Fragmented QRS in Prediction of Cardiac Deaths and Heart Failure Hospitalizations after Myocardial Infarction

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Background: Increased QRS fragmentation in visual inspection of 12-lead ECG has shown association with cardiac events in postmyocardial infarction (MI) patients. We investigated user-independent computerized intra-QRS fragmentation analysis in prediction of cardiac deaths and heart failure (HF) hospitalizations after MI.

Methods: Patients (n = 158) with recent MI and reduced left ventricular ejection fraction (LVEF) were studied. A 120-lead body surface potential mapping was performed at hospital discharge. Intra-QRS fragmentation was computed as the number of extrema (fragmentation index FI) in QRS. QRS duration (QRSd) was computed for comparison.

Results: During a mean follow-up of 50 months 15 patients suffered cardiac death and 23 were hospitalized for HF. Using the mean + 1 SD as cut-point both parameters were univariate predictors of both end-points. In multivariate analysis including age, gender, LVEF, previous MI, bundle branch block, atrial fibrillation, and diabetes FI was an independent predictor for cardiac deaths (HR 8.7, CI 3.0–25.6) and HF hospitalizations (HR 3.8, CI 1.6–9.3) whereas QRSd only predicted HF hospitalizations (HR 4.6, CI 2.0–10.7). In comparison to QRSd, FI showed better positive (PPA) and equal negative (NPA) predictive accuracy for both end-points, and PPA was further improved when combined to LVEF < 40%. Limiting fragmentation analysis to 12-lead ECG or a randomly selected 8-lead set instead of all 120 leads resulted in an almost similar prediction.

Conclusions: Increased QRS fragmentation in post-MI patients predicts cardiac deaths and HF progression. A computer-based fragmentation analysis is a stronger predictor than QRSd.

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QRS fragmentation; cardiac death; heart failure

Both short- and long-term prognosis of myocardial infarction (MI) has greatly improved during the past two decades with the introduction of means to effectively reduce infarct size and to treat residual ischemia. Yet, even without a recurrent MI the clinical course in a substantial number of patients is that of a progressing heart failure (HF), which has an adverse effect on survival.[1–3] The treatment of HF has recently advanced with the application of evidence-based medications and with the advent of resynchronization therapy.[4,5] Identification of patients at risk of worsening HF might allow a closer control of these patients and earlier application of the proven therapies. Several clinical parameters have shown association to cardiac death and HF progression including older age, prior MI, and diabetes. Increased fragmentation of QRS complex in 12-lead ECG has also shown prediction of cardiac events in patients with coronary artery disease (CAD).[6,7] However, the fragmentation analysis has been based on visual inspection only or the studies have not addressed patients with a recent MI.

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We investigated if user-independent computerized intra-QRS fragmentation analysis would predict cardiac deaths and HF hospitalizations after recent MI. QRS duration (QRSd) was registered for comparison since QRSd has shown association with cardiac events in patients with acute MI and also in patients with HF.[8,9]

METHODS

Study Patients

This prospective study was conducted in five hospitals in Helsinki district. Patients who had acute MI were screened consecutively from May 1997 until June 2000 and the study follow-up extended until June 2003, three years after the last enrolment. To exclude patients with only minor myocardial damage, only patients with left ventricular ejection fraction (LVEF) <50% and at least one local hypokinetic or akinetic left ventricular region were included in the study. The diagnosis of acute MI was confirmed by typical chest pain or ECG changes together with diagnostic elevation (twice the normal value) of serum troponin T, troponin I, or MB fraction of creatine kinase. All patients had left ventricular cineangiography or echocardiography performed at stable convalescent phase. Patients were excluded if they were unable to give informed consent or if they had a significant noncardiac co-morbidity likely to shorten their survival markedly. Also patients with a cardiac pacemaker were excluded. All patients gave their written informed consent and the institutional ethical review board approved the study protocol. The study complies with the Declaration of Helsinki.

