Risk stratification after myocardial infarction: a new method of determining the neural component of the baroreflex is potentially more discriminative in distinguishing patients at high and low risk for arrhythmias

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Aims We hypothesize that the neural component (NC) of the baroreflex sensitivity (BRS) is a better risk stratifier for ventricular tachycardia/fibrillation (VT/VF) than conventional BRS itself, because it is both independent of vessel wall stiffness and can be measured non-invasively.

Methods and results NC was determined by correlating spontaneous carotid artery diameter variations with R–R interval variations using spectral analyses. In consecutive outpatient populations with chronic coronary artery disease the ability of the NC to distinguish post-myocardial infarction (MI) patients at risk for VT/VF (post-MIHIGH RISK) from post-MI less prone to arrhythmias (post-MILOW RISK) was compared with the pressure-derived BRSphenyl and BRSspectral method. Ninety-six patients, i.e. 28 post-MILOW RISK, 28 post-MIHIGH RISK [a LVEF (left ventricular ejection fraction) <30% and/or history of VT/VF], and 40 healthy controls were enrolled. With NC, rather than with BRS methods, median values for post-MIHIGH RISK were smaller than for post-MILOW RISK patients (NC, \( P = 0.03 \); BRSspectral, \( P = 0.35 \); BRSphenyl, \( P = 0.63 \)). Variability of R–R interval (LF = 0.04–0.15 Hz) was significantly larger in the control group than in the post-MIHIGH RISK and post-MILOW RISK group (\( P < 0.01 \) and \( P < 0.01 \)). To separate post-MIHIGH RISK from post-MILOW RISK patients, a linear combination of age and the logarithm of the NC measurement was constructed as a risk index. By optimizing the intercept of this line, an optimal sensitivity and specificity pair was determined. The sum of optimal specificity and sensitivity was higher for NC (155) than for BRSspectral (133) and BRSphenyl method (132). With all methods, values for post-MI patients were significantly smaller than for controls.

Conclusion NC may be superior to conventional BRS measures in identifying post-MI patients at high risk for VT/VF.

Introduction

The primary aim of this retrospective pilot study is to compare the ability of the NC of the baroreflex with that of conventional BRS measures to distinguish between post-myocardial infarction (MI) patients with an accepted indication for primary or secondary preventive implantable cardioverter-defibrillator (ICD) therapy [i.e. LVEF (left ventricular ejection fraction) <30%; or survived ventricular tachyarrhythmic events] and post-MI patients who did not fulfil these criteria. In addition it was examined: (i) whether neural control of the heart is decreased in post-myocardial patients compared with controls; (ii) whether this decrease is greater in post-MI patients, who are vulnerable for ventricular fibrillation than those who are not; and (iii) whether the NC is better able to distinguish between post-MI groups and controls than conventional measures of BRS. This methodologic study was performed in consecutive coronary artery disease (CAD) patients selected during the chronic phase of the disease.
Currently the best risk stratifier for post-MI patients is LVEF.\textsuperscript{1,2} To further increase specificity and sensitivity, there is a need for additional risk stratifiers, which can be used in combination with LVEF. In particular, measures reflecting cardiac autonomic activity such as heart rate variability (HRV), and baroreflex sensitivity (BRS), as well as newer parameters such as heart rate turbulence and deceleration capacity of heart rate have yielded promising results in this regard.\textsuperscript{1,3–7}

