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# Sudden death and its predictors in myocardial infarction survivors in an Indian population

Raja J. Selvaraj [a, *], Sasinthar Rangasamy [b], Dhivya Priya [c], Sreekumaran Nair [c], Ajith Ananthakrishna Pillai [a], Santhosh Satheesh [a], Balachander Jayaraman [a]

[a] Department of Cardiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India
[b] Department of Cardiology, Mahatma Gandhi Medical College and Research Institute, Pondicherry, India
[c] Department of Medical Biometrics and Informatics (Biostatistics), Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India

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ABSTRACT

*Objective:* This study was conducted to assess the incidence of sudden cardiac death (SCD) in post myocardial infarction patients and to determine the predictive value of various risk markers in identifying cardiac mortality and SCD.
*Methods:* Left ventricular function, arrhythmias on Holter and microvolt T wave alternans (MTWA) were assessed in patients with prior myocardial infarction and ejection fraction $\leq$ 40%. The primary outcome was a composite of cardiac death and resuscitated cardiac arrest during follow up. Secondary outcomes included total mortality and SCD.
*Results:* Fifty-eight patients were included in the study. Eight patients (15.5%) died during a mean follow-up of 22.3 $\pm$ 6.6 months. Seven of them (12.1%) had SCD. Among the various risk markers studied, left ventricular ejection fraction (LVEF) $\leq$ 30% (Hazard ratio 5.6, 95% CI 1.39 to 23) and non-sustained ventricular tachycardia (NSVT) in holter (5.7, 95% CI 1.14 to 29) were significantly associated with the primary outcome in multivariate analysis. Other measures, including QRS width, heart rate variability, heart rate turbulence and MTWA showed no association.
*Conclusions:* Among patients with prior myocardial infarction and reduced left ventricular function, the rate of cardiac death was substantial, with most of these being sudden cardiac death. Both LVEF $\leq$30% and NSVT were associated with cardiac death whereas only LVEF predicted SCD. Other parameters did not appear useful for prediction of events in these patients. These findings have implications for decision making for the use of implantable cardioverter defibrillators for primary prevention in these patients.


## 1. Introduction

Patients who survive a myocardial infarction (MI) with depressed left ventricular (LV) function are a high-risk group for sudden death [1]. Antiarrhythmic drugs other than beta blockers do not improve survival in this population [2,3] and may even increase mortality [4]. The only effective preventive measure in patients at risk is the implantable cardioverter defibrillator (ICD). However, when used in all patients with depressed LV function after an MI, about 18 patients need to be treated to save one life at 2 years [5]. The implantation of an ICD also entails a significant financial burden, even in developed countries, but especially so in the developing countries.

Methods to refine risk assessment, allowing detection of a high-risk subgroup who will benefit from device implantation while avoiding implantation in those at low risk, are desirable. Various risk markers have been described, but none has shown consistent efficacy in different trials. Studies on risk markers in this population have also been hampered by the use of ICD therapies as a surrogate endpoint for sudden death. Use of this surrogate endpoint is known to skew the results of the trials [6,7].

There is limited data on incidence of sudden death after an MI in India [8]. Patients suffering an MI in India are different from those in the West, principally being younger and with a higher prevalence of diabetes [9]. Such differences in the population at risk may mean that the results of studies from the West may not apply to patients in south Asian regions [10].

* Corresponding author. Department of Cardiology, JIPMER, Dhanvantri Nagar, Puducherry, 605006, India.
*E-mail address:* raja.selvaraj@jipmer.edu.in (R.J. Selvaraj).
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Therefore, this study was designed to assess the incidence of sudden death among patients with a prior MI and impaired LV function. Various possible risk predictors were also assessed in this population.

## 2. Methods

### 2.1. Study design and population

This is a single center prospective cohort study conducted in a tertiary care hospital in South India. Patients were recruited between June 2012 and July 2015 and were followed up for 2 years. Patients of age 18–75 years with prior MI more than 40 days ago and LVEF ≤40% were included. Patients with a history of sustained ventricular arrhythmias, those who had undergone ICD implantation and those scheduled for an ICD implantation were not included. Patients who had undergone revascularization within the previous 30 days, those who would not be able to follow-up regularly and those with comorbidities with an expected longevity less than 1 year were also excluded from the study. Institute ethics committee approval was obtained, informed consent was taken from the participants.

