Clin. Cardiol. 23, 201–204 (2000)

Stability of the Noninvasive Baroreflex Sensitivity Assessment Using Cross-Spectral Analysis of Heart Rate and Arterial Blood Pressure Variabilities

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Summary

Background: Depressed baroreflex sensitivity (BRS), usually estimated using the invasive phenylephrine method or the nitroprusside test, is significantly and independently associated with an increased risk of malignant ventricular arrhythmias and sudden cardiac death in patients surviving acute myocardial infarction. Several investigators have compared the standard phenylephrine test and different noninvasive methods.

Hypothesis: This study evaluated the influence of different body positions with different breathing regimes on cross-spectral baroreflex indices (coherence between the spectral densities of blood pressure and cardiac cycle variabilities) in both low- and high-frequency bands.

Methods: The data were obtained in 103 patients (73 males, aged 53 ± 12 years) with coronary artery disease and/or hypertension. Simultaneous electrocardiographic and noninvasive blood pressure recordings were obtained in each subject in both supine and sitting positions during both spontaneous and slow and fast controlled respiration (0.1 and 0.33 Hz).

Results: The results show a significant bias and disagreement between noninvasive baroreflex sensitivity (BRS) indices. The mean values of the baroreflex in low frequency ranged from 5.0 ± 5.3 to 10.1 ± 7.9 ms/mmHg, while in high frequency, the mean values ranged from 6.6 ± 6.1 to 10.1 ± 7.9 ms/mmHg. The limits of agreement ranged from ± 1.7 to ± 4.1 ms/mmHg with bias from − 1.0 to + 0.7 ms/mmHg.

Conclusion: A comprehensive comparison of different methods shows that BRS estimated in low-frequency band in sitting position during spontaneous respiration is the most representative part of the global baroreflex gain.

Key words: baroreflex, noninvasive assessment, spectral analysis

Introduction

Depressed baroreflex sensitivity (BRS) is significantly and independently associated with an increased risk of malignant ventricular arrhythmias and sudden cardiac death in patients surviving acute myocardial infarction (MI).[1,2] It is usually estimated using the invasive phenylephrine method[3] or the nitroprusside test.[4] More recently, sophisticated data analyses have been proposed for BRS estimation that do not require the pharmacologic stimulus. They are based on the assessment of the correspondence between beat-to-beat oscillation of RR intervals (RR) and blood pressure (BP). The so-called "sequence analysis" scans the simultaneous record of RR and BP for every sequence of ≥ 3 beats, during which both BP and heart rate are systematically rising or falling. The mean linear regression between BP and RR in all such sequences serves as an index of BRS.[5] The frequency domain methods use cross-spectral (fast Fourier transform or autocorrelation) analysis of nonrandom oscillations of RR and BP in specific frequency bands. If an identical frequency of significant oscillation of both BP and RR is found in the range of 0–0.5 Hz, the ratio of amplitudes of linearly coherent fluctuations is an index of BRS. Previously, as originally described by Robbe *et al.*,[6] fluctuations in low-frequency band (around 0.1 Hz) were used for the analysis. More recently, refined methods have been proposed calculating BRS index in both low- (LF, 0.05–0.15 Hz) and high- (HF,

Supported by the Linkage Grant 972835 by NATO, Scientific and Environmental Affairs Division, Brussels, Belgium

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Received: April 26, 1999
Accepted: June 23, 1999

0.15-0.40 Hz) frequency bands. Often, the mean of both bands is used as a measure of the global baroreflex gain.[7]

Several investigators have compared the standard phenylephrine test and different noninvasive methods and reported a good agreement in small groups of normal and hypertensive subjects.[6–10] However, only correlation analysis, which may be highly misleading, was used to indicate the agreement. Recently, three studies have been published[11–13] employing an appropriate method[14] for assessing the agreement. The results of these studies are rather discouraging. The limits of agreement between invasive and noninvasive spectral methods were ± 5 ms/mmHg for elderly normotensive and hypertensive subjects.[12] Results in patients post infarction were even worse, with the limits of agreement between ± 8.3 and ± 13.0 ms/mmHg,[12] ranging from ± 13.3 to ± 18.3 ms/mmHg for different spectral indices.[13] Moderate improvement has been observed during controlled respiration (± 11.8 ms/mmHg).[13] Similar disagreement was found between the results of phenylephrine and the "sequence analysis" method. It was consequently implied that the phenylephrine method has no sufficiently reliable noninvasive surrogates. At the same time, the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study[1] demonstrated significant clinical value of phenylephrine-based BRS testing. Thus, finding noninvasive surrogates of the phenylephrine test would be of considerable practical importance.

