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Rapid Recovery of Baroreceptor Reflexes in Acute Myocardial Infarction is a Marker of Effective Tissue Reperfusion

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Abstract Baroreflex sensitivity (BRS) measured several days after myocardial infarction (MI) is a powerful predictor of cardiovascular mortality. No information is available on BRS in the early hours of MI. The possibility to reliably assess BRS in the acute phase of MI and its clinical correlates were evaluated in 45 patients treated with primary percutaneous coronary intervention (pPCI). BRS (sequence method) was assessed 1, 3, 6, and 12 h after PCI. ST resolution (STRes) was considered present if ST had decreased ≥70 % 3 h after PCI. BRS was 10.7±6.2 1 h after PCI; at 12 h it was 15.4±5.2 and 8.4±4.8 ms/mmHg in patients with and without STRes, respectively ($p<0.001$). STRes was an independent predictor of 12 h BRS ($p=0.005$) and of 1–12 h BRS difference ($p=0.002$). BRS can be reliably assessed in the first hours of MI; it shows a rapid recovery in patients with STRes and a significant depression in patients without STres.

Keywords Baroreflex control · Autonomic nervous system · Myocardial infarction · Vagal activity · Reperfusion injury

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Introduction

Patients with a healed myocardial infarction (MI) who show a depression of baroreflex sensitivity (BRS) have a high, total and arrhythmic, mortality as demonstrated in the large multicenter ATRAMI study [1, 2]. This autonomic marker was found to be largely independent from left ventricular function but influenced by the status of the infarct-related artery, with higher BRS values observed among patients with patent arteries [3]. Subsequently, BRS was shown to be a powerful risk stratifier also over the long term and among patients with preserved left ventricular ejection fraction (LVEF) [4].

In these studies BRS was assessed several days or weeks after MI, mostly because of the concerns of injecting vasoconstrictive agents, such as phenylephrine [5], in the acute phase of MI. However, BRS can be derived from the spontaneous fluctuations of systolic blood pressure and heart cycle after identification of sequences of systolic blood pressures and heart cycles that concurrently increase or decrease [6, 7]. The sequence method correlates well with the traditional phenylephrine method [8].

Goals of the present study, among MI patients treated with primary percutaneous coronary intervention (pPCI), were as follows: (1) to evaluate whether the baroreceptor reflex system operates in the acute phase of MI and whether BRS can be reliably assessed using the sequence method, (2) to investigate the clinical correlates of different BRS dynamic patterns in the first hours after MI, and (3) to assess the influence of effective tissue reperfusion in modulating the acute BRS pattern.

Methods

Patients aged 18–75 years who underwent pPCI for a first ST elevation myocardial infarction (STEMI) within 12 h from the onset of symptoms were eligible for the study. We excluded patients in atrial fibrillation, with 2nd or 3rd degree

atrioventricular block during the first 12 h, in Killip class III and IV, with systolic blood pressure (SBP) <90 mmHg, treated with amines including dopamine, mechanically ventilated or treated with continuous positive airway pressure, with severe chronic obstructive pulmonary disease, central or peripheral nervous system disease and a known thyroid dysfunction.

The study did not interfere with the usual care of the patients, including technique of pPCI and pharmacological treatment. The protocol was approved by the local ethical committee, and all patients gave informed consent for the study. After pPCI, a 6 F sheath was left in the femoral artery of all patients and served as source for beat-to-beat SBP assessment. Both BP and 12-lead ECG signals recorded with the Mortara Surveyor system (Mortara Ltd, Bologna Italy and Milwaukee, USA) were sampled at 500 Hz, digitized and saved in the dedicated review station for off-line analysis.

