Heart rate variability density analysis (Dyx) for identification of appropriate implantable cardioverter defibrillator recipients among elderly patients with acute myocardial infarction and left ventricular systolic dysfunction

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Abstract

Aims Dyx is a new heart rate variability (HRV) density analysis specifically designed to identify patients at high risk for malignant ventricular arrhythmias. The aim of this study was to test if Dyx can improve risk stratification for malignant ventricular tachyarrhythmias and to test if the previously identified cut-off can be reproduced.

Methods and Results This study included 248 patients from the CARISMA study with ejection fraction ≤40% after an acute myocardial infarction and an analysable 24 h Holter recording. All patients received an implantable cardiac monitor, which was used to diagnose the primary endpoint of near-fatal or fatal ventricular tachyarrhythmias likely preventable by an implantable cardioverter defibrillator (ICD), during a period of 2 years. A Dyx ≤ 1.96 was considered abnormal. The secondary endpoint was cardiovascular death. At enrolment 59 patients (24%) had a Dyx ≤ 1.96 and 20 experienced a primary endpoint. A Dyx ≤ 1.96 was associated with a significantly increased risk for malignant arrhythmias [hazards ratio (HR) = 4.36 (1.81–10.52), $P = 0.001$] and cardiovascular death [HR = 3.47 (1.38–8.74), $P = 0.008$]. Compared with important clinical risk parameters (age >70 years and QRS > 120 ms), Dyx ≤ 1.96 significantly added predictive value ($P = 0.0066$).

Conclusions Dyx was a better predictor of ventricular tachyarrhythmias than the traditional measures of HRV and heart rate turbulence, particularly in the elderly. Dyx might be a useful tool for better selection of ICD candidates in the elderly population, since a normal Dyx in this group was associated with a very low risk for malignant ventricular arrhythmias.

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Key words: Acute myocardial infarction; Heart rate variability; Multipole analysis; Cardiovascular risk; Malignant arrhythmias; CARISMA

What's new?

- We tested the new heart rate variability (HRV) density analysis Dyx in the CARISMA population, including post-myocardial infarction patients with left ventricular ejection fraction ≤40%, in order to identify patients at risk of fatal or near-fatal ventricular arrhythmias.
- The primary endpoints were documented by implantable cardiac monitor or implantable cardioverter defibrillator (ICD).
- A low Dyx was a better predictor of malignant ventricular arrhythmias than both traditional and newer measures of HRV and heart rate turbulence, particularly in the elderly population.
- Dyx might be a useful tool for better selection of ICD candidates in the elderly population, since a normal Dyx in this group was associated with a very low risk for malignant arrhythmias.

Introduction

Even though the prognosis has improved greatly in the last couple of decades, survivors of acute myocardial infarction (MI) constitute a major population of high-risk patients even in the modern era of percutaneous coronary interventions.[1] Since the general population has aged, elderly patients compose a growing proportion of post-MI patients. The results from MADIT-II have shown that as age advances, particularly in the context of renal and vascular comorbidities, the life-prolonging effect of implantable cardioverter defibrillator (ICD) therapy tapers off.[2] Although numerous attempts have been made to develop invasive and non-invasive risk stratification tests that can provide additional information after assessment of conventional risk factors, few tests have been shown to be clinically feasible. One of the promising techniques for additional risk stratification is the analysis of heart rate variability (HRV). Heart rate variability is closely linked to the autonomic control of cardiovascular functions, and a decreased HRV, as a marker of impaired cardiac autonomic regulation, has been shown to be associated with increased cardiac risk.

