Influence of residual ischaemia on heart rate variability after myocardial infarction

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Despite the growing evidence for the positive predictive value of depressed baroreflex sensitivity and/or reduced heart rate variability after myocardial infarction, the mechanisms involved in these autonomic alterations are not fully understood. Specifically, the possible influence of residual ischaemia has not been assessed.

To address this problem we studied the spectral analysis of heart rate variability in 21 patients with a first myocardial infarction in whom the only clinical correlate was the presence of residual ischaemia, as documented by the positive response to both an exercise stress test and an echocardiographic stress test. Data from these patients were compared with those obtained in a group of post-myocardial infarction patients similar for several risk factors, age, site of myocardial infarction, but without residual ischaemia. Patients positive for residual ischaemia had lower power in the whole spectrum (1146 ± 158 vs 1631 ± 159 ms², P=0.032) as well as in the low and high frequency bands of heart rate variability. A nocturnal increase in high frequency was observed in those without residual ischaemia (from 167 ± 35 to 242 ± 51 ms², +45%, P=0.034), but not in those with residual ischaemia (from 111 ± 19 to 141 ± 29 ms², +27%, ns).

Thus, residual ischaemia reduces heart rate variability after myocardial infarction. The autonomic effects of residual ischaemia probably contribute to its negative prognostic value after myocardial infarction.

Key Words: Myocardial ischaemia, autonomic nervous system, coronary artery disease.

Introduction

There is growing evidence documenting the positive predictive value of depressed baroreflex sensitivity and/or reduced heart rate variability in the identification of post-myocardial infarction patients at high risk for lethal events[1,2]. However, the mechanisms involved in the depression of heart rate variability and baroreflex sensitivity after myocardial infarction are not fully understood.

Experimental evidence from studies in which baroreflex sensitivity and heart rate variability were measured before and after myocardial infarction in the same animals, while conscious, indicates that myocardial infarction causes depression of these autonomic markers[3-5]. This information has been confirmed in clinical studies in which post-myocardial infarction patients were compared with age- and sex-matched control subjects[6-8]. We recently observed that such a reduction in heart rate variability is transient in low-risk subjects, as they later recover an almost normal autonomic control of the heart, while it is permanent in subjects destined to remain at high risk[9]. This high-risk condition can be profoundly improved by exercise training, an intervention that concomitantly increases heart rate variability and baroreflex sensitivity and greatly reduces risk for lethal arrhythmias[10].

Among the several factors potentially able to alter autonomic activity after myocardial infarction, depressed left ventricular function is probably a very important one. Nonetheless, either a lack of, or a weak, correlation has been documented between left ventricular ejection fraction and either baroreflex sensitivity[10] or heart rate variability[11,12]. The relationship between the site of the myocardial infarction and autonomic markers has also been evaluated and the data obtained are conflicting[10,12]. Furthermore, other factors such as hypertension or diabetes also influence cardiac autonomic activity and prognosis after myocardial infarction[12,13].


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To date, the autonomic consequences of inducible ischaemia, that is a predictor of higher mortality in the first year after myocardial infarction\(^{[8]}\), have not been clearly described. This is mostly due to the presence of multiple risk factors and/or of ongoing therapy in the patient population enrolled in the available studies in which the role of residual ischaemia was investigated. Recent clinical evidence confirms the experimental information that transient myocardial ischaemia acutely reduces baroreflex sensitivity\(^{[14]}\). Post-myocardial infarction patients with three-vessel coronary disease have a lower baroreflex sensitivity than those with single-vessel disease\(^{[10]}\). Furthermore, in patients with or without a prior myocardial infarction, respiratory sinus arrhythmia is also significantly lower in the presence of multi-vessel disease\(^{[15]}\). In apparent contrast with this latter information is the evidence that a positive response to an exercise stress test is not associated with lower heart rate variability\(^{[12]}\).

The present study was designed to address the issue of the influences of residual ischaemia on cardiac autonomic activity after myocardial infarction. With this aim, heart rate variability was evaluated in early post-myocardial infarction patients in which the only clinical correlate was acute myocardial ischaemia evoked by an exercise stress test and by an echocardiographical stress test. Data from these patients were compared with those obtained from a group of post-myocardial infarction patients comparable for several risk factors but without stress-inducible ischaemia.