The analysis of heart rate variability (HRV) was performed with the H-Scribe software (Mortara Ltd, Bologna Italy and Milwaukee, USA), assessing the traditional parameters [9] including standard deviation normal beat-to-normal beat (SDNN), root mean square successive difference (rMSSD) and percentage of normal-to-normal intervals differing from the preceding one >50 ms (pNN50). The analysis of BRS was made with the Heart Scope Software (AMPS Ltd, NY, USA). BRS was calculated with the sequence method [6, 7] as well as with the power spectral method. The methodology to assess BRS with the sequence method consists in assessing the slope of the linear relationship between systolic blood pressure and the subsequent RR-interval during series of ≥3 consecutive concomitant BP and RR increases or decreases. The former system provides BRS values for positive sequences, negative sequences, and overall. Positive sequences are those BRS sequences formed by increasing values of both blood pressure and RR-interval (i.e., those sequences in which blood pressure and RR-interval values increase concomitantly). Negative sequences are those in which blood pressure and RR-interval values decrease concomitantly from beat to beat. We have defined in the text BRS computation based on positive sequences as BRS+, while BRS computation based on negative sequences as BRS−. BRS, without any further specification is the average value derived from all BRS sequences.

BRS sequences were accepted with the following criteria:

- number of consecutive RR and SBP increases/decreases ≥3
- $|\Delta RR| \geq 5$ ms and $|\Delta SBP| \geq 1$ mmHg
- the slope of the regression line RR vs SBP has $r \geq 0.85$

The sequences were recorded 1, 3, 6, and 12 h after PCI. The analog signals were sampled at 500 Hz and digitized. This high frequency sampling leads to a very small and acceptable error in the determination of the RR interval making it appropriate for the evaluation of HRV also in case of expected SD values lower compared to the ones observed in this study. Once the RR values and systolic BP values were obtained, each hour period was divided into six 10-min periods and the corresponding six BRS values were obtained using a program leading always to 100 % accurate and reproducible results. The lowest and the highest BRS values were discarded and the remaining four were averaged to give the final value used for analysis. The choice of the segments to be used for the analysis was based on the operator. However, all choices were made by a single investigator and were very consistent and reproducible. We have assessed the reproducibility of the BRS values in 10 patients at 4 time points (overall 40 measures) and found that the 40 duplicate measures never differed more than 10 % and correlated with an r value of 0.97. A similar procedure was followed for the assessment of HRV, with the difference that the measures were derived from 5-min periods that showed a stationary heart rate. Overall, only segments that showed <5 premature beats per minute were accepted for the analysis.

ST segment resolution was evaluated as an index of tissue reperfusion after pPCI. ST segment deviation was assessed before and 3 h after pPCI in the lead showing the greatest ST displacement and ST resolution was considered complete if ST segment elevation had decreased ≥70 % [10]. Echocardiography was performed, with standard techniques, between 12 and 24 h after PCI.

Multivessel coronary disease was defined as the presence of a stenosis equal or greater than 70 % in one or more major epicardial coronary vessels, or surgical by-pass grafts, in addition to the infarct-related artery.

Statistical Analysis

The sample size calculation was based on the expected difference in BRS measured at 12 h between patients with ST resolution and patients without ST resolution. Our most recent study suggested an average BRS of 8.2±6.3 ms/mmHg [4]. We calculated that with 6.3 ms/mmHg SD, to detect a difference between the two groups of 5 ms/mmHg with α (two-tail) 0.05 and 90 % power, we required 17 patients in each group. However, since the ratio of patients with ST resolution/without ST resolution was around 2:1 on the basis of our experience, we decided to enroll 45 patients with valid tracings.

Continuous variables are presented as mean±SD and/or as median and interquartile range. Normality was assessed for all variables with the Kolmogorov–Smirnov test.

Comparisons were made by Student t test or Mann Whitney test, as appropriate. Categorical variables were described as frequencies and compared by chi-square test.

The behavior of the autonomic variables at 1, 3, 6, and 12 h was analyzed with ANOVA for repeated measures followed by Tukey tests for multiple comparisons. Multivariable models were constructed to assess the predictors of the 12-h value of BRS, of the change from 1 to 12 h, and of LVEF values.

Medcalc for Windows, Vers. 3.01 and SPSS for Mac Vers. 16.0 were used for the statistical analysis.

