for example), situations in which this relative motion results in significant over-exposure of critical organs must be avoided. More advanced 4D deliveries should aim at using motion as another degree of freedom available for sparing critical organs. Temporally optimized DMLC tracking is a promising tool to investigate in this context.

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CORRELATED POINCARÉ INDICES FOR MEASURING HEART RATE VARIABILITY

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Abstract

Poincaré indices are usually applied to HRV to summarise long data sets collected over 24 hrs. Many applications of HRV are interested in dynamic, short term changes (<1min). This study uses Poincaré indices published through the 1990's to the present, to determine which of them are correlated over the short term (25 beats). Dynamic changes were observed in 12 subjects pre-operatively receiving fentanyl and midazolam sedation with ECG collected for 5 mins before and 5 mins after fentanyl administration. Poincaré indices with a strong correlation ($r>0.85$) between the indices for each of the 12 subjects ($p<0.001$) (particularly with the common measures SDNN, RMSSD, pNN50 and meanRR) were identified. These indices will not be used for further investigation of dynamic effects of fentanyl and midazolam, two sedative drugs used in anaesthesia and intensive care. Indices that proved less suitable for short term analysis (eg. presence of outliers, inability to produce a valid index with smaller number of beats) were also identified. A shortlist of Poincaré indices that do not correlate strongly with commonly used measures may prove interesting in determining dynamic characteristics of the effect of sedative drugs on autonomic nervous system activity.

Key words Poincaré plot, heart rate variability, HRV, fentanyl, sedative

Introduction

Poincaré plot is the common name used for a scatter plot to analyse heart rate variability (HRV) where the time between R-waves on an ECG, the R-R interval (RRI) is plotted against the succeeding RRI. A typical plot can be seen in Fig 1. Traditionally, Poincaré plots are made with data collected over 24hrs[1-6] or 12 hrs[7]. Shorter time periods have also been used more recently: 5-20mins[8-13], and <2mins[14,15].

Many indices have been developed to characterise the nonperiodic behaviour of HRV displayed in Poincaré plots, particularly with 24hr data, and these have been compared

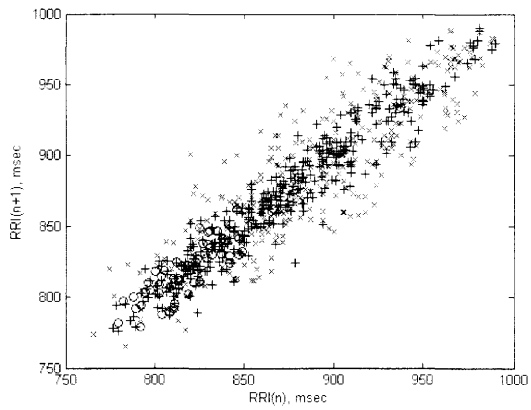

Figure 1. *Typical Poincaré plot (subject 3) for 10 mins of R-R intervals. Legend: x=baseline, o=fentanyl administration, +=post-fentanyl.*

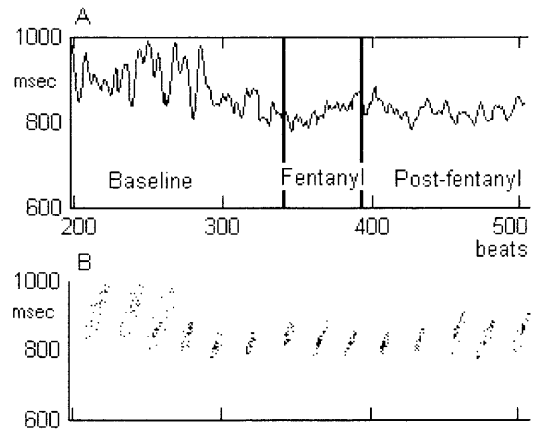

Figure 2. *A. Portion of typical data set (subject 3). B. Poincaré plots for each subset of 25 RRI.*

with known markers for autonomic nervous system activity: time-domain, and spectral power indices.

