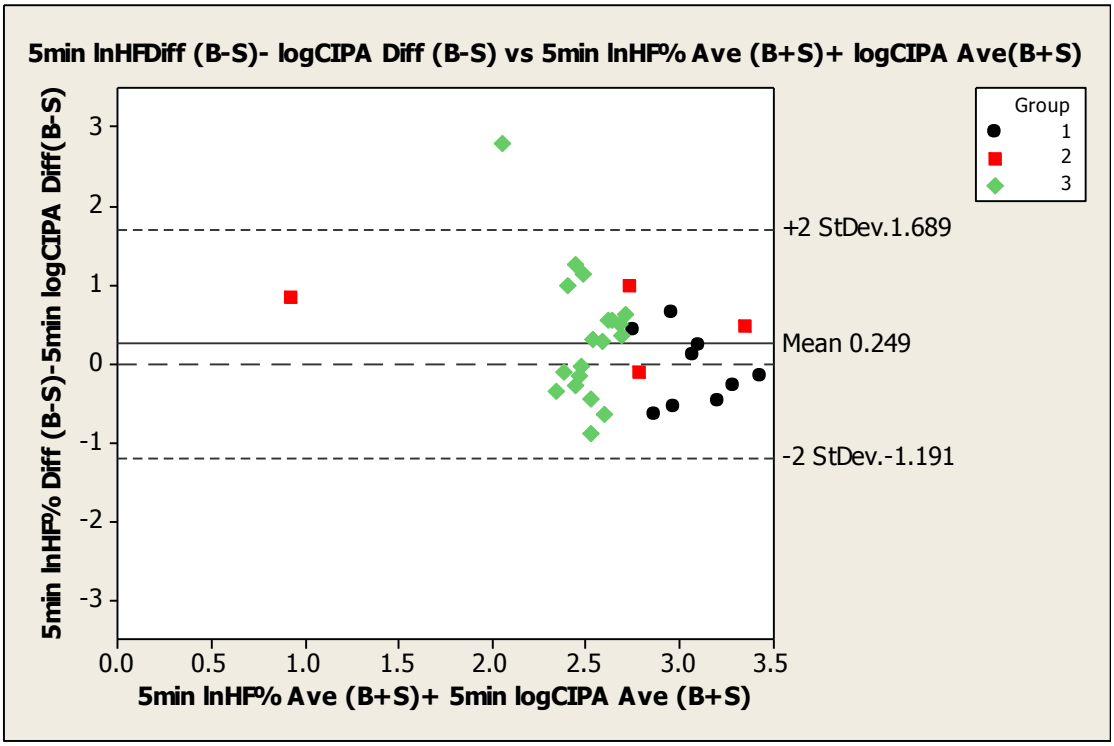


Figure 131 Bland & Altman scatterplot of difference (lnHF% difference minus log CIPA difference) versus average for total 5minute data

Limits of agreement are (-0.9) and 1.3. The Antilog of these values are 0.4 and 3.5 (range is 2.2). When lnHF% is compared to log CIPA, there is a mean difference of 0.2 ± 1.4 with limits of agreement 0.4 and 3.5 (range 3.1), (Figure 131).

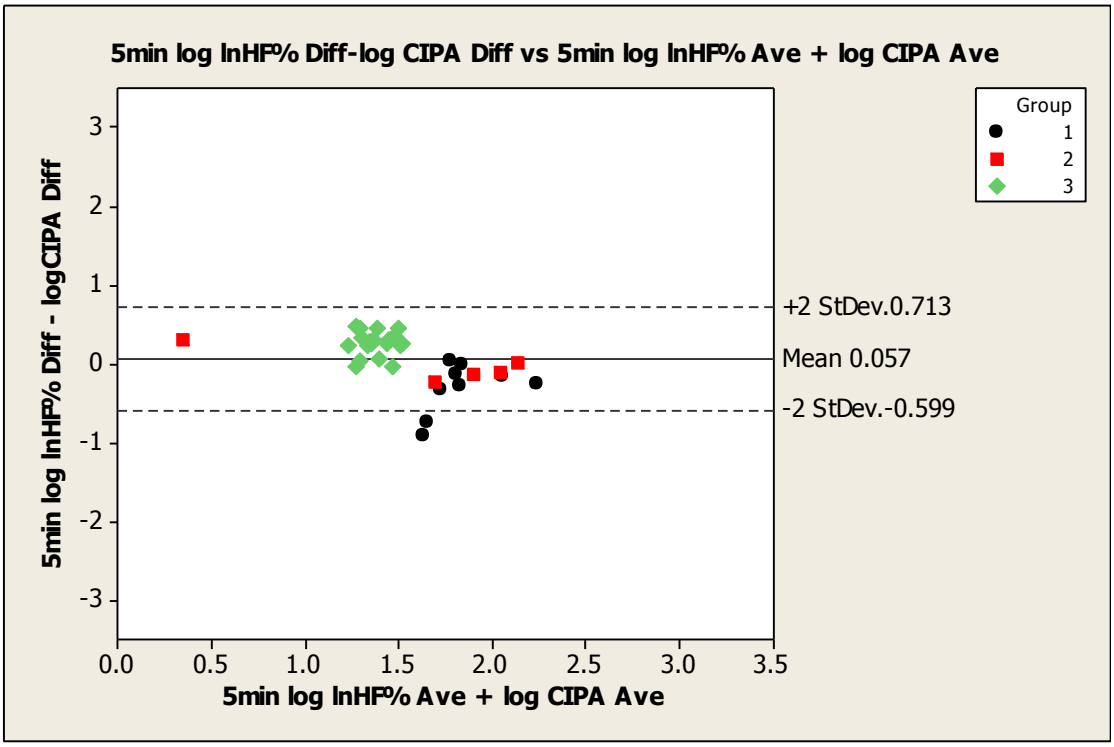


Figure 132 Bland & Altman scatterplot of difference (log lnHF% difference minus log CIPA difference) versus average for total 5minute data

Limits of agreement are (-0.3) and 0.5.The Antilog of these values are 0.7 and 1.6 (range is 0.9).

However, the closest comparable values are found when log lnHF% and log CIPA are used with a mean difference of 0.1 ± 0.6 with limits of agreement 0.7 and 1.6 (range 0.9), (Figure 132, Table 37). This would indicate that a difference of 10% would exist between the NeuroScope CIPA and BioSignal HRV using epochs of 5 minutes.

5 minute Mean Data Comparing BioSignal & NeuroScope Bland & Altman plot n=33	HF% Diff (B-S) minus CIPA Diff (B-S) vs HF% Ave +CIPA Ave	CIPA Diff (B-S) minus lnHF%Diff (B-S) vs CIPA Ave +lnHF% Ave	lnHF% Diff (B-S) minus logCIPA Diff (B-S) vs lnHF% Ave + logCIPA Ave	Log lnHF% Diff (B-S) minus logCIPA Diff (B-S) vs log lnHF% Ave + logCIPA Ave
Mean	8.5	-0.4	0.3	0.1
Standard Deviation	41	7.5	1.4	0.7
Lower limit of agreement	-32.2	-6.0	0.4	-0.3
Upper limit of agreement	41.4	5.9	3.5	0.4
Range	73.6	11.9	2.1	1.0

Table 43 Bland & Altman limits of agreement between NeuroScope & BioSignal total 5minute HRV data.

Pearson Correlation of log CIPA Difference (baseline minus sub-clinical) versus Counted log ln HF% Difference, 5minute log ln HF% Difference.

