Effects of Prolonged Bed Rest on the Total Peripheral Resistance Baroreflex

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Abstract

Orthostatic intolerance following prolonged exposure to microgravity continues to be a primary concern of the human space program. Reduced autonomic tone has been demonstrated to contribute to this phenomenon, and the heart rate baroreflex, in particular, has been repeatedly shown to be impaired. However, only the works of Yelle et al. have attempted to address the role of the total peripheral resistance (TPR) baroreflex, a potentially more significant contributor to blood pressure regulation. We applied a previously developed method for estimating the static gains of both the arterial and cardiopulmonary TPR baroreflexes to data obtained before and after 16-day bed rest. Reductions in the estimated static gains of the arterial (statistically significant) and cardio-pulmonary TPR baroreflexes were found after bed rest. This study supports the works of Yelle et al, which imply that the TPR baroreflex is reduced after spaceflight.

1. Introduction

Microgravity-induced orthostatic intolerance continues to be a primary concern of the human space program. It has been reported that about 25% of astronauts have experienced difficulty exiting the space shuttle or had orthostatic intolerance evidenced by presyncopal symptoms (nausea, vomiting, light-headedness) during stand tests after 8-14 days of flights [1]. The etiology of orthostatic intolerance is unclear, but it is the consequence of a failure to maintain normal arterial blood pressure (ABP) which results in inadequate cerebral perfusion. Various mechanisms, such as reduced blood volume, cardiac atrophy, and peripheral blood pooling associated with increased venous compliance have been shown to contribute to this phenomenon. A diminished heart rate (HR) baroreflex has also repeatedly been implicated as a contributing factor [1,2].

Circulatory baroreflex pathways have been studied to a significantly lesser degree due to difficulties in obtaining the relevant measurements. However, they may be more important to ABP regulation than cardiac baroreflex pathways. For example, according to Guyton [3], venous return is nearly saturated at non-elevated right atrial pressures and thus, ABP could not be substantially increased by enhancing cardiac function. The TPR baroreflex, in particular, may be the most important short-term contributor to ABP regulation as TPR affects ABP directly via Ohm's law and indirectly via venous return. Despite this possibility, the effects of microgravity on the TPR baroreflex are largely unknown, because there has been no practical technique available for its measurement.

We previously developed a system identification method aimed at quantitating the static gains of both the arterial TPR baroreflex (feedback transfer relationship from ABP to TPR) and the cardiopulmonary TPR baroreflex (feedback transfer relationship between right atrial trasmural pressure (RATP) and TPR) from beat-to-beat measurements of ABP and cardiac output (CO), each of which may be measured noninvasively in humans. At a conceptual level, the method seeks to infer the extent of the reflex control of TPR through the relationship between the fluctuations in the measured signals. For example, if there were no reflex control, then an X% step increase in CO would cause an X% increase in ABP in the steady-state due to Ohm's law. However, if there were a negative feedback TPR baroreflex, then the steady-state percent change in ABP would be less than the X% step increase in CO due to the reflex drop in TPR. Thus, the steady-state percent change in ABP would indicate the extent of the reflex control of TPR, with a smaller percent change associated with a larger TPR baroreflex static gain.

In this paper, we applied the identification method to noninvasively measured CO and ABP signals obtained prior to and after 16-day 4-degree head-down-tilt bed rest, an accepted ground-based model of microgravity [4].

2. Identification method

The identification method is employed in two steps. The first step is based on the block diagram of Figure 1 which includes two transfer functions (CO→ABP and SV→ABP) and an unobserved, perturbing noise source (N_{ABP}: the residual ABP variability not accounted for by

the transfer functions). The aim of the first step is to identify the two transfer functions and the perturbing noise source by analyzing the fluctuations in the measured signals normalized with respect to their mean values (see below). This is specifically achieved by utilizing an autoregressive moving average structure in conjunction with a parameters reduction algorithm [5]. In the second step, the static gains of CO→ABP and SV→ABP are utilized to compute the static gains of Arterial TPR Baroreflex and Cardiopulmonary TPR Baroreflex according to physiologic models as described below.