The time-domain indices are well described and extensively used as markers of autonomic system activity[16]. SDNN, the standard deviation of the RRI, reflects all cyclic components responsible for variability, the variance being mathematically equal to total power of spectral analysis. RMSSD, the square root of the mean squared differences of successive RRI, is a purely vagal index. pNN50, the proportion of intervals greater then 50 ms, is used as a reliable marker of vagal activity[17]. Furthermore, the RRI itself is an index of sympathovagal balance[18,19].

This study will compare these common measures of HRV with the published Poincaré indices. Indices which do not correlate strongly with commonly used measures may be useful in investigating dynamic and short-lived changes to HRV, such as those that occur during exercise[20] and fentanyl and midazolam sedation.

This study uses the dynamic effect of fentanyl on HRV to assess these indices. Fentanyl is a well-known depressor of the respiratory system, heart rate, and HRV power. Fentanyl was used because of its lipophilic nature; it enters the brain rapidly after intravenous injection. Contradictory results have been reported regarding the effect of fentanyl to cause a shift to increased parasympathetic dominance[21-24]. This study will determine indices that may be useful in further analysis of the effect of sedative drugs on autonomic nervous system activity.

Methods

Indices

A survey of published methods of Poincaré analysis with literature from the 1990's to the present day (Table 1)[25] found 48 indices applicable for short period HRV analysis. Indices not used were those using patterns, 3D, and density indices[1,2,6].

In addition to the surveyed Poincaré indices, three statistical time-domain indices (SDNN, RMSSD and pNN50), and an index of sympathovagal balance (mean RR interval[18], meanRR) were used to analyse the same data set: 12 subjects undergoing fentanyl and midazolam sedation.

Table 1. *Summary of Poincaré indices surveyed.*

Author	Index	Description
Ashkenkazy [33]	*A.mag|sd| *A.sgn(sd)	Magnitude and sign of differences
Contreras[34] Lagged plots	*SDsd8 *SDsd10	Lag of 8 beats Lag of 10 beats
Copie [3]	C.Area *C.pNN30	(pi.L.W)/4
D'Addio [5]	D.PLW	% length at Wmax
Ewing[35]	*E.pNN6.25	Percentage successive difference >1/16
Goldberger [18,19]	*meanRR *G.RMS	Sympathovagal balance Deviation of RRI from straight line
Griffin [36]	*p50	Median data point
Guzik[37] Assymetry	*Gz.acc *Gz,dec	Accelerations Decelerations
Hirose [38]	*Hi.SD/SDsd	Ratio SDNN to SDsd
Huikuri [4] Ellipse	nSD1 nSD2 H.D1 H.D2	Normalised SD Distances from mean to avg max diff & max diff
Kamen [9,10] Histogram variances	K.SD1 K.SD2 *K.NRR *K.Nsd	Width of RR histogram Width of delta RR Normality of RR and differences
Lewkowicz [39] Multipoles	*skew.RR *skew.sd *kurt.RR *kurt.sd	Skewness Kurtosis
Marciano [1] Radii of inertia	M.A M.B M.G	Max radius Min radius Gradient RR (avg)
Moraes [6] 3D	P2 P3	Max longitudinal & transverse ranges
Otzenberger [12] Pearson	rRR	Interbeat autocorrelation
Raetz [8] Quadrants	Qa-d *Qchi2	Distribution of sequences
Schechtman [7] Dispersion	W10 W90	Width at 10% Width at 90%
Toichi [11]	L T *log(L*T) L/T CV	4* SD longitudinal & transverse axis Coefficient of variation
Tulppo [30]	T.SD1 T.SD2 T.SD1/SD2 T.SDsd	Ellipse rotated +/- 45deg in polar coordinates, then SD along axis

Table 2. *Summary of patient data.*

	F n=10 Mean (SD)	M n=2 Mean (SD)	Total n=12 Mean (SD)
Age	40.5 (14.3)	36.0 (25.5)	39.8 (15.1)
Weight	75.6 (12.3)	93.0 (5.7)	78.4 (13.2)

