Patterns of ectopy leading to increased risk of fatal or near-fatal cardiac arrhythmia in patients with depressed left ventricular function after an acute myocardial infarction

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Aims
To identify potential new markers for assessing the risk of sudden arrhythmic events based on a method that captures features of premature ventricular complexes (PVCs) in relation to sinus RR intervals in Holter recordings (heartprint).

Methods and results
Holter recordings obtained 6 weeks after acute myocardial infarction from 227 patients with reduced ventricular function (left ventricular ejection fraction $\leq 40\%$) were used to produce heartprints. Measured indices were: PVCs per hour, standard deviation of coupling interval (SDCI), and the number of occurrences of the most prevalent form of PVCs ($S_{nib} \geq 83$). Predictive values, survival analysis, and Cox regression with adjustment for clinical variables were performed based on primary endpoint, defined as an electrocardiogram-documented fatal or near-fatal arrhythmic event, death from any cause, and cardiac death. High ectopy (PVCs per hour $\geq 10$) was a predictor of all endpoints. Repeating forms of PVCs ($S_{nib} \geq 83$) was a predictor of primary endpoint, hazard ratio $= 3.5$ (1.3–9.5), and all-cause death, hazard ratio $= 2.8$ (1.1–7.3), but not cardiac death. SDCI $\leq 80$ ms was a predictor of all-cause death and cardiac death, but not of primary endpoint.

Conclusion
High ectopy, prevalence of repeating forms of PVCs, and low coupling interval variability are potentially useful risk markers of fatal or near-fatal arrhythmias after myocardial infarction.

Keywords
Sudden arrhythmic event • Premature ventricular beats • Implantable cardioverter-defibrillator • Holter monitoring • Myocardial infarction

Introduction
A major clinical problem in cardiology is the lack of reliable non-invasive methods that could specifically predict which patients are at high risk of sudden cardiac death (SCD), with a goal of initiating appropriate therapy—such as the implantable cardioverter-defibrillator (ICD). Criteria must be developed to identify patients who would benefit from therapy, but who do not meet current guidelines for therapy. Likewise, these criteria could also identify patients who meet current guidelines for therapy, but who, in fact, do not have high risk for SCD.¹,²

We carried out analyses of 227 Holter records in the CARISMA (Cardiac Arrhythmia and Risk Stratification after Myocardial Infarction) dataset obtained 6-week following an acute myocardial infarction (AMI).³ The patients from this study had reduced ventricular function.⁴ The primary endpoint was identified as an electrocardiogram (ECG)-documented fatal or near-fatal arrhythmic event that was judged to be likely treatable by an ICD. Huikuri et al.³,⁴ have
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What’s new?

- This study tested new markers of the risk of sudden arrhythmic events based on a method that captures quantitative features of premature ventricular complexes (PVCs) in relation to sinus RR intervals in Holter recordings (heartprint).
- High prevalence of repeating forms of PVCs (≥83 events) was a predictor of primary endpoint (electrocardiogram-documented fatal or near-fatal arrhythmic event), hazard ratio = 3.5 (1.3–9.5) and all-cause death, hazard ratio = 2.8 (1.1–7.3), but not cardiac death.
- Coupling interval (CI) standard deviation ≤80 ms was a predictor of all-cause death and cardiac death, but not of primary endpoint.
- High ectopy, prevalence of repeating forms of PVCs, and low CI variability are potentially useful risk markers of fatal or near-fatal arrhythmias after myocardial infarction.

Methods

Study population, study protocol, and endpoints

A detailed description of the study population, study protocol, and endpoints of the CARISMA clinical trial is in Huikuri et al.1 Briefly, 1393 out of 5869 patients who were screened in 10 European centres complied with the inclusion criterion of left ventricular ejection fraction (LVEF) ≤40%, measured 3–5 days after AMI diagnosis. After exclusions, 3 312 patients were enrolled in the study. Each patient received an implantable loop ECG recorder 5–21 days after AMI to document arrhythmic events and was followed-up for 24 months (mean follow-up 22.2 ± 6.9 months). The loop-recorder was interrogated 6 weeks after implantation and thereafter at 3-month interval (during clinical follow-up visits). Day 0 was the time when AMI was diagnosed. Along with several techniques to test different risk stratification methods,2 all enrolled patients underwent a 24 h ambulatory ECG recording immediately after the index AMI (between 5 and 21 days). The Holter recording was repeated in 305 patients at 6 weeks post-AMI. The analysis of the current work is based on the analysis of Holters from 227 patients obtained at week 6 after AMI. A detailed description of exclusion criteria is shown in Figure 2, and clinical characteristics of included and excluded patients are compared in Table 1. The majority of the patients were treated according to current guidelines as regards medication and revascularization at the time of study. Compared with patients included in this study, patients from the excluded group were similar except that they were older, had more cases of congestive heart failure, lower LVEF after 6 weeks of AMI and had fewer cases with Q-wave AMI and thrombolysis during AMI. However, both groups had similar proportions of patients who reached the primary and secondary endpoints.