### 2.2. Baseline assessment

At study entry, assessment for major risk factors like diabetes, hypertension, smoking and renal disease were done for all the enrolled patients by history, physical evaluation and blood investigations as required. A brief drug history including usage of beta blockers, ACE inhibitors, statins, calcium channel blockers and antiarrhythmics was taken. A 12-lead electrocardiogram (ECG) was recorded at rest and analyzed for heart rate, QRS width, the presence of bundle branch blocks and atrial fibrillation. The LVEF was determined by echocardiography using the Simpson's biplane method.

#### 2.2.1. Holter

A 24-h ambulatory Holter recording was done for all patients using a 12-lead recording system (Mortara). At the workstation, beat annotation was reviewed and corrected manually when required. Mean heart rate, total premature ventricular contraction (PVC) count, and presence of non-sustained ventricular tachycardia (NSVT) were recorded. Heart rate variability (HRV) was analyzed using the standard deviation of normal to normal RR intervals (SDNN). Patients were said to have 'frequent PVCs' if the total PVC count by holter was >10 per hour [11]. NSVT was defined as at least 3 consecutive ventricular beats at a rate ≥ 120 beats per minute but lasting less than 30 s [12]. For HRV, SDNN below 70 ms was used as a cut-off to identify as abnormal [13].

The RR intervals were exported and heart rate turbulence (HRT) was measured offline using custom software using the algorithm as described previously [14]. Sequences of beats containing a PVC with at least two normal sinus beats before and 15 normal sinus beats after the PVC were chosen for measuring HRT. Only PVCs followed by a pause were included. At least five such sequences were required to obtain HRT measurements from a recording. Turbulence Onset (TO) was measured as the percentage change in the mean of two intervals after the PVC compared to the mean of two intervals just prior to the PVC, as follows:

$$TO\ (\%) = ((RR_1 + RR_2) - (RR_{-2} + RR_{-1}))\ x\ 100\ /\ (RR_{-2} + RR_{-1})$$

where $RR_{-2}$ and $RR_{-1}$ are the two RR intervals immediately preceding the PVC, and $RR_1$ and $RR_2$ are two RR intervals immediately following the compensatory pause. Turbulence Slope (TS) is defined as the maximum positive regression slope fitted to any 5 consecutive sinus rhythm RR intervals within the first 15 RR intervals after the PVC. TS is expressed as milliseconds per normal-to-normal interval (ms/NN). TO and TS were dichotomized at predefined cut points (TO – abnormal when >0%, TS – abnormal when < 2.5 ms/NN) [14]. Patients were classified into the following three HRT categories - category 0 when both TO and TS were normal, category 1 if either TO or TS was abnormal and category 2 if both TO and TS were abnormal.

#### 2.2.2. Electrophysiology study

Electrophysiology (EP) study was performed in all patients. Quadripolar catheters were placed in the right atrium and right ventricle through femoral venous access. Twelve lead ECG was recorded on the EP system (Bard) during atrioventricular pacing with an atrioventricular delay of 0 ms. Pacing was performed for 3 min each at rates of 90, 95, 100, 105 and 110 beats per minute. The ECG signals were exported, and custom software was used to analyze microvolt T wave alternans (MTWA) using the spectral method with 128 beats at each heart rate [15]. It was considered positive if the alternans amplitude was >1.9 $\mu$V with alternans signal-to-noise ratio k > 3 sustained for > 1 min [16,17]. Indeterminate tests, where T wave alternans measurement is not possible because of excessive noise or frequent PVCs were also classified as positive [18].

Single premature beats were delivered from the RV catheter, separated by 20 beats of sinus rhythm, starting at a coupling interval 100 ms shorter than the sinus cycle length, decrementing by 10 ms and ending at ventricular refractoriness. HRT was measured from these sequences using the same methodology as with Holter recordings.

