

Baroreflex Sensitivity Predicts Long-Term Cardiovascular Mortality After Myocardial Infarction Even in Patients With Preserved Left Ventricular Function

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Objectives	This study sought to assess the long-term predictive power of depressed baroreflex sensitivity (BRS) among post-myocardial infarction (MI) patients with preserved left ventricular function.
Background	Risk stratification after MI is primarily performed by identifying patients with depressed left ventricular ejection fraction (LVEF) because of their greater mortality. Autonomic markers can help refining risk stratification. Depressed BRS (<3 ms/mm Hg) correlated with cardiovascular mortality in 1,284 post-MI patients during a 21-month follow-up in the multicenter ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study, but had no significant predictive power in patients with LVEF >35% or above age 65 years.
Methods	Two hundred forty-four consecutive post-MI patients (age 59 ± 10 years) with LVEF >35% (average $54 \pm 8\%$) were enrolled. They underwent a complete assessment, including BRS 4 weeks after MI.
Results	During a 5-year mean follow-up, 14 (5.7%) patients died of cardiovascular causes. Multivariate analysis identified BRS ($p = 0.0001$), but not LVEF and age, as predictive of cardiovascular mortality. The relative risk (95% confidence interval [CI]) for depressed BRS was 11.4 (95% CI 3.3 to 39.0) for the overall population, 19.6 (95% CI 4.1 to 94.8) for patients ≤ 65 years, and 7.2 (95% CI 1.3 to 39.9) for patients above age 65.
Conclusions	Even among the large number of low-risk post-MI patients with preserved left ventricular function, depressed BRS identifies, independently of age, a subgroup at long-term high risk for cardiovascular mortality in which more aggressive preventive strategies should be considered. (J Am Coll Cardiol 2007;50:2285-90) © 2007 by the American College of Cardiology Foundation

Despite significant progress, risk stratification after myocardial infarction (MI) is still less than optimal. Most efforts have obviously and successfully focused on the high-risk groups, especially on the patients with depressed left ventricular ejection fraction (LVEF). However, as cleverly pointed out by Myerburg and Castellanos (1), such an approach identifies patients with a high risk for cardiovascular mortality, which is laudable, but because it does so only in a small fraction of the general population of post-MI patients, the number of absolute deaths

involved is actually small. To make an impact on overall cardiovascular mortality it would be necessary to identify individuals at increased risk among the much larger population at relatively low risk. This is what we attempted to do in the present study.

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Aside from depressed LVEF, several additional risk predictors have been proposed and validated, and among them significant prognostic value had been provided by autonomic markers (2), including baroreflex sensitivity (BRS) (2,3), heart rate variability (2,4), and heart rate turbulence (5). The background and rationale for these studies lies in the tight relationship between autonomic imbalance (i.e., increased sympathetic activity and/or decreased vagal activity) and life-threatening arrhythmias shown by a wealth of experimental (6-8) and clinical

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Manuscript received June 1, 2007; revised manuscript received July 9, 2007, accepted August 6, 2007.

Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
BRS	= baroreflex sensitivity
CI	= confidence interval
ECG	= electrocardiogram
IQR	= interquartile range
LV	= left ventricular
LVEF	= left ventricular ejection fraction
MI	= myocardial infarction
SDANN	= standard deviation of the average RR interval

studies (9–12). Among these, the largest was the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study (9,10), which showed that depressed BRS was associated with increased cardiac mortality over a 21-month follow-up period. However, the predictive value of depressed BRS did not reach statistical significance among patients over 65 years of age and among patients with preserved left ventricular (LV) function (LVEF >35%). This latter finding left a question about the potential of depressed BRS to help identify individuals at high risk within a

large low-risk population.

Accordingly, the present prospective study was designed to assess, during long-term follow-up, the predictive role of depressed BRS in the largest group of post-MI patients, namely those with preserved LV function who are at low risk of cardiac death.