BSPM Registration

BSPM registration was performed 1–2 weeks after the acute MI at stable convalescent period. Our 120-lead mapping system has been described previously.[10] In brief, 18 vertical straps containing 120 leads covering both anterior (63 leads) and posterior (57) thorax were used (Fig. 1). The limb leads were recorded conventionally and Wilson's central terminal was taken as the reference point for chest potentials. BSPM was recorded in supine position at rest for 5 minutes. Recordings were band-pass filtered at 0.16–300 Hz and digitized with a sampling frequency of 1 kHz.

Signal Processing and Parameter Computations

All the further data processing was done off-line with a custom-made program developed for BSPM data analyses in personal computer. Signal averaging of 150–250 beats was performed to improve signal quality and to reduce noise. A 20 Hz high-pass filter (Butterworth, 4th order) was applied. The beginning and end of the QRS complex were automatically defined based on the noise levels both before and after the QRS complex.[11] A 20 ms time interval from the PR interval and a 40 ms time interval from the ST segment of the filtered QRS complex were selected for noise reference. The QRS complex onset was defined as the midpoint of a 5 ms interval where the average first deviates 3 SDs over the noise level when approaching the QRS complex. The QRS complex offset was correspondingly defined backwards from the ST segment. The average of all channels was used to calculate QRSd.

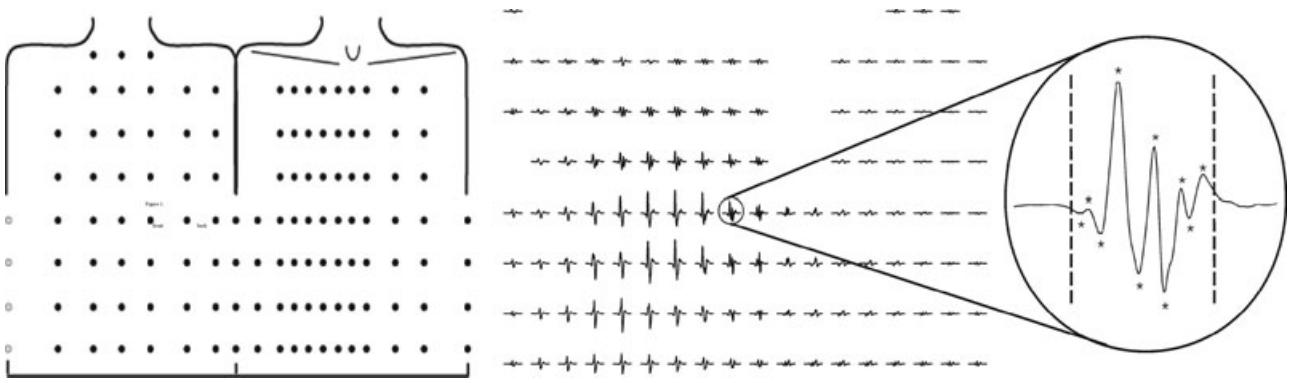

Figure 1. 120-lead body surface potential mapping lead positions (left) and the principle of the intra-QRS fragmentation analysis (right). After binomial filtering the number of polarity changes or extrema (*) are computed yielding the intra-QRS fragmentation index FI. The horizontal dashed bars indicate the onset and offset of the filtered QRS.

To compute intra-QRS fragmentation index, a binomial high-pass filter of 90th order with a cutoff frequency of 37 Hz was implemented in the same QRS complexes used for QRSd calculations. High-frequency components were removed by applying a binomial low-pass filter with 90 Hz cutoff frequency. Intra-QRS fragmentation index (FI) of these QRS complexes was computed by calculating the number of extrema within the filtered QRS complex (Fig. 1). For a mathematical description of the intra-QRS fragmentation analysis, see reference.[12] In the final analysis, the average of all channels was used. In addition, conventional 12-lead ECG was extracted from the same recordings using chest leads corresponding to leads V_1–V_6 and FI in 12-lead ECG was calculated as the average of the 12 leads. To check whether the differences between BSPM and conventional 12-lead ECG results could be due to difference in the number of leads or their positions, we also computed the average values for a large number of different combinations of 8 leads randomly distributed over body surface.