The most simple HRV techniques involves applying statistical methods such as the standard deviation of the distance between normal-to-normal beats (SDNN).[3] Spectral HRV analysis using fast Fourier transformation identifies particular subsets of the autonomic regulation.[4] However, neither this technique, nor SDNN, has been incorporated in clinical cardiology, mainly because it has not been possible to identify reproducible cut-off points, applicable across different populations. Newer non-linear methods, such as detrended fluctuation analysis (DFA)[5] and heart rate turbulence (HRT),[6] have opened a new approach to better understanding the underlying characteristics of RR-interval series with a highly complex time evolution and increased randomness, not easily detected by linear measure, and have been tested with success in post-MI populations.[7,8] The non-linear measures have more reproducible cut-off points but since both require meticulous analysis they are not used routinely. All the above-mentioned methods were recently tested and compared in the CARISMA trial.[9]

In this study we test a new non-linear HRV analysis, Dyx, in the CARISMA trial population. This method, previously described by Olesen *et al.*,[10] is a density analysis which, in addition to time-domain analysis, is susceptible to loss of density in areas where heart rate intervals would cluster in normal low-risk subjects. The Dyx analysis can be easily and automatically obtained using 24 h Holter monitoring and was developed specifically for risk stratification for malignant ventricular arrhythmias. The purpose of this study is two-fold:

1. To test if Dyx will improve risk stratification for malignant ventricular arrhythmias compared with regular clinical risk variables and conventional HRV analyses.
2. To test whether the previously identified cut-off point for Dyx can be reproduced in the CARISMA population.

Methods

Population

CARISMA was a multi-centre observational study conducted in 10 European centres between 2001 and 2006. A total of 5869 patients with enzyme verified MI were screened consecutively with 2D echocardiography in the acute phase (days 2–5 post-MI) and 312 patients with left ventricular ejection fraction (LVEF) ≤40% were included in the study.[9] All patients received an implantable cardiac monitor (ICM) within the first 21 days post-MI. Holter monitoring was performed between day 5 and 21. A total of 248 patients had an analysable Holter-recording made at enrolment and were included in the following analyses. Patients were followed in the outpatient clinic quarterly for 24 months. All patients gave written informed consent. The appropriate local ethics review board approved the protocol and the study was conducted according to the Declaration of Helsinki.

Device programming

The ICM (Reveal Plus™ 9526, Medtronic Inc.) was programmed as follows: Ventricular tachycardia or fibrillation (VT or VF) was recorded if the arrhythmia registered lasted ≥16 beats with a heart rate ≥125 bpm. Sustained VT was defined as arrhythmia lasting ≥30 s. During follow-up 47 patients were implanted with ICD for primary (n = 36) or secondary (n = 11) prevention and 12 patients received a pacemaker. In order to differentiate between sustained and non-sustained VT, the programming of the ICD was set for 'monitoring only during the first 30 s for cycle lengths of 480–310 ms, and in cases of fast VT or VF defined as cycle lengths from 194–220 bpm and >220 bpm, respectively, therapy was typically programmed to be delivered after a detection period of 18 intervals.

Holter monitoring

Holter monitoring was performed using two- or three-channel recorders with 1000 Hz RR interval sampling frequency for 24 h. Holter recordings were first analysed locally by an experienced technician, and later traditional measures of HRV and HRT were analysed centrally at the university of Oulu (Finland) using previously described methods and custom-made software.[7,8,11] The following HRV variables were analysed; average heart rate (meanRR), time domain measure of the standard deviation of normal-to-normal RR intervals (SDNN), frequency-domain measurements [very low frequency (VLF), low frequency (LF), and high frequency (HF)], short-term fractal scaling exponent α_1, and the onset (TO) and slope (TS) of HRT.

The Dyx density heart rate variability method

A detailed description of how to measure Dyx has been published earlier.[10,12] Briefly, Dyx HRV density analysis is a new way of investigating the Poincaré plot from complex time series and is derived from Multipole analysis. The Poincaré plot is interpreted as a two-dimensional body, where each data point in the plot is assigned a unit mass in order to describe the total mass distribution within the plot. The measures obtained from this kind of analyses bear intrinsic time dependence due to the very construction of the plot, as opposed to SDNN which does not include any time ordering (shuffling the RR intervals lead to the same value for SDNN). As a result, Dyx, as do other Poincaré plot indices, derives information from both the time and frequency domains as well as reflecting increased randomness in the RR interval time series. The density ratio Dyx is derived from the kurtosis and calculates the ratio between the peak-density on the y-axis (dy) and the x-axis (dx), respectively.

The optimal cut-off value for bad prognosis (Dyx ≤ 1.96) was defined in a prior post-MI population of 446 patients with LVEF < 35%,[10] and values above this are considered normal.

