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Prediction of heart rate variability on cardiac sudden death in heart failure patients: A systematic review

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Keywords

Prediction; Heart rate variability; Cardiac sudden death; Heart failure patients; Systematic review

Sudden cardiac death occurs frequently in patients with heart failure [1,2]. Determining suitable factors for identifying high risk heart failure patients is necessary. Heart rate variability (HRV) [3] was previously demonstrated to predict sudden cardiac death in heart failure patients, though findings have been inconsistent [4].

We conducted a systematic review for clarifying the predictive value of HRV. A comprehensive literature search up to December 2013 using the PubMed (MEDLINE) and CENTRAL with restrictions to humans' studies and English publications was carried out, with key words containing Sudden Cardiac Death, Heart Failure, and Heart Rate Variability. Among the 138 publications identified, 119 were excluded based on screening of titles and/or abstracts. 19 potential relevant articles and an additional article identified from references were fully reviewed. Six articles were excluded from our study due to different reasons. Jiang et al. included only death or a life-threatening cardiac event as the outcome but not covers sudden cardiac death [5]. Arsenos et al. included surrogate of sudden cardiac death as outcome [6]. Yamada et al. and Nessler et al. did not provide sufficient information [7,8]. La Rovere et al. did not provide specified data for outcome of sudden cardiac death [9]. Szabo et al. did not provide sufficient information for multivariate adjusted result of HRV parameters [10]. After excluding these 6 articles, 14 appropriate articles were retained (Fig. 1) [11–24]. Among them 4 articles have overlapping for participants of two studies [14,19,21,23]. We included all of them as in each article they demonstrated different variables/parameters of HRV. Further quality assessment in standardized manner [25] did not find deviations among these studies.

In total, 14 articles representing 12 prospective studies were included. Detailed information for these articles is demonstrated in Table 1. These studies used quite different variables/parameters of HRV in their report, making an overall quantitative evaluation challenging [26,27]. As the main variable of HRV, standard deviation of all normal-to-normal intervals (SDNN) was mostly studied. While this variable was presented as numerical variable in several studies [12,13,21,22], in other studies it was categorized according to different values, making an overall numerical estimation difficult [11,14,18,20,23]. However, in all these 9 studies, SDNN did not show a predictive role; thus, this variable should have a limited role in predicting sudden cardiac death among heart failure patients. Similarly, some other studied variables, including SD derived from time-domain analysis [12], NN [12,14,23], SDANN [12–14,23,24], pNN50 [12–14,20], rMSSD [12,13,18,23], HRV index [13], sNN50 [18], log HRV [17] and RR [21], were demonstrated to be not predictive in most studies except that one study supported a marginal predictive role of SDANN and rMSSD [20]. Thus, overall these variables are less likely to be predictive of sudden death in heart failure patients.

Several other variables of HRV were demonstrated to be potentially predictive in more studies. High frequency power (HF/HFP) was shown to be predictive in the 2005 Greece study [12], and night HFP seemed to be predictive in the 2005 Italy study [21], while a null effect was shown in the 2000 and 2009 Japan study [13,15], the 1996 and 2009 Netherlands study [14,23], and the 2000 France study [20]. It thus makes HFP being predictive of sudden cardiac death in heart failure patients less possible, since the 2009 Japan study with a long following-up (65 months) showed null result [13]. On the other hand, low frequency power (LF/LFP) was predictive in the 2003 Italy study (2 independent samples) [19], besides day-time LFP in the 2000 France study [20] and night-time LFP in the 2005 Italy study [21]. However, the prediction was not demonstrated in the 2005 Greece study [12], the 2000 and 2009 Japan study [13,15], and the 1996 and 2009 Netherlands study [14,23]; also the 2005 Italy study showed that all LFP did not have a predictive effect [21]. Thus overall evidences supporting the predictive effect of LFP are also weak. Another HRV variable, Poincare plot, demonstrated strong prediction in available studies (the 1996 Netherlands and the 1997 US studies) [14,24]. Though limited by a small number of studies, the relatively small sample size and short following-up make this effect is likely real.

To our knowledge, this is the first systematic review for the prediction value of heart rate variability on sudden cardiac death in heart failure patients. Although a quantitative meta-analysis is impossible due to that heart rate variability variables/parameters used in each study are quite different, all findings from these studies were carefully evaluated in our systematic review. We found that variables of SDNN, SD derived from time-domain analysis, NN, SDANN, pNN50, rMSSD, HRV index, sNN50, log HRV and RR should have limited predictive roles. Other two HRV variables, high frequency power and low frequency power, although showing a predictive value in several studies, are less likely to effectively predict sudden cardiac death in heart failure patients. On the other hand, Poincare plot can potentially predict well according to current evidences. Further studies are warranted to determine whether Poincare plot can really be a representative HRV variable in effectively predicting sudden cardiac death in heart failure patients.