Follow-Up and Study End Points

During the follow-up all data concerning hospital admissions were obtained. In addition, at the end of the study the patients or their relatives were contacted by phone. For any reported event, all available information was retrieved from hospital files, death certificates, and autopsy records. The study end points were cardiac death and HF hospitalization. The classification of cause and mode of death was based on the method used in the AIRE study.[13] For HF hospitalizations, data from all hospital admissions were obtained. HF hospitalization was defined as a hospital admission due to worsening heart failure requiring the use of medications to treat acute HF. HF hospitalizations due to a new infarction were not included. The criteria for a new infarction were the same as those of the study inclusion. The clinical adjudication committee reviewed all deaths and HF hospitalizations in a blinded fashion.

Statistical Analysis

Continuous variables are presented as mean ± SD values and discrete variables as percentages. Comparisons between the groups were made using the unpaired *t*-test or Mann-Whitney *U*-test when appropriate.

Kaplan-Meier curves were generated to describe the cumulative incidences of cardiac deaths and HF hospitalizations for each parameter showing significant difference between patients with and without events. The cut-point values chosen were the mean ± 1 SD of the parameter values in the whole group. The equality of the event distributions for each parameter was assessed with a log-rank test. To study the independent predictive values of the parameters showing univariate prediction, a multivariate Cox proportional hazards analysis was performed using stepwise selection for each parameter separately together with the clinical variables including age, sex, LVEF, atrial fibrillation, bundle branch block (BBB), previous MI, and diabetes. The hazard ratios (HR) with their 95% confidence intervals (CI) for each variable were computed. The receiver-operator characteristic (ROC) curves displaying sensitivity as the function of the complement of specificity were created to study the ability of the parameters to predict study end points. ROC curves were created separately for FI and QRSd in BSPM and also for FI in 12-lead ECG and in the 8-lead combinations.

Positive predictive value was calculated as the percentage of the patients with events among those who showed abnormal parameter values. Negative predictive value was calculated as the percentage of patients without events among those who showed normal parameter values.

Statistical significance was defined as a P-value < 0.05. The data analyses were performed with the Statistical Package for Social Sciences biostatistic software, version 11.5 (SPSS Inc., Chicago, IL, USA). The areas under the ROC curves were calculated with Matlab software (MathWorks, Natick, MA, USA).

RESULTS

Altogether 158 patients fulfilled the inclusion criteria and were recruited to the study. Characteristics of the study patients are delineated in Table 1. The mean age of the study patients was 61 ± 10 (range 34–79) years and the LVEF was 40 ± 6%. Coronary arteriography was performed for 92 (58%) patients, and 48 (30%) patients underwent percutaneous coronary intervention and 25 patients (16%) coronary bypass surgery either acutely or based on residual ischemia. Beta-blockers and aspirin were prescribed to all patients (100%) and ACE inhibitors to patients with marked left

Table 1. Clinical Characteristics of the Study Patients

Patient Characteristics (n = 158)	
Age (years)	61 ± 10
Men/women	129/29 (82%/18%)
Infarct location (anterior/inferior/undefined)	94/52/12 (60%/33%/7%)
Previous MI	58 (37%)
Ejection fraction (%)	40 ± 6
Diabetes	33 (21%)
Bundle branch block	13 (8%)
Atrial fibrillation	6 (4%)

Values are presented as means ± SD or as the number (percent) of patients.

ventricular dysfunction. At the end of the study follow-up, 95% of the patients were on beta-blockers, 94% on aspirin, and 72% on ACE-inhibitors.

