Heart Rate Variability During the Acute Phase of Myocardial Infarction

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Background. After acute myocardial infarction (AMI), several abnormalities of the autonomic control to the heart have been described. Heart rate (HR) variability has been used to explore the neural control to the heart. A low HR variability count measured 7–13 days after AMI is significantly related to a poor outcome. Little information is available on HR variability early after AMI and its relation to clinical and hemodynamic data.

Methods and Results. We studied 54 consecutive patients (42 men and 12 women; mean age, 60.4±11 years) with evidence of AMI by collecting the 24-hour HR SD from Holter tapes recorded on day 2 or 3. We also measured HR variability in 15 patients with unstable angina and in 35 age-matched normal subjects. HR variability was lower in AMI than in unstable angina patients (57.6±21.3 versus 92±19 msec; \( p<0.001 \)) and controls (105±12 msec; \( p<0.001 \)). Also, HR variability was greater in non–Q-wave than in Q-wave AMI (\( p<0.0001 \)) and in recombinant tissue-type plasminogen activator–treated patients with respect to the rest of the group (\( p<0.02 \)). No difference was found for infarct site. HR variability was significantly related to mean 24-hour HR, peak creatine kinase–MB, and left ventricular ejection fraction (all \( p<0.0001 \)). Patients belonging to Killip class >1 or who required the use of diuretics or digitalis had lower counts (\( p<0.004 \), \( p<0.001 \), and \( p<0.024 \), respectively). Six patients died within 20 days after admission to the hospital. In these patients, HR variability was lower than in survivors (31.2±12 versus 60.9±20 msec; \( p<0.001 \)), and a value <50 msec was significantly associated with mortality (\( p<0.025 \)).

Conclusions. HR variability during the early phase of AMI is decreased and is significantly related to clinical and hemodynamic indexes of severity. The causes for the observed changes in HR variability during AMI may be reduced vagal and/or increased sympathetic outflow to the heart. It is suggested that early measurements of HR variability during AMI may offer important clinical information and contribute to the early risk stratification of patients. (Circulation 1992;85:2073–2079)

Key Words • autonomic nervous system • death, sudden • myocardial infarction, acute • electrocardiography, ambulatory

Several abnormalities of the neurohumoral cardiovascular control have been described after acute myocardial infarction (AMI).\(^1\)–\(^5\) Full understanding and recognition of these changes is still lacking, but several investigations suggest that alterations in the level and kind of autonomic control to the heart do affect early and long-term prognosis of patients after AMI.\(^6\)–\(^8\)

Recently, it has been shown that computerized analysis of heart rate (HR) variability may provide valuable information on the underlying neural control to the heart that also possesses clinical relevance. Low HR variability counts can be observed in diabetic patients with autonomic neuropathy,\(^9\) in congestive heart failure,\(^10\)\(^,\)\(^11\) and after heart transplantation.\(^12\) HR variability is also decreased before ventricular fibrillation\(^13\) and has been shown to represent a powerful independent predictor of mortality when recorded after AMI.\(^14\)\(^,\)\(^15\)

The aim of this investigation was to evaluate HR variability during the early phase of AMI, to study its changes over time, and to relate this parameter with both clinical and instrumental data available in the coronary care unit (CCU).

Methods

Subjects

We studied 54 patients admitted to the CCU within 12 hours of the onset of a long-lasting chest pain. Diagnosis of AMI was based on currently accepted criteria (i.e., long-lasting chest pain accompanied by serum creatine kinase [CK]-MB elevation with or without typical ECG ST changes). Patients were admitted to this study consecutively with the exception of those having atrial fibrillation or atrial flutter. Patients >75 years old were also excluded from the study. There were 42 men and 12 women (mean age, 60.4±11 years; range, 36–75 years).

On the basis of the ECG site of the ST change, 26 patients had an inferior AMI and 28 an anterior AMI. Forty patients had a Q-wave and 14 patients a non–Q-wave AMI.
Seventeen patients suffered from hypertension, eight from type II diabetes, five had a peripheral obstructive arteriopathy, and four had chronic obstructive pulmonary disease. Six patients had had a myocardial infarct more than 6 months previously.