### 2.3. Follow up

Participants were followed up every 6 months for a total duration of 2 years. Optimal medical management was continued during the follow up. The primary outcome was a composite of cardiac death and resuscitated cardiac arrest. Secondary outcomes included total mortality and SCD. For patients who died during follow-up, an interview was conducted with a close relative who was with the patient around the time of death and the cause of death was classified as SCD, non-sudden cardiac death or non-cardiac death. Death was classified as SCD if death was natural with abrupt loss of consciousness within 1 h of symptom onset [19].

### 2.4. Statistical analysis

Baseline characteristics were described using mean and standard deviation for continuous variables and percentage or proportions for categorical variables. In univariate analysis, the characteristics of patients who reached the primary endpoint at the end of the follow up period were compared with that of the patients who did not reach the endpoint. Risk factors measured at the beginning of the study were also compared between the two groups in similar way. The factors found significant in univariate analysis were considered for survival analysis. Cox proportional hazard model was used to obtain hazard ratios for each of the risk predictors. Time to development of events was depicted using Kaplan-Meier time-to-event curves and comparison was done using the log-rank test. All statistical analyses were carried out at 5% level of significance.

## 3. Results

### 3.1. Patients and outcomes

A total of 58 patients (55 males and 3 females) were enrolled in the study. One patient died three months after enrollment. All other patients were followed up for a minimum period of 18 months. At the end of a mean follow-up of 22.3 ± 6.6 months, 8 patients reached the primary endpoint. Of these, 7 were SCDs which gives an incidence of 12.1% (95% CI = 6%–23%) and one was non-sudden cardiac death. One patient died of non-cardiac cause. No patient had resuscitated cardiac arrest or sustained ventricular tachycardia. The characteristics of the patients, overall and by whether they reached the primary outcome are listed in Table 1.

### 3.2. Risk predictors

Age, QRS width, heart rate, LVEF, frequent PVCs (>10 per hour), NSVT, HRV, HRT and MTWA were compared between patients who reached the primary endpoint and those who did not (Table 2). LVEF, NSVT and HRT onset measured during EPS were significantly different between the two groups.

LVEF, NSVT and EPS derived HRT onset were entered into a multivariate analysis. Both LVEF ≤30% and NSVT were found to be independent predictors of cardiac mortality. Hazard ratio for these risk markers is shown in Table 3. Fig. 1 shows the Kaplan-Meier plot for the primary outcome based on LVEF. LVEF and NSVT were also found to be significant predictors of total mortality. However, for SCD, only LVEF was found to have a significant association. Among 7 patients who developed SCD, 6 patients (85.7%) had LVEF ≤ 30% whereas among the remaining 51 patients, only 14 patients (27.4%) had LVEF ≤ 30%.

## 4. Discussion

In this prospective study of patients with a prior myocardial infarction and left ventricular ejection fraction less than 40%, we found that there was a 12% incidence of sudden cardiac death and 15.5% total mortality during a follow up of 2 years. Left ventricular ejection fraction ≤30% and non-sustained ventricular tachycardia in holter were the only independent predictors of risk of cardiac death. None of the other risk markers including heart rate variability, heart rate turbulence score and microvolt T wave alternans were predictive of cardiac death.

Previously available data from India suggests that SCD accounts for about 10% of all deaths and more than half of these had prior MI and/or LV dysfunction.9 However, prospectively collected data on incidence of sudden death in this population was not available. Tanno et al. reported in a Japanese population that the overall survival was better and sudden death rate was very low in a Japanese population conforming to the MADIT II inclusion criteria [9]. On the other hand, in a similar population in China, the sudden death rate was comparable to the MADIT study [20]. Therefore, it is important to assess for regional differences in outcomes to predict the benefit from ICD implantation. The mortality rate seen in our series (15.5%) is comparable to that in VALIANT [21] which had a total mortality of 19% at 2 yrs and the MADIT II trial [5] with a mortality of 19.8% at 20 months. This suggests that the magnitude of benefit with primary prevention ICD should be similar to MADIT II in an Indian population.

Although many studies have attempted to study the risk markers for sudden death in patients with a previous myocardial infarction, a major limitation of recent studies has been the use of ICD therapies as a surrogate endpoint. The number of ICD shocks overestimate and do not accurately reflect sudden death rates [6]. Use of this endpoint can result in skewed outcomes [7]. The patients in this study did not undergo ICD implantation due to financial limitations. This allowed the use of sudden death or arrhythmias as an outcome instead of using ICD therapy as a surrogate.