Follow-up Data

During a mean follow-up of 50 months (range 1–72) 15 patients suffered cardiac death and 23 were hospitalized due to decompensated heart failure. Of the cardiac deaths, six were sudden cardiac deaths, five were due to end stage heart failure, and three patients died of a recurrent MI. In one patient the death was classified as "other cardiac"; the patient was found dead with no discernible cause of death at the autopsy suggesting arrhythmic death yet the strict criteria for sudden cardiac death was not met. Of the patients who suffered cardiac death seven (47%) had been hospitalized due to heart failure during the follow-up. The average time from study onset to cardiac death was 32 ± 24 months (median 30 months) and 17 ± 19 months (median 6 months) to HF hospitalization. Twenty-three patients had a recurrent MI during the follow-up and six of them were later hospitalized for HF.

The patients who suffered cardiac death had more often diabetes, bundle branch block, and had more often had a previous MI. There was no difference in age whereas LVEF was lower almost significantly in those who suffered cardiac death (36 ± 8 vs 40 ± 5, P = 0.06). The patients who were hospitalized for heart failure were older, had lower LVEF, bundle branch block in ECG, and had more often suffered a previous MI.

Parameter Values and ROC Curves

Both study parameters were significantly different between patients with and without events (Table 2). Patients with HF death showed especially high FIs (11.8 ± 3.2) compared to patients with no HF during follow-up and even compared to patients who suffered sudden cardiac death (mean FI 9.2 ± 2.7) although the difference with the latter did not reach statistical significance due to small number of the patients. The ROC-curves showed areas under curves (AUC) between 0.71 and 0.77 with FI displaying better prediction for cardiac deaths and QRSd showing slightly better prediction for HF hospitalizations (Figs. 2 and 3). The corresponding values for FI in 12-lead ECG were 0.73 for cardiac deaths and 0.74 for HF hospitalizations and for the best 8 lead combination 0.77 and 0.73, respectively (curves not shown).

Univariate and Multivariate Analyses

In univariate analysis both parameters were significant predictors of both study end points: FI log-rank 36.6 ($P < 0.0001$) and 33.8 ($P < 0.0001$) for cardiac death and HF hospitalization, respectively (Fig. 4). In multivariate analysis including age, gender, LVEF, previous MI, bundle branch block, atrial fibrillation, and diabetes FI showed independent prediction (HR 8.7, CI 3.0–25.6) for cardiac death together with LVEF and diabetes. In contrast, QRSd failed to show prediction with the clinical parameters in the model.

On the other hand, both QRSd (HR 4.6, CI 2.0–10.7) and FI (HR 3.8, CI 1.6–9.3) predicted HF

Table 2. Parameter Values

Parameter	Cardiac Death + (n = 15)	Cardiac Death − (n = 143)	Heart Failure Hospitalization + (n = 23)	Heart Failure Hospitalization − (n = 135)
Fragmentation index FI	9.7 ± 2.9	7.1 ± 1.6*	9.2 ± 2.9	7.1 ± 1.5*
QRS duration	103 ± 29 ms	85 ± 19 ms*	107 ± 31 ms	83 ± 16 ms**

Values are presented as mean ± SD.
*$P < 0.01$; **$P < 0.001$ between patients with and without events.