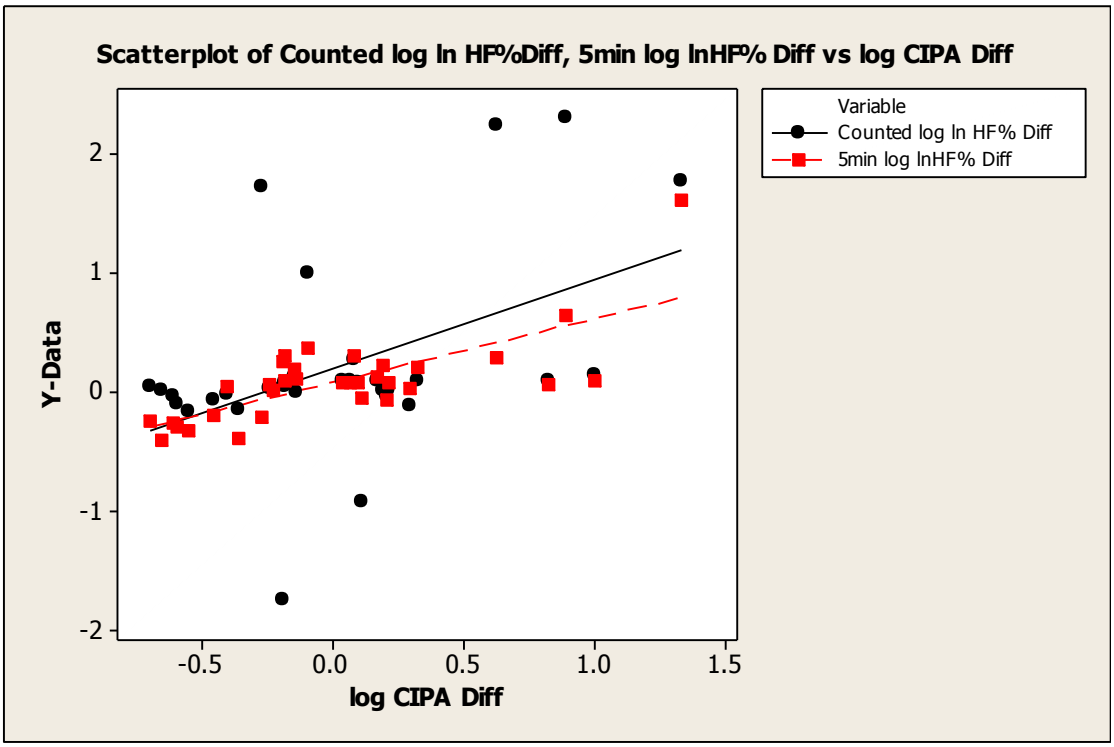


Figure 133 Scatterplot with regression log lnHF%(counted data) & log lnHF% (5minute data) on the Y-axis versus log CIPA.

High Pearson correlation is found for log CIPA Difference (baseline minus sub-clinical) and Counted log lnHF% Difference (baseline minus sub-clinical), (*p=0.006)*. However, log CIPA Difference (baseline minus sub-clinical) is more closely correlated to 5minute log lnHF% Difference (baseline minus sub-clinical), (*p<0.001).*

Different epochs measuring heart rate variability should not be compared but the purpose of one of the aims of this study is to deliberately ascertain if similar information can be achieved by using a shorter "counted" epoch compared to that of traditional short 5minute HRV. HRV HF% information has then been directly compared to CIPA to determine any similarity of

results to allow comparison of two different systems. CIPA and "counted HRV" are R-R matched and qualifies for direct comparison. There are limitations comparing data in this way and only general observations should be made. The agreement has been investigated by using Bland & Altman plots and the correlation co-efficient have been tested because a change in scale of measurement does not affect correlation but it does effect agreement.

Section Three

3.10.1 Discussion

Mortality rate is 2-3 times higher in a patient with epilepsy due to epilepsy related deaths compared to someone in the general population (Ansakorpi et al 2002, Nouri et al 2004). One thousand epilepsy-related deaths a year occur in the United Kingdom of which 60% is believed to be SUDEP (Hanna et al 2002). It is considered that pathogenic mechanisms underlying Sudden Unexpected Death in Epilepsy (SUDEP) are multi-factorial and are thought to include cortical control of the autonomic nervous system such as ictal bradyarrythmia and respiratory mechanisms such as ictal apnoea (Algra et al 1993, Nashef & Shorvon 1997, Al-Aweel et al 1999, Ansakorpi et al 2002, Leung et al 2006, Mameli et al 2006). Mameli et al (2006) concluded that cortical control of the autonomic nervous system appears to be the main factor in SUDEP. It has also been postulated that a predisposed patient could become a victim of SUDEP if there is a combination of reduced sympathetic tone during sleep, ictal bradyarrthymia or extreme fluctuations in heart rate resulting in autonomic instability. Ictal bradyarrthmia and sinus arrest have vagally mediated involvement during seizure discharges (Vaughn et al 1997). The "lockstep phenomenon" was proposed by Lathers et al (1987) and

proved synchronization between epileptogenic "sub-convulsant" discharges with abnormal sympathetic and vagal neural discharges with cardiac arrhythmia in anaesthetised cats. They believed that the lockstep phenomenon of synchronization of epileptogenic discharge with cardiac sympathetic neural discharge could be a contributing factor of SUDEP.

Variability of successive R-R intervals is generally considered to be an important protective mechanism of the autonomic nervous system being able to respond to sudden cardiovascular demands (Hohnloser et al 1994, Miller et al 2004). Loss of this variability increases the risk of sudden cardiac death and reduced HRV is a measure of risk stratification for myocardial infarction patients (Bigger et al 1984, Kleiger et al 1987, Malpas 2002, Miller et al 2004) of 2.5 years for approximately 50% of patients. Reduced vagal activity following myocardial infarction is believed to be due to the necrotic scar from the infarct altering the geometry of the beating heart. This altered geometry increases sympathetic afferent fibres in response to damage of sensory endings and inhibits vagal effect (Hohnloser et al 1994).

Heart rate variability is lost completely in brain death due to loss of central control where acute traumatic lesions have occurred in the brainstem compared with deep coma patients (Freitas et al 2000). These authors advocate that HRV could be used as part of the brain death criteria as HRV is fully sensitive and specific in this situation.

Other disease processes are increasingly being investigated using HRV parameters including diabetes (Miller et al 2004, Seyd et al 2008) and sleep apnoea (Park et al 2008). A large epidemiological study by Algra et al (1993) investigated 6,693 patients attending Rotterdam hospitals for 24hour

electrocardiography (ECG) who were followed up two years later. They concluded that patients with either low short-term (5minute) or low long-term (24hour) variation in HRV have double the risk of sudden death compared to patients with high HRV, independent from other risk factors. The Framingham Heart Study (Tsuji et al 1996) indicates that low heart rate variability is an independent marker for all causes of mortality in coronary events. Bilchick & Berger (2006) hypothesized that mortality from reduced HRV culminates from a combination of increased sympathetic tone and vagal withdrawal, increasing the risk of ventricular fibrillation. Applications of HRV analysis are also being applied to other areas such as anaesthesia, biofeedback and fitness training and Miller et al (2004) believe that the ability to monitor HRV as a non-invasive medical tool is a major breakthrough in patient welfare.

Very little research is present in the literature investigating loss of heart rate variability during epileptic discharges as a possible contributing factor of SUDEP. This is perhaps due to the difficulties of vagal measurement during a clinical seizure and the impossible interpretation of large alterations in autonomic control during what is a very physical event altering sympathetic and parasympathetic responses to the clinical seizure including changes in sleep to wake states, physical demand, body position (orthostatic), temperature changes etc. In this study, sub-clinical seizures were identified specifically to eliminate any physical element that a clinical seizure would have on vagal tone. Cardiac vagal tone measured during sub-clinical seizures and baseline studies selected from the same stage of sleep with regular respiration permitted patients to act as their own controls. This comparison of baseline and sub-clinical data aimed to give an indication of any alteration

of the parasympathetic activity being a result of direct neural influences from electro-cerebral seizure discharge on cardiac control.

Sub-clinical seizures are defined as "electrographic seizures without subjective or obvious objective neurological or somatic manifestation" (Babb et al 1987, Sperling & O'Connor 1990, Binnie & Marston 1992, Zangaladze et al 2008). A further definition of sub-clinical seizures is given by Weil et al (2005) "EEG seizure patterns not associated with any disturbances of sensory phenomena, motor functions, or consciousness in the wake patient, with any movements during sleep or arousals on EEG." Sub-clinical seizures were investigated in this study because even brief epileptiform discharges are suspected to cause changes in cardiac parameters (Wannamaker, 1958), are easily identified by EEG (electroencephalographic) video-EEG telemetry, originate from the same cortical area as clinical seizures (Zangaladze et al 2008) and have no clinical component to complicate the interpretation of any changes in vagal tone.