Methods

This was a single-center prospective study enrolling patients discharged from the hospital in the years 1999 to 2000 after an acute MI with preserved LV function (LVEF >35%). The diagnosis of acute MI was based on clinical course, serum creatinine kinase levels, and electrocardiogram (ECG) findings of ST-segment elevation.

All patients with an ST-segment elevation MI were scheduled for a follow-up outpatient visit at our post-MI clinic 30 to 40 days after MI. Only patients who could not come for the regular visits (usually because of logistical reasons such as distance from the hospital) or who underwent a surgical revascularization followed by a rehabilitation phase in specialized centers did not follow this schedule (these cases together represent <10% of the population). All consecutive patients presenting at the post-infarction clinic after an ST-segment elevation MI in the years 1999 to 2000 (n = 468) were screened for eligibility in the study. Exclusion criteria were: LVEF ≤35%, advanced valvular heart disease, unstable angina or congestive heart failure, atrial fibrillation or abnormal sinus node function, arterial blood pressure above 160/90 mm Hg at the time of BRS determination and any disease limiting survival, or refusal to give informed consent to the study. During the outpatient visit, the enrolled subjects underwent measurement of LV function by means of echocardiography, followed by autonomic assessment.

Autonomic assessment. The protocol was the same as used in previous studies (13–15). Patients were studied while supine at rest in a quiet temperature-controlled room,

3 h after a light meal, and they were asked to relax and to avoid talking and sleeping. The ECG recording was started after 10 to 15 min of acclimatization. The analog ECG signal was digitized at 500 Hz, and the QRS complex was recognized by cross-correlation with a template chosen by the investigator. A 10-min recording was performed and used to derive the standard deviation of the average RR interval (SDANN).

For the BRS assessment, phenylephrine (2 to 4 μg/kg) was given intravenously by at least 3 bolus injections, separated by ≥10-min intervals, to increase systolic arterial pressure by 15 to 40 mm Hg (in most cases 15 to 30 mm Hg) (3,16). Beat-to-beat systolic arterial pressure was measured noninvasively by means of infrared plethysmography with a finger cuff (Finapres 2300, Ohmeda, Finapres Medical Systems, Amsterdam, the Netherlands). Several thousand tests have been performed by our group with this protocol producing only rare, transient, and minor side effects (such as horripilation or mild headache). No serious or significant side effect has ever occurred. Custom-made software was used for detection of QRS and blood pressure signal and for calculating BRS as the slope of the regression line correlating systolic blood pressure and RR interval changes after phenylephrine injection. Baroreflex sensitivity was considered depressed, similar to previous studies (10), if it was <3 ms/mm Hg.

Statistical analysis. Continuous variables are presented as mean ± standard deviation or as median and interquartile range (IQR) for non-normal variables. Comparisons were made by Student *t* test or Mann-Whitney *U* test, as appropriate. Categorical variables were described as frequencies and compared by the Fisher exact test (2-tailed). The BRS was dichotomized using the pre-specified and validated (10) cutoff value of 3 ms/mm Hg. To compare its predictive value with that of LVEF, the latter was dichotomized using 45% as the cutoff value in some analyses. The pre-specified primary end point of the study was cardiovascular mortality; the secondary end point was all-cause mortality.

The main analyses were performed for the entire population as well as for the 2 pre-specified age subgroups (≤65 and >65 years). Kaplan-Meier estimates of event-free survival were plotted and compared by the log-rank test. The Cox proportional hazards model was used to evaluate the predictive value of BRS, LVEF (both continuous and dichotomized), age, and site of infarction on cardiovascular mortality. Further analyses were performed adding, as an additional factor to the model that included age, BRS, and LVEF, one of the following variables: gender, SDANN, beta-blocker use, angiotensin-converting enzyme (ACE) inhibitor use, and diuretic use.

