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The role of heart rate variability, heart rate turbulence, and deceleration capacity in predicting cause-specific mortality in chronic heart failure

Salah S. Al-Zaiti [a,*], Grzegorz Pietrasik [f], Mary G. Carey [c], Mohammad Alhamaydeh [d], John M. Canty [b,e], James A. Fallavollita [b,e]

[a] University of Pittsburgh, Pittsburgh, PA, United States of America
[b] State University of New York, Buffalo, NY, United States of America
[c] Strong Memorial Hospital at University of Rochester Medical Center, Rochester, NY, United States of America
[d] Conemaugh Memorial Medical Center, Johnstown, PA, United States of America
[e] VA Western NY Health Care System, Buffalo, NY, United States of America
[f] Rush University Medical Center, Chicago, IL, United States of America

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ABSTRACT

Background: The volume of regional denervated myocardium (D-M) on positron emission tomography has been recently suggested as a strong independent predictor of cause-specific mortality from sudden cardiac arrest (SCA) in chronic heart failure. We sought to evaluate whether ECG indices of global autonomic function predict risk of SCA to a similar degree as regional D-M.

Methods: Subjects enrolled in the *Prediction of Arrhythmic Events using Positron Emission Tomography* (PAREPET) study were included in this study. Patients completed a 24-hour Holter ECG at enrollment and were followed up at 3-month intervals. SCA events were adjudicated by two board-certified cardiologists. Other cardiovascular death events were classified as nonsudden cardiac death (NSCD). Eight measures of heart rate variability were analyzed: SDNN, RMSSD, low-frequency (LF) and high-frequency (HF) power, heart rate turbulence onset and slope, and acceleration and deceleration capacity. We used competing risk regression to delineate cause-specific mortality from SCA versus NSCD.

Results: Our sample included 127 patients (age 67 ± 12, 92% male). After a median follow-up of 4.1 years, there were 22 (17%) adjudicated SCA and 18 (14%) adjudicated NSCD events. In multivariate Cox-regression, LF power was the only HRV parameter to predict time-to-SCA. However, in competing risk analysis, reduced LF power was preferentially associated with NSCD rather than SCA (HR = 0.92 [0.85–0.98], $p = 0.019$).

Conclusion: Depressed LF power might indicate impaired vagal reflex, which suggests that increasing vagal tone in these patients would have a protective effect against NSCD beyond that achieved by the mere slowing of heart rate using β-blockers.

Introduction

Patients with ischemic heart disease and left ventricular dysfunction are at particularly high risk of sudden cardiac arrest (SCA). Non-invasive risk stratification to identify and manage such high-risk patients is a clinical priority [1,2]. A depressed left ventricular ejection fraction (i.e. LVEF ≤ 35%) remains the only risk stratification tool employed clinically to identify candidates of implantable-cardioverter defibrillation (ICD) therapy for the primary prevention of SCA. However, using LVEF to target ICD therapy has been found to be very inefficient [3,4]. Not only do most SCA events occur in people without an indication for an ICD, but only 25% of those with an ICD for the primary prevention of SCA will use their device within the next 5 years [5]. Therefore, more accurate risk stratification tools for cause-specific mortality from SCA constitute an unmet clinical need [6].

The analysis of heart rate variability (HRV) provides a non-invasive tool to characterize the sympathetic autonomic function, and has been shown to predict the risk of cardiovascular death in various clinical populations [7–9]. However, the majority of these studies have not evaluated cause-specific mortality from SCA and have primarily focused on populations at relatively low risk of SCA. In fact, it is still unknown if HRV plays any significant role in high-risk population (e.g., ischemic cardiomyopathy) due to the high prevalence of pacing and atrial fibrillation and the widespread clinical use of beta blockers in these patients [10].

* Corresponding author at: University of Pittsburgh, 3500 Victoria St., Pittsburgh, PA 15261, United States of America.
E-mail address: ssa33@pitt.edu (S.S. Al-Zaiti).

