New techniques in the management of Transient loss of consciousness (TLOC) or Blackout

A Thesis submitted to the University of Manchester for the degree of Doctor of Medicine in the Faculty of Medical and Human Sciences

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Abbreviations and keywords

AV	Atrioventricular
COPD	Chronic obstructive pulmonary disease
CRT	Cardiac resynchronization therapy
CSM	Carotid sinus massage
ECG	Electrocardiogram
EEG	Electroencephalogram
ENT	Ear, Nose and Throat
HRV	Heart rate variability
IVCD	Interventricular conduction delay
LAD	Left axis deviations
LAHB	Left anterior hemiblock
LBBB	Left bundle branch block
NEAD	Non-epileptic attack disorders
OH	Orthostatic Hypotension
PPM	Permanent pacemaker
PPS	Psychogenic pseudosyncope
QT	Interval between start of Q wave and end of T wave on ECG
RBBB	Right bundle branch block
RVH	Right ventricular hypertrophy
SECGC	Symptoms ECG correlation (Associated of symptoms with ECG findings)
SVB	Sympathovagal balance
TLOC	Transient loss of consciousness
TT	Tilt testing

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Abstract

Submission for the degree of Doctor of Medicine, The University of Manchester
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New techniques in the management of Transient Loss of Consciousness (TLOC) or Blackout
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Collapse is defined as an "abrupt loss of postural control" and is very common presentation to primary and secondary care. It accounts up to 3% of emergency department cases, and 6% of hospital admissions. Many patients are labelled with "collapse?cause". It should be appreciated that collapse can be with or without TLOC/blackout. Causes without TLOC include falls, transient ischemic attacks, cerebrovascular accidents, road traffic accidents, metabolic abnormalities and intoxication. However, most collapse patients have TLOC. Most common causes are syncope, epilepsy or psychogenic blackouts. There are many similarities and overlap of clinical features leading to misdiagnosis. There are huge variations in the ways TLOC patients are assessed and managed. Patients are dealt by different specialties in different clinical settings. There is lack of clinical tools for assessment and poor risk stratification. Most clinicians take a "safe approach" and as a result, TLOC patients are often admitted to hospital unnecessarily and over investigated, which can increase confusion and healthcare cost. We have therefore tried to approach these issues via a dedicated "Rapid Access Blackout Triage Clinic" (RABTC). In this thesis, we have addressed the problem of TLOC in five projects arising from the triage of patients seen in that clinic. Chapter 1 expands the scene-setting for the thesis. Chapter 2 reports outcomes of a specialist nurse-lead RABTC. The clinic uses custom clinical evaluation and risk stratification tools for patients with TLOC with cardiologist supervision (author). Nearly two thirds of patients presenting to the RABTC are over 65 years. Chapter 3 reports outcome of pacemaker insertions in elderly patients for minor ECG abnormalities that are not current indications for pacemaker insertion. We speculated that such abnormalities could progress suddenly and transiently at the time of TLOC. Patients underwent pacemaker implantation directly avoiding further investigations, delay, and the risk of further blackouts and injury. Large numbers of patients with blackouts referred to the RABTC have had many investigations elsewhere with no conclusion. In chapter 4, we studied the effect of long term insertable ECG monitor (ILR) which can help making early diagnosis and avoid unnecessary investigations. We explored the impact of the ILR on time to Symptom/ECG correlation and time-to-diagnosis. There remains nearly half of the patients where even ILR is unable to explain the TLOC. Ideally, ILR would detect ECG, Blood Pressure and the Electroencephalogram, (EEG). These physiological parameters would be sufficient to distinguish between syncope, epilepsy and psychogenic blackouts. In Chapter 5 the results of in-depth analysis of the ECG in these patients are presented. Heart rate variability was used to calculate sympathovagal balance. The patients were recruited using video telemetry data from a Regional epilepsy centre. Finally, treatment of TLOC depends on its underlying cause and by far the most common cause is reflex syncope. So far, no treatment has proven benefit in this situation. One drug, midodrine an alpha-adrenoceptor agonist, has had several albeit unsatisfactory randomised controlled trial. We describe our experience of midodrine in this condition in Chapter 6. Chapter 7 summarises what has been contributed by this thesis.

Declaration

No portion of this work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright statement

Dedication

This thesis is dedicated to Dr Adam Fitzpatrick, Consultant Cardiologist, Manchester Heart Centre, Manchester Royal Infirmary, Manchester. I have had the privilege of working under his supervision since 2012. He not only gave me the opportunity to do this research but also guided me for clinical activities. He is a great teacher and listener inspiring me to achieve greater heights and excellence. In addition, he is an exceptional human being.

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Amir Anwar, Allen S, Virag N, Sutton R, de Melis M, Cooper PN , Fitzpatrick AP: "Sympatho-Vagal Balance(SVB) During ECG Monitoring May "REVEAL" The Underlying Cause Of T-LOC. **British Cardiovascular Society Conference June 2014, UK.** *(doi:10.1136/heartjnl-2014-306118.2, Heart 2014;100(Suppl 3): A1–A138)*

Amir Anwar, Allen S, Virag N, Sutton R, de Melis M, Cooper PN , Fitzpatrick AP: "Sympatho-Vagal Balance(SVB) During ECG Monitoring May "REVEAL" The Underlying Cause Of T-LOC". **Heart Rhythm Society Conference, May 2014, San Francisco, USA** *(Heart Rhythm, Vol. 11, No. 5, May Supplement 2014*

Y. Saeed**, Amir Anwar**, A Fitzpatrick. "Effectiveness of ECG-Based Triage in Older Patients with TLOC Attending a Rapid Access Blackouts Triage Clinic: Conduction Tissue Abnormalities Predict a Higher Mortality, Recurrent TLOC and a Good Response to Cardiac Pacing". **Heart Rhythm Congress Oct 2014 UK** *(DOI: 10.1093/europace/euu239.8, Europace 16 Suppl 3(suppl 3): iii15 react-text: 57 · /react-text react-text: 58 October 2014*

Amir Anwar, S. Collitt1, P. Iddon, N. Rice, M. Dodd, A. Dunsdale, S. Petkar, J. Mudd, N. Linker, and A.P. Fitzpatrick. Specialist arrhythmia nurse-led rapid access blackouts triage clinic: experience in 2 centres. **Heart Rhythm Congress Oct 2013 UK** *(Europace Nov 2013, 15 (suppl 4) iv14-iv18; DOI: 10.1093/europace/eut316)*

Peer Reviewed Journal Publications

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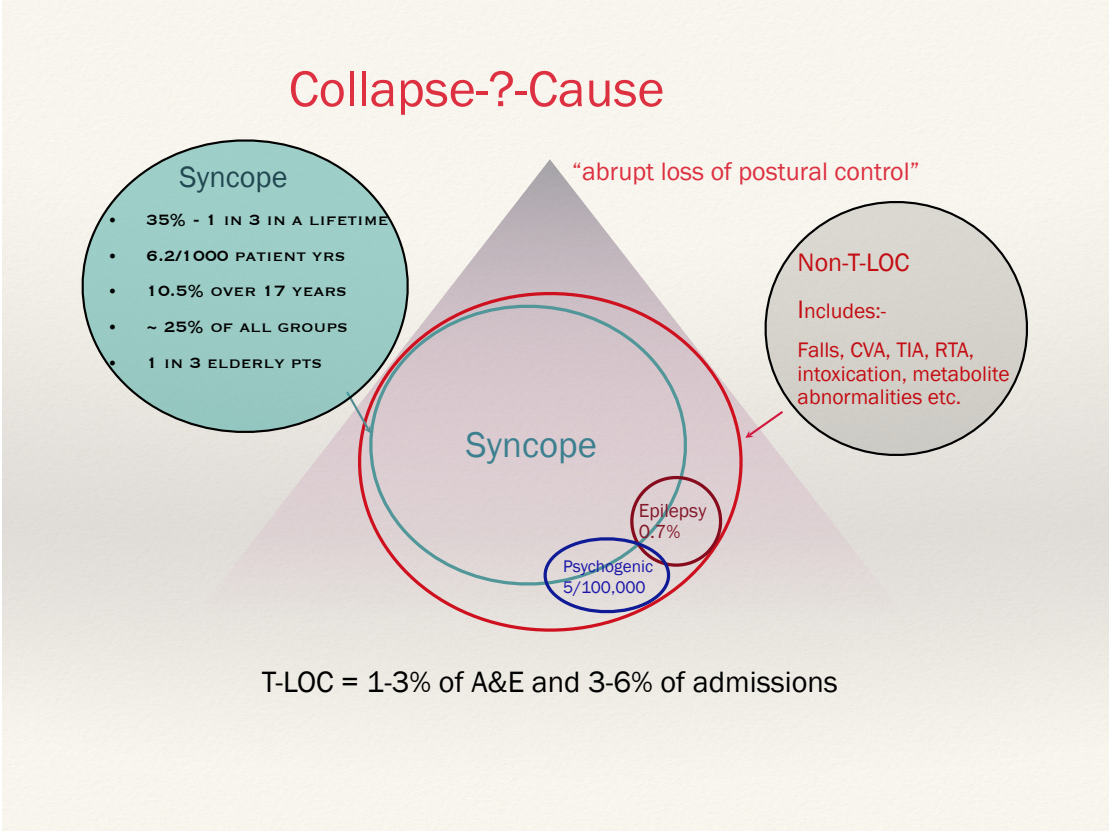
Chapter 1

1. General Introduction:

'Collapse ?cause' is common in both primary and secondary care. It is defined as abrupt loss of postural control. Collapse may occur with or without loss of consciousness/blackout (TLOC). The terminology is often confused. Collapse is often used when "loss of consciousness", is meant, but the two are different, because TLOC is one cause of collapse, not the only cause. Causes of TLOC (Figure 1.1). These include syncope and generalized epilepsy where there is associated TLOC. However in falls, cerebrovascular accidents (including transient ischaemic attacks), metabolic causes (hypoxia, hyperventilation and hypoglycemia) and intoxications(1), collapse usually occurs without a TLOC. TLOC or blackout is the most common cause of collapse, but whilst collapse can occur without losing consciousness, TLOC cannot occur without a collapse. Another critical distinction is between TLOC/blackout and TIA. TLOC is a transient loss of consciousness without neurological deficit, while a TIA is a transient neurological deficit without loss of consciousness. The definition of a TIA includes neurological deficit of vascular origin which lasts less than 24 hours. TLOC is also characterised by a short duration and the absence of an external cause serving to exclude an external injury causing concussion[3]. Prolonged loss of consciousness is coma, not TLOC.

Figure 1.1: Causes of collapse



1.1 Definitions and Derivation of Transient Loss of Consciousness (TLOC):

Consciousness is 'the state of awareness of the self and the environment(2) and has two components : content (awareness) and arousal (degree of wakefulness from deeply unconsciousness to fully awake. As a person cannot be aware without being awake, hence these two aspects are not independent. Considering this definition, unconsciousness might also have 'content' and 'arousal' parts but this is not clinically relevant. If 'unconsciousness' were also used for content, then the word would also cover the mental state during absence and partial complex seizures: wherein patients have impaired awareness, and content is affected. Such forms of epilepsy do not usually

cause collapse, however. Patients appear ‘awake’; meaning the ‘arousal’ aspect is unaffected. The term ‘unconsciousness’ is not used for these conditions and the international League Against Epilepsy (ILAE) uses ‘impaired’ consciousness to describe consciousness in these states. Partial complex seizures and absences therefore do not usually enter the differential diagnosis, needed to distinguish clinically between the principle causes of syncope and epilepsy.

“TLOC can be defined as a transient, self limited loss of consciousness usually leading to a collapse”. The Oxford English dictionary also defines blackout as “temporary loss of consciousness”, and “blackout” is valuable parlance for everyday communication with patients and between doctors. Blackout does not prejudice the underlying cause of loss of consciousness. Unlike TLOC it is commonly used in everyday English, and widely understood by patients, relatives and doctors.

1.1.1 Causes of TLOC:

Causes of collapse and TLOC are given in Figure 1.1. The causes of TLOC are syncope, epilepsy and psychogenic blackouts, with some very rare exceptions. Although psychogenic blackouts are not really blackouts, they only appear to be syncope. All these causes have distinguishing clinical features but misdiagnosis occurs frequently, and it is known that epilepsy is commonly diagnosed in patients with syncope(3). Misdiagnosis of epilepsy occurs because syncope is often convulsive with abnormal movements and incontinence(4). This is discussed later in detail.

a. Syncope:

Syncope is the most common cause TLOC. The word syncope is derived from the Greek words, ‘syn’ meaning ‘with’ and the verb ‘koptein’ meaning ‘to cut’ or more appropriately in this case ‘to interrupt’(1). There has been a lot of confusion in defining

syncope. Van Dijk(5) et al has described the condition in detail. Syncope must be distinguished from TLOC itself and recognized as a common cause of TLOC. In some conditions, consciousness appears to be lost, which is probably the case in psychogenic blackouts. Many causes of TLOC are not due to syncope (Fig 1.2), but many past definitions of syncope are very unhelpful, because they confuse syncope and TLOC. For example, in the Framingham study and in many medical textbooks, syncope is defined as a "sudden loss of consciousness associated with inability to maintain postural tone, followed by spontaneous recovery". This is not a definition of syncope, but a definition of TLOC/blackout. In some publications, even stroke, TIA and epilepsy were considered among causes of syncope, but TIAs specifically do not cause TLOC.

More recently, definitions more closely detail the underlying pathophysiology. Syncope is now defined by the European Society of Cardiology as a "TLOC due to transient global cerebral hypoperfusion characterized by rapid onset, short duration and spontaneous recovery"(1). Thus, syncope is only diagnosed if abrupt loss of cerebral blood flow is thought to be the cause of TLOC, and not simply in TLOC. Causes of syncope are mentioned in table 1.1.

Figure 1.2: Syncope in relation to real and apparent loss of consciousness

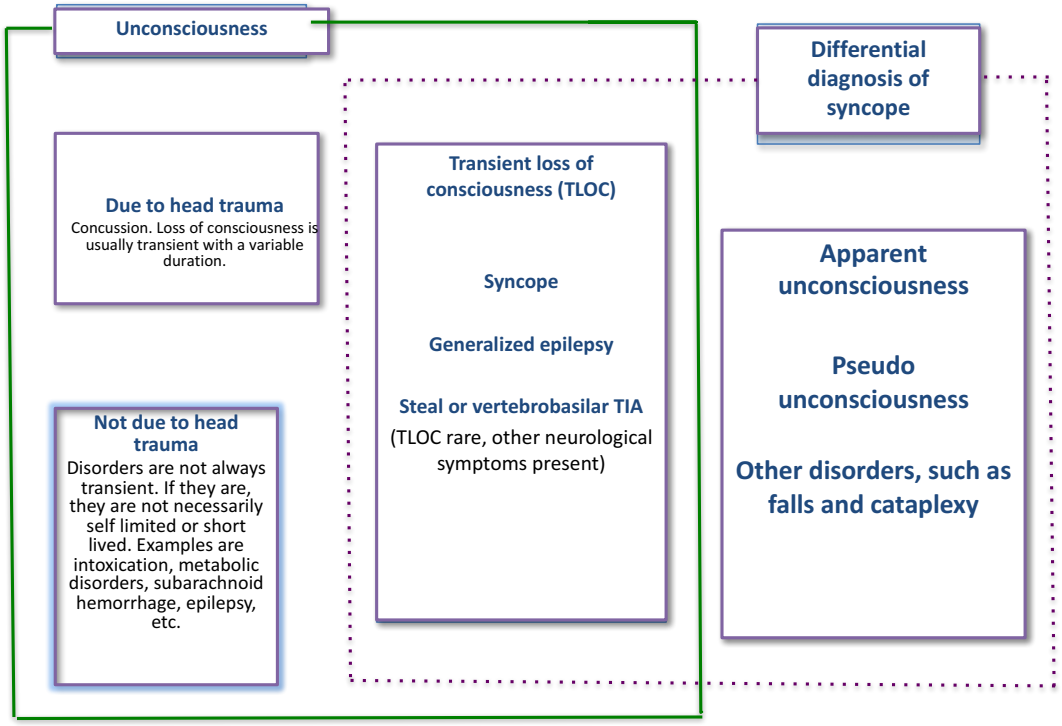


Table 1.1: Causes of Syncope(6)

Reflex (neurally mediated) syncope
Vasovagal: Mediated by emotional distress: fear, pain, instrumentation, blood phobia, or by orthostatic stress
Situational: cough, sneeze, gastrointestinal stimulation (swallow, defaecation, visceral pain), micturition (post micturition), post exercise, post prandial, others (e.g., laughter, brass instrument playing, weightlifting)
Carotid sinus syncope
Atypical forms (without apparent triggers and/or atypical presentation)
Syncope due to orthostatic hypotension

Primary autonomic failure: pure autonomic failure, multi-system atrophy, Parkinson's disease with autonomic failure, Lewy body dementia

Secondary autonomic failure: diabetes, amyloidosis, uraemia, and spinal cord injuries

Drug induced orthostatic hypotension: alcohol, vasodilators, diuretics, phenothiazines, antidepressants

Volume depletion: haemorrhage, diarrhoea, vomiting, salt depletion

Cardiac Syncope (cardiovascular)

Arrhythmia as primary cause:

Bradycardia: sinus node dysfunction (including bradycardia/tachycardia syndrome), atrioventricular conduction system disease, implanted device malfunction

Tachycardia: supraventricular, ventricular (idiopathic, secondary to structural heart disease, or to channelopathies)

Drug induced bradycardias and tachycardias

Structural disease: Cardiac: cardiac valvular disease, acute myocardial infarction/ischemia. Hypertrophic cardiomyopathy, cardiac masses (atrial myxoma, tumors etc.), pericardial disease/ tamponade, congenital anomalies of coronary arteries, prosthetic valve dysfunction

Others: pulmonary embolism, acute aortic dissection, pulmonary Hypertension

Three most common causes of syncope are: reflex syncope, syncope due to orthostatic hypotension, and syncope with cardiac/cardiopulmonary cause.

Reflex Syncope:

Normal cardiovascular reflexes maintain the blood pressure and cerebral perfusion, and a major component of this is the maintenance of peripheral arteriolar tone. Arteriolar

tone is maintained by sympathetic outflow, mainly to skeletal muscle capillary beds. Sudden loss of this tone causes blood to rush into skeletal muscle, and away from other organs. When the body is upright, the effect on the brain is maximised, because of the orthostatic effect which further reduces perfusion pressure to the upper parts of the body. Cerebral hypoperfusion, especially if marked and abrupt, results in loss of function with loss of consciousness, and affects the anti-gravity muscles supplied by the motor cortex which is the highest part of the brain. This characterises 'vasodepressor' of reflex syncope. However, there is a variable component of "cardioinhibition". This is characterised by abrupt vagal stimulation, slowing or even stopping the heart, transiently. If both mechanisms occur in same individual, it is called 'mixed' type of reflex syncope.

There has been much debate as to whether decreased cardiac output or vasodilation is the dominant hypotensive mechanism preceding vasovagal syncope. Wieling et al(7) did an analysis of classical papers and concluded that reduction in cardiac output, rather than vasodilation, may be the primary cause of hypotension of vasovagal syncope.

Reflex Syncope is characteristically spontaneous without a good explanation, or associated with certain stimuli, such as the sight of blood or a needle. Sometime there are other specific situations with specific provocateurs causing reflex syncope such as micturition or cough syncope. Different types are described in table1.

Conditions misdiagnosed as syncope:

The most important differential diagnoses for syncope are epilepsy and psychogenic blackouts. Metabolic disorders may cause collapse and altered consciousness, but they rarely correct themselves rapidly and spontaneously as syncope does. In other very rare

circumstances, such as cataplexy, there is no TLOC, although consciousness is affected. The most important principle in the differential diagnosis of patients with blackouts is that diagnosis is based predominantly on clinical evaluation. This should be backed up by a 12-lead ECG in all cases, and only a few patients are typically diagnosed with more sophisticated and expensive testing. Hence, the important clinical features are discussed below. Table 1.2 summarises the conditions misdiagnosed as syncope.

Table 1.2: Conditions incorrectly diagnosed as syncope

Disorders with partial or complete LOC but without global cerebral hypoperfusion
Epilepsy
Metabolic disorders including hypoglycaemia, hypoxia, hyperventilations with hypocapnia
Intoxication
Disorders without impairment of loss of consciousness
Cataplexy (Sudden and transient episode of muscle weakness due to some trigger such as laughing, crying and terror; consciousness is not affected)
Drop attacks (Sudden spontaneous falls while standing or walking with complete recovery in seconds or minutes)
Falls
Functional (Psychogenic pseudosyncope)
TIA of carotid origin

b. Epilepsy:

Epilepsy is conceptually defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition(8). There is requirement of at least one epileptic seizure, which is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity of the brain. More recently a practical clinical definition of epilepsy has been agreed by International League against Epilepsy (ILEA) and is described by any of the following conditions(9);

1. At least two unprovoked (or reflex) seizures occurring >24 hr apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to general recurrence risk (at least 60%) after unprovoked seizures, occurring over the next 10 years.
3. Diagnosis of an epilepsy syndrome

Epilepsy is not necessarily life-long and is considered to be resolved if a person has been seizure free for 10 years, with 5 years free of antiepileptic medications, or when that person has passed the age of an age-dependent epilepsy syndrome. Many clinicians believe that two documented unprovoked seizures are required for the diagnosis. Crucially, generalised epilepsy is a cause of TLOC, but there is no change to cerebral perfusion in the pathogenesis of it. Other forms of epilepsy should not cause confusion with syncope or psychogenic blackouts as they tend not cause collapse with TLOC.

c. Psychogenic seizures

The term ‘psychogenic syncope’ is a misnomer. "Psychogenic pseudosyncope’ (PPS), is a better term, but can still cause confusion. Using “syncope” can imply to some that cerebral perfusion is impaired, and to others that there is TLOC. Many different terms have been used, including ’self-induced syncope(5). Rueber and Elger(10) described it as ‘episodes of altered movement, sensation, or experience similar to epilepsy, but caused by psychological process and not associated with abnormal electrical discharges in the brain’. Unfortunately, whilst this excludes epilepsy, it doesn’t exclude syncope. ‘Psychogenic pseudosyncope’ refers to episodes when patients appear unconscious but are not. Related terms are ‘psychogenic seizure’, ‘psychogenic coma’ or ‘pseudo-unconsciousness’, depending on the clinical presentation. Three psychiatric conditions may underlie ‘psychogenic pseudosyncope’. One is conversion disorder, in which patients have unexplained somatic symptoms, suggesting a neurological or general medical condition. As a rule, the symptoms cannot, after appropriate investigation, be fully explained by a general medical condition, the effects of a substance, or as a culturally sanctioned behaviour or experience(5). Secondly, in a factitious disorder, symptoms are intentionally produced, with the motivation being to assume a sick role(5). In malingering, the motivation of symptom production is an external incentive, such as economic gain or legal responsibility(5). Malingering is probably very rare today and care should be taken not to label this a cause as it will be counterproductive.

Psychogenic blackouts usually last much longer than syncope: patients may lie on the floor for many minutes; 15 min is not exceptional. Other clues are a high frequency of attacks in a day, and the lack of a recognizable trigger. Injury does not exclude psychogenic blackouts: trauma was reported in 50% in pseudoseizures (11).

The eyes are often open in epileptic seizures and syncope but are usually closed in psychogenic blackouts. Full documentation of attacks is needed to aid diagnosis. This is extremely difficult to organize. Parameters required to assess fully are posture and muscle tone (video recording or neurological investigation), BP, HR, and EEG. "Functional" disorders combine apparent unconsciousness with loss of motor control, while normal BP, HR, and EEG rule out syncope and most forms of epilepsy. Increased heart rate in relation to the apparent loss of consciousness has been suggested by Leiden group(12) as important recognizing feature in patients with psychogenic syncope. Same group has also shown that frequent, long attacks with the eyes closed during apparent TLOC are pathognomonic for PPS(13,14). Having objective physiological data is extremely useful in confirming the diagnosis. Giving a 'psychogenic' diagnosis to patients may be difficult, but objective data are invaluable. A psychological explanation may imply to patients that they are personally responsible or that they simulate attacks on purpose. However, psychogenic blackout patients see their attacks as involuntary, (as they probably are). Stressing that attacks are as involuntary as syncope or an epileptic seizure avoids stigmatization, avoids counterproductive clashes, and provides a therapeutic opening. A further feature of psychogenic blackouts is that many sufferers have also been sufferers of physical and sexual abuse in childhood(4). Many patients, perhaps all, with psychogenic syncope have had and may continue to have reflex syncope(15).

1.1.2 Abnormal Limb Movements and distinguishing different types of TLOC:

Generalized seizures produce TLOC and should be distinguished from syncope. Generalized seizures may be tonic, clonic, myoclonic, tonic-clonic, or atonic, depending on the predominant muscle activity observed during the seizure. A generalized seizure is a seizure 'whose initial semiology indicates, or is consistent with, more than minimal involvement of both hemispheres'(16) and this is naturally a very expert judgement to make a clinical diagnosis. Although loss of consciousness is not included in the definition, abnormal neuronal activity of major parts of both hemispheres generally results in loss of consciousness. Myoclonic seizures are the sole exception, as these seizures usually present without affecting consciousness. 'Tonic' refers to a sustained increase in muscle contraction lasting a few seconds to minutes. Myoclonus is defined as 'a sudden, brief (< 100 ms) involuntary single or multiple contraction(s) of muscle(s) or muscle groups of variable topography (axial, proximal limb, distal)', and is thus flitting or random. Clonic refers to 'a myoclonus that is regularly repetitive, involves the same muscle groups, at a frequency of ~2–3/s, and is prolonged', so that these movements are more repetitive and regular. Tonic-clonic refers to 'a sequence consisting of a tonic followed by a clonic phase'. Finally, atonic seizures are characterized by 'a sudden loss or diminution of muscle tone without apparent preceding myoclonic or tonic event lasting 1 to 2 s, involving head trunk jaw, or limb musculature'. Atonic attacks are rare and occur almost only in small children.