### Methods

#### Study population

Fifty-three in-hospital patients (49 men and four women) with a recent non-complicated first myocardial infarction entered the study. The diagnosis of myocardial infarction was based on: (1) chest pain lasting more than 30 min, resistant to nitrates; (2) electrocardiographic changes suggestive of an acute coronary event; (3) elevation of cardiac enzymes (specifically creatinine kinase-MB).

The clinical characteristics of the selected patients are shown in Table 1. The two groups were comparable for factors known to influence autonomic activity, such as smoking habit\(^{[16,17]}\), age\(^{[2,10]}\), hyper tension or diabetes\(^{[13]}\). Both groups had a similarly preserved left ventricular ejection fraction and an acute myocardial infarction that was comparable for size (as estimated from cardiac enzymes) and site. Most of the patients were treated with thrombolytic agents in the acute phase of the myocardial infarction.

### Residual ischaemia

Presence of residual ischaemia was assessed by a dipyridamole-echocardiography test and by a symptom-

<table>
<thead>
<tr>
<th>R1−</th>
<th>R1+</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 9</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>18/21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10/21</td>
</tr>
<tr>
<td>Angina</td>
<td>1/21</td>
</tr>
<tr>
<td>NIDDM</td>
<td>0/21</td>
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<tr>
<td>Dyslipidaemia</td>
<td>3/21</td>
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<tr>
<td>Smokers</td>
<td>17/21</td>
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<tr>
<td>Inf-MI</td>
<td>18/21</td>
</tr>
<tr>
<td>Ant-MI</td>
<td>2/21</td>
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<tr>
<td>Lat-MI</td>
<td>1/21</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>58 ± 6%</td>
</tr>
<tr>
<td>CPK (U·L⁻¹)</td>
<td>1266 ± 922</td>
</tr>
<tr>
<td>CPK-MB (U·L⁻¹)</td>
<td>87 ± 56</td>
</tr>
<tr>
<td>SGOT (U·L⁻¹)</td>
<td>141 ± 59</td>
</tr>
<tr>
<td>LDH (U·L⁻¹)</td>
<td>704 ± 273</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>19/21</td>
</tr>
</tbody>
</table>

RI = residual ischaemia; NIDDM = non-insulin dependent diabetes mellitus; Inf, Ant, Lat = inferior, anterior, lateral; MI = myocardial infarction; CPK = creatinine kinase; SGOT = serum glutamic oxaloacetate transaminase; LDH = lactate dehydrogenase. No significant differences were observed between the two groups.

#### Echocardiographical stress test

Echocardiographical stress was performed by means of a combined atrial pacing and high-dose dipyridamole test, as already described\(^{[18]}\). During the procedure, arterial blood pressure was periodically measured and the 12-lead electrocardiogram was continuously recorded. Two-dimensional echocardiograms were also continuously monitored. The pacing protocol consisted of an initial rate of 110 beats min⁻¹ increasing every 2 min by increments of 10 beats min⁻¹, until a maximum rate of 150 beats min⁻¹ was achieved or chest pain occurred. After 5 min recovery, a 10 min infusion with dipyridamole to a total dose of 0.84 mg kg⁻¹ was performed. Positivity of the test was defined by the detection of transient asynergy/dysynchrony of contraction, which was absent or of a lesser degree in the baseline examination, or by the occurrence of chest pain and/or typical ECG changes. Aminophylline was administered (120–240 mg i.v. for 1–4 min) as soon as dysynchrony was evident or at the end of the test, to reverse or prevent side effects due to dipyridamole. Wall motion abnormalities were scored by dividing the left ventricle into 11 segments and by scoring wall motion from 1 to 4, 0 being normal and 4 dysynchrony. For this study, evaluation and scoring of wall motion was performed by the same physician.
Exercise stress test

Patients performed a multistage bicycle ergometer test, with an initial load of 25 Watt and increments of 25 Watt every 3 min. A 12-lead electrocardiogram and systolic and diastolic pressures, measured using a cuff sphygmomanometer, were recorded before the test and every minute during exercise and following recovery. End-points of the test were the occurrence of typical chest pain, diagnostic ST-segment shift, the achievement of a maximal age-related heart rate, or limiting dyspnoea or fatigue in the absence of signs of myocardial ischaemia.