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References

1. Kannel WB, Plehn JF, Cupples LA. Cardiac failure and sudden death in the Framingham Study. *Am Heart J*. 1988; 115:869–75. [PubMed: 3354416]
2. Lane RE, Cowie MR, Chow AW. Prediction and prevention of sudden cardiac death in heart failure. *Heart*. 2005; 91:674–80. [PubMed: 15831662]
3. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. *Med Biol Eng Comput*. 2006; 44:1031–51. [PubMed: 17111118]
4. Lorvidhaya P, Addo K, Chodosh A, Iyer V, Lum J, Buxton AE. Sudden cardiac death risk stratification in patients with heart failure. *Heart Fail Clin*. 2011; 7:157–74. vii. [PubMed: 21439495]
5. Jiang W, Hathaway WR, McNulty S, et al. Ability of heart rate variability to predict prognosis in patients with advanced congestive heart failure. *Am J Cardiol*. 1997; 80:808–11. [PubMed: 9315600]
6. Arsenos P, Gatzoulis K, Manis G, et al. Decreased scale-specific heart rate variability after multiresolution wavelet analysis predicts sudden cardiac death in heart failure patients. *Int J Cardiol*. 2012; 154:358–60. [PubMed: 22133464]
7. Yamada T, Shimonagata T, Fukunami M, et al. Comparison of the prognostic value of cardiac iodine-123 metaiodobenzylguanidine imaging and heart rate variability in patients with chronic heart failure: a prospective study. *J Am Coll Cardiol*. 2003; 41:231–8. [PubMed: 12535815]
8. Nessler J, Nessler B, Kitlinski M, et al. Sudden cardiac death risk factors in patients with heart failure treated with carvedilol. *Kardiol Pol*. 2007; 65:1417–22. [discussion 23–4]. [PubMed: 18181053]
9. La Rovere MT, Pinna GD, Maestri R, et al. Autonomic markers and cardiovascular and arrhythmic events in heart failure patients: still a place in prognostication? Data from the GISSI-HF trial. *Eur J Heart Fail*. 2012; 14:1410–9. [PubMed: 22851700]
10. Szabo BM, van Veldhuisen DJ, van der Veer N, Brouwer J, De Graeff PA, Crijns HJ. Prognostic value of heart rate variability in chronic congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol*. 1997; 79:978–80. [PubMed: 9104918]
11. Bilchick KC, Fetters B, Djoukeng R, et al. Prognostic value of heart rate variability in chronic congestive heart failure (Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure). *Am J Cardiol*. 2002; 90:24–8. [PubMed: 12088774]
12. Anastasiou-Nana MI, Terrovitis JV, Athanasoulis T, et al. Prognostic value of iodine-123-metaiodobenzylguanidine myocardial uptake and heart rate variability in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2005; 96:427–31. [PubMed: 16054475]
13. Tamaki S, Yamada T, Okuyama Y, et al. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction: results from a comparative study with signal-averaged electrocardiogram, heart rate variability, and QT dispersion. *J Am Coll Cardiol*. 2009; 53:426–35. [PubMed: 19179201]
14. Brouwer J, van Veldhuisen DJ, Man in 't Veld AJ, et al. Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. The Dutch Ibopamine Multicenter Trial Study Group. *J Am Coll Cardiol*. 1996; 28:1183–9. [PubMed: 8890814]

