

Effects of Lower Body Negative Pressure on Cardiac and Vascular Responses to Carotid Baroreflex Stimulation

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Summary

The aim of this study was to assess carotid baroreflex responses during graded lower body negative pressure (LBNP). In 12 healthy subjects (age 29 ± 4 years) we applied sinusoidal neck suction (0 to -30 mmHg) at 0.1 Hz to examine the sympathetic modulation of the heart and blood vessels and at 0.2 Hz to assess the effect of parasympathetic stimulation on the heart. Responses to neck suction were determined as the change in spectral power of RR-interval and blood pressure from baseline values. Measurements were carried out during progressive applications (0 to -50 mmHg) of LBNP. Responses to 0.1 and 0.2 Hz carotid baroreceptor stimulations during low levels of LBNP (-10 mmHg) were not significantly different from those measured during baseline. At higher levels of LBNP, blood pressure responses to 0.1 Hz neck suction were significantly enhanced, but with no significant change in the RR-interval response. LBNP at all levels had no effect on the RR-interval response to 0.2 Hz neck suction. The unchanged responses of RR-interval and blood pressure to neck suction during low level LBNP at -10 mmHg suggest no effect of cardiopulmonary receptor unloading on the carotid arterial baroreflex, since this LBNP level is considered to stimulate cardiopulmonary but not arterial baroreflexes. Enhanced blood pressure responses to neck suction during higher levels of LBNP are not necessarily the result of a reflex interaction but may serve to protect the circulation from fluctuations in blood pressure while standing.

Key words

Autonomic nervous system • Baroreflex • Blood pressure • Heart rate variability • Spectral analysis

Introduction

Lower body negative pressure (LBNP) is a widely used technique for studying the cardiovascular responses to simulated orthostatic stress. Studies have shown impaired responses to LBNP in patients with orthostatic intolerance and postural orthostatic tachycardia syndrome (Dietz *et al.* 1997, Brown and Hainsworth 2000, Bush *et al.* 2000). LBNP at levels up to -20 mmHg is considered to selectively unload

cardiopulmonary receptors, resulting in reflex peripheral vasoconstriction without changes in heart rate (Zoller *et al.* 1972). Higher levels of LBNP elicit cardiovascular responses that are mediated by the unloading of both arterial and cardiopulmonary baroreceptors (Furlan *et al.* 2001).

The arterial baroreflex is of major importance in regulating responses to orthostasis, as demonstrated by the fact that carotid baroreceptor denervation results in orthostatic intolerance. The so-called 'cardiopulmonary

receptors', which are located in the atria and ventricles of the heart and in the pulmonary artery and veins, are responsive to changes in central venous pressure (Roddie *et al.* 1957). Alterations in carotid baroreceptor sensitivity during LBNP might indicate an interaction between cardiopulmonary receptors and the arterial baroreflex. So far, the effects of cardiopulmonary receptor unloading by LBNP on the cardiac and vascular limbs of the arterial baroreflex are not clear.

Clarification of the role of baroreflexes and their interactions might provide greater insight into the pathophysiology of conditions in which baroreceptor abnormalities may be involved such as orthostatic intolerance and postural orthostatic tachycardia syndrome (Gulli *et al.* 2001, Stewart and Weldon 2001).

The aim of our study was to assess whether arterial baroreflex responses are influenced by orthostatic stress. Responses were studied during graded LBNP, from -10 to -50 mmHg to determine the effects of sequential 'cardiopulmonary' and arterial baroreceptor unloading. At each LBNP level we stimulated the carotid baroreceptors using neck suction, a technique that mechanically stretches the baroreceptors, eliciting reflex RR-interval and blood pressure responses. In order to study both heart rate and blood pressure responses to baroreceptor stimulation, the neck suction was applied in a sinusoidal fashion, using an algorithm that allows for separate identification of the sympathetic and parasympathetic limbs of the arterial baroreflex (Bernardi *et al.* 1995, Brown *et al.* 2002).

Methods

We studied 12 volunteers (9 males, 3 females) aged 20-35 years (mean \pm SD 29 \pm 4 years). All were healthy with no history of cardiovascular disorders or syncope, and none were taking medication. They were asked not to drink coffee on the day of the test nor to eat anything for at least 3 h before the start of the procedure. Average height and weight were 176 \pm 7 cm and 74 \pm 3 kg, respectively. The procedures were approved by the local ethics committee and informed consent was obtained from all subjects according to the declaration of Helsinki.