In some cases of SUDEP, the victim does not appear to have suffered a physical seizure but has died suddenly in the absence of any other pathology (Nashef & Shorvon 1997). This raises the question of a fatal arrthyhmia arising as a result of a sub-clinical seizure in a pre-disposed individual.

Heart rate variability reflects the dynamic interplay between cardiovascular function and the dynamic response of the cardiovascular regulatory systems (Algra et al 1993, Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996, Malpas 2002, Bilchick & Berger 2006) and can be used as a quantitative marker.

An analogy of HRV is offered by Bilchick & Berger "one learns only about the overall power from a star by measuring the intensity of light emanating from it, but by separating the light into its component colours with a prism, one may learn about the composition of chemical reactions within the star. HRV may similarly be broken into the frequency components that compose the overall variability."

A decrease in heart rate is not solely due to parasympathetic activity because heart rate is dually influenced by both the sympathetic and parasympathetic autonomic nervous system (Wittling et al 1998, Denver et al 2007, Nolan 2010). Brief changes in heart rate are also influenced by respiratory sinus arrhythmia (Denver et al, 2007). During inhalation, the vagus nerve is impeded and heart rate increases and then the situation reversed during exhalation (Katona & Jih 1975, Nolan 2010). Heart rate is mainly influenced by baroreceptor feedback from pulse stimulation at the aorta and carotid arteries to the medulla oblongata's nucleus ambiguus controlling signals to the sino-atrial node via the vagus nerve altering the level of inhibition and modulating heart rate.

The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996 states that efferent vagal activity is a major contributor to the HF component. Malpas (2002) exercises a word of caution in the interpretation of this parameter, as other influencing factors should be considered such as differences in vasculature but agrees that baroreceptors, brainstem and vagal activity are central to neural control and fundamental to changes in the heart rate tachogram. The time domain tachogram is then mathematically manipulated (MacArthur (1997) by representing the signal by a combination of sine and cosine waves

(usually following interpolation of the signal) with different amplitudes and frequencies by Fourier transform. The spectrum displays power densities of three main peaks known as Very Low Frequency, Low frequency (LF) and High Frequency (HF) for heart rate variability frequency domain analysis.

Low frequency (LF) components of heart rate variability are more controversial as to what they represent physiologically. Many scientists argue that LF does not simply reflect sympathetic activity as it also includes parasympathetic and renin-angiotensin hormonal changes (Akselrod 1981, Malpas 2002). Some studies advocate for LF/HF ratio to look at the sypatho-vagal balance of the autonomic nervous system (Miyashita et al 2003, Everingul et al 2005, Persson et al 2007)). This is generally considered to be an over-simplified interpretation of many complex biological processes and LF/HF ratio was not applied to this study.

Akselrod et al (1981) proved the HF power spectrum as parasympathetic activity when they abolished it by administering glycopyrrolate (0.01mg/kg) blocking muscarinic parasympathetic transmission in dogs. They also blocked sympathetic B-adrenergic receptors by administering propranolol (0.1mg/kg). They concluded that LF components are influenced by both sympathetic and parasympathetic activity but HF components are only parasympathetic. This is reinforced by the biological fact that the parasympathetic nervous system reacts rapidly, constituting high frequencies compared to slower sympathetic changes, which cannot contribute to the HF signal.

A study by Casadei et al (1995) examined the measure of HF and LF spectral analysis during exercise observed that the HF component fell at the

beginning of exercise consistent with a reduction on cardiac vagal activity but LF components diminished until no longer detectable during severe exercise. This adds to the controversy around what biological processes are represented by LF signal of the HRV.

Dexter (1997) explained how the HF signal may be affected pharmacologically during fast heart rates. Pulsed blood pressure causes oscillations in efferent vagal activity resulting in oscillations of acetylcholine release from postganglionic parasympathetic neurons. This in turn causes oscillations in the concentration of acetylcholine at sinus node neuroeffector junctions. Anticholinesterase prolongs the time required for acetylcholine to be broken down. This takes longer than the next cycle, which he believes decreases the magnitude of acetylcholine at these neuroeffector junctions and is expected to pharmacodynamically cause a decrease in high frequency variability. This may be a consideration during fast heart rates reducing HF HRV during clinical seizures. However, this is an unlikely scenario during sub-clinical seizures in this study, as heart rates are not elevated to the same heart rates as expected during clinical focal or generalised tonic clonic seizures. Taking Dexter's observation forward, a resultant decreased vagal effect at the neuroeffector junctions at the time of increased heart rate would prevent the intended autonomic control of slowing heart rate at critical or prolonged times of elevated heart rates during a clinical seizure and this may also be a contributing factor of SUDEP.

In this study HRV HF% was mainly analysed as it alters as a proportion with LF (incorporating sympathetic activity and VLF components. $Hfms^2$ is often quoted in HRV studies but the standard deviations compared to the mean values in this study were very large (mean baseline 383.1 ± 982.8 and mean

sub-clinical 489 ± 1364) making any interpretation of the mean values meaningless. Standard deviation is expected to improve with increased observations and $HFms^2$ may be useful in a much larger study. Additionally, 5minute $HFms^2$ were least correlated to CIPA (*p=0.359)* compared to 5minute HF% correlation to CIPA (*p<0.001).*

In 1876, Mayer recorded the first physiologically measured oscillations in blood pressure from anaethetised rabbits. Much later, Guyton & Harris (1951) described "vasomotor" waves as slow oscillations in blood pressure not related to respiration. Wittling et al's (1998) study, of 45 subjects, examined hemisphere asymmetry in parasympathetic control of the heart and monitored respiration. They concluded that HF power was uninfluenced by differences in respiration rate. However, Malik & Camm (1973) amongst other researchers do believe that HF power is directly affected by respiration.

Baroreceptors monitor changes in blood pressure and relay this information to the medulla oblongata, which then sends the signal via the vagus nerve to the sino-atrial node in the myocardium. An important distinction between baroreflex sensitivity and heart rate variability is that baroreceptor sensitivity measures *reflex* vagal activity and heart rate variability quantifies mainly *tonic* vagal activity (Malik & Camm 1973, Hohnloser et al 1994). Studies have shown vagal blockade with atropine abolishes this neural signal oscillation (Julu, 1992) rapidly controlling heart rate on a beat-by-beat basis. Julu et al claims that output from the NeuroScope is independent from respiration and heart rate.

Distinct from baroreflex measurement, Porges (2009) claims that in 1992, he proposed an estimate of vagal tone from measuring respiratory sinus

arrhythmia (RSA) using time series analyses to extract the *amplitude* of the RSA for an accurate index of vagal activity, representing the tonic functional outflow from the vagus to the heart. Denver et al (2007) showed in their study that respiratory sinus arrhythmia amplitude is not affected by respiration frequency. Grossman & Taylor (2007) describes the distinction between RSA and vagal tone as RSA being "phasic" and vagal tone being "tonic." They gave an example whereby respiration rate increased resulting in an increase in magnitude of RSA but the mean vagal discharge remained the same. Conversely, Bilchick & Berger (2006) and Tanaka et al (2004) amongst others describe the magnitude of HF power being highly dependent on respiration and suggest that respiration should be taken into account.

In this study, HRV measurements are selected during slow wave sleep where respiration is regular. Vanoli et al (1995) examined HRV over 5minute epochs and describe increased vagal tone during NREM sleep compared to wakefulness and REM sleep. These authors suggest that studies investigating HRV should also monitor sleep staging for interpretation of changes in HRV parameters. Paediatric studies of HRV by Grossman & Taylor (2007) did not use strict criteria in monitoring sleep stages electrographically.

The NeuroScope is based on the theoretical model proposed by Katona (Julu 1992). Chest respiration was not recorded in this study, as NeuroScope measures are independent from breathing and heart rates. However, in the case that HRV BioSignal HF signal is affected by respiration, chest respiration was not considered necessary in this particular study, as altered breathing rate during sub-clinical seizures is unlikely. Additionally, respiration rate is regular during slow wave sleep, equivalent or better than 'paced breathing techniques' suggested by Grossman & Taylor (2007) to

standardise respiratory rate during HRV studies. Therefore changes in HF% and CIPA in this study are more likely to be attributed to the effects of sub-clinical seizures rather than to altered respiration rate.