Results

Fifty-five eligible patients were screened for the study. Ten patients (18 %) were excluded because reliable values for BRS and HRV could not be obtained for every planned interval (1, 3, 6, 12 h). This occurred because of the presence of frequent atrial or ventricular arrhythmias or runs of atrial tachycardia/fibrillation or a damped or absent pressure waveform resulting from inadequate flushing of excessive bending of the intraarterial catheter. There was no complication related to the 12-h persistence of the catheter in the femoral artery in any patient. It should be underlined that leaving the femoral sheath for over 12 h was not done for the purpose of the study, being it the common practice after primary PCI in our center.

The characteristics of the 45 enrolled patients are shown in Table 1 that also shows the main variables related to the procedure. The evaluation of BRS with the sequence method proved to be possible in all 45 patients enrolled and was based on the average on 3.0 % of the overall number of beats, corresponding to an average of 31 measured sequences for each 1-h time period. The average value of BRS 1 h after PCI (see Table 2) was 10.7±6.2 ms/mmHg, resulting from an average of BRS+ of 11.6±7.8, and of BRS− of 10.2±5.9. The average values for SDNN, MSSD, and pNN50 were 55±41 ms, 68±42 ms, and 12.6±13.6 %, respectively (see Table 3). Tables 2 and 3 present also median values as well as the interquartile range for these autonomic markers, since most of them are positively skewed, although formal tests for deviation from normality show borderline significance only for baseline values of SDNN and pNN50. No autonomic variable was significantly correlated with age, although a weak trend was visible for a negative correlation between age and BRS (p=0.097).

Table 1 Clinical characteristics of the enrolled population

Male gender, *n* (%)	34 (76 %)
Age, years (mean±SD)	59±13
Hypertension (*n*, %)	25 (56 %)
Diabetes mellitus (*n*, %)	5 (11 %)
β-blocker treatment (*n*, %)	25 (56 %)
MI site, anterior, *n* (%)	19 (42 %)
Pain to balloon time, min (mean±SD)	3.5±1.4
Multivessel coronary disease (*n*, %)	19 (42 %)
Use of anti GP IIb/IIIa (*n*, %)	29 (64 %)
ST resolution present (*n*, %)	31 (69 %)
TIMI Flow III after PCI (*n*, %)	43 (96 %)
LVEF (%, mean±SD)	48±8
Peak CK (UI/L, mean±SD) [Median]	2129±1475 [1784]
Peak CK-MB (UI/L, mean±SD) [Median]	285±246 [248]

MI myocardial Infarction, *PCI* percutaneous coronary intervention, *LVEF* left ventricular ejection fraction

During the course of the observation from 1 to 12 h after PCI, BRS increased significantly to 13.2±6.0 ms/mmHg as a result of an increase in the baroreceptor gain of both positive and negative sequences (Table 2). On the other hand, no significant difference was observed in the three markers of heart rate variability analyzed (Table 3).

BRS at 1 h was not significantly different in men vs. women (10.9±6.3 vs. 10.1±6.0 ms/mmHg) in anterior vs. non-anterior MI (9.5±5.6 vs. 11.6±6.6 ms/mmHg), in single vessel vs. multivessel coronary artery disease, in patients treated <3.5 h vs ≥3.5 h from symptom onset, in patients treated and not treated with beta-blockers in the first 12 h as well as in patients with a peak CK value below or above the median value. The same pattern was found while comparing the BRS values observed at 12 h, with the exception of a lower BRS found in patients with anterior MI (10.9±5.1 vs 14.9±6.1 ms/mmHg, p=0.023, uncorrected for multiple comparisons).

In agreement with the goal of the study, we assessed whether BRS would be different between the group of patients with ST resolution following PCI (n=31) and the group of patients without ST resolution (n=14). Figure 1 shows the behavior of BRS in the two groups: they both start at similar average values, but while patients with ST recovery also have a recovery of BRS with values increasing from 10.9±6.4 to 15.4±5.2 ms/mmHg (p=0.03), patients with no ST resolution have a further depression in BRS from 10.4±6.0 to 8.4±4.8 ms/mmHg (p<0.001), a significantly divergent pattern (p<0.001). We assessed whether there was any difference in BRS recovery (expressed as the difference between BRS values 12 h after PCI and immediately after PCI) in several subgroups of patients on the basis of the site of myocardial infarction, of the culprit coronary artery, of the presence of single-vessel or multivessel coronary disease, and on the basis of the peak CK value (dichotomized by the median value). None of these comparisons yielded a statistically significant p value (all >0.1). BRS recovery was numerically, but not significantly lower in the seven patients (16 %) who did not receive statins in the first 12 h, compared with the remaining patients (−1.8±2.1 ms/mmHg vs. +3.5±1.5 ms/mmHg, p=0.11).