Lower body negative pressure

Progressive orthostatic stress was elicited by means of lower body negative pressure. Subjects were placed in a semi-cylindrical chamber that was sealed at the level of the iliac crests. Pressure within the chamber was indicated by a manometer and could be lowered

using a variable vacuum source. After a period of at least 40 min of quiet rest, the following graded orthostatic stress protocol was applied. Baseline recordings were initially made during 16 min without LBNP application. Then, graded LBNP was applied at -10 , -20 , -30 , -40 and -50 mmHg. The 0, -10 , -30 and -50 mmHg levels were each applied for 16 min to allow for simultaneous application of the carotid baroreceptor stimulation protocol, while the -20 and -40 mmHg levels were applied for 6 min only. The LBNP was terminated if the subject developed presyncope, which was defined as a drop in systolic blood pressure below 80 mmHg, accompanied by symptoms of impending syncope such as dizziness, light-headedness, nausea, pallor or visual disturbances (el-Bedawi and Hainsworth 1994).

Carotid baroreceptor stimulation

The carotid baroreflex was assessed during the 0, -10 , -30 and -50 mmHg levels of LBNP, using sinusoidal neck suction (Bernardi *et al.* 1995, Brown *et al.* 2002). The neck chamber consisted of a malleable lead collar edged with neoprene foam that was fitted to the anterior neck, over the carotid baroreceptors (Eckberg *et al.* 1975). Subatmospheric pressure was applied to the collar. The pressure within the chamber was monitored with a pressure transducer (Hugo-Sachs Elektronik, March, Germany) and could be set to oscillate between 0 and -30 mmHg at either 0.1 or 0.2 Hz. In order to exclude interference from respiratory influences on the responses to neck suction, respiration was maintained at 0.25 Hz (15 breaths per minute) by a visual stimulus. Oscillations in neck pressure at 0.1 Hz are transmitted to the level of the RR-interval (sympathetic and parasympathetic modulation) and to the blood pressure (sympathetic modulation) (Bernardi *et al.* 1995, Brown *et al.* 2002). Therefore, a response of blood pressure to 0.1 Hz neck suction is an index of sympathetic baroreflex activation (Bernardi *et al.* 1995, Brown *et al.* 2002) and a response of RR-interval to slow neck suction (0.1 Hz) is an index of both sympathetic and parasympathetic cardiac baroreflex activation (Bernardi *et al.* 1995, Brown *et al.* 2002).

Faster 0.2 Hz oscillations in neck pressure are transmitted only to the level of the RR-interval by parasympathetic nerves (Bernardi *et al.* 1995, Brown *et al.* 2002). Therefore, a response of RR-interval to 0.2 Hz neck suction is an index of vagal baroreflex activation (Bernardi *et al.* 1995). The 0.2 Hz oscillation in RR-interval induced by the 0.2 Hz neck suction is close to but distinct from the 0.25 Hz oscillation in RR-

interval caused by breathing (respiratory sinus arrhythmia).

The following protocol was used for each 16-min stage of LBNP (0, -10, -30 and -50 mmHg), during which carotid baroreceptor stimulations were performed: 3 min normal breathing, 3 min paced breathing at 0.25 Hz (control period), 3 min application of sinusoidal neck suction at 0.1 Hz (with breathing paced at 0.25 Hz), 3 min application of sinusoidal neck suction at 0.2 Hz (with breathing paced at 0.25 Hz) and 4 min paced breathing (0.25 Hz).

Recordings

We made continuous measurements of electrocardiogram (ECG) and non-invasive blood pressure in the radial artery at the level of the wrist by arterial tonometry (Colin-PilotTM, Colin Medical, San Antonio, TX, USA). Respiration was monitored by electrical inductance plethysmography (Respirace CalibratorTM, Ambulatory Monitoring, Ardsley, NY, USA).

Data acquisition and analysis

The signals of RR-interval, arterial pressure, respiration, and pressure within the neck chamber were digitized at a sampling rate of 300 Hz, fed to a computer and stored for off-line analysis. A computer program identified the peak of each R wave and constructed time series of RR-interval, systolic, mean and diastolic blood pressure, respiration and neck suction pressure. Oscillations in RR-interval, blood pressure, respiration, and neck suction pressure were characterized by applying power spectral analysis to these signals using an autoregressive algorithm (Bernardi *et al.* 1995). A coefficient of spontaneous baroreflex sensitivity was obtained by calculating the α -index (Pagani *et al.* 1988).