Five patients included in this study survived an episode of ventricular fibrillation that had occurred immediately before or soon after their admission to the CCU. After hospitalization, all patients were forced to bed and received conventional therapeutic measures (usually intravenous nitrates, aspirin, and subcutaneous heparin). None of the patients received β-blocking agents. Eighteen patients admitted within 6 hours from the onset of symptoms received 100 mg of intravenous recombinant tissue-type plasminogen activator (rt-PA) within 2 hours.

Blood samples for creatine phosphokinase determination were drawn three times a day starting from admission. Both total creatine phosphokinase and MB fractions were determined and expressed in IU/l. A two-dimensional echocardiographic exam was performed immediately before or soon after the 24-hour ECG recording. Simple measurements, such as end-diastolic left ventricular diameter and left ventricular ejection fraction (area–length method), were collected by use of either a 2.8- or a 3.5-MHz electronic transducer (Toshiba, Japan or Sonost 1000, Hewlett Packard, Andover, Mass.).

Holter Monitoring

A two-channel 24-hour ECG recording (Del Mar Avionics, Irvine, Calif.) was performed in all AMI patients on day 2 or 3 from admission to the CCU. We also studied 15 unstable angina patients (12 men, three women; mean age, 62±12 years) admitted to the CCU because of frequent myocardial ischemic episodes. These subjects also required medical therapy that in any case was similar to that of AMI patients. HR variability counts were performed on day 2 after admission to the CCU, with patients in bed.

Finally, we also collected the HR variability count of 35 subjects free from cardiac diseases who were able to perform moderate physical activity (28 men and seven women; mean age, 61±10 years). These subjects (who were matched for age and sex to the AMI group) were used as controls.

In all the patients surviving AMI, a long-term ECG recording was obtained 2 months after discharge from the CCU. In 22 patients, Holter monitoring was also performed 30 days after AMI. Monthly information on their clinical conditions was collected for all patients.

Tapes were stored and subsequently analyzed on a Del Mar Avionics 750A Innovator display unit (Irvine, Calif.). In addition to the usual information (arrhythmia and ST-T segment analysis), this computer-based system provides hourly and 24-hour mean HR values and also performs the HR variability analysis by determining the mean 24 hour R-R standard deviation. The acquisition and digital conversion rate of the unit is 256 samples per second (temporal resolution, 4 msec). Tapes were analyzed with the aim of including the major part of the recording in the HR study. For this purpose, the HR range of analysis was set at the highest and lowest mean HR value observed on the same tape.

Recording periods showing more than 5% of artifacts were removed from the analysis. To avoid the inclusion of artifacts and premature beats from the HR variability count, the system was set to remove all the cycles having a length duration >20% or <20% of the preceding r-r interval. This prevented the analysis of artifacts, premature beats, and postextrasystolic pauses. R-wave detection was checked by visual inspection to avoid the processing of artifacts. For each patient, recording time was exactly 24 hours, and no less than 95% of normal heartbeats were included in the HR variability count.

Tapes belonging to patients and controls were analyzed blindly by two different operators who were unaware of the design of the study. Interobserver variability was assessed by three different operators. Differences among operators for HR variability count was <5%. Intraobserver variability as assessed by a second count of HR variability on 15 tapes was again <5%.

Statistical Analysis

Comparisons of continuous data among groups or subgroups were made by Student’s t test for unpaired data. A χ² test was used to compare dichotomous data between groups. Comparison of data within a group over time was obtained by the paired Student’s t test. A linear regression analysis was used to assess the relation of continuous clinical data to HR variability. Where appropriate, results are expressed as mean±SD. A value of p<0.05 was required for statistical significance.