In animal studies (without myocardial infarction) baroreceptor measurements were more sensitive than HRV in showing risk of ischaemia induced ventricular fibrillation from increases in arterial blood pressure (Hohnloser et al 1994). The NeuroScope in this study also appeared to be more sensitive than "counted" HRV in terms of indicating vagal measurement over shorter epochs. More similar results to the NeuroScope are found from 5minute HRV as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) for HRV standardisation

Heart rate variability of different epochs should not be compared but the purpose of one of the aims of this study was to deliberately ascertain if similar information could be achieved by using a shorter "counted" epoch compared to that of traditional short 5minute HRV. HF% baseline compared to sub-clinical HF% for counted data showed a significant decrease in vagal tone for total data (*p=0.049)* and similarly but statistically more significant for 5minute HRV HF% for total data *(p=0.026).*

HRV HF% "counted" and 5minute data were then directly compared to CIPA to determine any similarity of results comparing two different systems. CIPA and "counted HRV" are R-R matched and qualified for direct epoch comparison under the recommendations from the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) for HRV matched epoch duration for data

standardisation. There are limitations comparing CIPA data in this way due to the necessity of calculating mean values to compare to HF% mean values and only general observations can be made. CIPA and 5minute HF% HRV are not epoch matched but this was a deliberate comparison to discover whether similar information could be provided by CIPA over shorter epochs compared to 5minute HF% HRV epochs. Pearson correlation was limited to the final comparison as it is generally misused in scientific papers. A high correlation between two methods does not always mean that the two methods necessarily "agree" but do have a relationship. This relationship could be poor but it would still show a correlation Data agreement has been investigated in this study by using Bland & Altman plots in this thesis and the correlation co-efficient was tested because a change in scale measurement does not affect correlation but it does effect agreement (Bland & Altman 1986). Closer comparisons of results were found between CIPA and 5minute HRV data. High Pearson correlation was found for log CIPA and Counted log lnHF% ($p=0.006$). However, log CIPA is more closely correlated to 5minute log lnHF% ($p<0.001$).

A limiting factor in comparing CIPA with HRV HF% is that CIPA measures efferent vagal tone from baroreceptor feedback and HRV HF% measures modulations of afferent parasympathetic activity. In extreme circumstances of vagal blockade or over-saturation effect on the sinus node by persistent high vagal tone can lead to a situation where an increase in high frequency components do not reflect increased vagal tone or vice versa (Malik and Camm 1993). However, in this study parameters were not measured during such extreme states.

For "counted" R-R analysis in this study, the sub-clinical data was clipped one minute prior to the onset of electrographic sub-clinical seizure activity and continued until the sub-clinical seizure had ended and the trace had resumed the previous resting trace. For "5 minute" R-R analysis, the sub-clinical seizure was sited in the middle of the clip as far as possible within the constraints of selecting data within the same sleep stage. Baseline clipped data for "counted" and 5minute data were selected from any section of the patient's trace that was in the same sleep stage for comparison to the sub-clinical clipped data. In a study by Novak et al (1999) clinical seizures were found to change time frequency analysis several minutes prior to the attack with rapid parasympathetic withdrawal approximately 30 seconds prior to the start of the seizure. It is difficult to estimate how long to analyse data prior to a sub-clinical seizure where relatively small populations of local neurons increase their firing rate (Babb et al 1987). One minute prior to the sub-clinical seizure was considered practical and likely to capture any parasympathetic changes that may have occurred prior to the electrographic change detected by full head coverage of scalp electrodes.

A null hypothesis of this study was that no changes in vagal tone would occur during sub-clinical seizures compared to baseline studies given that no obvious clinical changes occur or physical demands altering resting heart rate variability. However, clear altered vagal tone is observed during sub-clinical seizures compared to baseline studies in both CIPA ($p<0.001$) and 5minute HRV HF% ($p=0.026$) and "counted" HRV HF% ($p=0.049$) Therefore, statistically significant results are seen in HF% during even brief sub-clinical seizures when 5minute epochs are used and the same sub-clinical seizure data shows a slightly less statistically significant change of HF% HRV over a shorter "counted" epochs. CIPA showed the most statistically significant

change ($p<0.001$) in vagal tone over matched shorter epochs compared to counted HF% HRV ($p=0.049$).

In a study by Adjei et al (2009), mean HRV did not change during or after sub-clinical patterns. "Minimal" changes were described with "lower HRV" from left sub-clinical seizures than from right sub-clinical seizures. However, the study by this group is methodologically limited as 10 seconds HRV is too short a duration to quantify HRV fully unless vagal tone is measured using the NeuroScope (Hamilton et al 2004). Additionally, the SDNN was also calculated over 10 seconds in Adjei's study (2009) which is too short a duration to perform this time domain analysis effectively. As the period of monitoring decreases, SDNN will estimate a shorter cycle length (Task Force of the European Society of Cardiology & the North American Society of Pacing and Electrophysiology, 1996).

It is only since the 1970's that more precise stimulation techniques such as axonal tracer methods have been introduced to delineate cortical regions that have a direct effect on the autonomic nervous system Cechetto and Saper (1990) cite many authors who have performed this mapping. Prefrontal cortex and insular cortex have direct projections to areas of the amygdala, hypothalamus, brainstem and spinal cord that are involved in autonomic control. Stimulation of the insular cortex causes many changes including altered blood pressure, heart rate and respiration depending on the stimulation frequency. During seizures involving the insular cortex, often diagnosed as temporal lobe epilepsy but the seizure source is insular (Brotherstone, 2002), epigastric or gustatory symptoms are experienced and this is replicated by stimulation of the dysgranular insular area. Stimulation techniques of the posterior insular cortex are well described of the right

insular resulting in increased heart rate and the left insular causing decreased heart rate (Oppenheimer et al 1992). The amygdala receives direct projection from the insular cortex. Frysinger and Harper (1986) have shown a relationship between neuronal firing from the medial pre-frontal cortex to cardio-respiratory firing rate.

In a study of amygdaloid kindling in rats (Healy et al, 1995), increased vagal activity produced bradycardia and reduced heart rate variability. These authors postulate that prolonged bradycardia may be indicative of sinus node impairment and if there is no atrio-ventricular junctional pacemaker escape following significant delay of depolarisations at the sino-atrial node then sinus arrest may occur.

Do generalised sub-clinical seizures pose a greater risk of autonomic nervous system deregulation than temporal lobe seizures?

Persson et al (2007) analysed long term 24 hour HRV of 22 newly diagnosed epileptic untreated patients with a control group and found no statistically significant differences between the two groups. However, repeated seizures over a longer term are reported to have an effect on autonomic cardiac regulation and are associated with higher morbidity and SUDEP mortality in epileptic patients (Everingul et al 2005, Harnod et al 2008). From their study analysing heart rate variability in children with refractory generalised epilepsy they concluded that lower HRV was found during the inter-ictal period. Bulent et al (2010) also describe how long term abnormalities in the autonomic nervous system from repetitive seizures can cause a temporary impairment in autonomic functions by each epileptic discharge having an effect upon limbic structures, amygdala and periamygdaloid piriform cortex. Additionally, this group found that autonomic dysfunction became more

marked in the post-ictal period compounding an already existing dysfunction. Nouri et al (2004) describe how damage to the myocardium can occur when exposed to frequent increases of plasma catecholamines. This damage to the myocardium can then cause areas of fibrosis and render the myocardium more likely to trigger cardiac arrhythmias.

Al-Aweel et al (1999) reported a ringing effect lasting two to six minutes from low frequency heart rate oscillations following 11 partial seizures (2 with secondary generalisation) in 5 patients. They describe an increase in heart rate between 28-88/min and hypothesize that the ringing effect (not seen at any other time) could be the result of unstable cardiopulmonary dynamics as heart rate seeks to find equilibrium following the seizures. Cardiac arrhythmia is suspected in witnessed SUDEP victims, when the seizures have clearly ended, but the patient then suddenly collapses and dies.

Concordant with Everingul et al (2005) and Harnod et al (2008)), this study demonstrated inter-ictal or "baseline" HRV HF% lower in children with generalised epilepsy (faster baseline heart rate) compared to all other patients in this study for counted and 5minute epochs. R-R interval data during generalised sub-clinical seizures is different compared with R-R interval data during right or left temporal lobe sub-clinical seizures. Generalised sub-clinical seizures show a mean increase in R-R interval 628.9 to 686.95msec ($p<0.001$), indicating a decrease in heart rate with a mean difference of (-58) ± 138msec of baseline minus sub-clinical data. Generalised sub-clinical seizures also demonstrate a much tighter co-efficient of variation (scatter of data) of R-R interval data (n=9176) compared to right temporal lobe seizure data (n=5376) and left temporal lobe seizure data (n=2614).