Both syncope and psychogenic blackouts are commonly associated with limb and facial movements(4). Critically, stiffness and myoclonus are not restricted to epilepsy. They were observed in 90 % of healthy subjects who intentionally provoked syncope(17).

Observations of such movements is reported in 12 %(18) to 46 % (19) of fainting blood donors. Abnormal movements mimicking a 'seizure' can be produced because of cerebral anoxia and can be easily confused with tonic-clonic movements of epilepsy. This is 'convulsive syncope' which has resulted in misdiagnosis of epilepsy. Lempert et al induced this phenomenon in healthy medical students while observing the effect through video cameras(17). Similar movements can be produced during tilt table induced Reflex Syncope (Zaidi et al.(3)). Caution is needed therefore when using the word 'seizure' to describe abnormal movements in TLOC, since many physicians would equate seizure with 'epileptic attack' potentially giving rise to a misdiagnosis. Interestingly, the ILAE does not restrict the use of "seizure" to epileptic attacks.

With the focus on careful history taking and clinical diagnosis, expert working groups have defined distinguishing features. ESC guidelines (2009)(11) have described some distinguishing clinical features between epilepsy and syncope (Table 1.3).

Table 1.3: Clinical features distinguishing epilepsy and syncope

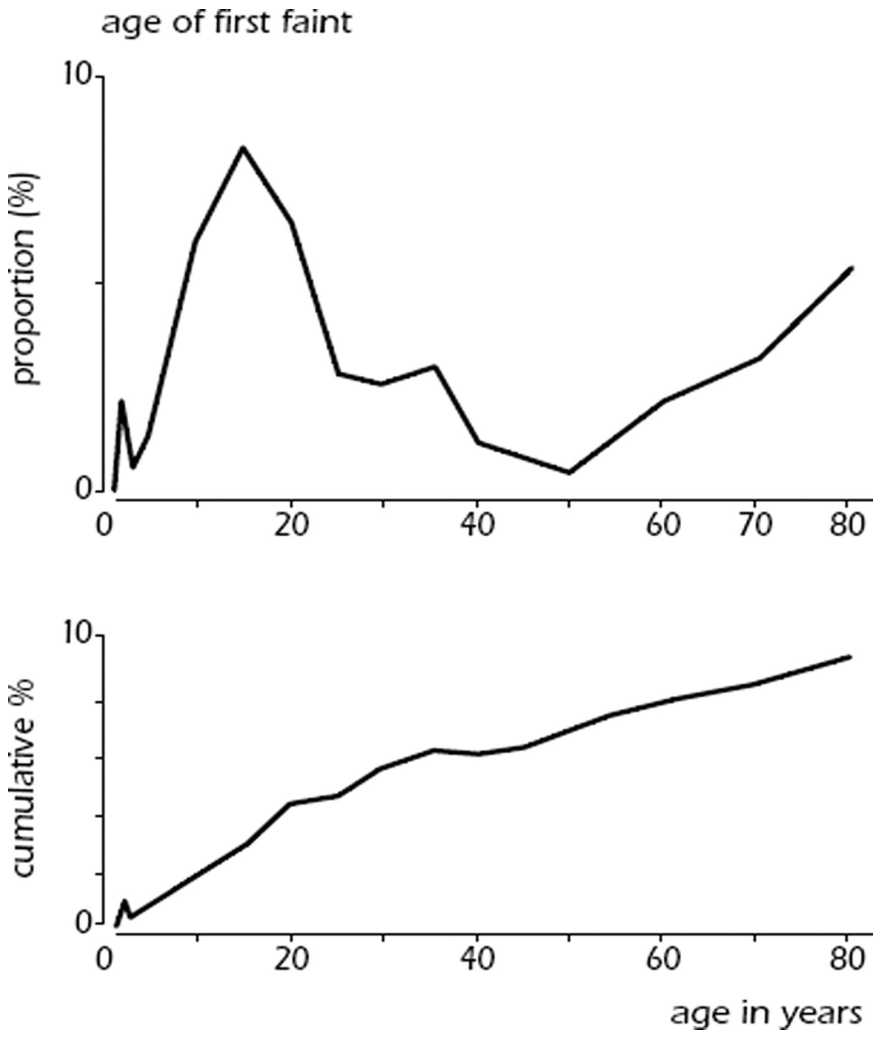
Clinical findings that suggest the diagnosis	Epilepsy likely	Syncope likely
Symptoms before the event.	Aura (such as funny smell)	Nausea, vomiting, abdominal discomfort, feeling of cold, sweating (neutrally mediated)
Findings during loss of consciousness (as observed by an eye witness)	Tonic-clonic movements are usually prolonged and their onset coincides with loss of consciousness.	Tonic clonic movements are always of short duration (<15 s) and they start after the loss of consciousness

	Hemilateral clonic movement Clear automatism such as chewing or lip smaking or frothing at the mouth (partial seizure) Tongue biting a) Lateral – epilepsy b) Tip –reflex syncope Blue face	
Symptoms after the event	Prolonged confusion Aching muscles	Usually of short duration Nausea, vomiting, pallor (neurally mediated)
Other clinic findings of less value for suspecting seizure (low specificity) Family history Timing of the event (night) Pins and needles before the event Incontinence during event (non-specific finding guiding neither toward epilepsy or toward reflex syncope) Injury resulting from event Headache after the event Sleepy after the event Nausea and abdominal discomfort		

1.2 Epidemiology of TLOC:

Syncope is common in general population and the first episode presents at characteristic age. Reflex syncope is very common at young age and there is high prevalence of first attack between 10 and 30 years of age, occurring at some time of life on 30-50% of individuals(20). In contrast, epileptic seizures in a similar age group are much lower (<1%) and syncope secondary to cardiac arrhythmia is even less common. Figure 1.4(21) showed distribution of age and cumulative incidence of first episode of syncope in general population.

Fig 1.3: Incidence of syncope in general population



The Framingham heart study(22) assessed 7814 participants and followed for an average of 17 years. Over 10% (822) reported TLOC. The incidence of a first reported event was 6.2 per 1000 person-years. The most frequently identified causes were vasovagal (21.2 percent), cardiac (9.5 percent), and orthostatic (9.4 percent); for 36.6 percent, the cause was unknown. The incidence of TLOC increases with age specially at 70 years. Cardiac syncope was likely to have recurrent episodes and only 17% of patients reported second events(22). There was no increased risk of cardiovascular morbidity or mortality associated with vasovagal (including orthostatic and medication-related) syncope.

In The Netherlands, Colman(20) studied the prevalence of TLOC in general practice and estimated it to be at 9.3 per 1000 encounter-years. The occurrence of syncope was twice as much in females compared to males. It was also much higher (up to 6%) in elderly(23). Recent studies report a remarkably constant frequency of TLOC in community based emergency departments with incidence around 1% of all emergency department attendances(24).

The prevalence of causes of TLOC depends not only on clinic settings and the age of the patient but also geographical factors and local care pathways, making a comparison between different studies difficult.

Table 1.4: Frequency of causes of syncope in general population, Emergency department and specialized clinical settings from recent studies(11)

Setting	Source	Reflex%	OH%	Cardiac%	Non-Syncopal TLOC%	Unexplained%
General Population	Framingham(22) studies	21	9.4	9.5	9	37
ED	Ammirati(25)	35	6	21	20	17
	Sarasin(24)	38	24	11	8	19
	Blanc(26)	48	4	10	13	24
	Disertori(27)	45	6	11	17	19
	Olde(28) Nordkamp	39	5	5	17	33
	Range	35-48	4-24	5-21	8-20	17-33
Syncope Unit (dedicated facility)	Alboni(29)	56	2	23	1	18
	Chen(30)	56	6	37	3	20
	Shen(31)	65	10	6	2	18
	Bringole(32)	65	10	13	6	5
	Ammirati(33)	73	1	6	2	18
	Range	56-73	1-10	6-37	1-6	5-20

Table 1.5: Frequency of causes of syncope according to age(11)

Age	Source	Reflex %	OH %	Cardiovascular %	Non syncopal TLOC %	Unexplained %	Settings
<40	Olde Nordkamp(28)	51	25	1.1	18	27	ED and chest pain unit
40-60 years	Olde Nordkamp(28)	37	6	3	19	34	ED and chest pain unit
<65years	Del Resso(34)	68.5	0.5	12		19	Cardiology Department
>60/65 years	Del Resso(34)	52	3	34		11	Cardiology Department
	Ungar(35)	62	8	11		14	Geriatric Department
	Olde(28) Nordkamp	25	8.5	13	12.5	41	ED and chest pain unit
>75years	Undar(35)	36	30	16		9	Geriatric department. In further 85 of patients, diagnosis was multifactorial or drug related

Above studies described in table 1.4 & 1.5, found syncope being the most common cause. Some general comments are however possible:

- Reflex syncope is the most common cause of syncope in any setting.
- Cardiac syncope is the second most common cause and higher prevalence in old age
- OH is frequent in the elderly and less frequent in those with age <40 years.
- Misdiagnosis of non-syncopal conditions is more common in emergency department and reflect the multifactorial complexity of the settings and urgency of the situation.

  A high rate of misdiagnosis and unexplained syncope justifies new approaches to evaluation and risk assessment.

  In UK, syncope is by far the most common cause of TLOC. Globally it accounts for around 3% of emergency room visits and up to 6% of general hospital admissions(25,26,36). Epilepsy is the commonest chronic disease but it is far less common than syncope. Stokes et al(37) reported its incidence as 50 per 100,000 with a life time prevalence of 0.5-1.0%.

  Psychogenic blackouts are much more common in young females(10) and usually represent previous stress, including a history of sexual abuse in childhood(38). Its incidence is estimated to be between 2 and 33 per 100,000 population(38). It coexists with epilepsy and diagnosis can be difficult(10). It is usually diagnosed after careful history and must be diagnosed by tilt testing with continuous beat-to-beat BP monitoring with heart rate and, if possible, an EEG(39).

1.3 Prognosis and importance of making a diagnosis of TLOC

In patients with TLOC, it is important to stratify their risk, to make a diagnosis and try to prevent recurrences. Correct treatment is only possible if the diagnosis is accurate. Misdiagnosis and delayed diagnosis have important implications. In Framingham Heart Study(22), risk of death was found to be increased by 31% among all participants with syncope and was doubled among participants with cardiac syncope, when compared with those without syncope. Syncope of unknown cause was associated with an intermediate increased risk of death while Reflex Syncope has a benign prognosis(22). In 2010. Fedorwoski et al(40) described orthostatic hypotension and its association with increased mortality. They found impaired diastolic response to be strongly associated with coronary disease. Sub-analysis of Sudden Cardiac Death in Heart Failure Study (SCD-HeFT)(41) and other similar reports(11,42) compared outcomes in patients with and without syncope. Patients typically had severe left ventricular systolic dysfunction (ejection fraction of ≤35%) of ischemic as well as non-ischemic aetiology.

They reported increased mortality, regardless of the treatment given (placebo, amiodarone or implantable cardioverter defibrillator).

Patient can get correct treatment only after correct diagnosis and the urgency of treatment depends on their correct risk stratification. However, at least 30% of adults and 40% of children treated for epilepsy are misdiagnosed(37,43–45), often because of misinterpretation of abnormal movements and urinary incontinence during attacks. A misdiagnosis of epilepsy can have very serious consequences. There have been instances of sudden death that have been shown to be due to unsuspected genetic heart disease, particularly where the congenital Long QT syndrome was present. Typically, in these cases, an ECG was not done or properly reported ante-mortem, but the patient had been wrongly diagnosed with, and treated for, epilepsy. In some cases, the Long

QT syndrome was demonstrated on the ECG channel of an EEG recording used to try and make the diagnosis of epilepsy. In another case, Long QT syndrome was diagnosed in the identical twin sister of a child who died suddenly 3 months after being diagnosed with epilepsy and treated with anticonvulsants. Globally, there are approximately <1-10 per 1000 person years sudden unexplained deaths in patients with epilepsy each year, and in many of these cases the cause of death is unknown(46). Other patients wrongly diagnosed with epilepsy may simply have reflex syncope with abnormal movements, not epilepsy, only to suffer the consequences of epilepsy for education, driving, childbearing and work, as well as the side effects of antiepileptic medications.

1.4 Methods of risk stratification

Many risk-stratification schemes have been suggested(11). In general, these schemes have been better at assessing risks where they were developed, rather than in other centres(11,47,48). An abnormal ECG, old age and history suggestive of cardiac syncope were found to carry worse prognosis at 1-2 year follow up. Several clinical factors to predict outcome have been identified in some prospective population studies involving a validation cohort and are summarized in Table 1.6.

Table 1.6: Risk stratification at initial evaluation in prospective population studies including a validation cohort(11)

Study	Risk factors	Score	Endpoints	Results of studies (Validation cohort)
S. Francisco syncope rule(49)	Abnormal ECG Congestive heart failure Shortness of breath Haematocrit <30% Systolic BP <90mmHg	No risk = 0 item Risk= ≥1 item	Serious events at 7 days	98% sensitive and 56% specific
Martin et al(50)	Abnormal ECG History of ventricular arrhythmia History of congestive heart failure Age >45 years	0 to 4 (1 point each item)	1-year severe arrhythmia or arrhythmic death	0% score 0 5% score 1 16% score 2 27% score 3 or 4
OESIL Score(51)	Abnormal ECG History of cardiovascular disease Lack of prodrome Age > 65 years	0 to 4 (1 point each item)	1 year total mortality	0% score 0 0.6% score 1 14% score 2 29% score 3 53% score 4
EGSYS score(52)	Palpitations before syncope (+4) Abnormal ECG/heart disease (+3) Syncope during effort (+3) Syncope while supine (+2) Autonomic prodrome (-1) Predisposing and/or precipitating factors (-1)	Sum of + and - points	2 years total mortality Cardiac syncope probability	2% score <3 21% score ≥ 3 2% score <3 13% score 3 33% score 4 77% score >4

1.5 Importance of Clinical Triage and Health-Economic Issues:

Amongst TLOC patients, about 90% will have syncope, but important minorities will have epilepsy or psychogenic blackouts or a very rare cause of TLOC or apparent TLOC. However, it is very easy for patients to be inadequately assessed clinically, to be misdiagnosed, and to be sent on the wrong care-pathway. If patients are embarked on the wrong journey, it is very difficult to start a thorough clinical history, risk-stratification and ECG. Therefore, appropriate clinical triage of TLOC patients is the first step in proper management, and should be available to every patient. TLOC triage sits in a space between “first responders" such as ambulance crews and emergency room staff, and referral for assessment by an appropriate specialist, such as a cardiologist or neurologist. Triage allows patients to be seen by the right specialist first time, and reduces the risk that omissions will occur or mistakes will be made. It also prevents unnecessary investigations and their financial implications. It is known that syncope has huge economic burden on the health care system. This is likely to reflect the fact that clinical triage and risk assessment, testing for a diagnosis and appropriate onward referral for specialist care are variable and delayed. Statistical data for England and Wales indicate 15 million emergency attendances a year to hospitals, with 1:200 cases being due to blackout (75,000 emergencies).(53) Elsewhere, syncope alone is widely reported to be responsible for 1–3% of emergency room visits and 3-6% of hospital admissions(54).

It is known that clinical evaluation and an electrocardiogram (ECG) give a diagnosis in 50–94% of syncope patients, and are far more cost-effective than complex testing e.g. with brain scanning, EEG and carotid Doppler imaging (55,56). T-LOC during recording of useful physiological data, such as ECG, blood pressure or EEG is very

unusual, and patients usually appear normal when they are subsequently evaluated. Often, diagnosis depends critically on information from an eyewitness. If possible, physician should call the witness by mobile phone. Witnesses are often well-known to the patient and are usually lay people and abnormal movements may be misconstrued as epilepsy. It is the physician's job to assess that. Hence the diagnosis and management of such patients continues to pose important diagnostic, therapeutic, and economic challenges(57).

Managing TLOC is costly. Local data collection by the Manchester Primary Care Trust prior to the start of our specialist nurse-lead Rapid Access Blackouts Triage Clinic showed that between April 2003 and March 2004, 305 patients (age: 65.6 ± 21.6 years) were admitted to the Central Manchester and Manchester Children's NHS Trust for Syncope and Collapse, (NHS Hospital Episode Statistics Code = R35). The mean length of stay was 7.61 ± 13.9 days at an average cost of £7500 (the cost is substantially more in 2016). All this cohort left the hospital without a diagnosis, and it was clear that their clinical triage and risk stratification was deficient.

Comparison of costs can be difficult due to differences between healthcare systems in different countries. In the USA, estimated total annual costs for syncope-related admissions, derived from the Medicare database, were US$2.4 billion, with a mean cost of US$5400 per hospitalization(58). In a US study by Calkins(59), a failure to diagnose Reflex Syncope clinically resulted in up to $16,000 of unnecessary diagnostic testing. If patients are not seen in the right specialty, unnecessary investigations will be done. This was noted by Pires et al(60). Costly low yield neurological tests were overused, higher yield cardiovascular tests were underused and untargeted use of specialist evaluations did not increase the rate of diagnoses. Pires et al(60) also suggested that, the increased use of specific tests directed by history and results of physical

examination could improve diagnostic yield and decrease the cost of evaluating TLOC, making the argument for appropriate clinical triage.

In a multicentre study performed in Italy(32), 929 patients evaluated according to usual practice were compared with 725 patients evaluated using a standardized guideline-based approach. In the usual practice group, the cost per diagnosis was €1753 ± 2326 per patient; it increased to €3506 ± 2729 for hospitalized patients. When compared with the usual-care group, the standardized-care group had a 17% lower hospitalization rate, 24% fewer tests performed, and 11% shorter in-hospital stay. Consequently, the mean cost per diagnosis was 29% lower (€1240 ± 521 $P = 0.0001$). In the UK(61), the overall cost per patient was £611, with 74% attributed to the costs of hospital stay. Cost per diagnosis of patients admitted to hospital was £1080.

The cost of misdiagnosis also needs to be considered. A report by the All Party Parliamentary Group on Epilepsy, chaired by David Cameron MP(62), found that 74,000 patients in England have been wrongly diagnosed with epilepsy and are wrongly taking antiepileptic drugs. This equates to over 100,000 patients in the whole of the UK. The cost of this was calculated at nearly £200 million a year, but the health, social, educational, employment and welfare costs are much higher for those misdiagnosed and their families(63). Data from neurological "First fit clinics" and geriatric "Falls clinics" established along NICE guidelines, have shown that many patients actually have syncope. When patients are seen in the wrong clinic, resources are wasted and there are delays, confusion and misdiagnosis(64–66).

Seventy per cent of UK patients receiving a pacemaker have presented with syncope or pre-syncope according to European Registry data, but the UK lags behind Western Europe in pacemaker implants, managing only 50-60% of the pacemaker implants of

Germany, France Spain and Belgium(67). It is very likely that the unstructured and unstandardised evaluation of TLOC, combined with a lack of early triage to the most appropriate specialist mean that patients who need a pacemaker are not getting one. This is confirmed by the findings of the National Pacemaker Group(68).

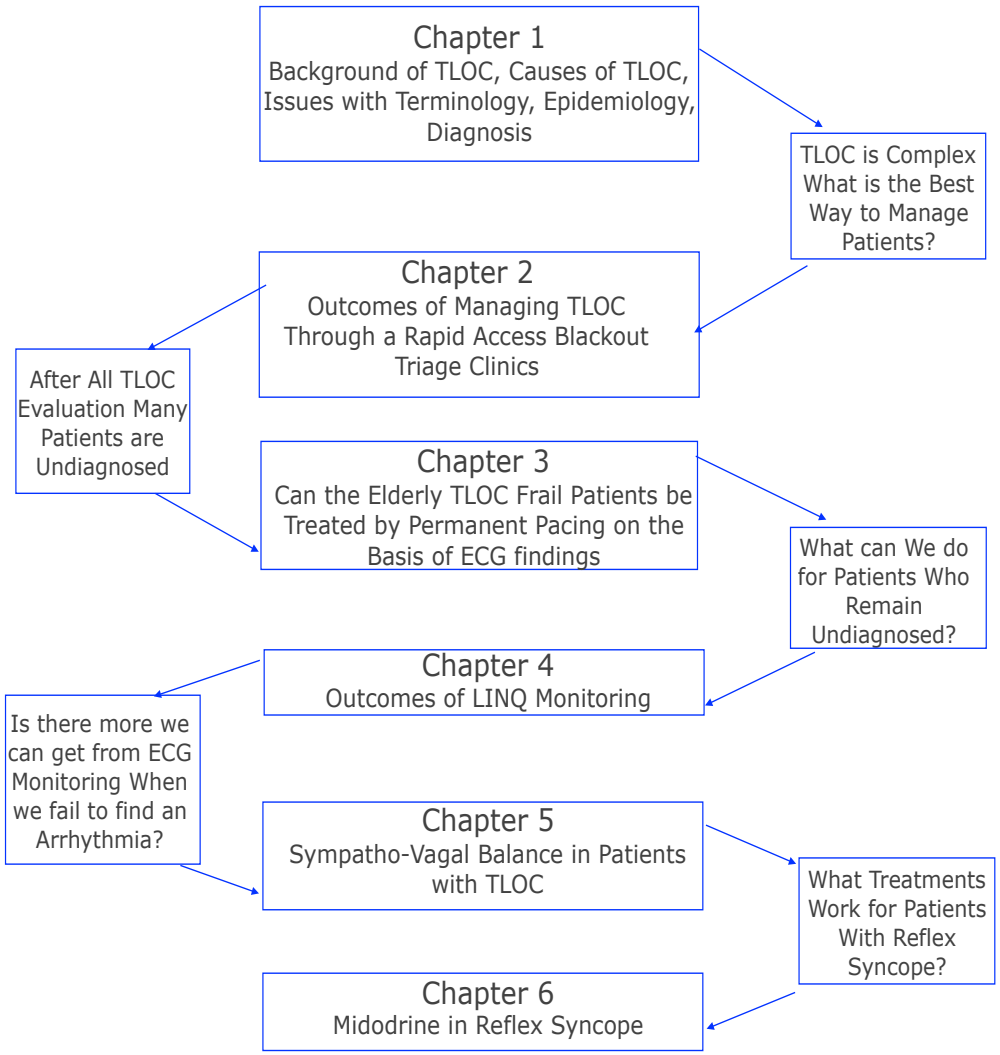
In order to address these shortcomings of care, we implemented a Rapid Access Blackouts Triage Clinic in 2007. This was run by specialist nurses in cardiac arrhythmias, epilepsy and falls, supervised by a junior cardiologist. Patients were seen in the clinic, evaluated using a web-based questionnaire, reviewed by the cardiologist and then discussed at a weekly MDT with a consultant cardiologist. We published our early experience in 2011(53). The aims of RABTC are;

1. To provide a care-pathway between first responder and specialist care
2. To undertake a detailed history, physical exam and 12 lead Electrocardiogram
3. To avoid unnecessary investigations
4. To undertake risk stratification to identify high risk patients
5. To make a diagnosis wherever possible
6. To refer onward to other specialties where necessary

1.6 Arrangement of Chapters in this Thesis

This thesis is arranged in Chapters following the introduction. The flow diagram below illustrates the way in which the chapters are arranged as a body of work. After the flow diagram, each chapter is briefly introduced.

Figure 1.4: Flow diagram of thesis



Below is the brief introduction of each chapter.

Project 1:

Analysis of the role and effectiveness of a specialist-nurse lead Rapid Access Blackout Triage Clinic.

The hypothesis was that effective triage between first-responders and specialist referral for TLOC/blackouts would best be managed clinically in a blackouts triage clinic. To provide evidence for this the results of risk assessment and follow up data were analysed. Since the RABTC was established, > 3000 patients have been assessed. Each patient has clinical evaluation and a 12 lead ECG. Patients are assessed by specialist nurses and then discussed with a supervising doctor for further management. An initial experience of just over 300 patients has been published(53) but without long term follow up. We have now analysed the data of over 1200 patients including their 6 year follow up and we will be assessing

a) Role of nurses in RABTC
b) Risk stratification
c) Outcome at follow up

Project 2:

Specific groups: pacing in elderly patients with blackouts with evidence of minor AV nodal disease.

A large proportion of patients in our RABTC are elderly. Often the clinical history is not as reliable as in young patients because of loss of memory for a TLOC episode(11). These patients may have more than one possible cause of TLOC, and cardiac syncope is much more likely than in younger patients and with much higher risks of recurrence, hospitalisation and death. This implies much higher health care costs. Elderly patients

commonly present with a putative "fall", when the real mechanism of TLOC was syncope and they are unable to recall the episode. These patients often have minor ECG abnormalities (first degree atrioventricular block (AV), hemiblocks). The full significance of these are not known in relation to TLOC and such ECG findings are not currently amongst accepted indications for pacemaker insertion. Nevertheless, early pacing in such patients based on the assumption of aggravated conduction problems during syncope could save recurrences, morbidity, hospitalisations and cost. The FUSE study(69) from Ireland detected 20% of falls in elderly patients are secondary to arrhythmia requiring permanent pacemaker insertion. In this chapter, we describe our experience of early pacemaker insertion in these circumstances.

Project 3:

High early yield of insertable ECG recorders in patients triaged through nurse-lead TLOC clinics.

This project is described in chapter 4. The RABTC relies on clinical evaluation and 12 lead ECG for assessment of patients as it carries highest yield. Despite this, there at least two thirds of the patients where diagnosis is uncertain and requires further investigations. Selection of appropriate tests is crucial to get the diagnosis. In hospitalized patients, a battery of investigations is frequently undertaken without justification instead of good clinical history in TLOC. These tests include echocardiogram, ambulatory ECG and blood pressure monitor, tilt tests, CT, EEG and MRI. All these tests have low diagnostic yield resulting in confusion and increasing cost(59,60). To make matters worse, many patients with low risk and likely reflex syncope are kept in hospital waiting for these tests to be done.

