Standing Revised: Assessing Baroreflex Sensitivity by the Modified Transfer Function Method

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Abstract

Baroreflex sensitivity (BRS) can be estimated non-invasively by computing the transfer function modulus (TF) between spontaneous oscillations of systolic arterial pressure (SAP) and RR interval within the LF band. In 21 healthy volunteers we tested the hypothesis that during standing the reliability of BRS-TF increases as a result of increased SAP power. We also assessed whether standing causes any change in BRS-TF.

BRS-TF was computed averaging the TF over the whole LF band and only within –3db points. We found that during standing the error of TF estimates markedly decreased compared to the supine posture. As this change was also accompanied by a decrease of BRS-TF, the reduction of the relative error was modest. Hence, standing is capable of reducing the uncertainty of TF estimates but this beneficial effect is partly offset by a simultaneous reduction of TF values. Of the two approaches for measuring BTS-TF, the average between –3db points showed the highest reliability.

1. Introduction

The baroreceptor-heart rate reflex (baroreflex sensitivity, BRS) can be estimated noninvasively by computing the transfer function modulus (from now on simply "TF") between spontaneous oscillations of systolic arterial pressure (SAP) and RR interval within the low frequency band (LF, 0.04-0.15 Hz) [1, 2]. We have shown recently that the reliability of TF estimates can be assessed accurately by computing 95% confidence intervals [3], and that this information can be used to define different criteria for measuring BRS [4]. Applying these concepts to real signals from normal and pathological subjects, large confidence interval are often observed [2]. Therefore, any method capable of reducing confidence intervals, and hence improve the reliability of TF estimates, would be highly desirable. A sensible procedure towards this end would be i) to careful examine which factors, from a theoretical point of view, are most important in determining the width of confidence interval, ii) to set some hypotheses accordingly, and iii) to test experimentally these hypotheses.

We have shown previously that the record length and the width of spectral window are two important parameters affecting the reliability of TF estimates [3]. Apart practical limitations, however, increasing record length beyond a certain value brings negligible improvements [3]. Similarly, the width of the spectral window can not be increased beyond a certain value without prejudicing the accuracy and resolution of spectral estimates [5].

A critical factor affecting the TF confidence intervals is the ratio between noise and SAP powers. As we have limited means to reduce noise sources, we should explore how to increase the variability of SAP oscillations (the input signal for the baroreflex) in a noninvasive way. A possible way could be making our recordings during standing instead of in the supine position.

The upright posture is a complex maneuver involving physical exertion, pooling of blood in the lower portions of the body, changes in respiration, changes in sensory inputs and a chain of autonomic and humoral responses. There is substantial direct evidence that arterial and cardiopulmonary baroreceptors are the main mediators of autonomic changes elicited by orthostatic stress [6].

A marked increase of LF oscillations of arterial blood pressure has consistently been observed in humans upon standing [7], and has been associated with the increased sympathetic activity which is responsible for major cardiovascular adjustments occurring in the upright posture [8].

In this study we tested the hypotheses that during standing the reliability of TF estimates, and hence the reliability of BRS measurements, increases as a result of increased SAP power. Moreover, as the standing maneuver has a physiological interest *per se*, an ancillary objective of this study was to assess whether standing causes any change in BRS as estimated by the TF method.

2. Methods

2.1. Theoretical background

Modelling spontaneous oscillations of the RR interval in the LF band as a linear time-invariant transformation of SAP oscillations through the baroreflex, plus uncorrelated noise [3], and using the weighted covariance spectral estimator [9], the confidence interval of the TF between SAP and RR interval is given by:

$$\left\| \hat{H}(f) \right| - \left| H(f) \right\| \le \sqrt{\frac{\hat{G}_N(f)}{\hat{G}_{SAP}(f)\cdot(2n-2)} \cdot F_{2,2n-2;\alpha}} \quad (1)$$

where $\hat{H}(f)$ and $H(f)$ are respectively the estimated and expected value of the TF at frequency f, and $\hat{G}_{SAP}(f)$ and $\hat{G}_N(f)$ are the spectral density functions of SAP and noise respectively. $F_{2,2n-2;\alpha}$ is the upper α point of the F distribution with the indicated degrees of freedom and $2n$ are the equivalent degrees of freedom of the spectral estimate, a parameter which depends on the record length and on the type and width of the spectral window. Half confidence interval for α=0.05 gives the range of the absolute error of the TF at each frequency with a probability of 0.95. Therefore, for practical purposes, we propose to use this function as error function of TF estimates.

2.2. Subjects

We considered for the study 29 healthy volunteers, 24 males and 5 females. Age and sex distributions were chosen so as to match demographic characteristics of cardiac disease patients referred to our hospital.

2.3. Experimental protocol

The experimental protocol included: 1) instrumentation and signal stabilization (about 20 min), 2) 8 min supine resting recording of ECG, instantaneous lung volume (ILV, Respitrace Plus) and noninvasive arterial blood pressure at the finger (Finapres 2300), 3) 8 min recording of the same signals in the standing position. Measurements in the standing position were undertaken after signal stabilization and Finapres recalibration (typically 3 min).