Multivariable models were constructed to assess the predictors of the 12 h value of BRS and of the change from 1 to

Table 2 Baroreflex sensitivity values

Time	BRS^{+} (ms/mmHg)	BRS^{-} (ms/mmHg)	Overall (ms/mmHg)
1 h (mean±SD)	11.6±7.8	10.2±5.9	10.7±6.2
Median (interquartile range)	10.5 (5.7–16.1)	9.5 (5.6–13.3)	10.5 (5.7–14.4)
3 h (mean±SD)	12.1±7.8	11.6±7.4	11.7±7.2
Median (interquartile range)	11.0 (7.0–14.7)	11.2 (5.4–15.5)	11.2 (6.2–15.2)
6 h (mean±SD)	12.4±7.4	12.9±6.5	12.7±6.4
Median (interquartile range)	9.7 (7.0–16.8)	12.0 (7.2–18.8)	12.7 (7.9–17.9)
12 h (mean±SD)	13.5±7.0	13.2±6.4	13.2±6.0
Median (interquartile range)	12.4 (8.7–15.9)	12.2 (8.3–17.6)	12.6 (8.5–17.0)
P value (ANOVA for repeated measures)	0.22	0.016	0.020

BRS^{+} Baroreflex sensitivity values for positive sequences, *BRS^{-}* Baroreflex sensitivity values for negative sequences

12 h. In both cases, the variables entered in the model were as follows: age, gender, site of MI (anterior/non anterior), pain to balloon time, LVEF, and ST resolution. ST resolution was shown to be the only independent predictor with a p value of 0.005 for 12 h BRS values and of 0.002 for the difference in BRS between 1 and 12 h. None of the other variables showed any predictive power (all p values >0.1).

Discussion

This study was the first, to our knowledge, to directly assess BRS in the initial hours after an acute myocardial infarction. The data show that despite the multiple inputs originating by acute ischemia, the baroreceptor reflex remains efficient already in the first hour after PCI. Furthermore, this reflex can be reliably quantitatively assessed with the sequence technique. The main finding is the demonstration of a very early separation between BRS recovery and BRS worsening associated, respectively, with a favorable or an unfavorable myocardial tissue perfusion following PCI. This early divergence is likely to carry an important prognostic role and to contribute to different clinical outcomes [1, 2, 4].

Presence of Active Baroreflex Control During Acute MI

This study shows that BRS sequences are present in all patients even in the first hour following PCI for an acute myocardial infarction, indicating that the baroreceptor control is altered but not lost in this condition. On the contrary, Airaksinen et al. [11] suggested the persistence of baroreceptor modulation of heart rate in only 59 % of patients undergoing coronary angioplasty.

Our finding of the persistence of this reflex regulation has potentially important consequences since elevated vagal activity or reflexes reduce the risk of malignant arrhythmias [12, 13] and increased the hemodynamic tolerability of ventricular tachycardia [14].

Clinical Correlates and Pathophysiology of BRS During Acute MI

BRS 1 h after PCI was similar in men and women (all postmenopause), anterior and non-anterior MI, single vessel and multivessel disease. At variance with markers of HRV, BRS increased significantly between 1 and 12 h by 23 % in the overall population. This rapid variation in BRS and its relationship with tissue myocardial perfusion appears in agreement with our hypothesis [15] that depressed BRS could be