Many patients evaluated in the RABTC remain undiagnosed, but risk-stratified, after visiting the clinic. Such patients in the RABTC will usually be offered long term ECG monitoring with an insertable ECG loop recorder, (ILR), instead of such investigations, particularly when;

- the diagnosis is unclear
- the diagnosis is reflex syncope but patients are not responding to simple measures, and asystolic syncope is suspected
- there is a mild degree or uncertain degree of structural heart disease, and its significance needs to be evaluated

Project 4:

Flux in sympatho-vagal balance (SVB) derived from heart rate variability (HRV) in ECG recordings during video telemetry suggests "signature" of different causes of TLOC

ILRs do not give a diagnosis in all patients. An ILR's value is in achieving symptom/ECG correlation, and these devices contributed significantly in the management of TLOC(70). An ILR can disclose an ECG abnormality at the time of TLOC, but substantial numbers of patients have TLOC with normal ECG. A serious brady- or tachyarrhythmia is ruled out, but the objective of a diagnosis is still unmet(71). In >40% of cases, ECG may be non diagnostic during TLOC(72). The three causes of TLOC, syncope, epilepsy and psychogenic blackouts would require simultaneous recordings of ECG, BP and EEG to diagnose with certainty. This is only available in epilepsy video telemetry units, which are expensive and scarce. The hypothesis in this project was that derived ECG parameters that might help to give us a better understanding of causes of TLOC. Heart rate variability (HRV) can be

measured by time and frequency domain variations in RR interval. Different groups of patients with diagnosed TLOC were studied using HRV from the ECG to derive sympathovagal balance. Marginal interval was used to calculate marginality in these different groups and is presented in Chapter 6. This project was done in collaboration with the North West Neurosciences Centre Epilepsy Monitoring Unit where we recruited data from 43 patients. Patients were admitted and were monitored by video, EEG and ECG. Diagnoses were made based on continuous data during TLOC episodes. For comparison, data from patients in a tertiary syncope clinic with tilt-induced reflex syncope were also used.

Project 5:

Midodrine is Safe and Effective in the Treatment of Reflex Syncope

Reflex syncope is by far the most common cause of syncope. Syncope usually occurs due to global cerebral hypoperfusion. First line of treatment should be with non-pharmacological measures, including increased fluid and salt intake, regular exercise and physical counter pressure manoeuvres(73). These manoeuvres help improving blood pressure and include leg crossing, whole body tensing and squatting. These are effective in some cases. However, symptoms may persist and be disabling, and further treatment may be needed. Commonly used drugs are b-blockers and fludrocortisone. However, both treatments have been found to be ineffective in recent trials(74,75). Midodrine, an alpha-adrenergic agonist, has been used in patients who are not responding to non-pharmacological treatments(73,76–78). Two randomized control trial by Ward et al(77) and Cleveland clinic study(78) have shown beneficial effects of midodrine. In both studies, number of patients were low (16 and 61 respectively) and

their recruitment criteria was positive tilt test. In addition, follow up duration was also low for both studies (1 month and 6 months respectively).

So far, less is known about midodrine treatment, particularly in younger patients with reflex syncope versus older patients with orthostatic hypotension(79). In chapter 6, we will be describing our experience of use of midodrine in 195 patients who came through the RABTC.

Chapter 2

2. Analysis of the role and effectiveness of a specialist-nurse lead Rapid Access Blackout Triage Clinic.

2.1 Introduction:

Management of patients with syncope has always been challenging. It should be aimed to differentiate from other causes of blackouts such as epilepsy, syncope, psychogenic and metabolic causes(57). Hence prognosis depends on underlying cause(20,22) and varies from simple faint to life threatening conditions such as arrhythmias. A major difficulty with evaluating patients with TLOC rests on the fact that patients are usually asymptomatic by the time they are first seen. There has been significant heterogeneity in the way TLOC patients are managed. Many physicians take a safety-first approach and admit the patients. This is because of diagnostic difficulties and the fact that syncope may be a harbinger of sudden death among patients(80). Although the rationale of this approach is understandable, the presumption that in-hospital evaluation improves a patient's clinical outcome has never been demonstrated, rather it is a costly exercise with little reward.

The main goals of evaluation and the experience of Rapid Access Blackout Triage Clinics are given below.

2.2 Goals of evaluation of patients presenting with Collapse ?cause:

The RABTC aimed to see patients with collapse ?cause, to identify the cause, risk stratify and to give appropriate treatment. It targeted to see patients within two weeks of referral although, we found it to be 48±29 days because of inability to adjust increasing number of patients due to financial issues required to run the clinic and to support staff salaries. There are 4 main steps of evaluation of these patients and the RABTC also aimed to follow these steps (Fig 2.1);

1. *Confirmation of loss of consciousness*:

It should be noted that not all patients referred to these services have loss of consciousness. Information should be obtained either from the patient or from any witnesses as non TLOC causes are different (TIA, CVA, RTA, Intoxications and metabolite abnormalities).

2. *Identify cause*

Once it is confirmed that there was loss of consciousness, the next aim should be to identify the causes of TLOC. As mentioned previously there are three main common causes of TLOC (syncope, epilepsy, and psychogenic). A good history with help of a clinical examination and 12 lead ECG will give a diagnosis in more than half of the patients(81,82). It should also be kept in mind that there are overlaps in causes mentioned above and some people might have more than one cause of TLOC. Here when detailed and structured history will come into play. Value of history and examination is well established in diagnosing TLOC(81). A good history provides clues to whether a blackout is due to syncope or epilepsy and may also help in differentiating various causes of syncope and epilepsy syndromes(1). Meta-analysis by Linzer et

all(81) showed at least 45% of patients could be diagnosed with history, examination and a 12 lead ECG. By far the most important and beneficial test is the 12 lead ECG. It has proven high yield when combined with history and physical examination in diagnosing TLOC. This was also shown in FAST study by Van Dijk et al(83). In contrast to previous studies, they used 'high likely diagnosis' patient group in addition to 'certain' and 'no diagnosis' groups. If former two groups are combined, diagnostic yield can be as high as 63% while accepting some uncertainty which ultimately will lead to more investigations. Diagnostic accuracy in this situation was 88%. Finding the balance between avoidance of unnecessary additional testing and acceptance of some uncertainty about the initial diagnosis remains one of the most difficult tasks in evaluating patients with TLOC.

3. *Risk stratification of uncertain causes*

There still remain nearly half of the patients where the cause was uncertain. The aim should be to identify high risk patients as urgent investigations and ultimately treatment is required. Treatment can be delayed in low risk patients until investigations are done. Some bedside investigations may help in making a diagnosis like carotid sinus massage (CSM) and measurement of lying and standing BP to look for postural drop. CSM is done in patients >40 years and is considered to be positive if syncope is reproduced in the presence of asystole longer than 3 seconds and/or a fall in BP >50 mmHg. It should be performed in a controlled environment where continuous ECG and blood pressure monitoring can be done. Caution should be taken to look for contraindications like previous TIA or stroke within the past 3 months and in patients with carotid bruits (except if carotid Doppler excluded significant stenosis). In the absence of compensatory mechanism, blood pressure drops and can cause syncope(84).

Measurement of supine blood pressure (BP) and during active standing of at least 3 minutes can be helpful in these circumstances as mentioned in consensus document by Freeman et al(85). This test is considered to be positive if there is symptomatic fall in systolic BP from a baseline value ≥ 20mmHg or diastolic BP ≥ 10mmHg and if this phenomenon occurs without symptoms, it can be considered diagnostic. The RABTC measures postural BP in almost every patient and there are dedicated sections on our web based questionnaire.

A less commonly used test is a tilt table test. The RABTC has used this test initially to confirm suspected diagnosis of reflex syncope(86,87) and also to differentiate syncope with jerky movements from epilepsy(3). In recent times, it has been recognized that tilt-tests results are not reproducible. A negative tilt table response does not exclude the diagnosis of reflex syncope. The clinical significance of the type of response to tilt testing in predicting the behavior of BP and heart rate during spontaneous syncope has been questioned in different studies including ISSUE 2(88,89). It should be used to assess hypotensive susceptibility and not to diagnose vasovagal syncope(90). Tilt-testing remains valuable in assessing some conditions, such as delayed orthostatic hypotension, postural orthostatic tachycardia syndrome and psychogenic pseudosyncope, which remains undiagnosed after the initial evaluation(11).

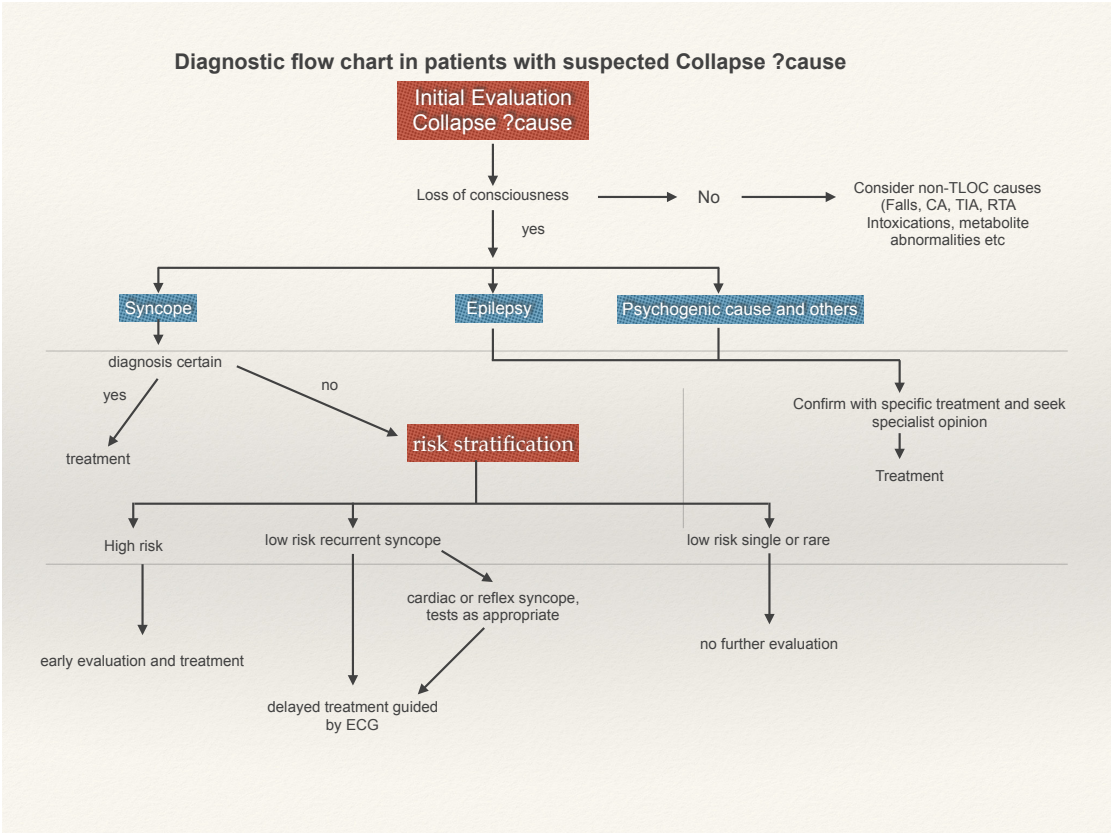
4. *Initiation of treatment and onward referral*

Life threatening conditions (arrhythmia and AV blocks) require urgent attention and treatment. There will be patients who have suspected epileptic seizures who should be referred for specialist management. As RABTC works in collaboration with neurology, a proportion of patients are referred for specialist advice for patients; where history is suggestive of epilepsy or there is history of brain injury. Orthostatic hypotension can

be associated with abnormalities in autonomic system. It should be appreciated and where appropriate referral should be made to neurology. Similarly, patients who suffer from migraine have a higher life time prevalence of syncope(91) although they do not usually occur together. Some patients, after neurological opinion, are referred onward for psychiatric evaluation of psychogenic blackouts.

An initial experience with the RABTC has been reported, but with very limited follow-up data to endorse the approach(53). In this chapter, a much greater number of patients with longer follow up is described. The aim is to demonstrate that patients with TLOC can be managed effectively and quickly, avoiding unnecessary investigations.

Figure 2.1: Summary of diagnostic flow chart in patients with Collapse ?cause



2.3 Multidisciplinary approach for assessment of TLOC patients:

Literature has also shown the beneficial role of nurses in epilepsy(92). It is also well recognised that elderly patients who suffer from 'falls' may actually have syncopal events. They have poor memory of the events and are usually unable to recall losing consciousness because of retrograde amnesia(1). Specialist Falls nurses bring their expertise to RABTC. Most patients with TLOC have syncope justifying the involvement of specialist cardiac nurses. The nursing staff therefore comprised specialist nurses in cardiology, epilepsy and falls.

2.4 Rapid Access Blackout Triage(RABTC) clinic in Manchester Royal Infirmary:

In Manchester Heart Centre, we adopted a multidisciplinary approach as mentioned in the previous section. The RABTC was set up in 2007 in order to assess the patients with blackouts as suggested by the National service framework (NSF) for heart diseases and department of health's 18th week commissioning pathway for blackouts. Although it was set up by the cardiology department, other specialties (Emergency department, Care of the elderly and neurology) became integrated within it. The unique point of RABTC is not to aim at only subset of syncope patients but patients with TLOC. Referrals were encouraged with collapse ?cause who were suspected to have a blackout/TLOC and who were suitable to have assessment in the outpatient settings. Primary care referrals were also accepted.

Main aims of RABTC are to

- provide a rapid clinical assessment with ECG within two weeks of referral
- assess and where possible diagnose the cause of blackouts

- triage patients into high and low risk groups and ensure early treatment for high risk patients
- decrease hospitalisation of low risk patients by providing early assessment
- use the clinical assessment to determine the cause of blackouts, investigate and treat accordingly and refer to other specialty where indicated.

RABTC team:

The team consists of three specialist nurses from arrhythmia, falls and epilepsy teams. Medical cover is provided by one of the cardiology doctors. There are two new clinics every week and up to 8 patients in each clinic are assessed by two nurses and one follow-up clinic accommodating 12-14 patients by a cardiology doctor (author). Each week an MDT (multidisciplinary team) meeting was held with a consultant cardiologist/electrophysiologist to discuss uncertain cases.

Triage consists of the specialist nurses taking a detailed history from patients. The nurses use a custom-designed web-based questionnaire designed in Manchester Heart Centre with embedded video clips to aid eye-witnesses, who are questioned wherever possible. All patients have a physical examination and 12 lead ECG, ensuring that all patients go through same assessment. These nurses then discuss the history and ECG with the supervising cardiology doctor (author) for further management plans. Further advice is obtained from the cardiology consultant supervising the clinic. Patients were risk stratified to high (Red flag) and low risk (Green flag). This risk assessment segmentation was built into the web-based questionnaire, (see Figure 2.3). Onward referral to another specialty like neurology or falls were made depending on the results of TLOC triage.

We assessed the impact of this approach on patient care including cost implications to the UK healthcare system and outcomes.

Figure 2.2: Specialist nurse (Falls) using the customised web based questionnaire

3 Specialist nurses: Falls, EP, epilepsy

Sr Sarah Collitt Bell, Arrhythmia/Electrophysiology Nurse

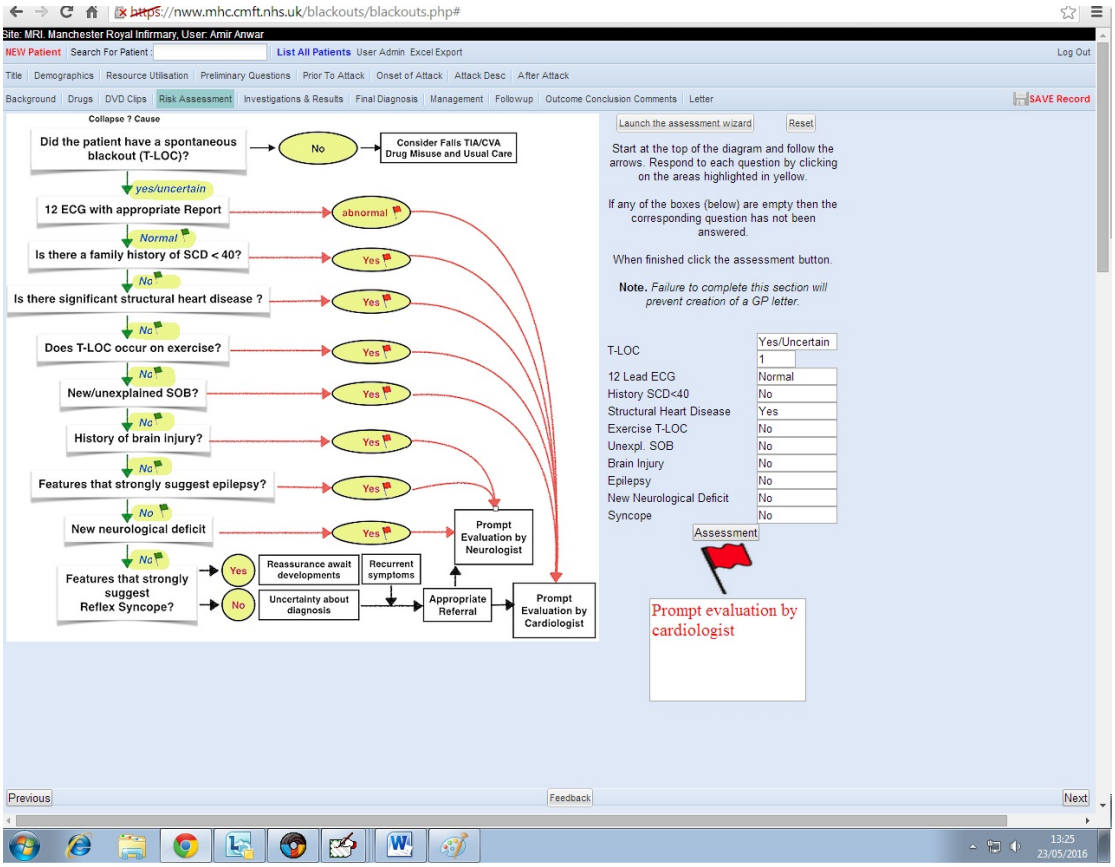
Sr Nicola Rice, Falls Nurse

Sr Pamela Iddon, Epilepsy Nurse

One of the assessment pages involves risk assessment, where required information are entered and the system automatically gives you the assessment (Figure 2.3). Risk assessment involves presence of high risk features and includes five cardiac and 4 neurological features (figure 2.4). This risk assessment tool was designed when RABTC was set up after literature review. If any of these features is present, patient is

classed as high risk and “red flag” ( )appears. If none of these features are present, patient is at low risk and is given green flag . No red flag = green flag.

Figure 2.3: Risk assessment page



Red flag features are given in Figure 2.4. Investigations were only done if strictly indicated, for example 24hr ECG monitoring if patients had daily symptoms. Echocardiography was done if the 12-lead ECG was abnormal, or if the heart sounds were abnormal. In these cases, there was a low threshold for use of an insertable ECG loop recorder for symptom/ECG correlation rather than other tests, (see Chapter 4). Assessment of outcome included diagnosis in the RABTC, diagnosis made from further

tests, and management following referral to other specialties. Follow up was based on case notes review and computer records.

Figure 2.4: Cardiac and neurology red flags features

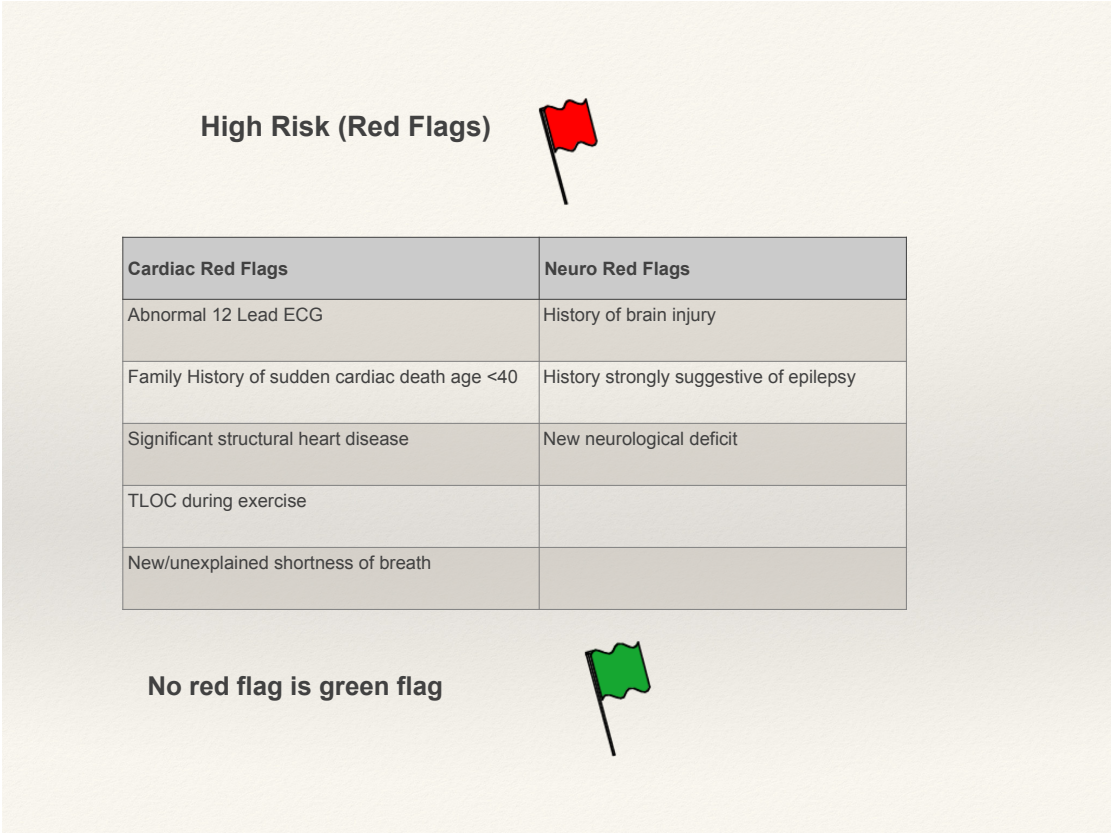
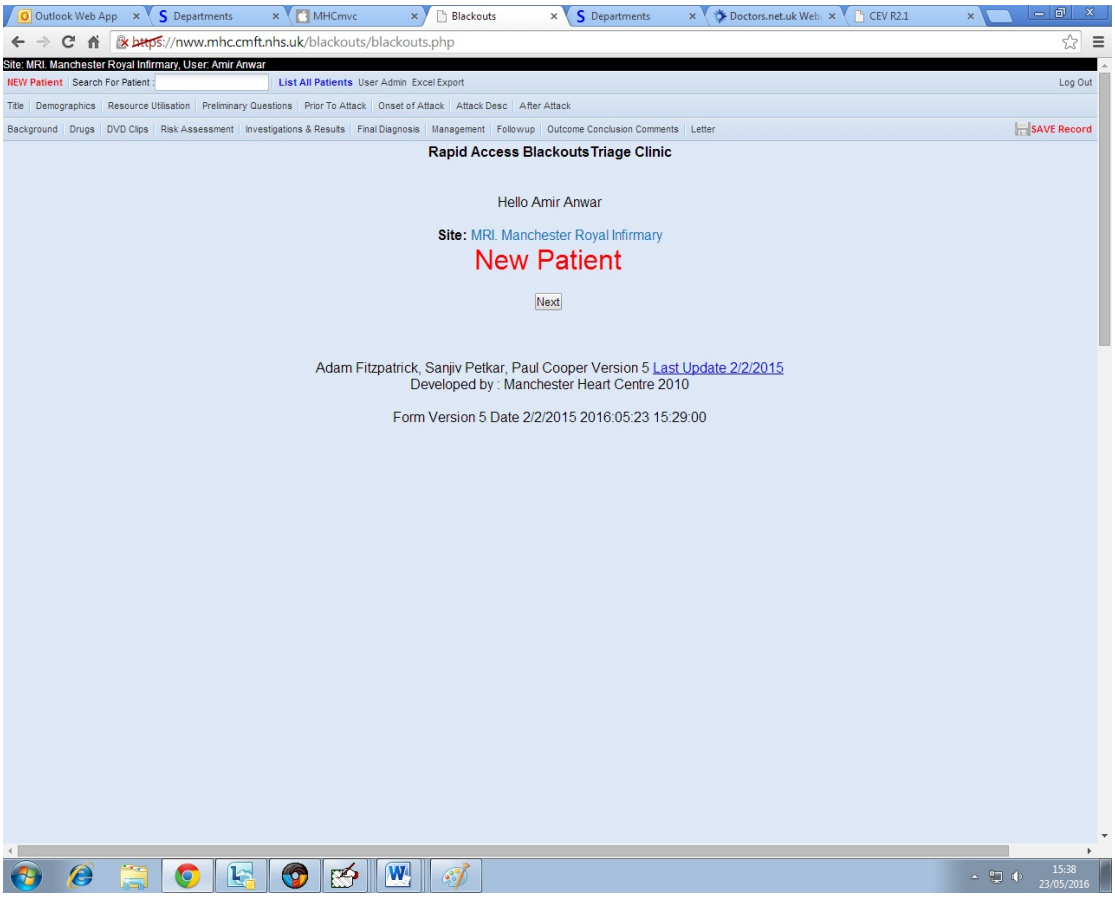


Figure 2.5: Screen shot of RABTC data base showing customised questionnaire



2.5 Methodology:

Over 3000 patients have been assessed in the RABTC. This study aims to analyse:

- The initial and follow-up performance of the built-in "Risk Assessment" in identifying high-risk (Red Flag) patients, and researching their outcomes at a minimum of two years' follow-up after initial assessment.
- It aims to analyse the clinical characteristics of a cohort of these patients, including: where they come from, who refers them, what is their symptom burden, and the proportions of syncope, epilepsy and psychogenic blackouts.
- The results of the long term follow-up.

2.5.1 Hypothesis/Primary question

Does the use of a risk assessment tool in Nurse Lead Rapid Access Blackout triage clinic differentiate between high/low risk patients?

2.5.2 Patient cohort

We analysed the data of 1226 patients who were seen between May 2007 and March 2014.

2.5.3 Data collection and analysis

Data was collected on an Excel spreadsheet from an electronic database and paper case notes.

Clinical judgment and assessment tools were assessed by reviewing patient's symptoms and diagnosis made at triage with subsequent visits. This also helped in measuring the effectiveness of existing tool. A consecutive sample of patients was taken who had at least 1 year of follow-up.