2.4. Measurements

RR (resolution 1 ms) and SAP time series were obtained from raw signals. All signals were resampled at 2 Hz. The widest sub-record free from artifacts, large transients or marked changes in the fluctuation pattern of the signals was interactively selected in both supine and standing recordings. In order to avoid the confounding effect of different record lengths between supine and standing, the longest recording was cut (center justified) to the length of the shortest. To be eligible for the study, the latter had to be ≥ 180 s.

Breathing frequency was obtained by computing the barycentric frequency of ILV spectral components (AR spectral decomposition, Johnsen and Andersen algorithm) in the high frequency band (HF, 0.15-0.45 Hz). Patients having i) an irregular or slow breathing pattern in either recording (≤ 80% of the power in the HF band) were discarded from analysis. This was done to avoid the confounding effect of respiratory components in the LF band [10].

The power of SAP and RR interval in the LF band was computed by integration of corresponding power spectral densities (weighted covariance method, 0.015 Hz bandwidth Parzen window [5]). The TF between SAP and RR interval time series was obtained from bivariate spectral analysis (weighted covariance method, 0.03 Hz-bandwidth Parzen window [3]). BRS was finally computed using two slightly different approaches: i) averaging the TF over the whole LF band (BRS-TF_w) and ii) averaging the TF only at those frequencies comprised between its –3db points (BRS-TF_{3db}). This second approach is based on the observation that the shape of the TF usually resembles a band-pass filter; therefore, following a common engineering practice, its transfer properties are better described by the gain in the pass-band region.

A comprehensive measure of the reliability of TF estimates (and hence of BRS) was obtained by averaging the error function over the entire LF band and between –3db points, depending on the approach used. Accordingly, the two error figures will be referred to as Err-TF_w and Err-TF_{3db}.respectively. Normalizing these figures by the corresponding BRS value, we obtained relative errors, namely RelErr-TF_w and RelErr-TF_{3db}.

2.5. Statistical analysis

Since some variables showed a markedly skewed distribution, descriptive statistics are given as median (interquartile range). Paired comparisons were performed by the Wilcoxon signed rank test. A P level < 0.05 was considered statistically significant.