Statistica 6.1 (StatSoft, Tulsa, Oklahoma) was used for the analysis. A value of *p* < 0.05 was considered significant.

Results

Study population characteristics. The study enrolled 244 patients who met the inclusion/exclusion criteria and signed the informed consent (mean age 59 ± 10 years) (Table 1). As expected from the inclusion criteria, the average LVEF was normal ($54 \pm 8\%$). The median BRS was 6.9 ms/mm Hg in the entire population. It was higher among patients ages ≤ 65 years (median 7.6 ms/mm Hg, IQR 5.0 to 10.9 ms/mm Hg) compared with patients > 65 years old (median 5.3 ms/mm Hg, IQR 2.8 to 7.7 ms/mm Hg, $p < 0.0001$). A moderate negative correlation was found between BRS and age ($r = 0.39$, $p = 0.0001$). Patients with depressed BRS (i.e., < 3 ms/mm Hg) were 35 of 244 (14%). This occurred more frequently among patients > 65 years (21 of 76, 28%) compared with younger patients (14 of 168, 8%, $p = 0.0001$). An LVEF $< 45\%$ was present in 11% (28 of 244) of the overall population, and tended to be more frequent among the older than the younger patients (15 of 76, 20% vs. 13 of 168, 8%, $p = 0.06$). Ninety-eight percent of patients were treated with aspirin, 84% with beta-blockers, 62% with ACE inhibitors, and 19% with diuretics. Beta-blockers were given to 91% of patients with depressed BRS and 83% of patients with preserved BRS.

Follow-up and survival analysis. The average follow-up was 61 ± 19 months. During this period, 19 patients (7.8%) died. The primary end point of the study, cardiovascular death, occurred in 14 patients (5.7%). Cardiovascular death occurred in 4.2% of men and 11% of women ($p = 0.09$); in 6.1% of reperfused versus 4.6% of nonreperfused patients ($p = 0.65$); in 4.6% versus 12.1% of patients treated and not treated with beta-blockers, respectively ($p = 0.11$); in 7.8% versus 3.2% of patients treated and not treated with ACE inhibitors, respectively ($p = 0.24$); and in 16.1% versus 3.7% of patients treated and not treated with diuretics, respectively ($p = 0.02$).

The patients who died of cardiovascular causes, when compared with survivors, had similar LVEF ($52 \pm 9\%$ vs. $54 \pm 8\%$, $p = 0.26$) and prevalence of reperfusion (78% vs.

72%), but tended to be older (64 ± 8 years vs. 58 ± 11 years, $p = 0.06$). They also had a slightly but significantly lower SDANN: median 18.5 ms (IQR 12.4 to 37.1 ms) versus 30 ms (IQR 22.3 to 40.3 ms), $p = 0.03$. Compared with survivors, patients with a primary end point had a markedly lower BRS: median 2.6 ms/mm Hg (IQR 1.6 to 5.2 ms/mm Hg) versus 7.0 ms/mm Hg (IQR 4.5 to 10.3 ms/mm Hg), $p = 0.0002$. Cardiovascular mortality was significantly and strikingly greater among patients with depressed BRS, as shown in Figure 1, which illustrates the progressive divergence of the 2 survival curves. Cardiovascular mortality for patients with depressed BRS was much greater in the overall population and in the 2 different age subgroups (Fig. 2). On the other hand, no difference in cardiovascular mortality was found by comparing patients with LVEF between 35% and 45% ($n = 28$) versus $\geq 45\%$ ($n = 216$). Multivariate analysis of predictors of cardiovascular mortality was performed entering in the model age, gender, site of infarction, LVEF (both continuous and dichotomic), and BRS. This analysis identified depressed BRS as the sole statistically significant predictor ($p = 0.0001$). The relative risk and 95% confidence interval (CI) associated with depressed BRS was 11.4 (95% CI 3.3 to 39.0, $p = 0.0001$) for the overall population, 19.6 (95% CI 4.1 to 94.8, $p = 0.0002$) for patients ≤ 65 years old, and 7.2 (95% CI 1.3 to 39.9, $p = 0.02$) for patients > 65 years old.