Results

HR Variability and HR in AMI

In the 54 patients studied, we found a mean 24-hour HR value of 78.5±10.3 beats per minute. This value was significantly higher than that recorded both in controls during unrestricted activity (68.4±13 beats per minute; p<0.001) and in unstable angina patients in the CCU (69.5±18 beats per minute; p<0.001). This higher mean HR value appeared related to a low day-to-night HR variation compared with both unstable angina patients and controls.

In the AMI group, we found a mean HR variability count of 57.6±21.3 msec (range, 14–107 msec). This value showed wide interindividual variations but was significantly reduced compared with both controls (105±12 msec; p<0.001) and unstable angina patients (92±19 msec; p<0.001) (Figure 1).

HR variability in AMI was related to age (r=−0.26; p<0.05), as older patients tended to have lower HR variability values than younger AMI patients. Also, HR variability was inversely related to mean 24-hour HR. A highly significant inverse (r=−0.7; p<0.001) linear relation was indeed present between HR and HR variability.

According to the ECG site of AMI, we compared HR variability of inferior AMI patients (n=26) with that of anterior AMI patients (n=28). Although patients with anterior AMI tended to have lower HR variability values than the group with inferior AMI (56.1±25 versus 60.6±18 msec), the difference was not statistically significant.
HR Variability, Infarct Size, and Left Ventricular Function

To evaluate the relation between infarct dimensions and HR variability, we compared the HR variability count with several parameters that are known to relate to the infarct size and left ventricular function. We found a significant inverse linear relation between HR variability and peak CK-MB value \( (r = -0.54; p < 0.001) \), so that patients with large CK plasma levels tended to show low HR variability counts and vice versa (Figure 2). The slope of the regression did not differ when anterior and inferior infarcts were compared.

HR variability was also significantly higher in non-Q-wave AMI than in Q-wave AMI \( (80.3 \pm 13.5 \text{ versus } 50.3 \pm 17.8 \text{ msec}; p < 0.0001) \) (Figure 3). Patients belonging to Killip class II–IV had significantly lower HR variability values than those in class I \( (p < 0.004) \). Also, patients who required the use of diuretics and digitalis had lower HR variability values than those patients who did not require the use of these drugs \( (p < 0.001 \text{ and } p < 0.024, \text{ respectively}) \). HR variability was significantly related to left ventricular ejection fraction \( (r = 0.44; p < 0.0001) \) and end-diastolic left ventricular diameter \( (r = -0.34; p < 0.014) \) (Table 1).

HR Variability and Systemic Thrombolysis

Eighteen AMI patients admitted to the hospital within 6 hours from the initial symptoms received rt-PA (100 mg i.v.; Actylise, Boehringer Ingelheim) within 2 hours. HR variability was higher in these patients than in those not receiving thrombolysis \( (67.4 \pm 19 \text{ versus } 52.7 \pm 21 \text{ msec}; p < 0.02) \) (Figure 4). To evaluate the effect of early thrombolysis on the relation between HR variability and CK elevation, we evaluated rt-PA-treated and nontreated patients separately. The slope of regression improved in both groups with respect to that observed for the whole AMI population (Figure 5). No significant difference in age and gender was present in the two groups.

Other Holter Variables and HR Variability

Four patients showed evidence of transient myocardial ischemia during Holter monitoring in the CCU. Myocardial ischemic episodes were defined as a transient ST depression \( \geq 1 \text{ mm } 80 \text{ or more msec after the J point and lasting more than } 1 \text{ minute. Two patients had one silent episode, one had three episodes (two asymptomatic), and one had only one episode during the occurrence of chest pain. HR variability in these patients did not differ from that of the remaining AMI group not showing transient myocardial ischemia.}

A low-grade ventricular ectopic activity was recorded in all the AMI patients on day 2 or 3. Polymorphic isolated ventricular ectopic beats were recorded in 52 of the 54 patients studied. Ventricular couplets were seen in 12 patients, and nonsustained ventricular tachycardia was recorded in eight subjects. No significant HR variability difference was found among AMI patients having different kinds of ventricular ectopic activity.