Generalised baseline data has coefficient of variation (6.9%), which is approximately half or less than half of that seen during right temporal lobe baseline data (12.8%) and left temporal lobe baseline data (15.1%). All data shows an overall increase in coefficient of variation during sub-clinical seizures compared to baseline measurement but generalised data still remains much tighter with an average value of 12.9% compared to right temporal sub-clinical seizures (18.1%) and left temporal sub-clinical seizures (19.5%). Generalised sub-clinical seizures demonstrate less variable R-R interval data compared to focal sub-clinical data. This finding would need to be further analysed in a larger study including generalised sub-clinical seizure data from adults. Paediatric baseline heart rates are higher and this may have influenced results. However Analysis of Variance (ANOVA) compared baseline variance between individuals and within individuals. The data from paediatric patients with generalised sub-clinical seizures were not inherently different to the other patients.

A proposed SUDEP mechanism.

Autonomic instability and reduced variability of successive beats may put a pre-disposed individual at more risk during sleep (Shorvon 1997) when vagal tone is already increased, especially with generalised seizures. Instead of responding with a decrease in vagal tone and increased heart rate ready to meet the physical demands of the seizure, there could be instead an initial further increase in vagal tone resulting in a further initial decrease in heart rate (as indicated from this study's findings and described by others) potentially leading to ictal bradyarrythmia. Clinical generalised seizures are then characteristically followed by a massive acceleration of heart rate (sudden vagal withdrawal) and marked catecholaminergic sympathetic

activity with resultant effect on the myocardium. This initial mismatch between vagal tone and seizure demand could make the myocardium vulnerable leading to possible SUDEP in some pre-disposed individuals with low heart rate variability. Massive sympathetic discharge can trigger fatal cardiac arrhythmias during seizures (Noval 1999, Nouri 2004). O'Regan & Brown (2005) also describe a rapid but short lived rise in cardiac vagal tone associated with some seizures but consider that this may be an inbuilt mechanism to protect the myocardium from possible fatal cardiac arrhythmias caused by unbridled sympathetic or massive catecholamine activity. Delamont et al (1999) also describe an increase in cardiac parasympathetic activity just prior to secondary generalised complex partial seizures and proposed that pre-ictal elevation of cardiac parasympathetic activity may be a marker for secondary generalised seizures.

A study by Vaughn et al (1997) recorded asystole lasting 3-17 seconds during five generalised tonic clonic seizures in an infant. They found increases in both sympathetic and parasympathetic spectral frequencies and therefore suggested epileptic induced asystole resulted from both arms of autonomic outflow. However, it is not clear from Vaughn et al's study at which point in the clinical seizure the 10 seconds epoch selected, whether artefact-free ECG was possible during a clinical seizure and how interpretation of HRV analysis was possible during a clinical epileptic seizure when complicated by physical exertion , change in body position and temperature alteration and only 10 seconds epochs were selected despite being too short for HRV traditional methods of 5 minute epochs as recommended by The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). In this study, increased vagal tone is described in generalised seizures also but low frequency HRV was not

analysed due to the controversy of what contributes to the LF frequency. Vaughn et al (last author) produced a further paper in 2003 examining the "lockstep relationship" between scalp electroencephalographic spikes and alteration in the R-R interval at that moment, comparing spike discharges from the right and left hemispheres. Due to normal sinus arrhythmia I would have expected this group to examine R-R intervals from samples of the recording that did not have any electrographic spike discharges to quantify the effects of RSA on their sampling methodology.

Leung et al (2006) and Hiroso et al (2005) consider that a channelopathy is involved as a possible mechanism of SUDEP particularly for generalised epilepsy leading to both seizure and cardiac arrhythmia. Activation techniques of hypothalamic and mesencephalic epileptic foci, induced a significant increase in vagal nerve firing that was strictly correlated to ECG impairments and hypotension in hemipherectomized rats (Mameli et al 2006). In Mameli et al's study when both the hypothalamic and mesencephalic epileptic foci were co-activated, 25% of rats had vagal hypertone, cardiac arrhythmia leading to hyperkalemia, acidosis, pulmonary hypertension and death. The authors could not establish why some animals developed severe clinical symptoms leading to death and others did not. They hypothesized that the non-surviving animals had a low threshold of excitability whose central structures were unable, during an epileptic seizure, to maintain a balanced ratio between sympathetic and parasympathetic activities. De-regulation of the autonomic nervous system is believed to have a functional cause rather than a cause due to structural abnormality of the hippocampus (Ansakorpi et al 2004). A group of patients with temporal lobe epilepsy, some of whom had hippocampal sclerosis had no significant differences in HRV compared to a control group.

The comparison of the NeuroScope & BioSignal HRV.

One of the main aims of this study was to compare the cardiac index of parasympathetic activity (CIPA) produced by the NeuroScope that gives a continuous cardiac vagal tone measurement on a beat-by-beat basis with a more traditional measure of cardiac vagal (high frequency spectral analysis) Heart Rate Variability as produced by BioSignal software. This is useful if the NeuroScope is to be considered as another reliable method of measuring parasympathetic activity instead of more traditional methods of HRV in clinical practice. However, only mean values per study are produced by BioSignal heart rate variability software and therefore mean CIPA was calculated to allow a direct comparison. By using mean values, less data is available for statistical analysis as the amount of data is greatly reduced, compared to total CIPA results. CIPA derived during right temporal lobe sub-clinical seizures analysed a total of 2688 beats for baseline and a total of 2688 beats for sub-clinical data. For comparison to BioSignal HF%, only one mean value was calculated per baseline study and for each sub-clinical seizure study. Therefore data was greatly reduced to a total of 9 values instead of 2688 for right temporal sub-clinical seizures. CIPA derived during left temporal lobe sub-clinical seizures included a total of 1307 baseline and 1307 sub-clinical data but became a mean output of 5 matched data values CIPA derived during generalised sub-clinical seizures included 4588 beats for baseline and 4588 beats for sub-clinical data became 19 mean data values to allow direct comparison to BioSignal data. Due to this restricting effect of using mean values only general comparisons can be made and a much larger study would be required to be analysed in order to give adequate quantitative comparison between the NeuroScope and BioSignal software. Despite this restricting effect of using mean values for CIPA to compare to

BioSignal HF%, clear similarities in all results were found in both sets of data.

The NeuroScope uses an index of parasympathetic activity giving proportional representation on a scale of 1-10 (and above in this study and reported by others). BioSignal quantifies High Frequency as HF% proportion of total HRV, essentially also providing an index of 1-100%.

An obvious scale difference was encountered when comparing data from the NeuroScope to that of HF% HRV BioSignal software. This scale difference had to be mathematically altered to bring the outputs closer to allow comparison of results from the two systems that had identical input data.

A second question was whether cardiac vagal tone could be measured over shorter 'counted' epochs rather than 5 minutes as determined by traditional HRV methods.

By systematic analysis of mathematically altering scale, log CIPA data was similar in magnitude to that of 'counted' log lnHF% with a mean difference of 0.02 ± 1.0. Similarly, the closest comparison of scale between the NeuroScope CIPA and BioSignal for 5 minute data was also log CIPA and log lnHF%. Mean difference is 0.1 ± 0.6.

The comparison of results from both systems after scale adjustment in this limited study suggest that there is a 2% difference between NeuroScope log CIPA and BioSignal log lnHF% for short 'counted' epochs. This difference increases to 10% for 5 minute epochs. This result is based on limited data from this pilot study and can only be used as general observation for comparing NeuroScope and BioSignal data.

CIPA results for grouped data derived during right, left and generalised sub-clinical seizures, show similar findings to an HF% HRV parameter but CIPA is able to do this over a shorter epoch. Generally, some patients are considered to be more pre-disposed to cardiac arrhythmia and sudden death than others. A study by Schwartz et al (1988) demonstrated that a group of susceptible myocardial post infarction dogs had reduced baroreflex sensitivity prior to the infarction compared to resistant surviving dogs. La Rovere et al (1998) concluded from a large prospective study 30 days post-infarction, that baroreflex sensitivity was a powerful predictor of mortality for these patients over the following 2 years.

