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Statistical analysis of the DIAMOND MI study by the multipole method

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Abstract

We present a new method to describe the dynamics of the beat-to-beat RR time series. The classification of the phase-space plots obtained from RR time series is performed by a calculation of parameters which describe the features of the two-dimensional plot. We demonstrate that every parameter has its specific consequence on the evaluation of the state of the cardiac function. By applying the method to the DIAMOND MI study we demonstrate that these parameters have more prognostic power than previously suggested risk markers. The results suggest that the RR intervals constitute a highly complex time series which necessitates the use of refined mathematical–statistical methods in order to reveal pathologies in the heart rate.

Keywords: heart rate variability, recurrence plot, multipoles, DIAMOND MI study

1. Introduction

Reduced heart rate variability (HRV) is an important prognostic factor predicting sudden arrhythmic death after acute myocardial infarction (AMI) (Task force of The European Society of Cardiology 1996, Tapanainen *et al* 2002, Wessel *et al* 2000b, Kleiger *et al* 1987, Schwartz *et al* 1992, Meyerburg *et al* 1992, Malik *et al* 1990, Makikallio *et al* 1999). Several studies have demonstrated increased arrhythmic as well as non-arrhythmic mortality in AMI populations with low HRV. Those studies included traditional methods based on time- or frequency-domain analysis and newer fractal analysis techniques which are based on time-domain analysis (Thurner *et al* 1998a, 1998b, Peng *et al* 1995, Mäkikallio *et al* 2001, Saermark *et al* 2000,

Ashkenazy *et al* 2001, Wilson *et al* 2002, Voss *et al* 1996, Schmidt *et al* 1999, Wessel *et al* 2000a).

Two methods have separated themselves exhibiting more prognostic power than the others in comparative studies. One is the short-term fractal scaling exponent α_1 which evolved as a powerful predictor of death in the survivors of AMI (Peng *et al* 1995). In a comparative study it was shown that α_1 is a better predictor of death than the traditional measures of HRV among patients with AMI and a low wall motion index. It also predicted independently arrhythmic death which neither of the traditional HRV measures did after adjustment for clinical risk factors (Huikuri *et al* 2000).

The other is the multipole method, a recently developed method to describe time series with a highly complex time evolution computing various parameters (the multipoles) descriptive of the time series (Lewkowicz *et al* 2002, Bloch Thomsen *et al* 2001). In clinical medicine, the dynamics of the RR time series is commonly represented by the so-called recurrence plot (Huikuri *et al* 1996, Kamen *et al* 1995, 1996, Brennan *et al* 2002), where each RR interval is plotted against the previous one. The method replaces the classification of the recurrence plot by visual inspection with the computation of the various multipoles. The two-dimensional recurrence plot is interpreted as a two-dimensional body where each data point is assigned a unit mass; the origin of the coordinate system is chosen in the centre of mass. Therefore one does not ignore the varying density of data points in the recurrence plots which might lead to similar contours for different heart dynamics, which has been the major obstacle for bedside application (Malik 1998). Each of these multipoles constitutes a measure exhibiting its particular facet for assessing the heart function. It includes, but also extends beyond, the integrative measures of HRV.

1.1. The DIAMOND MI study

The DIAMOND MI was a randomized double-blind-controlled study of Dofetilide in post-MI patients (The DIAMOND Study Group 1997). The study included screening of consecutive patients with left ventricular dysfunction in association with recent myocardial infarction. It included patients with an acute MI and a left ventricular wall motion index (WMI) $<$ 1.2. A substudy of the DIAMOND MI was designed in order to determine and compare the prognostic power of traditional HRV measures with those of new fractal measures (Huikuri *et al* 2000). HRV was obtained from consecutive RR intervals from 24 h ECG recordings 5–10 days after AMI. Results were reported on 446 patients who fulfilled the criteria for meaningful RR interval variability analysis. The mortality was 25.6% after a follow-up of 685 + 360 days (114 died). 75 deaths (17%) were classified as arrhythmic and 28 (6.3%) were classified as non-arrhythmic cardiac deaths.

2. Methods

The present study makes use of four different multipoles: one of the quadrupole moments, two of the octupole moments and a hexadecapole-related moment.

The quadrupole moment Q_{yy} describes the overall distribution of the data points along and vertical to the diagonal of the recurrence plot. It vanishes for an elliptically shaped distribution with an axis ratio of $\sqrt{2}/1$, where the data points are Gaussian distributed along the principal axes.

One of the octupole moments (T_{xxx}) expresses the skewness of the two-dimensional body along the x-axis and the other (T_{yyy}) on the y-axis.

Table 1. Predictive accuracies of the various HRV measures.

