Comparison Between Noninvasive Indices of Baroreceptor Sensitivity and the Phenylephrine Method in Post–Myocardial Infarction Patients

Maria Vittoria Pitzalis, MD, PhD; Filippo Mastropasqua, MD; Andrea Passantino, MD; Francesco Massari, MD; Luana Ligurgo, MD; Cinzia Forleo, MD; Cataldo Balducci, RN; Federico Lombardi, MD; Paolo Rizzon, MD

Background—Depressed baroreflex sensitivity obtained by means of a phenylephrine test plays a prog nostic role in patients with a previous myocardial infarction. Our purpose was to evaluate the correlation and agreement between the baroreflex sensitivity obtained with phenylephrine and that obtained by two noninvasive methods: the α-index and sequence analysis.

Methods and Results—The α-index was measured by means of the spectral analysis of RR and systolic blood pressure variabilities in both the high- and low-frequency bands; sequences were identified from simultaneously recorded time series in which the RR and systolic blood pressure concurrently increased or decreased. Noninvasive baroreflex sensitivity tests were performed during both spontaneous and controlled respiration. Fifty-two consecutive patients with recent myocardial infarction underwent the analyses. Although the correlations between phenylephrine and either of the noninvasive methods were always significant, those found during controlled respiration had the highest r values (r = .70). However, the limits of agreement calculated by means of the Bland and Altman method were wide for both noninvasive methods.

Conclusions—The results obtained by means of noninvasive baroreflex sensitivity assessments should not be used in clinical practice as an alternative to those obtained by the phenylephrine method. (Circulation. 1998;97:1362-1367.)

Key Words: myocardial infarction • baroreceptors • phenylephrine

It has been shown that BRS plays a prognostic role in patients who have suffered a recent myocardial infarction, with depressed BRS being associated with an increased incidence of death and malignant ventricular arrhythmias.1–3 Baroreflex sensitivity (an index of reflex vagal activity) and not heart rate variability (an index of tonic vagal activity) is able to identify patients with malignant ventricular arrhythmias among those with an old myocardial infarction.4,5 Furthermore, the evaluation of BRS has been shown to provide information on the patency of the infarct-related artery.6 In all of these studies, BRS has been evaluated according to the method proposed by Smyth et al,7 which consists of the administration of phenylephrine (a drug that increases blood pressure and therefore induces baroreflex-mediated bradycardia) and is still considered the standard technique for assessing BRS to stratify the risk of patients who have survived a myocardial infarction. However, its invasiveness and the fact that it cannot be used in patients with high resting values of SBP may limit its application. Other (noninvasive) methods of measuring BRS have recently been proposed, some of which are based on the use of the spectral analysis of both RR and SBP variabilities (α-index)8,9 and others on the analysis of simultaneously recorded RR and SBP time series to identify those sequences in which the two variables concurrently increase or decrease.10,11 Both the α-index and the sequence method have been shown to correlate with the BRS evaluated by use of phenylephrine in both normal subjects8,12 and hypertensive patients.13,14

The aim of the present study was to evaluate the correlation and agreement between the BRS values calculated by the two noninvasive methods and those calculated with phenylephrine in post–myocardial infarction patients.

Methods

Study Population
Fifty-two consecutive patients (48 male, 4 female; mean age, 53 ± 9 years) were studied 11 ± 5 days after a first acute Q-wave myocardial infarction. The diagnosis was made on the basis of chest pain and ECG modifications and then confirmed by serial ECGs and serum enzyme changes. Patients were excluded from the analysis if they...
had had a previous myocardial infarction or suffered from diabetes, thyroid dysfunction, alcoholism, or central or peripheral nervous system diseases; if they were taking β-blockers or showed second- or third-degree atrioventricular block, intraventricular conduction defects, atrial and/or ventricular tachyarrhythmias, atrioventricular preexcitation, or pacemaker-induced rhythm; if they had concomitant valvular disease, cardiomyopathy, or unstable angina; or if they were >80 years old or had a blood pressure of >160/90 mm Hg.

