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How to measure baroreflex sensitivity

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Introduction

In normal subjects arterial baroreflexes play a key role in short-term blood pressure adjustments to a variety of environmental stresses, thereby maintaining circulatory homeostasis. These responses are mediated by the sympathetic and parasympathetic nervous systems through their effects on heart rate, venous return, contractility and peripheral resistance. The evaluation of baroreflex sensitivity (BRS) has recently found unexpected exploitations as alterations in the baroreflex control of heart rate have been associated with an increased propensity for cardiac mortality and sudden cardiac death [1].

Among several quantitative approaches developed for evaluating BRS including the analysis of reflex responses to pharmacological or mechanical manipulations of baroreceptors, this article describes the use of vasoactive drugs and the analysis of spontaneously occurring changes in blood pressure and heart rate.

Vasoactive drugs

An increase in systemic arterial pressure increases the firing rate of baroreceptors which causes vagal excitation and sympathetic inhibition, thus decreasing heart rate; BRS can be quantified as the measure of the reflex bradycardia which follows the blood pressure rise induced by injection of an alpha-adrenoreceptor stimulant [2]. Generally, an increase in systolic arterial pressure by 20–40 mm Hg activates baroreceptors to operate in the linear portion of their reflex response.

In normal subjects 25–100 mcg of phenylephrine are flushed into a vein to increase systolic arterial pressure (SAP) by 20–40 mm Hg. The administration of the drug is performed in standardized laboratory conditions including a quiet, temperature controlled environment, during a continuous and simultaneous recording of one lead electrocardiographic signal and beat-to-beat arterial pressure. Heart rate and blood pressure are recorded continuously because, given the rapidity of vagal responses, it is commonly assumed that at normal resting heart rates each heart period value is mainly related on a cause-effect basis to the previous systolic pressure peak, and that this relation is linear. Prolongations of successive RR intervals with respect to baseline values (i.e. pre-injection) are therefore plotted as a function of preceding SAP changes and an analysis window is selected between the beginning and the end of the first significant (> 20 mm Hg) increase in SAP. The slope of the regression line fitted to the selected points (expressed as ms/mm Hg) — that is, the absolute increase in RR interval produced by a 1 mm Hg rise in SAP — represents BRS. Pearson's correlation coefficient is used to test the goodness of the linear association between SAP and RR interval changes.

Several injections are generally repeated at intervals of a few minutes and the corresponding slopes are averaged in order to reduce measurement variability between tests. The final slope is generally obtained by at least three slopes with the higher correlation coefficients. Estimates of BRS are very similar when SAP is measured directly from the radial or brachial artery or from a noninvasive pressure monitor [3, 4].

In normal young subjects average BRS values of 14.8 ± 9.2 ms/mm Hg (SD) [5], 16.0 ± 1.8 ms/mm Hg (SEM) [6] and 16.4 ± 4.2 ms/mm Hg [7] have been reported. When analyzing a test of BRS such a slope is generally interpreted as the result of the inter-