Endpoints

The primary endpoint (PE) of the CARISMA study was fatal or near-fatal ventricular tachyarrhythmias, which are most likely preventable by an ICD. Deaths were first adjudicated by the treating physician and later submitted to consensus adjudication by a five-member endpoint committee blinded to results of the different risk stratification tests undertaken in the study. The primary endpoints (PEs) included resuscitated cardiac arrest due to documented primary arrhythmia, symptomatic sustained ventricular tachycardia (VT), or documented arrhythmic death which had to be ECG-documented either by the implanted ICM, ICD, or pacemaker, or by a Holter-recording or telemetry strip. The secondary endpoints were cardiac death or the combined endpoint of near-fatal cardiac arrhythmias or cardiac death. Cardiac death and the combined endpoint were included, since the PE contains non-fatal events. Cardiac and non-cardiac deaths were adjudicated by the endpoint committee using the modified Hinkle–Thaler criteria.

Statistical analyses

Clinical and Holter variables were tested for normality using histogram plots and differences between patients with normal vs. abnormal Dyx were tested using paired t-test, Wilcoxon rank-sum test, and χ^2-

test wherever appropriate. Linear correlation between Holter variables was tested using Pearson correlation analysis. Cox-proportional hazards regression analysis was used to assess the association between different risk predictors and the endpoints.

Important clinical variables were tested for interactions with Dyx. When tested for additive predictive value, Dyx was compared with known important clinical risk variables (age > 70 and QRS > 120) as well as all the included HRV/HRT parameters. Due to the limited number of endpoints, no more than three variables were included in the model at any given time. Since age was the strongest independent clinical risk parameter, Dyx was compared with the other HRV/HRT parameters by including age +1 HRV/HRT parameter at a time in the model. The additive value was calculated as the χ^2-probability of [Likelihood (LH) of model including Dyx – LH of model without Dyx]. Sensitivity, specificity, and predictive values were calculated for all HRV parameters. Kaplan–Meier graphs of the cumulative risk were used for visual presentation of univariate comparisons. *P*-values <0.05 were considered statistically significant and all analyses were performed using SAS 9.3® for windows (SAS Institute).

Results

Baseline characteristics of patients with and without abnormal Dyx

An abnormal Dyx (≤1.96) was found in 59 (24%) of the population. Differences in baseline characteristics between patients with and without abnormal Dyx were subtle, as shown in *Table 1*. Patients with abnormal Dyx were older and more often suffered from diabetes and symptoms of heart failure, whereas other cardiovascular risk factors were identical in the two groups including echocardiographic parameters. In the group with abnormal Dyx, there was a higher proportion of patients that did not receive any kind of revascularization after the index MI (51% vs. 37%, $P < 0.01$).

Table 1: Baseline clinical variables for all patients and for patients with normal Dyx (>1.96) or abnormal Dyx (≤1.96)

Clinical variables at enrollment	All patients, *n* = 248	Dyx ≤ 1.96, *n* = 59 (24%)	Dyx > 1.96, *n* = 189 (76%)
Age (years)	63.4 ± 10.7	67.0 ± 9.3[a]	62.2 ± 10.9
Male gender	191 (77%)	37 (63%)[a]	154 (82%)
Prior MI	94 (38%)	22 (37%)	72 (38%)
Prior CHF	20 (8%)	2 (3%)	18 (10%)
NYHA class II–IV	189 (76%)	51 (86%)[a]	138 (73%)
Diabetes	47 (19%)	21 (36%)[a]	26 (14%)
Hypertension	109 (44%)	31 (53%)	78 (41%)
Previous or current smokers	159 (64%)	36 (61%)	123 (65%)
Hypercholesterolaemia	104 (42%)	25 (42%)	79 (42%)
BMI	27 ± 4	28 ± 5	27 ± 4
Renal insufficiency	13 (5%)	3 (5%)	10 (5%)
QRS > 120 ms (surface ECG)	32 (13%)	12 (20%)	20 (10%)
n	22 (9%)	4 (7%)	18 (10%)
LBBB	23 (9%)	8 (14%)	15 (8%)