All patients underwent two-dimensional echocardiography. All patients gave informed consent, and the study was approved by the local Ethics Committee.

**BRS Assessments**

The evaluations were made in the morning in a quiet and light-attenuated room whose ambient temperature was kept at approximately 24°C. The subjects were asked to remain resting in a supine position throughout all of the study phases. The following signals were continuously recorded during each session: ECG by means of a conventional bedside monitor (Hewlett Packard model 78354C); the respiratory signal by means of an impedance pneumograph (Hewlett Packard model 78354C); and blood pressure by means of a photoplethysmographic finger transducer (Finapres model 2300, Ohmeda).

Before each evaluation, patients lay supine for 30 minutes to allow their cardiovascular mechanisms to reach steady state. The study protocol consisted of a first phase of 10 minutes, during which the patients were asked to breathe spontaneously (BS); a second phase of 10 minutes, during which they were asked to pace their breathing in time with a metronome set at a frequency of 16 bpm (CR); and a third phase, during which they underwent phenylephrine testing.

**Spectral Method**

The data obtained during the BS and CR phases were stored on a personal computer equipped with signal conditioning, an antialiasing low-pass filter, and a 12-bit analog-digital interface.

The ECG signal was acquired at a sampling rate of 1 kHz and the other signals at a sampling rate of 250 Hz. A real-time program detected the ECG R-wave signal and measured the beat-to-beat systolic pressure. When present, artifacts were removed and then corrected by means of linear interpolation with the previous and following beats. Periods of 256 beats were selected from the visual inspection time series of the tachogram, systogram, and respirogram and used for the subsequent analysis. Frequency-domain variability was analyzed by an autoregressive model on the RR intervals, SBP, and respiratory signals, and the model order was selected according to the Akaike information criterion. Spectral components of RR intervals and SBP were obtained by means of a decomposition method to measure the power and centered frequency of each peak.

The following components were considered: LF power, in the 0.03- to 0.15-Hz band; and HF power, in the 0.15- to 0.40-Hz band. The α-index (α) (ie, the gain in the relationship between the RR period and SBP variabilities) was obtained by means of the simultaneous spectral analysis of RR and SBP variabilities, with the calculation being made from the square root of the ratio between RR and SBP variability in the two major bands of LF (αLF) and HF (αHF); the coherence between the RR interval and either systolic pressure or respiratory signal variabilities was assessed by means of cross-spectral analysis. The α-index was calculated only when the magnitude of squared coherence (K^2) between the RR and SBP signals exceeded 0.5 (range, 0 to 1) in both the LF and HF bands.

The data obtained during CR were considered if K^2>0.5 in a cross-correlation analysis of respiration and RR-interval variabilities at the frequency of breathing, αLF(BS), αHF(BS), and their mean value (αM) were calculated during BS, and the α-index in the respiratory band (αCR) was calculated during CR (Fig 1). The phase shift (in degrees) between RR and SBP oscillations was also calculated.

**Sequence Method**

The time series of RR and SBP recorded during the BS and CR phases were scanned with a software capable of identifying the sequences in which RR and SBP concurrently increased (up sequence) or decreased (down sequence) over three or more beats. The minimum change had to be 1 mm Hg for SBP and 4 ms for RR. The indicated correlation between RR and SBP was computed for each sequence (Fig 2); if r<0.8, the software calculated the regression coefficient or slope, which was taken as a measure of BRS and expressed in ms/mm Hg. UpBRS, DownBRS, and SeqBRS were computed for each phase.

**Phenylephrine Method**

After having undergone the noninvasive assessments, the patients underwent phenylephrine testing according to the method described by Smyth et al. The RR interval and SBP were continuously recorded as described and then digitally converted in a personal computer. A bolus of phenylephrine (2 μg/kg IV) was given to raise SBP variability in the two major bands of LF (αLF) and HF (αHF); the coherence between the RR interval and either systolic pressure or respiratory signal variabilities was assessed by means of cross-spectral analysis. The α-index was calculated only when the magnitude of squared coherence (K^2) between the RR and SBP signals exceeded 0.5 (range, 0 to 1) in both the LF and HF bands.