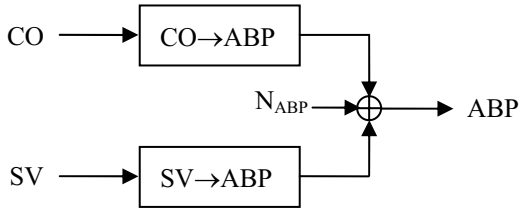

Figure 1. Block diagram upon which the TPR baroreflex identification method is based.

In particular, CO→ABP encompasses the dynamical properties of the Arterial TPR Baroreflex as well as the Systemic Arterial Tree according to the physiologic model in Figure 2. (This model assumes that the considered ABP variability is small.) As its name suggests, Systemic Arterial Tree characterizes the mechanical properties of the systemic arteries and specifically couples CO fluctuations to ABP fluctuations as well as TPR fluctuations to ABP fluctuations. The physiologic model of Figure 2 indicates, for example, that an increase in CO would initially cause ABP to increase via Systemic Arterial Tree. This would, in turn, excite the Arterial TPR Baroreflex/Systemic Arterial Tree arc to decrease TPR so as to maintain ABP.

According to the physiologic model of Figure 2, the static gain of Arterial TPR Baroreflex may be exactly computed from the static gain of CO→ABP, since the static gain of Systemic Arterial Tree is identically one due to the normalization of the analyzed signals with their respective mean values. The computed static gain of Arterial TPR Baroreflex is unitless and indicates, for example, that if ABP increases by X% with respect to its mean value, then TPR will change, in the steady-state (with respect to its mean value), by the product of the computed static gain and X%.

SV→ABP encompasses the dynamical properties of the Arterial TPR Baroreflex and Cardiopulmonary TPR Baroreflex as well as Inverse Heart-Lung Unit and Systemic Arterial Tree according to the physiologic model in Figure 3. (This model assumes that SV fluctuations are completely accounted for by RATP fluctuations [5], and the considered ABP variability is small.) Inverse Heart-Lung Unit couples SV fluctuations to RATP fluctuations and thus represents the *output-input* relationship of the heart-lung unit. This physiologic model suggests, for example, that an increase in SV would indicate that an increase in RATP had occurred through Inverse Heart-Lung Unit. This RATP increase would excite the Cardiopulmonary TPR Baroreflex to decrease TPR which would then stimulate the Arterial TPR Baroreflex/Systemic Arterial Tree arc in order to increase TPR and maintain ABP.

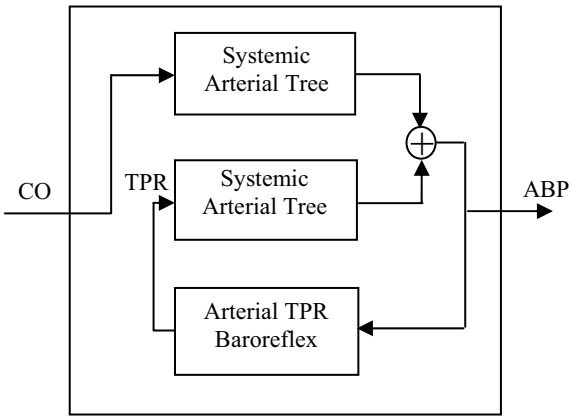

Figure 2. Physiologic model representing CO→ABP.

