

Pressure and time dependence of the cardiopulmonary reflex response in patients with hypertensive cardiomyopathy

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Abstract

The first minutes of the time course of cardiopulmonary reflex control evoked by lower body negative pressure (LBNP) in patients with hypertensive cardiomyopathy have not been investigated in detail. We studied 15 hypertensive patients with left ventricular dysfunction (LVD) and 15 matched normal controls to observe the time course response of the forearm vascular resistance (FVR) during 3 min of LBNP at -10, -15, and -40 mmHg in unloading the cardiopulmonary receptors. Analysis of the average of 3-min intervals of FVR showed a blunted response of the LVD patients at -10 mmHg ($P = 0.03$), but a similar response in both groups at -15 and -40 mmHg. However, using a minute-to-minute analysis of the FVR at -15 and -40 mmHg, we observed a similar response in both groups at the 1st min, but a marked decrease of FVR in the LVD group at the 3rd min of LBNP at -15 mmHg ($P = 0.017$), and -40 mmHg ($P = 0.004$). Plasma norepinephrine levels were analyzed as another neurohumoral measurement of cardiopulmonary receptor response to LBNP, and showed a blunted response in the LVD group at -10 ($P = 0.013$), -15 ($P = 0.032$) and -40 mmHg ($P = 0.004$). We concluded that the cardiopulmonary reflex response in patients with hypertensive cardiomyopathy is blunted at lower levels of LBNP. However, at higher levels, the cardiopulmonary reflex has a normal initial response that decreases progressively with time. As a consequence of the time-dependent response, the cardiopulmonary reflex response should be measured over small intervals of time in clinical studies.

Key words

- Baroreflex
- Essential hypertension
- Heart failure
- Cardiopulmonary reflex
- Baroreceptors

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Introduction

Hypertension is considered to be a major health problem, with clear evidence that it is one of the most important causes of heart failure (1). Indeed, heart failure (2-7) and hypertension (8-13) are associated with abnormalities in cardiovascular reflexes and neurohumoral regulation, each of which are

independent risk factors for increased cardiovascular morbidity and mortality (14-19).

Studies on animals and humans have shown that both the cardiopulmonary and the arterial baroreflex play important roles in regulating the cardiovascular system (20-24). Clear evidence exists that the cardiopulmonary reflex control is impaired in humans with severe left ventricular dysfunction (LVD,

2,5-7) and hypertension (9,10,25,26). However, most studies of cardiopulmonary reflex control in humans have used data averaged over several minutes, without including the 1st min of progressive levels of lower body negative pressure (LBNP) to analyze the nature of this impairment in patients with hypertension (9,10,25) and LVD (5,7). We are not aware of studies that analyzed the cardiopulmonary reflex minute-to-minute, including the 1st min of stimulation, which could be an important parameter to understand the mechanism of reflex impairment because the neural reflex response is very rapid at its onset. Therefore, the analysis of the average of several minutes might mask transient changes.

More recently, Hisdal et al. (27) observed transient changes in cardiovascular variables after the rapid onset and release of low levels of LBNP in normal volunteers, which clearly demonstrates that the intensity and time of stimulus application are important to the activation of the different receptors. Furthermore, the reflex response is very rapid at its onset, and when the overall response is analyzed as an average over several minutes, transient changes in the reflex response cannot be detected.

Our objective was to determine in patients with hypertensive cardiomyopathy whether minute-to-minute analysis of the forearm vascular resistance (FVR) in comparison with averaging over several minutes, as reported by many studies, is able to detect differences in the time course of the cardiopulmonary reflex and to provide information about the mechanism of the reflex.