Subjects

Ethics approval for the study was given by Flinders Medical Centre Ethics Committee. Consenting subjects were recruited if they were scheduled for minor surgical procedures, aged between 18 and 80 years, weight 40-120 kg, with a low frequency of ventricular arrhythmias (<10 premature complexes/hr), no recent history of cardiac-rate controlling drugs, and no clinical signs of peripheral neuropathy. They were studied in the ten minutes before anaesthesia was induced. Before testing they had been supine for at least 15mins, however, they were not all relaxed. As could be expected before surgery, they were often anxious. Baseline ECG, SpO2 and spirometry was recorded (Datex-Ohmeda AS/3 Anaesthetic monitor with S/5 Collect) for 5 minutes then a standard dose of midazolam (2.5 milligram) was given, followed by a randomly selected bolus of fentanyl (50, 75, 100 or 150 microgram). A further 5 minutes was then recorded. Oxygen was administered by facemask throughout.

Data collection

The analog ECG, lead II (Hewlett Packard 78353B, CA, USA) was digitised at 1000 Hz with 12 bits resolution (NI 6035E DAQ, National Instruments Corp, TX, USA) and stored (LabVIEW, National Instruments Corp, TX, USA) for off-line analysis.

Analysis of the data was performed using custom software developed for this study on a PC using MatLab (The MathWorks Inc., Natick, MA, USA). The ECG R-waves were identified by whichever of two methods produced the least artifacts: simple threshold or mean of backward differences[26]. Artifacts were automatically identified if the RRI was more than 30% from the mean RRI and then visually verified and corrected to the actual ECG R-wave peak. The few remaining artifacts were visually identified and manually corrected.

Data analysis

The indices were measured over data sets of 25 beats. This window size was selected as a trade-off between a small window size that captures dynamic changes, and the ability to generate meaningful indices from the number of beats. This provided at least 26 observations for each subject (some data sets were longer than 10 minutes).

The linear relationship strength between variables was determined by measuring Pearson correlation coefficients between the common indices and the Poincaré indices, and also between the Poincaré indices. For a correlation coefficient to be meaningful there are some conditions that must be met[27]: a) the relationship is linear, b) no outliers, c) no subgroups, and d) one of the variables has a normal distribution. Visual analysis of the index values confirmed linear relationship and no subgroups. Normal distribution of the main indices was assessed with Shapiro-Wilks test. Outliers were recorded for analysis. The criteria for a strong correlation was an average coefficient $r>0.85$ (explained variance of 72%) and $p<0.001$ for each of the 12 subjects.

Results

Summary of the patient data is shown in Table 2. Female subjects predominated in the scheduled operating lists available for this study.

The Shapiro-Wilks test showed the main indices were normally distributed for most subjects. Normal distribution was rejected in only a few subjects for each of the main indices: SDNN 1, RMSSD 2, meanRR 3, rRR 2. The test for pNN50 could not be calculated due to the low number of counts in some subjects.

Strong correlations with an average coefficient $r>0.85$ (explained variance of 72%) and $p<0.001$ for each of the 12 subjects with total variance (SDNN) and vagal activity (RMSSD, pNN50), and sympathovagal balance (meanRR), were seen in 18 of the 48 published indices(Table 3). In the (Table 3) column headed Subjects $p<0.001$, an asterisk indicates all 12 subjects had $p<0.001$. Where a number is written it indicates the number of subjects who had $p<0.001$. However for the mean correlation coefficients given, all subjects at least had a $p<0.05$.

One other index was observed to have multiple strong correlations: rRR, the correlation of each RR interval with the subsequent RR interval. This was strongly correlated with 3 other indices (Table 3).

Table 3 also includes four less-strongly correlated indices: C.Area, E.pNN6.25, M.A & M.B. These indices failed to meet the criteria of $r>0.85$ and $p<0.001$ for each of the 12 subjects. These indices also had the highest counts of outliers.

The surveyed Poincaré indices that were not strongly correlated with SDNN, RMSSD, meanRR or rRR are listed in Table 4.