In most clinical studies, BRS has been defined as the linear component of the relation between changes in pressure and changes in R–R interval, expressed as change in R–R interval per change in arterial pressure (ms/mmHg). First, arterial pressure changes cause stretch and thus diameter changes of the aortic arch and the carotid body. This relationship is influenced by vascular wall stiffness.\textsuperscript{8,9} Secondly, these diameter changes induce changes in the output of stretch-sensitive nerve cells in these vessel walls. These changes in output are translated by the autonomic nervous system into vagal outflow to the heart influencing R–R interval duration. BRS is smaller if the vessel wall is stiffer and although the vessel wall becomes stiffer with age\textsuperscript{10} not all aged persons will suffer arrhythmic events. Although vessel wall stiffness is correlated with coronary heart disease and stroke,\textsuperscript{11} it is not yet known to our knowledge if it is correlated with arrhythmias. The NC is defined as the relationship between the diameter changes (input) and R–R interval changes (output). The NC is not influenced by absolute diameter changes and vascular wall stiffness, if assessed during spontaneous rather than drug induced pressure changes, which is within the linear part of the relation between stretch and BRS activity.\textsuperscript{8,9} It is known that deterioration of the neural components (NCs) of the baroreflex is responsible for the decrease of BRS in post-MI patients and is correlated with the occurrence of ventricular arrhythmias.\textsuperscript{4,12–15} Therefore, by excluding the mechanical component of BRS (i.e. the pressure/stretch component), one can postulate that the remaining NC (i.e. the stretch/R–R component) is a more reliable predictor of arrhythmia risk in post-MI patients. Furthermore, peripheral finger pressures (Finapress\textsuperscript{TM}), used in most BRS methods, are not a precise representation of carotid pressures, especially with advancing age.\textsuperscript{16–18}

In contrast to the conventional BRS measure, where an injection of a vasoconstrictor is necessary, the assessment of the NC can be performed non-invasively by extending the routinely performed cardiovascular ultrasound measurements to assess spontaneous vessel wall diameter changes. Using long recordings of carotid wall movements and simultaneous measurements of arterial pressure and ECG signal, the relation between arterial pressure and carotid diameter (vessel wall component BRS) and carotid diameter and R–R interval (NC BRS) as well as total BRS can be determined non-invasively\textsuperscript{4,9,19,20} in the low-frequency (LF) range (0.04–0.15 Hz),\textsuperscript{21} where baroreflex modulation of heart rate occurs.\textsuperscript{22–24}

**Methods**

**Study population**

In 2003, consecutive patients scheduled for a regular follow-up visit to undergo clinical assessment and risk stratification for chronic CAD were selected. During the same period, healthy volunteers were asked to participate in the study protocol. Patients with chronic CAD following prior MI could be included if they fulfilled the following criteria: (i) LVEF lower than 30% (primary indication for ICD prevention) and/or a history of VT or VF (secondary prevention for ICD prevention); designated post-MI\textsuperscript{HIGH RISK} group; (ii) LVEF > 30% and no history of ventricular tachyarrhythmias; designated post-MI\textsuperscript{LOW RISK} group. All patients had undergone extensive non-invasive and invasive evaluation to establish the underlying heart disease. From all patients and volunteers informed consent was obtained before they entered the study. The study was approved by the medical ethical committee of the hospital. In total 96 patients were enrolled. Twenty-eight post-MI\textsuperscript{HIGH RISK} patients (primary prevention n = 14, and secondary prevention n = 14; average = 19 ± 1 months after the infarct), 28 post-MI\textsuperscript{LOW RISK} patients (average = 17 ± 11 months after the infarct), and 40 healthy normotensive, non-diabetic, non-hypercholesterolemic, non-smoking volunteers (controls) were enrolled.

**Protocol**

Subjects were tested in the morning between 9:00 a.m. and 12:00 noon and refrained from exercise and caffeine consumption prior to the tests. Beta blockers were withheld 2 days prior to testing. In each subject common carotid artery distension waveform, systolic diameter and the peak of the R-waves of the ECG waves were recorded simultaneously for 5 min three times without prior intervention and three times during an injection of a bolus of phenylephrine hydrochloride (Oxford technique, starting dose 200 μg) to induce changes in pressure of at least 15 mmHg (31 ± 17 mmHg).\textsuperscript{25} The cross-sectional common carotid artery diameter was measured 1 cm distal from the carotid body. The frequency of data acquisition of the arterial wall movements was 200 Hz. During the ultrasound recordings arterial finger pressure was assessed simultaneously by means of a Finapress\textsuperscript{TM} (Ohmeda).