All the patients in our study were on optimum medical management including beta blockers and ACE inhibitors. Thus, the mortality rate reflects what is seen in patients on optimal therapy. It is also possible that the use of beta blockers could have affected the

**Table 1**
Study population characteristics.

| Variables | All patients (n = 58) | Cardiac death (n = 8) | Remaining patients (n = 50) |
|---|---|---|---|
| Male sex (%) | 55 (95%) | 8 (100%) | 47 (94%) |
| Age (years)[a] | 46.8 ± 10.1 | 44.6 ± 9.4 | 47.2 ± 10.3 |
| Hypertensives (%) | 8 (13.8%) | 0 | 8 (16%) |
| Diabetics (%) | 19 (32.7%) | 3 (37.5%) | 16 (32%) |
| Smokers (%) | 37 (63.8%) | 6 (75%) | 31 (62%) |
| Time since last MI (months)[b] | 7 (1, 96) | 5 (2, 24) | 8 (1, 96) |
| Previous revascularization (%) | 22 (38%) | 3 (37.5%) | 19 (38%) |
| LVEF (%) | 35 (18, 50) | 27.5 (18, 36) | 36 (18, 50) |
| NYHA class (%) | | | |
| I | 23 (40%) | 3 (37.5%) | 20 (40%) |
| II | 32 (55.2%) | 4 (50%) | 28 (56%) |
| III | 2 (3.4%) | 0 | 2 (4%) |
| IV | 1 (1.7%) | 1 (12.5%) | 0 |
| Drug | | | |
| Beta Blockers | 58 (100%) | 8 (100%) | 50 (100%) |
| ACEI | 58 (100%) | 8 (100%) | 50 (100%) |
| Calcium blockers | 58 (100%) | 8 (100%) | 50 (100%) |
| Digitalis | 10 (17.24%) | 3 (37.5%) | 7 (14%) |
| Furosemide | 51 (87.93%) | 6 (75%) | 45 (90%) |
| Aldosterone antagonists | 58 (100%) | 8 (100%) | 50 (100%) |
| Impaired renal function (%) | 1 (1.5%) | 0 | 1 (2%) |
| Wide QRS (%) | | | |
| RBBB | 3 (5.2%) | 2 (4%) | 1 (12.5%) |
| LBBB | 0 | 0 | 0 |
| IVCD | 1 (1.7%) | 1 (2%) | 0 |

ACEI- angiotensin converting enzyme inhibitors; RBBB- right bundle branch block; LBBB- left bundle branch block; IVCD-intraventricular conduction defect.
[a] Mean with standard deviation (Normally distributed).
[b] Median with Range (Non-normally distributed).

**Table 2**
Comparison of risk markers between the two groups.

| S.no | Parameter | N | Cardiac death | N | Remaining patients | Statistical Significance |
|---|---|---|---|---|---|---|
| 1 | Age (years)[a] | 8 | 44.6 ± 9.43 | 50 | 47.2 ± 10.27 | p > 0.05 |
| 2 | QRS width (ms)[b] | 7 | 100 (80, 150) | 48 | 100 (80, 120) | p > 0.05 |
| 3 | Mean heart rate (bpm)[a] | 7 | 72.7 ± 10.8 | 46 | 74.3 ± 11.4 | p > 0.05 |
| 4 | LVEF ≤ 30% | 8 | 6 (75%) | 50 | 14 (28%) | p = 0.009 |
| 5 | PVC >10/hr | 7 | 3 (42.9%) | 48 | 11 (22.9%) | p > 0.05 |
| 6 | NSVT in holter | 8 | 4 (50%) | 50 | 6 (12%) | p = 0.008 |
| 7 | HRV (SDNN <70 ms) | 7 | 6 (85.7%) | 46 | 42 (91.3%) | p > 0.05 |
| 8 | Mean HRT onset (Holter)[b] | 6 | −0.017 (−0.02, 0.05) | 27 | −0.0125 (−0.08, 0.12) | p > 0.05 |
| 9 | Mean HRT slope (Holter)[b] | 6 | 5 (3, 31) | 27 | 5 (0, 21) | p > 0.05 |
| 10 | Mean HRT onset (EPS)[a] | 7 | −0.0057 ± 0.02 | 43 | −0.0335 ± 0.023 | p = 0.004 |
| 11 | Mean HRT slope (EPS)[b] | 7 | 6.5 (4, 23) | 43 | 6 (0, 28) | p > 0.05 |
| 12 | HRT (Holter) | 6 | 5 (83.3%) | 27 | 12 (44.4%) | p > 0.05 |
| | Score 0 | | 1 (16.7%) | | 15 (55.5%) | |
| | Score 1& 2 | | | | | |
| 13 | HRT (EPS) | 7 | 5 (71.4%) | 43 | 36 (83.7%) | p > 0.05 |
| | Score 0 | | 2 (28.6%) | | 7 (16.3%) | |
| | Score 1 & 2 | | | | | |
| 14 | Positive MTWA | 8 | 2 (25%) | 40 | 12 (30%) | p > 0.05 |