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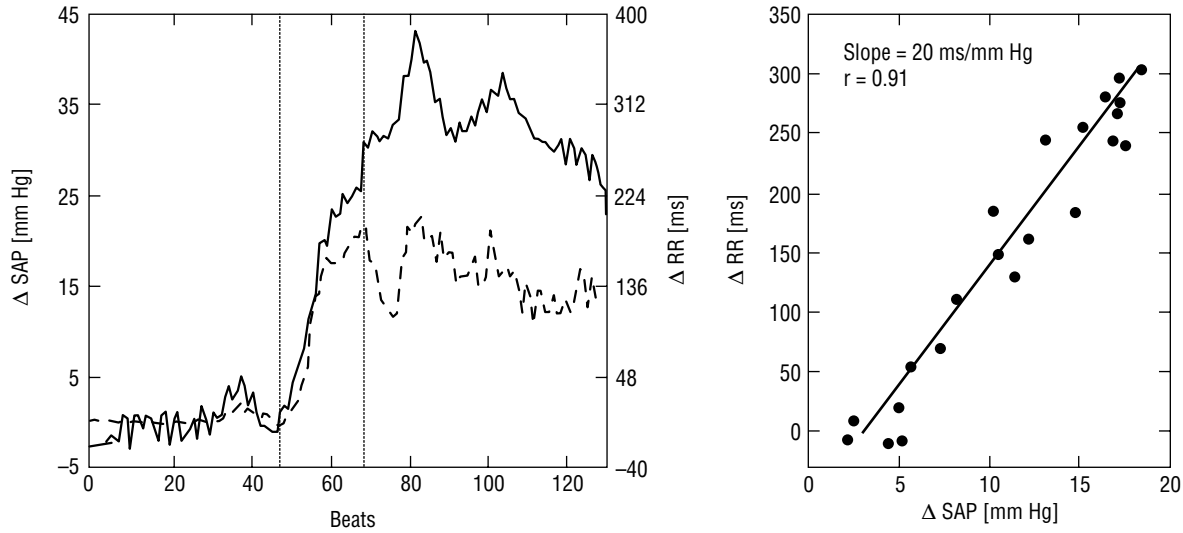

Figure 1. Example of a sensitive BRS. On the left beat-to-beat changes in systolic blood pressure (SAP) (dotted line) and in RR interval (continuous line) with respect to baseline values are reported. Analysis is limited to the first major increase in systolic arterial pressure with the attendant changes in RR interval (points included between dotted lines). These points are used for calculation of the regression line (on the right). The increase in SAP is greater than 20 mm Hg and is accompanied by a consistent increase in RR interval. Accordingly the slope of the regression line is 20 ms/mm Hg and represents a response primarily characterized by an increase in efferent vagus nerve activity to the sinus node.

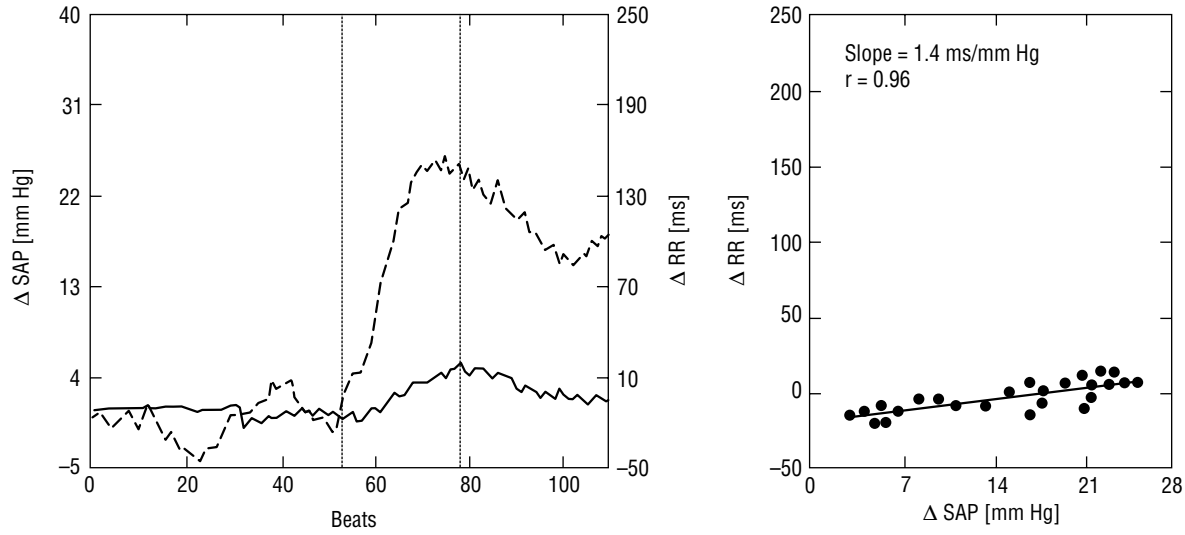

Figure 2. Example of a poor BRS. Detailed description as in Figure 1. The increase in SAP is accompanied by a modest increase in RR interval and the slope of the regression line is 1.4 ms/mm Hg and represents a response characterized by weak vagal reflexes.