**Ultrasound method**

The ultrasound echo system in combination with dedicated signal processing (ATL Mark 9, HDI, Advanced Technology Laboratories, Bothell, WA, USA) allowed the continuous assessment of systolic diameter and distension waveform, i.e. the change in diameter per cardiac cycle, and has been described in detail elsewhere.\textsuperscript{26} In brief, the common carotid artery was visualized in B-mode using the C9-5 curved array probe (operating frequency 5–9 MHz). After positioning the M-line 10 mm from the bifurcation and visualizing the intima-media transition to check for perpendicular positioning, the ultrasound system was switched to echo M-mode with a pulse repetition frequency of 500 Hz. The spatial variation in end-diastolic diameter along this M-line, using raw radio frequency data, is 40 μm.\textsuperscript{27} Recording was started synchronously with a trigger derived from the simultaneously recorded peak of the R-wave of the ECG signal. This facilitates the detection of distension as well as systolic diameter.

**Spectral analysis**

The relationship between signals was evaluated by means of spectral analysis.\textsuperscript{28} For example, the relation between systolic diameter and R–R interval (NC) is described as follows: First, the frequency contents of the diameter and the R–R interval signal were obtained by means of Fourier transformation. A very LF trend (<0.005 Hz), which is the distensibility coefficient (DC) component, was removed so that only variations were considered. Next the transfer function \( H(f) \) between the two signals was calculated as

\[
H(f) = \frac{S_d(f)}{S_r(f)}
\]

where \( S_d(f) \) is the estimate of the autospectrum of the diameter of the common carotid artery and \( S_r(f) \) the complex cross-spectrum between the two signals. The transfer function magnitude

\[
\text{DC} = \frac{\text{Real}(H(f))}{\sqrt{\text{Real}^2(H(f)) + \text{Imag}^2(H(f))}}
\]
\(|H(f)|\), i.e. gain, reflects for a specified frequency the relative amplitude of the relation between the systolic diameter of the common carotid artery and R–R interval. The gain \(|H(f)|\) was derived from the real part \(H_R(f)\) and the imaginary part \(H_I(f)\) of the complex transfer function as

\[H(f) = (|H_R(f)|^2 + |H_I(f)|^2)^{0.5}\]  

(2)

The linearity and reliability of the transfer function between both signals was estimated by a magnitude-squared coherence (C) function. In Figure 1 an example of power spectra of systolic diameter, R–R interval and corresponding transfer function are given. The peak between 0.04 and 0.15 Hz (between dashed lines) has been attributed to the baroreflex. Additional details about data analyses have been previously published.

Data analysis

The relation between change in pressure and change in R–R interval as assessed after an injection of a bolus of phenylephrine hydrochloride (Oxford technique, starting dose 200 µg) was used to determine BRSphenyl. The average transfer function between systolic pressure and R–R interval variation (BRSspectral) was calculated in the LF range between 0.04 and 0.15 Hz. In addition, the average transfer function between systolic diameter and R–R interval variation (NC) was calculated in the same frequency range. Furthermore, the LF variation of systolic pressure, systolic diameter and R–R interval was quantified between 0.04 and 0.15 Hz. A correction function to exclude outliers in the systolic diameter, pressure and R–R interval signal due to artefacts, ventricular premature beats, and measurement errors was applied.

Statistics

Median values of the three methods (BRSphenyl, BRSspectral and NC) were calculated for the three patient groups by means of descriptive statistics. For further statistical analysis we performed log transformations on the data (BRSphenyl, BRSspectral and NC) to obtain normal distributions. In the primary analyses the effect of age was not considered. We, therefore, first assessed the relation to age using least squares linear regression on the measures vs. age. Additionally, a risk index for each of the three BRS measurements was constructed, which separated the generally higher log transformed values in post-MI LOW RISK patients from lower log transformed values in post-MI HIGH RISK patients or higher values in controls from lower values in post-MI LOW RISK as much as possible: an optimal slope was determined with logistic regression for a linear combination of age and the logarithm of the measurement (Figure 2A). Sensitivity and specificity pairs for distinguishing patient groups were determined retrospectively. These sensitivity and specificity values were used to construct a ROC curve, in which the optimal sensitivity, specificity is visualized (Figure 2B). Wilcoxon test was used to test for non-trivial area under the ROC curve. P-values were adjusted for multiple comparisons using a Hochberg correction.