This is the square root of the ratio of low frequency power of RR-interval to the low frequency power of systolic blood pressure (expressed as $\text{ms}\cdot\text{mmHg}^{-1}$) and can be applied when there is significant (>0.5) coherence between the oscillations of RR-interval and systolic blood pressure in the low frequency range (Pagani *et al.* 1988).

Responses to neck suction were evaluated by relating the power (magnitude) of the oscillations at 0.1 Hz and at 0.2 Hz during neck suction to those recorded during the control period. We assessed responses to neck suction as the absolute increase in the power but also as the percentage increase in power from the control value.

Cross-spectral analysis was used to determine whether there was a stable relationship between pairs of signals. Significant coherence (>0.5) between the oscillations of pressure within the neck chamber and the oscillations of heart rate or blood pressure during the control period indicate that the heart rate or blood pressure response is caused by the neck suction application (Bernardi *et al.* 1995, Brown *et al.* 2002). However, if there is significant coherence between respiration (paced at 0.25 Hz) and either heart rate or blood pressure at the frequency of neck suction (0.1 or 0.2 Hz), this indicates that part of the measured heart rate or blood pressure response may be due to spurious slow breaths (Bernardi *et al.* 1995, Brown *et al.* 2002).

Statistical analysis

All values reported are means \pm S.E.M., unless otherwise stated. Time and frequency-domain responses to each level of LBNP were evaluated using repeated-measures analysis of variance with Bonferroni test when a significant P-value was found. The level of statistical significance was set at $P < 0.05$.

Table 1. Hemodynamic parameters recorded at each stage of lower body negative pressure (LBNP).

	LBNP level (mmHg)					
	0	-10	-20	-30	-40	-50
Heart rate (bpm)	60 \pm 3	59 \pm 3	61 \pm 3	65 \pm 3*	71 \pm 4**	84 \pm 4**
Systolic BP (mmHg)	125 \pm 3	127 \pm 4	125 \pm 5	120 \pm 4	121 \pm 5	121 \pm 5
Diastolic BP (mmHg)	67 \pm 3	68 \pm 4	68 \pm 3	68 \pm 2	72 \pm 3	76 \pm 3**
Mean BP (mmHg)	86 \pm 2	88 \pm 3	87 \pm 3	86 \pm 2	88 \pm 2	91 \pm 2
Pulse pressure (mmHg)	59 \pm 3	59 \pm 4	57 \pm 3	51 \pm 4*	50 \pm 5**	45 \pm 4**

Results

Effects of LBNP

Four of the 12 subjects experienced presyncope during the LBNP, all during the final level (-50 mmHg). One of these subjects became presyncopal during the 0.1 Hz neck suction and three during 0.2 Hz neck suction.

Steady-state hemodynamic responses, expressed as average values recorded during the last 3 min of each level of LBNP are listed in Table 1 for heart rate, systolic, diastolic and mean blood pressure. Low level LBNP (-20 mmHg) caused no significant changes in heart rate or blood pressure. Higher levels of LBNP significantly

increased heart rate, but mean blood pressure did not change significantly at any level of LBNP (with the exception of the subjects in whom presyncope occurred). Pulse pressure did not change in the early stages of LBNP, but decreased significantly from the -30 mmHg LBNP level onwards.

All subjects maintained their breathing frequency at 0.25 Hz during the neck suction stimulations. Low frequency powers of systolic, mean and diastolic blood pressure increased significantly at the higher levels of LBNP, but there was no significant change in RR-interval LF powers.

