

Sequential Modulation of Cardiac Autonomic Control Induced by Cardiopulmonary and Arterial Baroreflex Mechanisms

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Background—Nonhypotensive lower body negative pressure (LBNP) induces a reflex increase in forearm vascular resistance and muscle sympathetic neural discharge without affecting mean heart rate. We tested the hypothesis that a reflex change of the autonomic modulation of heartbeat might arise during low intensity LBNP without changes of mean heart rate.

Methods and Results—Ten healthy volunteers underwent plasma catecholamine evaluation and a continuous recording of ECG, finger blood pressure, respiratory activity, and central venous pressure (CVP) during increasing levels of LBNP up to -40 mm Hg. Spectrum and cross-spectrum analyses assessed the changes in the spontaneous variability of R-R interval, respiration, systolic arterial pressure (SAP), and CVP and in the gain (α_{LF}) of arterial baroreflex control of heart rate. Baroreceptor sensitivity was also evaluated by the SAP/R-R spontaneous sequences technique. LBNP began decreasing significantly: CVP at -10 , R-R interval at -20 , SAP at -40 , and the indexes α_{LF} and baroreceptor sensitivity at -30 and -20 mm Hg, compared with baseline conditions. Plasma norepinephrine increased significantly at -20 mm Hg. The normalized low-frequency component of R-R variability (LF_{R-R}) progressively increased and was significantly higher than in the control condition at -15 mm Hg.

Conclusions—Nonhypotensive LBNP elicits a reflex increase of cardiac sympathetic modulation, as evaluated by LF_{R-R} , which precedes the changes in the hemodynamics and in the indexes of arterial baroreflex control. (*Circulation*. 2001; 104:2932-2937.)

Key Words: nervous system, sympathetic ■ baroreceptors ■ hemodynamics ■ pressure

Lower body negative pressure (LBNP) is a recognized technique to mimic and modulate the effects of gravity, particularly on central venous pressure (CVP) and arterial pressure. It has been used to study cardiopulmonary and arterial baroreceptor mechanisms in a number of physiological and pathological conditions including orthostatic intolerance.¹⁻³

There is agreement that values of LBNP > -20 mm Hg induce reflex autonomic changes, including an increase of heart rate mediated by both cardiopulmonary and arterial baroreceptor areas⁴ to maintain blood pressure. On the other hand, reduction of cardiopulmonary afferent discharge activity by low-intensity nonhypotensive lower body suction elicits a reflex increase in the forearm vascular resistance^{5,6} and muscle sympathetic nerve activity (MSNA)^{6,7} but has no effect on heart rate. From this observation, there might appear to be a lack of autonomic modulation to the heart in response

to a mild decrease of CVP. The present study was undertaken to reexamine the experimental evidence that a mild decrease of CVP has no reflex effect on cardiac autonomic profile.

Spectral methodologies have been used during the last decade to infer information on the functional state of both cardiac autonomic modulation⁸ and arterial baroreflex control of heart rate.⁹ Within physiological ranges, the low-frequency (LF_{R-R}) and high-frequency (HF_{R-R}) components of heart rate variability may provide, when measured in normalized units (nu) or as an LF/HF ratio, quantitative markers of the cardiac sympathetic and vagal modulation,^{10,11} respectively. Conversely, the absolute value of LF_{R-R} does not furnish an index of cardiac sympathetic modulation.^{8,11,12} Importantly, power spectrum analysis techniques have shown that a change in the spontaneous variability of R-R interval, suggestive of a change in the neural control of the heart, may not be mirrored by concomitant modifications of the mean R-R values.

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Indeed, in a group of subjects with neurally mediated syncope, we observed that the loss of consciousness was preceded by a long-lasting slow decay of normalized values of LF_{R-R} and a concomitant increase of HF_{R-R} in the presence of unchanged heart rate values.¹³

In the present study, we addressed the hypothesis that any reflex change in the cardiac autonomic modulation induced by low-intensity, nonhypotensive LBNP would have been reflected in an early change of the pattern of R-R spontaneous variability without necessarily being attended by concomitant modifications of mean heart rate.