15. Soejima K, Akaishi M, Meguro T, et al. Age-adjusted heart rate variability as an index of the severity and prognosis of heart failure. *Jpn Circ J*. 2000; 64:32–8. [PubMed: 10651204]
16. Kuch M, Janiszewski M, Mamcarz A, Cudnoch-Jedrzejewska A, Dluzniewski M. Major adverse cardiac event predictors in survivors of myocardial infarction with asymptomatic left ventricular dysfunction or chronic heart failure. *Med Sci Monit*. 2009; 15:PH40–8. [PubMed: 19478711]
17. Tereshchenko LG, Cygankiewicz I, McNitt S, et al. Predictive value of beat-to-beat QT variability index across the continuum of left ventricular dysfunction: competing risks of noncardiac or cardiovascular death and sudden or nonsudden cardiac death. *Circ Arrhythm Electrophysiol*. 2012; 5:719–27. [PubMed: 22730411]
18. Nolan J, Batin PD, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation*. 1998; 98:1510–6. [PubMed: 9769304]
19. La Rovere MT, Pinna GD, Maestri R, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation*. 2003; 107:565–70. [PubMed: 12566367]
20. Galinier M, Pathak A, Fourcade J, et al. Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. *Eur Heart J*. 2000; 21:475–82. [PubMed: 10681488]
21. Guzzetti S, La Rovere MT, Pinna GD, et al. Different spectral components of 24 h heart rate variability are related to different modes of death in chronic heart failure. *Eur Heart J*. 2005; 26:357–62. [PubMed: 15618038]
22. Shehab AM, MacFadyen RJ, McLaren M, Tavendale R, Belch JJ, Struthers AD. Sudden unexpected death in heart failure may be preceded by short term, intraindividual increases in inflammation and in autonomic dysfunction: a pilot study. *Heart*. 2004; 90:1263–8. [PubMed: 15486117]
23. Smilde TD, van Veldhuisen DJ, van den Berg MP. Prognostic value of heart rate variability and ventricular arrhythmias during 13-year follow-up in patients with mild to moderate heart failure. *Clin Res Cardiol*. 2009; 98:233–9. [PubMed: 19219394]
24. Woo MA, Moser DK, Stevenson LW, Stevenson WG. Six-minute walk test and heart rate variability: lack of association in advanced stages of heart failure. *Am J Crit Care*. 1997; 6:348–54. [PubMed: 9283671]
25. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000; 283:2008–12. [PubMed: 10789670]
26. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*. 1996; 93:1043–65. [PubMed: 8598068]
27. Crawford MH, Bernstein SJ, Deedwania PC, et al. ACC/AHA Guidelines for Ambulatory Electrocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography). Developed in collaboration with the North American Society for Pacing and Electrophysiology. *J Am Coll Cardiol*. 1999; 34:912–48. [PubMed: 10483977]

Fig. 1.
Articles identified through comprehensive literature search.

Table 1

Studies investigating predictive value of heart rate variability on cardiac sudden death in heart failure patients.

First author, publication year (reference), country	Cases/subject (age), duration of follow-up	Method for obtaining data	Exposure categories	RR/HR (95% CI)	Adjusted factors
Bilchick et al., 2002 ¹¹ , US	21/127 (mean 64.7 y), mean 34 months	24 h Del-Mar Holter recording	SDNN: SDNN >65.3 ms (Ref) SDNN < 65.3 ms	2.40 ($p = 0.088$)	LVEF, systolic BP, HR, age, treatment group, presence of ischemic cardiomyopathy
Anastasiou-Nana et al., 2005 ¹² , Greece	4/52 (56 ± 12 y), 2 years	24 h ambulatory ECG monitoring	High frequency power SD derived from time-domain analysis Mean NN, SDNN, SDANN, pNN50, rMSSD, low power, total power, normalized low or high power, low/high power ratio	0.31 (0.101-0.954) 0.913 (0.831-1.004) All NS	None
Tamaki et al, 2009 ¹³ , Japan	18/106 (~64y), 65 ± 31 months	24 h ambulatory ECG monitoring	Mean RR, SDNN, SDANN, SDNN index, rMSSD, pNN50, HRV index, TP, ULFP, n-ULFP, VLFP, n-VLFP, LFP, n-LFP, HFP, n-HFP, LFP/HFP	All NS	Age; sex; underlying causes (ischemic or nonischemic); New York Heart Association (NYHA) functional class; heart rate; systolic and diastolic blood pressure; LVEF; presence of nonsustained ventricular tachycardia on Holter monitoring; echocardiography data; plasma noradrenaline concentration; serum uric acid, sodium, and creatinine levels; and the results of cardiac MIBG imaging, SAECG, HRV, and QT dispersion
Brouwer et al, 1996 ¹⁴ , Netherlands	11/95 (~60 y), 2-4y	24 h ambulatory Holter recording	Poincare plot: normal (REF) abnormal plot Mean NN interval (<750 ms), SDNN (<110ms), SDNN (<50 ms), SDANN (<100 ms), pNN50 (<2.0%), total power (<2500 ms ²), very low frequency power (<1500 ms ²), low frequency power (<300 ms ²), high frequency power (<100 ms ²)	5.3 (1.0-27.5) All NS	LVEF (<0.30), plasma norepinephrine (> 450 pg/ml), ventricular premature beats (>20/h), ventricular tachycardia (present) None
Soejima et al, 2000 ¹⁵ , Japan	7/52 (mean 61.5 y), mean 3.8 y	24 h Holter monitoring	LF, HF: normal (Ref) Abnormal LF, HF	NS	Age
Kuch et al, 2009 ¹⁶ , Poland ^a	33/158 (49-80 y), 2 y	24 h ECG monitoring	HRV: normal (Ref) Low	$P < 0.001$	Diabetes status, AMI location