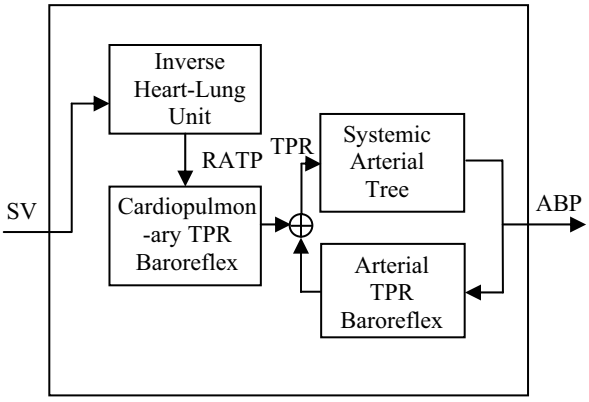

Figure 3. Physiologic model representing SV→ABP.

The physiologic model here may appear to be counter-intuitive, since the increase in SV does *not* cause an increase in CO and thus ABP through Systemic Arterial Tree. The reason for this is that SV→ABP is mathematically defined to characterize the effects of SV fluctuations on ABP fluctuations while all other considered inputs to ABP fluctuations (which includes CO fluctuations here) are held perfectly constant. This implies that the increase in SV must be accompanied by a commensurate decrease in HR. Since the static gain of Inverse Heart-Lung Unit is also equal to one here, a unitless static gain of Cardiopulomonary TPR Baroreflex

may be exactly computed from the static gains of both SV→ABP and CO→ABP according to the physiologic models of Figures 2 and 3.

We have validated this method with respect to a realistic cardiovascular model [6]. We have also demonstrated that the method could track (nearly statistically significant) increases in the static gain of the TPR baroreflex resulting from a modest 30 degree tilt in posture (unpublished data). In a parallel study, the promise of the method has been shown with respect to conscious sheep preparations [7].

3. Bed rest protocol

Twelve male subjects (age: 32.8±9.9 (SD) years, height: 70.0±2.2 (SD) inches, weight: 78.3±8.2 (SD) kilograms) were recruited for this study. All potential subjects were screened via physical and psychological examinations. Subjects with sleep disorders, drug/alcohol abuse history, evidence of psychopathology history and any symptoms of active illness (e.g. fever, leukocytosis, hypertension, coronary artery disease, renal insufficiency, thyroid disease, anemia) were excluded from the study. All subjects were required to maintain a regular sleep/awake schedule for three weeks prior to the start of the study. The Brigham and Women's Hospital (Boston, MA) Research Committee approved the protocol and all subjects provided written, informed consents.

The subjects were admitted into the hospital for a 5-day pre-bed rest ambulatory period when baseline testings were performed and an isocaloric diet was maintained (200 mEq sodium, 100 mEq potassium and 2500 ml fluid). Then the subjects underwent 16 days of 4-degree head-down-tilt bed rest with the same diet. Lastly, three days of post-bed rest period were scheduled for recovery when they were allowed ad lib activity but must continue the constant diet. Throughout the in-patient course, the subjects maintained a constant light/dark cycle (16-hour light/8-hour dark).

On the day prior to bed rest (pre-bed rest day) and the last day of bed rest (end-bed rest day), standard surface ECG, ABP, and CO were recorded continuously and non-invasively for about eight minutes with each subject in the supine posture. Continuous blood pressure was recorded from the middle finger of the right or left hand using a fingertip cuff transducer (Portapres, TNO, or Finapres, Ohmeda). CO was recorded with a previously described Doppler ultrasound technique [8]. Briefly, aortic velocity was measured with a bi-directional ultrasound Doppler velocimeter (CFM-750 Vingmed Sound A/S, Horten, Norway) which was operated in pulsed mode at 2MHz with the hand-held transducer placed on the suprasternal notch. The aortic diameter of the rigid aortic ring was determined in a separate session by parasternal sector-scanner imaging (CFM-750 Vingmed Sound A/S, Horten, Norway). The CO data, combined with HR determined from ECG, was processed offline to obtain stroke volume (SV). During data collection, the subjects were instructed to breathe in response to auditory tones spaced at random intervals ranging from 1-15 seconds with a mean of 5 seconds. The subjects controlled their own tidal volume in order to maintain normal ventilation. This random breathing protocol excites a broad range of frequencies thereby facilitating system identification [9].