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SBP by 15 to 40 mm Hg; if SBP did not increase as desired, the dose was increased by 25 to 50 μg. The bolus injection was repeated at least three times at whatever dose was found to be efficacious, and then the linear regressions of RR and SBP were calculated, including all of the points between the beginning and end of the increase in SBP. If the correlation coefficients were statistically significant, the results of the test were considered for the analysis (see example in Fig 3). The final slope (PheBRS) was the mean of at least three tests and was considered to be an index of BRS (ms/mm Hg).

**Statistical Analysis**

The data are expressed as mean values±SD. Correlation coefficients (r) were computed to compare BRS measurements: if r was statistically significant (P<.05), the limits of agreement were calculated according to the method proposed by Bland and Altman. A plot was drawn of the differences between the methods against their mean values, and then the lack of agreement was computed by calculating the bias, ie, the mean difference (d) and its SD. The limits of agreement are given by d±2 SD (ie, the range containing 95% of differences).

**Results**

The clinical characteristics of the study population are shown in Table 1.

The mean value of PheBRS calculated in the patients as a whole was 9.76±6.15 ms/mm Hg. The aLF during BS was calculated in 36 patients and had a mean value of 10.29±7.2 ms/mm Hg; in the remaining 16 patients, the coherence between RR and SBP was <0.5. aHF could be calculated in only 46 patients for the same reason. The αM (mean value, 12.5±8.5 ms/mm Hg) was calculated in 32 patients. Conversely, it was possible to calculate αCR in all of the patients (mean value, 8.6±8.3 ms/mm Hg). No significant differences were found among the spectral indices, but there was a statistically significant correlation (P<.01) between PheBRS and aLF (0.51), aHF (0.53), and αM (0.64) during BS and between PheBRS and αCR (0.70) (Fig 4A); however, despite the good linear correlation, the limits of agreement were broad (Table 2) (Fig 4B). The phase shift between RR and SBP oscillations during BS in the LF and HF bands was −83.54° and −4.38°, respectively; during CR the phase shift in the respiratory band was −20.36°.

The percentage of beats in the sequences was 28.39±14.92% during BS and 30.38±18.03% during CR. During BS, UpBRS was calculated in all but one patient, who did not show any up sequence; DownBRS and SeqBRS could be calculated in all patients. The mean values of UpBRS, DownBRS, and SeqBRS during BS were 10.78±8.33, 10.24±7.01, and 10.39±7.43 ms/mm Hg, respectively. During CR, one patient did not show any down sequence; the mean values of UpBRS, DownBRS, and SeqBRS during CR were 9.20±8.09, 9.22±7.48, and 9.17±7.69 ms/mm Hg, respectively. No differences were found among the different indices. As with the α-index, the sequence measurements correlated well with PheBRS (Fig 4C), but the limits of agreement were broad (Table 3) (Fig 4D). Table 4 shows the values in the 32 patients in whom BRS was always measurable.

**Discussion**

Our data show that both of the tested noninvasive methods of measuring BRS correlate well with the PheBRS results in patients who had suffered a previous myocardial infarction. A good correlation between noninvasive measurements of BRS and the phenylephrine test was also shown in a previous study involving both normotensive and hypertensive subjects. However, close correlation does not necessarily mean that there is agreement between the two methods, as can be seen from the fact that the use of the Bland and Altman method of both spectral and sequence analysis revealed only broad
TABLE 2. Comparison of PheBRS With the α-Index