All-cause mortality was also significantly higher among patients with depressed BRS, as shown in Figure 3. Multivariate analysis of predictors of all-cause mortality identified depressed BRS as the sole statistically significant predictor with a relative risk of 4.9 (95% CI 1.8 to 13.4, $p = 0.002$).

Discussion

The present study provides the first evidence that an autonomic marker, depressed BRS, is a powerful predictor of long-term cardiovascular mortality after MI even among the large population of patients with well-preserved LV function generally considered to be all at low risk. This predictive power was not limited to specific age groups because it was also present among older patients. These data markedly extend our previous findings (10) and may pave the way toward targeted aggressive preventive strategies for selected patients within the vast population generally thought to be at low risk.

Post-MI prognosis and the role of depressed BRS. The current approach for primary prophylaxis after MI focuses on patients with depressed LV function (17). However, the use of a single risk predictor, especially one burdened by a large measurement error, as occurs with LVEF (18), has 2 significant drawbacks (19). On the one hand, not all patients with depressed LVEF are truly at high risk (19), as suggested also by the relatively low mortality of those with well-preserved BRS (10). On the other hand, a significant minority of patients with an LVEF above 30% to 35% may be at high risk and are not correctly identified (19). Because the

Table 1 Characteristics of the Enrolled Patients

Patients	244
Men	190 (78%)
Age (yrs)	59 ± 10
Infarct site	
Anterior	107 (44%)
Nonanterior	127 (56%)
Reperfusion therapy	
Primary PCI	91 (37%)
Pharmacological	89 (37%)
None	64 (26%)
LVEF (%)	54 ± 8
BRS (ms/mm Hg)	
Mean \pm SD	8.2 ± 6.3
Median	6.9

BRS = baroreflex sensitivity; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

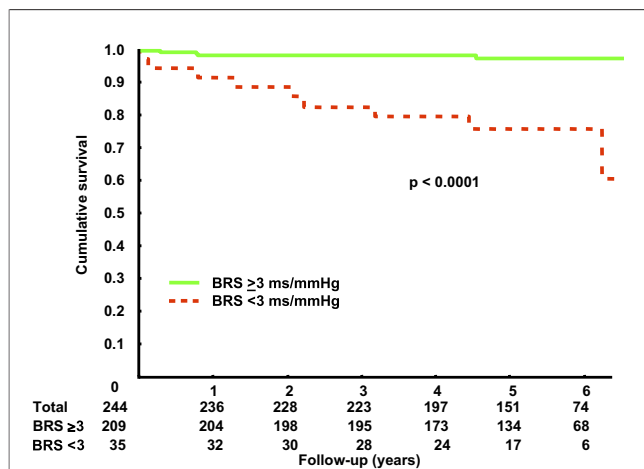


Figure 1 Survival Curve for Freedom From Cardiovascular Death

Kaplan-Meier event-free survival curves relative to the primary end point (cardiovascular death) in the 2 groups of patients. **Broken red line** = patients with depressed baroreflex sensitivity (BRS); **solid green line** = patients with preserved BRS.

total number of patients with preserved LV function after MI greatly exceeds that of patients with depressed LV function, this approach actually fails to identify the majority of patients at risk for cardiovascular mortality in the follow-up.

This study was indeed designed to assess whether a depressed BRS could be of value in identifying the subgroup at relatively higher long-term risk among post-MI patients deemed to be at low risk because of preserved LV function.