Coronary angiography

Coronary angiography was routinely performed in all patients with evidence of residual ischaemia. Furthermore, coronary angiography was also offered to all patients without residual ischaemia. Overall, angiographic data were collected in 17 of 20 patients with residual ischaemia and in 16 of the 21 patients without residual ischaemia.

Long-term electrocardiographic monitoring

Twenty-four hour electrocardiographic monitoring was carried out by conventional techniques. An ICR 6201 and ICR 7200 Holter Recorder (Instrument for Cardiac Research, East Syracuse, NY-13057, U.S.A.) were used. ECG files were analysed by a Marquette Holter analysis system (series 8000/T). RR intervals were calculated as the time between each two consecutive normal QRS complexes. The ST segment was also analysed from the 24-h recording. This was done to exclude the presence of silent ischaemic episodes that could have affected our findings.

Heart rate variability spectral analysis

Spectral analysis was performed on 5 min RR interval sequences extracted from the 24-h Holter recording. A computer program was designed that automatically discarded sequences containing artifacts or a number of ectopics greater than 2%.

In all 5 min RR interval sequences which fulfilled the described criteria, the residual ectopic beats present were automatically corrected by an interpolating algorithm. The original 5-min sequence and the corrected one were then plotted superimposed on one another. The analyst could then interactively decide to either accept or discard the resulting series. At least five sequences per hour suitable for analysis were selected in each patient. All accepted series were linearly detrendized by a least-square first-order polynomial fitting. For computational efficiency, the power spectrum density of each segment was estimated by the Blackman-Tukey method, that is the Fourier transform of the windowed autocovariance function. The signal variance (total power) was computed. The power in the very low frequency (0-0.03 Hz), low frequency (0.03-0.15 Hz) and high frequency (0.15-0.40 Hz) bands was then computed by numerical integration of the power spectral density function.

Data from the 5 min segment were then averaged for each patient over the 24 h. Day and night (from 2200 h to 0600 h) heart rate variability in the three different spectral bands was also calculated.

Statistical analysis

For each parameter considered, a repeated measures analysis of variance (ANOVA) was used to assess differences between the two groups of patients (between-subjects effect) and between day and night (within-subject effect). A \( P < 0.05 \) was considered significant. All statistical analysis was performed using version 6.04 of the SAS/STAT package (SAS Institute Inc. 1987). Data are reported as mean ± SE.

Results

Of the 53 patients enrolled in the study, 21 (40%) had a negative response to both the exercise and stress-echocardiography tests and 20 (38%) had a positive response to both tests. Twelve (22%) patients had an inconsistent response to the two tests. Only patients with positive and negative tests were considered for the analysis.

Wall motion abnormalities during the stress echocardiography test

The study population had a similar asynergy score at the baseline evaluation, prior to dipyridamole infusion. Asynergy score was 3.93 ± 0.75 in the positive patients and 4.6 ± 0.88 in the negative patients (ns). With dipyridamole, the asynergy score remained unchanged in the negative group while it increased (\( P < 0.001 \)) to 7.14 ± 0.88 in the positive group. As a consequence, under stress wall motion scoring in the two groups of patients showed a significant difference (\( P < 0.003 \)).

Coronary angiography findings

On average, the number of diseased coronary vessels was higher in the positive patients (1.9 ± 0.9 vs 1.3 ± 0.7, \( P = 0.045 \)). Specifically, in the group with residual ischaemia three patients had three-vessel disease, one had four-vessel disease while none of the patients without residual ischaemia had more than two diseased vessels.
Residual ischaemia and heart rate variability

Heart rate variability

No ST-segment changes suggestive of silent ischaemia that could have influenced heart rate variability\cite{19,20} were detected in any recording at analysis of the ST segment.