These aspects may be of paramount clinical importance in patients who have spells of orthostatic intolerance because the prompt recognition of abnormalities in the early changes of cardiac autonomic profile attending mild reductions of CVP, as achieved also by low angles of a stepwise head-up tilt,¹⁴ may result in differently tailored therapeutic approaches based specifically on the use of fluid and salt loads instead of vasoconstrictor agents.

Methods

The present study was performed in 10 healthy volunteers (7 women and 3 men, 34 ± 2 years of age) without evidence of organic disease on the basis of the interview and physical examination. A negative pregnancy test was required of women to be enrolled.

In every subject, we recorded the ECG with an AC amplifier. Noninvasive blood pressure was continuously assessed by a volume-clamp technique (Finapres, Ohmeda 2300). Respiratory activity was evaluated by a thoracic bellows connected to a pressure transducer. High-fidelity CVP recordings were obtained by a miniature (3F, diameter 0.8 mm) catheter-tipped pressure transducer (Millar Instruments Inc) in 8 subjects. After calibration, the pressure transducer was introduced into a vein of the antecubital fossa by the Seldinger technique and advanced near the right atrium. An intravenous line was positioned in the opposite arm for blood sampling.

ECG, arterial pressure, respiratory activity, and CVP signals were recorded on the paper of an optic chart recorder, concomitantly digitized at 300 samples/s by an analog-to-digital board (AT-MIO 16E2, National Instruments), and stored onto the hard disk of a personal computer for off-line analysis.

High-performance liquid chromatography with electrochemical detection was used to assess plasma epinephrine and norepinephrine on venous blood samples.

Protocol

The lower body suction device consisted of a steel cylindrical chamber connected to a Statham pressure transducer for negative pressure values monitoring and to a rheostat-controlled vacuum engine.

In the supine position, the lower body of each subject was placed into the suction chamber that was sealed at the iliac crest level. Thirty minutes after instrumentation, baseline data acquisition was initiated and a blood sample was withdrawn for catecholamine evaluation. Thereafter, suction was applied at levels of -5 , -10 , -15 , -20 , -30 and -40 mm Hg for 4 minutes at each level, and a venous sample was obtained to assess plasma catecholamine.

The experimental protocol was approved by the Vanderbilt University Institutional Review Board, and written informed consent was provided by all subjects.

Data Analysis

CVP values were referenced to atmospheric pressure; no transmural CVP values are provided because intrathoracic esophageal pressure was not evaluated concomitantly.

The methodology we used for signal processing, autoregressive spectrum and cross-spectrum analysis of R-R interval and systolic

arterial pressure (SAP) variability and of respiratory activity, have been described in detail elsewhere.^{9,11} Taking into account the marked influence of breathing in modulating intrathoracic venous pressure oscillations, the CVP signal was processed as a respiratory signal, that is, it was resampled once per cardiac cycle synchronously with the R-wave peak of the ECG, obtaining the series of consecutive CVP values. These latter in turn underwent autoregressive spectrum and cross-spectrum analyses.

The power of the LF and HF oscillatory components of R-R variability is provided in both absolute units (ms^2) and normalized units.^{8,11} Normalization is achieved by dividing the absolute power of each component by total variance (minus the power of the very-low-frequency component) and multiplying by 100.¹⁰ The LF_{R-R}/HF_{R-R} ratio may furnish a further index to evaluate the sympathovagal interaction to the sino-atrial node activity.^{10,11} SAP and CVP fluctuations in the LF and HF bands are expressed in absolute units (mm Hg²).

Global (carotid and aortic) arterial baroreflex function was assessed by both a time-domain and a frequency-domain approach. The first method is based on the detection of spontaneous sequences of three or more SAP and R-R values that simultaneously increase (positive sequences) or decrease (negative sequences).¹⁵ Sequences were considered to reflect baroreceptor activity if the following criteria had been matched: (1) R-R interval variations were >5 ms; (2) SAP changes were >1 mm Hg; and (3) sequences were longer than 4 beats. For each sequence, a linear regression between the two variables was computed and the slope of the regression line calculated. In every subject, all the slopes characterized by a correlation coefficient >0.85 were averaged and the final value taken as the gain of arterial baroreflex control of heart rate (BRS).