Clinical variables at enrollment	All patients, *n* = 248	Dyx ≤ 1.96, *n* = 59 (24%)	Dyx > 1.96, *n* = 189 (76%)
Characteristics of index MI			
Anterior MI	147 (59%)	33 (56%)	114 (60%)
No revascularization at index MI	99 (40%)	30 (51%)[a]	69 (37%)
Thrombolysis at index MI	94 (38%)	18 (31%)	76 (40%)
Primary PCI at index MI	77 (31%)	15 (25%)	62 (33%)
Echocardiography			
Ejection fraction (%)	35 (30–37)	35 (31–37)	35 (30–37)
Medical treatment at discharge			
Betablockers	241 (97%)	184 (97%)	57 (97%)
ACE-inhibitors	222 (90%)	168 (89%)	54 (92%)
Statins	205 (83%)	163 (86%)	42 (71%)
Holter parameters			
SDNN	95 (±33)	73 (±31)[a]	101 (±30)
ln HF	4.9 (±0.98)	4.8 (±1.2)	4.9 (±0.91)
ln LF	5.1 (±1.2)	4.2 (±1.4)[a]	5.4 (±0.94)
ln VLF	6.4 (±0.96)	5.5 (±1.1)[a]	6.7 (±0.69)
DFA (α_1)	1.1 (±0.24)	0.83 (±0.19)[a]	1.2 (±0.2)
HRT slope	6.8 (±7.7)	4.9 (±5.6)[a]	7.4 (±8.1)
HRT onset	−0.9 (± 2.2)	−0.7 (±1.9)[a]	−1.0 (±2.3)
MeanRR	68 (±10)	71 (±12)[a]	67 (±9)
VPBs/24 h	34 (7–204)	34 (7–167)	34 (7–209)

- MI, myocardial infarction; NYHA, New York Heart Association; COLD, chronic obstructive lung disease; BMI, body mass index; PCI, percutaneous coronary intervention; VPB, ventricular premature beats; RBBB, Right Bundle Branch Block; LBBB, Left Bundle Branch Block.
- Indicates $P < 0.05$ for difference between groups.

Correlation of Dyx with other heart rate variability parameters

Before clinical comparison, we tested the correlation between Dyx and the other included Holter variables, as shown in *Table 2*. The strongest correlations were found with VLF ($r^2 = 0.47$) and DFA1 ($r^2 = 0.51$), whereas correlations with HF ($r^2 = 0.02$) and HRT slope ($r^2 = 0.03$) were weak.

Table 2: Correlation between Dyx and conventional measures of HRV

Parameter	R^2	*P*
SDNN	0.26	<0.01
ln(HF)	0.02	0.02
ln(LF)	0.34	<0.01
ln(VLF)	0.47	<0.01
DFA1	0.51	<0.01
HRT slope	0.03	0.01

Abnormal Dyx and risk of malignant arrhythmias and cardiac death

During the study, 20 patients experienced a PE of which nine were fatal. Additionally, nine suffered a cardiovascular death ($n = 18$) which was not classified as PE (i.e. not due to ventricular tachyarrhythmias preventable by an ICD). A Dyx ≤ 1.96 was associated with a significantly increased risk for malignant arrhythmias [hazards ratio (HR) = 4.36 (1.81–10.52), $P = 0.001$] and cardiovascular death [HR = 3.47 (1.38–8.74), $P = 0.008$] (see *Table 3*). *Figure 1A* shows the Kaplan–Meier risk for PE, while *Figure 1B* shows the accumulated risk for cardiac death in patients with normal and abnormal Dyx, respectively. *Figure 1C* shows the accumulated risk for near-fatal ventricular tachyarrhythmias or cardiac death.