Table 3 Heart rate variability values

Time	SDNN (ms)	MSSD (ms)	pNN50 (%)
1 h (mean±SD)	55.4±41.5	67.7±42.2	12.6±13.6
Median (interquartile range)	39.0 (32.0–64.0)	61.0 (38.5–83.0)	8.5 (2.0–15.0)
3 h (mean±SD)	49.1±32.1	65.0±35.2	12.5±13.2
Median (interquartile range)	37.5 (27.5–59.5)	58.0 (43.0–83.5)	9.0 (2.5–17.5)
6 h (mean±SD)	49.3±27.6	65.1±32.0	12.4±13.5
Median (interquartile range)	42.5 (27.0–63.0)	63.0 (39.8–83.0)	7.0 (2.0–18.3)
12 h (mean±SD)	47.4±26.0	67.2±28.1	13.7±16.6
Median (interquartile range)	42.0 (28.8–61.0)	61.0 (44.0–85.8)	8.0 (2.5–17.0)
P value (ANOVA for repeated measures)	0.11	0.59	0.53

SDNN standard deviation normal beat to normal beat, *MSSD* mean square successive difference, *pNN50* percentage of normal-to-normal intervals differing from the preceding one >50 ms

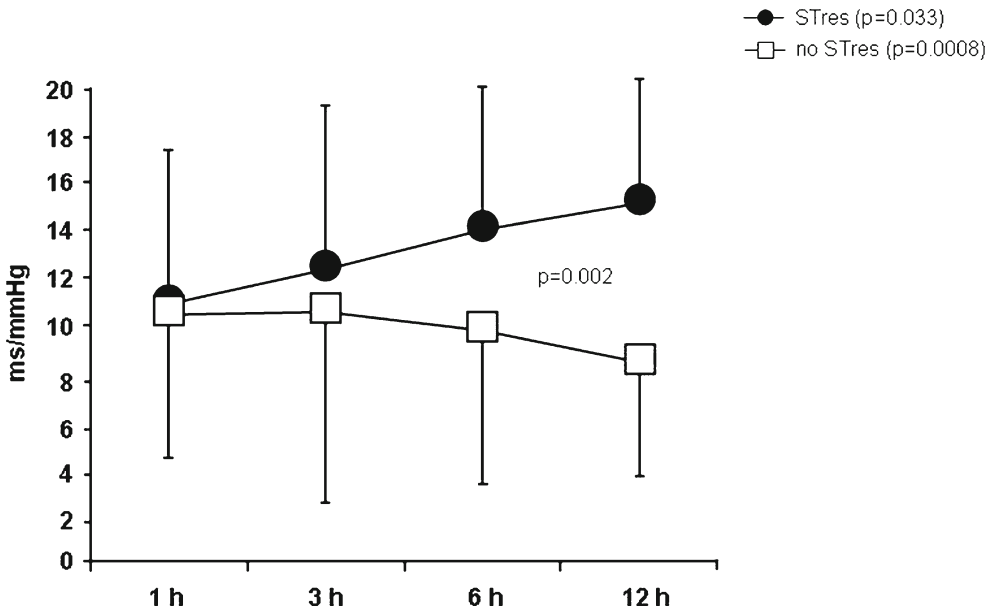

Fig. 1 Baroreflex sensitivity pattern in patients with (*full circles*) and without (*empty squares*) ST resolution. *STres* ST resolution present (ST decrease ≥70 % 3 h after PCI), *no STres* ST resolution absent

related to augmented afferent input from the altered geometry of left ventricle, a possibility confirmed by subsequent experimental studies [16].

Relationship Between Vagal Activity and Myocardial Perfusion

Mortara et al. [3] showed that BRS, evaluated on the average 17 days after MI, was higher among patients with patent infarct-related artery. Bonnemeier et al. [17] studied heart rate turbulence (HRT) in patients undergoing pPCI and found that turbulence onset and slope (but not turbulence timing) were "improved" in the first 24 h among patients with TIMI 3 flow but not among patients with TIMI 2 flow. HRT measurement requires the presence of spontaneous premature ventricular complexes (PVCs). Despite the fact that just two PVCs were considered sufficient to measure HRT in their study, many patients (37 %) could not be assessed. Also, average pain-to-balloon time was 7 h not reflecting current practice and guidelines. The present study markedly extends the significance and the reliability of the conclusions by Bonnemeier et al. [17]. We assessed BRS directly rather than a surrogate marker. We enrolled a population of STEMI patients treated within current standards (3.5 h average pain to balloon time) and excluded only 18 % of patients, mostly because of the presence of very frequent arrhythmias. Also, the BRS values shown are the average of a very high number of reflex sequences each, thus providing an accurate estimate. Finally, ST resolution, a more reliable marker than TIMI flow, was used to identify adequate tissue perfusion after PCI [18]. Interestingly, a recent experimental study shows that depressed BRS is associated with reduced angiogenesis in the ischemic myocardium [19]. This finding, associated with our own, suggests the possibility of a vicious circle by which reduced tissue perfusion depresses BRS, which in turn hinders an improvement in perfusion.

