Heart rate variability as a predictor of sudden cardiac death

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ABSTRACT

Different noninvasive approaches have been developed for risk stratification of patients with myocardial infarction and heart failure with aim to select patients at high risk of sudden cardiac death who might mostly benefit from preventive therapy. Reduced heart rate variability (HRV) was a strong predictor of mortality in myocardial infarction and heart failure in early studies. However, in the era of modern treatment strategies the prognostic significance of HRV indices has been challenged. We thought to review the role of conventional, nonlinear and novel spectral indices of HRV in prediction of sudden cardiac death in patients with myocardial infraction and heart failure.
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Key words: myocardial infarction, heart failure, sudden cardiac death, heart rate variability

Introduction

Epidemiological and population based studies reported that annually about 1-2 of 1000 people die suddenly, though there has been a significant decline in mortality due to coronary artery disease in past 20 years (1-3). Early risk stratification of patients with heart disease carrying the risk of sudden cardiac death (SCD) is important since the preventive therapy with implantable cardioverter defibrillator (ICD) is effective in reducing mortality (4, 5). Different noninvasive approaches have been developed for risk stratification of patients with myocardial infarction (MI) and heart failure (HF) with aim to select patients who might mostly benefit from preventive therapy (5-10).

Heart rate variability (HRV), the indicator of the cardiac autonomic modulation was low in survivors of cardiac arrest (11-13) and abnormal HRV patterns preceded the episodes of life-threatening arrhythmias on Holter monitoring and ICD storing electrograms (14, 15).

Reduced HRV was a strong predictor of mortality in patients with MI (7, 16-18). However, in the era of modern treatment strategies that have modifying role in prognosis of patients with MI like treatment with beta-blockers and revascularization (19, 20, 21, 22), the prognostic significance of conventional HRV indices has been challenged.

Time-domain, frequency-domain and geometric indices of HRV and SCD

Time-domain indices of HRV were strong predictors of total mortality after MI in early studies (16-18), however there was no association of SDNN (standard deviation of normal-to-normal RR intervals) with SCD in 700 patients with acute MI, 97% of whom were treated with beta-blockers (19).

Bigger et al. (17, 23) described the relationship of HRV spectral indices with arrhythmic death and SCD in patients with MI. In the MPIP study (17, 23), which included 715 patients with acute MI, long-term 24-hour and short-term frequency-domain indices of HRV predicted development of arrhythmic death and SCD during 31 months of follow-up.

The prognostic significance of HRV index, a geometric measure of RR variability, was studied in patients with low left ventricular ejection fraction (LVEF) soon after MI (24, 25), however HRV index did not predict arrhythmic death, though it was a significant multivariate predictor of mortality in patients with MI (25).

In heart failure, the data on prognostic significance of time-domain HRV indices in prediction of SCD are somewhat controversial (26-29). In UK-Heart prospective study, SDNN was found to be a significant multivariate predictor of total mortality, however it could not predict development of SCD in 18 of 433 patients with HF, NYHA class I-III and LVEF≤45% during mean 482±161 days of follow-up (26). While Bilchik et al. (28) showed that SDNN ≤65.3 ms was the significant predictor of SCD and worse survival in patients with HF presented with NYHA class II-IV, LVEF ≤40% and ventricular ectopic beats on Holter monitoring during 50 months of follow-up period.

Spectral indices of HRV, specially low frequency power (LF) estimated from 24 –hour Holter monitoring during day (30), during night (31) or extracted from short-term recording during controlled breathing (32) have been shown to have high prognostic value in prediction of SCD in patients with HF. The day-time LF≤3.3 ln(ms)^2 (30) was a significant multivariate predictor of SCD (RR=2.8, 95%CI 1.2-8.6, p<0.05) during 3 years of follow-up period in 190 patients with HF, NYHA class II-IV, and mean LVEF ≤45%. Guzetti et al. (31) have demonstrated that night-time LF ≤20 ms^2 is significantly associated with SCD in a larger population of patients with HF and LVEF ≤30%. The night-time LF below cut-off value carried a 2.6 fold higher risk (95%CI 1.2-5.5, p=0.012) of SCD

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during 3 years of follow-up (9% of patients died suddenly). The LF, extracted from short-term recordings during controlled breathing had even stronger association with SCD (32). La Rovere et al. (32), in a derivation sample of 202 patients with HF, have shown that LF ≤13 ms^2 (RR=3.7 95% CI 1.5-9.3, p=0.005) and LV end-diastolic dimension ≥77 mm (p=0.04) were the only independent multivariate predictors of SCD, while in validation model (242 patients) the patients with LF≤11 ms^2 were 3 times more likely to die suddenly during follow-up period (95% CI 1.2-7.5, p=0.01). Combination of ventricular premature complexes and low LF had negative predictive value of 97% and positive predictive value of 18% in prediction of SCD.