Analysis was made using SPSS and graph pad prism. Categorical variables are expresses in percentages and continuous variables (mean±SD, median and range) are presented where appropriate. Chi square test was used to calculate associated p values.

Outcome Measures

Comparison was made between initial and subsequent evaluation.

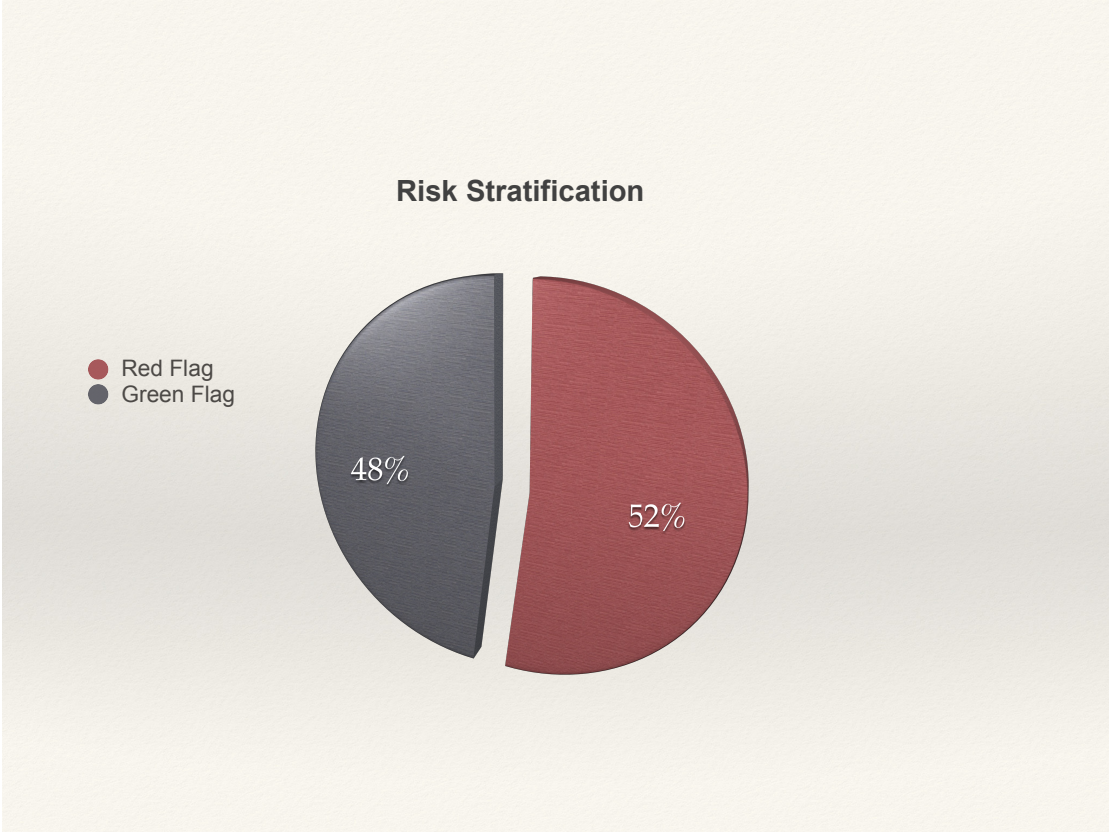
2.6 Study Results:

2.6.1 Patients:

Of 1226 patients, nearly 8 % (133) patients had an episode of collapse without losing consciousness. Patients were risk stratified using 'Red Flag' features mentioned above

in figure 2.4, into high and low risk. A small majority of patients had Red flags, 52% (Figure 2.6).

Figure 2.6: Distribution of high and low risk patients



Demographics:

There was wide variation in age in the RABTC. The age range was 16-94 years with mean age of 47±21 years. More than 60% patients were between 25-75 years (Figure 2.7). In keeping with other reports, a small majority of the cohort were female, 58% (Figure 2.8). Patients were referred from primary and secondary care. There was a gradual and steady growth in referrals from A&E from an initial rate of 4% in 2007, to over 25% by current date, and 22% over the whole period, (Figure 2.9).

Figure 2.7: Age range of cohort

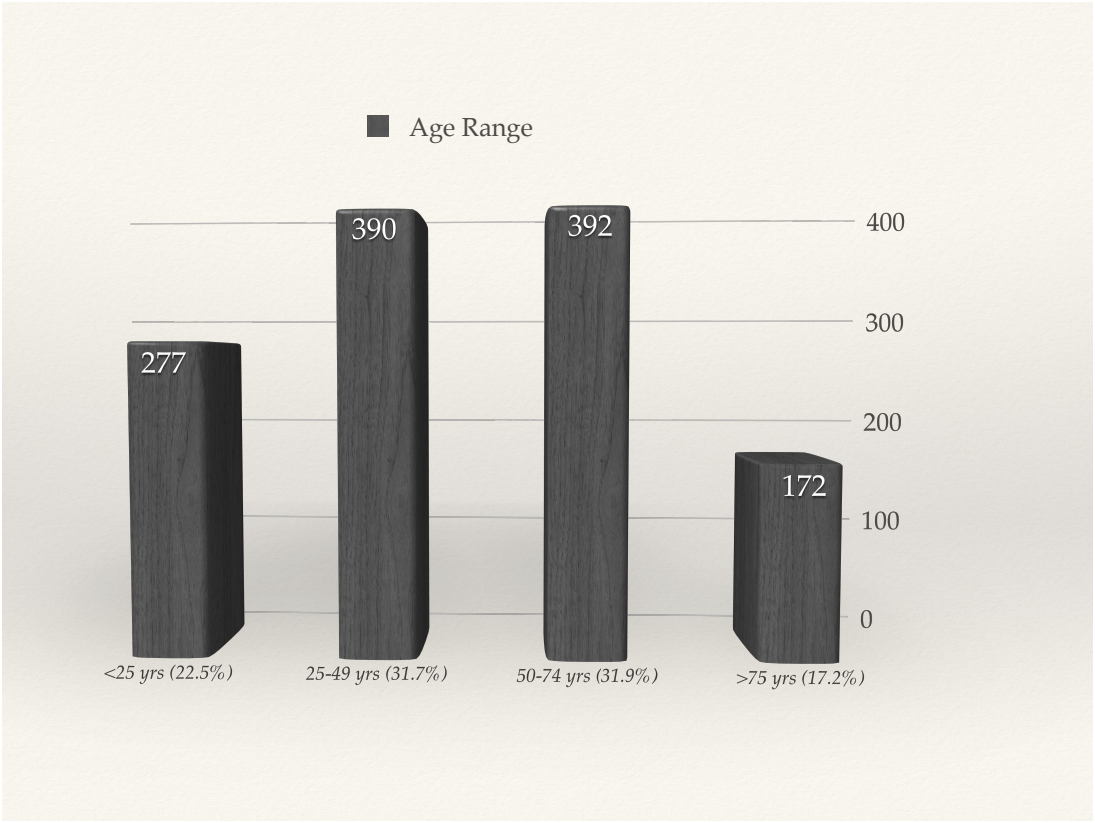
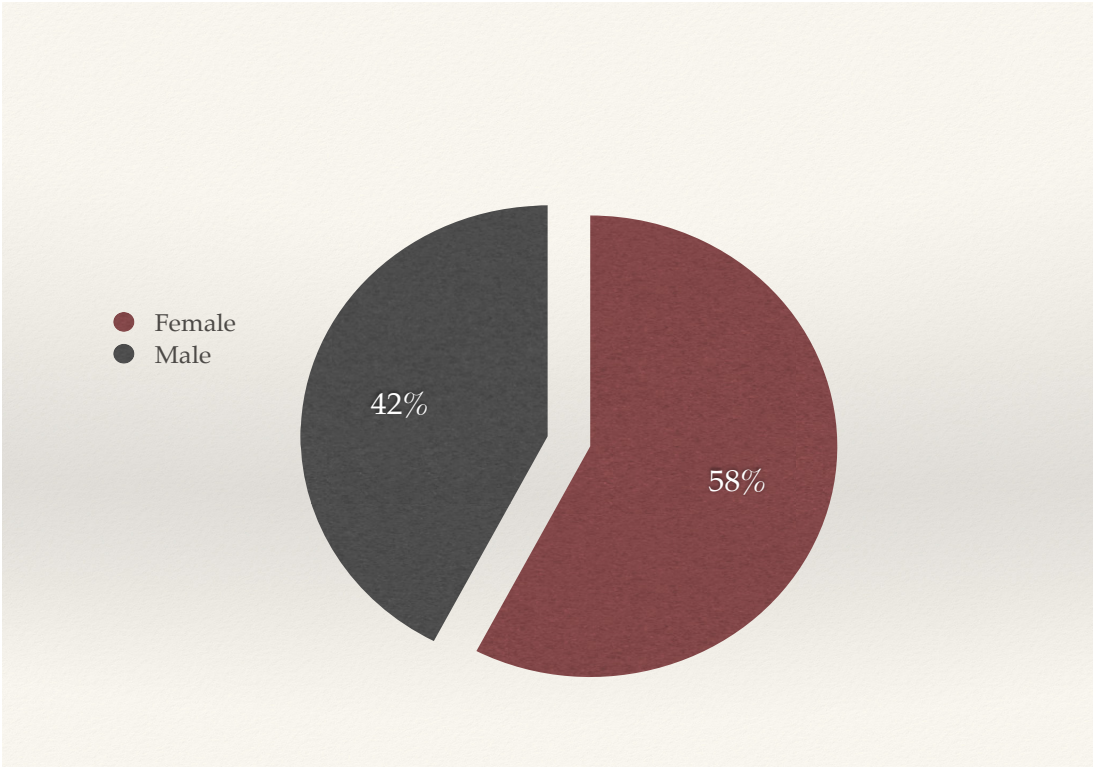


Figure 2.8: Gender distribution

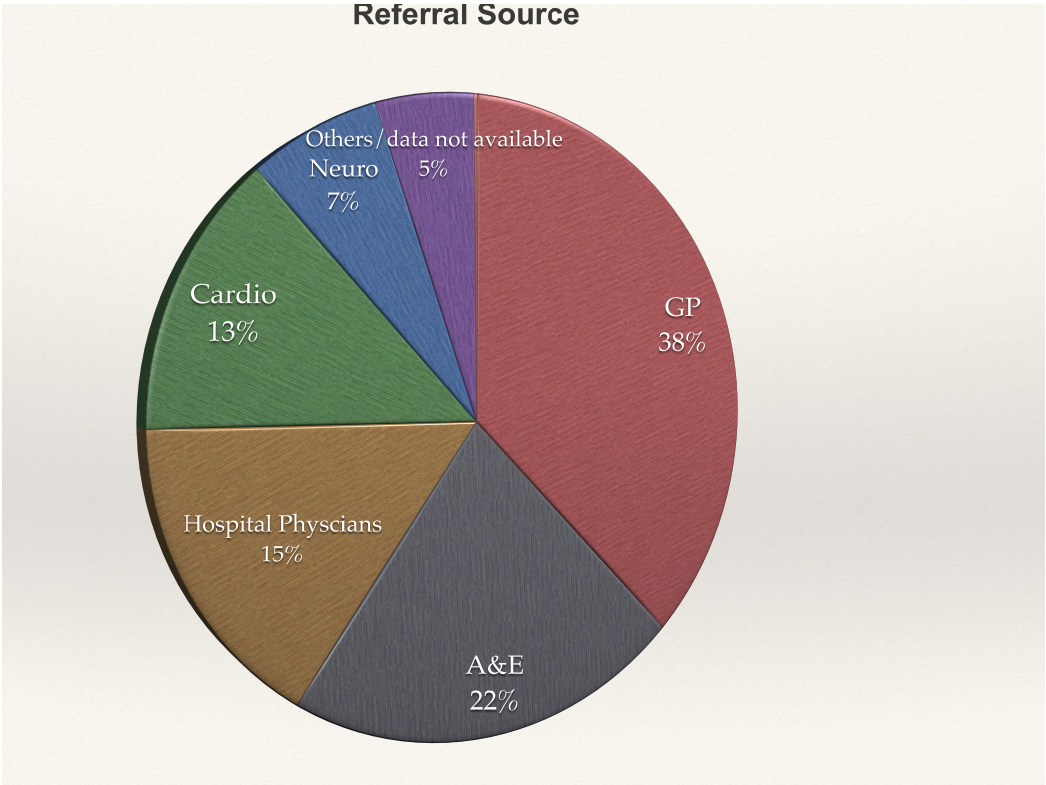


2.6.2 Referrals to RABTC:

RABTC received referrals from primary care as well as other specialties. The majority of the referrals received were from GPs followed by accident and emergency (A&E) department. Initially there were quite a few referrals from A&E but after more information via local and regional meetings we started to get an increasing number of patients from other sources. Primary care remains the highest source. From the electronic record, details of referral source for 5% of patients were not available. Figure 2.9 explains different percentages from main referral sources.

RABTC has expanded since it was established and we have two weekly clinics for new patients accommodating 8 patients each. In addition, a new dedicated follow up clinic was set up. A target of 2 weeks from referral to RABTC was planned and the average time was 48±29 days.

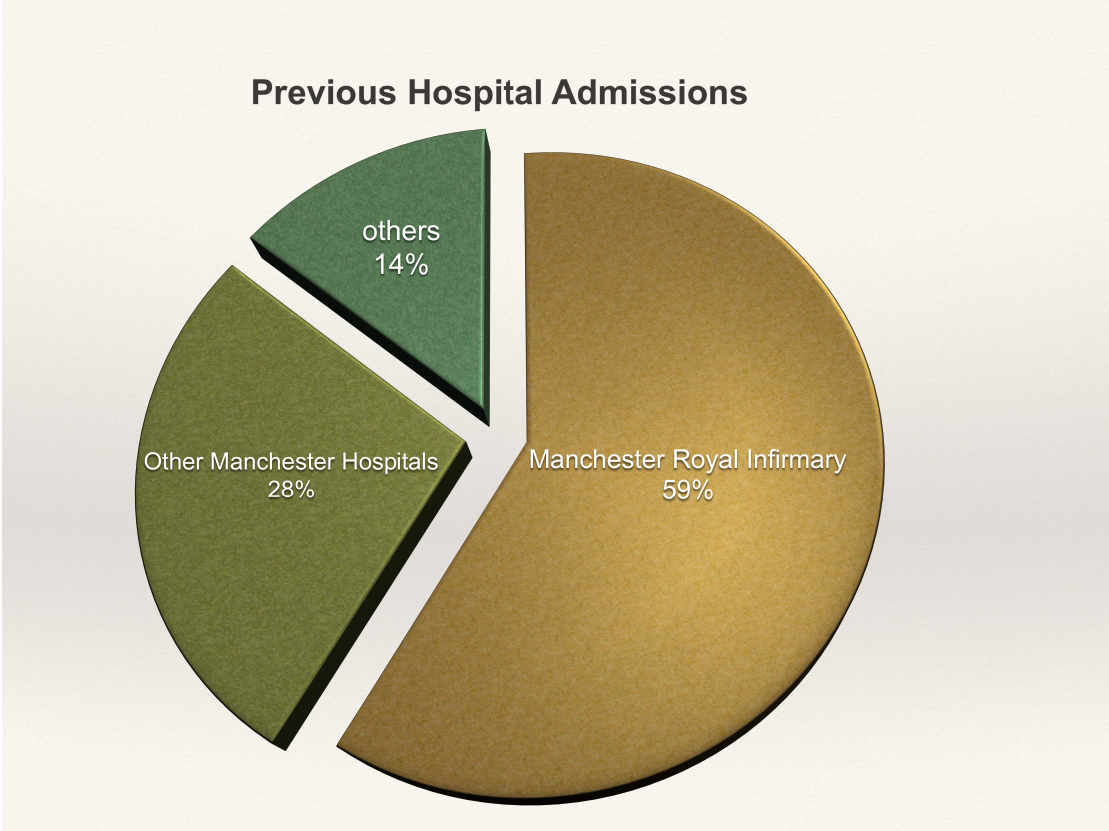
Figure 2.9: Referral sources



2.6.3 Previous Hospital admission

A significant proportion had previous hospital admissions. We found that 472 of 1226 (38%) were previously admitted with TLOC. These patients had typically had multiple investigations with no clear diagnosis despite multiple investigations. The admission profile is shown in figure 2.10.

Figure 2.10: Previous hospital admission



2.6.4 Initial assessment and risk stratification

The results of risk stratification, and the type of risk factor found are shown in Figure 2.11. 12 lead ECG abnormalities are described in table 2.1. An initial diagnosis was made in almost 60% of patients. Syncope was the most common cause and reflex

syncope was diagnosed in almost 32%. Importantly, cardiac syncope was found in 10% of patients. These are detailed in table 2.2.

Figure 2.11: Percentage of different Red flag features

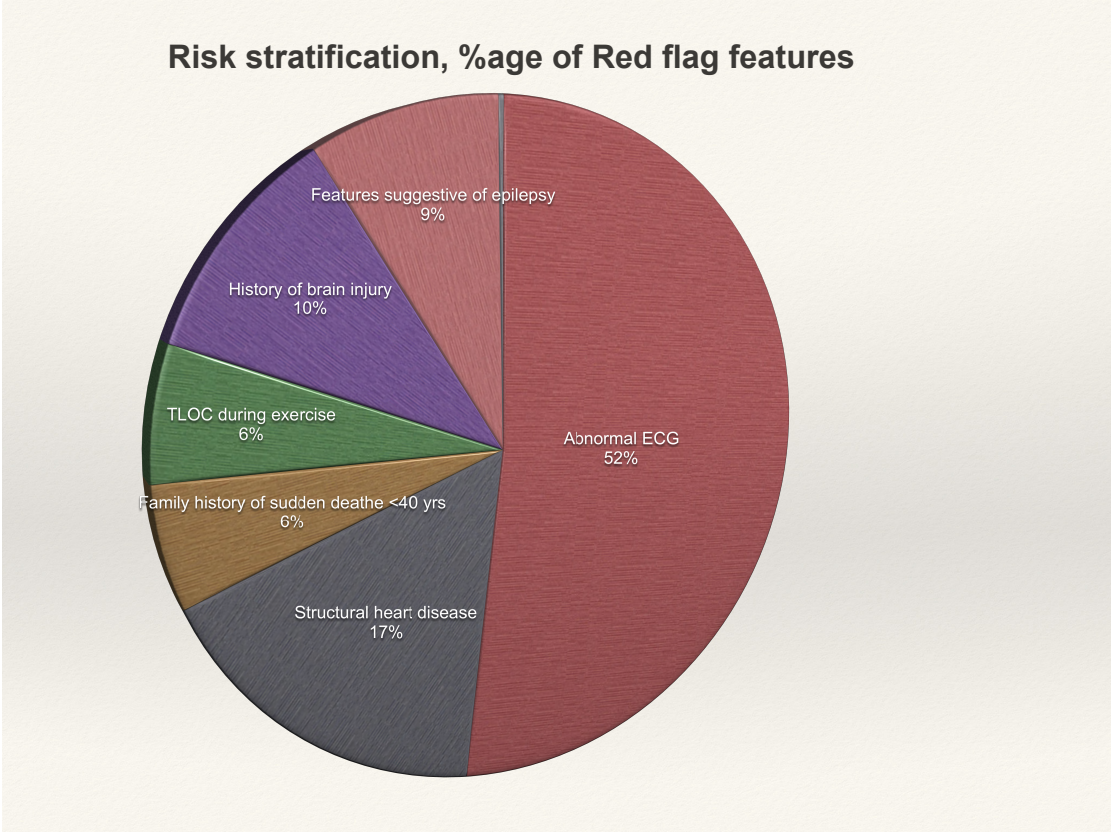


Table 2.1: ECG abnormalities in our cohort

ECG Findings	No of Patients	ECG findings	No of patients
Prolonged PR Interval >200 msec	79	Incomplete RBB	24
Sinus tachycardia	19	Suspicious of Brugada	5
Pre- excitation	8	Pathological Q waves (Previous MI)	35
Prolonged QT interval	16	IVCD	7
T wave inversion	39	LAD	41
Atrial Flutter	2	LBBB	27
Atrial fibrillation	27	LAH	9
Atrial ectopics	13	Poor R wave progression	21
Paced rhythm (Previous PPM)	5	ST segment changes	16
Left atrial enlargement	11	Sinus rhythm	593
Right atrial enlargement	4	Low voltage	13
Early transition of R in V3	12	RBBB+LAD	17
Voltage criteria for LVH	56	RBBB	42
Ventricular ectopic	46	Short PR Interval	5
Abnormal p wave morphology	5	RVH	7
Early repolarisation	10	Sinus arrhythmia	8
Sinus bradycardia	39	Trifascicular block	8

Table 2.2: Diagnosis after initial evaluation

Initial Diagnosis after RABTC assessment	Number of patients N =1226	High Risk N=637	Low Risk N=589	P value
Cardiac Syncope	115 (9.3%)	113 (17.7%)	2 (0.5%)	<0.001
Reflex syncope	391 (31.8%)	89 (13.9%)	302 (51.2%)	<0.001
Epilepsy	27 (2.2%)	27 (4.2%)	0	0.0043
Orthostatic Hypotension	43 (3.5%)	31 (4.8%)	12 (2%)	0.0071
Falls	19 (1.5%)	16 (2.5%)	3 (0.5%)	0.0046
Drug Induced	12 (1%)	9 (1.4%)	3 (0.5%)	NS
Alcohol Related	27 (2.2%)	13 (2%)	14 (2.3%)	NS
Cough syncope	6 (0.5%)	4 (0.6%)	2 (0.33%)	NS
NEAD	27 (2.2%)	8 (1.2%)	19 (3.2%)	0.01
Others	31 (2.5%)	9 (1.4%)	22 (0.33%)	0.009
Uncertain	528 (43%)	318 (49.9%)	209 (35.4%)	<0.001

2.6.5 Follow up and subsequent management:

Out of 1226 patients who were seen in RABTC between May 2007 and March 2014, 133 patients did not suffer from further loss of consciousness. There were more females than males and age range was range16-94 and mean age was 47±21 years. Nearly 26% patients lost to follow up. A large majority of these patients were young with diagnosis

of reflex syncope and were given life styles modifications advice during initial consultations. Average duration of symptoms was 26±59 months and average follow up duration was 15±20 months. Number of episodes of TLOC was 5.3±8 per 12 months. Follow up diagnoses are mentioned in table 2.3. The management of onward care after RABTC assessment is summarized in Table 2.4.

Table 2.3: Follow up Diagnosis

Follow up diagnosis	Number of patients N =1226	High Risk N=637	Low Risk N=589	P value
Cardiac Syncope	154 (12.5%)	151(23.7%)	3 (0.5%)	<0.001
Reflex syncope	519 (42.3%)	80 (12.5%)	439 (74.5%)	<0.001
Epilepsy	53 (4.3%)	44 (6.9%)	9 (1.5%)	<0.001
Orthostatic Hypotension	59 (4.8%)	47 (7.3%)	12 (2%)	<0.001
Falls	23 (1.8%)	16 (2.5%)	7 (1.1%)	NS
Drug Induced	22 (1.79%)	13 (2%)	9 (1.5%)	NS
Alcohol Related	27 (2.2%)	13 (2%)	14 (2.3%)	NS
Cough syncope	8 (0.6%)	5 (0.78%)	3 (0.5%)	NS
NEAD (Non epileptic attack disorders)	37 (3%)	8 (1.2%)	29 (4.9%)	<0.001
Others	25 (2%)	11 (1.7%)	14 (2.3%)	NS
Uncertain	299 (24%)	90 (14%)	209 (35.4%)	<0.001

Table 2.4: Different treatments offered in the RABTC

Follow up management	Number of patients N =1226
Treatment given	892 (73%)
Discharged to GP	406 (33%)
Drug addition	289 (23%)
Drug withdrawal	19 (1.5%)
ILR Insertion	205 (16.7%)
PPM Insertion	104 (8.4%)
ICD/CRT	6 (<1%)
EP study/Ablation	8 (<1%)
Referred for surgery	5 (<1%)
Life style changes	217 (17.6%)
Other specialty referral	139 (11.3%)
Rehospitalisation	127 (10%)
Cardiac related	26
Deaths	39 (3%)
Cardiac related	7 (all red flag)

In majority of the cases initial and final diagnosis remained the same. Follow-up outcomes suggested that the triage in the RABTC made a correct diagnosis in many patients where the initial diagnosis was uncertain in spite of extensive testing elsewhere. A comparison between initial and final diagnosis is shown figure 2.12 & 2.13. Outcomes suggested a high degree of accuracy in the diagnosis of reflex syncope,

cardiac syncope, orthostatic hypotension and falls (Table 2.5).