**TABLE 1. Correlation of Heart Rate Variability With Some Clinical and Laboratory Data**

<table>
<thead>
<tr>
<th></th>
<th>( r ) or ( t )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>( r = -0.26 )</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Heart rate</td>
<td>( r = -0.7 )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK-MB (IU/l)</td>
<td>( r = -0.54 )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF</td>
<td>( r = 0.44 )</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EDVD</td>
<td>( r = -0.34 )</td>
<td>&lt;0.014</td>
</tr>
<tr>
<td>Killip class I vs. II–IV</td>
<td>( t = 3.047 )</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Use vs. no use of digitalis</td>
<td>( t = 2.325 )</td>
<td>&lt;0.024</td>
</tr>
<tr>
<td>Use vs. no use of diuretics</td>
<td>( t = 3.635 )</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\( r \), Correlation coefficient of linear regression analysis; \( t \), unpaired Student's \( t \) test value; CK, creatine kinase; EF, left ventricular ejection fraction; EDVD, end diastolic left ventricular diameter.
Brief episodes of atrial fibrillation or supraventricular tachycardia (three to 11 consecutive beats) were recorded in six patients. HR variability in these patients was significantly lower than in those who did not have these arrhythmias (46±12 versus 58±19 msec; p<0.05).

**Major Arrhythmic Events in the CCU and HR Variability**

Within the first 24 hours, 12 patients showed one or more episodes of ventricular tachycardia as recorded from the CCU monitors. Of these, eight patients developed a slow ventricular tachycardia at the end of the rt-PA infusion. HR variability on day 2 or 3 in these patients was not significantly different from that of patients without ventricular tachycardia (61.7±19 versus 57.1±22 msec; NS).

Five patients had one episode of ventricular fibrillation within 24 hours of admission to the CCU (range, 0–18 hours) and were successfully treated by DC shock cardioversion. In all these subjects, HR variability data were not available until 1 or 2 days later because of the design of the study. HR variability in this group of patients was lower than in the rest of the AMI group (47.2±26 versus 59.2±21 msec; NS), but the difference was not significant. One patient who had the lowest HR variability value measured in this group (14 msec) experienced an episode of pulmonary edema 10 days later. The remaining four patients had a regular and uncomplicated recovery.

Two patients having an inferior AMI developed a symptomatic bradycardia on days 4 and 5, respectively, which required temporary cardiac pacing. HR variability in these patients was 41 and 45 msec, respectively, values that were not significantly different from those of the remaining AMI patients.

**HR Variability and Mortality**

During a mean follow-up period of 12 months (range, 8–19 months), six deaths were either observed or reported (overall mortality, 11.1%). Mortality was concentrated over the first 20 days after AMI. Four patients died suddenly, and two died from cardiogenic shock. Three patients died in the CCU (two sudden deaths from cardiac rupture; one cardiogenic shock). The remaining three patients died within 1 month. Patients who died after AMI showed significantly lower values of HR variability than the survivors (31.2±12 versus 60.9±20 msec; p<0.001) (Figure 6). These patients also had significantly higher values of HR (p<0.001), lower values of left ventricular ejection fraction (p<0.001), and higher Killip class (p<0.02) than the survivors (Table 2).

We analyzed the probability of death in AMI patients as a function of HR variability. On the basis of a previous study from Kleiger et al., we considered an HR variability value <50 msec as a risk factor. A value of HR variability <50 msec was present in all of the patients who died. This value was significantly associated with mortality (p<0.025; Table 3). A low HR variability value also increased the likelihood of death in patients having other altered parameters. Decreased left ventricular ejection fraction (<50%) was present in 14 patients and in four out of those who died (mortality, 29%). However, a low ejection fraction and an HR variability count <50 msec were present in nine patients, four of whom subsequently died (mortality, 44%) (Figure 7).