Counted SDNN HRV data.

The SDNN is the standard deviation of the NN intervals, which is the square root of variance and is an overall estimate of HRV. It is possible to compare counted baseline studies and matched counted sub-clinical studies as they are of equal number of NN intervals. It is inappropriate to compare individual patient SDNN studies as each event is of a different duration. Using Bland & Altman plots to analyse the difference versus the average for matched total counted baseline R-R studies and total counted sub-clinical R-R studies, the smallest range in limits of agreement for SDNN is seen in association with generalised sub-clinical seizures 0.5 and 0.8 (range 0.3) indicating the smallest variability, compared to SDNN derived during right temporal lobe sub-clinical seizures with limits of agreement 0.7 and 2.0 (range 1.3) and SDNN derived during left temporal lobe sub-clinical seizures with limits of agreement 0.5 and 1.2 (range 0.7) sub-clinical seizure manifestations in HRV. Generalised sub-clinical seizures again are characteristically different for SDNN50 and pNN50 compared to sub-clinical

seizures derived during either the right or left temporal lobes. NN50 and pNN50 data approximately halve during right temporal sub-clinical (NN50 1064 to 626, pNN50 39.7 to 23.3) and left temporal sub-clinical (NN50 615 to 356, pNN50 47.2 to 27.3) but generalised sub-clinical seizures increase markedly (NN50 64 to 315, pNN50 1.4 to 6.9).

5minute HRV SDNN data.

Generalised data again shows the smallest SDNN limits of agreement 0.6 and 1.0 (range 0.4) compared to SDNN derived during right temporal sub-clinical seizures limits of agreement 0.8 and 1.2 (range 0.4) and SDNN derived during left temporal sub-clinical seizures limits of agreement 0.5 and 1.0 (range 0.5). However, all groups show more similar limits of agreement for SDNN when using 5minute epochs compared to results from counted SDNN. This demonstrates that analysing the SDNN variability during sub-clinical seizures is diminished over longer epochs i.e. 'averaged out' as it is combined with non-event data. In this case the counted HF% may be more sensitive than 5minute epochs.

The NN50 count and pNN50 during generalised sub-clinical seizures is low during both baseline and sub-clinical data compared to temporal lobe data. This reflects less variability between successive beats from patients with generalised epilepsy in the study compared to temporal lobe epilepsy.

A study by Murray et al (2001), recruited 50 subjects to assess and compare traditional heart rate variability measures with output from the NeuroScope. They concluded that the short-term reproducibility of a 5minute recording of CIPA is moderate and better than simple time domain but not frequency domain measures of HRV. They felt that the NeuroScope provided a simple

alternative for measuring parasympathetic activity and may have a widespread application if the clinical usefulness of its measure can be established.

Where HRV measures are standardised to 5minute epochs as the spectral analyses requires stationarity to analyse its component parts, it would be useful to be able to use a shorter epoch for more transient phenomenon. Hamilton et al 2004 measured three epochs of 10 seconds within a 5minute sample of R-R interval using the NeuroScope in fifty patients. They concluded that results (RMSSD) from 10 seconds of CIPA were highly correlated to and predictive of data from 5minute epochs. This would suggest the NeuroScope could produce heart rate variability measures over epochs as short as 10 seconds unlike traditional methods of 5minute or 24hour heart rate variability software.

Age effect on cardiac vagal tone.

Loss of heart rate variability occurs with increasing adult age (De Meersman & Stein 2007). These authors have shown that increasing level of fitness, particularly of post-menopausal women and elderly men improves vagal modulation. Numbers are small in this study so alternatively data was divided into paediatric and adults and re-analysed. Statistically significant differences were found comparing baseline and sub-clinical mean data for counted epochs for each group but this was not the case for data of 5minute epochs. Changes in baseline CIPA to sub-clinical CIPA were more marked in adults ($p<0.001$) than in paediatrics ($p=0.203$) with a mean difference of 6.5 (adults) compared to 0.4 (paediatrics). When data was analysed over 5minute epoch significant differences were lost. Mean difference in HF% baseline

minus sub-clinical was calculated for paediatrics (n=27) and adults (n=6) for 5minute epochs HRV. The mean difference for paediatrics data was 7.5 ± 47.9 (*p=0.28*) Adult mean difference is 17.7 ± 31.5 (*p=1.0*) Therefore, when data is analysed over a 5minute epoch, no statistical significance is demonstrated comparing adult data with paediatric data. Age Effect on CIPA & HRV HF Data could not be assessed in this study because of small group data. Normal data for standardised HRV has not been sufficiently established in paediatrics in all age ranges. It has been reported (Finley & Nugent 1993, Goto et al 1997) that there is an age-related alteration in cardiac vagal tone of an increase in cardiac vagal tone between the ages of 3 to 6 years and then a decrease from 6 to 15 years. However, numbers of patients included in this normal data are also small and do not give account of the wide intra and inter-subject variation in HF (Grossman & Taylor 2007) and these studies did not use strict criteria in monitoring sleep stages electrographically. The generalised data derived from two patients in this study (aged 5 years) had lower cardiac vagal tone compared to the other patients but they had severe generalised epilepsy and therefore their data may not be comparable to normal data. Case studies of these two patients are supplied in the appendix.

Harnod et al (2008) compared heart rate variability in children who had refractory generalised epilepsy with a control group. They reported decreased resting HRV (faster resting heart rate) in the epileptic children and postulated that this was due to reduced vagal tone. They believed that epileptic adults have reduced HRV via a different mechanism of increased sympathetic activity. Generalised sub-clinical seizures were not recorded in adults in this study and therefore a comparison could not be made between paediatrics and adults.

Limitations of the study

This study included eleven patients due to strict inclusion criteria. Manual measuring of 27,151 R-R intervals (33 sub-clinical seizures with 5minute matched baselines) also presented time limitations of what is possible during this research period. Most studies use automated peak detection software to identify and measure R-R intervals. Automated peak detection software was considered for 5 minute R-R interval but when checked and re-measured manually, there were marked errors and so manual measurement was preferred. No statistical differences were found between R-R measurements made either by Inter-observer analysis ($p=0.809$) or intra-observer analysis ($p=0.976$). Some authors advocate for manual measurement due to automated peak detection software unreliability but manual measurements are particularly time consuming and will limit performing a larger study in this way. In a report by the American Heart Association (1990), a consortium of European investigators found systematic errors in measurement of 16 computer programs for ECG analysis.

Comparison of reflex vagal tone and modulated tonic vagal tone.

A limiting factor in comparing CIPA with HRV HF%, is that CIPA measures efferent vagal tone from baroreceptor feedback and HRV HF% measures overall modulations of parasympathetic activity and they have a different basis for parasympathetic measurement. Respiration rate effects this modulation of HF frequency whereas CIPA is independent from changes in respiration due to series of low and high pass filters during data acquisition. In the study, data was analysed during slow wave sleep where respiration rate is constant and believed to be more constant than paced breathing. In extreme circumstances of vagal blockade or over-saturation effect on the

sinus node by persistent high vagal tone leads to a situation where an increase in high frequency components do not reflect increased vagal tone or vice versa (Malik and Camm 1993). However, for the purposes of this study parameters are not measured during such extreme states.

Effects of anti-epileptic drugs and CIPA

The patient receiving topitamate and phenobarbitone polytherapy has a low mean CIPA (4.2 and ranges from 0.9 - 5.2).This result indicates that this patient has an elevated resting heart rate and in the main study was also found to have low beat-to-beat variability. This child would be considered to have risk factors associated with low heart rate variability (HRV), Bilchick & Berger (2006). However, this finding is impossible to relate specifically to medication as only one patient is being treated on these drugs in this study. The results may instead be due to his refractory generalized epilepsy with the effect on his autonomic nervous system from repeated frequent seizures. Bulent et al (2010).