Bivariate spectrum analysis of R-R interval and SAP variabilities⁹ provided the index α , which was computed as the square root of the ratio between the powers of corresponding spectral components of R-R interval and SAP variabilities.

Data are expressed as mean \pm SEM. One-way repeated-measures ANOVA and the Dunnett's post test were used to evaluate differences between each different level of lower body suction and the baseline value. Differences were considered significant at values of $P < 0.05$.

Results

Hemodynamic and Respiratory Changes

Heart rate increased with increasing levels of suction and, over the range of -20 mm Hg to -40 mm Hg, was significantly higher than baseline (Table 1). SAP was reduced compared with the baseline value at -40 mm Hg, whereas diastolic pressure was unaffected by the suction procedure. CVP decreased simultaneously with the enhancement of lower body suction reaching values lower than those observed in control condition over the range of -10 to -40 mm Hg of LBNP. Both the respiratory frequency and the amount of breathing modulation on intrathoracic venous pressure, as assessed by HF_{CVP} , did not change during the procedure.

Autonomic and Baroreflex Changes

Figure 1 depicts an example of the changes in the power spectra of R-R variability and in the hemodynamics attending the different levels of LBNP. Notice the increase of the relative power of the LF spectral component of R-R variability (LF_{R-R}) and the decrease of the HF component (HF_{R-R}), beginning with the lower level of intensity of the suction. At -40 mm Hg of stimulation, concomitantly with the minimum of arterial pressure and R-R interval values, the spectrum shows the maximum of the normalized LF_{R-R} component.

TABLE 1. Hemodynamic and Respiratory Parameters During Increasing Levels of Lower Body Suction

	Control	-5 mm Hg	-10 mm Hg	-15 mm Hg	-20 mm Hg	-30 mm Hg	-40 mm Hg	Recovery
HR, bpm	65±3.6	65±3.4	68±3.8	71±4.2	75±4.4*	86±5.6*	94±9.1*	63±3.5
SAP, mm Hg	105±3.2	107±3.7	104±3.4	104±2.8	102±2.1	99±1.7	90±3.3*	101±2.1
DAP, mm Hg	67±1.4	68±1.5	67±1.3	67±1.3	68±1.2	68±1.2	63±3.8	66±1.8
CVP, mm Hg†	3.9±0.4	2.8±0.6	2.0±0.7*	0.8±0.7*	0.3±0.7*	-0.9±1.0*	-1.9±1.5*	3.9±1.0
CVP σ , mm Hg†	0.5±0.1	0.4±0.1	0.3±0.1	0.3±0.1	0.3±0.1	0.5±0.2	0.8±0.2	0.5±0.1
HF _{CVP} , mm Hg†	0.2±0.1	0.1±0.1	0.1±0.1	0.2±0.1	0.1±0.0	0.3±0.1	0.3±0.1	0.2±0.0
Resp, cycles/min	15±1.0	15±0.8	14±0.7	15±0.8	15±1.0	16±1.2	14±1.1	15±1.0

HR indicates heart rate; SAP, systolic arterial pressure; CVP σ , variance of CVP; HF_{CVP}, high-frequency respiratory component of CVP variability; and Resp, respiratory frequency.

Data are mean±SEM.

* P <0.05 vs control.

†In 8 subjects.

The mean values of the indexes of cardiovascular autonomic control and of baroreflex gain during LBNP are summarized in Table 2 and Figure 2. Plasma norepinephrine increased and reached a value higher than in baseline conditions beginning at -30 mm Hg of lower body suction. The spectral index of cardiac sympathetic modulation, LF_{R-R} nu, progressively increased and reached values higher than in the control condition, at -15 mm Hg up to -40 mm Hg of suction.