The primary endpoint was ‘ECG-documented fatal or near-fatal cardiac arrhythmia, adjudicated as ‘most probably treatable’ by an ICD’, which included resuscitated cardiac arrest due to primary arrhythmia, symptomatic sustained ventricular tachycardia (VT), or arrhythmic death. Sustained VT was defined as an episode of consecutive PVCs with heart rate ≥125 beats per minute that lasted 30 or more seconds. Each arrhythmia had to be ECG documented either by implantable loop recorder, ICD, or any other rhythm strip at the time of the event. Secondary endpoints were all-cause mortality and cardiac death. A separate endpoint committee blinded to the test results defined the causes of death and arrhythmic events that were considered the primary endpoint, as described in detail previously.3,9 An arrhythmic event was excluded as the primary endpoint if any member of the endpoint committee considered that it could not have been successfully treated by an ICD. This excludes events that occurred in end-stage chronic heart failure or during refractory ischaemia. The prophylactic indication for the implantation of ICD at the time of the CARISMA study was according to the results of the MUSTT (Multicenter Unsustained Tachycardia Trial) study in Europe, i.e. LVEF <40%, non-sustained VT on Holter recording, and the inducibility of sustained VT during the electrophysiological study.10 This study complies with the Declaration of Helsinki, locally appointed ethics committees approved the research protocol and informed consent was obtained from the patients.

Recording characteristics and beat identification

The current work is based on the analysis of 227 Holter recordings obtained at week 6 after AMI. Each recording was 24 h long and had the following information: (i) a binary data file with the 24-hour ECG recordings (2 or 3 simultaneous channels digitized at 180 samples per second), (ii) a header file with basic format and content information, and (iii) an annotation file with the identification information of each beat—QRS complex time occurrence and type of beat. The ECG records were processed by the ADAPT analysis engine (Medilog Darwin Holter Analysis, Schiller Medilog). The automated detection of the beats was verified through visual inspection by an investigator who was blinded to clinical outcomes. Typical Holter analysis criteria were utilized to address the suitability of Holter recordings. These criteria include the removal of Holter segments in which noise was visible such as saturated signals, significant artefact due to technical reasons (such as loose electrode, wiggling of Holter cable, and motion artefact). Normally conducted beats were identified as normal beat (N) and multiform PVCs were identified as V.
Runs of atrial tachycardia or irregular sinus RR intervals were identified and corresponding beats were categorized as N, since these represented normally conducted beats. Records with predominant non-sinus rhythm were excluded (persistent or chronic atrial fibrillation, pacemaker, or second degree atrioventricular block).

Heartprints

The heartprint (Figure 1B) is a visual display for the analysis of ventricular arrhythmias from RR intervals over an extended period of time.6–8 The ‘heartprint’ represents dependencies between the sinus RR interval and (i) VV interval, (ii) NIB, and (iii) the CI. The ordinate of the three coloured plots in the heartprint is the sinus RR interval which precedes the first PVC of each VV interval. The incidence of the VV intervals, NIB values, and the CI are indicated in the coloured plots, respectively, where the relative frequency of occurrence is indicated by the colour, (red is associated with the highest incidence). The plots above the coloured plots give the histograms of the VV intervals, the NIB values, and the CI, respectively. The histogram to the left of the coloured plots gives the histogram of sinus RR intervals. Heartprints are generated using custom written software in C or in Matlab (The MathWorks, Inc.) software. A C-language code is available at http://www.physionet.org/physiotools/heartprints/).11

Various patterns of arrhythmias are defined based on the repetition patterns of PVCs and sinus RR intervals. These patterns include bigeminy (NIB = 1), trigeminy (NIB = 2), concealed bigeminy (NIB values are all odd numbers), and concealed trigeminy (the NIB values are taken from the sequence 2, 5, 8, ...).

Quantitative indexes

The following characteristics were measured from the heartprints to identify potential risk markers for the primary and secondary endpoints: (i) total ventricular ectopy (PVCs per hour), (ii) CI variability [standard deviation of the CI (SDCI)], and (iii) the NIB index, SNIB, which is the number of incidences (i.e. the height of the histogram in the heartprint) of the most prevalent NIB values in the range 1–8.