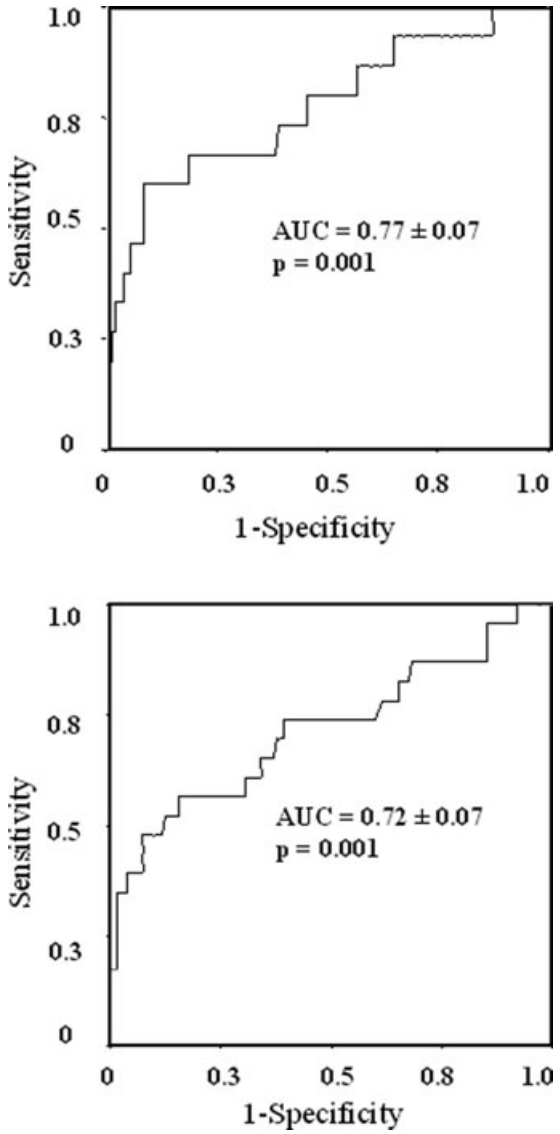

Figure 2. Receiver-operator characteristics for fragmentation index FI in predicting cardiac deaths (top) and heart failure hospitalizations (bottom).

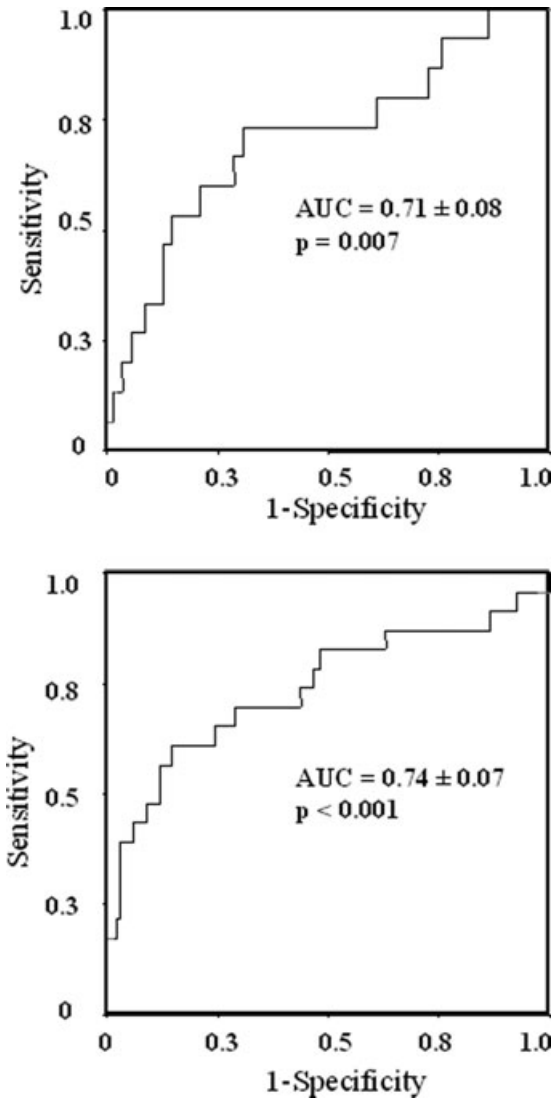

Figure 3. Receiver-operator characteristics for QRS duration in predicting cardiac deaths (top) and heart failure hospitalizations (bottom).

hospitalization independently of clinical variables. Of the clinical variables both age and LVEF entered the model together with FI or QRSd in prediction of HF hospitalization.

FI displayed markedly better PPA for cardiac deaths in comparison to QRSd and slightly better PPA for HF hospitalization (Table 3). NPAs were of the same magnitude varying from 91% to 96%. The combination of FI > 9.3 and LVEF < 40% further improved PPA especially for HF hospitalization without markedly reducing NPA.