Figure 2.12: Initial and follow up diagnosis

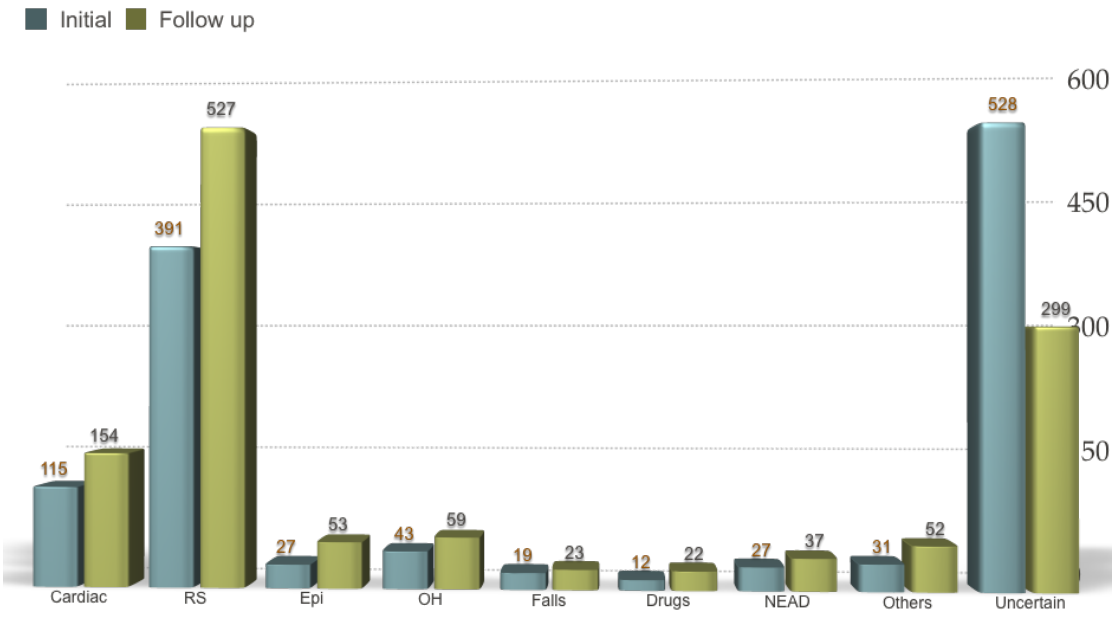


Figure 2.13: Comparison of initial and follow up diagnosis

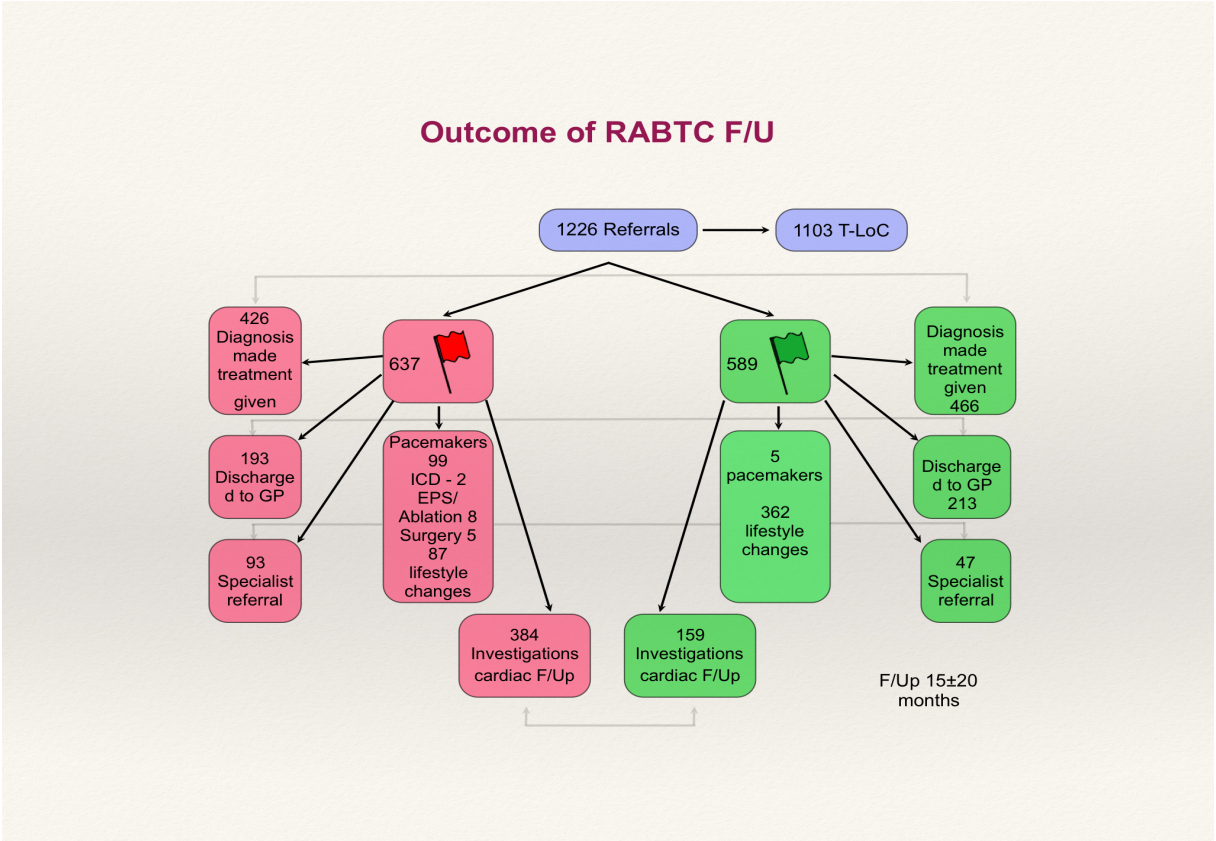


Table 2.5: Accuracy of initial diagnosis compared to final diagnosis

Initial Diagnosis	**Diagnosis on Follow up**							**Accuracy of initial diagnosis %**
	Reflex syncope (527)	Cardiac syncope (154)	OH (59)	Epilepsy (53)	NEAD (37)	Falls (23)	Uncertain (299)	
Reflex syncope (391)	353	3	12	2	6	2	13	90.2
Cardiac syncope (115)	5	103	3	0	0	0	4	90
OH (43)	4	1	38	0	0	0	0	88.3
Epilepsy (27)	3	0	0	17	5	0	2	63
NEAD (27)	6	0	0	0	19	0	2	70.3
Falls (19)	0	0	0	0	0	19	0	100
Uncertain (528)	156	47	6	34	7	2	278	53

2.6.6 Outcome of referral to other specialties:

As a part of the triage and uncertainties in diagnosis, one hundred and forty (11%) from total cohort were referred to different specialties. The majority (80%) of these referrals were made to neurologists. Follow up data showed 17 out of 27 suspected epilepsy patients had epilepsy (63%). A further 2 patients from initial reflex syncope group

(0.56%) were diagnosed with epilepsy, when symptoms continued and a late referral to neurology was made. Amongst 156 cases of uncertain diagnosis but possible epilepsy, 34 (22%) were diagnosed with epilepsy. Respiratory referrals were made for 3 cases of cough syncope with COPD, and one patient with sleep apnoea. All referrals to ENT lead to positive diagnosis and treatment. Results are explained in Table 2.6.

Table 2.6: Referral to other specialties

Specialty	Number of patients N =140
Neurology	113 (9.3%)
Falls clinic	4 (31.8%)
ENT	5 (2.2%)
Respiratory	8 (3.5%)
Stroke team	2 (1.5%)
Vascular surgery	1 (1%)
Endocrinology	7

2.6.7 Outcome of Device treatment:

110 out of 1226 patients had pacemaker or related device inserted, (9%). A large proportion (95%) had a permanent pacemaker. Two patients had an ICD and 4 patients a pacemaker for cardiac resynchronisation, (CRT). Forty-three patients were identified on the initial RABTC evaluation, (39%). Others, with uncertain diagnosis or indication, had investigations or prolonged insertable ECG monitoring before a clear device

indication was found, (see Chapter 4). Six patients had pacemaker implantation because of reflex asystolic syncope not responding to other measures. In the group treated with implantable devices, all but 11 patients had a Red flag on initial assessment including 6 who were paced for reflex syncope. All these 6 had an initial Green flag at triage. In the 60% of patients receiving implantable devices after the initial RABTC triage the insertable loop recorder played important role in identification of the need. In addition, a large number of patients >65yrs of age received a pacemaker for minor conduction tissue abnormalities found at initial triage without further investigation, and this is discussed in Chapter 3 in detail.

2.6.8 Rehospitalisation and Mortality:

472 (38%) patients had been hospitalised for TLOC before RABTC assessment. 127 patients (10%) had further admissions during follow up period. However only 26 (20%) were cardiac related admissions. Three were due to TLOC and had sinus node disease during corresponding TLOC captured on their ILR. There were a total of 39 (39/1226, 3.1%) deaths during follow up. Among these patients, 7 deaths were deemed to be from a cardiac cause according to death certification. These were related to heart failure and myocardial infarction. None of these deaths was associated with TLOC, and all these patients were red flag on their initial RABTC assessment.

2.7 Discussion:

There are many key points by which RABTC is different from other similar models. This is the largest study to date in terms of numbers of presenting patients with their follow up over a substantial period. RABTC acts as triage between first responder and the specialist referral hence it attracted patients with all causes of TLOC. Previous

models have described their experience with syncope only while RABTC dealt with patients with TLOC or blackouts and not the subset of syncope.

The RABTC is different from other models of care. The RABTC aims to triage TLOC cases between first responder and specialist care, and it attracts patients with varying causes of TLOC. Most published reports have described the experience with Syncope Clinics. Sometimes it is unclear whether the aim is to attract patients fitting the tight definition of syncope given in Chapter 1. The RABTC has patients with TLOC or blackouts and not the subset of syncope. RABTC stands out from other models because it has three experienced nurses one of which is an arrhythmia specialist nurse who has a cardiology background with further training in electrophysiology. The 'Falls specialist nurse' helps in assessing elderly patients. Since at least one third of patients with falls had TLOC with memory loss a falls specialist nurse brings helpful experience of dealing with elderly patients. It is common for patients seen in RABTC to report a "seizure" during their episodes. This may not be epilepsy but its recognition is extremely important to avoid misdiagnosing epilepsy. Reflex syncope often present with abnormal movements and this is the most common cause of misdiagnosis(3,93). Epilepsy specialist nurses in the RABTC contribute their expertise and experience (92).

Even if a diagnosis cannot be made immediately, risk stratification is important for outcomes. Over 50% of patients in this cohort had a Red flag at first assessment. Many of these patients had an abnormal ECG. In some cases, existing evidence helps guide management. For patients presenting with high degree AV block and TLOC, existing knowledge dictates that they should receive a pacemaker without further investigation but should have echocardiogram. Many other patients have either a "mild" ECG

abnormality, or a “mild degree” of structural heart disease. This poses a problem in deciding not just if a Red flag confers high risk, but how significant the Red flag is and how much of a risk the patient faces in the future. Further work on risk stratification and outcomes is needed to address these questions.

Despite many guidelines, the assessment of TLOC varies widely amongst physicians and hospitals. This often results in a lack of careful attention to the clinical assessment and the ECG, and inappropriate use of diagnostic tests. These in turn seem to result in many misdiagnoses, repeated episodes, admissions and cost. There appear to be good grounds for replacing this haphazard approach with cohesive and structured care pathways delivered in a dedicated service for TLOC. Since multiple specialties need to be involved, the service would ideally be multidisciplinary. However, the vast majority of TLOC cases have a cardiac or cardiovascular pathogenesis, and the seriously high risk cases all have cardiac syncope due to valve disease or life-threatening arrhythmias. It makes sense, therefore for the RABTC to be “cardiology-based” involving different specialty expertise as mentioned above. Also, the main reasons for wasted resources in TLOC care are lack of gold standard pathways and investigations(57). These should aim to get the right patients to the right specialist promptly, and the outcomes of this cohort of RABTC cases suggest this is done efficiently and with appropriate results. Furthermore, the management of psychogenic blackouts reflects the fact that sufferers have often had extremely traumatic experiences in their young lives and need very careful expert mental health handling(94–96). No such service exists in cardiology, but can be accessed, where available, via regional neurological referral. With dedicated TLOC/blackout clinics, management of these patients will be costly. There have been multidisciplinary teams described in syncope management units. These units are based

in Emergency department (ED) or in other inpatient or outpatient based practices. These clinics focus on recurrent syncope and mortality(31).

The idea of "syncope units" has also been supported in European society of cardiology (ESC) 2009 guidelines and the recommendations were that there should be availability of syncope experts and easy access to all referring physicians as well as preferential access to all contemporary cardiac investigations(11). There are numerous syncope models and risk stratification systems. Among different syncope rules are the San Francisco syncope rule (SFR)(36,97,98), STePS (Short term prognosis of syncope) study(99) and ROSE (Risk stratification of syncope in emergency department)(100,101). More recently in 2015, European Heart Rhythm association (EHRA) presented a pragmatic approach to the rationale and requirement for syncope units(102). This was based on specialist consensus, existing practice and scientific evidence and was also endorsed by Heart Rhythm Society (HRS). Similarly there were long term risk stratification studies such as Italian study *Osservatorio Epidemiologicodella sincope nel Lazio* (OESIL)(51).

The Boston Syncope Criteria (BSC)(103) were developed by Grossman et al. This was an ED based study recruiting 362 patients with a short follow up of 30 days. They showed this rule might be helpful to identify high risk syncope and near syncope patients(104). This pathway may be useful in reducing hospital admissions(105). Limitations of this study include single centred, small sample size and lack of long term follow up. In addition, external validation was not available.

The Calgary syncope scores have been introduced by R Sheldon(106,107) and its specificity was found to be much lower on external validation by Romme J(108) and

did not fare well in an elderly population compared to a young population (109). Plasek et al(110) compared OESIL, EGSYS-M (multivariant) and EGSYS-univariant and found all three scoring system capable of classifying cardiac syncope, reducing unnecessary hospital admissions and improving syncope risk evaluation. By means of uni- and multi-variate logistic regression, the most important independent predictors of a cardiac syncope were identified in a list of 52-item formulary. They found EGSYS-U to have high sensitivity and specificity. Martin et al(50) did two studies for derivation and validation of the risk classification system. They found that historical and ECG factors available at the time of presentation can be used to stratify risk of arrhythmias or mortality within 1 year in ED patients presenting with syncope. The Turkish group (Kayayurt K et al)(111) compared San Francisco syncope rule with EGSYS and OESIL. They developed a new Anatolian syncope rule and found to be equally good for short term risk stratification. No validation study was done.

In the *Syncope Evaluation in the Emergency Department Study* (SEEDS)(31), the investigators compared the outcome of the patients managed through a syncope unit with those evaluated through standard care. The central hypothesis of this study was that a syncope unit equipped with diagnostic resources that target common causes of syncope would improve the diagnostic yield and reduce the hospital admission rate compared with standard care (controls) at the conclusion of the ED evaluation. It was postulated that the reduction in hospital admissions would not negatively affect patient outcomes in terms of survival and recurrent symptoms of syncope. This was a prospective, single-centre, un-blinded randomized study, conducted at the Mayo Clinic in Rochester, Minnesota, a tertiary care medical centre. The syncope management unit was designed based on a multidisciplinary clinical practice model including ED physicians, electrophysiologists, allied staff and other specialists such as neurologists

when needed. After initial evaluation, intermediate risk patients were randomly assigned to standard care or to the syncope unit evaluation. They found that the novel syncope unit designed for this study significantly improved diagnostic yield in the emergency department and reduced hospital admission and total length of hospital stay although all-cause mortality and recurrent syncopal events were similar between the standard care patients and syncope unit patients(112). In a series of *EGSYS*(52) (*Evaluation of Guidelines in Syncope study*) studies including pilot *EGSYS*(27)*, EGSYS 2*(80,113) and follow up study of *EGSYS*(112), a hospital-based syncope unit was compared with standard care in different hospitals in Italy. The management of patients through a syncope unit was shown to be effective. The investigators concluded that the standardized approach improved the diagnostic yield, reduced hospital admissions and was less costly. The risk stratification scheme, by Canadian Cardiovascular Society review, provided standardised pathway in syncope management and perhaps is the most utilised approach(114).

Kenny et. al(61)., from Newcastle UK, proposed a model *Falls and Syncope Services (FASS)* to differentiate falls from syncope which comprised a specialised team. They audited all acute admissions to the general Internal Medicine service at a single hospital. After implementing FASS protocols, the admission rate for syncope and fall patients decreased from 10.6% at baseline to 8.2%. Although the length of hospital stay was unchanged but readmission (30-day) rate decreased from 12% to 0%. Importantly, the messages were broadcast, and appropriate use of clinical investigations and management strategies improved. The investigators concluded that the easy-to-use algorithms could improve clinical practice in this patient population. The FASS model was subsequently used in outpatient settings and found to be helpful in making early

diagnosis, preventing unnecessary investigations and hospital admission and eventually reducing cost.

Effect of syncope unit has been studied in Sweden by A Fedorowski(115) (Syncope Study of Unselected Population in Malmo-SYSTEMA I). They established that a systematic approach to patients presenting with unexplained syncopal attacks considerably increased diagnostic efficacy and accuracy. Potential syncope diagnoses have a tendency to overlap and show diversity in demographic, clinical evaluation, and pharmacological determinants. This unit focussed on TLOC and not on syncope which is also the approach of the RABTC(53).

As clinical practice, expertise and patient demographic vary in different areas, these syncope models may not produce consistent findings. The EaSyAS (Eastbourne Syncope Assessment study)(116) found that despite widespread use of a syncope protocol, unnecessary admission and investigations do still occur. Similar findings were also found by an Italian group in 2005(117). The common themes of these reports are a small number of patients studied and short duration of follow up. They aim to deal with syncope but it is unclear to what extent they see TLOC cases. They do not aim to provide basic clinical triage, and ECG and a risk stratification, whereas the value of history and physical examination along with 12 lead ECG for TLOC patients is well known(81). Our study is the largest study with the longest follow-up and the only study of TLOC patients.

Diagnostic accuracy in different studies has been variable. Linzer et al(81) showed that good clinical evaluation and 12 lead ECG can make diagnosis in up to two thirds of the patients. In "StePS(99) study", the accuracy of original diagnosis was 76%. In the "FAST study"(83), attending physicians could make a diagnosis, based on initial

evaluation, in 63% of patients with TLOC, with an overall diagnostic accuracy of 88%. In comparison, our study showed overall diagnostic accuracy of around 80%. Diagnostic uncertainty was around 23%, with main reason being patients lost to follow up. Other studies show diagnostic uncertainty in the region of 13-54% with only one up to 5%(32), but without detailed follow up and validation.

A multidisciplinary approach to TLOC is important. The RABTC has collaborations with different specialties for prompt evaluation when required. One hundred and forty (11%) from the total cohort were referred to different specialties. A majority (80%) of these referrals were made to neurologists. A majority of these patients had an uncertain diagnosis and nearly 50% secured a diagnosis following referral. No other published study has reported the outcome of referral to different specialties.

A significant number of RABTC patients deemed to require a pacemaker or device implantation. Pacemaker implantation rates in the UK lag far behind Western European countries. At the same time, 70% of patients receiving a pacemaker in the UK do so for reason of syncope or pre-syncope, according to the European Pacemaker Registry. It is likely therefore, that many deserving candidates for pacing are suffering TLOC, but are not being brought forward for a pacemaker in a timely fashion. The National Pacemaker Survey team have highlighted this deficiency, and it is clear that this arises from a failure of medical teams to identify indications for pacing. Our high rate of pacemaker success shows that more deserving candidates for pacing could be identified through a dedicated service such as the RABTC. In our study, of 106 patients who received a pacemaker, 43 were identified on initial consultation. Failure to identify indications for pacing inevitably result in delays and recurrences, admissions and higher

costs of care. An additional 39 patients had indications on their loop recorder findings. All these patients had Red flags on their risk assessment at triage but did not have convincing ECG abnormalities. In 6 patients, there was an initial diagnosis of reflex syncope, and initial Green flag risk. Unresolving symptoms at follow-up lead to ILR insertion, and these patients later showed reflex asystolic syncope and received pacemakers. Pacing for reflex syncope is controversial. However, some good evidence exists. A meta-analysis(118) and ISSUE 3(119) study showed a beneficial effect of pacing in reflex syncope in patients >40years, identified through ILR symptom/ECG correlation. However, no data are available in younger patients, and 4 of these patients were <40 years. These patients showed a significant improvement in syncope burden but in some symptoms are not fully resolved. This relates to continuing vasodepressor components during syncope which pacing cannot correct. This phenomenon has been highlighted in the literature(11,11,90).

RABTC care reduced rehospitalisation significantly (38% to 10%) with anticipated savings in healthcare cost(99,103). No TLOC related death was discovered. Overall mortality, at 3%, was less than published data.

2.8 Conclusion:

The RABTC provides structured clinical assessment and an ECG by nurses in a cardiology-base for TLOC, before specialist referral where appropriate. It is a rapid, cost-effective and efficient way of assessing patients using a custom web-based assessment tool/database, minimising the training required while allowing comprehensive case records. The RABTC makes a quick and accurate diagnosis, limiting unnecessary investigations but providing appropriate onward referral. Hospital

admission for TLOC appears to be reduced after assessment. The overall impact on costs of triage for TLOC using this model cannot be stated with certainty on these data. However, several areas for savings can be identified. Hospital admissions fell. Patients did not get a swath of unnecessary investigations. Access to the RABTC, while not achieving the 2 week target, was fast, and much better than for conventional outpatients where nurses are not used to deliver assessment. Such rapid access should limit the potential for further TLOC while patients wait. A significant effect can be seen in the growth of A&E referrals from a low rate of 4%, to around a quarter at current status. This may reflect willingness to trust a rapid nurse-lead triage rather than calling the medical team and "risking" admission. Other impact includes the emphasis on avoidance of the misdiagnosis of epilepsy and attendant financial and social costs. Widespread use of the blackouts tool could provide the UK NHS with a performance map. A number of other UK centres are using the web-based tool, which is available using a hospital code, a user account and N3 connection (a secure NHS network). For example, nurses in Middlesbrough run one central and several satellite clinics, have 19 user accounts, and have seen over 4000 patients.

More information is needed about the meaning of certain non-specific ECG abnormalities. An RABTC may reduce hospital admissions, with risk stratification reducing costs, but more data are needed to confirm this.

Chapter 3

3. Specific groups: pacing in elderly patients with blackouts with evidence of minor AV nodal disease.

3.1 Introduction:

In chapter 1 & 2, we have discussed overall management of patients with transient loss of consciousness (TLOC). We see a large proportion of elderly patients in the RABTC. The incidence of syncope increases with age, and 1 in 3 elderly patients suffer from syncope. The Framingham heart study(22) described incidence of TLOC as 6.2 per 1000 person-years. Some studies have reported even higher incidence(120) and it increases with age until at 70 years of age it has doubled. The most common causes of syncope in the elderly are orthostatic hypotension (OH), reflex syncope and cardiac arrhythmias(121,122). Different forms may often co-exist in a patient making diagnosis difficult but cardiac syncope carries the worst prognosis(22) and is likely to be recurrent.

In evaluating TLOC, the history and physical examination, along with 12 lead ECG give the highest yield(81) but may be less reliable in the elderly because they often have a poor memory for TLOC episodes(123). It is also well recognised that elderly patients who suffer from 'falls' may actually have syncope, but they are unable to recall losing consciousness because of retrograde amnesia(11). At least 30% of blackouts in patients >65 years present with falls without memory for the TLOC event(6). To make things more complicated, elderly patients are often living alone or in small households, and

more than two thirds of blackouts in the elderly are not witnessed. This may increase the number and duration of hospitalizations and hence raising health care costs(124). Bhangu et al studied the role of ILR and demonstrated at least 20% of unexplained falls secondary to cardiac arrhythmia (125). They concluded that patients with cardiac arrhythmia are more likely to have future falls.

Both American(126) and European guidelines(11) have recommended 12 lead ECG in evaluating TLOC. In elderly patients, the ECG might show some relatively minor conduction tissue abnormality, such as first degree atrioventricular (AV) block (PR interval >200msec, which conventionally may not convincingly explain the TLOC episode. Moreover, first degree AV block is not amongst the indications for pacing as evident from ESC guidelines(127).

Figure 3.1: Indications of pacing (ESC guidelines(127))

Recommendations	Class	Level
1) Sinus node disease. Pacing is indicated when symptoms can clearly be attributed to bradycardia.	I	B
2) Sinus node disease. Pacing may be indicated when symptoms are likely to be due to bradycardia, even if the evidence is not conclusive.	IIb	C
3) Sinus node disease. Pacing is not indicated in patients with sinus bradycardia which is asymptomatic or due to reversible causes.	III	C
4) Acquired AV block. Pacing is indicated in patients with third- or second-degree type 2 AV block irrespective of symptoms.	I	C
5) Acquired AV block. Pacing should be considered in patients with second-degree type 1 AV block which causes symptoms or is found to be located at intra- or infra-His levels at EPS.	IIa	C
6) Acquired AV block. Pacing is not indicated in patients with AV block which is due to reversible causes.	III	C

Other conduction tissue abnormalities that are often found on the 12-lead ECG in elderly patients include; left axis deviation (LAD), left and right bundle branch block (LBBB, RBBB) and LAHB (left anterior hemiblock). In electrocardiography, left axis deviation (LAD) is a condition where the mean electrical axis of ventricular contraction of the heart lies in a frontal plane direction between −30° and −90°. This is reflected by a QRS complex positive in lead I and negative in leads aVF and II. LAHB is caused by defective anterior half the left bundle and ECG findings include left axis deviation and negative QRS complexes in inferior leads (II, III, aVF) on ECG. However, these are not considered justifiable reasons for taking action without more investigations. In the ISSUE(128) study ILRs were used to show that one or more prolong pauses were mainly due to sinus arrest in around third of the patients with isolated syncope group as well as tilt positive group and the most frequent mechanism was bradycardic reflex. The ISSUE group investigators also showed that in patients with bundle branch block, syncope is associated with prolong asystolic pauses, mainly attributable to sudden onset paroxysmal AV block(129).

Whilst the impact of bundle branch block on the resting ECG can lead to pacing without further investigation, the significance of first degree AV block is not known. If first degree AV block proved to be a significant marker for paroxysmal high grade AV block with syncope, early pacing would spare elderly patients unnecessary investigations and delays before treatment, and unnecessary hospitalisations for recurrences. Furthermore, studies have shown that a prolonged PR interval is associated with increased risk of atrial fibrillation (AF), pacemaker implantation and all cause mortality(130,131). With this in mind, we studied the effect of pacing in elderly patients (>65 years) with minor AV conduction disease (prolonged PR interval and hemiblocks)

who were presented to our Rapid access blackout triage clinic (RABTC) with episodes of TLOC. These patients would not usually be offered pacemaker implantation without further investigation. Typically, this would involve external ambulatory monitoring, which could delay treatment.

3.2 Methodology:

Patients attended a Rapid Access Blackout Triage Clinic (RABTC) from different referral sources. These patients were assessed by specialist nurses using the web-based tool and risk stratification as described in previous chapter. From our cohort of RABTC we first calculated the number of patients >65 years who attended the clinic. We then counted the number of patients who were offered a pacemaker and noted the indications for pacing among these patients. For the purpose of analysis, we used those patients who had a pacemaker implantation on the basis of history and 12 lead ECG only with no further investigations. We then compared the hospitalisation pre- and post-pacemaker insertion and noted any deaths over follow up duration.