First author, publication year (reference), country	Cases/subject (age), duration of follow-up	Method for obtaining data	Exposure categories	RR/HR (95% CI)	Adjusted factors
Tereshchenko et al, 2012 ¹⁷ , Spain	52/533 (mean 62.8 ± 12 y), median 44 months	High-resolution orthogonal ECG recordings	Log HRV: 3 higher quartile (Ref) Lowest quartile of log HRV	1.53 (0.85-2.77)	None
Nolan et al, 1998 ¹⁸ , UK	18/433 (62 ± 9.6 y), 484 ± 161 days	24 h ECG recording	SDNN (> 100ms), sNN50, rMSSD	All NS	Cardiothoracic ratio, LVEDD, NSVT, potassium
La Rovere et al, 2003 ¹⁹ , Italy	19/202 (52 ± 9y), 3 y (derivation sample)	ECG recording	Controlled-breathing LF power: >13 ms ² (Ref) 13 ms	3.7 (1.5-9.3)	Left ventricular end-diastolic diameter
	20/242 (~54 y), 3 y (validation sample)		Controlled-breathing LF power: >11 ms ² (Ref) 11 ms ²	3.0 (1.2-7.6)	Ventricular premature contractions
Galinieret al, 2000 ²⁰ , France	21/190 (mean 61 ± 12 y), mean 22 ± 18 months	24 h Holter ECG recordings	Day-time low frequency power: 3.3 ln (ms ²) (Ref) <3.3 ln (ms ²)	2.8 (1.2-6.8)	Aetiology (CAD)
			SDANN (<55 ms)	2.5 (1-5)	None
			RMSSD (<14 ms)	2.4 (1-5.5)	None
			Day-time total power (<4.8 ln (ms ²))	2.4 (1-5.6)	None
			Mean heart rate (>89 beats/min), SDNN (<67 ms), SD (<30 ms), pNN50 (<2%), night-time total power (<5.3 ln (ms ²)), night-time low frequency power (<3.6 ln (ms ²)), day-time high frequency power (<2.7 ln (ms ²)), night-time high frequency power (<3.1 ln (ms ²))	All NS	None
Guzzetti et al, 2005 ²¹ , Italy ^b	29/352 (47-59 y), median 34 months	Holter ECG recordings	LF night(20 ms ²) HF night((60 ms ²)	2.7 (1.3-5.6) 2.2 (1.0-4.6)	None None
			RR 24-h, RR night, SDNN 24-h, SDNN night, VLF 24-h, VLF night, LF 24-h, HF 24-h, LF 24-h nu, LF night nu, HF 24-h nu, HF night nu, LF/HF 24-h, 1/f slope	All NS	None
Shehab et al, 2004 ²² , UK	5/34 (mean 68 y), 1 y	24 h ECG monitoring	SDNN (mean)	NS	None

First author, publication year (reference), country	Cases/subject (age), duration of follow-up	Method for obtaining data	Exposure categories	RR/HR (95% CI)	Adjusted factors
Smilde et al, 2009 ²³ , Netherlands ^c	28/90 (mean 60 ± 8 y), mean 11.7 y	Holter ECG recordings	Mean NN (<750 ms), SDNN (<110 ms), SDNN (<50 ms), SDANN (<100 ms), RMSSD (<25 ms), total power (<2500 ms ²), very LF power (<1500 ms ²), LF power (<300 ms ²), HF power (<100 ms ²)	All NS	None
Wooetal, 1997 ²⁴ , US	19/113 (53 ± 10 y), 1y	24 h Holter monitoring	Poincare plot (nonlinear method) SDANN	$P < 0.0001$ NS	Mean right atrial pressure at hemodynamic optimization, serum level of sodium, LVEF, results of the 6-minute walk

RR: relative risk; HR: hazard ratio; CI: confidence interval; NA: not available; NS: not statistically significant.

^a Studied patients are post myocardial infarction patients with heart failure.

^b Part of La Rovere et al., 2003 as shown above.

^c Part of Brouwer et al., 1996 as shown above.