Relationship Between Vagal Activity and Reperfusion Damage

The effects of vagal activity on the consequences of ischemia and reperfusion have recently become an argument of great interest. Vagal activity has been shown experimentally to produce profound anti-inflammatory effects, in the context of the so-called vagal anti-inflammatory reflex first described by Tracey [20]. Accordingly, in reperfused myocardial infarction, vagal stimulation markedly limits the inflammatory response and infarct size [21]. Vagal reflexes play a major role in the protective effect achieved by remote ischemic conditioning [22, 23] a new attractive cardioprotective technique [24]. Also, the feasibility of direct electrical vagal stimulation in man [25–27] may now offer the opportunity of increasing parasympathetic activity at the time of coronary reperfusion by angioplasty, a novel concept that is worth testing [28].

Prognostic Implications

Abundant data support the protective role of vagal activity against life-threatening ventricular arrhythmias particularly in the setting of myocardial ischemia [12, 13, 29] or reperfusion [30]. Clinically, La Rovere et al. and Farrell et al. [31, 32] suggested, over 20 years ago, that depressed baroreflex sensitivity correlated with an increased incidence of life-

threatening ventricular arrhythmias in the first 1 to 2 years after myocardial infarction. Among remote post-MI patients, depressed BRS is similarly correlated with a greater probability of ventricular tachycardia [33] as well as with a higher risk for hemodynamic deterioration during the tachycardia [14]. Recently, attenuated recovery of heart rate turbulence (an autonomic marker strongly related to BRS) in the first weeks after MI was associated with a 9.4-fold higher risk of sustained ventricular tachycardia or fibrillation [34]. In the accompanying editorial, Hirose [35] advocates the opportunity to assess whether a recovery of heart rate turbulence and BRS may occur also in an earlier phase of MI. The present study suggests that recovery of BRS may indeed occur very early on and that knowledge about this process may help in tailoring the therapeutic approach to the single patient.

Potential Limitations

We deliberately did not enroll patients in Killip classes III and IV, for since these patients are often treated with intraortic balloon pump, positive airway pressure and IV amines, conditions that alter the autonomic balance and the relationship between blood pressure and heart rate. Furthermore, while it is known that patients in Killip class III and IV have an unfavorable prognosis, it is among the group of patients with relatively good prognosis that we have recently shown that a low BRS identifies a subset of patients at very high long-term risk [4]. The present data suggest that it is possible to identify these patients as early as 24 h after MI.

The study did not have adequate power to assess whether early depression of BRS has prognostic value that is additive to that provided by the usual risk predictors. However, the goal of this pilot study was to demonstrate, for the first time, that it is possible to evaluate BRS in the first hours after MI and to assess its behavior relative to tissue reperfusion.

Conclusions

This study provides the first evidence that baroreflex sensitivity can be reliably assessed in the early hours after myocardial infarction. The findings indicate that the baroreflex is efficient and that within 12 h of reperfusion, it increases its gain modestly, but significantly as a result of two divergent behaviors: a marked increase in patients with effective myocardial tissue reperfusion and a significant decrease among patients without effective myocardial reperfusion.

The determination of baroreflex sensitivity very early after myocardial infarction may help in risk stratification and tailored therapeutic approach to patients with myocardial infarction.

Conflict of Interest Doctor De Ferrari G.M. declares that he is a Member of the Steering Committee of a cardiovascular medical device trial sponsored by Boston Scientific. Professor Schwartz P.J. declares that he is serves as consultant to BioControl Medical Ltd. Doctors Sanzo A., Castelli G.M., Turco A., Ravera A., Badilini F. declare that they have no conflict of interest.

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