The data was collected retrospectively from hospital electronic records. This also included information from pacemaker follow up clinics. Microsoft Excel for Mac 2011 and Prism version 6 was used for data analysis. Non parametric tests were used for analysis and associated ρ-value was calculated using Wilcoxon signed-rank test.

3.3 Results:

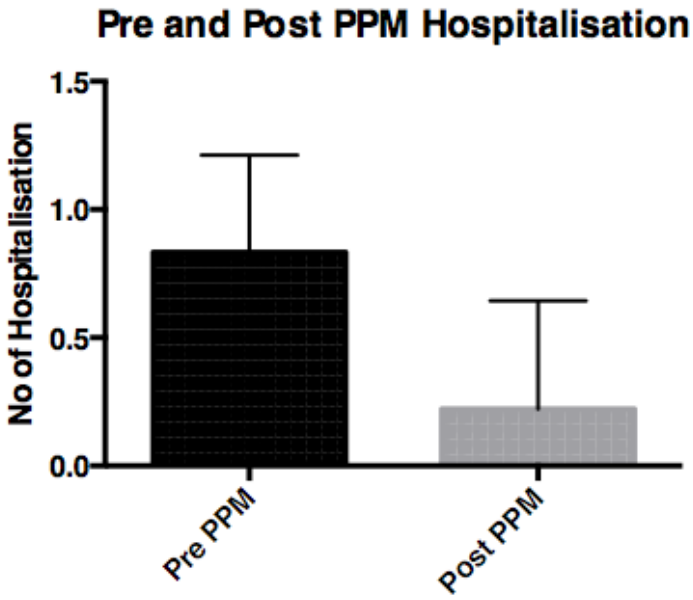
Of 1226 of the total cohort, 306 (25%) patients were above 65 years of age. Age range was 65-92 years (mean age 78±7years). Total of 81 patients (male 39 and female 44) had pacemaker (PPM) insertion. Thirty-eight (38) patients were offered pacemakers on the basis of initial consultation and “soft” ECG findings (Prolonged PR, LBBB, LAD and LAHB). Two patients declined and 36 patients received pacemaker implants. ECG

abnormalities in these patients were first degree AV block with or without left axis deviation (24), LBBB with left axis deviation (11) and RBBB and LAHB (3). Baseline characteristics are described in table 3.1. Further 6 patients have PPM on ECG findings of trifascicular block and complete heart block. Forty-two patients had an abnormal echocardiogram, 29 had normal and no information was available for the rest of the 10 patients. Over follow up duration of 39±31months we noted 7 patients to have rehospitalisation due to cardiac cause. There was significant reduction in hospitalisation (83% to 19 %, P <0.05) post PPM insertion (Figure 3.2). Total number of deaths (all cause) was 7.

Table 3.1: Baseline characteristics of study population

Variable	**No. of patients**
First degree AV block left axis	83 (female 44, Male 39
Left bundle and left axis	11
RBBB with LAHB	3
Clear PPM indications on ECG	6
Holter indications for PPM	17
Implantable loop recorder implantation	22
Pre PPM Hospital admissions (of 36)	30
Post PPM Hospital admissions (of 36)	7
Injury/fracture	14
No of deaths (all cause)	7

Figure 3.2: Comparison between Pre and Post PPM Hospitalisation



3.4 Discussion:

We studied the effect of pacing in the elderly patients presenting with TLOC and ECG abnormalities which are conventionally considered as "soft" findings. Among these, a prolonged PR interval is the commonest and others included left axis deviation (LAD), bundle branch block (RBBB, LBBB). These ECG abnormalities could suggest more serious conduction abnormalities especially in the elderly at the time of syncopal attack but are not among current guidelines for pacing.

Different studies(132–135) have evaluated the prognostic implications of a prolonged PR interval and found it to be a transient and benign in young people. Aro et al(136) showed similar results and found it to be transient, and with no association with increased mortality. In contrast a different study(137) found an association between fist degree AV block and coronary artery disease. Finally, Cheng et al analysed the Framingham Heart Study patients and found an association of PR prolongation with

increased risks of AF, pacemaker implantation, and death(130).

In our study, amongst patients with a prolonged PR interval on ECG, at least 4 patients also had high degree AV block. This was found on external heart monitors which were requested by referring clinicians and were available at RABTC appointment. This suggests that elderly patients have high degree AV block when they are syncopal. Furthermore, from our elderly cohort, 17 patients with near normal ECG also had high degree AV block or sinus arrest on external heart monitors.

There is a greater imperative to offer a pacemaker for a prolonged PR if the history suggests cardiac syncope. Our study mainly relies on history, examination and 12 lead ECG and we particularly noted patients who had injuries associated with TLOC and found 14 patients with injuries including fractures. Ahmed et al(138) has shown a history of injury secondary to syncope without conduction abnormalities on the ECG to be a strong indication for pacemaker implantation. Other significant clinical predictors were female sex, PR interval > 200msec, and age >75 years(138). In our cohort, we have no patient with a completely normal ECG and TLOC and injury. However, from our cohort, we were able to demonstrate decreased morbidity as indicated by reduced rates of hospitalization and decreasing healthcare costs. One might argue that pacemaker actually treated reflex syncope with asystole or bradycardia rather than advancing conduction tissue disease. However, our patients had abnormal findings on ECG, mentioned above, along with unexplained episodes of TLOC which were likely due to conduction tissue abnormalities. In addition, history was not suggestive of reflex syncope. In our study, we could not show a mortality benefit, this would require a longer duration of follow up. In the setting of the RABTC, if elderly patients have

TLOC episodes with or without injuries and which are otherwise unexplained, “more trivial” ECG findings could lead to permanent pacing and reduced healthcare costs without further investigation. If an RABTC assessment and an ECG are all the resources required to offer pacing, this could speed up care and save other tests, with effective treatment without delay. In our patients, these hospitalizations were attributed to postural hypotension and mechanical fall. Studies have shown presence of more than one causes of TLOC in elderly patients(12).

In our study, data collection was done from electronic records entered by specialist nurses, junior doctors and a cardiologist. Every effort was made to ensure complete and robust data. More data is required before it can be included in pacing guidelines.

3.5 Conclusion:

Elderly patients presenting with TLOC with ECG abnormalities (first degree AV block or hemiblocks), which otherwise are not indications for pacing, should be considered for a pacemaker, especially where frailty, poor social conditions and frequent TLOC make it desirable to speed up treatment to try and prevent recurrence. These data show that pacing will give symptomatic benefit, reduce hospitalization and reduce healthcare costs.

Chapter 4

4. High early yield of insertable ECG recorders in patients triaged through nurse-lead Rapid Access blackout Triage (RABTC) clinics.

4.1 Introduction:

In previous chapters, we described the RABTC assessment on the basis of clinical evaluation and 12 lead ECG. This technique helped in making diagnosis at least half of the patients. There is still a substantial number of patients with uncertain diagnosis. Careful thoughts and targeted investigations rather than a battery of tests help in these situations. This can avoid unnecessary investigations and reduce healthcare cost. We detected many patients attending the RABTC who had previous investigation for TLOC without conclusion. This typically consists of repeated ambulatory ECG monitoring, which is usually inconclusive, and other tests such as echocardiography, tilt table tests and EEG. However, symptom/ECG correlation (SECGC) is very rare with external ECG monitoring because the monitoring period is relatively short, and symptoms are infrequent. Since in most of the patients, symptoms do not recur during the monitoring period, the true yield of Holter in syncope may be as low as 1-2% in unselected patients. Bass et al showed in 15% of patients symptoms were not associated with arrhythmia(139). Holter monitoring in syncope can be beneficial if symptoms are frequent and daily single or multiple episodes of TLOC may increase the chances of symptom ECG correlation. Extended ECG monitoring is recommended when there is high pre-test probability of finding arrhythmia associated with syncope. However, studies have shown at least 50% of patients at age above 40 years can have arrhythmia

mainly asystole associated with syncope despite normal 12 lead ECG and no structural heart abnormality(128,140). In these circumstances, a test with high diagnostic yield is required and insertable ECG monitors (ILR) are recommended in these patients. NICE (National institute of clinical excellence) recommends ILRs in patients with infrequent (<2weekly) episodes https://www.nice.org.uk/guidance/cg109/chapter/Key-priorities-for-implementation. The PICTURE registry(141) and others(142) have also shown the high diagnostic yield of ILRs in TLOC.

Implantable ECG monitors are small devices which are implanted underneath the skin under local anaesthesia. Battery life is around 3 years. It works in 2 ways by automatically recording ECG abnormality as well as allowing patients to make recordings at the time of symptoms. This helps in correlating patient's symptoms with ECG findings on ILR. An ILR has a high initial cost. However, if symptom–ECG correlation can be achieved in a substantial number of patients during the active life of the device, then analysis of the cost per symptom–ECG yield has shown that the implanted device may be more cost-effective than a strategy using conventional investigation(143,144).

Until recently, ILRs have been used for diagnosis of unexplained syncope at the end of a completely negative work-up. Symptom-ECG correlation has been found to be around 35 % when used at the end of conventional testing(128,145–147). With newer versions of insertable ECG monitors which are tenth the size of previous versions, there is a trend to offer these early at the stage of TLOC investigations. These insertable ILRs, because of their smaller size, allow insertion in a treatment room. They provide more memory and improved algorithms, and there are no restrictions on magnetic resonance scanning. In this study, we describe our experience with insertable ILRs early in the

management of patients presenting with TLOC to our RABTC between May 2014 and January 2016.

4.2 Methods:

Every effort is made to make full use of clinical evaluation and 12 lead ECG to reach the diagnosis. It is known that history, examination and ECG obtain the greatest diagnostic yield in TLOC patients, while more sophisticated and costly tests have a low yield(83). The clinical assessment protocol in the RABTC is designed with this knowledge in mind and chapter 2 has mentioned the outcome. Using risk stratification mentioned in previous chapters, patients are classified high and low risk. These patients are discussed in our weekly Multi-disciplinary meeting (MDT) where decision on further management including ILRs takes place.

4.2.1 Indications to offer ILR in RABTC:

There was a low threshold for advising long-term ECG monitoring. ILRs were not used to try to make a diagnosis of reflex syncope, since this was a considered a clinical diagnosis, as is the case with epilepsy. The indications for offering an ILR were as below (reflecting ESC guidelines(11));

1. Uncertain diagnosis,
2. Reflex syncope with continuing disabling symptoms and suspected asystole
3. ECG suggestion of possible conduction tissue problems or arrhythmia

4.2.2 ILR Insertion:

LINQ ILRs were inserted in an "office" setting in a clean treatment room in the non-invasive cardiology area. The room was equipped with a supine couch and patients walked in after consent and removed upper-body clothing. The skin was cleaned with Chloroprep, and 0.5% bupivacaine used for local anesthesia. A medium-sized, fenestrated, adhesive drape was used. The implanter undertook a full surgical scrub for a minimum of 3 minutes, and then donned a surgical gown and surgical gloves and approached the patient from the right side. Local anesthetic was infiltrated subcutaneously in the left lower parasternal area. Using the proprietary implant tools, a Medtronic Linq was implanted subcutaneously and angled slightly towards the right shoulder from below to above to align with the long axis of the heart and principal ECG vector. The wound was closed with medical glue and steristrips, and a waterproof dressing retained for 5 days from implant. Signal quality was assessed immediately for R-wave magnitude and P-wave detection.

4.3 Results:

A total of 597 patients were seen in the RABTC between May 2014 and January 2016. This group was seen during the period when insertable ILRs were being implanted in a clean room. 273 patients had been previously investigated elsewhere. ILR was inserted in 141 patients (Female = 71, Male 70). Age range was 16-88 with a mean age of 50.46 ±19.21 years. An ILR was offered to these patients because; there was uncertainty about the diagnosis, reflex syncope had been confidently diagnosed but simple measures had failed to relieve symptoms, or the history and ECG raised the possibility of conduction tissue disease or syncope due to an arrhythmia.

Table 4.1 : Number of patients with ILR (LINQ) and ECG Abnormalities (Pre-ILR)

Description	**No. of patients**
Total number of ILR Implanted	141
Female)	71
Male)	70
Age range (yrs.)	16-88
Mean Age	50.46 ±19.21 yrs.
Patients with Abnormal ECG or structural heart disease	84
Diagnostic uncertainty	57
Patients with Bundle branch block	12
Abnormal QT	5
T wave changes	13
Previous Ablation for Supra ventricular tachycardia (SVT)	4
Atrial Fibrillation (AF)	8
Abnormal PR	8
Left axis deviation	6

One ILR had to be explanted due to discomfort but without evidence of infection. Another ILR was removed because of a wound infection.

4.3.1 Examples of ILR download:

Here are few examples from loop recorder findings

Figure 4.1: ILR download showing Pause

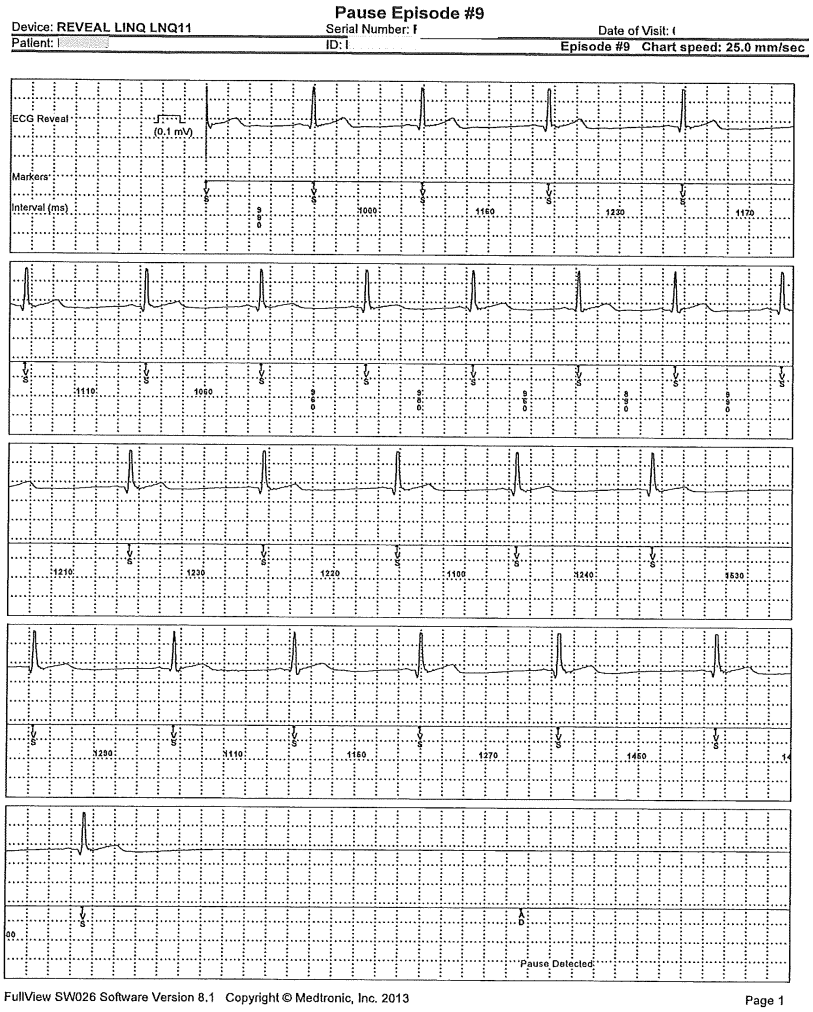


Figure 4.2: ILR download showing Atrial fibrillation

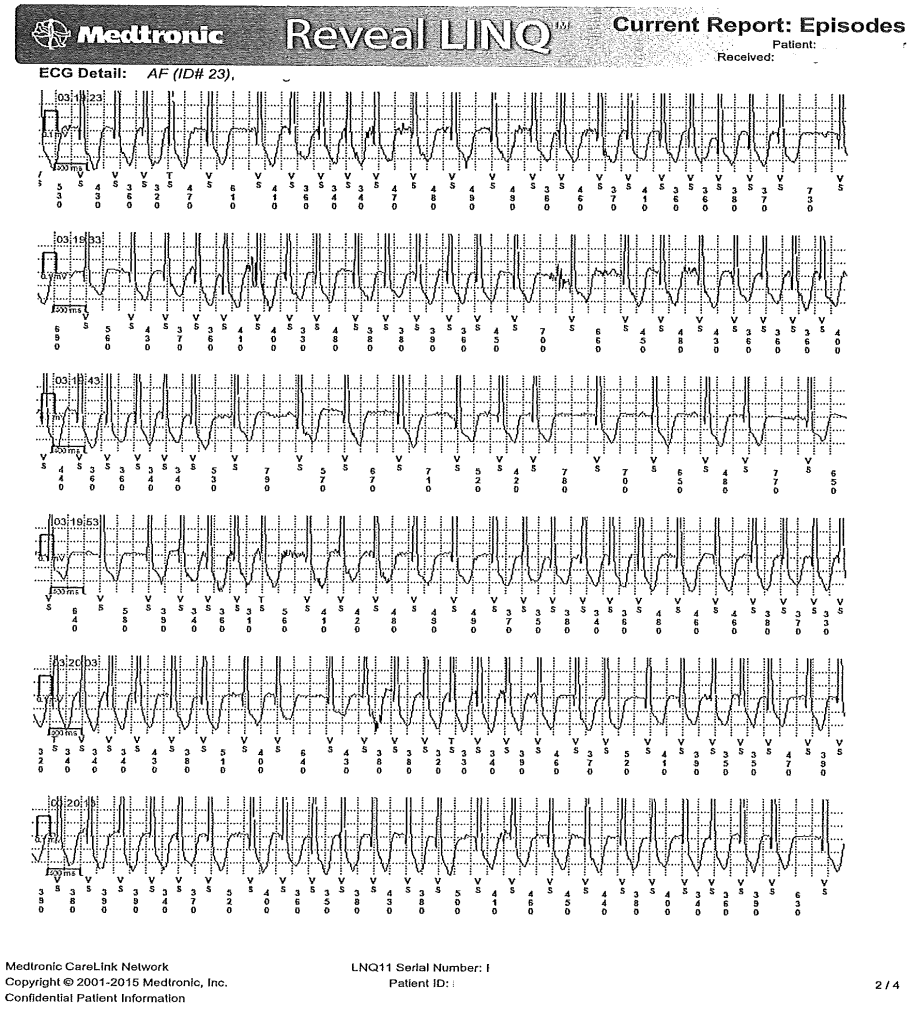
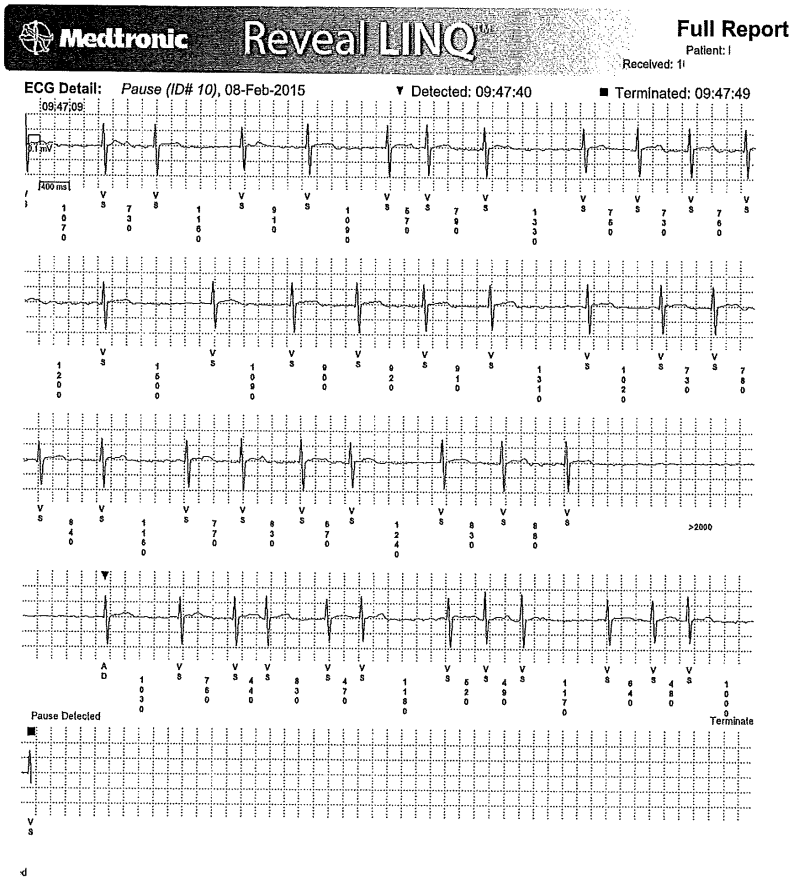


Figure 4.3: ILR download showing AF with Pause



4.3.2 Symptom/ECG Correlation:

A Positive symptom/ECG correlation (SECGC) was defined as ILR findings during symptoms leading to a diagnosis or change in treatment. SECGC was also noted when a symptomatic recording was made whether or not there were diagnostic features leading to a change of management. Of 141 patients with insertable ILR for TLOC, 57 had symptom/ECG correlation. Thirty of these had positive SECGC with an abnormal ECG leading to a diagnosis and action. In 27 patients with SECGC there were no diagnostic features that warranted a change of management. The average monitoring period was 117±104 days. Thirty (30) patients with an abnormal ECG had an active change of treatment plan. Eighteen patients (18) received a pacemaker. Five (5) patients had EP study because the ILR showed a narrow complex tachycardia, and one of these had an AF ablation. In 3 patients who had failed to respond to midodrine, reflex asystolic syncope was associated with asystole > 6 seconds at the time of TLOC. Nearly half of the patients have symptoms/ECG correlation within 8 weeks of ILR insertion and more than 90% within 10 months. A number of patients had SECGC but no diagnostic ECG finding, and were suspected to have epilepsy or psychogenic disturbances and apparent TLOC. In these cases, SECGC with a normal ECG was helpful in facilitating triage initially to neurological services in the regional neurosciences centre.

Results are given in Table 4.2. Figure 4.4 explains time to positive symptoms. The curve suggests increased occurrence of SECGC few weeks after ILR insertion. SECGCs appeared to occur with greater frequency within first 3 months, and plateau after 6 months.

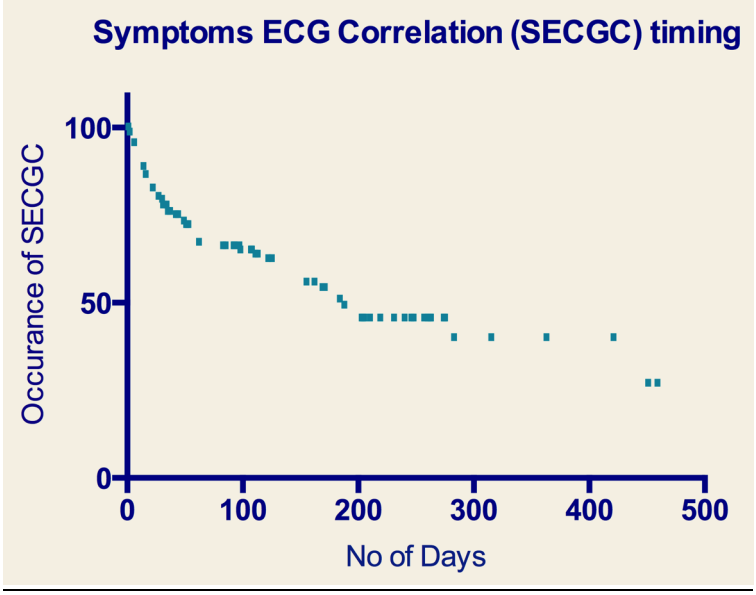
SECGC was also achieved in 33 (42.8%) of 77 patients with inconclusive investigation elsewhere. Many of these patients had repeated external Holter ECG monitoring for short periods of time. This suggests that there is too much reliance on external monitoring for short periods of time for symptoms that typically occur infrequently, and that long-term implanted monitoring at an earlier stage could save time and resources.

Another observation was that very early SECGC soon after implantation typically showed a normal ECG. 21 of 30 patients with SECGC in the first 8 weeks showed no diagnostic rhythm abnormality, and typically had sinus rhythm or sinus tachycardia. Very early and frequent activation with normal ECG on the ILR could be an indication of psychogenic blackouts.

Table 4.2 : Results showing Number of patients with SECGC including ILR findings and treatment received.

Description/Treatment	**Results**
Number of patients with LINQ for TLOC	141
No of patients with positive Symptom ECG correlation	57
No of patients with normal ECG	27
No of patients with abnormal ECG	30
Mean monitoring period	117±104 days
Positive symptom ECG correlation within 8 weeks	30
Positive symptom ECG correlation within 10 months	56
Pauses/AV block	16
AF	8
AF with Pauses	6
Non-diagnostic findings	27
PPM	18
Electrophysiology Study Ablation	5
Treatment with medication	7
ILR explanted because of painful site / infection	2

Figure 4.4: Time to symptom/ECG corrélation (SECGC)



4.4 Discussion:

Triage of TLOC patients through an RABTC helps to get a full range of TLOC patients to the right specialist in a timely fashion. Our multidisciplinary specialist nurse-led RABTC uses a structured clinical assessment tool, allowing uniform questioning. It has been shown previously that a systematic approach to patients presenting with TLOC increases diagnostic efficacy and accuracy(115). However, despite the well-proven value of clinical assessment and a 12-lead ECG, in patients with continuing uncertainty of diagnosis, understanding of the heart rhythm during TLOC is critical. Where patients attending the RABTC had been previously investigated, there was a common story of multiple non-invasive tests, particularly repeated Holter monitoring for periods of 1-7 days, without symptoms during testing. Many patients also had other tests repeatedly, such as transthoracic echocardiography. In our study, 273 out of 597 patients have had investigations either in primary care or through secondary care without a diagnosis

being made. In recent years, the ineffectiveness of investigation through conventional channels has led to the development of multidisciplinary TLOC clinics(148). These have shown improved diagnostic rates, however, some clinics emphasize only the management of syncope, which could deter referrals where other causes of TLOC are suspected. In the UK, the term "blackout" is widely used by doctors and patients, and understood to be synonymous with TLOC. We believe that using the term "blackouts triage clinic" makes it clear to referring doctors and patients what is available.