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Value</th>
<th>PheBRS</th>
<th>r</th>
<th>P</th>
<th>Mean Difference±SD (Bias)</th>
<th>Limits of Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>αLF(BS)</td>
<td>36</td>
<td>10.29±7.2</td>
<td>10.2±6.3</td>
<td>.51</td>
<td>&lt;.01</td>
<td>−0.073±6.78</td>
<td>13.5 to −13.65</td>
</tr>
<tr>
<td>αHF(BS)</td>
<td>46</td>
<td>12.25±11</td>
<td>10.18±6.38</td>
<td>.53</td>
<td>&lt;.01</td>
<td>−2.063±9.15</td>
<td>16.25 to −20.38</td>
</tr>
<tr>
<td>αCR</td>
<td>52</td>
<td>8.6±8.3</td>
<td>9.76±6.15</td>
<td>.7</td>
<td>&lt;.01</td>
<td>1.159±5.91</td>
<td>12.99 to −10.68</td>
</tr>
<tr>
<td>αM(BS)</td>
<td>32</td>
<td>12.56±8.5</td>
<td>10.57±6.59</td>
<td>.64</td>
<td>&lt;.01</td>
<td>−1.988±6.66</td>
<td>11.35 to −15.32</td>
</tr>
</tbody>
</table>

αLF(BS) indicates α-index evaluated in the LF band during baseline (spontaneous respiration); αHF(BS), α-index evaluated in the HF band during baseline; αCR, α-index evaluated in the respiratory band during CR; and αM(BS), average value of αHF and αLF during baseline.

levels of agreement. For this reason, the clinical information provided by means of the phenylephrine test cannot be extrapolated by use of these alternative methods.

Nevertheless, although phenylephrine testing is considered the only accepted method of stratifying risk in post–myocardial infarction patients, it has a number of limitations: there is a different individual response to the administration of the bolus, and phenylephrine induces changes in venous compliance and venous return and may stimulate baroreceptor pathways regardless of the increase in arterial pressure. The possibility of analyzing BRS under spontaneous conditions remains intriguing and offers clear advantages, such as the fact that the test can be repeated several times and under different experimental conditions; however, the prognostic value of noninvasive BRS has not yet been prospectively evaluated.

Spectral Analysis

In accordance with the results of previous studies, we found a good correlation between α-index and PheBRS, but the agreement between PheBRS and the α-index was far from good. There are various possible explanations for this finding. PheBRS explores the vagal fast arm of baroreflex control of circulation in an open-loop fashion, but it is more complicated to identify the physiological correlates of the spectral components of RR and SBP variabilities. Given that the α-index can be measured in both the HF and LF bands and that the baroreflex control of the cardiovascular system may affect the different peaks of the spectral analysis of the RR interval, the fact that baroreflex gain is analyzed separately in different frequency bands may represent a limitation of this method. Furthermore, baroreflex control may generate non-rhythmic oscillations that determine no peaked power in a broad frequency band.

Conversely, a number of factors can generate RR and SBP oscillations in each band. HF reflects predominantly respiratory oscillations, which are mediated partly by vagal activity but also partly by mechanical factors: there is still a reduced RR variabil in the HF band after pharmacological parasympathetic blockade as well as after cardiac transplantation. Disagreement exists concerning the LF component of the RR spectrum: some studies suggest that it is the expression of both sympathetic and vagal activity, but according to some authors, it is a result of baroreflex-mediated adjustments, although other factors (such as thermoregulation and periodic breathing) have also been shown to be associated with LF band oscillations. To overcome these limitations, it is possible to analyze a spectral index of the overall gain of the RR/SBP relationship by calculating αM, an averaged index that accounts for both LF and HF components. Using this index, we obtained a closer correlation and an improved agreement with PheBRS.

One limitation of this kind of analysis is that the baseline α-index cannot be measured in all patients because of the lack of coherence between SBP and RR in both the LF and the HF bands. Under baseline conditions, the respiratory pattern may be irregular, and so the respiratory frequency may move above the limits of the HF band; for this reason, the RR and SBP spectra may be differently modified in each patient. During CR, the respiratory component of the RR and SBP variabilities remains in the HF band, which may explain why it was possible to measure the α-index in all of our patients, thus improving the correlation and agreement with PheBRS; however, even in this controlled condition, the limits of agreement with PheBRS remained too broad to allow the α-index to be used instead of phenylephrine for clinical purposes.