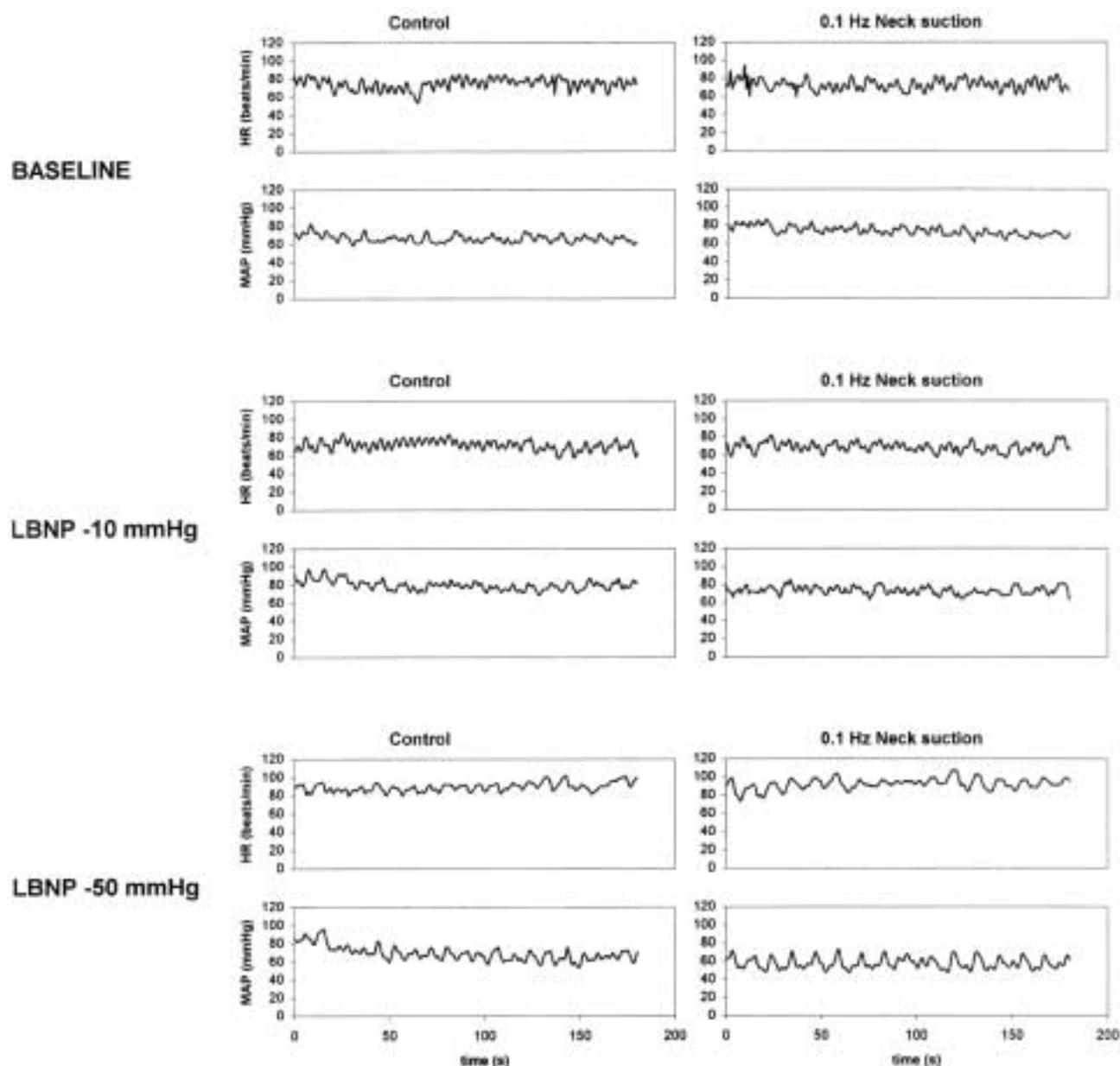


Fig. 1. Original traces from one subject showing responses of heart rate and blood pressure responses to 0.1 Hz (a) without LBNP application, (b) during -10 mmHg LBNP and (c) during -50 mmHg LBNP.

