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System identification of baroreflex response to mild lower body negative pressure

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***Abstract*—The effect of mild lower body negative pressure (LBNP) on baroreflex control of arterial blood pressure (ABP) has long been thought to affect cardiopulmonary baroreflex only, although recent studies have pointed out that arterial baroreceptors may be transiently unloaded too after the rapid onset of mild LBNP. This paper presents a spectral decomposition method for the black box identification of the contribution of arterial and cardiopulmonary baroreflexes to beat-by-beat variability of ABP in response to mild LBNP levels. The significant decrease of mean and diastolic arterial pressure and of the arterial baroreflex mediated contribution to overall variability of ABP which was found, suggested that the unloading of arterial baroreceptors may be reflected by an altered dynamic response of arterial baroreflex, too. In addition, arterial baroreflex mediated modulations were found to be the main player in the modulation of beat-by-beat fluctuations of ABP, while the role of cardiopulmonary baroreflex mediated responses appeared to contribute very little.**

I. Introduction

MILD lower body negative pressure (LBNP) has long been considered a stimulus able to selectively unload cardiopulmonary baroreceptors, by acting on small variations of venous return (VR). However, it has been recently reported that a transient change in arterial blood pressure (ABP) occurs following the onset of mild LBNP, consisting of a decrease followed by an increase and recovery of basal values within ~ 15 beats [1,2,3]. This simple observation of the time domain course of ABP, which had been overlooked because mean arterial pressure (MAP) is not changed by mild LBNP (< 20 mmHg), was interpreted as a compensatory response due to the action of the arterial baroreflex (ABR), thus questioning the belief that only cardiopulmonary baroreflex (CPBR) is affected by mild LNBP, as a consequence of selective unloading of low pressure baroreceptors. Although the effects of the ABR response on vascular resistance can be found by very simple and straightforward analysis of MAP series in the time domain, a more thorough mathematical modeling of baroreflex regulation of ABP could enable to better interpret the mechanisms of baroreflex mediated responses to the changes induced by LBNP. In particular, system identification of ABR and CPBR control of ABP could shed light on the effects of mild LBNP and the potential impairment of neural and non neural responses to it, which can characterize orthostatic intolerance, for instance in patients who experience baroreflex failure, or in astronauts upon return on Earth after prolonged exposition to a low gravity environment.

In this paper, a model for the identification of ABP variability will be presented, and applied to data from a protocol of mild LBNP, with the purpose of investigating the ABR and CPBR responses in the frequency domain, by means of spectral analysis and spectral decomposition techniques.

II. Materials and Methods

A. Experimental Protocol

Hemodynamic recordings were selected from the database of the WISE (Women International Space Simulation for Exploration) study [4,5,6,7]. The WISE protocol entailed 20 days of ambulatory control period followed by 60 days of -6° head down bed rest. For the purpose of this paper, we analyzed data from four subjects (age 33±1 years, height 165±3 cm, weight 59.5±2 kg), taken from the control epoch. Intra- and post- bed rest recordings were not analyzed. One of the experiments which were carried out in the WISE study was the application of cycles of continuously increasing LBNP. After recording spontaneous hemodynamic variability for about 2 minutes, LBNP was rapidly applied to a level of -10 mmHg and maintained for approximately 2 minutes, then increased to -20 mmHg and maintained for approximately 2 minutes, then further increased to -30 mmHg for approximately 2 minutes, then discontinued.

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Measurements included ECG, ABP measured by means of finger cuff method (Finometer®, Finapress Medical Systems, The Netherlands), central venous pressure (CVP) measured by means of a catheter in the left antecubital vein, and respiration (RESP) measured by a thoracic belt.

B. Pre-processing of signals

Standard algorithms were used to extract the R peak from the electrocardiographic signal and identify the cardiac beats. Within each cycle, the systolic and diastolic value were then extracted from the ABP waveform.

In order to study the hemodynamic variability, zero-mean normalized beat-by-beat series ($y(i)$) were built from the original raw signal ($y_r(i)$) after subtracting the mean ($\bar{y}_r$) and dividing by the mean:

$$y(i) = \frac{y_r(i) - \bar{y}_r}{\bar{y}_r} \quad (1)$$

In this way, beat-by-beat variability series were obtained for: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure (PP), calculated as the difference between SBP and previous DBP, central venous pressure (CVP) and RR. Evenly spaced time series were subsequently derived by resampling of beat-by-beat series in the time domain, by means of an anti-aliasing low pass filter. Sampling frequency was 1 Hz.

C. System identification of baroreflex control of arterial blood pressure

We previously proposed a model for the black-box identification of ABP variability and its spectral decomposition [8] for the estimate the input-output relationship between cardiovascular variables and, therefore, to model the control mechanisms responsible for short term regulation of blood pressure.