Little is known about the influence of different body positions and respiration patterns on baroreflex in both low- and high-frequency bands. Thus, it is not obvious to what extent poor stability of the proposed noninvasive surrogates contributed to the difficulties in reproducing the results of the phenylephrine test. It might be speculated that slow controlled respiration at frequency close to the inherent baroreflex frequency around 0.1 Hz will yield the most reproducible BRS estimates. The aim of the present study was to evaluate the mutual correspondence of BRS indices estimated by the cross-spectral analysis influenced by different body positions with different respiration regimes.

Methods

The study investigated 103 patients (73 men, aged 53 ± 12, range 20–82 years) referred for the management of coronary artery disease and/or hypertension. Coronary artery disease was present in 63 patients, 42 of whom had suffered previously from MI, 59 patients were hypertensive, and 18 had Type II diabetes mellitus. Each patient underwent a battery of standardized recordings of a single precordial electrocardiographic (ECG) lead and a noninvasive continuous finger arterial pressure (Finapres, Ohmeda, Englewood, Colo.). Both signals were sampled at 250 Hz/12-bit and stored in a computer-readable format for an off-line analysis. The following recordings were obtained in both supine and sitting positions: 5 min at rest, 3 min of controlled respiration at 0.1 Hz, and a 3-min period of controlled respiration at 0.33 Hz. Sufficient time for stabilization and/or recovery was used to separate individual procedures. Both ECG and pressure signals were carefully scanned visually to confirm all detected QRS complexes, to remove all beats of nonsinus origin, and to exclude incidental noise likely to interfere with the spectral analysis.[6] The frequency at which a distinct peak of maximum coherence of both signals occurred was searched between 0.033–0.133 Hz and 0.200–0.400 Hz to obtain low- (BRS-LF) and high-frequency (BRS-HF) baroreflex gain, respectively. Of all detected cross-spectral gains only those with coherence > 0.5 (arbitrary threshold) were accepted. For each subject, the global baroreflex sensitivity (G-BRS) was calculated as the average of all accepted baroreflex gains of both body positions, all respiration regimes, and both frequencies.

TABLE I Baroreflex sensitivity and percentage of valid assessment of all subjects examined in both body positions and during three respiration regimes

Body position	Supine			Sitting		
Respiration	Spont	Slow	Fast	Spont	Slow	Fast
BRS-LF (ms/mmHg)	6.8 ± 5.1	10.1 ± 7.9[b]	6.0 ± 4.8[a]	5.4 ± 4.3[c]	8.8 ± 8.6[b]	5.0 ± 5.3[c]
Valid BRS-LF (%)	79	100	85	74	99	86
BRS-HF (ms/mmHg)	10.1 ± 7.9[d]	—	9.8 ± 9.1[d]	8.6 ± 12.7[c]	—	6.6 ± 6.1[c,e]
Valid BRS-HF (%)	32	—	84	27	—	90

Statistics (Student's *t*-test for dependent samples):
[a] $p < 0.05$.
[b] $p < 0.0001$ vs. spontaneous respiration.
[c] $p < 0.01$ vs. supine position.
[d] $p < 0.01$ vs. corresponding BRS-LF value.
[e] $p < 0.05$ vs. corresponding BRS-LF value.
Abbreviations: Spont = spontaneous respiration; Slow = controlled respiration at frequency 0.1 Hz (6 cycles/min); Fast = controlled respiration at frequency 0.33 Hz (20 cycles/min); BRS-LF and BRS-HF = mean ± standard deviation (SD) of baroreflex sensitivity in low-(0.033–0.133 Hz) and high-frequency band (0.200–0.400 Hz), respectively; Valid-BRS-LF and Valid-BRS-HF = percentage of valid baroreflex gains of all examined patients in low-frequency and high-frequency band, respectively. Note that BRS-HF is not applicable during slow controlled respiration as there is no physiologically meaningful oscillation at this frequency under that condition.

Results

The numerical results are shown in Table I. The averaged G-BRS value was 7.5 ± 5.1 ms/mmHg. The BRS-LF gain in supine position was lower during fast controlled than during spontaneous respiration ($p<0.05$). All values of BRS-LF in the sitting position were lower than corresponding values in the supine position ($p<0.01$) except for slow controlled respiration. The BRS-LF values during slow controlled respiration were higher in both positions than the corresponding resting values ($p<0.0001$). All BRS-HF values in supine position were significantly higher than the corresponding BRS-LF values ($p<0.01$). In the sitting position, the BRS-HF value was higher than the corresponding BRS-LF value only during fast controlled respiration ($p<0.05$). Both BRS-HF values were lower in sitting than in supine position ($p<0.01$). The BRS-HF values did not decrease significantly during fast controlled respiration. Percentages of valid results were almost 100% during slow controlled respiration in both positions and the lowest for BRS-HF during spontaneous respiration.