Variable	High risk values	Sensitivity	Specificity	PPA	NPA	OPA
Q_{yy}	$Q_{yy} \geqslant -750$	64	62	36	83	60
κ_{yx}	$\kappa_{yx} < 1.96$	69	63	39	86	64
T_{xxx}	$T_{xxx} \geqslant -25$	70	54	35	84	60
T_{yyy}	$T_{yyy} \geqslant -3.567$	69	43	29	80	55
SDNN	SDNN < 65	39	75	34	78	56
LF	(ln) < 5.5	58	60	36	79	58
HF	(ln) > 5.5	58	58	35	79	57
LF/HF	<1.6	59	59	34	78	56
CMP_3	$CMP_3 > -2.5$	79.8	55.4	38.1	88.9	65
CMP_4	$CMP_4 > -1.4$	73	64	43	90	67
α_1	$\alpha_1 < 0.75$	62	73	46	84	65

PPA: positive predictive accuracy, NPA: negative predictive accuracy, OPA: overall predictive accuracy.

The hexadecapole-related moment we employ is the ratio of the kurtosis along the y-axis and the kurtosis along the x-axis, κ_{yx}. The kurtosis vanishes for a Gaussian distribution and is increasingly positive for progressively more peaked distributions.

2.1. Univariate analysis

The outcome variable was death within the follow-up period (685 + 360 days).

For each of the four variables (multipoles) the cut-point which maximizes the sum of sensitivity and specificity was chosen.

2.2. Multivariate analysis

After fixing the cut-points each variable was considered as a binary one. We used the multiple logistic regression. The appropriate model assumed that $\log(p/(1-p))$, where p is the probability of death, is the linear combination of the four multipole variables and their paired interactions (products). We used the backward elimination approach, which started with the model with all four multipole variables and all six interactions and step by step excluded one of the variables or interactions, which did not significantly improve the goodness-of-fit (the agreement between the model and the data).

The final model included only effects significant on the standard level of 0.05. In section 3 we show the odds ratio (i.e. the ratio of the odds of the death in patients with high-risk values versus low-risk values) and the 95% confidence limits for all the variables in the final model.

All calculations were performed using SAS 8.12. (SAS Institute, Cary, NC).

3. Results

The dichotomized variables for bad prognosis, i.e. death within the follow-up period, were defined as $Q_{yy} \geqslant -750$, $T_{xxx} \geqslant -25$, $T_{yyy} \geqslant -3.567$ and $\kappa_{yx} < 1.96$.

Table 1 compares the sensitivity, specificity and predictive accuracy values of the various measures: the quadrupole moment Q_{yy}, the hexadecapole moment ratio κ_{yx}, the two octupole moments T_{xxx} and T_{yyy}, the combination of the three multipole parameters T_{xxx}, T_{yyy} and κ_{yx} (CMP_3) as derived by the multivariate analysis and the combination of all four multipole

Table 2. Ten patients from the DIAMOND MI study with low-risk Q_{yy} values and elevated risk kurtosis ratio (<2.5).

Patient	Patient status	Q_{yy}	κ_{yx}
1	Deceased	−1828	1.97
2	Deceased	−1560	2.01
3	Deceased	−1797	2.25
4	Deceased	−1856	2.27
5	Deceased	−2101	2.31
6	Deceased	−2637	2.36
7	Alive	−1635	2.37
8	Deceased	−1525	2.38
9	Deceased	−1926	2.40
10	Deceased	−1702	2.43
11	Deceased	−1426	2.48

parameters (CMP_4). The predictive power of these measures is compared with those of the other, more traditional HRV measures (α_1, SDNN, HF, LF and LF/HF) (Huikuri *et al* 2000).

The final model of the multiple logistic regression included the dichotomized variables:

κ_{yx} (OR = 3.255, 95% CI = (2.020, 5.243))
T_{yyy} (OR = 1.936, 95% CI = (1.196, 3.136))
T_{xxx} (OR = 2.168, 95% CI = (−1.333, −3.525))
(OR: odds ratio, CI: confidence interval).

This combined model of three multipole parameters (CMP_3) achieves the sensitivity of 79.8%, the specificity of 55.4% and an overall predictive accuracy of 65%.

By combining all of the four multipole parameters (CMP_4) one obtains an overall predictive accuracy of 67%.

Table 2 lists ten patients from the DIAMOND MI study which have low-risk Q_{yy} values but an elevated risk kurtosis ratio (<2.5). The mortality in this group was 90%, remarkably high relative to the overall mortality of 25.6%.

Figure 1 shows Kaplan–Meier survival curves for the scaling exponent α_1, the SDNN and the combined parameter CMP_4.

In order to demonstrate the relevance of the octupoles we include figure 2 which shows recurrence plots for two of the recordings from the DIAMOND MI study with similar quadrupoles. Figure 2(a) shows a survivor with the highest concentration of data points on the positive part of the x-axis (negative octupole), whereas figure 2(b) shows the plot of a deceased individual with the major part of data points concentrated on the negative part of the x-axis (positive octupole).