play between effective vagal reflexes and tonic sympathetic activity (Fig. 1). By contrast, a flat slope may be due to abnormal vagal response or is the result of the inability of vagal reflexes to counterbalance sympathetic activation (Fig. 2). The major criticisms the phenylephrine test has been subjected to is that the phenylephrine injection, by acutely increasing left ventricular afterload, may activate other receptors such as cardiac mechanoreceptors and that the observed response is the results of multiple factors (including the stiffness of the arterial wall and transduction processes, the central integration, the sensitivity of the sinus node etc.). However, when BRS is used to draw inferences on the

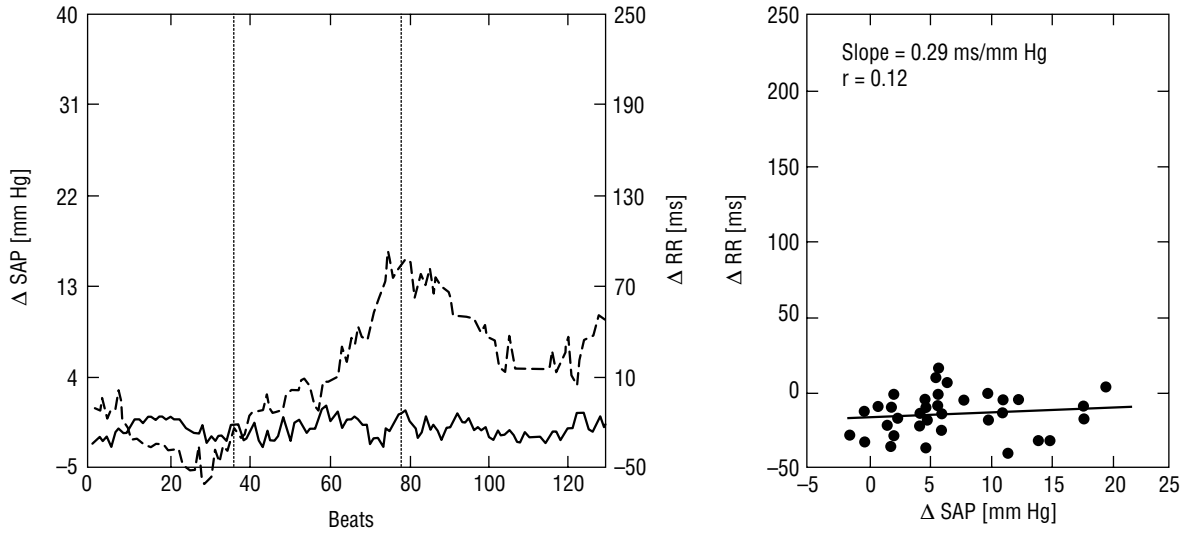

Figure 3. Example of a poor BRS in a patient with severe congestive heart failure. Detailed description as in Figure 1. The increase in SAP (> 30 mm Hg) is accompanied by small, erratic changes in RR interval. The slope of the regression line is near to 0 and the correlation coefficient is not statistically significant.

amount of autonomic mediators (acetylcholine, norepinephrine) released at cardiac level, a most important question for cardiac electrophysiology, this is no longer a limitation. Indeed, the fact that vasoactive drugs induce a simultaneous activation of multiple reflexogenic areas is actually an advantage for the purpose of using BRS as a measure of net autonomic balance to the heart.

Several methodological aspects of the phenylephrine technique deserve some comments and considerations when dealing with the application of this test in patients.

Rate of infusion

In patients after a recent myocardial infarction [8], for "safety reasons", phenylephrine has been injected over 30 s. However, provided that patients with unstable angina and uncontrolled arterial hypertension (> 160/90 mm Hg) are not tested, no ischemic episodes have been reported as a consequence of phenylephrine administration. At variance, in patients with heart failure in stable clinical condition it may be necessary to increase the rate of infusion of the drug as these patients show slower blood pressure changes [9].