TABLE 3. Comparison Between the Sequence and Phenylephrine Methods

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Value±SD</th>
<th>PheBRS±SD</th>
<th>r</th>
<th>P</th>
<th>Mean Difference±SD (Bias)</th>
<th>Limits of Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>UpBS</td>
<td>51</td>
<td>10.78±8.33</td>
<td>9.88±6.16</td>
<td>.63</td>
<td>&lt;.01</td>
<td>−0.81±6.51</td>
<td>12.22 to −13.84</td>
</tr>
<tr>
<td>DownBS</td>
<td>52</td>
<td>10.24±7.01</td>
<td>9.76±6.15</td>
<td>.64</td>
<td>&lt;.01</td>
<td>−0.471±5.65</td>
<td>10.83 to −11.77</td>
</tr>
<tr>
<td>SeqBS</td>
<td>52</td>
<td>10.39±7.43</td>
<td>9.76±6.15</td>
<td>.64</td>
<td>&lt;.01</td>
<td>−0.622±5.85</td>
<td>11.09 to −12.33</td>
</tr>
<tr>
<td>UpCR</td>
<td>52</td>
<td>9.20±8.09</td>
<td>9.76±6.15</td>
<td>.65</td>
<td>&lt;.01</td>
<td>0.558±6.17</td>
<td>12.9 to −11.79</td>
</tr>
<tr>
<td>DownCR</td>
<td>51</td>
<td>9.22±7.48</td>
<td>9.88±6.16</td>
<td>.71</td>
<td>&lt;.01</td>
<td>0.719±5.26</td>
<td>11.25 to −9.81</td>
</tr>
<tr>
<td>SeqCR</td>
<td>52</td>
<td>9.17±7.69</td>
<td>9.76±6.15</td>
<td>.69</td>
<td>&lt;.01</td>
<td>0.593±5.62</td>
<td>11.85 to −10.66</td>
</tr>
</tbody>
</table>

BS indicates baseline.
TABLE 4. BRS in the Patients in Whom It Was Calculated by All Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>n</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>PheBRS</td>
<td>32</td>
<td>10.57 ± 7</td>
</tr>
<tr>
<td>aLF(BS)</td>
<td>32</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>aHF(BS)</td>
<td>32</td>
<td>14.12 ± 12</td>
</tr>
<tr>
<td>aCR</td>
<td>32</td>
<td>9.82 ± 9</td>
</tr>
<tr>
<td>aM(BS)</td>
<td>32</td>
<td>12.56 ± 9</td>
</tr>
<tr>
<td>SeqBRS(BS)</td>
<td>32</td>
<td>11.55 ± 8</td>
</tr>
<tr>
<td>SeqBRS(CR)</td>
<td>32</td>
<td>9.91 ± 9</td>
</tr>
</tbody>
</table>

Abbreviations as in previous Tables.

One possible limitation to the use of the frequency-domain measure of baroreflex sensitivity has been underscored by Taylor and Eckberg,25 who, using bivariate spectral analysis, showed that SBP oscillation follows RR-interval oscillation in supine, healthy humans; in the same subjects, cardiac pacing did not increase but rather actually reduced SBP oscillations. According to the authors, these findings minimize the direct baroreflex buffering role of short-term SBP-interval oscillations. On the contrary, during 40° tilt, the phase between the two signals was negative, with RR oscillation following SBP oscillation, and cardiac pacing was able to increase SBP oscillations. The authors suggest that the link between RR and SBP oscillations may be baroreflex-mediated only when sympathetic outflow is increased. In our patients, we found a negative phase between RR and SBP oscillations in both the LF and HF bands during BS and in the HF band during CR: ie, the RR-interval oscillations followed the SBP oscillations, thus confirming the probable baroreflex link between the two signal variabilities. This may be explained by differences in sympathetic tone between patients with a previous myocardial infarction and healthy subjects.