4. Discussion

The series of RR intervals is an excellent example of a non-stationary and non-linear time series with a very complex behaviour. It seems reasonable to expect that the regulation of the heart rhythm, which is a very complex mechanism due to its dependence on many subsystems in the body, can be described optimally only by a method which has a diversity of different parameters describing partly different behaviours of those subsystems.

The quadrupole moment, although resembling a standard deviation for the two-dimensional distribution, differs fundamentally from the one-dimensional standard deviation

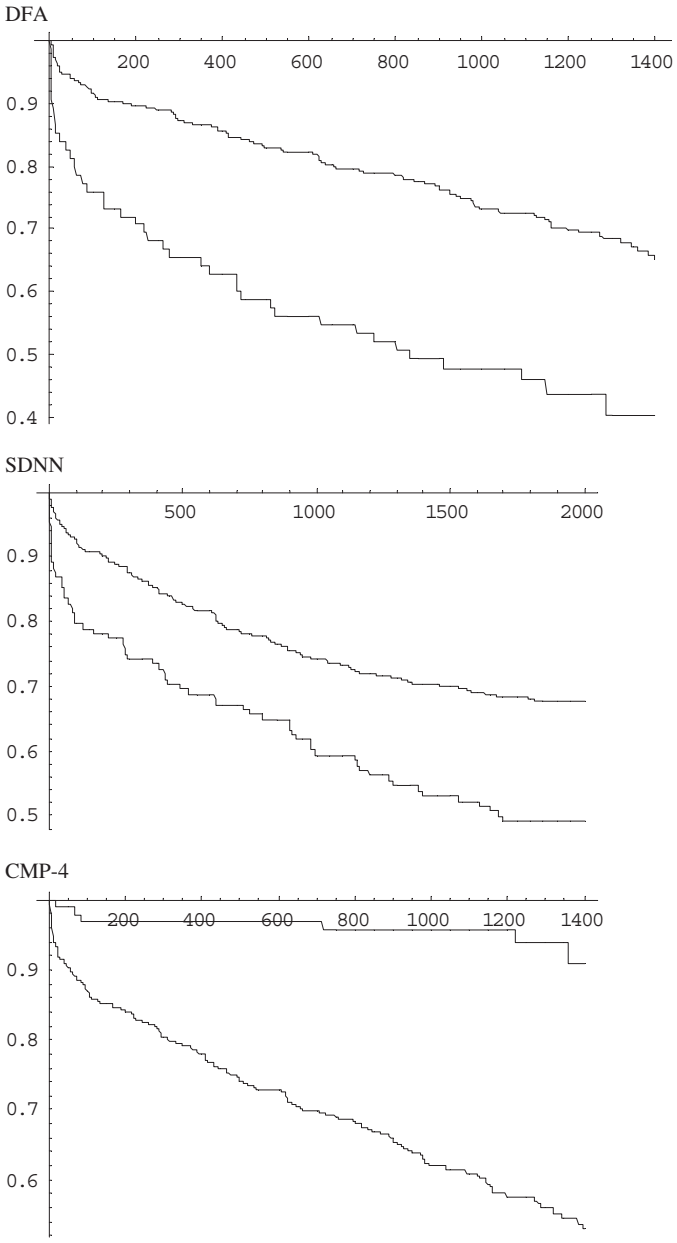

Figure 1. Kaplan–Meier survival curves for the DIAMOND MI study: (a) by the fractal scaling exponent α_1 (upper branch $\alpha_1 \geqslant 0.75$; lower branch $\alpha_1 < 0.75$), (b) by the SDNN (upper branch SDNN $\geqslant$ 65 ms; lower branch SDNN $<$ 65 ms) and (c) by the CMP_4 (upper branch $CMP_4 \leqslant -1.4$; lower branch $CMP_4 > -1.4$).

of the RR interval time series, the SDNN, which does not include any time ordering (shuffling the RR intervals will result in the same value for SDNN). The various multipoles due to the very construction of the recurrence plot bear intrinsic time dependence and thus convey a quantification of the cardiac system's dynamical properties. This explains why Q_{yy} is superior to SDNN as a prognostic indicator.