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In the PAREPET trial (Prediction of Arrhythmic Events using Positron Emission Tomography), we reported that the volume of regional denervated myocardium (D-M) is a predictor of cause-specific mortality from SCA in patients with ischemic cardiomyopathy [11]. The PAREPET dataset is unique since it has both PET data and Holter ECG data. As such, we sought to evaluate whether ECG indices of global autonomic function predict risk of SCA to a similar degree as regional D-M. Given that patients need to be stratified on optimal medical therapy (e.g., ICD), we used a competing risk regression approach to delineate cause-specific mortality from SCA versus mortality due to non-sudden cardiac death (NSCD).

Methods

Setting and subjects

This analysis was based on subjects enrolled in the *Prediction of ARrhythmic Events with Positron Emission Tomography* (PAREPET) study. PAREPET was a prospective observational study sponsored by the National Heart Lung and Blood Institute designed to determine whether denervated and/or hibernating myocardium as quantified with PET could predict SCA among subjects with ischemic cardiomyopathy who were eligible for a primary prevention ICD [2]. Eligible subjects had coronary artery disease, pre-enrollment LVEF ≤ 35%, and NYHA Class I–III heart failure symptoms. The IRB-approved study design and methods have been reported in detail [2,12] and are summarized here. After informed consent, eligible patients underwent echocardiography, PET scans, and 24-hour ambulatory ECG monitoring. Subjects were followed at 3-month intervals for the development of cardiac events (defined below). LVEF and LV end-diastolic volume index (LVEDVI) were quantified by biplane transthoracic echocardiography [2].

PET data and endpoints determination

Our analysis included subjects from PAREPET (n = 127) after exclusion of: [1] those with persistent pacing (n = 43) or atrial fibrillation (n = 20); and [2] those without high-fidelity ECG recordings (n = 14). Total volume (% of LV) of D-M, viable D-M, and infarcted myocardium (infarcted and denervated) were quantified with PET, as previously described [2].

The primary endpoint was SCA. This included [1] arrhythmic death using modified Hinkle-Thaler criteria [13,14] or [2] documented ICD discharge for ventricular fibrillation or rapid ventricular tachycardia (>240 beats/min), which approximates the reduction in SCA in primary prevention ICD trials [15]. Therapies for ventricular tachycardia at lower rates were excluded since they substantially overestimate the benefit of an ICD and are frequently self-terminating [16]. Any other cardiovascular death but not due to SCA was classified as NSCD. Endpoints were independently adjudicated by two board-certified cardiologists. Disagreements were resolved by consensus with a third cardiologist.

Electrocardiography

Continuous 24-hour ambulatory ECG monitoring was performed using H12+ Holter recorders (V3.12, Mortara Instrument) on all subjects at baseline. High-frequency recordings (1000 Hz) using the Mason-Likar configuration (i.e., limb leads on body) were preprocessed using H-Scribe v 5.11 (Mortara Instrument). After the automated pre-processing, ECG streams were manually annotated (noise and artifacts deleted) by a blinded reviewer to ensure that ECG quality was adequate for subsequent analysis. Non-sinus beats were manually labeled for exclusion. This resulted in 23 ± 3 h of monitoring per eligible patient. All measures were computed according to the methods recommended by the European Society of Cardiology [17].

The annotated ECG streams were then analyzed using Super-ECG (Mortara Instrument), which provided global HRV estimates for time-domain (i.e., SDNN, RMSSD) and frequency-domain (i.e., normalized low- and high-frequency power) measures. Measures of heart rate turbulence (i.e., onset and slope) and acceleration/deceleration-related modulations of heart rate were computed using a custom-written algorithm as previously described [18]. HRT onset was computed as the percentage difference between the heart rate immediately following and immediately preceding a PVC. HRT slope was computed as the steepest regression slope for each sequence of five consecutive sinus rhythm R-R intervals within the first 15 sinus rhythm R-R intervals after a PVC. Acceleration capacity (AC) and deceleration capacity (DC) of the heart rate were quantified using phase rectified signal averaging (PRSA) as previously described [7]. Computer processing of heart period sequences generates the PRSA curve and the center deflection of this curve characterizes the average capacity of the heart rate to accelerate or decelerate from one beat to the next.