The two groups of patients had similar mean heart rates over the 24 h. The mean RR interval was 904 ± 19 ms in the negative patients and 896 ± 24 ms in the positive patients (ns). The total power was significantly lower in the positive group (1146 ± 158 vs 1631 ± 159 ms², \( P = 0.032 \)). Power spectral analysis showed no difference between positive and negative patients in the very low frequency band (516 ± 71 vs 643 ± 74 ms², \( P = 0.2178 \), Fig. 1).

A lower power was measured in the low frequency band in the positive patients (420 ± 67 vs 600 ± 58 ms², \( P = 0.045 \), Fig. 1). Neither group showed day-night (night is 2200 h to 0600 h) variations in the low frequency band (positive: 403 ± 80 ms² day-time vs 436 ± 111 ms² night-time, \( P = 0.495 \); negative: 582 ± 83 ms² vs 617 ± 82 ms², \( P = 0.399 \)).

The power in the high frequency band was also significantly lower in the positive patients (126 ± 17 vs 204 ± 31 ms², \( P = 0.034 \), Fig. 1). At variance with the low frequency band, a significant nocturnal increase in high frequency power was evident in the negative group (from 111 ± 19 to 141 ± 29 ms², +27%, ns, Fig. 2). This different nocturnal pattern led to a significant reduction in the low frequency/high frequency ratio during the night in the negative patients (from 4.3 ± 0.5 to 3.3 ± 0.4, -23%, \( P < 0.01 \)) but not in the positive patients (from 5.1 ± 1.7 to 4.6 ± 1.4, -10%, ns).

Discussion

The present study documents that residual ischaemia contributes to reduce heart rate variability after myocardial infarction. Indeed, patients with residual ischaemia showed a loss of power both in the low and the high frequency bands. In this latter band, a lack of nocturnal increase in power significantly contributed to the observed results. The present findings provide new information for the understanding of mechanisms involved in the genesis of autonomic imbalance observed after myocardial infarction.

Study population

The study group consisted of patients with a recent myocardial infarction free of additional correlate but residual ischaemia. At the time of the testing, all patients were in hospital but ambulatory and in wash-out from the therapy used in the acute phase of the myocardial infarction. This was feasible because of the absence of any event complicating the myocardial infarction. Daytime activity and sleep time were similar in all patients due to the hospital schedule. Consequently, the observed differences in heart rate variability pattern were not due to different levels of activity among the two groups of patients.

As described in Table 1, patients with and without residual ischaemia shared several risk factors. Left ventricular function was preserved in both groups (57–58% left ventricular ejection fraction) and all but three patients were treated with thrombolysis, an intervention known to reduce both heart rate variability\cite{21} and baroreflex sensitivity\cite{22,23}. The incidence of other factors known to influence heart rate variability

**Figure 1** Power distribution in the VLF (very low frequency), LF (low frequency) and HF (high frequency) bands of the spectral analysis of heart rate variability in patients with (RI+) and without (RI-) post-myocardial infarction residual ischaemia. \(*=P<0.05\).

**Figure 2** Day (■) and night (●) power in the high frequency band of the spectral analysis of heart rate variability in patients with (RI+) and without (RI-) post-myocardial infarction residual ischaemia. Only RI- patients had a significant nocturnal increase in the high frequency power. \(*P=0.034\).
such as age, arterial hypertension\cite{13} or smoking\cite{17} were also similar in the two groups. Only one patient, in the negative group, had angina at rest prior to the index myocardial infarction. Abnormalities of the ST segment were not observed on specific analysis of this aspect of the 24 h ECG recordings.

Overall, the population selected for the present study suited the objective of describing the relationship between residual ischaemia after myocardial infarction and heart rate variability in an environment relatively free of other confounding factors.

\textbf{Angiographic findings and heart rate variability}

Residual-ischaemia positive patients had a greater number of diseased vessels than the negative patients. Hayano \textit{et al.} showed that the coefficient of component variance, which provides the amplitude of the variance relative to the mean RR interval, in the band between 0.04 and 0.15 Hz, was significantly lower in patients with three or more diseased vessels than in patients with normal coronary angiography. Furthermore, in the same work by Hayano \textit{et al.} there was a progressive reduction of respiratory sinus arrhythmia as a function of the number of diseased coronary vessels. In agreement with this finding, is the evidence that patients with a three- vessel coronary artery disease have a lower baroreflex sensitivity, a marker of vagal reflexes, than patients with one-vessel disease\cite{10}.