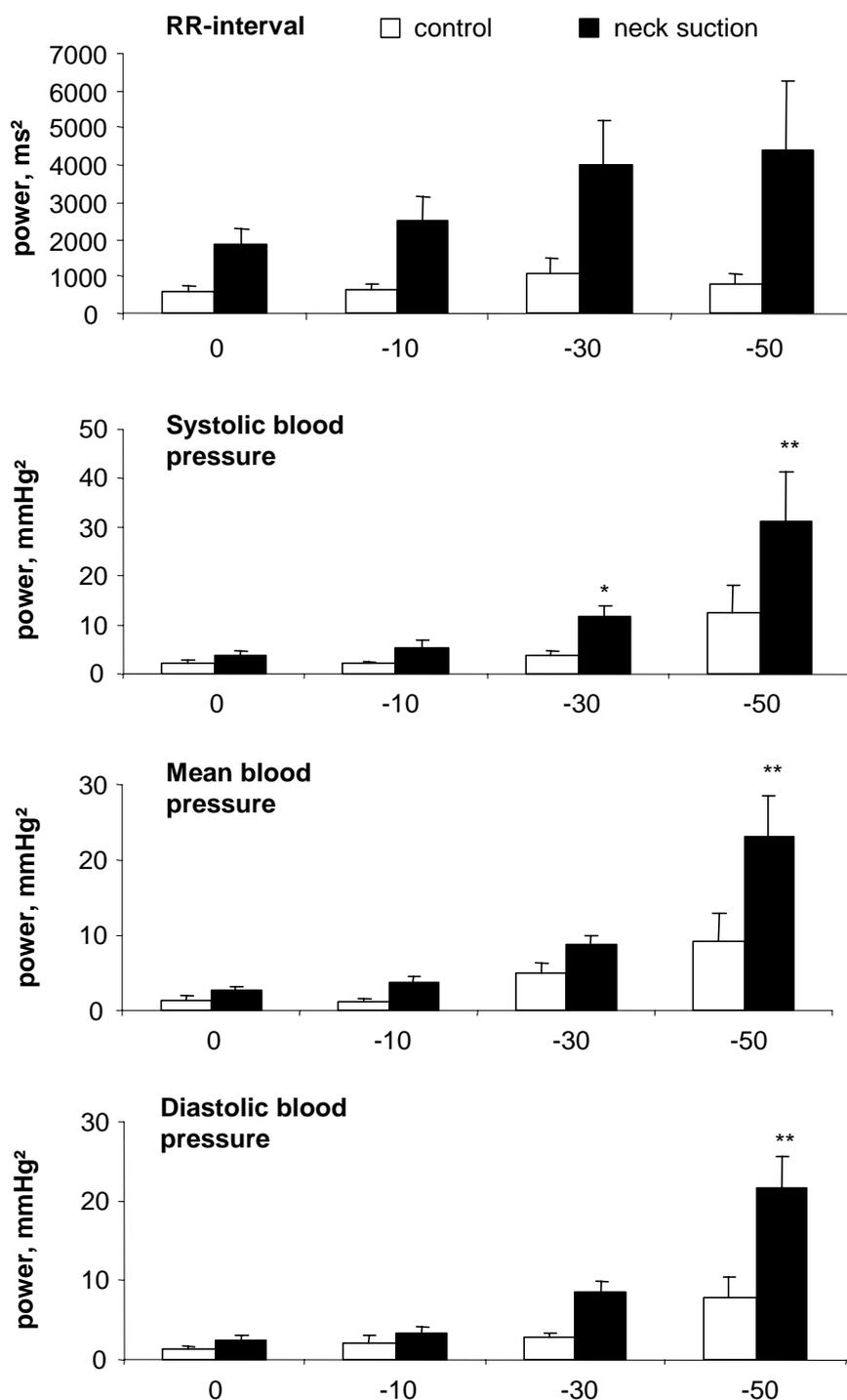


Fig. 2. Effect of 0.1 Hz neck suction on low frequency powers of RR-interval and systolic, mean and diastolic blood pressure during graded levels of LBNP. LBNP at -10 mmHg had no effect on the responses to neck suction. Blood pressure responses, assessed as absolute change of power during 0.1 Hz neck suction were significantly greater during -50 mmHg LBNP than during baseline (* $P < 0.05$, ** $P < 0.01$). However, when assessed as percentage changes from control values, responses to 0.1 Hz neck suction did not differ at any level of LBNP.

Responses to 0.1 Hz neck suction

An example of heart rate and blood pressure responses to 0.1 Hz neck suction during baseline, -10 mmHg LBNP and -50 mmHg LBNP is shown in Figure 1. Overall, there were no significant changes in either the RR-interval or the blood pressure responses to 0.1 Hz neck suction during -10 mmHg LBNP (selective cardiopulmonary receptor unloading) as compared with baseline (Fig. 2). When responses to 0.1 Hz neck suction were assessed as the increase in absolute powers of LF

oscillations, mean and diastolic blood pressure responses were significantly enhanced at the -50 mmHg LBNP level, but the systolic blood pressure response was also enhanced at the -30 mmHg level (Fig. 2). Although the response of RR-interval LF power to 0.1 Hz neck suction was increased during -50 mmHg LBNP, this did not reach statistical significance. However, when responses to 0.1 Hz neck suction were assessed as the relative (percentage) increases in LF power, LBNP at any level had no effect.