Statistical analysis

Values are reported as mean ± SD or as n (%). All analyses were conducted using STATA v 14.0 for Windows, with $p < 0.05$ considered statistically significant. Demographic and clinical characteristics of subgroups were compared using ANOVA with Tukey posthoc for continuous variables and chi-square for categorical variables. The independent relationship between predictors and time-to-event data was evaluated using Cox proportional-hazards regression models. Variables significant at $p < 0.1$ in the bivariate analysis were entered in the multivariate models with backward selection method. The goodness-of-fit of the final model was assessed using the simple test previously reported by O'Quigley and Moreau [19]. Then, a competing risks analysis was then performed to simultaneously assess factors associated with SCA vs. NSCD [20]. The variables that resulted from the multivariable Cox-regression analyses of the individual end points (SCA or NSCD) were included in this competing risks analysis. Sub-hazard ratio was computed for the predictors significant at the competing risk model.

Results

After excluding patients with pacing or atrial fibrillation (33%), the final sample included 127 subjects (age 67 ± 12 years, 92% male). The majority of patients were in NYHA heart failure classes II and III (83%), and the majority were on β-blockers (96%) and angiotensin inhibition therapy (93%). After a median follow-up of 4.1 years (range 2.5–7.2 years), there were 22 (17%) adjudicated SCA cases and 18 (14%) adjudicated NSCD cases. Table 1 compares the clinical and ECG characteristics between patients with endpoints and survivors.

Table 2 shows the univariate and multivariate predictors of time-to-event data. At the univariate level, left ventricular end-diastolic volume (LVEDV), regional D-M, RMSSD, LF power, and DC were associated with time-to-SCA; while age, LF power, and DC were associated with time-to-NSCD. At the multivariate level, LVEDV, regional D-M, and LF power predicted time-to-SCA; and only age and LF power predicted time-to-NSCD.

Table 3 shows the results of the competing risk analysis for predicting cause-specific mortality from SCA versus NSCD. In this competing risk model, we used variables significant at $p < 0.10$ at the multivariate Cox-regression. Overall, we found that LVEDV and regional D-M were preferentially associated with SCA, while age and LF power were preferentially associated with NSCD. For each 1% increase in LF power, the risk of NSCD decreased by 8%. Fig. 1 shows the Kaplan-Meier events probability curves of NSCD for tertiles of LF power in this sample.

Finally, to better understand the relationship between total D-M and autonomic dysfunction by means of HRV, we explored whether a model of autonomic markers could adequately estimate the amount of D-M (Table 4). We found that HRV correlates with viable, but not infarcted, myocardium, with LF/HF power components being the only independent correlates of D-M.

Table 1
Demographic and clinical characteristics of study sample.

Parameter	All patients (n = 127)	Endpoint		
		SCA (n = 22, 17%)	NSCD (n = 18, 14%)	Survivors (n = 87, 69%)
Clinical parameters				
Age (years)	66.6 ± 12.0	65 ± 8	73 ± 10*	66 ± 13
Sex (male)	117 (92%)	22 (100%)	17 (94%)	78 (90%)
LV ejection fraction (%)	28 ± 9	26 ± 8	25 ± 11	29 ± 9
LVEDV index (ml/m^2)	90 ± 31	114 ± 20***	96 ± 34	82 ± 29
Total D-M (% of LV)	27 ± 12	32 ± 10*	27 ± 13	0.26 ± 0.11
Viable D-M (% of LV)	7 ± 5	9 ± 5	8 ± 6	0.07 ± 0.05
Infarcted myocardium (% of LV)	20 ± 9	21 ± 7	19 ± 8	0.21 ± 0.10
ECG parameters				
Average heart rate (bpm)	71 ± 10	74 ± 11	68 ± 7	71 ± 10
SDNN (ms)	45.6 ± 22.1	48 ± 22	47 ± 32	45 ± 20
RMSSD (ms)	64.4 ± 47.2	83 ± 42**	79 ± 64	57 ± 43
LF power (nu)	25.8 ± 5.8	23 ± 5**	23 ± 6*	27 ± 5
HF power (nu)	38.8 ± 7.2	40 ± 7	40 ± 8	38 ± 7
HRT onset (%)	0.00 ± 0.02	0.00 ± 0.01	0.00 ± 0.01	0.00 ± 0.02
HRT slope (ms)	3.1 ± 3.6	2.2 ± 2.0	2.8 ± 4.6	3.5 ± 3.5
AC (ms)	−6.9 ± 4.0	−6.2 ± 2.7	−6.6 ± 2.6	−6.3 ± 2.5
DC (ms)	3.0 ± 3.3	1.7 ± 2.5**	1.7 ± 3.5*	3.7 ± 2.6