Nonlinear indices of HRV and SCD

The analysis of MPIP data (33) has demonstrated that power law regression parameters of HRV in patients after MI have significant multivariate association with arrhythmic death (RR- 3.21, p<0.001), which was stronger than predictive power of 24-hour Holter spectral indices, after adjustment for clinical variables.

The nonlinear short-term fractal scaling exponent α_1 (DFA α_1) was the only parameter independently associated with increased risk of SCD in 446 patients with MI and LVEF ≤35% (39-45% were treated with beta-blockers), 75 of whom died due to arrhythmia during mean follow-up of 685 +360 days (35). In multivariate analysis DFA α_1 after adjustment for clinical variables like age, NYHA class, wall motion index, medications, ventricular arrhythmias on 24-hour Holter monitoring and randomization for dofetilide and placebo predicted arrhythmic death with RR of 1.4 (95% CI 1.1-1.7, p<0.05). The DFA α_1<0.75 was the most powerful predictor of worse cumulative (arrhythmic and nonarrhythmic cardiac deaths) survival during 1200 day of follow up as compared with SDNN and very low frequency spectral component (p<0.001).

In the study by Makikallio et al (36), which included 2130 patients with acute MI, undergoing contemporary treatment, DFA α_1 along with turbulence slope and NSVT were significant predictors of SCD in multivariate analysis after adjustment for age, diabetes and LVEF. Patients with MI and DFA α_1 <0.75 were 1.9 times (HR 1.9 95% CI 1.0-3.6, p=0.04) more likely to die suddenly during 1600 days of follow-up. Interestingly, the predictive significance of HRV was different in subgroups of patients dichotomized by LVEF: none of the HRV indices were predictive for SCD in patients with LVEF≤35% (226 patients), while in patients with LVEF ≥35% (1094 patients) the DFA α_1 <0.75 predicted SCD with HR of 2.7 (95% CI 1.3-5.7, p=0.0088).

In patients with HF, among nonlinear indices the abnormal Poincare plot was a significant, multivariate and independent of LVEF, norepinephrine levels, ventricular tachycardia and ventricular premature complexes predictor of SCD (HR 5.3, 95% CI 1.0-27.5, p<0.05) in 95 patients with HF, of whom 11 died suddenly during 4-year follow-up period (37, 38).

Novel spectral indices of HRV and SCD

Two novel spectral indices have been recently introduced (39-41). The prognostic significance of prevalent LF oscillation (PLF) of HRV was investigated in ATRAMI study population (39), which included 1139 patients after MI and mean LVEF-49.0±1.8%. In this study, only presence of PLF along with reduced LVEF≤35% could predict the combined end-point during mean 674±234 days of follow-up. The patients with frequency of PLF ≥0.1 Hz have 3.61 fold (95% CI 1.25-10.5, p<0.02) higher risk of death, including cardiac arrest and ventricular fibrillation. However, PLF was present only in 80% of patients, which may limit its use as a risk marker in patients after MI. Further it has been shown that the combination of PLF with heart rate turbulence slope improved prediction of arrhythmic death with RR of 5.1 (95% CI 2.8-9.3, p=9.8*10^{-8}) in patients of placebo group in EMIAT study population (40).

Kiviniemi et al. (41) have recently demonstrated that new HRV spectral parameter - Vi, derivative of high frequency (HF) spectral component and RRi intervals, had a strong prognostic power in prediction of SCD in 700 patients with MI, among them 17 patients (2.9%) died suddenly during mean 39±14 months of follow-up period. In univariate analysis SDNN, LF, HF and new index Vi were significant predictors of SCD, however, after adjustment for clinical variables and LVEF, the Vi was a sole multivariate predictor of SCD; the patients with Vi <4.45ms^2 had 4.2-fold (95% CI 1.2-15.2, p=0.02) higher risk of SCD during follow-up period. It worth mentioning, that Vi parameter was a significant predictor of worse survival in patients with low LVEF (p=0.03).