Results

Patient group description

Table 1 summarizes patient characteristics of controls, and low and high risk patients. The patient groups did not differ with respect to diastolic and systolic blood pressure, resting heart rate (mean R–R interval), Q–T interval duration and its dispersion. Distension, i.e. the change in

![Figure 1](https://academic.oup.com/europace/article/10/2/227/504429/figurefile_18229096)

Figure 1 Example of power spectra of systolic diameter, R–R interval and corresponding transfer function. The peak between 0.04 and 0.15 Hz has been attributed to the baroreflex.
diameter per cardiac cycle, decreased significantly with age (linear regression) and this age-dependent decrease was not significantly different between the groups. End-diastolic diameter increased significantly with age in the three groups and the increase was significantly higher in post-MI LOW RISK and post-MI HIGH RISK patients than in controls (linear regression, slopes compared). Intima-media thickness (IMT) increased significantly with age and the increase with age was not significantly greater in the post-MI LOW RISK and post-MI HIGH RISK group compared with the control group. However, a significantly greater IMT was found in the post-MI LOW RISK and post-MI HIGH RISK group compared with the control group. Medication for the post-MI LOW RISK and post-MI HIGH RISK group is given in Table 2. Only the use of diuretics was different between the post-MI LOW RISK and post-MI HIGH RISK group. The controls did not use any medication related to cardiovascular disease.

**Baroreflex sensitivity methods and neural component method**

In Figure 3 plots with median, 25 and 75% percentile values for the NC (A), BRSphenyl (B) and BRSspectral (C) are shown of controls, post-MI LOW RISK and post-MI HIGH RISK patients. A significant difference is present between post-MI LOW RISK and post-MI HIGH RISK patients if the NC is used ($P = 0.03$, Wilcoxon test), but not if conventional BRS measures were used. These differences were not found for the BRS methods.

With all three measures median values of the control group could be distinguished significantly from median values of post-MI patients.

A significant decrease in the NC vs. age was found in the control group ($P$ (slope) = 0.0009) and the post-MI LOW RISK group ($P$ (slope) = 0.006), but not in the post-MI HIGH RISK group ($P$ (slope) = 0.82). For the BRSphenyl and BRSspectral methods no significant relation to age was found.

**Ability of the methods to distinguish patient groups**

As described above, this study has shown that high and low risk post-MI groups can be better distinguished using the median NC than the median BRS values. To correct for the influence of age and assess how good the individual data could predict if a patient belongs to the high or low risk groups, a risk index was calculated. In order to obtain normal distributions, a log transformation on the measurements obtained with the three methods was performed. Since we found a significant relation to age for the NC, a linear combination of age and the logarithm of the measurement was constructed as a risk index for the three methods using logistic regression. With this technique an optimal slope of a line depending on age was determined, which separates the value of a parameter determined in high and low risk post-MI patients as well as possible. By varying the intercept, various sensitivity-specificity pairs were obtained and a ROC curve was calculated using these pairs. Table 3 presents the indices and performance characteristics: area...
under ROC curve, $P$-value for non-triviality, the intercept that achieved the highest sum of sensitivity and specificity, the achieved sensitivity and specificity and the sum of the two. The area under the ROC curve and the sum of the optimal specificity and sensitivity to distinguish post-MILOW RISK from post-MIHIGH RISK patients was greater for the NC (sum = 155, areaROC = 81) than for the BRSspectral and BRS phenyl method for the three groups [BRS spectral (ms/mmHg) = $1.18 \times$ BRS phenyl (ms/mmHg) + 0.95], $N = 59$.

Correlations between methods
A moderate correlation ($R^2 = 0.29$) was found between the NC and BRSspectral values for the three groups [NC (ms/μm) = $0.05 \times$ BRSspectral (ms/mmHg) + 0.003, $N = 76$] if a linear regression was performed on all data of patients and controls together. Furthermore, a moderate correlation ($R^2 = 0.27$) was found between the BRSspectral and BRSphenyl method for the three groups [BRS spectral (ms/mmHg) = $1.18 \times$ BRS phenyl (ms/mmHg) + 0.95], $N = 59$.