Statistical analysis

Most variables were not normally distributed ($P < 0.05$, Kolmogorov–Smirnov test). Therefore, we give the median, and in parentheses the percentile 25–percentile 75. The median between groups was compared using the Mann–Whitney U test. The difference between
Predictive values (sensitivity, specificity, and predictive accuracy) were estimated according to predefined cut-off values: PVCs per hour $\geq 10$, $12-15$ PVCs per hour $\geq 30$, $16-17$ and SDCI $\leq 80$ ms. There are no established cut-off values for SNIB. To establish cut-off values, we carried out a linear regression analysis of log (SNIB) vs. log (PVCs per hour). The data were well fit by the expression PVCs per hour $= 0.77 \times$ SNIB ($R = 0.88$; Figure 3). Based on linear interpolation of this expression, we have determined the cut-off values of SNIB $= 20$ and 83 corresponding to 10 and 30 PVCs per hour, respectively; 10 PVCs per hour $= 20^{0.77}$ SNIB and 30 PVCs per hour $= 83^{0.77}$ SNIB.

To consider the effect of time on the predictive values of the indexes, we performed a survival analysis that involves the time to event (e.g. days to primary endpoint or days to death). The time to development of the event (e.g. primary endpoint, death, or cardiac death) was displayed by constructing Kaplan–Meier curves and the significance estimated by a log-rank test (which compares the survival distributions between groups defined by the indices). Cox proportional hazard models were used to calculate hazard ratios for dichotomized risk factors to identify predictors of the primary endpoint and secondary endpoints. Models were adjusted for age, prior AMI, history of congestive heart failure, and diabetes mellitus. Multivariate Cox regression models were used to examine whether combinations of indices added predictive value.

**Results**

Table 2 displays a summary of the measured characteristics, which are grouped according to the primary endpoint and secondary endpoints. For each of the three endpoints, there were significantly more PVCs/hour in the group that reached the endpoint compared with the group that did not reach the endpoint. SNIB was significantly higher in the group that reached the primary endpoint, compared with the group that did not reach the primary endpoint. In addition, the SDCI was significantly shorter in the group that experienced cardiac death compared with the group that did not reach that endpoint.

Prognostic values (sensitivity, specificity, positive predictive value, and negative predictive value) of these ventricular arrhythmia characteristics for primary endpoint, overall mortality and cardiac death are displayed in Table 3. These prognostic values are similar to the ones based on heart rate variability indexes that were previously tested on recordings from the CARISMA study.

Kaplan–Meier curves of selected indexes are displayed in Figure 4. Significant $P$ values (log-rank test) indicate that those indexes are associated with a lower probability of being free of the primary endpoint, all-cause death, or cardiac death during the 2-year follow-up period. After controlling for clinical variables, Cox regression analyses confirmed PVCs per hour $\geq 10$ and SNIB $\geq 83$ as independent predictors for the primary endpoint (Table 4). The following characteristics are independent predictors of both all-cause death and cardiac death: high ectopy (PVCs per hour $\geq 10$) and SDCI $< 80$ ms. SNIB $\geq 20$ and SNIB $\geq 83$ were predictors of all-cause death, but not cardiac death.

Multivariate Cox regression results showed that PVCs $\geq 10$ and SNIB $\geq 83$ are each independently related to an increase risk of the
primary endpoint, but there was no additive effect. This is likely due to these factors being highly associated, as well as due to the small number of primary events. For all-cause death, multivariate analyses identified only PVCs $\geq 10$ as being associated with an increased risk. In the multivariate analyses for cardiac death, PVCs $\geq 10$ were also associated with increased risk, and

Table 1  Clinical characteristics of eligible participants (all enrolled participants except for seven who died before evaluations at week 6)