Subjects and Methods

Subjects

The study included 15 patients (8 men and 7 women), 35 to 59 years of age, mean body mass index 27.3 ± 2.5 kg/m², with mild-to-moderate LVD determined by cal-

culatation of the ejection fraction by echocardiography using Simpson's method (group with LVD). The ejection fractions ranged from 36 to 50%, and the mean left ventricle diameter was 63 ± 2.3 mm. All patients were asymptomatic at rest and during exercise and none showed evidence of lung congestion on the day of the study. The LVD group was compared to 15 healthy controls (7 men and 8 women), mean body mass index 26.5 ± 2.0 kg/m², 31 to 58 years of age (normal control group). All subjects had normal laboratory tests that included a complete blood count as well as blood glucose, blood urea nitrogen, and serum creatinine levels. Total cholesterol levels (normal = 203 ± 7 vs LVD = 197 ± 11 , P = NS) and triglyceride levels (normal = 106 ± 8 vs LVD = 107 ± 8 , P = NS) were also similar in both groups. None of the patients were diabetic, had any other associated disease or used any medications, including hormonal therapy for the women in both groups. Written consent was obtained from all subjects before the study, and the Medical Ethics Committee of the University of São Paulo Medical School, São Paulo, Brazil, approved the study protocol.

Hemodynamic measurements

The following hemodynamic measurements were performed: arterial blood pressure, heart rate, central venous pressure (CVP), forearm blood flow (FBF), and FVR. All measurements were recorded simultaneously on a Gould strip-chart recorder (RS 3800; Gould Inc., Recording System Division, Valley View, OH, USA) and on a computer (Gateway 2000 4DX2-66V) with a CODAS system for data analysis (Computer Operated Data Acquisition Software: AT-CODAS; DATAQ Instruments, Inc., Akron, OH, USA).

Arterial blood pressure was measured with a digital photoplethysmograph, which provides accurate beat-to-beat systolic and diastolic values in mmHg (Finapres, Omeda

2300, Monitoring Systems, Englewood, CO, USA). Heart rate was calculated by analysis of the peak systolic interval of the arterial pressure curves obtained with the digital photoplethysmograph. CVP (mmHg) was obtained with a polyethylene catheter (Intracath, 16 gauge/24"; Jonhson & Jonhson, Waterloo, Belgium) inserted percutaneously through an antecubital vein into the left arm and advanced to the right atrium under fluoroscopy in the Hemodynamic Laboratory. This device was connected to a Gould P23 transducer in the Hypertension Laboratory, and the CVP values were determined; the zero reference was estimated at the subjects' midaxillary level in the fourth intercostal space. FBF (ml/100 ml forearm volume per minute) was measured in the right arm by venous occlusion plethysmography using a double-stranded mercury-in-silastic strain gauge designed by Whitney (28). The venous occlusion pressure was 35 to 40 mmHg. The circulation in the hand was blocked by inflating a wrist cuff above the systolic pressure for 1 min before limb blood flow was determined. Venous occlusion was performed every 10 s and 3 curves of FBF per min at baseline and increasing levels of LBNP were determined. The average was then calculated as the mean value of data collected during 1 min of each stimulus. FVR (units) was calculated as mean arterial pressure/FBF.

Humoral measurements

Humoral measurements consisted of determining norepinephrine concentration in blood samples withdrawn from the right atrium at the end of the baseline period and at each level of LBNP. Blood was stored in pre-chilled tubes and processed at low temperatures by high performance liquid chromatography.

Protocol

Hypertensive patients had their medica-

tion regimens changed with the progressive withdrawal of beta-blockers, angiotensin converting enzyme inhibitors and central alpha-blockers over a 3-week period. During the last week before the experiment, they received only vasodilators with short half-lives (nifedipine or hydralazine) and loop diuretics (furosemide). Administration of these medications was discontinued 24 h before the study. Patients did not consume alcohol or caffeine 24 h before the protocol, and no smokers were included in the study.

The experimental protocol was similar to that used in a previous study performed in our laboratory (29). Hemodynamic variables were continuously measured during the 3-min baseline period and during sequential applications of LBNP at -10, -15, and -40 mmHg, with a 5-min rest between stimuli. Each LBNP stimulus was preceded by 1 min of baseline measurements to confirm that these parameters were stable.

Statistical analysis

Data were processed with JMP 5.0 software (a business unit from the SAS Institute). Baseline values, the average of 3 min of each stimulus, and the norepinephrine response were compared between groups by the unpaired Student *t*-test. Analysis of variance for repeated measures was used to compare the minute-to-minute responses of the FVR during the 3 min of LBNP at -10, -15 and -40 mmHg. *P* values of <0.05 were considered to be significant. Data are reported as means \pm SEM.