Table 3: Univariate and multivariate Cox proportional hazards regression analysis

Parameter	PE	*P*	CD	*P*
Univariate analyses				
Dyx ≤ 1.96	4.36 [1.81–10.52]	0.001	3.47 [1.38–8.74]	0.008
SDNN < 70	2.88 [1.16–7.16]	0.023	3.26 [1.29–8.27]	0.013
ln(HF) < 3.5	1.39 [0.32–6.00]	0.66	2.43 [0.70–8.41]	0.16
ln(LF) < 5.5	0.74 [0.30–1.82]	0.51	1.38 [0.52–3.67]	0.52
ln(VLF) ≤ 5.7	2.05 [0.81–5.22]	0.13	2.26 [0.88–5.84]	0.091
DFA1 < 0.75	3.78 [1.36–10.50]	0.011	4.1 [1.46–11.5]	0.007
HRT (T-slope <2.5)	1.89 [0.76–4.71]	0.17	2.07 [0.82–5.26]	0.12
Age >70 years	3.64 [1.51–8.78]	0.004	2.89 [1.15–7.28]	0.024

Parameter	PE	*P*	CD	*P*
QRS > 120 ms (surface ECG)	3.06 [1.17–7.95]	0.022	3.54 [1.33–9.44]	0.012
LVEF per 5% increase	0.71 [0.53–0.97]	0.030	0.87 [0.61–1.23]	0.42
Multivariate analyses				
Dyx ≤ 1.96	3.53 [1.43–8.68]	0.006	2.76 [1.07–7.12]	0.036
DFA1 < 0.75	3.05 [1.06–8.77]	0.038	3.24 [1.11–9.43]	0.024
SDNN < 70	2.89 [1.16–7.21]	0.022	3.25 [1.28–8.26]	0.013
Age >70 years	3.10 [1.24–7.75]	0.015	2.37 [0.91–6.16]	0.077
QRS > 120 ms (surface ECG)	2.17 [0.81–5.87]	0.13	2.81 [1.02–7.76]	0.045

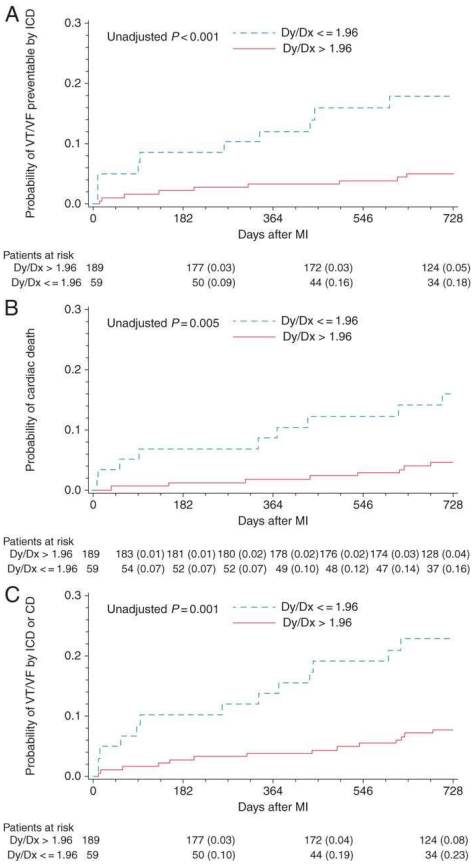


Figure 1

(*A*) Kaplan–Meier graph showing cumulative risk for the combined endpoint of VT/VF preventable by ICD. (*B*) Kaplan–Meier graph showing cumulative risk for cardiac death. (*C*) Kaplan–Meier graph showing cumulative risk for the combined endpoint of VT/VF preventable by ICD or cardiac death.

In multivariate Cox regression analysis including the risk variables and HRV/HRT parameters presented in *Table 3*, Dyx remained the strongest predictor for malignant arrhythmias [HR = 3.53 (1.43–8.68), *P* = 0.006].

The overall predictive accuracy was highest for Dyx, with sensitivity 55% and specificity 79% for PE (*Table 4*).

Table 4: Sensitivity, specificity, and predictive accuracies of Holter variables in predicting PE

	Identified by cut-off *N* (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV(%)
Dyx ≤ 1.96	59 (24%)	55	79	19	95
SDNN < 70	57 (23%)	45	79	16	94
DFA1 < 0.75	27 (11%)	30	91	22	94
HRT slope <2.5	86 (35%)	45	66	10	93
ln(VLF) ≤ 5.7	61 (25%)	40	77	13	94
ln(LF) < 5.5	152 (61%)	55	38	7	91
ln(HF) < 3.5	25 (10%)	15	90	12	92
MeanRR ≤ 750	39 (16%)	20	85	10	92

- PPV, positive predictive value; NPV, negative predictive value.