Sequence Analysis

During BS, the correlation with PheBRS was closer and the limits of agreement slightly less broad than those of the spectral indices. Furthermore, this kind of analysis is easier to perform and makes it possible to obtain information about BRS under all of the studied conditions. However, the limits of agreement with PheBRS remain broad. The baroreflex nature of sequences has been demonstrated in a previous study, which revealed a dramatic reduction in both up and down sequences after sinoaortic denervation in unanesthetized cats.26 In accordance with the results of previous studies,10,27,28 we did not find any difference between the up and down slopes, and the analysis made without separating them made it possible to obtain information on BRS in the whole study population.

A significant positive correlation between the sequence method and phenylephrine has been found in healthy subjects12 and in hypertensive patients.13 However, Watkins et al27 have also shown that there are differences between the two methods in subjects with irradiated baroafferents, in whom BRS was found to be reduced only when evaluated by use of the vasoactive drug, despite the good correlation found between the two measurements.

One possible explanation of the differences between these two methods is that they explore BRS at different operating points: during a maximal stimulus (ie, at the higher SBP reached after the injection of a phenylephrine bolus) and during a lower stimulus (ie, at the normal SBP present in spontaneous conditions). The stimulus-response (SBP-RR) curve for baroreflex is sigmoidal, with the gain being different point by point as the RR or SBP changes.23 Parati et al10 found that the slopes of the up and down sequences in both hypertensive and normal subjects were inversely related to the SBP and pulse interval existing at the beginning of the sequence, a finding that was confirmed by Parlow et al,12 who obtained the sigmoidal baroreflex curve in healthy men with both vasoconstrictive (phenylephrine) and vasodepressive (nitroprusside) drugs. From this curve, it was possible to calculate drug-induced BRS at a mean resting pressure that agreed well with the slope of the BRS sequence. Conversely, only a broad level of agreement was found when the BRS sequence was compared with phenylephrine injection. Like ours, these results suggest that PheBRS reflects a part of the baroreflex curve that offers an incomplete estimate of baroreflex sensitivity, and so a more physiological evaluation may be obtained by measuring the reflex response at different pressure levels.

In summary, there are two main reasons for explaining the differences observed between invasive and noninvasive methods: first, noninvasive methods explore baroreflex gain during minimum spontaneous beat-to-beat oscillations of SBP, whereas the phenylephrine method gives an estimation of baroreflex gain during an increase (>15 mm Hg) of SBP; second, the differences observed may be interpreted on the basis of the completely different methodological approach. In particular, whereas the phenylephrine method is based on an open-loop model, in which RR-interval changes are related to SBP increase according to a linear model, noninvasive techniques provide a closed-loop estimation of BRS, in which blood pressure oscillations induce changes of RR interval that in turn are able to modify blood pressure.

Limitations of the Study

There are some possible limitations of this study. We used noninvasive SBP measurements at finger level, which may be different from measuring SBP at the level of baroreceptors by means of an intra-arterial catheter, even though its use during phenylephrine testing has been validated in previous studies.29,30

The phases of the experiments were not randomly assigned: the invasive BRS assessment always followed the noninvasive evaluations because we wanted to avoid the possibility that the drug used during phenylephrine testing could in some way influence the spontaneous test results. As in previous studies,10,11 we used a zero lag between RR and SBP when calculating the sequence slope, but the latency of vagal efferent response to baroreceptor stimulation may vary depending on the heart rate.31 Although the mean value of RR in our study population was 902 ms at baseline and 892 ms during CR, allowing us to use a zero lag on the basis of the
results of Blaber et al., some patients showed shorter RR intervals, and we cannot exclude the possibility that a higher lag (ie, 1 or 2) may be more appropriate for the measurement of BRS in these patients. We decided to standardize the analysis by always using the zero lag adopted for $\text{Phe}_{\text{BRS}}$.

Conclusions
Despite their good correlation with $\text{Phe}_{\text{BRS}}$, noninvasive measurements of BRS cannot be used as an alternative for stratifying risk in patients with a previous myocardial infarction; an ad hoc prospective study should be made to evaluate the prognostic value of BRS measured by noninvasive methods.

References
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