Values are mean ± standard deviation (SD), or n (%).
SCA: Sudden Cardiac Arrest, D-M: Denervated Myocardium, LV: left ventricle, LVEDV: left ventricle end-diastolic volume SDNN: standard deviation of normal-to-normal RR intervals, RMSSD: root mean square of the standard deviation of RR intervals, LF: low frequency, HF: high frequency, HRT: heart rate turbulence, AC: acceleration capacity, DC: deceleration capacity.
* $p < 0.05$ against survivors using post-hoc Tukey test.
** $p < 0.01$ against survivors using post-hoc Tukey test.
*** $p < 0.001$ against survivors using post-hoc Tukey test.

Discussion

In this study, we evaluated whether ECG indices of global autonomic function predict risk of SCA to a similar degree as regional D-M. Despite the limitations induced by our small sample size, we found that LF power was the only HRV parameter in multivariate analysis to predict time-to-SCA. This finding suggests that LF power possesses some prognostic information not covered by total D-M; especially given that power analysis of HRV could only explain 9% of the variability observed in viable D-M in this study. However, in competing risk analysis, reduced LF power was preferentially associated with NSCD rather than SCA. This is the first study to evaluate the role of ECG indices of global autonomic function in predicting cause-specific mortality in patients at very high-risk of SCA.

Table 2
Bivariate and multivariate Cox-regression of time-to-event data.

Predictors	Time-to-SCA		Time-to-NSCD	
	Bivariate	Multivariate[¥]	Bivariate	Multivariate[£]
Clinical parameters				
Age (per 10 years)	NS	–	$p = 0.013$	**$p = 0.02$**
Sex (male)	NS	–	NS	–
LV ejection fraction (%)	NS	–	NS	–
LVEDV index (per 10 ml/m^2)	$p = 0.001$	**$p = 0.001$**	NS	–
Total D-M (per 1% of LV)	$p = 0.018$	**$p = 0.05$**	NS	–
Viable D-M (% of LV)	NS	–	NS	–
Infarcted myocardium (% of LV)	NS	–	NS	–
ECG parameters				
Average heart rate (bpm)	NS	–		NS
SDNN (ms)	NS	–	NS	–
RMSSD (ms)	$p = 0.022$	$p = 0.07$	NS	–
LF power (nu)	$p = 0.001$	**$p = 0.03$**	$p = 0.003$	**$p = 0.02$**
HF power (nu)	NS	–	NS	–
HRT onset (%)	NS	–	NS	–
HRT slope (ms)	NS	–	NS	–
AC (ms)	NS	–	NS	–
DC (ms)	$p = 0.001$	NS	$p = 0.001$	NS

SCA: sudden cardiac arrest, NSCD: nonsudden cardiac death; D-M: denervated myocardium, LV: left ventricle, LVEDV: left ventricle end-diastolic volume SDNN: standard deviation of normal-to-normal RR intervals, RMSSD: root mean square of the standard deviation of RR intervals, LF: low frequency, HF: high frequency, HRT: heart rate turbulence, AC: acceleration capacity, DC: deceleration capacity.
Bold indicates the variable remained significant in the final multivariate model.
[¥] Goodness-of-fit Chi-square = 6.121, $p = 0.1903$.
[£] Goodness-of-fit Chi-square = 5.024, $p = 0.2848$.

Cause-specific mortality from SCA

Despite controversy in the literature, the prognostic value of HRV has been repeatedly emphasized in heart failure patients. Nolan et al. [21] evaluated time-domain HRV parameters in 433 heart failure patients and found that SDNN was the most powerful predictor of the risk of death due to progressive heart failure. La Rovere et al. [22] evaluated time- and frequency-domain HRV parameters in 444 heart failure patients and found that LF power was an independent predictor of SCA. Similar results were also obtained by Galinier et al. [23] who found that LF is an independent predictor of SCA in 190 heart failure patients. Yet,

Table 3
Competing risk model for SCA versus NSCD.