To the other extreme, those patients receiving carbamazepine have a high mean CIPA (16.2 and ranges from 4.2 to 50.3). Maximum CIPA for this group is much higher than any group receiving other AED's. The autonomic nervous system is finely balanced on a beat-to-beat basis. Any extremes whether transient or long-term can cause cardiovascular imbalance. Sustained tachycardia can lead to hypertension and low HRV as a consequence of down-regulation of cardiac sympathetic receptors. La Rovere et al (1998). At the other extreme, bradycardia due to high vagal tone can lead to cardiac arrhythmia if combined with other contributing factors e.g seizures and sudden increases in heart rate where cardiac hysteresis may

cause a 'lag' effect of the Q-T shortening/re-polarising and too slow for the tachycardiac sinus rhythm. Bradycardia itself can also lead to Early After Depolarisations (EADs), occurring in late stages of ventricular re-polarisation and can occur due to partial inhibition of K channels as a result from hypokalemia. If the sinus pace-maker occurs at the same time as ventricular re-polarisation then this can be pro-arrhythmic and trigger ventricular fibrillation Bers (2001).

Ansakorpi et al (2002) did not find any alteration in heart rate variability in their study of patients with temporal lobe seizures compared to normal controls in relation to AEDs but still suspected some changes may be found in some patients due to blocking of sodium channels from AED medication.

In this study, one patient receiving Topiramate and Phenobarbitone polytherapy had very low cardiac index of vagal tone and indicated a high resting heart rate and low beat-beat variability. The multivariate analysis also indicated that patients in this group being treated with carbamazepine tend to have a high index of cardiac vagal tone. Bradycardia is not a risk factor in itself but can lead to cardiac arrhythmias during a seizure where sudden increases in heart rate may give rise to cardiac hysteresis where the ventricles are slow to repolarise proportionally for rate and Early After Depolarisations may lead to cardiac arrhythmia especially if there are contributing factors of ionic disturbance e.g Na channel blockade hypothetically resulting from carbamazepine especially during acidosis from hypoxia during a seizure.

It is difficult to know just what true contributing effects of medication have on an individual and maybe a pre-disposed individual in the physiological extremes of seizures and when particularly prolonged. There may not be

many clues in patients who are studied while at rest or during brief sub-clinical seizures. This is perhaps one of the reasons why SUDEP remains unexplained to date. This pilot study is small in terms of numbers of patients are no clear correlations between the index of cardiac vagal tone and AEDs was possible.

Ansakorpi et al (2002) did not find any changes in heart rate variability from effects of anti-epileptic drugs (AED) in their study of temporal lobe epilepsy patients compared to controls but they acknowledge that AED are anticipated to cause changes in cardiovascular regulatory function in some patients due to blocking of sodium channels. Any effects of AED cannot be fully evaluated in this study due to the limited number of patients.

CIPA in relation to Gender

Differences in cardiac vagal tone and Gender were assessed by ANOVA and no differences in CIPA were found. A study by Valladares et al (2008) showed the only gender difference in nocturnal vagal tone occurred in men during REM sleep where there was a marked increase in cardiac sympathetic drive. The data in this study was sampled during slow wave sleep only.

3.9.2 Further studies

Indications from this study have offered a good basis for further investigation of the differences between generalised and temporal lobe sub-clinical seizures in the continued investigation of possible autonomic mechanisms of SUDEP. Nouri et al (2004) underlines the importance of evaluating autonomic cardiovascular and respiratory reflexes in people with epilepsy and believes that it will provide invaluable insight into some of the

mechanisms of SUDEP. Further verification is also required for the comparison of the NeuroScope with traditional heart rate variability software with a larger study. An increase in cardiac vagal tone is measured during generalised sub-clinical seizures but not in temporal lobe sub-clinical seizures in this study. Further investigation is required for evaluating cardiac vagal tone in line with European HRV standards in people with epilepsy to allow quantification and comparisons of cardiac vagal tone and HRV to other diseases. The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996 believe that the task of assessing transient changes in HRV seem to be more important than further refinements of HRV technology.

3.9.3 Conclusion

One of the main aims of this study was to investigate if there were any changes in parasympathetic activity during sub-clinical seizures. This study involved a small number of patients (11) but a large amount of R-R interval (27,151) manual measurement for 33 sub-clinical seizures and baseline studies. It has shown increased vagal tone and low R-R variability during generalised sub-clinical seizures compared to decreased vagal tone and higher R-R variability during temporal lobe sub-clinical seizures. This study has also demonstrated a good relationship between NeuroScope log CIPA data with log lnHF% Heart Rate Variability (HRV) BioSignal data.

Chapter 28

Final Discussion

It is documented that sleep itself increases the occurrence of seizures with 10-45% of patients with epilepsy having seizures that may occur predominantly or exclusively in sleep or in relation to sleep deprivation' (Walker et al 2004). Undetected prolonged nocturnal seizures can be fatal or result in significant morbidity due to hypoxic brain damage (Brown & Hussain 1991).

Some seizures resulting in death are accidental and death could have been avoided if someone was alerted to the situation and intervened with rescue medication and body re-positioning to prevent an obstructive airway (Langan et al 2000).

However, other seizures resulting in death from SUDEP may not have been prevented even with intervention (Dasheif & Dickinson 1986).

The knowledge that we are dealing with two separate problems which both result in death in patients with epilepsy, namely 'extrinsic factors' of circumstantial compromise e.g. suffocation due to obstructive apnoea or drowning and 'intrinsic factors' of SUDEP, have been considered for over one hundred years. 'Epileptologists at the turn of the century were well aware of the dangers from seizures and recognised that seizure deaths could be accidental or due to intrinsic mechanisms during a single seizure or serial seizures and status' (Nashef 2000). However, very little is understood of what exactly happens during these 'intrinsic mechanisms.'

Final Discussion

In this thesis, a novel epilepsy alarm system is proposed and two possible intrinsic mechanisms of SUDEP were investigated. In the first section, the main aim was to determine whether epileptic seizures could be distinguished from normal events using percentage heart rate change and oxygen saturation measurement. In section two, a possible intrinsic mechanism of SUDEP was investigated to discover if clinically significant lengthening of the corrected Q-T occurred during seizures. The main aim of section three was to measure parasympathetic activity during sub-clinical seizures to discover whether altered cardiac vagal tone and heart rate variability was detected in any particular type of sub-clinical seizure. Altogether, approximately 180,000 manual measurements were made from 527 seizures in the investigation of percentage heart rate change and oxygen saturation, Q-T interval analysis, cardiac vagal tone and heart rate variability.

A reliable alarm system may not prevent true SUDEP cases but many seizures that are amenable to intervention, if detected, will be prevented from causing bodily injury, hypoxic brain damage and in some cases death. My view is supported by others ' timely assistance at the time of a seizure is likely to reduce the risk of death or injury' and 'un-witnessed seizures carry a higher risk of death' (Nashef 2000) and 'positioning of the patient or stimulation of respiration may prevent a fatal outcome in some cases. This raises the important issue of supervision' (Langan et al 2000).

Percentage Heart Rate Change and Oxygen Saturation.

In this study, my main aim was to discover if epileptic seizures could be distinguished from normal events using heart rate percentage change and oxygen saturation measurement. I compared manually measured

consecutive R-R intervals (approximately 99,200 measurements) and calculated percentage heart rate changes and oxygen saturation before and during 527 epileptic events and 496 normal events using 9second epochs. Diagnostic testing of this data gives a sensitivity of 79% and specificity of 75% of distinguishing epileptic events from normal events with a trigger level of 25.5% percentage heart rate change. Combined percentage heart rate change and oxygen saturation increases the sensitivity to 86%. The same trigger level is optimum for the detection of temporal lobe seizures with a sensitivity of 75% and specificity of 75%. Frontal lobe seizure detection trigger level is optimum at 30.5% percentage heart rate change to give a sensitivity of 83% and specification of 82%. For the detection of generalised tonic clonic seizures, the trigger level is 32.5% percentage heart rate change. Diagnostic testing suggests a sensitivity of 88% and specificity of 85%.

An alarm system based on these parameters can be set to trigger for individual seizure types depending on the patient's habitual seizures. A second trigger level is proposed which is not adjustable and would indicate a life threatening status of the patient if pulse is lost and oxygen saturation drops to severe hypoxic levels. Abnormal pulse and reduced pulse oximetry are listed as part of the identified risk factors for cardiac arrest (Hodgetts et al 2002). This second trigger level would act as a 'safety net' and both types of alarms would alert parents or carers via an audible alarm and/or a radio page receiver unit.