**Changes in HR Variability Count Over Time**

A second Holter tape was recorded in 22 patients 30 days after discharge from the CCU, and a third record-
ing was performed 60 days later in all the patients who survived (n=48). HR variability greatly increased at 60 days (Figure 8), and near normal HR variability counts could be observed (92.1±21 msec versus the count on day 2 or 3; p<0.0001). Intermediate values were obtained at 30 days (78.3±19 msec versus the count on day 2 or 3; p<0.001), indicating a progressive increase of HR variability over time. At 60 days, only two patients still showed an HR variability ≤50 msec. One of them had experienced repeated episodes of pulmonary edema after AMI, and the other patient developed congestive heart failure.

**Discussion**

In this investigation, we found that HR variability is low compared with both controls and unstable angina patients when measured early after AMI. We also found that low HR variability at an early stage of AMI is significantly associated with early mortality and major complications and that this parameter is significantly related to clinical, hemodynamic, and laboratory data, which are known to reflect infarct size and ventricular performance. Finally, we observed a significant increase in the HR variability count over time.

HR variability possesses the theoretical basis to be a very important parameter, as it represents the integrated response of the cardiovascular system to several different influences. Being a biological signal and depending on several factors (some of which are independently associated with mortality in cardiac patients) such as plasma levels of catecholamines, baroreflex activation, and sympathetic and vagal activity, HR variability may reflect the true relevance of hemodynamic damage better than any of the other currently used parameters. HR variability can be measured by different methods. In the present investigation, we used the 24-hour SD of the R-R interval, as this index was shown to possess a predictive value in a large study in postinfarction patients at the time this study was designed. Since then, another index based on the frequency distribution of duration of normal-to-normal RR intervals has been shown to have a similar prognostic value.

Several data in this study indicate that the degree of HR variability reduction we found is related to clinical severity and infarct size: 1) HR variability was greater in non-Q-wave than in Q-wave AMI; 2) there was an inverse relation between HR variability and peak CK-MB discharge; and 3) low counts were associated with Killip class >1, use of digitalis and diuretics, faster HR, and lower left ventricular ejection fraction values. The greater HR variability in patients who received systemic thrombolysis than in those who were not treated also supports these conclusions. In fact, early thrombolysis is known to improve left ventricular function by decreasing infarct size. Thrombolized patients in our study had higher ejection fraction values than nonresponding patients (63±11% versus 45±14%; p<0.001). Therefore, it is conceivable that the higher HR variability counts observed in the rt-PA–treated group are to be related to a smaller infarct size.

Our data also show that HR variability changes in time after AMI and usually increases progressively over a 2-month follow-up. These results are compatible with previous data reporting the presence of a temporary decrease of vagal activity after AMI. As it improves in time after AMI, HR variability should be regarded as a

**TABLE 3. Heart Rate Variability and Mortality**

<table>
<thead>
<tr>
<th></th>
<th>Patients (n)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>54</td>
<td>11</td>
</tr>
<tr>
<td>HRV &gt;50 msec</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>HRV &lt;50 msec</td>
<td>21</td>
<td>29</td>
</tr>
</tbody>
</table>

HRV, heart rate variability. 
χ²=5.6, p<0.025.

**FIGURE 7. Scatterplot of heart rate (HR) variability and left ventricular ejection fraction (EF) in acute myocardial infarction (AMI). An arbitrary line has been traced on the horizontal plane corresponding to an HR variability <50 msec. On the vertical plane, a line has been traced at a level of EF <50%. □, AMI patients who died. Note that all the patients who died had HR variability counts <50 msec.
dynamic parameter, and investigations on postinfarction patients should consider the fact that counts are not constant at different time intervals after AMI.

Finally, we found that HR variability as recorded early in the CCU is related to subsequent events and mortality. In fact, AMI patients with very low HR variability counts developed significantly more events than patients with higher counts. Kleiger et al. found a value of HR variability <50 msec to be a significant risk factor of mortality when recorded in the early convalescent phase of AMI. In our study, all the patients who died showed values under this limit. Although a count below 50 msec was often present in AMI patients who survived, patients with HR variability >50 msec had a significantly smaller probability of death than those with a value <50 msec. The association of decreased HR variability and low ejection fraction was particularly ominous, as mortality increased significantly from 29% to 44% in those having both parameters altered.