Considering the findings reported in [8] and the relationship between diastolic decay and total peripheral resistance [9], it could be assumed that beat-by-beat fluctuations of DBP reflect beat-by-beat fluctuations of total peripheral resistance, which depend on sympathetic and baroreflex vasomotor tone control.

Thus, short term variability of DBP can be predicted by a multi input model:

$$DBP(i) = \sum_{j=i}^{n} h_{ds}(j) \cdot SBP(i-j) + \sum_{j=i}^{n} h_{dv}(j) \cdot CVP(i-j) + h_{dt} \cdot HP(i-1) + u_d(i) = DBP_{/sbp} + DBP_{/cvp} + DBP_{/hp} + u_d \quad (2)$$

In addition to the inputs given by SBP and HP (heart period, computed from the RR interval) [8], the model in equation (2) also utilizes CVP as an input to DBP prediction.

The black-box input-output relationships in (2) are assumed to be representative of different effects on the beat-by-beat variability of DBP:

- SBP → DBP: sympathetic and arterial baroreflex vasomotor tone control
- CVP → DBP: afterload resistance control by cardiopulmonary baroreflex
- HP → DBP: effect of diastolic runoff on the diastolic end point
- The residual error on the model prediction may account for sources of variability that are not measured, such as autoregulation mediated control of peripheral resistance.

D. Time domain analysis

The mean values of RR interval duration and heart rate, of MAP, SBP,DBP, PP, and of CVP were computed in each epoch of the experiment.

E. Spectral analysis

Autoregressive (AR) spectra were computed for all variability series.

To quantify the contribution of ABR and CPBR to the modulation of afterload resistance, the power content in the low frequency (LF, ~ 0.1 Hz) band of DBP, of DBP/SBP, and of DBP/CVP was observed in its changes from baseline, due to the applications of the LBNP stimulus.

F. Statistical analysis

Paired Student's t-test was applied to data to compare each LBNP epoch with spontaneous variability as recorded during baseline.

Table I: Time domain and frequency domain indices
(mean±se; * indicates statistically significant difference from BL with p-value < 0.05)

	BL	LBNP = -10 mmHg	LBNP = -20 mmHg	LBNP = -30 mmHg
RR (s)	0.890 ± 0.021	0.913 ± 0.027	0.882 ± 0.012	0.841 ± 0.014*
MAP (mmHg)	94 ± 4	91 ± 4*	89 ± 4	89 ± 3
SBP (mmHg)	124 ± 4	120 ± 4	116 ± 4*	115 ± 4
DBP (mmHg)	74 ± 4	72 ± 4*	72 ± 3	72 ± 3
LF ($DBP_{/SBP}$) / LF(DBP)	48 % ± 11 %	36 % ± 14 %*	29 % ± 2 %	31 % ± 7 %
LF ($DBP_{/RR}$) / LF(DBP)	12 % ± 7 %	12 % ± 4 %	22 % ± 2 %*	19 % ± 5 %
LF ($DBP_{/CVP}$) / LF(DBP)	22 % ± 16 %	6 % ± 3 %	2 % ± 0.4 %	9 % ± 3 %

III. Results

A. Time domain

Mean values of RR, MAP, SBP, DBP in the different epochs of the protocol are summarized in table I.

MAP was significantly lower at -10 mmHg than in baseline, DBP decreased significantly at -10 mmHg, while SBP decreased at -20 mmHg, and RR was reduced at -30 mmHg.

B. Frequency domain

Spectral computation of DBP variability series and the components derived from system identification showed that the largest contribution to DBP power is conveyed by SBP in all epochs of the experiment. A clear peak about 0.1 Hz was always estimated and total power and LF power tended to increase with incremental values of LBNP (figures 1-4, obtained from the same subject).

The components of DBP variability predicted by CVP and RR only marginally contributed to overall variability of DBP. However, the contribution of RR appeared to become larger with increasing levels of LBNP. On the other hand, $DBP_{/CVP}$ never conveyed a great amount of power and its power was mainly concentrated in the very low frequency (VLF, $f < 0.04$ Hz) band of its spectrum.

No significant variation from baseline was found in either the LF or total power of DBP and its components in any of the LBNP epochs. The power in the high frequency (HF, $0.15 < f < 0.5$ Hz) was disregarded because of the largely predominant concentration of DBP power in the LF band. As regards the contribution of the three inputs to DBP variability, the respective weight of SBP, RR, and CVP on DBP power at LF was equal to 48%±11%, 12%±7%, 22±16% during baseline. The contribution of SBP was significantly lower at -10 mmHg, while RR increased its relevance for the prediction of SBP power at -20 mmHg.