Nocturnal Seizures and SUDEP

Sudden and extreme changes in heart rate can occur during nocturnal seizures. This seizure induced cardiac instability during sleep may cause

sudden and extreme fluctuations in autonomic tone, which may precipitate lethal cardiac arrhythmias and be one of the causes of SUDEP. (Nei et al 2004), Nei et al reported 14/21 people died from SUDEP in sleep and studying seizure EEG/ECG data of these patients retrospectively discovered that much higher increases in heart rate occurred during seizures arising from sleep than from wakefulness in the SUDEP group compared to the non-SUDEP group. Additionally, 'Ictal cardiac re-polarization and rhythm abnormalities occurred in 56% of SUDEP.' Forced awakening occurs during nocturnal seizures and the effects of sudden waking with associated increase in heart rate is compounded by the seizure itself at a time of suspected autonomic instability and therefore could leave some pre-disposed individuals more vulnerable to an induced cardiac arrhythmia during early waking hours.

Marked changes in T-wave morphology, signalling an alteration in ventricular re-polarisation was demonstrated when subjects were unexpectedly woken from deep sleep (Dweck et al 2006). Increased autonomic instability is described during early waking hours corresponding to a reported period of increased vulnerability to ventricular tachycardia and sudden death (Pater 2005). Cardiological effects during seizures can be the result of autonomic instability because of a nocturnal seizure presenting when vagal tone is high or an undiscovered channelopathy triggered by the seizure, directly affecting the heart (Lathers et al 1987, Wannamaker 1985, Cheung & Hachinski 2000, Ansakorpi et al 2004). Another consideration is that some susceptible individuals may develop an intracellular ionic flux disturbance in the myocyte because of changes in ionic environment due to the physiological demands of the seizure. This disturbance in ionic flux may

deteriorate over time in cases of undetected prolonged nocturnal seizures and this could also be a contributing factor in some cases of SUDEP.

Corrected Q-T Analysis

Lengthening of the corrected Q-T was investigated in this study as cardiac arrhythmia is considered to have a possible role in SUDEP (Soonhak et al 2003, Tavernor 1996). Prolonged corrected Q-T re-polarisation time can lead to fatal cardiac arrhythmias (Morganroth and Pyper 2001, Tavernor et al 1996).

A total of 156 seizures had consecutive R-R and Q-T intervals manually measured (approximately 49,920 measurements) and Q-T corrected for rate according to Bazett's (Bazett 1920), Hodges (Hodges 1997), Fridericia's (Fridericia 1920) and Framingham's (Sagie et al 1992) corrective formulae, before and during each epileptic seizure. The 156 analysed seizures were composed of:- generalised tonic-clonic seizures (9), absences (34), tonic seizures (12), temporal lobe seizures (27), frontal lobe seizures (58) and 16 sub-clinical seizure events were clinically and electrographically identified.

There were only two patients who were identified by all four corrective formulae as having prolongation of the corrected Q-T during epileptic seizures. The corrected Q-T prolongation occurred as the seizure progressed and as the heart rate changed each formulae demonstrated prolongation during different epochs within the same seizure The first patient (9M) was a 2 years old male during a right sub-clinical seizure with prolonged QTc (Bazett's 492 milliseconds (heart rate 119.5/min), Hodge's 475 milliseconds (heart rate 127.3/min), Fridericia's 454 milliseconds (heart rate 92.8/min) and Framingham's 451 milliseconds (heart rate 88.8/min). The second patient

(20M) was a 21 years old male during a right temporal lobe seizure with prolonged QTc (Bazett's 495 milliseconds (heart rate 66.7/min), Hodge's 479 milliseconds (heart rate 66.7/min), Fridericia's 463 milliseconds (heart rate 65.9/min) and Framingham's 462 milliseconds (heart rate 65.9/min).

One of the main aims of this study was to determine if there was any lengthening of the corrected Q-T during epileptic seizures. This study has indicated that significant lengthening of the corrected Q-T beyond normal limits in children and adults transiently occurs during some epileptic seizures. Prolonged corrected Q-T is associated with an increased risk of cardiac arrhythmia and this study supports the possibility that this cardiological mechanism may be involved in SUDEP.

Cardiac vagal tone & Heart Rate Variability

A measure of autonomic changes during different types of seizures may give some insight as to a possible mechanism involved during sudden unexpected death in epilepsy. It has also been postulated that a predisposed patient could become a victim of SUDEP if there is a combination of reduced sympathetic tone during sleep, ictal bradyarrthymia or extreme fluctuations in heart rate resulting in autonomic instability. Ictal bradyarrthmia and/or sinus arrest have vagally mediated involvement during seizure discharges (Vaughn et al 1997). The "lockstep phenomenon" was proposed by Lathers et al (1987) proved synchronization between epileptogenic "sub-convulsant" discharges with abnormal sympathetic and vagal neural discharges with cardiac arrhythmia in anaethetised cats. They believed that the lockstep phenomenon of synchronization of epileptogenic discharge with cardiac sympathetic neural discharge could be a contributing factor of SUDEP.

Variability of successive R-R intervals is generally considered to be an important protective mechanism of the autonomic nervous system being able to respond to sudden cardiovascular demands (Hohnloser et al 1994, Miller et al 2004). Loss of this variability increases the risk of sudden cardiac death and reduced HRV is a measure of risk stratification for myocardial infarction patients (Bigger et al 1984, Kleiger et al 1987, Malpas 2002, Miller et al 2004) of 2.5 years for approximately 50% of patients. Reduced vagal activity following myocardial infarction is believed to be due to the necrotic scar from the infarct altering the geometry of the beating heart. This altered geometry increases sympathetic afferent fibres in response to damage of sensory endings and inhibits vagal effect (Hohnloser et al 1994).

One of the main aims of this study was to investigate if there were any changes in parasympathetic activity during sub-clinical seizures. This study involved a small number of patients (11) but a large amount of R-R interval (27,151) manual measurement for 33 sub-clinical seizures and baseline studies. It has shown increased vagal tone and low R-R variability during generalised sub-clinical seizures compared to decreased vagal tone and higher R-R variability during temporal lobe sub-clinical seizures. This study has also demonstrated a good relationship between NeuroScope (Julu & Little 2002) log CIPA data with lnHF% Heart Rate Variability (HRV) BioSignal (Niskanen et al 2002) data of 2% difference in CIPA and HF% for short ‘counted ‘epochs and 10% difference for 5 min epochs.

Conclusion

SUDEP mechanisms have yet to be proven by experts in epilepsy. Proposed mechanisms underlying SUDEP of lengthening of the corrected Q-T and

altered parasympathetic activity have been investigated during epileptic seizures in this study. Significant changes have been identified in each section but none of the study patients have become a victim of SUDEP (to date). SUDEP is believed to be multi-factorial and may only occur in individuals who have a pre-disposition of physiological vulnerability. A total of fifty patients took part in this study, three patients would be categorised as "at risk" from lengthened corrected Q-T or altered parasympathetic activity. It may be the case that none of them are predisposed and are physiologically able to cope with the effects of seizures and will hopefully not become a SUDEP victim.

Pre-disposition of individuals can alter over time with aging effect and the accumulative damage to cardiac myocardium and autonomic nervous system from repetitive seizures (Everingul et al 2005, Harnod et al 2008).

Re-polarisation disturbances are accepted as risk factors for sudden death in various diseases. Reduced heart rate variability is used in risk stratification in myocardial infarction patients. Most researchers and experts in SUDEP believe there has to be intrinsic cardio-respiratory mechanisms involved.

This study describes significant transient lengthening in the corrected Q-T during right temporal lobe seizures (Brotherstone et al, 2010, appendix), increased cardiac vagal tone and reduced co-efficient of variation during generalised sub-clinical seizures compared to right or left temporal sub-clinical seizures (paper accepted for publication, appendix) and created a patent sensitive method for an epileptic seizure alarm system that will distinguish clinically significant epileptic seizures from normal events using heart rate percentage change and oxygen saturation trigger levels.

As an outcome from this thesis, the proposed seizure alarm device method is being patented by NHS Lothian. Grant applications are being submitted to build a prototype device to test proof of concept prior to clinical trials in the future.

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