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(ms²) (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 ms² is significantly associated with SCD in a larger population of patients with HF and LVEF ≤30%.

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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 ms² (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 ms² 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 α1 (DFA α1) 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 α1 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 α1 <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 α1 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 α1 <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 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 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


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