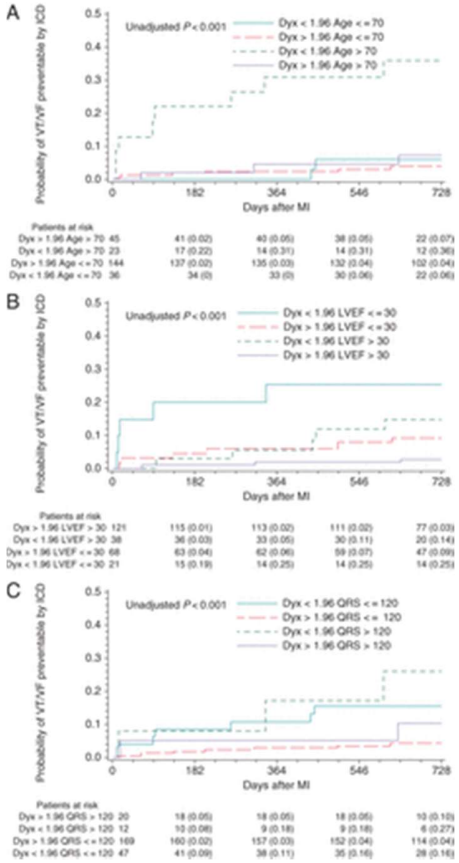
Compared with the two clinical risk factors age and QRS width (from 12-lead ECG), Dyx added substantial predictive value to the model (LH without Dyx = 10.16, LH with Dyx = 17.53, *P* for difference = 0.006). When testing Dyx in models including age and one HRV/HRT parameter, Dyx significantly added predictive value except when the model included age and DFA (which was the strongest independent HRV parameter next to Dyx), where the added predictive value was only borderline significant (LH without Dyx = 11.17, LH with Dyx = 14.61, *P* = 0.064).

Abnormal Dyx is very sensitive to increased risk for malignant arrhythmias in the elderly but not in younger patients

In-depth analysis revealed that a Dyx ≤ 1.96 was highly associated with age. While 20% of patients aged ≤70 had abnormal Dyx, this was found in 34% of patients aged >70 years (*P* = 0.023). In addition, we found a marked difference in the association of an abnormal Dyx and malignant arrhythmias between younger and elderly patients. In patients aged >70 years, an abnormal Dyx was associated with severely increased risk of malignant arrhythmias [HR = 6.4 (1.7–24.0), *P* = 0.04], whereas it was not in patients aged 70 or younger [HR = 2.1 (0.53–8.4), *P* = 0.30] (*Figure 2A*). This interaction was not statistically significant (*P* = 0.26), probably due to a low number of events in some of the groups. We tested other significant risk factors such as LVEF and QRS width both visually and statistically but did not find similar interactions (see *Figure 2B* and *C*).

Figure 2

(A) Relation between age, Dyx, and risk of near-fatal or fatal ventricular arrhythmias. (*B*) Relation between left ventricular ejection fraction, Dyx, and risk of near-fatal or fatal ventricular arrhythmias. (*C*) Relation between QRS width from surface ECG, Dyx, and risk of near-fatal or fatal ventricular arrhythmias.



Discussion

The present study shows that the HRV density measure, Dyx, is a powerful predictor of ECG-documented fatal or near-fatal ventricular arrhythmic events likely to be treatable by ICD, when measured early after an acute MI. Our results imply that this method could be particularly effective in elderly patients and less so in the young. Dyx was a better predictor than the traditional measures of HRV and HRT. This is important since the elderly is becoming an increasingly larger cohort and Dyx might be a useful tool for better selection of ICD candidates in the elderly population eligible for an ICD, since a normal Dyx in this group was associated with a very low risk for malignant arrhythmias.