The linear relation between the amount of CVP decrease during the different steps of LBNP and the corresponding changes in LF_{R-R} nu are presented in Figure 3 as regression lines. In each of the 8 volunteers, the increase of LBNP was attended by a corresponding enhancement of the relative power of LF_{R-R}.

The gain of the arterial baroreflex control of heart rate computed by the sequences technique (BRS) progressively declined during the suction procedure and was significantly lower than in the control condition, beginning at -20 mm Hg (Table 2 and Figure 2). The index α_{LF} also decreased during LBNP and was significantly reduced compared with baseline at -30 mm Hg (Table 2 and Figure 2).

Discussion

In the present study, we addressed the hypothesis that nonhypotensive, mild reductions of CVP obtained by a progressive LBNP procedure might affect cardiac autonomic control before the onset of major changes in the hemodynamics and arterial baroreflex modulation. The actual biological effect of the suction procedure on the great veins of the thorax was assessed by high-fidelity venous pressure recordings obtained on a beat-by-beat basis with the use of a pressure transducer-tipped catheter. In addition, power spectrum analysis of CVP variability permitted a precise assessment of possible modifications in both the frequency and the mechanics of breathing previously observed during a similar procedure.¹⁶

We found that R-R interval underwent early changes in its variability pattern during LBNP consisting of a progressive increase of the normalized power of the LF_{R-R} component that mirrored the CVP drop and preceded any hemodynamic modification. In addition, the finding that the gain of carotid and aortic arterial baroreflex control of heart rate, assessed by the time- and frequency-domain indexes BRS and α_{LF} , remained unchanged up to -20 and -30 mm Hg of suction

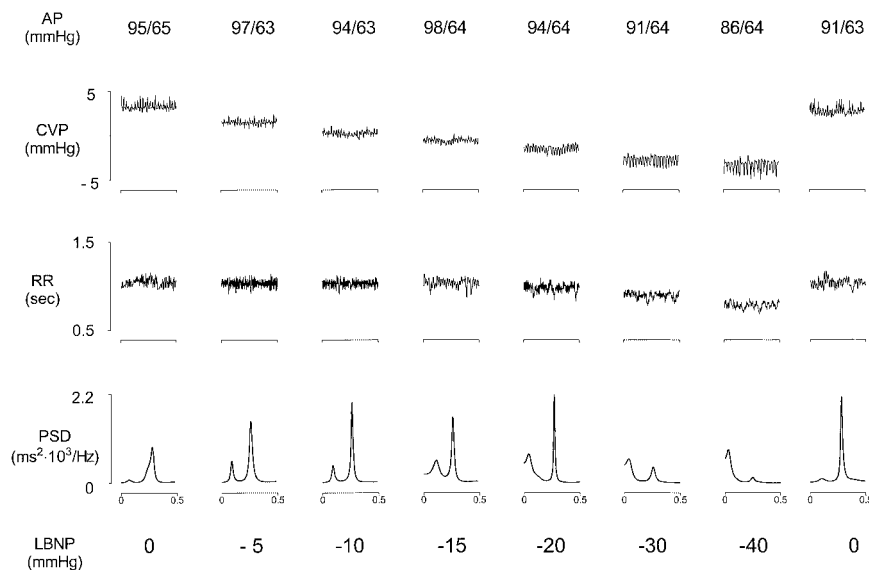


Figure 1. Modification of the spectra of R-R variability (PSD) and concomitant changes in hemodynamic parameters in a subject during lower body suction. Notice progressive drop in CVP in absence of major changes of systolic arterial pressure (AP) values up to -40 mm Hg of negative pressure. Slow fluctuations take place in R-R series from -15 up to -40 mm Hg of suction. PSD indicates power spectrum density.