Dosage of phenylephrine

In post myocardial infarction patients a dose of 2 mcg/kg is generally sufficient to obtain the required blood pressure change. If blood pressure does not increase as required additional injections will be made, increasing the dosage of phenylephrine by increments of 25 mcg. In patients with congestive heart failure [9] even higher doses (up to 10 mcg/kg) have been used to elicit baroreceptor responses.

Correlation coefficient

The value of the correlation coefficient also deserves several comments. When the correlation coefficient is higher than 0.7–0.8, and the pairs of data included in the analysis are greater than 10, a test of significance is not required since this correlation is obviously statistically significant. For lower values a test of significance is required to test the association between systolic arterial pressure and RR interval changes. When BRS values are near zero (–0.5 ÷ +0.5 ms/mm Hg) as it is commonly observed among patients with severely depressed left ventricular function and congestive heart failure, the correlation coefficient is obviously not significant. However, provided an adequate (> 15 mm Hg) systolic arterial pressure increase has been obtained, the BRS value is retained, independently of the not significant correlation coefficient (Fig. 3) [9]. In fact, this slope faithfully describes the observed phenomenon, namely the virtual absence of response between pressure elevation and RR interval. Paradoxically in some cases, (as in the transplant patient of Fig. 4), a BRS value near to 0 may have a statistically significant correlation coefficient. Finally, the correlation coefficient is not simply related to the scatter of data in the regression analysis as in some cases it can be improved by changing the lag between systolic pressure

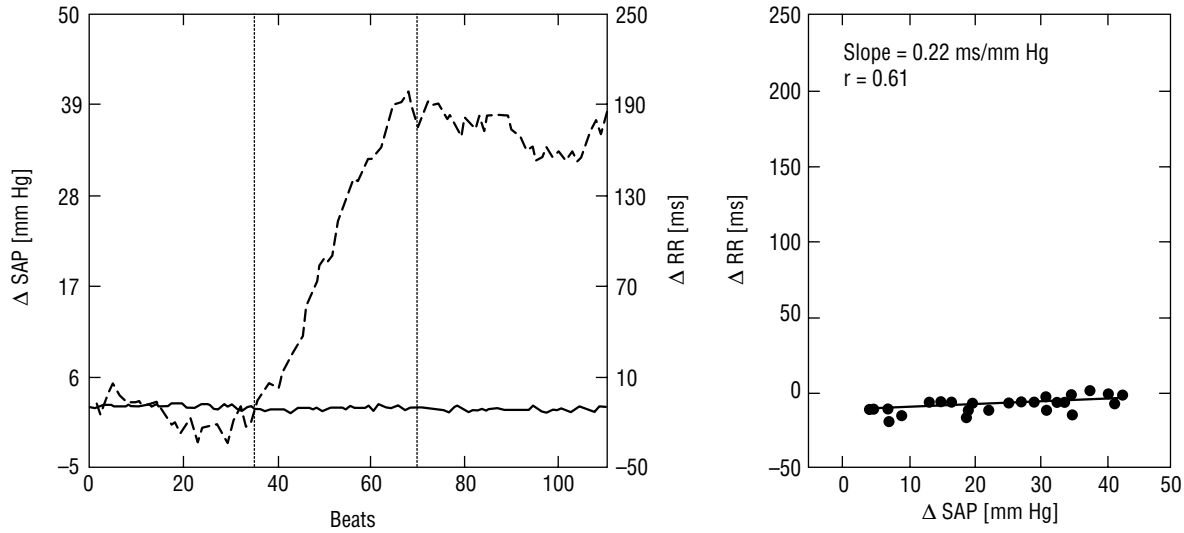

Figure 4. Example of a poor BRS in a patient with recent heart transplantation. Detailed description as in Figure 1. The increase in SAP is accompanied by a negligible change in RR interval. The slope of the regression line is near to 0, however the correlation coefficient is statistically significant ($p < 0.05$).

pulses and RR intervals. Abnormal respiratory patterns such as periodic breathing or Cheyne-Stokes respiration which are often observed in patients with heart failure [10] frequently induce such an erratic behavior of heart rate that definitely affects the correlation coefficient. In such cases this erratic behavior of heart rate can be markedly attenuated and a measurable BRS is obtained by the use of controlled breathing.