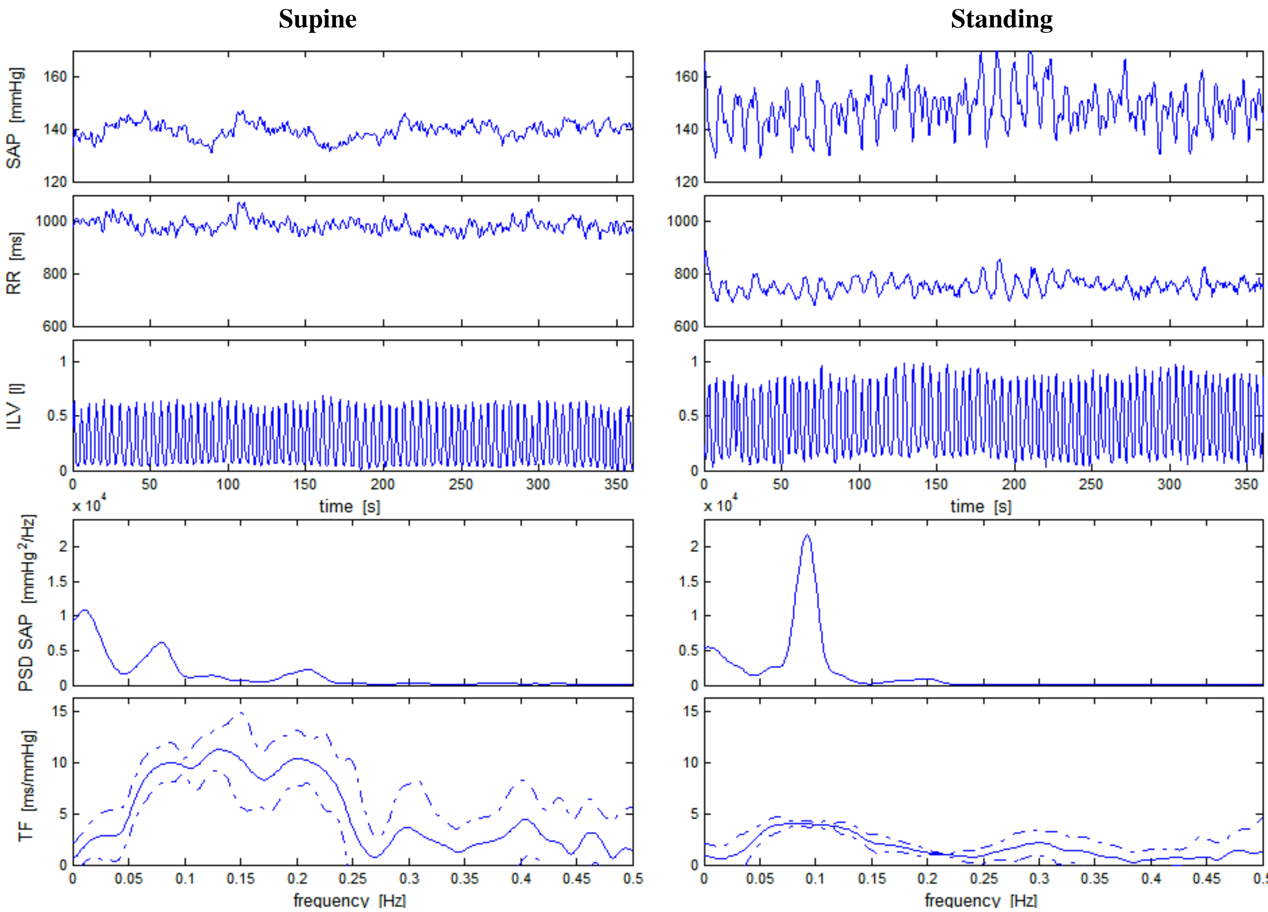

Fig. 1. Representative example of recorded signals, power spectral density (PSD) of systolic arterial pressure (SAP) and transfer function modulus (TF) with 95% confidence intervals (dashed-dotted line), in the supine and standing position.

Table 1. Descriptive statistics of study results.

	Supine	Standing
Mean SAP (mmHg)	111 (101-121)	116 (106-130)[a]
Mean RR (ms)	878 (737-933)	749 (652-884)[b]
SAP LF power ($mmHg^2$)	5.1 (3.4-7.6)	12.4 (7.8-14.5)[b]
RR LF power (ms^2)	165 (127-348)	215 (81-611)[c]
BRS-TF_w (ms/mmHg)	4.6 (3.3-7.1)	3.6 (2.2-5.8)[d]
BRS-TF_{3db} (ms/mmHg)	5.3 (3.5-8.0)	4.0 (2.5-6.4)[e]
Err-TF_w (ms/mmHg)	1.8 (0.0-2.0)	0.9 (0.7-1.8)[b]
Err-TF_{3db} (ms/mmHg)	1.9 (1.0-2.1)	0.9 (0.6-1.7)[b]
RelErr-TF_w (%)	39 (31-46)[h]	31 (28-41)[f]
RelErr-TF_{3db} (%)	33 (25-43)	26 (23-33)[g]

a) P =0.04, b) P <0.0001, c) P =0.16, d) P =0.003, e) P=0.001, f) P =0.14, g) P =0.013, h) P < 0.0001 compared to RelErr-TF_{3db}

3. Results

Recordings from 21 subjects were adequate for the study (20 males, 1 female). Record duration was 414 (295-440) s, spanning from 191 s to 518 s. Breathing frequency was remarkably similar in the two experimental conditions (supine: 0.25 (0.21-0.28) Hz, standing: 0.24 (0.22-0.27) Hz, P=0.58).

A representative example of recorded signals, SAP spectrum and TF (with 95% confidence interval) in the supine and standing conditions is given in fig. 1.

A marked increase of spontaneous LF oscillations can be appreciated in the standing condition compared to supine. This is accompanied by a marked decrease of the TF and by the narrowing of confidence intervals in the LF band.

Descriptive results for cardiovascular parameters, BRS estimates and error figures are reported in table 1.

4. Discussion and conclusions

As expected, passing from the supine to the upright posture elicited a tachycardic response and a marked increase of SAP oscillations in the LF band. A similar increasing trend, not reaching statistical significance, was observed in LF oscillations of the RR interval. The increase in SAP variability was accompanied by a marked reduction of the estimation error and by a decrease of BRS (using both computational approaches). As a consequence, relative errors showed a modest reduction (≈ -20%) passing from supine to standing, and this change was statistically significant only using BRS-TF_{3db}. The latter approach was also capable of providing the lowest relative error between the two approaches.

The finding of a reduced baroreceptor-heart rate reflex during standing is in agreement with the classical study from Pickering et al. using the pharmacological approach (phenylephrine test) to measure BRS [11]. This decrease in BRS is likely to be caused by sympathetic activation during standing.

We found an average increase in SAP of about 5 mmHg in the upright posture compared to the supine condition. This result is in agreement with a previous study using an head-up tilt protocol [12], and could be explained as the net effect of the different loading/unloading conditions of aortic and carotid baroreceptors during standing.

In conclusion, the theoretical expectation of a marked reduction of the magnitude of the error of TF estimates during standing as compared to the supine position, has been confirmed experimentally in this study using two slightly different approaches of BRS estimation. Yet, as standing was also accompanied by a reduction in BRS, the improvement in terms of percentage error was modest. Hence, standing is capable of reducing the uncertainty of TF estimates but this beneficial effect is partly offset by a simultaneous reduction of TF values.

Of the two approaches for measuring BRS considered in this study, the one based on averaging the TF between –3db points in the LF band showed to provide a better reliability and to achieve greater benefits from standing.

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