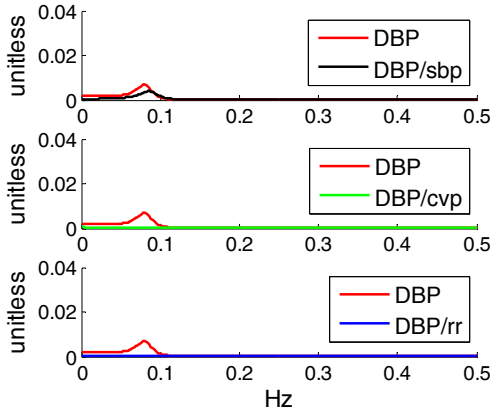

Fig. 1. Spectra of DBP, and components derived from system identification, from one subject during baseline

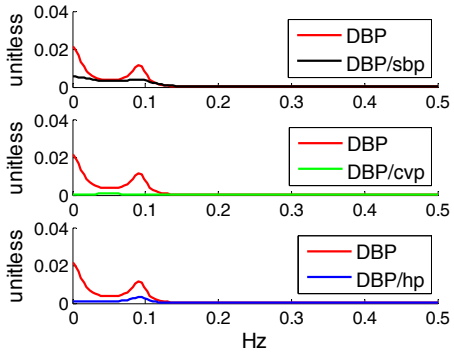

Fig. 2. Spectra of DBP, and components derived from system identification, from one subject during LBNP = - 10 mmHg

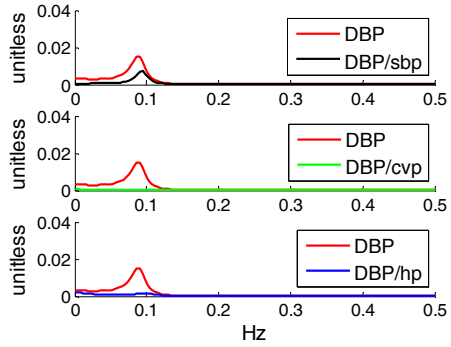

Fig. 3. Spectra of DBP, and components derived from system identification, from one subject during LBNP = - 20 mmHg

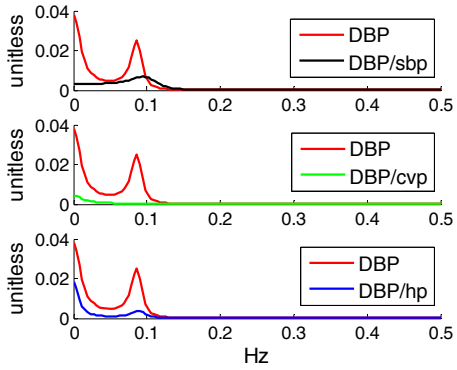

Fig.4. Spectra of DBP, and components derived from system identification, from one subject during LBNP = - 30 mmHg

IV. Discussion

The changes of mean values in the time domain appeared consistent with the previously reported effect of rapid onset mild LBNP. The decrease in DBP and MAP suggested that the control of peripheral resistance by baroreflexes is actually affected by LBNP, although such reduction was rather small for a very mild level of LBNP. The control of circulating volumes and heart rate, on the other hand, may come into play with higher levels of LBNP, as hinted by the diminished SBP at -20 mmHg, which could reflect an effective reduction in circulating volumes caused by the limitation in venous return due to LBNP. As a compensation to the ensuing reduction in beat-by-beat stroke volume, heart

rate was increased at -30 mmHg, and it may be hypothesized that stronger LBNP stimuli would produce a much larger effects on volumes and on heart rate compensations, as long as the system is able to compensate to the shift of volumes to the venous side. The goal of this paper was to interpret these phenomena in the frequency domain, thus opening a window on the black box identification of the response of autonomic control of ABP and HR. The prediction of DBP from SBP, CVP, and RR showed that most of DBP power is predicted by SBP, that RR has little effect, and that CVP contributes very marginally to DBP power. This result, which was found in all epochs of the protocol, points to the importance of the arterial baroreflex in the control of total peripheral resistance, particularly in spontaneous variability. The impairment of the arterial baroreflex following the onset of LBNP may therefore explain the reduction in MAP and DBP observed in the time domain, consistently with the trends observed by [1,2,3], which prompted those authors to conclude that mild LBNP not only affects CPBR as a result of a diminished venous return, but it also has an impact on the arterial baroreflex. Consistently with these comments, the spectral decomposition presented in this paper showed that the role of SBP in the prediction of DBP was reduced at LBNP = - 10 mmHg, which may hint that the tightness of arterial baroreflex control of vascular resistance is actually affected by mild LBNP. In addition, the increased role of RR in presence of a blunted baroreflex control of pressure, indicated that the variability of the duration of the diastolic interval assumed greater importance in determining the end diastolic value.

In conclusion, although our indices provide a black-box, indirect identification of baroreflex dynamic responses to LBNP, their importance may rely in a greater level of detail in describing the unloading of both low pressure and arterial baroreceptors, and may help understanding the basic patho-physiological changes associated with stimuli such as simulated microgravity or simulated orthostatic stress, utilizing non invasive or minimally invasive hemodynamic recordings.

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