All subjects showed significant coherence (>0.5) between the neck suction pressure and RR-interval at the frequency of neck suction (0.1 Hz). No coherence was found between the respiratory signal and RR-interval at 0.1 Hz, indicating that the increased power was not due to occasional slow breaths (Bernardi *et al.* 1995, Brown *et al.* 2002).

Responses to 0.2 Hz neck suction

Neck suction at 0.2 Hz resulted in the appearance of a high frequency peak (0.2 Hz) in the spectrum of RR-interval that was distinct from the one caused by breathing (0.25 Hz). The magnitude of this peak did not change significantly during any level of LBNP (Fig. 3).

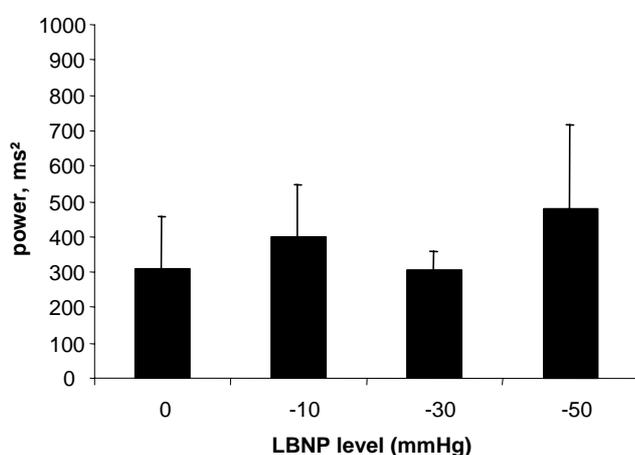


Fig. 3. RR interval responses to 0.2 Hz neck suction during graded LBNP. Responses are expressed as the magnitude of the peak at 0.2 Hz induced in the RR-interval by neck suction application. The level of LBNP had no significant effect on the responses.

Each subject showed significant coherence (>0.5) between the neck suction pressure and the RR-interval signal at the neck suction frequency (0.2 Hz). None of the subjects had significant coherence between respiration and RR-interval at 0.2 Hz, indicating that the 0.2 Hz peak in RR-interval was due to the applied neck suction, not to spurious slow breaths.

Cross-spectral analysis

Baroreflex sensitivity, as calculated using the α -index, is shown in Figure 4, for the 7 subjects who had significant coherence between LF oscillations in systolic

blood pressure and RR-interval. The α -index gain did not change consistently or significantly at any level of LBNP.

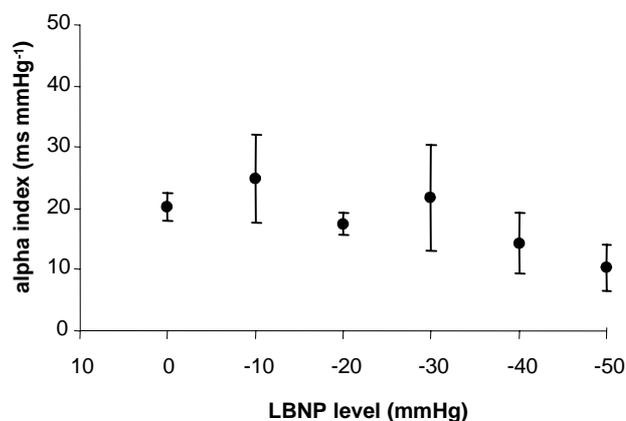


Fig. 4. Spontaneous baro-reflex sensitivity (BRS), as assessed by the alpha-index during graded LBNP. The alpha-index was not significantly affected by increasing levels of LBNP.

Discussion

The aim of this study was to assess the effects of graded LBNP on cardiac and blood pressure responses to carotid baroreceptor stimulation. We found that high levels of LBNP (> -30 mmHg) resulted in enhanced sympathetically-mediated blood pressure responses to 0.1 Hz carotid baroreceptor stimulation. However, responses of RR-interval during 0.1 Hz and 0.2 Hz baroreceptor stimulation were unchanged at all levels of LBNP. These results indicate that orthostatic stress does not affect the sympathetic or parasympathetic baroreflex control of the heart rate. However, the increased sympathetically-mediated blood pressure responses to carotid baroreceptor stimulation during high-level LBNP might have a role in protecting against blood pressure fluctuations during orthostasis.