Results

Baseline hemodynamic data

Systolic, diastolic and mean blood pressures and heart rate were significantly higher in the LVD group (Table 1). The CVP, FBF, and FVR were similar in both groups (Table 1).

Hemodynamic responses to LBNP: analysis of the 3-min average data

LBNP at -10 mmHg. In response to -10 mmHg of LBNP, both groups showed a similar decrease in CVP (Table 2). Systolic, diastolic, mean blood pressures, and heart rate did not change significantly compared to baseline values (Table 2). In the normal

group, FBF decreased and FVR increased significantly from baseline (Table 3). The decrease in FBF variation and the percent increase in FVR variation were markedly reduced in the LVD group (Table 3).

LBNP at -15 and -40 mmHg. The decrease in CVP was similar in both groups at -15 and -40 mmHg of LBNP (Table 2). Systolic, diastolic, and mean blood pressures did not change significantly from baseline values in either group (Table 2). However, heart rate increased significantly from baseline in both groups at -40 mmHg of LBNP (Table 2). The percent variation in FBF decrease and FVR increase did not differ significantly from baseline for either group (Table 3).

Table 1. Baseline hemodynamic data of normotensive controls and hypertensive patients with left ventricular dysfunction.

Variable	NL	LVD
Systolic blood pressure (mmHg)	134 ± 3	181 ± 10*
Diastolic blood pressure (mmHg)	73 ± 2	105 ± 7*
Mean blood pressure (mmHg)	93 ± 2	129 ± 8*
Heart rate (bpm)	65 ± 3	74 ± 3*
CVP (mmHg)	6 ± 1	8 ± 1
FBF (ml/100 ml tissue per minute)	3 ± 0.3	5 ± 1
FVR (U)	37 ± 5	33 ± 4

Data are reported as mean ± SEM for 15 subjects in each group. NL = normotensive control subjects; LVD = left ventricular dysfunction patients; CVP = central venous pressure; FBF = forearm blood flow; FVR = forearm vascular resistance. *P < 0.05 compared to NL (unpaired Student *t*-test).

Hemodynamic responses to LBNP: analysis of the 1-min average data

Minute-to-minute FVR analysis showed that the LVD group has a blunted response during all 3 min at -10 mmHg of LBNP without differences between minutes (Figure 1). Conversely, at -15 and -40 mmHg of LBNP, the LVD group had a normal response in the 1st min, but a marked decrease in FVR up to the 3rd min of each stimulus (Figure 1).

Table 2. Absolute changes in cardiovascular variables during lower body negative pressure.

Variable	-10 mmHg LBNP		-15 mmHg LBNP		-40 mmHg LBNP	
	NL	LVD	NL	LVD	NL	LVD
Systolic blood pressure (mmHg)	1.2 ± 1.6	-0.5 ± 1.6	2.6 ± 1.6	0.9 ± 1.7	-0.2 ± 2.5	-2.3 ± 3.7
Diastolic blood pressure (mmHg)	0.4 ± 0.4	0.6 ± 1.1	2.4 ± 0.9	0.8 ± 0.9	5.1 ± 1.3	2.4 ± 2.2
Mean blood pressure (mmHg)	0.4 ± 0.5	-0.4 ± 1.2	2.0 ± 0.9	-0.3 ± 0.8	2.5 ± 1.7	-1.6 ± 2.6
Heart rate (bpm)	0.1 ± 0.7	-0.4 ± 0.8	2.1 ± 0.9	0.7 ± 1.4*	7.5 ± 1.2*	4.3 ± 2.2*
Central venous pressure (mmHg)	-2.4 ± 0.2*	-1.8 ± 0.3*	-3.8 ± 0.5*	-2.9 ± 0.4*	-6.0 ± 0.7*	-4.6 ± 0.6*

Data have been compared to those in Table 1. Data are reported as means ± SEM for 15 subjects in each group. LBNP = lower body negative pressure; NL = normotensive control subjects; LVD = left ventricular dysfunction patients.

*P < 0.05 compared to baseline values (unpaired Student *t*-test).