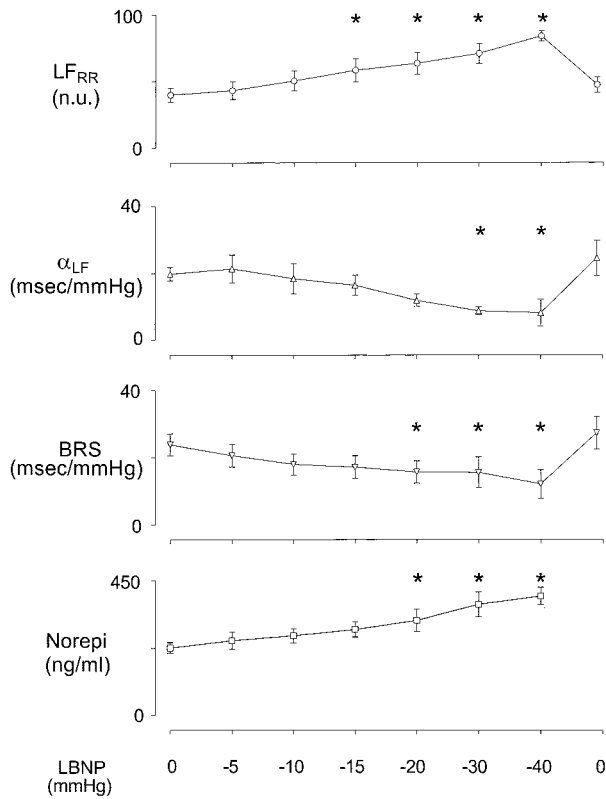


Figure 2. Graphs synthesize modifications in volunteers' autonomic profile as evaluated by changes of plasma norepinephrine levels (Norepi), of the spectral marker of cardiac sympathetic modulation LF_{R-R} , and of BRS and α_{LF} indexes of arterial baroreflex control of heart rate. Notice that LF_{R-R} already increased at level of suction of -15 mm Hg, whereas BRS and α_{LF} remained unchanged up to -20 and -30 mm Hg of LBNP, respectively.

raises the possibility that the increase of cardiac sympathetic modulation observed beginning at -15 mm Hg might be mostly due to a disengagement of cardiopulmonary neural afferents without a major contribution of the arterial baroreceptor areas.

Hemodynamic Changes and Heart Rate Variability During LBNP

The results of the present study indicate that LBNP affects R-R interval and SAP at levels of suction of -20 mm Hg or

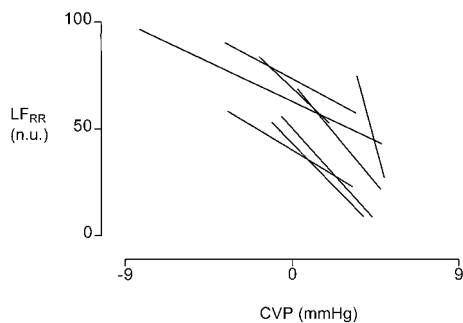


Figure 3. Relation between changes in CVP values and corresponding modifications of LF_{R-R} in normalized units during LBNP. Individual regression lines obtained from 8 volunteers are shown. Notice progressive increase of LF_{R-R} attending the decrease of CVP.

higher, in keeping with previous findings.⁴ Conversely, they conflict with another report indicating a decreased breathing activity during the suction procedure, possibly related to the interference exerted by LBNP on the diaphragm movements.¹⁶ In our volunteers, respiratory rate remained unchanged during the entire procedure. However, CVP mean values (see Table 1) and the respiratory component of CVP variability, HF_{CVP} , showed more pronounced fluctuations during the highest levels of suction (see Figure 1 and Table 2) compared with baseline conditions, suggestive of initial, mild changes in the depth of breathing.

In keeping with other investigations,¹⁷ in our study the stepwise increase of lower body suction induced a gradual enhancement of plasma norepinephrine levels, suggesting an overall increased sympathetic activity. Importantly, that neurohumoral pattern was accompanied by a lack of modification in mean R-R interval up to -20 mm Hg but was paralleled by a progressive increase of the relative power of LF_{R-R} that became higher than in control conditions at -15 mm Hg, thus suggesting an early reflex increase of sympathetic modulation to the sino-atrial node activity at low levels of LBNP.