<table>
<thead>
<tr>
<th></th>
<th>All eligible ($n = 305$)</th>
<th>Included ($n = 227$)</th>
<th>Excluded ($n = 78$)</th>
<th>$P$ value$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 (57–72)</td>
<td>64 (55–72)</td>
<td>70 (63–76)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Male gender</td>
<td>232 (76%)</td>
<td>176 (78%)</td>
<td>56 (72%)</td>
<td>0.306</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>113 (37%)</td>
<td>82 (36%)</td>
<td>31 (40%)</td>
<td>0.568</td>
</tr>
<tr>
<td>Prior congestive heart failure</td>
<td>30 (10%)</td>
<td>17 (7%)</td>
<td>13 (17%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Diabetes</td>
<td>59 (19%)</td>
<td>42 (19%)</td>
<td>17 (22%)</td>
<td>0.525</td>
</tr>
<tr>
<td>Hypertension</td>
<td>131 (43%)</td>
<td>92 (41%)</td>
<td>39 (50%)</td>
<td>0.145</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>292 (96%)</td>
<td>219 (96%)</td>
<td>73 (94%)</td>
<td>0.276</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At discharge</td>
<td>35 (30–37)</td>
<td>35 (30–37)</td>
<td>34 (28–36)</td>
<td>0.131</td>
</tr>
<tr>
<td>Week 6</td>
<td>37 (30–44)</td>
<td>37 (32–45)</td>
<td>34 (28–42)</td>
<td>0.048</td>
</tr>
<tr>
<td>ACE-inhibitor/AT blocker</td>
<td>272 (89%)</td>
<td>204 (90%)</td>
<td>68 (87%)</td>
<td>0.510</td>
</tr>
<tr>
<td>Statins</td>
<td>250 (82%)</td>
<td>185 (81%)</td>
<td>65 (83%)</td>
<td>0.716</td>
</tr>
<tr>
<td>Antiplatelet agent</td>
<td>274 (89%)</td>
<td>208 (92%)</td>
<td>68 (87%)</td>
<td>0.182</td>
</tr>
<tr>
<td>Characteristics of AMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q-wave AMI</td>
<td>181 (59%)</td>
<td>147 (65%)</td>
<td>34 (44%)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Anterior location</td>
<td>171 (56%)</td>
<td>128 (56%)</td>
<td>43 (55%)</td>
<td>0.847</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>106 (35%)</td>
<td>87 (38%)</td>
<td>19 (24%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Reached endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>21 (7%)</td>
<td>17 (8%)</td>
<td>4 (5%)</td>
<td>0.338</td>
</tr>
<tr>
<td>All-cause death</td>
<td>31 (10%)</td>
<td>20 (9%)</td>
<td>11 (14%)</td>
<td>0.133</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>21 (7%)</td>
<td>13 (6%)</td>
<td>8 (10%)</td>
<td>0.136</td>
</tr>
</tbody>
</table>

Data were gathered at discharge, unless stated otherwise.
AMI, acute myocardial infarction; ACE, angiotensin converting enzyme inhibitor; AT, angiotensin.
$^*$Comparison between included and excluded groups.

Figure 3  Regression analysis of PVCs/hour as a function of $S_{\text{VMB}}$. The plot with logarithmic scale does not include 38 recordings which had $S_{\text{VMB}} = 0$. 
PVCs \(\geq 30\) were associated with a decreased risk. Both factors were identified in the analysis because the cardiac death rate was 19.2\% in patients with PVCs between 10 and 30, while the rate was only 5.4\% in patients with PVCs \(\geq 30\).

**Discussion**

A major clinical problem is to identify post-myocardial infarction patients at risk of tachyarrhythmic SCD who might be aided by ICD. Earlier work has identified an increased frequency of PVCs per hour as a risk factor for a variety of endpoints including death and cardiac death.\(^{10,12,14–16,19–22}\) Although these studies were promising, they have not led to improved risk stratification procedures. In particular, after CAST (Cardiac Arrhythmia Suppression Trial) and some other trials, the enthusiasm of counting PVCs declined in risk stratification.\(^{23}\) This may be because the number of PVCs seems to reflect the severity of the underlying disease rather than a specific marker for risk of life-threatening arrhythmia events.

By analysis of data collected on implantable loop recorders, the CARISMA study allows us to identify patients who experience life-threatening tachyarrhythmias and hence should benefit from an ICD.\(^3\) When we examine the hazard ratio based on scores 10 and 30 PVCs per hour, we observe an increased hazard for PVCs/hour \(\geq 10\) and PVCs/hour \(\geq 30\) for primary, all-cause death, and cardiac death.
either death and/or cardiac death compared with the primary endpoint. In contrast, when we examine the hazard ratio for the comparable SNIB scores of 20 and 83 (corresponding to the 2 PVC per hour scores), we found that SNIB > 83 specifically identifies an increased hazard ratio = 3.51 (P = 0.013) for the primary endpoint compared with death and cardiac death.
Of the 19 risk factors evaluated in the earlier study by Huikuri et al.,3 there were only five criteria (power spectra at very low frequencies <5.7, power spectra at high frequencies <3.5, standard deviation of the NN intervals <70, QT dispersion >90 ms), and programmed electrical stimulation (leading to sustained monomorphic ventricular tachycardia) that had their hazard ratios at a higher level. Interestingly, three of those earlier criteria reflect lower heart rate variability (related to sympathetic tone) and only two of the criteria, inducibility of ventricular tachycardia and QT dispersion, reflect on arrhythmia substrate. Therefore, the $SNB > 83$ may have potential utility to be used as a non-invasive tool in risk stratification, especially since this index appeared to be more valuable for predicting specifically arrhythmia events, not only non-arhythmic deaths or all-cause mortality. This is opposite to heart rate variability, heart rate turbulence, the number of PVCs, and many other non-invasive indexes, which predict better the occurrence of non-sudden than SCD.3,4