Several previous studies have investigated the Poincaré plot of RR interval time series.[13–16] It is well established that there is a strong correlation between standard time- and frequency-domain measurements and Poincaré indices. The SDNN correlates with the length of the Poincaré plot along the line of identity, describing the overall RR interval variability or total spectral power. The width of the plot measured on the axes vertically to the line of identity is correlated to RMSSD (square root of the mean squared differences of successive NN intervals) and HF power, describing short-term variability attributed to parasympathetic vagal tone.

Dyx calculates a ratio between density measured along the short (Dx) and the long (Dy) axes of the Poincaré plot. The parameter describes the skewness in densities within the plot and thereby reflects the increased randomness in the RR interval time series and integrates measures of both vagal and sympathetic activation. The correlation between Dyx and HF power in this study is low, both indicating lower sensitivity to vagal than sympathetic modulation, but probably more so reflecting the influence of erratic rhythms on the HF measures, that do not reflect better parasympathetic function. Dyx is less sensitive to variation in rare RR intervals, i.e. periods with very high or low heart rates, and more sensitive to loss of variation at the most common heart rates. In addition, Dyx presumably performs better than previous Poincaré plot measures, because it is more accurate to calculate exact densities than length or standard deviation when describing the individual specific features of the plot. We suggest that Dyx should be considered as a new, important, non-linear HRV measure of altered sympathovagal balance and increased randomness of the RR intervals, leading to increased risk of death after an acute myocardial infarction. However, further prospective studies are needed to confirm this hypothesis.

The association between age and changes in HRV is well described. With increasing age, the HRV decreases, which may reflect an attenuated response to external stimuli with aging.[17,18] Akatsu *et al.* exemplified this by exposing a young and an elderly population to head-up tilt testing and found that the elderly showed greater changes in the LF (a marker of baroreceptor activity) than in the HF (a marker of vagal activity) components of spectral HRV, indicating that a given orthostatic stimulus induces greater autonomic stress in the elderly than in the young.[19] This explains why low HRV may be such a

sensitive marker for increased risk in the elderly. The HRV is generally lower in the elderly leaving less resources for adaptation to external stimuli, but elderly patients are also more dependent on autonomic stimulation during haemodynamic stress, making the elderly population more susceptible to consequences of dysfunctional autonomic regulation of the cardiovascular system.

Several linear and non-linear Holter-based measures of HRV and HRT have been shown to predict both all-cause and sudden cardiac death in different post-MI populations,[6,7,11] but there has been difficulties in finding significant predictive value of these indexes for sudden cardiac death in post-MI populations with depressed LVEF, when measured early after MI.[11,20,21] In this study Holter monitoring was performed within the first 21 days after index MI, but was done mostly at discharge. Hence, our results indicate that Dyx could be a mean of early risk stratification after MI.

Limitations

This study is subject to several limitations. First, HRV can only be calculated from the R–R intervals between sinus beats excluding all patients with, e.g. atrial fibrillation. In the elderly population, these patients constitute a relatively large proportion. Against this one may argue that patients with atrial fibrillation already are at significantly increased risk probably partly due to attenuated autonomic control of the cardiovascular system. Secondly, the ICM used in this study had limited memory available, meaning that if patients had many arrhythmic events, only events from a short part of the observation period were available for analysis. Also, the ICD may not always document a potential fatal arrhythmic event reliably, because some tachyarrhythmias may terminate spontaneously after the pre-defined delay setting for onset of therapy of the device.

Conclusions

The new multipole derived HRV measure, Dyx, is a powerful predictor of ECG-documented fatal or near-fatal ventricular arrhythmic events likely to be treatable by ICD when measured early after an acute MI. Dyx was a better predictor than the traditional measures of HRV and HRT, particularly in the elderly, and Dyx might be a useful tool for better selection of ICD candidates in the elderly population, since a normal Dyx in this group was associated with a very low risk for malignant arrhythmias. This result should be tested in larger cohorts.