The finding that modifications in the spontaneous variability of heartbeat might precede modifications in the mean R-R value has already been described during both physiological and pathophysiological conditions. Indeed, a decrease in the HF_{R-R} component of R-R variability in the absence of significant variations of mean heart rate has been found after a mild reduction in central blood volume obtained by blood donation.¹⁸ The LF nu and HF nu component of R-R variability showed marked reciprocal changes before a tilt-induced syncope, being the heart rate unchanged as compared with the early phase of the gravitational stimulus.¹³ Finally, a more pronounced increase of the 0.1 Hz component of R-R variability was observed during a second head-up tilt in volunteers in whom heart rate did not differ between the two subsequent tilt tests.¹⁹

Taken together, these observations suggest that the reflex control of heart rate may partially differ from the autonomic modulation of its variability, which, in certain conditions such as during low-intensity lower body suction, seems to lead. Thus, by decreasing CVP, low values of LBNP might mediate a reflex increase in cardiac sympathetic modulation affecting primarily R-R interval variability. Reflex changes of mean R-R values would take place only after high levels of lower body suction are applied, possibly entailing the crucial contribution of arterial baroreflex mechanisms.

Arterial Baroreflex Control of Heart Rate

An important finding of the present work is the observation that the indexes BRS and α_{LF} , which assess the gain of the carotid and aortic baroreflex control of heart rate both in the time and frequency domain, did not change significantly during low levels of lower body suction. BRS and α_{LF} decreased significantly only at the highest values of LBNP, as already observed during physiological conditions characterized by cardiac vagal withdrawal and sympathetic activation such as physical exercise⁹ and 75° head-up tilt.¹⁴ This finding is in keeping with the hypothesis⁴ that a high level of LBNP elicits reflex changes in the neural control of heart rate that

TABLE 2. Indexes of Autonomic Activity and Arterial Baroreflex Gain During Increasing Levels of Lower Body Suction

	Control	-5 mm Hg	-10 mm Hg	-15 mm Hg	-20 mm Hg	-30 mm Hg	-40 mm Hg	Recovery
Norepinephrine, pg/mL	226±18	251±29	267±24	288±25	318±37*	371±41*	398±28*	
Epinephrine, pg/mL	20±4.9	22±6.1	26±6.6	25±5.9	36.8±8.6	39±11.9	61±22.7	
RR σ , ms ²	2958±1029	2833±1140	3014±854	2494±737	2670±935	1210±230*	956±243*	3976±1206
LF _{RR} , ms ²	516±128	540±134	633±171	688±167	528±111	434±69	482±165	824±212
nu	39.6±5.4	42.9±6.6	50.0±7.4	57.9±8.8*	63.0±8.2*	70.4±7.5*	83.5±3.8*	46.9±5.7
HF _{RR} , ms ²	737±238	621±184	679±232	482±199	406±159	174±68*	70.6±29*	800±172
nu	49.2±5.4	41.0±5.9	39.2±6.8	37.0±9.1	33.2±7.8*	21.8±5.0*	12.6±3.3*	41.2±7.2
LF/HF	1.02±0.3	1.61±0.6	1.86±0.5	5.89±3.2*	3.89±1.4*	8.77±4.2*	11.86±4.8*	2.25±1.0
SAP σ , ms ²	14.8±3.8	10.4±1.7	12.7±2.3	11.8±2.0	9.5±1.5	13.8±3.5	13.9±2.9	14.9±4.4
LF _{SAP} , mm Hg ²	1.4±0.3	2.0±0.5	3.3±1.0	3.6±1.1	4.3±0.8	8.6±3.1*	8.9±2.2*	3.8±1.4
HF _{SAP} , mm Hg ²	1.6±0.7	0.8±0.2	0.96±0.3	0.9±0.1	1.0±0.2	1.4±0.6	1.4±0.4	1.0±0.2
α_{LF} , ms/mm Hg	19.8±1.9	21.3±4.1	18.3±4.4	16.4±3	11.9±1.8	8.8±1.1*	8.2±4.0*	24.5±5.2
BRS, ms/mm Hg	23.8±3.3	20.6±3.4	17.9±3.1	17.1±3.4	15.7±3.3*	15.6±4.6*	12.1±4.3*	27.3±4.8

σ indicates variance; LF, low-frequency component; HF, high-frequency component; nu, normalized units; α_{LF} , α index in the LF band; and BRS, slope of spontaneous baroreflex sequences.