The merit of conventional HRV predictors of mortality and SCD has changed during the past decade, with gaining in value of spectral, nonlinear and novel HRV indices as the potential risk markers in patients with MI and HF. However, the positive predictive value of HRV in prediction of SCD remains low. Further prospective investigations including combination of HRV indices with other noninvasive risk markers (4) in prediction of SCD should be addressed.

References

1. Smith TW, Cain ME. Sudden cardiac death: epidemiologic and financial worldwide perspective. J Interv Card Electrophysiol 2006; 17: 199–203.
2. Priori SG, Aliot E, Blomstrom-Lundqvist C, Bossaert L, Breithardt G, Brugada P, et al. Task force on sudden cardiac death of the European Society of Cardiology. Eur Heart J 2002; 22: 1374–450.
3. Goraya TY, Jacobsen SJ, Kottke TE, Frye RL, Weston SA, Roger VL. Coronary heart disease death and sudden cardiac death: a 20-year population-based study. Am J Epidemiol 2003; 157: 763-70.
4. Al-Khatib SM, Sanders GD, Bigger JT, Buxton AE, Califf RM, Carlson M, et al; Expert panel participating in a Duke's Center for the Prevention of Sudden Cardiac Death conference. Preventing tomorrow's sudden cardiac death today: part I: Current data on risk stratification for sudden cardiac death. Am Heart J 2007; 153: 941-50.
5. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005; 352: 225-37.
6. Denes P, el-Sherif N, Katz R, Capone R, Carlson M, Mitchell LB, et al. Prognostic significance of signal-averaged electrocardiogram after thrombolytic therapy and/or angioplasty during acute myocardial infarction (CAST substudy). Cardiac Arrhythmia Suppression Trial (CAST) SAECG Substudy Investigators. Am J Cardiol 1994; 74: 216-20.
7. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 1998; 351: 478-84.
8. Haigney MC, Zareba W, Gentlesk PJ, Goldstein RE, Illovsky M, McNitt S, et al; Multicenter Automatic Defibrillator Implantation Trial II investigators. QT interval variability and spontaneous ventricular