The prognostic value of depressed BRS had been suggested first in an established animal model of sudden cardiac death (6,20) and subsequently in 2 relatively small clinical studies (9,21). It was then conclusively shown by the ATRAMI study (10), which showed that depressed BRS (<3 ms/mm Hg) significantly predicts cardiac mortality. However, during the 21-month average follow-up, despite a trend toward possible differences, BRS failed to reveal a different mortality risk among patients with either age >65 years or LVEF >35%. For this reason we decided to focus our attention on patients with preserved LV function, who in the current era of aggressive reperfusion constitute the vast majority of the population, and to study them over a long follow-up period. We found depressed BRS to be an extremely powerful predictor of cardiovascular mortality over the long term in this low-risk population of patients. Two additional clinical features were found to be unequally distributed among patients with and patients without cardiovascular mortality. They were the SDANN (a time-domain measure of heart rate variability, largely an expression of vagal tone) that was lower among patients with cardiovascular death, and the use of diuretics that was more frequent among patients with cardiovascular death. Neither of these variables had a predictive power at multivariate analysis.

Cardiovascular mortality among patients with depressed BRS was 26%, compared with 2.4% in the remaining population, with a relative risk of 11.4. This predictive role was present also in patients >65 years of age who had a relative risk of 7.2. Thus, depressed BRS correctly identifies patients at high risk for cardiovascular events over the long term, independently of age, gender, site of infarction, and LV function, within patients with normal or mildly depressed ejection fraction. The statistical power of the multivariate and of the subgroup analyses was somewhat reduced by the relatively small number of cardiovascular deaths.

Importantly, the survival curves of patients with normal or depressed BRS continue to diverge over the long term. This points to the fact that BRS provides information on an individual characteristic likely to maintain its predictive value over time. This observation raises the intriguing possibility that the level of BRS may represent a genetic trait, a sort of autonomic fingerprint containing information on the likelihood of developing life-threatening events especially during an acute ischemic episode. This autonomic fingerprint would provide information valid even over extended periods of time. Two independent sets of data already support this concept. Increases in BRS induced by exercise training are associated with a significant protection from cardiovascular mortality over a period of 10 years (22). Heart rate changes during an exercise stress test in healthy subjects carry information predictive for the risk of sudden cardiac death over 2 decades (23).

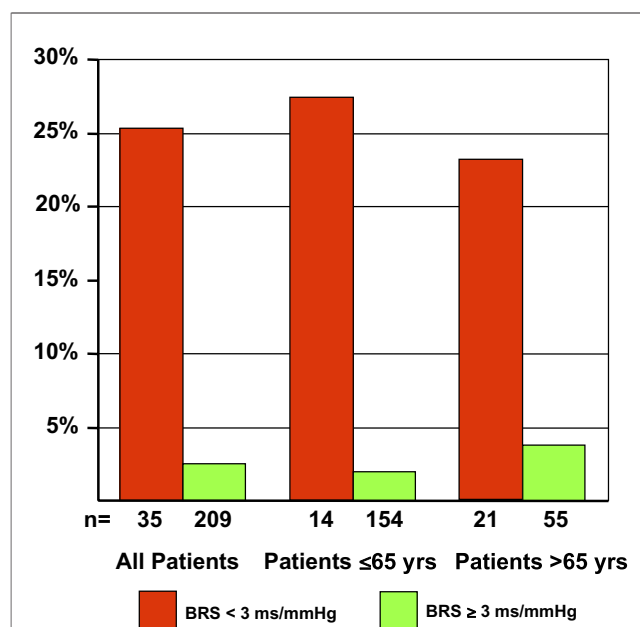


Figure 2 Occurrence of Cardiovascular Death on the Basis of Age and BRS

Cardiovascular mortality on the basis of baroreflex sensitivity (BRS) in the different age groups. The number of patients in each group is listed below the bar. **Red bars** = patients with depressed BRS; **green bars** = patients with preserved BRS.