Overall, BRS decreases whenever the autonomic balance shifts toward sympathetic dominance and increases whenever the autonomic balance shifts toward parasympathetic dominance. Cardiovascular disease may alter baroreceptor function, primarily because of a decreased capability to activate vagal reflexes [6]. A case in point is represented by myocardial infarction that often significantly impairs baroreflex sensitivity. The underlying mechanism has not yet been demonstrated; however, a tenable hypothesis has been advanced [11, 12]. It was specifically proposed that myocardial infarction could often augment sympathetic afferent traffic and that this, in turn, would reduce vagal efferent activity. The presence of a necrotic and noncontracting segment may indeed alter the geometry of the beating heart and increase beyond normal the firing of sympathetic and vagal afferent fibers by mechanical distortion of their sensory endings [13]. Excitation of cardiac sympathetic afferent fibers inhibits tonic vagal efferent activity and blunts the baroreceptor-mediated reflex increase in vagal activity elicited by a blood pressure rise. The mean BRS was 7.2 ± 4.6 ms/mm Hg (SD) and 3.9 ± 4.0 ms/mm Hg (SD) in two large series of patients with a previous myocardial infarction [14] and with congestive heart failure [9] respectively.

While vasoconstrictor drugs mainly explore the vagal component of the baroreceptor control of heart rate, vasodilators have been used to obtain information on the sympathetic branch of heart rate control [15]. Baroreflex slopes obtained by vasodilators are lower than those obtained by increasing arterial pressure to a similar extent, suggesting that the two responses are not symmetric [16].

Analysis of spontaneous baroreflex sensitivity

Based on the evidence that the baroreflexes do not act only to control abrupt changes in arterial pressure, but are continuously activated by small variations of systolic arterial pressure, more recent — computer based-techniques, have allowed to evaluate baroreflex cardiovascular control without externally induced changes in arterial pressure, by the analysis of spontaneously occurring fluctuations in arterial pressure and heart rate. Two basic approaches have been proposed and validated: one based on "time domain" and one based on "frequency domain" measurements.

At variance with the previously described measures of BRS which have been standardized in supine position, use of these new approaches has offered a detailed assessment of the interaction between baroreflex function and the daily life

modulation of cardiovascular parameters [17]. However for clinical purposes, one ECG lead and beat-to-beat blood pressure recordings are continuously obtained for a given period of time in supine resting position during spontaneous breathing and/or during paced breathing.

Sequence methods of baroreflex sensitivity evaluation

The sequence method, described by Parati et al. [18], is based on the identification of three or more consecutive beats in which progressive increases in systolic blood pressure are followed by progressive lengthening in RR interval or, progressive decreases in systolic blood pressure are followed by a progressive shortening in RR interval. The threshold value for including beat-to-beat systolic blood pressure and RR interval changes in a sequence are set at 1 mm Hg and 6 milliseconds, respectively. Similarly to that which is done when vasoactive drugs are injected, information on the sensitivity of baroreflex control of heart rate can be obtained by computing the slope of the regression line between changes in systolic arterial pressure and the following changes in RR interval.

The advantages of this method are: strict automatically used criteria, which significantly restrict the subjective evaluation of BRS, and allows to separate calculation of BRS for short-term increasing and decreasing SAP sequences.

The baroreflex nature of these spontaneous RR interval/SAP sequences was demonstrated by showing that in cats the number of sequences markedly dropped (–89%) after the surgical opening of the baroreflex loop obtained by a sino-aortic denervation.

Spectral methods of baroreflex sensitivity evaluation

BRS evaluation using the spectral method is based on the concept that each spontaneous oscillation in blood pressure elicits an oscillation of similar frequency in the RR interval by the effect of arterial baroreflex activity. Two major oscillations are usually considered: that centered around 0.1 Hz, within the low frequency (LF) band (0.04 ÷ 0.15 Hz), and that associated with respiratory activity in the high frequency (HF) band (0.15 ÷ 0.40 Hz).