Discussion
Although primary preventive therapy with an ICD is evidence based in post-MI patients with reduced ejection fraction, many of these patients will never use their ICD. There is thus a need for additional non-invasive methods to identify those patients who may derive a particular benefit from such treatment. In the past, several autonomic measures have been investigated with respect to arrhythmia risk stratification after MI.3,5–7 The predictive value of measures reflecting BRS seems to be superior to that of HRV. However, conventional BRS3,5 has the disadvantage of injecting a vasoactive agent. Newer methods such as heart rate turbulence and deceleration capacity of heart rate—both determined from Holter recordings—yield a high predictive value in MI patients treated according to contemporary guidelines.6,7 In this retrospective pilot study, post-MI patients at high risk for ventricular arrhythmias (LVEF lower than 30% or previous ventricular tachycardia/fibrillation (VT/VF) i.e. approved indication for primary or secondary preventive ICD therapy)1,30 could be better distinguished from post-MI patients at low risk for ventricular arrhythmias (LVEF > 30%) with the non-invasively determined NC than with the BRSphenyl and BRSspectral method. The NC reflects BRS as modulated by the sensing and vagal components without the influence of changes in artery wall properties, since the NC reflects the relationship between stretch and R–R interval variations and not absolute vessel wall stretch values. However, the concept of NC as a better predictor of ventricular arrhythmias compared with the conventional BRS measures and the additional value of NC in combination with other risk stratifiers needs confirmation in a future prospective study. The added value of the NC compared with total BRS methods may be explained by the elimination of the vessel wall component, i.e. the transfer of pressure variations to diameter variations, which is influenced by the stiffness of the vessel wall. Vessel wall stiffness increases with age.10 Although high vessel wall stiffness is correlated with coronary heart disease and stroke,11 its relation to ventricular tachyarrhythmias is not yet known. Another advantage of the NC is the elimination of the extrapolation of arterial finger pressure (LF) and age or patient groups was found.

Variabilities
Average variability of R–R interval (LF = 0.04–0.15 Hz) assessed from the short-time measurements was significantly larger in the control group than in the post-MIHIGH RISK and post-MILOW RISK group ($P < 0.01$ and $P < 0.01$). No influence of age could be detected on variability of R–R interval in post-MILOW RISK ($P = 0.13$), post-MIHIGH RISK patients ($P = 0.97$) and controls ($P = 0.09$). Assessment of standard HRV from Holter recordings was not part of the present study protocol. No relation between variability of systolic arterial finger pressure (LF) and age or patient groups was found.
arterial finger pressure to central pressure. Prior work has demonstrated that variations in carotid diameter correlated significantly better with variations in R-R interval than variations in arterial finger pressure due to elimination of the noise of incorrect pressure measurements.

In this study, a smaller NC was found in post-MI LOW RISK patients than in controls. The NC was particularly low in post-MI patients with a low ejection fraction or previous VT/VF, i.e. patients prone to life threatening tachyarrhythmias. The pivotal role of deterioration of the NCs of the baroreflex in the decrease of BRS, has been demonstrated in studies of myocardial infarction patients, where areas of sympathetic denervation exceeding the limits of myocardial necrosis have been demonstrated. This denervation has been considered a substrate for ventricular tachycardia and fibrillation. Furthermore, impaired reflex control of heart rate is related to the central effects of altered afferent input from the heart on the baroreceptors after a myocardial infarct. In an experimental model in 191 dogs with a healed myocardial infarction, Schwartz and coworkers demonstrated that reduced BRS (total pathway) is associated with a greater susceptibility to ventricular fibrillation during subsequent ischemic episodes. In these animals electrical vagal stimulation markedly reduced the incidence of VF in a high-risk subgroup, whereas muscarinic blockade increased VT/VF in low risk animals. Furthermore, it was found that a muscarinic agonist significantly reduced malignant arrhythmias during acute myocardial ischaemia in 17 felines. The ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) trial with 1071 post-MI patients demonstrated that markers of reduced autonomic tone such as BRS and HRV, are strong predictors of sudden cardiac death. The power of BRS remained significant even after adjusting for LVEF and number of premature ventricular complexes on Holter monitoring. Among patients with LVEF < 30%, BRS but not HRV remained a powerful predictor.