tachycardia or fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. J Am Coll Cardiol 2004; 44: 1481-7.
9. Berkowitsch A, Zareba W, Neumann T, Erdogan A, Nitt SM, Moss AJ, et al. Risk stratification using heart rate turbulence and ventricular arrhythmia in MADIT II: usefulness and limitations of a 10-minute holter recording. Ann Noninvasive Electrocardiol 2004; 9: 270-9.
10. Bloomfield DM, Steinman RC, Namerow PB, Parides M, Davidenko J, Kaufman ES, et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: a solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. Circulation 2004; 110: 1885-9.
11. Molnar J, Weiss JS, Rosenthal JE. Does heart rate identify sudden death survivors? Assessment of heart rate, QT interval, and heart rate variability. Am J Ther 2002; 9: 99-110.
12. Dougherty CM, Burr RL. Comparison of heart rate variability in survivors and nonsurvivors of sudden cardiac arrest. Am J Cardiol 1992; 70: 441-8.
13. Huikuri HV, Linnaluoto MK, Seppanen T, Airaksinen KE, Kessler KM, Takkunen JT, et al. Circadian rhythm of heart rate variability in survivors of cardiac arrest. Am J Cardiol 1992; 70: 610-5.
14. Lombardi F, Porta A, Marzegalli M, Favale S, Santini M, Vincenti A, et al; Implantable Cardioverter Defibrillator-Heart Rate Variability Italian Study Group. Heart rate variability patterns before ventricular tachycardia onset in patients with an implantable cardioverter defibrillator. Participating Investigators of ICD-HRV Italian Study Group. Am J Cardiol 2000; 86: 959-63.
15. Pruvot E, Thonet G, Vesin JM, van-Melle G, Seidl K, Schmidinger H, et al. Heart rate dynamics at the onset of ventricular tachyarrhythmias as retrieved from implantable cardioverter-defibrillators in patients with coronary artery disease. Circulation 2000; 101: 2398-404.
16. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59: 256-62.
17. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 1992; 85: 164-71.
18. Zuanetti G, Neilson JM, Latini R, Santoro E, Maggioni AP, Ewing DJ. Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. Circulation 1996; 94: 432-6.
19. Huikuri HV, Tapanainen JM, Lindgren K, Raatikainen P, Makikallio TH, Airaksinen J, et al. Prediction of sudden cardiac death after myocardial infarction in the beta-blocking era. J Am Coll Cardiol 2003; 42: 652-8.
20. Stein PK, Domitrovich PP, Kleiger RE; CAST Investigators. Including patients with diabetes mellitus or coronary artery bypass grafting decreases the association between heart rate variability and mortality after myocardial infarction. Am Heart J 2004; 147: 309-16.
21. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al; DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004; 351: 2481-8.
22. Bilchick KC, Bigger RD. Heart rate variability. J Cardiovasc Electrophysiol 2006; 17: 691-4.
23. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. Circulation. 1993; 88: 927-34.
24. Malik M, Camm AJ, Janse MJ, Julian DG, Frangin GA, Schwartz PJ. Depressed heart rate variability identifies postinfarction patients who might benefit from prophylactic treatment with amiodarone: a substudy of EMIAT (The European Myocardial Infarct Amiodarone Trial). J Am Coll Cardiol 2000; 35: 1263-75.
25. Camm AJ, Pratt CM, Schwartz PJ, Al-Khalidi HR, Spyt MJ, Holroyde MJ, et al; AzimiLide post Infarct surVival Evaluation (ALIVE) Investigators. 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.
26. Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, et al. Prospective study of heart rate variability and mortality in chronic heart failure. Circulation 1998; 98: 1510-6.
27. 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.
28. Bilchik KC, Fetics B, Djoukeng R, Gross Fisher S, Fletcher RD, Singh SN, et al. Prognostic value fo 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.
29. Fauchier L, Babuty D, Cosnay P, Fauchier JP. Prognostic value of heart rate variability for sudden death and major arrhythmic events in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1999; 33: 1203-7.
30. Galinier M, Pathak A, Fourcade J, Android C, Curnier D, Varnous S, 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.
31. Guzzetti S, La Rovere MT, Pinna GD, Maestro R, Borroni E, Porta A, et al. Different spectral components of 24h heart rate variability are related to different modes of death in chronic heart failure. Eur Heart J 2005; 26: 357-62.
32. La Rovere MT, Pinna GD, Maestro R, Mortara A, Capomolla S, Febo O, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation 2003; 107: 565-70.
33. Bigger JT Jr, Steinman RC, Rolnitzky LM, Fleiss JL, Albrecht P, Cohen RJ. Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. Circulation. 1996; 93: 2142-51.
34. Makikallio TH, Hoiber S, Kober L, Torp-Pedersen C, Peng CK, Goldberger AL, et al. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. TRACE Investigators. TRAndolapril Cardiac Evaluation. Am J Cardiol 1999; 83: 836-9.
35. 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. Circulation 2000; 101: 47-53.
36. 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. Eur Heart J 2005; 26: 762-9.
37. Makikallio TH, Huikuri HV, Hintze U, Videbæk J, Mitrani RD, Castellanos A, et al; for the DIAMOND Study Group. Fractal analysis and time- and frequency-domain measures of heart rate variability as predictors of mortality in patients with heart failure. Am J Cardiol 2001; 87: 178–82.
38. Brouwer J, van Veldhuisen DJ, Man in't Veld AJ, Haaksma J, Dijk WA, Visser KR, 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.
39. Wichterle D, Simek J, La Rovere MT, Schwartz PJ, Camm AJ, Malik M. Prevalent low-frequency oscillation of heart rate: novel predictor of mortality after myocardial infarction. Circulation 2004; 110: 1183-90.
40. Wichterle D, Simek J, Camm J, Malik M. Predictive characteristics of Holter-based postinfarction risk stratifiers appear superior to electrophysiological testing. Pacing Clin Electrophysiol 2005; 28: S182-6.
41. Kiviniemi AM, Tulppo MP, Wichterle D, Hautala AJ, Tiinanen S, Seppanen T, et al. Novel spectral indexes of heart rate variability as predictors of sudden and non-sudden cardiac death after an acute myocardial infarction. Ann Med 2007; 39: 54-62.