Little information is available on HR variability early after AMI. So far, only two studies have investigated this parameter during the early hours of AMI, showing a lower HR variation in anterior wall AMI than in inferior AMI and a lower count in patients with complications. We did not find any difference in HR variability based on AMI location. With regard to AMI location, our results are similar to those reported by Lombardi et al., who studied patients only 15 days after AMI. It can be hypothesized that differences in HR variability dependent on infarct site are limited to the very early hours of AMI, possibly to the first 24 hours.

The causes for decreased HR variability in AMI may be different and can only be inferred. Decreased HR variability is usually considered a marker of impaired vagal activity to the heart. However, low HR variability has also been observed in congestive heart failure, a condition that is characterized by increased adrenergic drive. AMI is also frequently associated with signs of sympathetic activity. Plasma catecholamine levels increase significantly a few minutes after experimental coronary occlusion and are related to the extent of myocardial damage. Also, a sympathetic reflex elicited by ischemia has been described. Therefore, increased adrenergic drive, impaired parasympathetic outflow to the heart, or both may contribute to the low HR variability count that we found in AMI. Further investigations with heart rate spectral analysis may help to cover this subject.

Because low vagal activity and increased sympathetic discharge are considered predisposing factors for major arrhythmic events or may represent an unfavorable condition in patients with left ventricular dysfunction, correction of the autonomic disturbance present after AMI would be advised. However, as several data in this report suggest, the autonomic impairment reflected by the decrease in HR variability is not a primary or unpredictable event after AMI but rather is associated with the degree of myocardial damage. Therefore, to modify the autonomic disturbance present, therapeutic efforts should be directed to the reduction of AMI size and preservation of myocardial function.

Our findings may have clinical relevance. Previous data on the clinical importance of HR variability as a predictor of mortality in patients after AMI have been collected between 7 days and 11±3 days after the acute event. Our data suggest that prognostic information based on HR variability in AMI can be obtained earlier than previously reported. Furthermore, as HR variability changes over time after AMI, repeated measurements may be required to assess postinfarction patients. HR variability is easily obtained and can be measured on the same Holter tape while evaluating other prognostic factors such as residual ischemia and ventricular ectopic beats.

There are some limitations to this study. Although we attributed the reduction of HR variability only to the presence of AMI, we cannot exclude that some changes could be caused by environmental factors. Also, therapy by itself may have caused some HR variability changes. Although these factors may have influenced the HR variability count, it is unlikely that they played a relevant role in our findings. In fact, we studied both unstable angina patients and controls in an attempt to obviate these limitations. Therapeutic interventions (apart from thrombolysis, which, however, increased HR variability) were similar in AMI patients and the unstable angina group. In spite of the similar therapy, AMI patients had a much lower HR variability than unstable angina patients. Also, two-dimensional echocardiography was performed on day 1 in 41 patients and on day 3 in 13 subjects. During the acute phase of AMI, several changes might be expected in both left ventricular dimensions and function. Therefore, the different timing of the examination may have influenced our results. Another potential limitation is the fact that we did not match the controls for the preexisting conditions of AMI patients. Of these conditions, only diabetes is known to decrease HR variability. Nevertheless, in six of eight diabetic patients surviving AMI, we observed a significant increase in HR variability over time. It is thus unlikely that diabetes per se could have influenced our results significantly.

Although we found a strict relation between HR variability reduction and signs of impaired left ventricular function, we cannot establish with certainty that this association was the cause for the observed HR variability behavior in AMI. In fact, some patients had
either low variability counts and good ejection fraction values or vice versa. Neural sympathetic disruption within the heart and sympathetic reflexes, both promoted by ischemia, can alter the normal autonomic regulation of the heart and may also account for the changes that we observed. Nevertheless, it should also be stressed that normal ejection fraction values do not necessarily reflect a normal ventricular function. Also, the fact that HR variability was strongly related to several indices of the extent and clinical severity of AMI raises a strong suspicion that changes in ventricular performance play a primary role in the observed results.

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References

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