DISCUSSION

The results of the study show that increased QRS fragmentation in postinfarction patients with cardiac dysfunction predicts both cardiac deaths and hospitalizations due to progressing heart failure. A computer-based automatic fragmentation analysis is a stronger predictor than QRS duration. The combination of increased fragmentation with markedly decreased LVEF further improved predictive ability. Increased fragmentation displayed predictive ability independently of clinical variables.

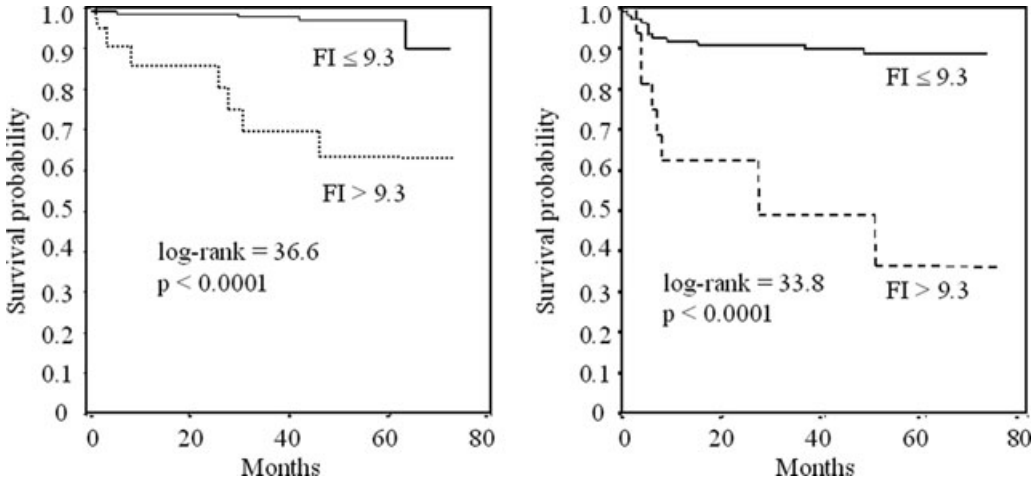

Figure 4. Kaplan-Meier actuarial curves for cardiac deaths (left) and heart failure hospitalizations (right) based on fragmentation index FI.

Previously, QRS fragmentation has shown association with adverse prognosis in CAD but also in diseases such as hypertrofic cardiomyopathy and Brugada syndrome.[14,15] Das et al. in their retrospective study found fragmented QRS a predictor of cardiac events in patients with CAD.[6] Using an automated analysis Lander et al. reported abnormal intra-QRS potentials in signal-averaged ECG to predict arrhythmic events after MI.[16] Although their method was somewhat different from the present study it is conceivable that both intra-QRS fragmentation and abnormal intra-QRS potentials are markers of the same phenomenon, namely delayed and anisotropic conduction, which is associated with arrhythmia vulnerability. This is also suggested by the relatively high percentage of sudden cardiac deaths (40%) in the present study. Similarly, increased fragmentation might also serve as a marker of abnormal spread of ventricular activation leading to dyssynchronous contraction and impending HF. Of interest, patients who died of HF had higher FIs than patients who suffered sudden cardiac death. This suggests that intra-QRS fragmentation in ECG might be a stronger predictor of heart HF deaths than sudden cardiac deaths although the small number of patients in these subgroups prevents statistical assessment. The fractionated electrograms could be caused by electrical barriers formed by increased fibrous tissue as was shown in patients with end stage heart failure due to dilated cardiomyopathy.[17] To the best of our knowledge, this is the first prospective study to probe electrocardiocraphic QRS fragmentation determined during the convalescent phase of MI in prediction of cardiac deaths and heart failure hospitalizations.