As expected amongst TLOC patients, most patients referred to our RABTC had syncope. In the group of 597, 220 patients also had red flags, and in many cases an ILR was not required. At least 12 additional patients required a pacemaker, based on 12 lead ECG findings, directly from RABTC after MDT discussion. Similarly, 2 patients were listed for ablation. Around 10% of patients were referred for neurological opinion where epilepsy or a psychogenic cause of TLOC was suspected. It could be expected that ILRs were used selectively, as reflex syncope, epilepsy and psychogenic blackouts are all clinical diagnoses(55,81) and clinical features are the requirement for diagnosis and treatment. However, for recurrent and unexplained syncope, ILRs are a useful diagnostic tool(149). They should be considered early in the management of syncope where the diagnosis is unclear, in patients with unresponsive reflex syncope and in patients with structural heart disease or ECG abnormalities of uncertain significance. They are also cost effective in unexplained TLOC(150). In our study, 57 patients had diagnostic uncertainties. These included; patients with no warning or preceding palpitations, ongoing symptoms despite life style measures (adequate hydration and salt intake) and 9 patients were on antiepileptic medications but ongoing symptoms. At least seven of the above patients had symptoms during driving.

The graph of time to SECGC correlation suggests a majority of recordings in first few weeks, in between a "blanking period" and finally a plateauing of recordings after approximately 6-7 months. These data may be useful in planning future devices. Battery consumption, for example, could be diverted to powering other sensors rather than prolonging device implant life. However, other centres(151) have reported continuing diagnostic data up to 4 years from implantation, and our data do not extend far enough to make a comparison. Amongst "early SECGC" cases, there was a high rate of non-diagnostic/no ECG abnormality. The majority of patients with positive SECGC within few days of ILR insertion showed no arrhythmia. This probably reflects a high rate of psychogenic TLOC, and these patients were referred to specialist services via the regional neurosciences centre.

Patients with TLOC need a systematic risk assessment. Our "Red Flag" features are embedded in the web-based TLOC Assessment Tool, and are therefore never neglected. With effective assessment tools to risk stratify high and low risk patients, hospital admissions can be avoided, which otherwise could result in unnecessary cost(58). However, an "abnormal ECG" covers a very wide range of possibilities. The ECG in TLOC patients may show subtle abnormalities such as 1st degree heart block, bundle branch block and T-wave inversion. ILR is the best way of finding out if these mean that TLOC is due to conduction tissue disease or an arrhythmia if these subtle abnormalities show much clearer abnormalities of rhythm during symptoms(152). It can avoid unhelpful external monitoring, and can significantly shorten the time to diagnosis and treatment(153). ILRs are also of proven value in patients where a diagnosis of epilepsy is in question(154). Its high diagnostic yield has been described in the elderly(155). There is an increasing trend to offer ILR early in the TLOC

management, which ultimately help achieve a quick diagnosis and hasten targeted treatment.

In our centre and elsewhere, ILRs were traditional implanted in a minor surgical procedure in a catheter laboratory. This was believed to be necessary to avoid infection, and was required because of the size of the implant. However, new ILRs are genuinely "insertable", and easily be implanted in an "office" setting. Implantation by nurses and physiologists has also been described(156). In this study complications were rare.

There are few points which make our study stand out. We offered insertable loop recorders (ILRs) early in the management of patients with high diagnostic uncertainties despite multiple previous investigations elsewhere. ILRs were implanted in an "office" setting, in a clean room outside a cardiac catheter laboratory. After ILR insertion, we calculated timing of symptoms and corresponding ECG findings and found a high diagnostic yield at a relatively early stage. It has impact on clinical practice. Our study provides guidance that structured assessment of TLOC patients and early use of ILRs in patients with unclear diagnosis can help in improving the outcome. We include a "time to symptom/ECG correlation" plot, which suggests high correlation in initial few weeks from insertion, and plateaus at about 6 months from insertion. This might be useful in designing future implants.

Whilst our report suggests that ILRs are safe when implanted in an office setting, a randomised study versus catheter laboratory placement would be more convincing. We have not compared management of uncertain diagnosis, unresponsive reflex syncope and "minor" structural heart disease by conventional care versus ILR-guided care.

4.5 Conclusions:

Rapid access blackout triage clinic (RABTC) helps to provide a single care-pathway and structured assessment for patients with TLOC. Early use of ILRs in patients with unclear diagnosis can help in improving the outcome. It can help achieving high symptom/ECG correlation and high early diagnostic yield. ILRs can be safely implanted in “office” conditions. The symptom/ECG correlation” plot suggests high correlation in initial few weeks from insertion, and plateaus at about 6 months from insertion. This might be useful in designing future implants.

Chapter 5

5. Flux in sympatho-vagal balance (SVB) derived from heart rate variability (HRV) in ECG recordings during videotelemetry suggests “signatures” of different causes of transient loss of consciousness - TLOC

5.1 Introduction:

The RABTC, by virtue of its reliance on clinical assessment, has contributed to TLOC management and ILRs have helped in uncertain cases. But there is still a proportion of patients with TLOC, where diagnosis remains uncertain. Good clinical assessment and an ECG, as done in the RABTC, provide the most cost-effective triage(81). Often diagnosis depends on clinical skills, and baseline and provocative tests may help. However, clinical skills are variable, baseline tests may be misleading, and provocative tests are prone to poor specificity, especially in unselected populations with TLOC(157). We know that costly tests tend to add little(81). Because of these shortcomings, 30% of adults and 40% of children may be misdiagnosed with epilepsy and wrongly treated(37,43–45). This is usually as a consequence of misinterpretation of reflex syncope with abnormal movements(3,158). In these cases, abnormal movements or incontinence may be witnessed during TLOC, but they are due to cerebral anoxia and not a primary brain disturbance of cerebral neurons(3). In most studies, about 50% of patients remain undiagnosed(159), and about 50% of these will continue to have symptoms(160). The ILR is a departure from clinical skills and typical tests. It has contributed significantly to the management of TLOC(70). It can record symptom/ECG correlation, (SECGC), both retrospectively (patient-triggering) and

automatically during TLOC(161). However, in many instances, the ECG recorded is not diagnostic and has been found to be inconclusive during TLOC in >40% of cases(72), and only disclosing normal sinus rhythm with little rate variation, unlikely to account for TLOC. A secure diagnosis of syncope, epilepsy or psychogenic TLOC would be confirmed by recording ECG, BP and EEG (electroencephalogram) during TLOC.

Because of this limitation, and because existing technologies cannot provide continuous EEG, ECG and BP during TLOC as in video telemetry units, we considered whether derived ECG parameters might provide insight into the cause of TLOC. Heart rate variability (HRV) can be measured by time and frequency domain variation in RR intervals(162). In this project, we examined HRV and derived a marginality index (MI), reflecting cardiac hyperexcitability. Sympatho-vagal balance (SVB) was then computed from HRV. We studied HRV and derived marginality for different types of TLOC which had been diagnosed during video telemetry or reflex syncope provoked by tilt-table testing.

5.3 Methodology:

This study was conducted in collaboration with Salford Royal Foundation Trust (SRFT) and Medtronic, BRC, Maastricht. Patients were admitted to the epilepsy-monitoring unit (EMU) of SRFT for up to a week for video –telemetry (VdT) during which we continuously recorded their EEG and ECG, and observed what happens to them, their EEG and ECG, during TLOC. For comparison, data from patients with tilt-induced syncope from a tertiary syncope clinic were also used.

5.3a: Hypothesis:

Our hypothesis was that HRV and SVB derived from ECG monitoring at; baseline, before, during and after TLOC, could distinguish between syncope, epilepsy and psychogenic causes of TLOC, by providing typical SVB "signatures".

5.3b: Aims and objectives:

- Primary objectives:

To determine heart rate variability (HRV) in different types of TLOC patients using a parametric spectral estimation with sliding window of 60-240s shifted in 5-20s increments.

To derive sympatho-vagal balance from HRV as the ratio of low frequency (LF:0. 04-0.15Hz) to high frequency components (HF:0. 15-0.4Hz).

To show a marginality index (MI), reflecting cardiac hyperexcitability computed as the % of RR values outside a confidence interval (over 40 consecutive beats).

- Secondary objective:

To determine if differences in marginality index are seen in different causes of TLOC.

5.3c: Intended outcomes:

To examine the possibility of HRV, SVB and marginality index derived "signatures" could be implemented in an ILR to improve the discrimination of the device in the diagnosis of different causes of TLOC.

5.3d: Study design:

Data for the study was obtained by examining the EMU patient database. We selected cases with TLOC, and looked for EEG evidence of a confirmed epileptic seizure with TLOC during VdT for epilepsy patients. We looked for lack of evidence of epilepsy or syncope in EEG, BP or ECG data during TLOC and VdT for psychogenic patients. Patient data was used for the study where the ECG recordings were of adequate quality for HRV analysis. Patients were excluded if they had a medical condition, medical treatment affecting HRV or autonomic function.

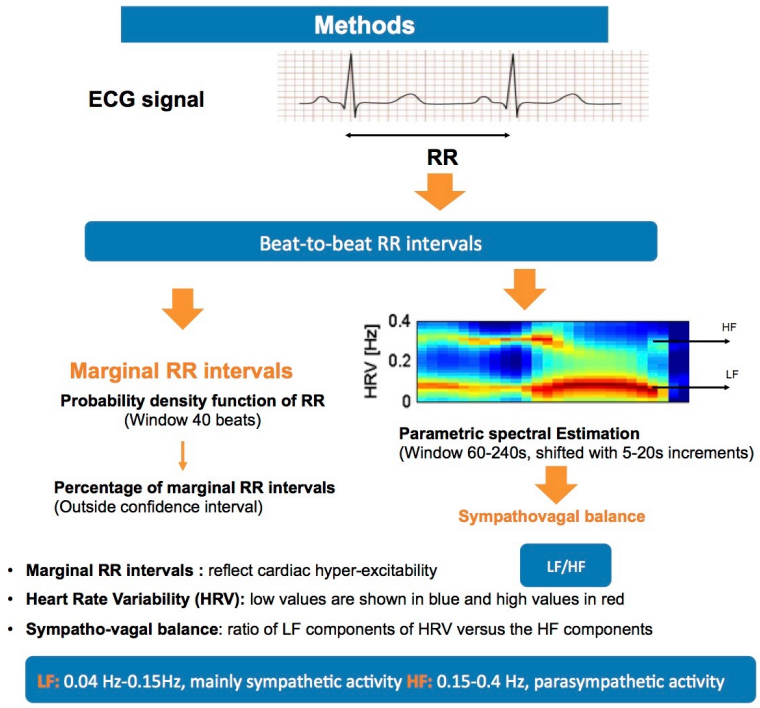
5.3e: Data Collection and handling:

In this pilot study, I made regular trips to Salford Royal NHS Trust to the Neurophysiology Unit. I personally selected patients from the cohort undergoing Video Telemetry. These were patients with EEG proven epilepsy, syncope or presumed psychogenic blackouts. I reviewed all the clinical details, and reviewed all the ECG studies. Sampling was done by me in conjunction with the EEG staff. I personally insured correct labelling and anonymisation of data with a unique identifier kept safely by the Principal Investigator. This would allow re-identification of the patient should anything of clinical significance become evident from the subsequent analysis. We selected three different recordings (10-20 minutes each); a) baseline (6-8hr prior to seizure), b) seizure (15 minutes prior including throughout the seizure and up to 15 minutes post seizure), c) post seizure 4-6hr post seizure. Anonymised data were transferred for analysis to Medtronic scientist (NV) using dropbox.

5.3f: Data analysis:

Data was analysed in Medtronic, Tolochenaz, Switzerland using standard methods(162). This method analysed HRV and marginality for different groups." Beat-to-beat RR intervals were extracted from the ECG signals. Marginal RR intervals (reflecting cardiac hyperexcitability) were analysed using a statistical assessment of the percentage of RR values outside a confidence interval (window size of 40 beats). This confidence interval was determined during a baseline recording of 10 minutes where the parameter alpha was calculated as 0.196 times the median baseline RR. For each analysis window of 40 beats, an RR interval was considered marginal if it fell outside the confidence interval "median RR of the analysis window plus or minus alpha". Marginality was computed as the percentage of marginal intervals in each analysis window. HRV was assessed with a parametric spectral estimation using a sliding analysis window of 60-240s, shifted with 5-20s increments. The sympatho-vagal balance was computed as the ratio of the low frequency components (LF: 0.04 Hz-0.15Hz, mainly sympathetic activity) versus the high frequency components (HF: 0.15-0.4 Hz, parasympathetic activity), (Fig 5.1).

Figure 5.1: Schematic representation of methods used



5.3g Sample size and power considerations:

The primary focus of this study was clinical feasibility. The concerns in relation to sample size were a) that there should be sufficient replications of the video-telemetry analysis to test the integrity of the method for use in future studies, and to highlight any unknown areas of difficulty and b) that there are sufficient numbers in each diagnosis group to give an early indication of potential systematic differences ('signatures'). A sample size of 60 patients, with approximately 20 per group, was judged to be suitable and achievable.

5.4 Results:

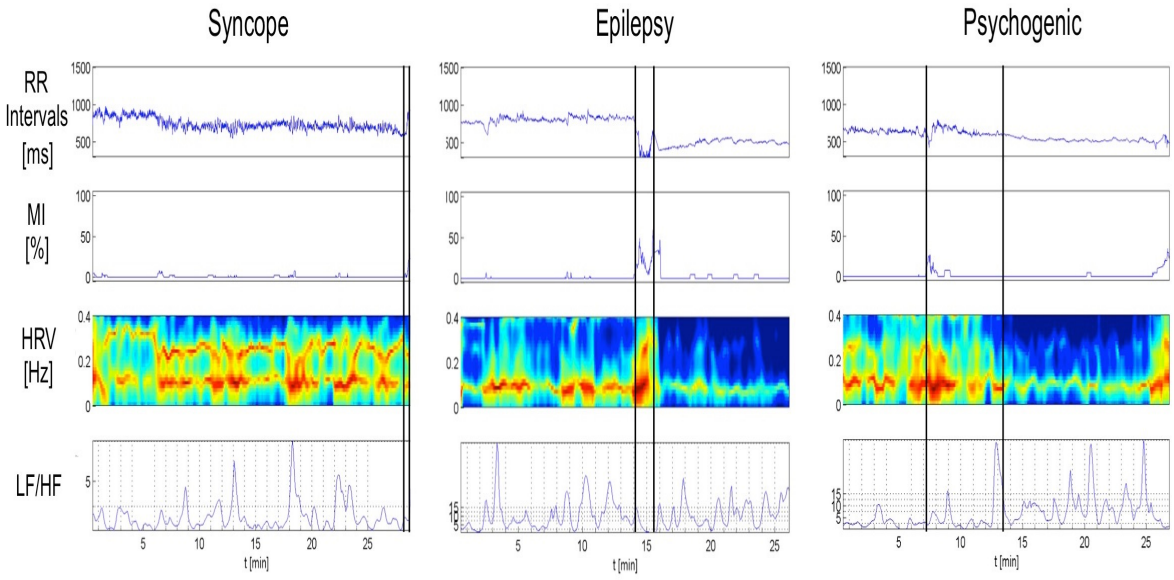
Sixty-three (63) patients were included. Of these, 43 patients had VdT at the EMU of SRFT, continuous EEG and ECG and intermittent BP. Among these 43 patients twenty-seven (27) were found to have an epileptic disturbance on their EEG during TLOC, and 16 had neither EEG abnormality, BP drop or ECG change and were labeled psychogenic TLOC. Twenty patients studied in a tertiary Syncope Clinic had tilt-induced syncope with an abrupt collapse in BP and some slowing of heart rate on ECG(163) at the time of TLOC.

The marginality index (MI) is normally very low, and prior to tilt-induced syncope MI was <5% in all 20 reflex syncope patients. Much larger values were found prior to epileptic seizures. Twelve (12) out of 27 patients with epilepsy had MI above 40%. Patients with psychogenic TLOC had much variation in MI, but only 5 patients showed an MI <5%. Results are given in table 5.1 and Fig 5.2.

Table 5.1: Marginality Index in different types of TLOC

Type of Blackout	Marginality Index (MI)				
	0-10%	10-20%	20-30%	30-40%	>40%
Epilepsy	1 (4%)	1 (4%)	6 (22%)	7 (26%)	12 (44%)
Psychogenic	5 (31%)	4 (25%)	4 (25%)	2 (12%)	1 (6%)
Syncope	20 (100%)	0	0	0	0

Fig. 5.2: Examples of colour plots of findings in HRV, SVB and MI for 3 patients each from a different group.



5.5 Discussion:

This study shows that derivations from ECG at the time of transient loss of consciousness have different patterns in epilepsy, psychogenic apparent loss of consciousness and reflex syncope. The ECG-derived index is capable of being implemented in an insertable loop recorder.

TLOC is a common clinical problem, and clinical assessment together with an ECG commonly leaves about 50% of patients undiagnosed(81). After more costly tests, relatively little additional diagnostic yield can be expected(141). Baseline tests, such as echocardiography, can be useful, where structural heart disease exists(164). Provocative tests may provide insight, but do so at the cost of loss of specificity with

more false positive results(165). The more aggressive a provocative protocol in pursuit of higher sensitivity, the more likely it is that specificity will fall(165). The most reliable diagnostic data for paroxysmal symptoms is where the symptoms coincide with recording of the critical physiological data, and this is true for the EEG in epilepsy, blood pressure in syncope and EEG, blood pressure and ECG in psychogenic TLOC. Unfortunately, opportunities to record all these parameters in TLOC of uncertain cause are limited by the cost of appropriately equipped laboratories, and the long periods of hospital admission that may be required(17,166).

The ECG may be monitored for several years, and acquired in conjunction with symptoms, (symptom/ECG correlation, SECGC), using insertable ECG loop recorders. A high rate of SECGC, with a high rate of diagnostic findings leading to therapy can be achieved. Around 35% of patients have SECGC within 6-12 months(141). However, in >50% of patients with SECGC, the best that can be concluded currently is that TLOC is not accompanied by a significant bradycardia, pause or tachycardia that could cause TLOC. The diagnosis remains unclear, and treatment cannot be started with confidence.

Some authors have reported HRV and autonomic changes during epilepsy. Brotherstone et al(167), studied parasympathetic changes during sub-clinical seizures. They showed that generalised sub-clinical seizures may be associated with more autonomic instability compared with temporal lobe sub-clinical seizures. Jeppesen et al(168) reported analysis of HRV as a promising method of non-invasive seizure detection in early phase as well as preceding the onset of seizures. Another study(169) looked at the effect of absence seizures on HRV. HRV has been used to differentiate complex partial seizures from “non epileptic attack disorders” (NEAD), and healthy

volunteers from patients with epilepsy and NEAD. However, in these studies, resting HRV measures alone did not differentiate between patients with NEAD and those with epilepsy(170).

Long term monitoring (LTM), either in the form of ambulatory electroencephalography (aEEG) or video telemetry (VT), is recommended by the International League Against Epilepsy and the National Institute for Health and Clinical Excellence (NICE) for patients in whom seizure or syndrome type is unclear, and in patients in whom it is proving difficult to differentiate between epileptic and non-epileptic conditions. The use of LTM within the context of a comprehensive epilepsy programme incurs costs in terms of personnel, time and resources. In addition to the need for appropriate hospital beds and expensive monitoring equipment, a highly skilled multidisciplinary team consisting of EEG technicians, neurophysiologists and trained nursing staff is also needed. Thus, it is important to be able to demonstrate the utility of LTM. The study from the Gower unit experience(171) revealed beneficial effect of LTM but it is relatively expensive, time consuming and of limited availability; this needs to be balanced against the considerable financial and social cost of misdiagnosed and uncontrolled seizures. Their study supported the use of performing LTM (either video or ambulatory) in a specialist setting in patients who present diagnostic difficulty.

Salaamed et al(172) also reported that HRV could help in the evaluation of syncope of unknown aetiology by comparing patients with recurrent syncope and positive tilt tests with healthy volunteers. They assessed autonomic function using time domain analysis of 24 hours ambulatory ECG. In another report(173), night-time SVB was used to assess autonomic control of HRV to avoid external stimuli. HRV was examined using

time domain parameters, indexes of vagal tone and frequency domain parameters and concluded that there was a reduction in HRV and vagal tone in vasovagal patients, together with increased sympathetic activity. In another study, HRV before and during postural tilt and their relationship to ageing and risk of syncope was explored. Older subjects have reduced supine HR variability and absent or attenuated low frequency activation during tilt. Young subjects who develop syncope during tilt demonstrate prominent low-frequency activation, which may be associated with heightened sympathetic activity. However, it is unclear whether these findings are unique to tilt-induced syncope patients or simply seen in different age groups.

In this pilot study, we sought additional information from the ECG, sampled at baseline, before, during and after TLOC, that might help to discriminate between the three causes of TLOC, epilepsy, syncope and psychogenic TLOC. We have shown there might be more discriminative information available in SECGC when HRV is derived, SVB is computed, and different causes of TLOC are identified by the degree of cardiac hyperexcitability expressed as the Marginality Index. Whilst these data are preliminary, and further studies are needed for validation, this study suggests that different causes of TLOC could be further discriminated using existing ILR technology by processing HRV prior to TLOC and deriving different levels of cardiac hyperexcitability in TLOC due to epilepsy, syncope or psychogenic causes.

This is a study of a small number of patients and the data analysis performed was retrospective. The study is intended to be regarded as a pilot study. The small number of patients did not allow the accumulated data to undergo meaningful statistical analysis.

5.6 Conclusions :

An EMU admission for VdT is costly, and capturing a patient's typical episode in a short admission may not be possible. Continuous ECG monitoring is available in ILRs for long periods, but SECGC may not be diagnostic and may not guide treatment in a significant proportion of patients. By deriving measures of autonomic tone by analysis of RR variability, cardiac excitability may be computed in different causes of TLOC. This preliminary study suggests that data extracted from the ECG during TLOC may provide a typical "signature" that could discriminate between common causes of TLOC.

Chapter 6

6: Midodrine is Safe and Effective in the Treatment of Reflex Syncope

6.1 Introduction:

In previous chapters, we have described diagnostic techniques for different causes of TLOC. Once diagnosis is made, treatment can be targeted depending on the underlying cause. Among three common causes of TLOC, syncope is the commonest. Reflex syncope is by far the most common cause of syncope. The European Society of Cardiology (ESC) has defined syncope as "T-LOC due to transient global cerebral hypoperfusion characterized by rapid onset, short duration and spontaneous complete recovery"; and reflex syncope results from "impairment of cardiovascular reflexes that are normally useful in controlling the circulation"(11). There are two main types of reflex syncope;

a) vasodepressor
b) cardioinhibitory

In most of the circumstances these types co-exist with one component being dominant. Vasodepressor is the name given to blood pressure fall while cardioinhibitory is applied where there is intense bradycardia or asystole.

The treatment options for reflex syncope are

1. Counselling and life style measures

2. Non pharmacological measures
3. Pharmacological
4. Cardiac pacing

The management of reflex syncope has always posed challenges to physicians. The patient's education is the mainstay of treatment. They must be informed about the benign nature of this condition, occurrence in clusters as well as chances of injuries if preventive measures are not taken seriously(22). Patient should be informed about the mechanism and importance of recognizing warning signs so that chances of injuries can be avoided. Physical counter pressure manoeuvres(174–176) should be explained to recurrent fainters, who are aware of warning symptoms, to avoid frequent syncopal attacks. The presence of psychiatric and psychological factors have been reported(177,178) in these patients and hence they should be identified and dealt with. The ESC has given recommendations for the management of reflex syncope (Figure 6.1).

Figure 6.1: ESC Recommendations for the treatment of reflex syncope(11)

Recommendations	Class[a]	Level[b]
• Explanation of the diagnosis, provision of reassurance, and explanation of risk of recurrence are indicated in all patients	I	C
• Isometric PCMs are indicated in patients with prodrome	I	B
• Cardiac pacing should be considered in patients with dominant cardioinhibitory CSS	IIa	B
• Cardiac pacing should be considered in patients with frequent recurrent reflex syncope, age >40 years, and documented spontaneous cardioinhibitory response during monitoring	IIa	B
• Midodrine may be indicated in patients with VVS refractory to lifestyle measures	IIb	B
• Tilt training may be useful for education of patients but long-term benefit depends on compliance	IIb	B
• Cardiac pacing may be indicated in patients with tilt-induced cardioinhibitory response with recurrent frequent unpredictable syncope and age >40 after alternative therapy has failed	IIb	C
• Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex	III	C
• β-Adrenergic blocking drugs are not indicated	III	A

Advice and education on the various factors that influence systemic blood pressure help reducing episodes. Counselling should be supplemented with education on the physical counter-manoeuvres to increase blood pressure and increase in fluid and salt intake to expand intravascular volume. In appropriate subjects, these interventions may be supplemented by physical exercise programs, tilt- table training, and abdominal binders.