Age

The trend observed in the decrease of R-R variability with age is in agreement with the significant decrease in R-R variability found in 2722 subjects by Tsuji et al. A significant increase in variability of carotid diameter with age was found in this study. This increase can be explained by the deterioration of the NC with age resulting in a decrease in buffering capacity of the heart on blood pressure variations. An increase in blood pressure variability with age leads to an increase in carotid diameter variability. However, no relation was found between variability of arterial finger pressure and age. It should be noted that the bias in the measurement of arterial finger pressure variability (caused by the effect of wave reflections) changes with age and, therefore, disturbs a possible relation between pressure variability and age.

End-diastolic diameter increased significantly with age in the control, post-MI LOW RISK and post-MI HIGH RISK group. This increase was more pronounced in post-MI patients than in controls irrespective of their ejection fraction and history of ventricular arrhythmias. Also intima-media thickness was greater in post-MI patients than in controls. These findings indicate that the effect of vessel wall aging is more pronounced in post-MI patients than in controls.

Comparison between spectral and phenylepinephrine methods

A moderate correlation between the NC and BRSphenyl and between BRSphenyl and BRSspectral was found. The latter corresponds to the results of Maestri et al. Furthermore, the variation in BRSphenyl and BRSspectral in this study was comparable with that found by Maestri et al. This moderate correspondence was found despite the possible influence of phenylepinephrine on the baroreceptors and the possibility that BRS, as determined by drug induced changes in pressure, was measured in the non-linear part of the stretch-BRS activity curve; whereas BRS as determined with the spectral method using small spontaneous changes in pressure was determined in the linear part of the curve.

Limitations and future studies

Although the NC performed better than the conventional BRS measures in distinguishing post-MI patients at risk for ventricular arrhythmias (as indicated by a low EF and/or a prior ventricular arrhythmic event) from those less prone to arrhythmias in this retrospective pilot study, the concept of the NC being a better predictor of ventricular arrhythmias than conventional BRS measures needs confirmation in a prospective study with a long duration of follow-up. Groups were too small to determine a potential relationship between NC and future arrhythmic events. Furthermore, patients were not consequently followed for the purpose of this methodological study. The predictive value of the NC combined with other risk factors on the occurrence of VT/VF thus needs further prospective investigation.
Particularly, the value of the NC in comparison with ejection fraction needs to be studied. In addition, it should be noted that in the control group of this study the possibility of background arrhythmia could not be excluded.

The area under the ROC curve obtained with the NC method had a significant P-value of 0.011. However, it should be noted that the P-value for the area under the ROC curve was not significant for the BRS methods. Thus, to obtain a statistically significant difference between sensitivities and specificities of the various methods to distinguish patient groups, larger sample sizes would be required. Cut-off values for identification of patients at risk, and sensitivity and specificity estimates for the proposed risk-stratification are based on the data of the population used in this study. Thus, sensitivity and specificity might be biased. Furthermore, the intra-individual reproducibility of NC measurements is not known and was not tested in the present study.

With respect to the medication, beta blocker therapy was withheld 2 days prior to the measurements, i.e. five half-lives of drug action. This may not allow for all effects to resolve. However, the procedure was in adherence to the protocol of other studies investigating autonomic risk stratifiers in post-MI patients. Although arrhythmia risk stratification should in clinical practice be performed in patients on full protective medication, we decided to withhold beta blockers in order to better compare the results between patients and healthy volunteers in the present study.

Clinical implications
The results of the present study indicate that assessment of NC of the baroreflex may more accurately reflect vagal reflex activity. Furthermore, this measure is less invasive than conventional BRS assessment since there is no need to inject a vasoactive agent. In this pilot study, the NC better separates post-MI patients at risk of ventricular arrhythmia as indicated by a low LVEF and/or history of ventricular arrhythmia from those less prone to arrhythmia than the conventional BRS measures. There is therefore a potential of NC to identify patients at particular high risk of arrhythmic events. Future studies are warranted to define the value of the NC in selecting patients who may benefit from primary preventive ICD therapy.

Conflict of interest: B.G. and L.K. are employees of Medtronic Inc.

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References