Modified Bland-Altman plots revealed that the differences between individual BRS indices and G-BRS significantly and disproportionally increased with increasing values of G-BRS. The limits of agreement ranged from ± 7.3 to ± 16.6 ms/mmHg with bias from −2.6 to + 2.8 ms/mmHg. For G-BRS <5 ms/mmHg, the individual BRS indices agreed with G-BRS rather closely. The limits of agreement ranged from ± 1.7 to ± 4.1 ms/mmHg with bias from −1.0 to +0.7 ms/mmHg, and the best agreement (for an index with satisfactory percentage of validity) was achieved using BRS-LF of spontaneous respiration in the sitting position (Fig. 1).

Discussion

As a matter of measurement principle, the G-BRS estimate of BRS must be superior to individual indices of baroreflex gain. From a practical point of view, the main goal of baroreflex testing is to identify the subjects with a pathologically low BRS, e.g., < 3 ms/mmHg.[1] In this sense, the range of 0–5 ms/mmHg for G-BRS, where we observed a good stability, seems to be suitable.

It is not obvious to what extent the poor stability of noninvasive tests contributed to the poor correspondence between these tests and the phenylephrine-based assessment as previously reported.[11–13] This lack of stability suggests that very strict procedural standards need to be developed before the results of the noninvasive tests may be trusted. Only when such standards are in place, systematic examinations of the correspondence between the noninvasive and pharmacologically induced tests will be of practical value. It was surprising that the BRS-LF obtained during slow synchronized deep respiration in both supine and sitting position, during which the most pronounced BP and RR oscillation and the best coherences were achieved, were least comparable to G-BRS. On the other

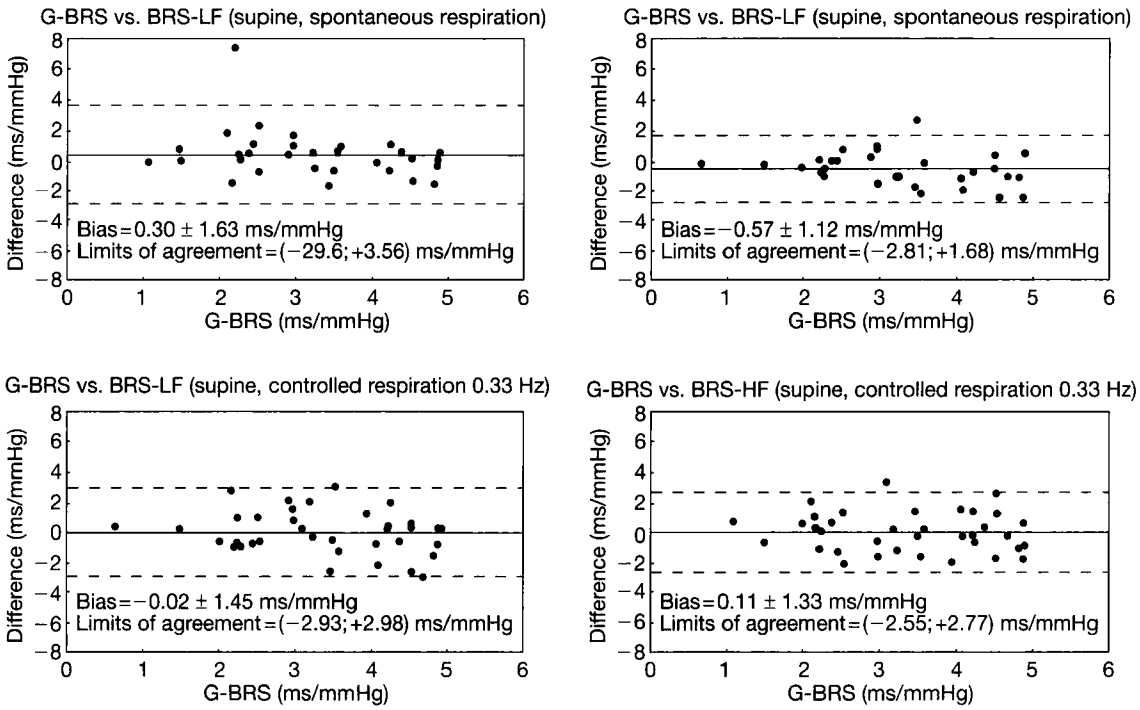

FIG. 1 Modified Bland-Altman plots for the comparison of different baroreflex sensitivity indices and the global baroreflex gain (G-BRS) in ms/mmHg (differences against the G-BRS). Bold line = mean difference (bias), dashed lines = limits of agreements (± 2 standard deviation). BRS-LF, BRS-HF = baroreflex gain in low- and high-frequency band, respectively.

hand, the best agreement was obtained for the BRS-HF during spontaneous respiration in supine position. However, valid BRS-HF was obtained only in 32% of all subjects on this condition (for this reason, these results are not shown here).

Hence, there is a significant bias and disagreement between different noninvasive BRS indices, which are similar to previously reported discrepancies between noninvasive BRS indices and the phenylephrine-based estimation. The analysis suggests that BRS estimated in the low-frequency band in sitting position during spontaneous respiration is the most representative and most reliable part of the global baroreflex gain.

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