Figure 6.2: Non pharmacological treatment options for reflex syncope(179)

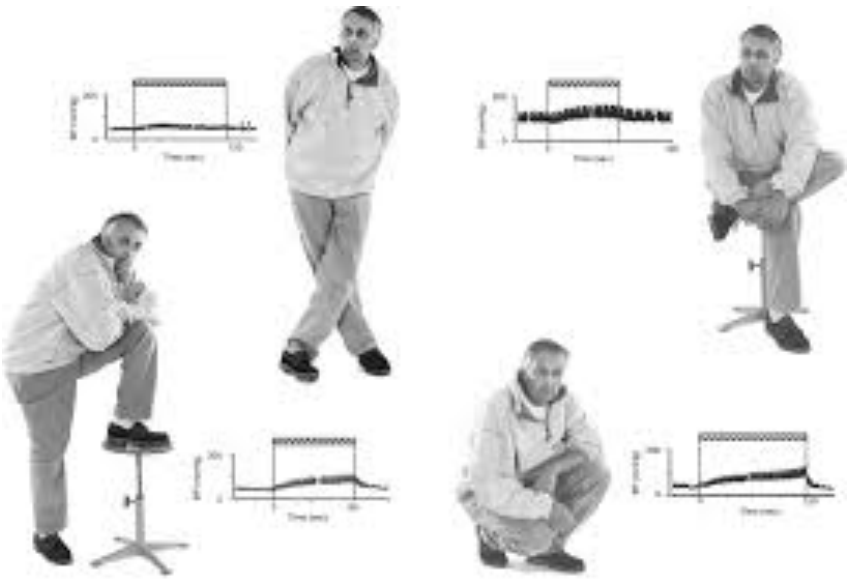
Initial approach

1. Counseling and reassurance
   – explanation
   – avoidance of triggering events:
      standing still for prolonged periods
      high environmental temperature (including hot showers and baths) sudden head-up postural change (especially on waking)
      straining during micturition and defecation
      hyperventilation
      fasting
      excessive alcohol intake
      drugs with vasodepressor properties
   – normal salt/water intake
2. Physical counter-maneuvers
   – leg crossing and muscle tensing
   – squatting
3. Psychological deconditioning

To be considered in recurrent syncope

4. Increase in dietary salt intake
   – daily salt intake of at least 10 grams (180 mmol) a day – weight gain of about 1–2 kg
5. Water drinking
   – 2–2.5 liter fluid/day
   – avoidance of dark urine
6. Physical exercise
7. Head-up sleeping
8. Tilt training
9. Abdominal binders and elastic stockings

Figure 6.3: Examples of physical counter pressure maneuvers(179)



The ESC guidelines recommend non-pharmacological measures as first line treatment which include emphasising fluid and salt intake, regular exercise and physical counter pressure manoeuvres(73). Non-pharmacological are effective in some cases. However, symptoms may persist and be disabling, and further treatment may be needed. Commonly used drugs are beta-blockers and fludrocortisone. However, both treatments have been found to be ineffective in recent trials(74,75). Midodrine, an alpha-adrenergic agonist, has been used in patients who are not responding to non-pharmacological treatments(73,76). However, less is known about midodrine treatment, particularly in younger patients with reflex syncope versus older patients with orthostatic hypotension(79). Furthermore, midodrine was not being prescribed as it was unlicensed but this has recently changed. The FDA has previously tried to delicense midodrine (2010 - FDA Proposes Withdrawal of Low Blood Pressure Drug (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm222580.htm). The European Society of Cardiology has recommended midodrine, but only as a class IIa indication(11). Information on when, why and how to prescribe midodrine in order to get good results without side effects is needed. We have been using midodrine in RABTC for more than 10 years and we analysed retrospective data of nearly 200 patients and in this chapter, we will be providing our experience.

6.2 Methodology:

We report a single-centre experience of midodrine in patients with reflex syncope, no clinical "Red Flags" (mentioned in thesis previously) and a normal or near-normal ECG. A large proportion of patients had a diagnosis of reflex syncope based on history, examination and normal ECG. Initial management strategies for these patients included

life style modification, adequate fluid and salt supplementation and counterpulsation manoeuvres(179,180). Patients with continuing syncope were offered midodrine as first-line treatment.

Midodrine is an α-adrenoceptor agonist. It increases arteriolar tone at skeletal muscle arterioles. This action inhibits the abrupt loss of tone in these arterioles when sympathetic outflow is suddenly shut off at the onset of a reflex syncopal attack. Blood pressure can be shown to rise during midodrine treatment(181). Midodrine also increases venous tone in the splanchnic bed(182) which may be more important given the pathophysiology of young syncope(7,183). Midodrine has been unlicensed in UK and was only prescribed on patient named basis. Although it has recently been licensed. It is still being prescribed in a similar way because of lack of expertise. There is a hope, with more experience and evidence, like our paper, it will be widely prescribed when required.

In the USA, the FDA has tried to unlicense the drug due to lack of evidence of efficacy, and concerns about a hypertensive response. This caused widespread protests from patients. As a result, the FDA issued an update, confirming that midodrine "remains approved and available in the marketplace" (http://www.fda.gov/Drugs/DrugSafety/ucm225444.htm). However, there is currently no good evidence to support its use in reflex syncope, particularly in younger patients, and no evidence that shows a reduction in spontaneous episodes of syncope in reflex syncope patients.

6.2a Study Protocol:

As mentioned above, not much evidence is available regarding midodrine use in reflex syncope but we have been using midodrine in Reflex Syncope in the Manchester Heart

Centre for over 10 years, and it has been highly effective. We have around 200 patients maintained or helped by the drug. There is very scanty evidence for its use in this type of patients. At the same time B-blockers, fludrocortisone and a number of other drugs have one-by-one been shown to be no better than placebo(54,184).

6.2b Hypothesis

Midodrine is effective pharmacological treatment in the management of reflex syncope.

6.2c Patients

We have nearly 200 patients maintained on this therapy. We assessed case notes to see the effectiveness of this medicine and will provide evidence based data of its effectiveness by providing our experience.

6.2d Data collection and analysis

Data was collected from the electronic database and case notes and prepared for a descriptive analysis. Syncope rates before and after midodrine were compared. The primary end point of the study was the difference in number of syncopal episodes before and after midodrine. These were assessed at follow up visits and documented in study notes. These are then compared with their frequency of syncopal episodes pre-midodrine. Using SPSS software, non-parametric tests were used for descriptive analysis. Associated significance values were based on Wilcox signed rank test.

6.2e Outcome Measures

It was measured by assessing frequency of syncopal episodes before and after starting midodrine.

6.2.1 Patients:

We analysed our use of midodrine in 195 consecutive patients with reflex syncope seen in our RABTC over 10 years. Reflex syncope was diagnosed clinically from a history of syncope, and recognised features of reflex syncope. Most such patients had a normal or near-normal 12-lead ECG. No cardiac Red Flags were present to suggest a cardiac or arrhythmic cause of syncope, or neurological Red Flags that might suggest a diagnosis of epilepsy. In some cases, we assessed patients with a previous diagnosis of epilepsy. In these cases, lack of response to multiple epilepsy drugs trials had made that diagnosis in doubt. In these cases, a new diagnosis of convulsive syncope (reflex syncope with abnormal movements) was made. In some patients there were minor ECG abnormalities, these all had normal echocardiography, and the clinical diagnosis of reflex syncope was convincing.

6.2.2 Treatment:

Patients with reflex syncope were advised to increase fluid and salt intake and practice other non-pharmacological measures as above. The number of syncopal episodes and the duration of symptoms, along with lying and standing blood pressure, were recorded. Those who continued to have episodes of reflex syncope were prescribed midodrine as a first line drug treatment. If patients had already tried fluid and salt, midodrine was prescribed at their initial consultation. The usual starting dose was 2.5mg three times daily. Regular blood pressure monitoring was arranged. Side effects such as tingling and numbness of the scalp were explained. Evening doses were prescribed a few hours prior to sleep in order to avoid supine hypertension. Patients were advised to avoid midodrine in pregnancy if possible. Regular follow up assessed symptoms and side effects. Response to medication was assessed by the number of syncopal episodes and

by blood pressure. Gradual increments in dose were made, up to maximum of 10 mg (in some15 mg) three times daily, depending upon response. Patients were told to stop treatment if unbearable side effects occurred, and contact the centre.

6.3 Results

6.3.1 Effect on rate of syncope.

Of 195 patients, majority were female (n=151, 78%). The age range was 13-90, (mean 40±18 years). Seventy-five patients were under 30 years of age, (37%). Patient characteristics are given in table 6.1. Sixty-one patients (31%), seen with reflex syncope had been avoiding salt because of an over-zealous response to public health messages and responded to salt supplementation alone, and are not included in the midodrine treatment data.

Table 6.1: Baseline characteristics of Patients

Parameter	Number	Results
Age (years)	Range 13-90 years	Mean± SD 40±18 years
Duration of symptoms	Median 28 months	1st Quartile 12 3rd Quartile 60
PPM previously implanted	14	7%
Previous diagnosis of epilepsy	43	22%
Had previously avoided salt	61	31%
Good Response to midodrine	143	73%
Symptoms abolished by midodrine	69	35%
Sodium tablets also prescribed	50	25 %
Fludrocortisone also prescribed	40	20 %

All patients had had syncope. The duration of symptoms prior to RABTC assessment varied from 4 to 300months. Thirty-nine patients had previously been diagnosed with epilepsy and treated with anti-convulsants to which there had been no response, resulting in referral to the RABTC. Anticonvulsants were weaned off in these patients

before midodrine was commenced. Follow up data was available for 184 patients (93%), while 11 were lost to follow-up. One hundred and fifty six (156) patients had a normal ECG, (ECG abnormalities in 35 patients are shown in Table 6.2.

Table 6.2: ECG Abnormalities

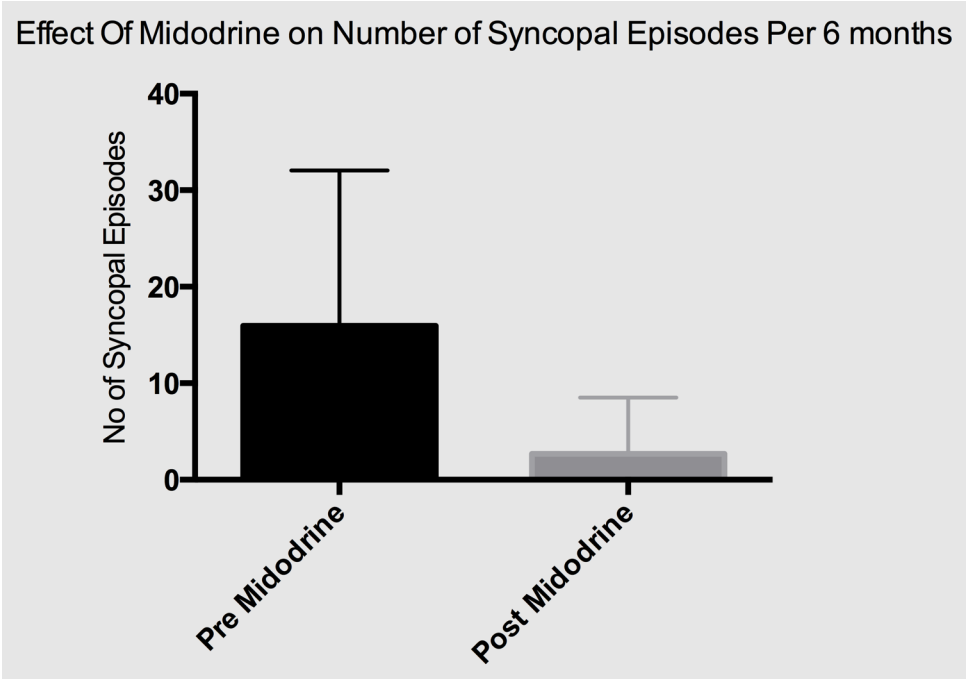
ECG Abnormality	Patients
Sinus tachycardia	2
Right bundle branch block (complete/incomplete)	9
Sinus bradycardia (<60, >50bpm)	2
Poor R wave progression in pre-cordial leads, but no Q-waves	4
Pre-excitation	3
Frequent ventricular ectopic beats	2
Voltage criteria for LVH	2
Left axis deviation	2
Dominant R-wave in V1	1
Inferior T-wave inversion	4
Unusual QT segment appearance	1
U wave	1
1st Degree AV block	1
Inferior Q-waves	1

There was improvement in symptoms of 143 patients (73%) treated with midodrine titrated upwards from 2.5mgs three times a day. The mean daily total dose of midodrine was 10mg. Sixty-nine (35%) patients had complete resolution of symptoms. A quarter (24%) of patients were already taking salt supplements as sodium chloride tablets. Forty patients (20%) had taken fludrocortisone without improvement. Nineteen patients (13% of responders) were able to stop treatment when symptoms resolved completely after 52±42 months of treatment. Fifteen patients (7%) could only tolerate the starting dose of midodrine, (2.5mg tds), because of side effects with increased dose. Twenty (20) of forty-one (41) of non-responders had to stop midodrine because of side effects. Seventeen patients (9%) had no response at all. Results are explained in table 6.3 & Figure 6.4.

Table 6.3: Descriptive analysis of Difference in number of syncopal episodes and Blood pressure pre and post midodrine per 6 months

	Number of patients	Mean	P value
Syncopal episodes pre midodrine	184	15.9±16.0	<0.05
Syncopal episode post midodrine	183	2.6±5.8	
Systolic BP Pre-mid	193	114±17	<0.05
Systolic BP Post-mid	190	121±18	

Fig 6.4: Effect of Midodrine on syncopal episodes pre and post midodrine per 6 months



6.3.2 Effect of midodrine on blood pressure.

We measured the effect of midodrine on blood pressure. As discussed above, all patients have measurement of blood pressure at the start of midodrine with subsequently regular monitoring. Mean systolic blood pressure rose from 114mmHg to 121 mmHg with midodrine treatment, (Table 6.3 & 6.4).

Table 6.4: Difference in Systolic blood pressure pre and post midodrine

Parameter	Pre Midodrine BP Systolic mmHg (n=193)	Post Midodrine BP systolic mmHg (n=191)
Mean	114	121
No	193	191
SD	17	18
Min	80	90
Max	174	180
Median	115	119
Lower 95% CI	112	118
Upper 95% CI	117	124

6.4 Discussion:

The management of reflex syncope can be difficult. Patient education is important, especially when there is a constant public health message warning against salt intake, and in spite of the fact that salt is an essential component of a healthy diet. The American Heart Association recommends 1.5g -2g of salt per day for a healthy person but more in a fainter from ~6g/day and could be as much as 10g/day. Caution should

be taken in prescribing Slow Sodium tablets as they may make the situation worse by retaining fluid in the bowel. Counterpulsation measures and the avoidance of prolonged standing may be useful(73), but only if there is sufficient warning before an attack. Whilst reflex syncope seems to be benign, the risk of accidents and injuries is clear, and counterpulsation may be ineffective if there is little warning before syncope. Patients should be informed about the mechanism and importance of recognising warning signs so that chances of injuries can be avoided. However, there is currently no treatment for reflex syncope that has been proven conclusively in a double-blind randomised, placebo-controlled trial. Many treatments have been advocated, and volume expansion has been the foundation for medical therapy and the conventional treatment include increased dietary salt and fluid intake(185).

Among prescription drugs for volume expansion, fludrocortisone is widely used, especially in younger patients. Scott et al(186) compared atenolol versus fludrocortisone in paediatric patients and found no beneficial effect over atenolol in preventing recurrence of syncope. Salim and Di Sessa(187) failed to demonstrate beneficial effect versus placebo in preventing syncope or pre-syncope in children. POST II(75) trial found no benefit from fludrocortisone when used as monotherapy for reflex syncope. However the recent randomized control trial (POST 2) by Sheldon et al (188) has found its beneficial effect. Beta-blockers are widely prescribed in reflex syncope but the evidence for benefit is scanty. It is thought that beta-blocker reduces myocardial inotropy. This then prevents the stimulation of left ventricular mechanoreceptors culminating in a Bezold-Jarisch Reflex, which is thought to be responsible for triggering reflex syncope. They might also block the effects on inotropy of increases in circulating adrenaline, and blunt the heart rate increase prior to

sympathetic withdrawal and syncope in many patients. However, conclusive evidence for all these theoretical effects in humans is missing. The majority of studies of β-blocker therapy in reflex syncope have been open-labeled and unblinded(189). Furthermore, where trial design includes randomisation and placebo-control, outcomes have only been measured in terms of reduction the number of positive tilt tests. However, the reproducibility of tilt-table testing is well known to be poor, and hampers its use both in diagnosis and in the assessment of treatments(190,191). There are currently no studies comparing the rate of syncope before treatment with the rate of syncope on treatment. In other studies, follow-up periods have been very short. Metoprolol(192), pindolol(193), propranolol(194,195), esmolol(189,196), and atenolol(197–199) have all shown benefit in uncontrolled studies, but, again, benefit was reliant on repeat tilt-testing in the majority of these, not long-term symptom review. In contrast, two reports show no benefit, with one described worsening of symptoms on atenolol treatment. Metoprolol was studied in the randomised, placebo-controlled, double-blinded, multi-centre POST trial(74), and this showed no benefit in prevention of long-term syncope recurrence. Despite the attractiveness of the pathophysiological rationale for β-blocker therapy in reflex syncope, as well as safety and relative tolerability, there is no good evidence in their favour. The trials of Fitzpatrick *et al*(200) and Brignole *et al*(201) used a variety of pharmacological therapies which included atenolol, scopolamine, clonidine, cafedrine, domperidone and dihydroergotamine; and found no differences between placebo and treatment arms(200,201) although few firm conclusions can be drawn because of the small numbers of patients and the even smaller number on each treatment. Theophylline can antagonize adenosine receptors shown to mediate vasodilatation. It has also been tested in two small-uncontrolled studies showing modest benefit(202). An abnormally

hypersensitive serotonin response within the central nervous system has been suggested as the cause of reflex syncope. Different studies have trialed selective serotonin reuptake inhibitors in reflex syncope. One randomised trial showed reduced syncope recurrence in 30 patients taking active medication compared with placebo(203), a subsequent study showed no benefit(204). Enalapril was also studied by Zeng et al(205) in 1998 and they found that it can prevent reflex syncope in patients, presumably because of its part in the inhibition of Cathecholamine release from sympathetic nerve endings (thought to be the cause of reflex syncope).

Studies have shown that hypotension as a result of abrupt sympathetic withdrawal resulting in vasodilatation and decreased peripheral resistance, could be the cause of reflex syncope(206–208). Peripheral venous pooling, implying a reduction in venous return has been shown to be the main factor on tilt to cause pre-syncope. Therefore failure of venoconstriction could be the cause of hypotension in these patients(209–211). Etilefrine which is a potent vasoconstrictor has no proven benefit(212).

So far midodrine (alpha agonist) is the only vasoconstrictor which has some beneficial effect in some studies although large randomised studies are lacking. Kaufman H(213) in 2002 studied the effect of midodrine in twelve patients with recurrent neurally mediated syncope and found it to be beneficial in improving orthostatic tolerance during head-up tilt, but without long-term symptom review. Another study(77) also recommended midodrine in extremely symptomatic patients, but follow-up was only for one month. A beneficial effect of midodrine in paediatric patients has been claimed(214), but outcomes were based on tilt test responses, and bias was introduced by addition of fludrocortisone therapy. In another study(78) midodrine had good effect

but it was open labeled. Romme et al (*STAND Trial)*(215) found no added beneficial effect over non-pharmacological treatment. Doyle et al(216) has also studied its efficacy comprehensively. A multicenter, international randomised placebo control trial (POST 4) is in progress to study role of midodrine in vasovagal syncope(217) and is expected to finish by next year. However, there will be no guidance for physicians looking after patients with troublesome reflex syncope for several years from this trial. Meanwhile many patients with severely limiting symptoms of recurrent syncope may be denied effective treatment. This is especially the case in the UK where midodrine has been unlicensed although things have changed recently. Physicians have to assume the risk of prescribing, and in the USA where the FDA has shown a desire to delicence the drug.

So far, no teratogenic data is available for midodrine and many patients who seem to require it are young women of fertile age. They need contraceptive advice. They should also be informed to stop this medication if they find themselves pregnant. However, reflex syncope tends to improve during pregnancy because of haemodynamic changes in the body caused by increased intravascular volume.

Our study found that midodrine gave a statistically significant benefit in over 70% of our patients, and complete resolution of syncope in 35%. Syncope rates fell very significantly. There was a clearly defined group who could not tolerate midodrine and a group whose symptoms resolved completely. At the same time, there were no instances of a hypertensive response to treatment. Mean systolic blood pressure rose by a small but significant amount. The study end-point was not dependent on tilt-test responses, which are unreliable. In the current absence of large randomised clinical

trials, our retrospective analysis provides beneficial evidence in reflex syncope. If simple lifestyle measures, avoidance of precipitating circumstances and salt and fluid supplementation prove to be inadequate, some patients might be deemed untreatable where midodrine might be effective.

6.5 Conclusion:

Reflex syncope is the most common cause of transient loss of consciousness. Simple measures like fluid and salt supplementation are the mainstay of treatment. Some patients with recurrent and frequent episodes require more than fluid and salt. No drug treatment has been proven beneficial so far. Midodrine can be helpful but evidence is lacking. In the absence of randomised control trials, our study provides some evidence of its efficacy. It has been unlicenced but this status has changed recently.

Chapter 7

7.1 Summary and future directions

Collapse is defined as an "abrupt loss of postural control" and is very common presentation to primary and secondary care. It accounts for up to 3% of emergency department cases, and 6% of hospital admissions. Many patients are labelled with "collapse?cause". It should be appreciated that collapse can be with or without TLOC/blackout. Causes without TLOC include falls, transient ischemic attacks, cerebrovascular accidents, road traffic accidents, metabolic abnormalities and intoxication. However, most collapse patients have TLOC. With the exception of a few very rare causes, TLOC is due to syncope, epilepsy or psychogenic blackouts. There are many similarities and overlap of clinical features in TLOC patients, and these can lead to misdiagnosis.

A potent cause of misdiagnosis is the huge variation in the ways TLOC patients are assessed and managed. Patients are commonly dealt with by a range of different specialties in different clinical settings, including GPs, A&E staff, acute medicine, neurology and cardiology. There is lack of a common clinical approach to assessment and poor risk stratification. Most clinicians take a "safe approach" as a result, and TLOC patients are often admitted to hospital unnecessarily and overinvestigated, which can increase confusion and healthcare cost. We have therefore tried to approach these issues via a dedicated "Rapid Access Blackout Triage Clinic" (RABTC). In this thesis, we have addressed the problem of TLOC in five projects arising from the triage of

patients seen in that clinic.

Chapter 1 expands the scene-setting for the thesis. Chapter 2 is a report of outcomes of a specialist nurse-lead RABTC in 1226 out of >3000 patients assessed since 2008. The clinic uses custom clinical evaluation and risk stratification tools for patients with TLOC with cardiologist supervision (author). Analysis of follow up data has revealed that clinical evaluation along with 12 lead ECG should be able to make diagnosis in majority of the cases. It can effectively triage patients, avoid unnecessary investigations, can initiate treatment and seek other specialty advice where necessary. Widespread use of an RABTC assessment is recommended for TLOC patients.

Nearly two thirds of patients presenting to the RABTC are over 65 years. Chapter 3 reports a cohort of these elderly patients with minor ECG abnormalities that are not accepted indications for pacemaker insertion under current guidelines. We speculated that such abnormalities could progress suddenly and transiently at the time of TLOC. Patients underwent pacemaker implantation directly, in the hope of sparing patient's exhaustive investigations, delay, and the risk of further blackouts and injury. The outcome of early pacing in these patients is given. Results have revealed decreased hospitalisation after pacemaker insertion reducing healthcare cost. Mortality benefit cannot be concluded because of follow up duration. Our results can be an initial step and more data is required before these ECG abnormalities can become part of the pacing guidelines.

TLOC patients typically undergo very extensive but unfruitful investigation. Large numbers of patients with blackouts referred to the RABTC have had many investigations elsewhere with no conclusion. In Chapter 4, we studied the outcome of long-term ECG monitoring in such blackout patients using a new insertable ECG loop

recorder, (ILR). We explored the impact of the ILR on time to Symptom/ECG correlation and time-to-diagnosis, and the potential to avoid wasteful and unhelpful investigations. The findings were that 57 of 141 patients, most of whom had had extensive investigations elsewhere before referral, had symptom/ECG correlation within an average of 4 months from insertion. We concluded that early use of ILRs in patients with unclear diagnosis can help in improving the outcome. It can help achieving high symptom/ECG correlation and high early diagnostic yield. ILRs can be safely implanted in "office" conditions.

Such results are compelling and advocate for the early use of ILRs rather than low yield and costly tests. However, our data showed that fewer and fewer patients sent useful recordings after the early months. In this and many other blackout cohorts, about 50% of patients still defy diagnosis. In ILR patients this is partly because only a single lead ECG is recorded. This is sufficient for abnormal tachycardias and bradycardias to be detected, but cannot give a diagnosis where there is, for example, a mild sinus tachycardia during TLOC, although vasodepressor component of reflex syncope also contributes to the TLOC episodes. Ideally, implantable monitors for patients with blackouts would detect ECG, Blood Pressure and the Electroencephalogram, (EEG). These physiological parameters would be sufficient to distinguish between syncope, epilepsy and psychogenic blackouts. In Chapter 5 the results of in-depth analysis of the ECG in these patients are presented. Heart rate variability was used to calculate sympathovagal balance in patients known to have reflex syncope, epilepsy and psychogenic blackouts. The technique used derived a measure of the degree of "turbulence" in the balance between these limbs of the autonomic nervous system, and we were able to show that this differed between each type of blackout patient. The cohort of patients were recruited using video telemetry data from a Regional epilepsy

centre. We showed that epilepsy, psychogenic TLOC and syncope patients have different degrees of SVB marginality at TLOC. This suggests that derived ECG parameters could be used to enhance the capabilities of insertable loop recorders at distinguishing between causes of TLOC where symptom ECG correlation is not diagnostic and cannot guide treatment. More data with large number of patients is required to get statistically significant results.

Finally, the treatment of TLOC depends on its underlying cause, clinical and test evaluation, certainty about a diagnosis and any perceived risks a patient may have. By far the commonest cause is reflex syncope. Reflex syncope is responsible for fainting, but can be convulsive and mimic epilepsy. In a significant subset of patients with reflex syncope, there is little response to the usual measures of salt and fluid supplementation and counter-measures such as avoidance of prolonged standing. A good number of drugs have been proposed as helpful for the treatment of reflex syncope in these patients over the last 30 years, but one-by-one, they have failed to show significant benefit when put to rigorous testing. One drug, midodrine an alpha-adrenoceptor agonist, has not yet been tested in a double blinded randomised controlled trial, but is being tested by a group in Canada, and will report in about 2 years time. We describe our experience of midodrine (an alpha agonist) of nearly 200 patients in this condition in Chapter 6. So far, this is the only study with largest number of patients and we concluded that it is safe and can effectively reduce number of syncopal episodes in reflex syncope.

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