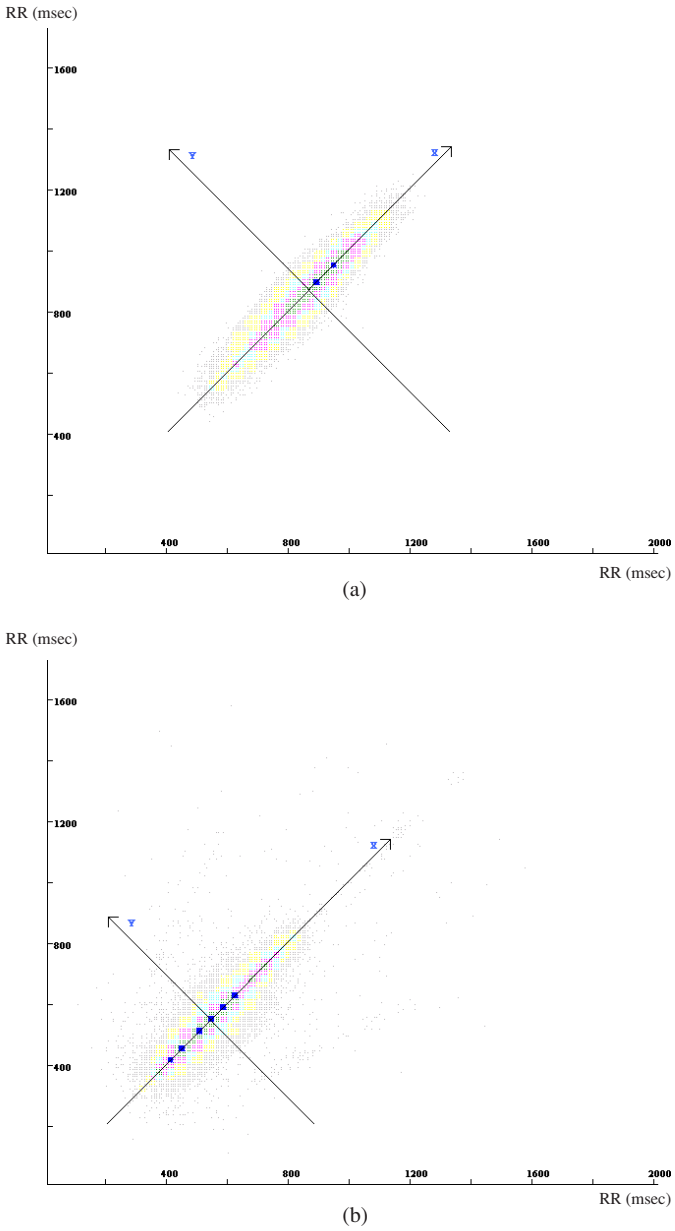

Figure 2. Phase-space plots for survivor (a) and non-survivor (b). They have approximately the same quadrupole moments but different octupole moments. (a) is an example of positive x-skewness, and (b) is an example of a negative x-skewness.

(This figure is in colour only in the electronic version)

Nevertheless, a low-risk quadrupole, indicating a considerable spread of data points, might also be obtained by large concentration of data points near the average value (the heart beats for extended periods with a low variability) together with spots of high density of points far away from the average (the heart beating some periods with a very high variability, as typical

for arrhythmia). This configuration results in a high-risk kurtosis ratio. This combination of low-risk quadrupole with a high-risk kurtosis ratio appears in the DIAMOND MI study in ten individuals, listed in table 2.

A similar analysis can be applied to the octupole moments. Two different distributions with the same mean and the same variance may differ with respect to the position of their maxima relative to their common mean. Skewness is a quantitative measure of this lack of symmetry. A distribution with the position of its maximum below the mean is said to be positively skewed, and vice versa. For a two-dimensional distribution as the RR recurrence plot, the octupole moments in respect with a principal axis can be connected to the skewness of the projection of the distribution along this axis. A negative octupole/skewness along the x-axis implies that the heart beats for extended periods with a low pulse rate (large RR intervals), while a positive octupole/skewness along the x-axis implies that the heart beats with a high pulse rate for extended periods.

A high concentration of data points on the negative y-axis (positive y-skewness) indicates a slow decrease and a fast increase in the heart rate which is a sign of an impaired sympathetic and/or parasympathetic nervous system. Negative skewness on the y-axis, implying a slowly increasing and a fast decreasing pulse, is hence one of the indications for a well-functioning heart function.

The first relevant multipole moment, the quadrupole (the dipole vanishes due to the choice of the origin), turns out to be a stronger risk indicator than SDNN (overall predictive accuracy 60 versus 56). Combining the other multipoles that were used in this study into a single measure by a multivariate analysis results in a measure which is a much more potent predictor than SDNN (65 versus 56) and similar to α_1. Combining all four measures results in a predictor (CMP_4) superior to all other predictors used in the DIAMOND MI study (Huikuri *et al* 2000).

5. Conclusion

The study shows that the multipole method provides more prognostic information on patients after acute myocardial infarction than previously suggested risk markers.

The method includes all the integrative measures of heart rate variability, but exceeds the predictive ability of traditional HRV due to the additional dynamic information gained by the individual moments obtained by expanding the RR recurrence plot.

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