Discussion

Technical problems

Some index calculations proved difficult to determine with smaller window length, and some required changes to the published method (previously published[25]).

Correlation

The criteria for a strong correlation were set high for this small sample of subjects undergoing limited dynamic change in heart rate variability. Using $r>0.85$ explained 72% of the variance in the sample. Requiring a $p<0.001$ for all 12 subjects reduced the likelihood of chance correlation.

The number of outliers varied between indices: the highest (12) in Table 4 is only 2.2% of data points. Useful indices would be expected to have fewer outliers.

Table 3. *Pearson correlation coefficients, mean of 12 subjects, for well correlated (r>0.75) indices.*

Index	Corr with[a]	r[b] (avg 12)	Subjects p<0.001[c]	Outliers
A.mag|sd|	R	0.97	*	3
C.Area	R	0.77[d]	11‡	8
CV	S	0.98	*	2
E.pNN6.25	P	0.88[d]	10	6
G.RMS	M	1.00	*	1
Hi.SD1/SD2	C	0.89	*	6
K.SD1	S	1.00	*	2
K.SD2	R	1.00	*	4
L	S	0.98	*	2
L/T	C	0.91	*	4
log(L*T)	S	0.92	*	5
M.A	S	0.76[d]	10‡	5
M.B	R	0.85[d]	11‡	9
nSD1	S	0.94	*	2
nSD2	R	0.98	*	4
P2	S	0.94	*	1
P3	R	0.92	*	7
p50	M	0.99	*	1
SDsd10	R	0.89	*	1
SDsd8	R	0.88	*	4
T	R	1.00	*	4
T.SD1	S	0.98	*	2
T.SD1/SD2	C	0.91	*	4
T.SD2	R	1.00	*	4
T.SDsd	R	1.00	*	4

[a] C=rRR, M=meanRR=G.RR, P=pNN50, R=RMSSD, S=SDNN
[b] n = 26, number of 25 beat observations
[c] *all subjects p<0.001, ‡all subjects p<0.05
[d] correlation not considered strong by criteria

Table 4. *Shortlist of indices for very short periods (25 beats): common measures and uncorrelated indices.*

Index	Outliers	Correlated with
SDNN	2	See Table 3
RMSSD	4	See Table 3
meanRR	1	See Table 3
rRR	1	See Table 3
A.sgn(sd)	0	Qb, Qc (r=0.78)
K.NRR	11	
K.Nsd	8	
Qchi2	10	
W10	3	
W90	6	
Qa	3	
Qd	3	
D.PLW	0	
H.D1	3	H.D2 (r=0.86)
M.G	8	
skew.RR	2	
skew.sd	6	
kurt.RR	12	kurt.sd (r=0.97)
Gz.acc	0	Gz.dec (r=-0.92)

Agreement

Strong correlations with vagal markers predominate as found by Hayano et al[28]. Vagal effects on the sinus node occur faster than sympathetically mediated effects[4], causing instantaneous changes in RRI that are easily measured over short windows. This is demonstrated by the number of indices strongly correlated with RMSSD.

This study finds correlations in agreement with published studies for: E.pNN6.25, K.sd1, K.sd2, L, T, M.A[1], nSD1 & nSD2[4], P2 & P3[6], T.SDsd, T.SD1 & T.SD2[29,30].

The index rRR was known not be equivalent to SDNN or RMSSD; Otzenberger[12] claiming it revealed a different characteristic of dynamic behaviour.

In this study the set of pNN50, pNN30 and pNN6.25 showed no correlation with RMSSD. This was due to the absence of intervals greater than 50 msec in many of the 25 beat windows.

Some unexpected strong correlations were found with:
RMSSD: A.mag|sd|, C.Area[3], M.B (not M.G[1]), SDsd8 & SDsd10 (not sympathetic)
SDNN: CV[11], log(L*T) & S (not vagal activity[11])
meanRR: G.RMS (not RMSSD), p50
rRR: Hi.SD1/SD2, L/T (not sympathetic activity[11]), T.SD1/SD2[12].