Variable	SCA		NSCD	
	Sub-hazard ratio [95% CI]	p value	Sub-hazard ratio [95% CI]	p value
Age (per 10 years)	–	–	**1.82 [1.05–7.70]**	**0.034**
LVEDV (per 10 ml/m^2)	**1.29 [1.14–1.45]**	**<0.001**	–	
Denervated myocardium (per 1%)	**1.03 [1.00–1.07]**	**0.05**	–	
RMSSD	NS	0.108	–	
Low-frequency power (per 1%)	NS	0.107	**0.92 [0.85–0.98]**	**0.019**

SCA: sudden cardiac arrest, NSCD: nonsudden cardiac death; LVEDV: left ventricle end-diastolic volume RMSSD: root mean square of the standard deviation of RR intervals.
Bold indicates the variable remained significant in the final multivariate model.

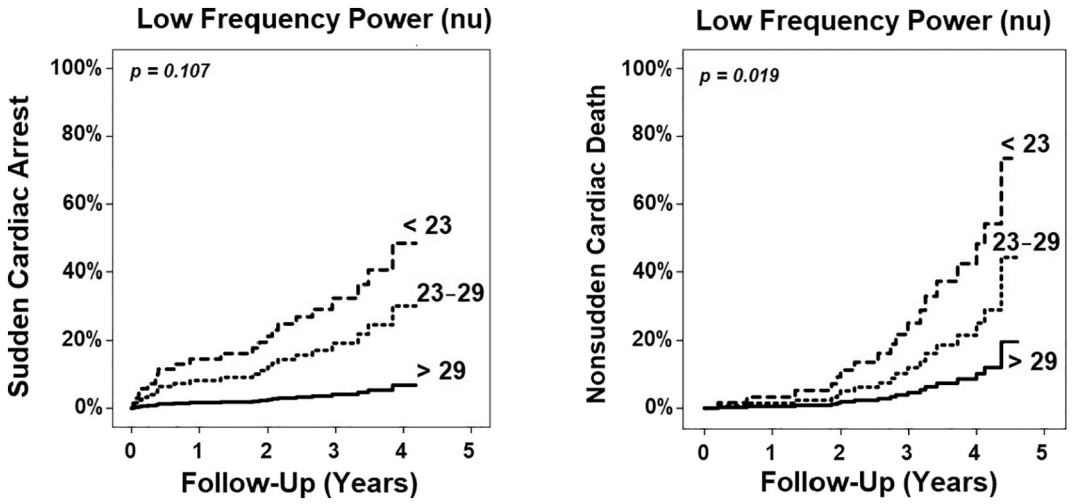

Fig. 1. Kaplan-Meier events probability curve. This figure illustrates that tertiles of LF power are preferentially associated with non-sudden cardiac death but not sudden cardiac arrest (*p* values based on competing risk analysis). Those with depressed LF power have the highest rate of events during follow up period.

Tamaki et al. [24] evaluated time- and frequency-domain HRV parameters in 106 heart failure patients, but found none to be predictive of SCA.

These studies have one limitation in common; they either did not evaluate both SCA and NSCD endpoints in the same study, or they did not simultaneously evaluate both endpoints in a competing risk model. Competing risk analysis accounts for participants who experience one outcome during follow up period before they reach a study endpoint. Using this approach is critical to accurately determine level of risk to best inform clinical decision-making [20]. In our study, we found that LF power is preferentially associated with NSCD rather than SCA in heart failure patients. This finding is interesting and suggests that simple frequency-domain HRV analysis can help target specific therapies to those at the greatest risk of non-arrhythmic heart failure death.