Hormonal responses to LBNP

Plasma norepinephrine responses to LBNP at -10, -15, and -40 mmHg were measured in 13 patients of the LVD group and 9 patients of the normal group. There was a trend to higher baseline plasma levels of norepinephrine (in pg/ml) in the LVD group (LVD: 342.6 ± 43.5 vs normal: 245.0 ± 23.2 ; $P = 0.06$). Percent variations in plasma norepinephrine during LBNP were attenuated in the LVD group at -10 mmHg (LVD: 7 ± 6 vs normal: $38 \pm 9\%$, $P = 0.013$), -15 mmHg (LVD: 35 ± 6 vs normal: $54 \pm 11\%$, $P = 0.032$), and -40 mmHg (LVD: 40 ± 7 vs normal: $104 \pm 13\%$, $P = 0.004$).

Discussion

The most important finding of this study was the accurate minute-by-minute characterization of the time course of the cardiopulmonary reflex control during 3 min of LBNP in hypertensive cardiomyopathy. Important information was lost when the analysis averaged 3-min data. In contrast to previous studies, by using a minute-to-minute analysis of FVR we observed a sustained blunted response in the LVD group during 3 min of LBNP at -10 mmHg, but a normal initial response at the 1st min of -15 and -40 mmHg of LBNP, with a marked decrease up to the 3rd min for each stimulus.

The present study is the first to characterize the temporal behavior of the cardiopulmonary reflex response in patients with hypertensive cardiomyopathy using a minute-to-minute analysis. We included data for the 1st min of the stimulus, in contrast to the studies which used the average of several minutes and which did not include the 1st min of LBNP (8-10).

Normal volunteers submitted to rapid low levels of LBNP showed a decrease in mean arterial blood pressure during the first seconds of receptor unloading (27). These premature hemodynamic alterations caused by

LBNP may cause an early deactivation of the cardiopulmonary reflex. The present data revealed the importance of minute-to-minute analysis of the response from the 1st min for a better characterization of the physiology and pathophysiology of the cardiopulmonary reflex regulation. In the present data, unlike the minute-to-minute analysis of FVR, the analysis of the average of 3 min failed to show the impairment of the reflex response indicated by a blunted norepinephrine re-

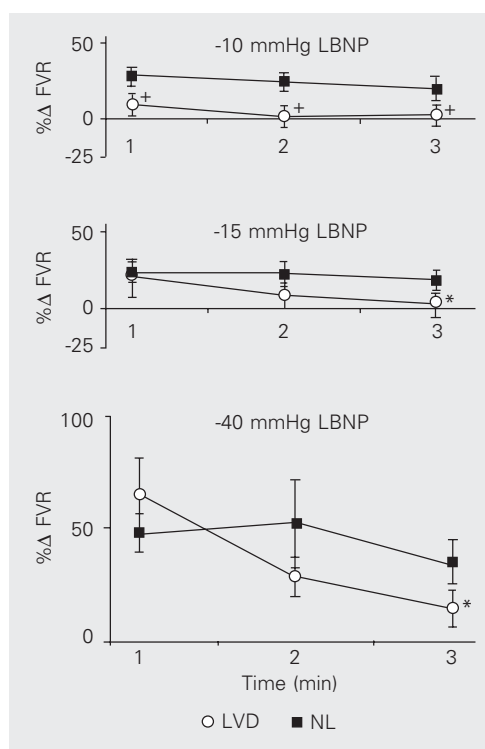


Figure 1. Minute-to-minute changes in forearm vascular resistance during the first 3 min at -10, -15 and -40 mmHg of lower body negative pressure. Each minute was compared to data presented in Table 1. FVR = forearm vascular resistance; LBNP = lower body negative pressure; LVD = left ventricular dysfunction group; NL = normal group. + $P < 0.05$ compared to NL; * $P < 0.05$ compared to previous minutes (analysis of variance for repeated measures).

Table 3. Three-minute interval average measurements of variations in forearm vascular resistance and forearm blood flow during lower body negative pressure.