Various analysis methods have been described. According to the technique described by Pagani et al. [19], the autoregressive approach is used to perform univariate and bivariate spectral analysis. The baroreflex gain is quantified by performing the following steps: 1) estimation of the spectrum of heart period and SAP and computation of spectral components in the LF and HF bands; 2) estimation of the coherence function; and 3) computation of the square root of the ratio between the heart period and the SAP spectral components in both bands provided that the coherence between these components was ≥ 0.5. These two indexes are usually called alpha-LF and alpha-HF, respectively. In the method described by Robbe et al. [20], BRS is computed as the mean value of the transfer function in the frequency region around 0.07 to 0.14 Hz where the coherence is ≥ 0.5. In one of the modifications of this method, described by Pinna et al. [21], BRS is evaluated by averaging the estimated gain function between 0.04 and 0.15 Hz (LF band) using all curves regardless of the coherence. Representative examples are reported in Figure 5. The minimum recording time necessary for BRS evaluation in this method amounts about 4 minutes.

Several investigators have proposed that spectral estimations of baroreflex gain are reliable alternatives to the phenylephrine test [19, 20, 22, 23]. However these results have been obtained only in small groups of normal subjects or hypertensive patients and have been based on simple correlation analysis. Moreover, when comparing different methods for assessing BRS, it is important to emphasize that the "true" value of cardiac BRS is unknown: all the existing methods offer an indirect estimation of its "true" value. Simply due to the large amount of clinical data gathered with the phenylephrine test, this technique is still regarded as the "gold standard" in the assessment of BRS.

We have compared spectral measurements and the phenylephrine measured BRS in patients with a previous myocardial infarction and different degrees of left ventricular dysfunction [24] and analyzed the "agreement" between the two approaches using a method more appropriate than the correlation coefficient testing for simple linear dependence [25]. We found that despite a substantial linear association, the agreement between spectral measurements and phenylephrine in the estimation of baroreflex gain is weak because the difference can be as large as the BRS value being estimated. It is not surprising that the phenylephrine and spectral methods do not provide similar quantification of baroreflex gain in cardiac patients. Besides theoretical and methodological differences, from a clinical point of view, the phenylephrine baroreflex gain — which is the result of the complex interplay of multiple receptor areas and the hemodynamic burden produced by the after-load increase — yields information on the „whole"