Clinical significance of LF power

The sympathetic and parasympathetic systems work in an opposing yet complementary fashion. The interaction between both systems is complex, ranging from centrally-mediated baroreceptors to local neuronal interactions [25]. While sympathetic activation is known to be pro-arrhythmic, parasympathetic activation is not. The LF oscillation signal in heart rate behavior was historically thought to represent the cardiac sympathetic tone, which explains the association between reduced LF power and SCA in some previous studies [22,23]. However, recent literature suggests that LF power is not a measure of cardiac sympathetic tone but rather a measure of parasympathetic tone and baroreceptor reflex function [26,27]. This new paradigm for understanding the LF power component of HRV can explain two interesting observations in the current study. First, LF power was preferentially associated with NSCD rather than SCA. This can be explained by the well-known relationship between baroreceptor-heart rate reflex sensitivity and the severity of heart failure progression (NYHA class) [28]. Second, the majority (96%) of patients in this study were on β-blockers, which are known to blunt the sympathetic function and limit the value of HRV parameters, yet, LF power remained a significant prognostic variable in predicting mortality in this study. This can be explained by the fact that baroreceptor-heart rate reflex sensitivity possesses a prognostic value independent from the modification of sympathetic dysfunction brought about by β-blockers [29].

This study has some important clinical implications. Depressed LF power remains a strong predictor of NSCD in our current beta blockade era. Given that depressed LF power could indicate an impaired vagal reflex, then it follows that increasing the vagal activity would have a protective effect against cardiovascular death beyond that achieved by the mere slowing of heart rate using β-blockers [28]. Any additional sympathetic inhibition produced by vagal stimulation would add an incremental protective effect against cardiovascular death [30].

Although the direct electrical stimulation of the vagal nerve was thought to improve baroreceptor sensitivity, recent findings from the INNOVATE-HF trial (*Increase of Vagal Tone in Heart Failure*) have shown that vagal nerve stimulation does not reduce the rate of death or heart failure events [31]. Alternatively, exercise training has been shown to reduce 10-year cardiovascular mortality, provided that it is associated with a clear shift of the autonomic balance toward an increase in baroreceptor sensitivity [32]. This means that exercise training remains the only clinically plausible mechanism to increase vagal activity in heart failure.

Table 4
Exploratory analysis of the relationship between denervated myocardium and autonomic dysfunction.

Predictors	Viable denervated myocardium		Infarcted myocardium	
	Bivariate	Multivariate[¥]	Bivariate	Multivariate
ECG parameters				
SDNN (ms)	NS	–	NS	–
RMSSD (ms)	$p = 0.011$	NS	NS	–
LF power (nu)	$p = 0.033$	**$p = 0.008$**	NS	–
HF power (nu)	$p = 0.100$	**$p = 0.010$**	NS	–
HRT onset (%)	$p = 0.097$	NS	NS	–
HRT slope (ms)	NS	–	NS	–
AC (ms)	NS	–	$p = 0.065$	NS
DC (ms)	$p = 0.091$	NS	NS	–

SDNN: standard deviation of normal-to-normal RR intervals, RMSSD: root mean square of the standard deviation of RR intervals, LF: low frequency, HF: high frequency, HRT: heart rate turbulence, AC: acceleration capacity, DC: deceleration capacity.
Bold indicates the variable remained significant in the final multivariate model.
[¥] Simple linear regression model: $r = 0.296$, $R^2 = 0.09$; $F = 5.394$, $p = 0.006$.

Limitations

This paper has few limitations. First, HRV cannot be analyzed in patients with pacing and atrial fibrillation which are prevalent in ischemic cardiomyopathy [33]. As a result, we excluded nearly one third of subjects in the original PAREPET cohort (n = 63/204, 31%). While this could introduce selection bias into the findings reported in this paper, the prior multivariate parameters we identified for predicting SCA including volume of denervated myocardium and left ventricular end-

diastolic volume were retained in the competing risks analysis. Second, our sample size was very small. Out of the 127 patients included in this study, only 22 reached the primary endpoint. As such, our results should be viewed as suggestive rather than conclusive. Finally, this analysis was based on patients with chronic heart failure due to ischemic cardiomyopathy, so our findings may not apply to those with non-ischemic cardiomyopathy.

Conclusions

This study demonstrates that depressed LF power of HRV is preferentially associated with NSCD in ischemic cardiomyopathy. Depressed LF power might indicate impaired vagal reflex, which suggests that increasing vagal tone in these patients would have a protective effect against cardiovascular death beyond that achieved by the mere slowing of heart rate using β-blockers.

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