$ Significant at 5% level of significance.
LVEF- left ventricular ejection fraction; PVC- premature ventricular contraction; NSVT-non-sustained ventricular tachycardia; HRV- heart rate variability; SDNN- standard deviation of normal to normal RR intervals; HRT-heart rate turbulence; EPS- electrophysiology study; MTWA-micro T wave alternans.
[a] Mean with standard deviation (Normally distributed).
[b] Median with Range (Non-normally distributed).

**Table 3**
Hazard ratio for selected risk markers based on Cox Proportional hazard model.

| Parameter | Hazard ratio (95% CI) | Statistical Significance |
|---|---|---|
| LVEF ≤ 30% | 5.6 (1.39, 23) | p < 0.01 |
| NSVT | 5.7 (1.14, 29) | p < 0.01 |

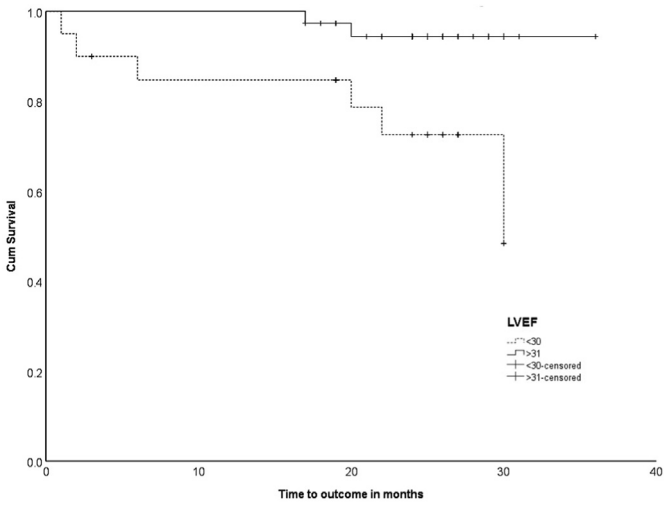


**Fig. 1.** Kaplan Meier curves for primary outcome based on ejection fraction Kaplan Meier curves are plotted for the primary outcome of cardiac death for subgroups with LVEF ≤30% and those with LVEF >30%.

predictive value of some markers like HRV, HRT and MTWA, which had better predictive value in previous studies where beta blocker use was less.

LVEF emerged as a strong predictor of cardiac death in our study. This is consistently seen in all previous studies. Although the patients with LVEF less than 40% have an elevated risk of sudden death, the increase in risk is markd with LVEF less than 30% [22]. We found the same in our patients with LVEF ≤ 30% the strongest predictor of cardiac death. Among 20 patients with LVEF ≤30%, cardiac death was seen in 6 patients (30%), while among 38 patients with LVEF > 30%, cardiac death was seen only in 2 patients (5.3%). The LVEF cutoff of 30% below which the SCD death risk increases substantially, was also validated in ISAR-risk [23] and REFINE [24] trials. LVEF is also an independent predictor of SCD and total mortality.