4. Results

To evaluate the effect of prolonged bed rest on the TPR baroreflex, the estimated static gains of each subject obtained before bed rest and after bed rest were compared using a paired t-test. Table 1 shows the group average results. The estimated Arterial TPR Baroreflex static gain decreased significantly after bed rest. The estimated Cardiopulmonary TPR Baroreflex static gain also diminished on average with a nearly significant *P* value.

Table 2 shows the group average results for average TPR (computed as the ratio of average ABP to average CO) prior to and after bed rest. Importantly, average TPR did not change as a result of the prolonged bed rest.

Table 1. Comparison of pre-bed rest (Pre) and end-bed rest (End) estimated static gains of Arterial (Ar.) TPR Baroreflex and Cardiopulmonary (CP) TPR Baroreflex (paired *t*-test).

Static Gain (unitless)	Pre (mean±se)	End (mean±se)	*P* value
Ar. TPR Baroreflex	-9.24±3.08	-1.50±0.45	0.03
CP TPR Baroreflex	-1.52±0.36	-1.07±0.09	0.13

Table 2. Comparison of pre-bed rest (Pre) and end-bed rest (End) TPR (average ABP / average CO) (paired *t*-test).

	Pre (mean±se)	End (mean±se)	*P* value
TPR (mmHg·min/l)	16.5±7.17	16.0±4.50	0.44

5. Discussion

The TPR baroreflex is potentially the most important pathway through which the autonomic nervous system maintains blood pressure. Its malfunctioning may play a major role in the orthostatic intolerance seen in patients undergoing prolonged bed rest or in astronauts returning from spaceflight. In this study, we applied a previously

developed, noninvasive method to estimate the static gains of the Arterial and Cardiopulmonary TPR Baroreflex in twelve healthy volunteers before and after 16-day bed rest. We found that prolonged bed rest significantly decreased the estimated static gain of the Arterial TPR Baroreflex and decreased the Cardiopulmonary TPR Baroreflex on average. On the other hand, average TPR did not change after prolonged bed rest. Thus, these results stress the importance of being able to measure the TPR baroreflex rather than just average TPR.

Among the numerous studies conducted in the past to evaluate the effect of simulated or actual microgravity on the cardiovascular control system, to our knowledge, only a couple have presented results pertaining to TPR baroreflex function. In particular, Fritsch-Yelle et al [10,11] studied astronauts before and after 5-16 day spaceflight. They showed that average TPR (ratio of average ABP to average Doppler ultrasound CO) among all the subjects at supine and standing postures were the same before and after spaceflight. Their data also indicate that for a given reduction in systolic blood pressure caused by a supine to standing postural shift, the average TPR increased less after spaceflight than before spaceflight. This implies that the TPR baroreflex static gain was blunted after spaceflight. These results are consistent with the present study. Our study adds to that of Fritsch-Yelle et al by attempting to distinguish the contributions of the arterial and cardiopulmonary TPR baroreflex. Furthermore, our method requires only a supine measure of CO, while that of Fritsch-Yelle et al requires an additional standing measure of CO, which is a significantly more difficult measurement to make via Doppler ultrasound.

In a parallel study [12], which is possibly relevant to the present study, the pharmacologic agent midodrine, an alpha-sympathetic agonist, was tested as a countermeasure to orthostatic hypotension following prolonged bed rest. The results of the study showed that subjects who were treated with midodrine one hour before a tilt-stand test following 16-day bed rest had a 71.4% rate of presyncope-free survival, whereas untreated control subjects had only a 25% rate of syncope-free survival (P = 0.036). However, these results do not necessarily imply that the TPR baroreflex is impaired following prolonged bed rest.

We conclude that the present study supports the previous works of Fritsch-Yelle et al which suggest that TPR baroreflex control is reduced after exposure to microgravity, while average TPR is unchanged.

Acknowledgements

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