Advantages

Poincaré plot indices were chosen because the data has no requirement for normal distribution as with summary statistics, no requirement for stationarity[30], minimum data set (e.g., the low frequency peak needs 2 mins[16]) or special processing that spectral analysis requires, and is more resistant to the influence of ectopic beats and other arrhythmias[9]. Measures of chaotic behaviour have been found to be reliable on samples as short as 500 beats[31], however the application of these indices on shorter 25 beat samples has not been investigated.

The commonly used time domain indices are recognised by Carrasco[32] as simple-to-calculate surrogates for many indices that are difficult to measure (including frequency domain variables).While SDNN reflects total power of variation, and RMSSD reflects vagal tone, there are no indices for measuring sympathetic tone. Indexes that do not correlate strongly with SDNN or RMSSD may prove useful in determining dynamic characteristics of cardiac nervous system activity.

Limitations

Throughout this study, all subjects received oxygen using a facemask to ensure adequate oxygenation after fentanyl administration. The application of a facemask does affect the HRV, but this effect should be consistent over the 10 mins of the study.

This study uses only a limited range of HRV over a short time (10 mins) to assess correlations of the indices. This is in agreement with the proposed application: further assessment of the dynamic effect of fentanyl on HRV.

Conclusion

The use of Poincaré indices over shorter time periods may require different methods for calculating for the indices due to the smaller sample sizes, but even small windows of only 25 RR intervals can still hold useful information.

This study using subjects undergoing fentanyl and midazolam sedation has shown that many published Poincaré indices are strongly correlated over short periods with commonly used indices SDNN, RMSSD, meanRR and rRR. Strongly correlated indices can be set aside and not used in further analysis of the fentanyl effect.

Further investigation of the Poincaré indices that do not correlate strongly with commonly used indices may prove interesting in determining dynamic characteristics of the effect of sedative drugs on autonomic nervous system activity.

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CORRELATION BETWEEN PARAMETERS DESCRIBING TUMOUR MOTION AND ITS LOCATION IN THE LUNGS

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Abstract

Characterizing respiratory-induced tumour motion is an important step in the effective image-guided radiation treatment of moving tumours, especially for tumours in the lung and lower abdomen. This study characterized tumour motion based on a piecewise linear model representing tumour motion at defined stages of the breathing cycle. Lung tumour locations were categorized based on broncho-pulmonary segments. Association rules between tumour motion characteristics and their locations in the lung were discovered and parameterized through statistical analysis. Results show there is a correlation between tumour motion characteristics and tumour location in the lungs. Generally, tumours with small motion (amplitude < 10mm) are observed most frequently in the apex region of lung or when attached to a fixed structure, such as the chest wall or aorta. Tumours with relatively large motion (amplitude > 20mm) are located close to the diaphragm or mid-level periphery of the lungs close to the chest wall.

Key words tumour locations, respiratory motion, correlations

Introduction

The goal of radiation therapy is to ensure precise and accurate delivery of a curative radiation dose to a tumour while limiting the exposure of surrounding healthy tissues and critical structures to radiation and so avoid serious treatment complications[1]. Radiation therapy for localized cancers of the lung is common and often applied in daily fractions over a few weeks. Intra-fraction tumour motion is often induced by the patient's respiration and it is this motion that poses a major challenge for precise radiation treatment delivery, especially when the amplitude of tumour motion is greater than a centimeter[1-3]. Understanding and characterizing the natural tumour motion behavior in various locations is of some importance to precision radiation treatment delivery. Once understood and characterized, prediction of this tumour motion behavior will facilitate advanced real-time treatment of patients under free breathing conditions.

It is known that tumours of the lung, kidney, liver or prostate have distinctive respiratory-induced motion properties[4]. The objective of this work is to identify the correlation between respiratory-induced tumour motion characteristics and its location in the lungs. Establishing reliable correlations between the motion characteristics and tumour location will enable refinement of the predictive