Thus, the evidence of reduced heart rate variability in positive patients could simply reflect the number of the diseased vessels. However, in our study two of the four patients in the positive group with more than two (four and three respectively) diseased coronary vessels had heart rate variability values within the highest levels observed in the whole population studied (total power 2777 and 5413 ms²). The two other patients (both with a three- vessel disease) had, respectively, a total power of 1069 and 527 ms². Overall, the number of diseased vessels did not appear to be a critical element for the lower heart rate variability observed in the positive patients.

\textbf{Potential mechanisms}

The combined analysis of the two tests used in the present study involved detection of residual ischaemia by two different criteria. They were the occurrence of ECG changes during a standard exercise stress test and the inducible wall motion abnormalities during the dipyridamole echo-stress test. Thus, mechanisms related both to ischaemia and to mechanical abnormalities were concomitantly described in the present study. Specifically, stress revealed wall motion differences among the two groups that were not otherwise detectable in baseline conditions.

Based on this information, a tenable hypothesis to explain the decrease in vagal control of the heart after myocardial infarction is that the altered geometry of contraction of the damaged heart may result in augmented activity of sympathetic afferent fibres due to mechanical distortion of their sensory endings\cite{41}. Such an increase in afferent sympathetic activity may lead to reflex inhibition of vagal and stimulation of sympathetic activity directed to the heart. The autonomic alteration consequent to these reflex mechanisms may result in depression of baroreflex sensitivity and heart rate variability. The whole hypothesis is based on several experimental observations. Acute myocardial ischaemia activates afferent sympathetic fibres and triggers an excitatory cardio-cardiac reflex\cite{24}. The electrical stimulation of afferent sympathetic fibres depresses afferent cardiac vagal activity\cite{25} and removal of cardiac sympathetic afferent fibres increases both cardiac vagal activity\cite{26} and baroreflex sensitivity\cite{27}. Thus, the possibility exists that the presence of an area of unstable perfusion and mechanical activity could have caused an increased discharge of afferent sympathetic fibres, leading to decreased vagal outflow to the heart.

It is of interest that the loss of high frequency heart rate variability in positive patients was specifically evident during the night. At this time the typical rise in power in the high frequency band consequent to the surge in cardiac vagal activity associated with sleep occurred in negative patients only. In contrast, positive patients showed a loss in this circadian pattern of high frequency power. A depressed circadian variation of heart rate variability after myocardial infarction has already been documented\cite{8,28}. We recently observed that such a loss in circadian variations of heart rate variability is dependent upon a lack of rise of power in high frequency during non rapid eye movement sleep\cite{29}, a condition in which high frequency power is at the highest level\cite{29}.

Coronary artery disease impairs the vagal component of the autonomic control of heart rate\cite{10,12}. In our study, such a negative influence of residual ischaemia could have been revealed specifically in the condition associated with the highest expression of cardiac vagal activity, such as sleep.

The present study was not designed to determine the relationship between residual ischaemia and risk for cardiovascular events after myocardial infarction. The prognostic value of a positive response to an exercise stress test has been documented in different studies\cite{2} although it has been recently questioned, specifically after thrombolytic therapy\cite{30}. Nonetheless, the present data suggest that residual ischaemia may worsen prognosis by altering cardiac autonomic control after an acute myocardial infarction.

\textbf{Conclusions}

Residual ischaemia is an important factor contributing to autonomic derangements after myocardial infarction,
even in the presence of preserved global left ventricular function. A possible mechanism of this autonomic alteration may involve increased afferent sympathetic activity originating from the area of unstable perfusion and mechanical function.

The reduction in heart rate variability, and specifically the loss of the circadian pattern of high-frequency components (indicative of a derangement in cardiac vagal activity), represents a factor likely to contribute to the negative prognostic value of residual ischaemia after myocardial infarction.

References


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