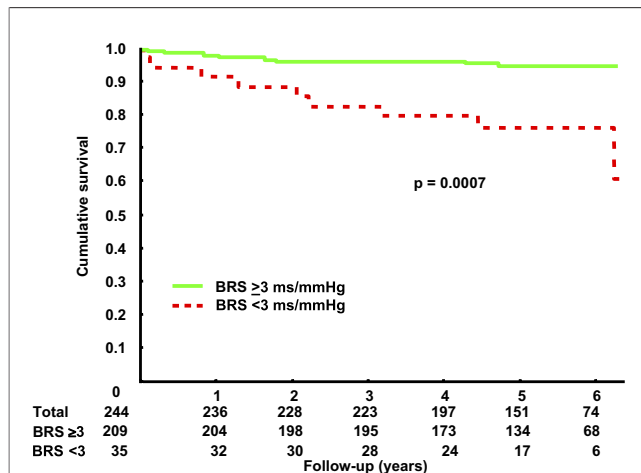


Figure 3 Survival Curve for Freedom From All-Cause Mortality

Kaplan-Meier survival curves in the 2 groups of patients for total mortality.
Broken red line = patients with depressed baroreflex sensitivity (BRS); **solid green line** = patients with preserved BRS.

Taken together, these studies and the present results strongly suggest, as previously proposed (24), that the individual autonomic make-up is at least in part genetically controlled and that, accordingly, the analysis of meaningful autonomic parameters may be of prognostic value also for events distant in time.

Depressed BRS and increased cardiovascular mortality. Multiple mechanisms contribute to the explanation of the strong association between low BRS values and increased mortality.

A post-MI depressed BRS suggests that sympathetic activity is increased (either in absolute or in relative terms) and/or unopposed by adequate vagal activity, thus identifying a shift of the autonomic balance toward a sympathetic predominance (3). The deleterious role of increased sympathetic activity in triggering cardiovascular mortality by a variety of mechanisms is well recognized (25). Also, abundant data support the protective role of vagal activity against life-threatening ventricular arrhythmias, particularly in the setting of myocardial ischemia (26,27). Indeed, animal experiments indicate that the presence of adequate vagal reflexes may represent the main mechanism preventing ventricular fibrillation during acute myocardial ischemia (28). Among post-MI patients, depressed BRS is also correlated with a greater probability of ventricular tachycardia and with a higher risk of hemodynamic deterioration during the tachycardia (15).

Depressed BRS post-MI may be a marker of increased neurohormonal activation, a condition favoring LV remodeling and the development and progression of heart failure (29). This concept has played a role in the ongoing assessment of the effects of vagal stimulation in patients with heart failure (30). Finally, unopposed sympathetic activity may also facilitate myocardial ischemia by increasing

shear stress and by increasing the propensity of platelets to aggregate (25).

Potential implications. The most relevant potential implication of these findings is represented by the novel opportunity to implement preventive measures destined to affect truly large numbers of individuals. Indeed, they indicate that it is possible to identify, even among low-risk post-MI patients with preserved LV function and with an overall cardiovascular mortality just above 1% per year, a group with 5-year mortality of 25%. These persons deserve a targeted and more aggressive approach.

Beta-blockers with doses adequate to counter the early morning surge in sympathetic activity, ACE inhibitors, and dual antiplatelet treatment (31) should all be considered for the pharmacological approach. Exercise training may have a special role for post-MI patients with depressed BRS. Exercise-induced increases in BRS post-MI are associated with reduced risk for sudden death both experimentally (32) and clinically (22), provided that it produces an adequate shift of the autonomic balance toward an increase in vagal activity. For patients with persistence of depressed BRS despite exercise training, further stratification of arrhythmic risk, including microvolt T-wave alternans (33), may be warranted.

Conclusions

Among post-MI patients with preserved LV function, representing the large group at very low risk, those with depressed BRS have a high incidence of cardiovascular mortality during long-term follow-up irrespective of age and of site of MI. Their risk for cardiovascular death is more than 11 times higher than that of patients with preserved BRS. For their protection, a more aggressive preventive strategy should be considered.

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