We found that decreased variability of CI (SDCI < 80 ms) was a predictor of death and cardiac death, but not arrhythmia events. This is in contrast to a previous report of increased variability of CI (SDCI > 80 ms) as a risk factor for cardiac death in patients with coronary artery disease and frequent PVCs.18 The opposite findings may be explained by differences in target population (in that study selected patients included cases with preserved LVEF and cases with coronary artery disease but no myocardial infarction, while patients with indication for an ICD implantation were excluded). Previous studies have documented the association between the variability of CI and the occurrence of PVCs in repetitive rhythms,24 and the potential use of the relation between CI and heart rate for the identification of different mechanisms of PVCs.25 However, further studies are required to assess the predictive value of variability of CI for patients with frequent PVCs from different aetiologies.

The heartprint is a novel method of looking at characteristics of ventricular ectopy and the interdependence between sinus beats and PVCs on the risk for life-threatening arrhythmias.5,8 The rationale for examining these characteristics relates to the possibility to understand better the mechanisms of arrhythmias and to use this understanding to help assess the utility for ICD intervention in individual patients. It has been recognized at an early stage that some mechanisms of arrhythmias, such as parasystole, might lead to a high frequency of PVCs, but may not confer high risk of SCD.20 In our previous work,8 we demonstrated how mechanisms of re-entry, or strong or weak coupling of ectopic pacemakers, could lead to patterns similar to those that were observed in the current dataset. More recently, we discussed the possibility that repetitive bigeminy patterns in patients with long QT might be a signature of early afterdepolarizations.6 Although the primary endpoint group had a greater incidence of repetitive rhythms, further research is needed to help identify the mechanism of the arrhythmia in an individual patient.

To date, clinical studies have dominated the evaluation of markers for risk of SCD.1 According to this strategy a statistic, often based on a single non-invasively measured quantity is used to stratify risk—indeed the underlying physiology of the transition from sinus rhythm to the terminal rhythm. Although the notion that different physiological mechanisms of PVCs confer different levels of risk is not new,20 there are not yet good methods to assess the risk in an individual patient. Since different markers are based on different hypotheses for the underlying mechanism for transition to terminal rhythm,5 we believe that it will be essential to better understand the mechanisms of arrhythmias in the individual patient before we are able to carry out better risk stratification. The methods presented here appear to be correlated with risk of tachyarrhythmic events, death, and cardiac death, and thus may provide insight into mechanisms of arrhythmia and prove to be clinically useful.

Limitations

Although the annotations are overall of high quality, there are some recordings with mislabelled beats. In view of the large number of beats, a small percentage of mislabelled beats is not expected to have a large significance. The dataset is over a limited time frame. Consequently, a patient who experienced life-threatening arrhythmia immediately following the two-year study period would presumably be at a high risk, but would not be correctly identified. Similarly, the anatomical and physiological substrate of the patient can be different between the time of the Holter recording and the endpoint. Since many patients with very strong repetitive arrhythmias on the ECG do not experience life-threatening arrhythmia or death over the course of this study, further study is needed to determine if some patterns of arrhythmia may be benign.

Recordings with predominant non-sinus rhythm were excluded. Although they were similar to the studied group in most clinical characteristics, excluded patients were older and had poorer cardiac function. Finally, a relatively small number of patients were included in these analyses, and the present findings should be confirmed and replicated in other similar populations. The present results suggest that these novel analyses of the characteristics of PVCs, not only their frequency, might provide a new approach for risk stratification of post-infarction patients.

Conclusion

Several quantitative indexes evaluated from the heartprint 6 weeks after myocardial infarction are potentially useful to identify patients with increased risk of potentially fatal arrhythmia and cardiac death. This analysis of risk associated with characteristics of ventricular arrhythmias in post-myocardial infarct patients identifies repetitive patterns of ventricular rhythms as a potentially useful marker for ICD candidates.

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Conflicts of interest: C.L. and L.G. hold a patent in the subject matter. R.N.G. is an employee and stock holder in Medtronic Inc.

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