In humans, there are conflicting results regarding evaluation of arterial baroreflex function during cardiopulmonary unloading by LBNP (Bevegard *et al.* 1977, Takeshita *et al.* 1979, Ebert 1983, Victor and Mark 1985, Pawelczyk and Raven 1989, Vukasovic *et al.* 1990). Some studies report increases (Bevegard *et al.* 1977, Ebert 1983, Victor and Mark 1985, Cooper and Hainsworth 2001) and some no change (Takeshita *et al.* 1979, Vukasovic *et al.* 1990) in arterial baroreflex sensitivity. Altered baroreflex sensitivity during LBNP

might indicate an interaction between cardiopulmonary receptors and the arterial baroreflex. However, under conditions when sympathetic activity is high, as is the case during high-level LBNP, one would anyway expect a greater capacity for lowering sympathetic tone by neck suction. Similar to the findings of Bevegard *et al.* (1977), we also observed enhanced blood pressure responses to 0.1 Hz neck suction and non-significant increases in the RR-interval response during high levels of LBNP (> -30 mmHg). However, we additionally evaluated carotid baroreceptor sensitivity during low level LBNP, at -10 mmHg and found no changes in carotid baroreceptor responsiveness compared with baseline. Furthermore, when we examined the percentage changes in the power of the fluctuations induced by sinusoidal neck suction, we found no effect of LBNP at any level on the response. Assessing the level of response by the percentage, rather than absolute changes in fluctuations might be more appropriate because it takes into account any effects of LBNP on spontaneous RR-interval and blood pressure variability.

A potential drawback of these methods is that even low-level LBNP may potentially stimulate arterial baroreflexes in addition to cardiopulmonary receptors. Although studies have indicated that low levels of LBNP do not alter arterial pressure (Zoller *et al.* 1972), it cannot be ruled out that the stimulus to the arterial baroreceptors does change but is not manifested as a measurable change in arterial pressure. Even during -5 mmHg LBNP, aortic pulse area (measured by magnetic resonance imaging) has been shown to decrease (Taylor *et al.* 1995), indicating that arterial baroreceptors may be stimulated even at very low levels of orthostatic stress. This raises the possibility that reflex responses that were previously attributed to cardiopulmonary receptor unloading may

actually be due to arterial baroreflexes. However, this is a controversial point since many authors still consider cardiovascular responses at low levels of LBNP to be exclusively due to cardiopulmonary reflexes (Zoller *et al.* 1972, Victor and Leimbach 1987, Desai *et al.* 1997, Furlan *et al.* 2001).

Animal studies allow more direct investigations on the characteristics of the different baroreflex branches. Mancina *et al.* (1976) demonstrated the dominance of the carotid baroreflex in the interplay between cardiopulmonary and arterial baroreflexes, showing that cardiopulmonary responses are inhibited by carotid baroreceptor activation. Other studies in animals have demonstrated that baroreceptor sensitivity can be altered by stimulation of cardiac afferent nerves (Koike *et al.* 1975, Chen 1979) or by hypotension (Sawano *et al.* 1995). These findings are supportive of the concept of an interaction between cardiopulmonary reflexes and arterial baroreflexes. However, the studies in quadruped mammals might not necessarily relate to baroreflex physiology in humans.

In conclusion, we found that LBNP affects the blood pressure, but not heart rate, responses to carotid baroreceptor stimulation. However, our results indicate that cardiopulmonary reflexes do not influence the sensitivity of the carotid arterial baroreflex. In contrast to previous studies (Bevegard *et al.* 1977, Takeshita *et al.* 1979, Ebert 1983, Victor and Mark 1985, Pawelczyk and Raven 1989, Vukasovic *et al.* 1990), we measured both cardiac and blood pressure responses to low and high levels of LBNP. Since the arterial baroreflex does not seem to have any input from receptors in the cardiopulmonary regions, the role, if any, of cardiopulmonary reflexes in orthostatic regulation remains a matter for speculation.

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Reprint requests

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