Langner and Geselowitz first described notches and slurs in ECG after MI.[18] Later, Flowers et al. postulated anisotropic, zigzag-like propagation of ventricular activation as the most plausible explanation for fragmentation. They found increased fragmentation in connection with previous MI as well as with ventricular enlargement.[19,20] More recent studies have associated abnormal QRS

Table 3. Positive and Negative Predictive Values of Fragmentation Index (FI) and QRS Duration (QRSd)

Parameter	Cardiac Death PPA	Cardiac Death NPA	Heart Failure Hospitalization PPA	Heart Failure Hospitalization NPA
FI > 9.3	43%	96%	52%	91%
QRSd > 107 ms	25%	93%	46%	91%
FI > 9.3 + LVEF < 40%	50%	94%	67%	90%
QRSd > 107 ms + LVEF < 40%	36%	93%	54%	88%

PPA = positive predictive accuracy; NPA = negative predictive accuracy; LVEF = left ventricular ejection fraction.

fragmentation to local perfusion defects in patients with CAD.[21] Most of the studies on QRS fragmentation have focused on the end of the QRS complex for abnormal notching. This is logical since intra-QRS fragmentation is difficult to evaluate in visual inspection only. However, data from combined ECG and invasive registrations have shown the major part of the myocardium displaying abnormal slow conduction to activate during the "normal" QRS.[22] Thus, it is worthwhile looking for signs of abnormal conduction during the whole QRS.

The average of all 120 channels did not perform markedly better than 12-lead ECG. Likewise, the results of the randomly chosen 8 leads resulted in quite equal prediction. The similar results indicate that intra-QRS fragmentation is robust with respect to positioning of the ECG leads and attempting to discover subsets of significantly more informative BSPM channels does not enhance the predictive properties. The slightly better performance of 120 leads is probably due to reduction in the measurement noise as the number of averaged leads increases.

QRSd was a strong independent predictor of HF hospitalizations but not of cardiac deaths. Previous studies on QRSd have showed somewhat conflicting results. Bauer et al. found QRSd to be an independent predictor of cardiac mortality.[9] Compared to present study their patients had well preserved left ventricular functions (mean LVEF > 50%) and they used 120 ms as the cut point for QRS prolongation. In another post-MI study with patient characteristics similar to our study QRSd did not show prediction in multivariate analysis.[23] The comparison with many of the previous studies is in part hampered by their exclusion of patients with a BBB. We did not exclude these patients (n = 13, 8%) since BBB is a recognized risk factor in HF patients. The results of this study confirm that QRSd indeed has value as a risk marker especially for worsening HF. The higher predictive accuracy of intra-QRS fragmentation may be due to its ability to better display myocardial damage leading to abnormal conduction, which in turn may lead to re-entrant arrhythmias and dyssynchronized contraction leading to HF.

Clinical Implications

Intra-QRS fragmentation analysis performed soon after the acute event identifies post-MI patients with moderately impaired left ventricular function who are at risk of cardiac death and worsening heart failure. This could be used to select patients for more intensive follow-up and timely application of evidence based therapies such as cardiac resynchronization therapy. The results of the present study suggest that the user-independent fragmentation analysis of conventional 12 ECG leads is sufficient in prediction of cardiac death and significant progression of heart failure rendering the method applicable for clinical work.

Study Limitations

The number of study patients was relatively small but this is in part offset by a lengthy follow-up period. We did not repeat the BSPM measurements during the follow-up and therefore the natural course of the intra-QRS fragmentation and its impact on the results is not known. The parameter cut-points were created in this study and they might not be applicable as such in another patient population.

The majority of the patients did not have acute invasive evaluation and treatment for MI and therefore the results may not be directly applicable in patients who had percutaneous intervention at the acute phase of MI. On the other hand, only 14% of the patients had as recurrent MI during follow-up indicating successful evaluation and treatment of residual ischemia. Yet we cannot rule out the role of ischemia in the development of HF at least in part of the patients.

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