Data are mean±SEM.

* P <0.05 vs control.

are likely to be mediated by a reduction of the inhibitory activity of arterial baroreceptor afferents, as indicated in our study by the decrease of BRS and α_{LF} , and by the disengagement of cardiopulmonary receptors already present at low levels of LBNP.^{5,7}

The relative contribution of cardiopulmonary and arterial baroreflex mechanisms controlling heart rate has been addressed specifically by Desai and colleagues²⁰ in a study that used neck chamber pressure and suction, LBNP, and different pharmacological probes. They found that their modeling of baroreflex control of heart rate was accounted for by 63% of aortic, 14% of carotid, and 23% of cardiopulmonary baroreceptor mechanisms, thus highlighting the major role played by arterial (carotid and aortic) baroreflex mechanisms in controlling heart rate response to high values of LBNP, in keeping with the results of the present study.

Although the evaluation of arterial baroreflex gain by spectrum analysis of R-R and systolic pressure variabilities entails the advantage of avoiding the administration of pressure drugs that may directly affect baroreceptor sensitivity, it must be pointed out that α computation may be overestimated as the result of the interference of variables unrelated to arterial baroreflex mechanisms, separately affecting arterial pressure and R-R variabilities.²¹ For example, respiration may produce a certain amount of R-R variability unrelated to arterial pressure fluctuations²² by inducing a direct central modulation on the efferent cardiac sympathetic activity. In this context, we may not exclude that in the subjects of our study rhythmic respiratory activity might have enhanced the corresponding values of α_{LF} , thus masking its possible reduction during values of LBNP <30 mm Hg. However, the finding that a similar pattern was also observed in the BRS index during analogous lower body levels of suction makes that hypothesis unlikely.

Finally, it is still debated whether a pure stimulation of cardiopulmonary afferents might be obtained in humans without simultaneously affecting the high-pressure barore-

ceptor district.⁴ In an elegant study based on nuclear magnetic resonance techniques, Taylor and coworkers¹⁶ found a deformation of the ascending aorta even at very low levels (-5 mm Hg) of lower body suction, thus inferring a possible contribution of aortic baroreflex mechanisms in producing early adaptation of the cardiovascular system to LBNP. Although the role of arterial baroreflex mechanisms in producing early changes of R-R variability cannot be directly excluded in the present study, the observation that the indexes of baroreflex sensitivity, BRS and α_{LF} , were unchanged during low levels of LBNP leaves the problem open.

Conclusions and Clinical Implications

In the present study, a low-intensity, nonhypotensive lower body suction procedure appeared to mediate a reflex increase of cardiac sympathetic activity that was mirrored by an early enhancement of the LF_{R-R} component of R-R variability. Reflex changes of mean R-R values would take place only after high levels of lower body suction are applied, thus largely involving arterial baroreflex mechanisms, as suggested in our study by the decrease of the indexes BRS and α_{LF} .

The detection of early signs of autonomic modifications, such as an increase of LF_{R-R}, preceding global changes in the cardiovascular system, might be of clinical value to clarify the uncertain pathophysiology of different forms of orthostatic intolerance, thus optimizing therapy. A blunted increase of the postganglionic neural sympathetic discharge during progressive reduction of CVP obtained by incremental tilt was described in habitual fainters.²³ It is conceivable that early changes in R-R variability, as found in our healthy volunteers, would not be observed in that population. Conversely, an earlier modification of LF_{R-R}, possibly taking place at values of LBNP <-15 mm Hg, is likely to characterize R-R variability of subjects who have orthostatic intolerance caused by mild dehydration or abnormal interstitial loss of fluid during standing.²⁴ We hypothesize that the different therapeutic approaches to orthostatic intolerance, such as the

use of water and salt loading or vasoconstrictor agents, might be more effective if they are matched to possible abnormalities in the early increase of LF_{R-R} during mild CVP reductions.

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