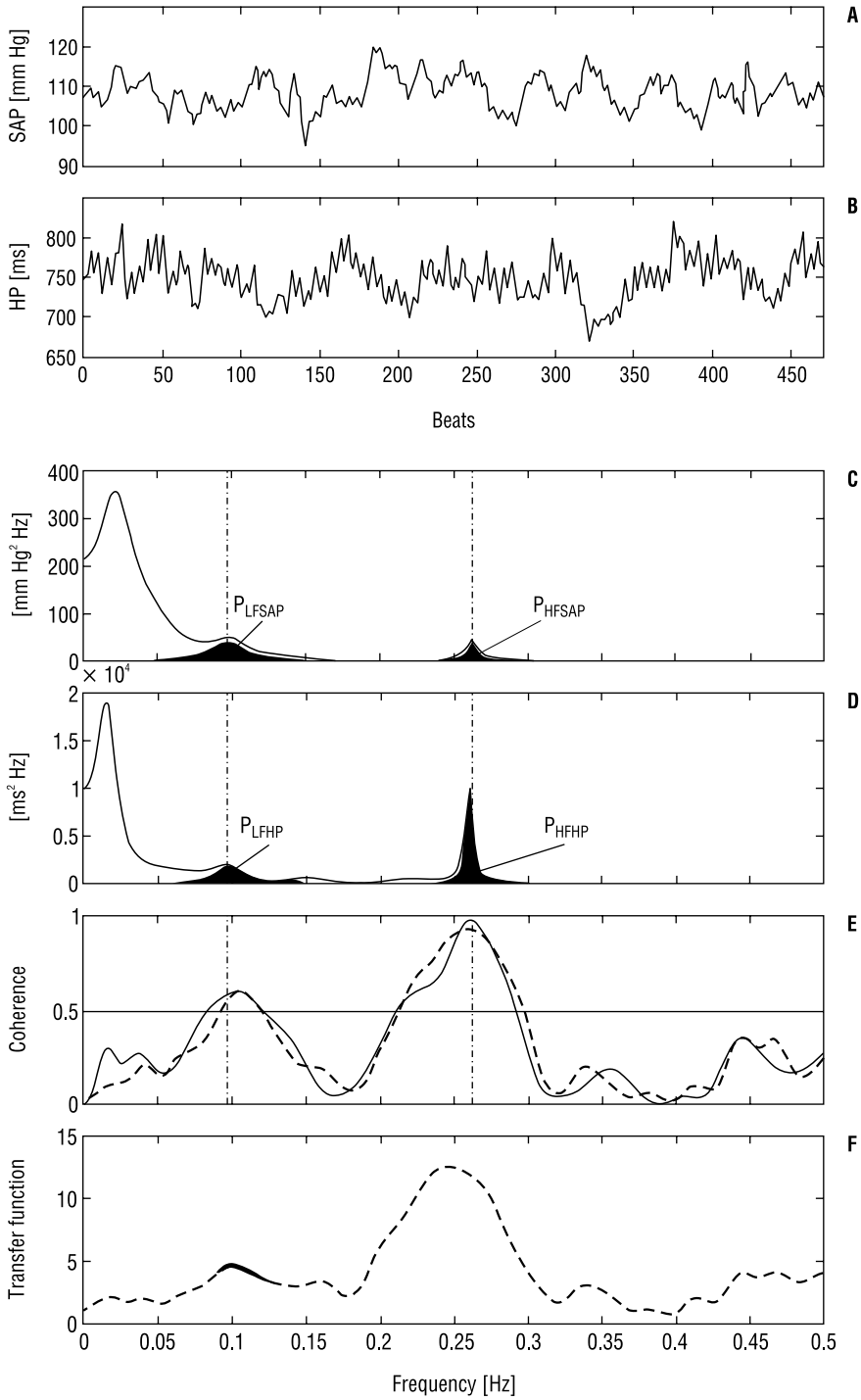

Figure 5. Example of the computation of the spectral indexes of Robbe et al. and Pagani et al. Panel **A** and **B** show representative examples of systolic arterial pressure (SAP) and heart period (HP) time series. The corresponding autoregressive spectra are shown in panels **C** and **D**, respectively; the coherence function between SAP and HP in panel **E** and the transfer function in panel **F**. The portion of the transfer function in the frequency region 0.07 to 0.14 Hz, where the coherence is ≥ 0.5, is plotted in bold. The mean value of this line is the baroreflex gain computed according to the Robbe technique. The darkened areas P_{LFSAP}, P_{HFSAP}, P_{LFHP} and P_{HFHP} in the two spectra represent the spectral components involved in the computation of the alpha-LF and alpha-HF, and the dashed-dotted lines in panels **C**, **D** and **E** indicate the LF and HF central frequencies. The alpha-LF is computed by dividing P_{LFHP} (corresponding to the LF component of SAP) by the P_{LFSAP} and taking the square root. The same holds for alpha-HF, considering the areas P_{HFHP} and P_{HFSAP}.

capability of the system to evoke an increase in vagal activity, whereas the spectral baroreflex gain yields information on the level of autonomic modulation on a continuous basis. Despite these differences, in a large series of 317 stable heart failure patients, we have found that non invasive BRS conveys relevant clinical and prognostic information [26].

In summary several methods have been developed to measure the baroreflex control of heart rate and blood pressure. Despite theoretical and practical differences both the invasive and non invasive estimates of baroreflex sensitivity have been demonstrated to carry prognostic information. However differences in clinical relevance should be addressed in wide populations.

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