Variable	-10 mmHg LBNP (%)		-15 mmHg LBNP (%)		-40 mmHg LBNP (%)	
	NL	LVD	NL	LVD	NL	LVD
FBF	-15.1 ± 5.2	$0.8 \pm 5.0^*$	-10.7 ± 5.5	-0.1 ± 5.3	-22.6 ± 4.4	-18.4 ± 6.1
FVR	23.8 ± 6.2	4.2 ± 6.0	20.8 ± 6.5	10.4 ± 9.5	45.2 ± 10.7	36.0 ± 14.1

Data have been compared to those in Table 1. Data are reported as means \pm SEM for 15 subjects in each group. FBF = forearm blood flow; FVR = forearm vascular resistance; LVD = left ventricle dysfunction patients; NL = normal control subjects.

* $P < 0.05$ between LVD and NL (unpaired Student t -test).

sponse at -15 and -40 mmHg of LBNP in the LVD group.

The similar decrease in CVP observed during the application of increasing levels of LBNP indicates an equivalent receptor unloading in both groups. Changes in FVR were observed without significant changes in arterial blood pressure or heart rate during -10 mmHg of LBNP, suggesting that the vascular responses were mainly due to the cardiopulmonary reflex. During -40 mmHg of LBNP, the small increase in heart rate indicated that the arterial baroreceptors, in addition to the cardiopulmonary baroreceptors, were unloaded, in agreement with previous reports that the application of LBNP higher than -20 mmHg also engages arterial baroreceptors in the final response (23,30). Nevertheless, this small increase does not exclude the participation of the arterial baroreceptors in the hemodynamic responses induced even by low levels of LBNP, such as -15 mmHg (23,30).

The impaired norepinephrine responses to LBNP in the LVD group constitute additional evidence for an altered cardiopulmonary reflex response. Similar findings of an impaired norepinephrine response to LBNP were obtained in patients with LVD (5) and hypertension (10,25).

The minute-to-minute analyses of FVR at -10, -15 and -40 mmHg of LBNP were able to demonstrate a different pattern of response in the LVD group. There was a parallel, but blunted response of FVR in the LVD group compared to control at lower levels of LBNP (-10 mmHg), when the reflex response is mainly a consequence of cardiopulmonary receptor unloading. However, at higher levels of LBNP (-15 and -40 mmHg), when the arterial baroreceptors in addition to the cardiopulmonary receptors are participating in the reflex response, the LVD group had an increase in FVR similar to the control group in the 1st min, but a significant decrease over 3 min. In contrast, the control group showed a small change in

the reflex response along minutes, probably as a consequence of normal interaction of the two reflexes and a normal sympathetic activation response.

The mechanisms associated with impairment of the cardiopulmonary reflex and baroreflex sensitivity (2,31-33) in patients with LVD and hypertension are not clear. To understand the mechanism underlying the present findings, we speculate that at higher levels of LBNP, the unloading of arterial baroreceptors could initially compensate the impairment of the cardiopulmonary reflex resulting in the initial normal response. However, as a consequence of the limitations of the methodology of reflex analysis applied to humans, it is not possible to precisely separate the responses of cardiopulmonary receptors and baroreceptors and the exact time of their initial influence on the final response. In addition, the impaired response observed in hypertensive patients with left ventricle dysfunction might be also the consequence of alterations in the neurohumoral regulation of other substances, such as atrial natriuretic peptide and renin, each of which is also regulated by the cardiopulmonary reflex (34,35).

There is clear evidence that LBNP is a good test for orthostatic tolerance (36), and that the cardiopulmonary response is attenuated in these patients. Especially considering the characteristics of progressive deterioration, the prevalence of orthostatic intolerance in these patients could be increased. Therefore, frequently used medications to treat hypertension and LVD, such as vasodilators and diuretics, should be prescribed with caution to patients whose cardiopulmonary reflex is impaired.

The present data agree with previous reports that the cardiopulmonary reflex and plasma norepinephrine responses are impaired in patients with hypertensive cardiomyopathy. However, the present results characterize the time course of the progressive impairment of the reflex response during

periods of LBNP and the normal initial response at higher levels of LBNP, showing the importance to monitor the time-course of the FVR response from the 1st min of stimulation and at subsequent 1-min intervals.

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