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References

1. Garcia-Garcia C, Subirana I, Sala J, Bruguera J, Sanz G, Valle V, et al . Long-term prognosis of first myocardial infarction according to the electrocardiographic pattern (ST elevation myocardial infarction, non-ST elevation myocardial infarction and non-classified myocardial infarction) and revascularization procedures. Am J Cardiol2011;**108**:1061-7.
2. Goldenberg I, Vyas AK, Hall WJ, Moss AJ, Wang H, He H, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2008;**51**:288-96.
3. Fei L, Copie X, Malik M, Camm AJ. Short- and long-term assessment of heart rate variability for risk stratification after acute myocardial infarction. Am J Cardiol 1996;**77**:681-4.
4. Lombardi F, Sandrone G, Pernpruner S, Sala R, Garimoldi M, Cerutti S, et al. Heart rate variability as an index of sympathovagal interaction after acute myocardial infarction. Am J Cardiol 1987;**60**:1239-45.
5. Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. Chaos 1995;**5**:82-7.
6. Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999;**353**:1390-6.
7. Huikuri HV, Makikallio TH, Peng CK, Goldberger AL, Hintze U, Moller M. Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction 3. Circulation 2000;**101**:47-53.
8. Bauer A, Barthel P, Schneider R, Ulm K, Muller A, Joeinig A, et al. Improved stratification of autonomic regulation for risk prediction in post-infarction patients with preserved left ventricular function (ISAR-Risk). Eur Heart J 2009;**30**:576-83.
9. Huikuri HV, Raatikainen MJP, Moerch-Joergensen R, Hartikainen J, Virtanen V, Boland J, et al. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction. Eur Heart J 2009;**30**:689-98.
10. Olesen RM, Thomsen PEB, Saermark K, Glikson M, Feldman S, Lewkowicz M, et al. Statistical analysis of the DIAMOND MI study by the Multipole method. Physiol Meas 2005;**26**:591-8.
11. Makikallio TH, Barthel P, Schneider R, Bauer A, Tapanainen JM, Tulppo MP, et al. Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era 4. Eur Heart J2005;**26**:762-9.
12. Lewkowicz M, Levitan J, Puzanov N, Shnerb N, Saermark K. Description of complex time series by Multipoles.Physica A: Stat Mech Appl 2002;**311**:260-74.
13. Huikuri HV, Seppanen T, Koistinen MJ, Airaksinen KEJ, Ikaheimo MJ, Castellanos A, et al. Abnormalities in beat-to-beat dynamics of heart rate before the spontaneous onset of life-threatening ventricular tachyarrhythmias in patients with prior myocardial infarction. Circulation 1996;**93**:1836-44.
14. Kamen PW, Tonkin AM. Application of the Poincare plot to heart rate variability: a new measure of functional status in heart failure. Aust N Z J Med 1995;**25**:18-26.
15. Brennan M, Palaniswami M, Kamen P. Poincare plot interpretation using a physiological model of HRV based on a network of oscillators. Am J Physiol Heart Circ Physiol 2002;**283**:H1873-86.
16. Stein PK, Domitrovich PP, Huikuri HV, Kleiger RE. Traditional and nonlinear heart rate variability are each independently associated with mortality after myocardial infarction. J Cardiovasc Electrophysiol 2005;**16**:13-20.
17. Reardon M, Malik M. Changes in heart rate variability with age. Pacing Clin Electrophysiol 1996;**19** (11 Pt 2):1863-6.
18. Felber Dietrich D, Schindler C, Schwartz J, Barthélémy JC, Tschopp JM, Roche F, et al. Heart rate variability in an ageing population and its association with lifestyle and cardiovascular risk factors: results of the SAPALDIA study.Europace 2006;**8**:521-9.
19. Akatsu J, Kumashiro M, Miyake S, Komine N, TakahashiI Y, Hashimoto M, et al. Differences in heart rate variability between young and elderly normal men during graded head up tilt. Ind Health 1999;**37**:68-75.
20. Huikuri HV, Tapanainen JM, Lindgren K, Raatikainen P, Makikallio TH, Juhani Airaksinen KE, et al. Prediction of sudden cardiac death after myocardial infarction in the beta-blocking era. J Am Coll Cardiol 2003;**42**:652-8.
21. Camm AJ, Pratt CM, Schwartz PJ, Al-Khalidi HR, Spyt MJ, Holroyde MJ, et al. Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. Circulation 2004;**109**:990-6.