NSVT was also independently associated with risk of cardiac death. The prevalence of NSVT by holter in our study was 17% (10/58 patients). Cardiac deaths were seen in 40% of these patients while it was seen only in 8.3% of patients without NSVT. Older studies highlighted the importance of NSVT as an independent prognostic factor associated with arrhythmic death [11], [[,25] but the studies which came later on such as the GISSI-2 [26] and ESVEM [27] trials failed to establish NSVT as an independent predictor, even though it predicted outcomes in univariate analyses. Interestingly in the ATRAMI study [28], NSVT was found to adversely affect prognosis independent of decreased LVEF. In our study NSVT was found to predict cardiac death and total mortality. It was also associated with SCD but did not reach statistical significance in multivariate analysis.

Markers of impaired autonomic tone such as abnormal HRV and HRT have been linked to arrhythmias and cardiac death [29]. In the ATRAMI study, impaired HRV (SDNN≤70 ms) was independently associated with increased mortality [13]. However, in a large study, low HRV was only weakly associated with total mortality and did not predict arrhythmic deaths [26]. HRV was not associated with either primary or secondary outcomes in our study.

HRT assesses short term fluctuations of the heart rate in response to a PVC [30]. HRT can be measured by ambulatory ECG, pacing from an implanted device or during an EP study. Two large prospective trials suggested that HRT is a strong predictor of death [24,31]. In our study, HRT was not measurable using Holter in 43% of patients, either due to inadequate PVCs or inadequate sequences where PVCs were followed by a sufficient number of sinus beats. Our patients were also younger than the typical post myocardial infarction patients in other trials. It is possible that this could have contributed to the low predictive value of HRT in our study.

Several clinical studies have showed that a positive MTWA is associated with adverse outcomes [24,32–34]. MTWA is most commonly measured by one of two methods – the spectral method

and the modified moving average method (MMA). Our findings of poor predictive value of T wave alternans with the spectral method is consistent with MASTER I study which has not shown consistent predictive value [35]. The MMA method measurement is influenced by other periodicities rather than strictly alternans [36] and it is possible that this results in better predictive value in patients with cardiomyopathy. Most of the recent trials showing significant predictive accuracy of MTWA have used the MMA method [24]. The problem with this method has, however, been the absence of a uniform threshold to define abnormal values.

### 4.1. Limitations

All patients were taking beta blockers in our study which may blunt the predictive value of some of the arrhythmic risk markers. Not all patients underwent coronary angiography in a systematic manner and coronary anatomy or revascularization status was not studied as a predictor of sudden death. The cause of death was determined only by verbal autopsy. Autopsy, hospital records or death certificates were not used. The sample size is low because of the need for an invasive electrophysiology study and technical problems with the recording system which led to recruitment being stopped for a year in between. The small sample size and number of events leads to wide confidence intervals. While the finding of a significant association for LVEF and NSVT with cardiac mortality despite this is proof of the strength of the association, it is likely that a weaker association with some of the other risk markers may have gone undetected.

## 5. Conclusions

Among patients with a previous myocardial infarction and left ventricular dysfunction, there is a significant mortality of 15.5% at 2 years with most of these being sudden cardiac deaths. LVEF and NSVT were significant markers for cardiac mortality whereas LVEF was the only predictor for SCD. Other markers like QRS width, PVC count, HRV (SDNN), HRT slope, HRT score and MTWA did not predict cardiac death or SCD in our study. Our findings of a high mortality in these patients, with many of the deaths being sudden cardiac deaths, suggest that ICDs may be useful for primary prevention. NSVT recorded on Holter may be used as an additive marker when making a decision regarding ICD implant.

## 6. Key messages

### 6.1. What is already known on this subject?

Patients who survive a myocardial infarction with depressed LV function are a high-risk group for sudden death. LVEF is a consistent marker of SCD and cardiac mortality in these patients.

### 6.2. What does this study add?

This study provides data on incidence of SCD in patients with MI and depressed LV function in the Indian population and predictive value of various risk markers in these patients. NSVT on Holter was found to have value in addition to LVEF.

### 6.3. How might this impact on clinical practice?

Our study suggests that the incidence of SCD in Indian patients with a previous MI and LV dysfunction is at least as high as that in the western world. Therefore, ICD implantation for primary prevention should be considered. LVEF $\leq$30% is the strongest predictor of sudden death. This could be combined with NSVT on holter to identify patients at risk.

## Declaration of competing interest

None for any of the authors.

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