Dissociation between reflex sympathetic and forearm vascular responses to lower body negative pressure in heart failure patients with coronary artery disease

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Notarius CF, Morris BL, Floras JS. Dissociation between reflex sympathetic and forearm vascular responses to lower body negative pressure in heart failure patients with coronary artery disease. Am J Physiol Heart Circ Physiol 297: H1760–H1766, 2009. First published September 4, 2009; doi:10.1152/ajpheart.00012.2009.—Many heart failure (HF) patients exhibit paradoxical forearm vasodilation when central blood volume is reduced by lower body negative pressure (LBNP). We tested the hypothesis that this response results from reflex sympathetic withdrawal. We recorded simultaneously forearm blood flow, muscle sympathetic nerve activity (MSNA), and plasma norepinephrine (PNE) during four random applications of LBNP, −5, −10, −20, and −40 mmHg, in 12 men with HF (mean left ventricular ejection fraction = 24 ± 2%) and 10 healthy, normal, age-matched men (N). Compared with N, MSNA burst frequency (P = 0.001) and PNE (P = 0.005) were significantly higher in the HF group, both at rest and during LBNP. As anticipated in N, LBNP −40 mmHg significantly increased MSNA (+14.2 ± 2.5 bursts/min; P < 0.05) and PNE (+0.83 ± 0.22 mmol/l; P < 0.05) and decreased forearm vascular conductance (FVC) (−11.7 ± 3.2 ml·min⁻¹·mmHg⁻¹; P < 0.05). In the HF group, LBNP elicited similar increases in MSNA (+11.5 ± 2.0; P < 0.05) and PNE (+0.85 ± 0.12; P < 0.05), without affecting FVC significantly (−4.1 ± 2.4; P = 0.01 vs. N, interaction P = 0.03). However, within the HF group, responses were bimodal: LBNP −40 mmHg increased MSNA in all subjects (P < 0.001), yet the six patients with nonischemic or dilated cardiomyopathy (DCM) exhibited significant vasoconstriction (decrease in FVC; P = 0.001), whereas the six patients with ischemic cardiomyopathy (ICM) exhibited significant vasodilation (increase in FVC; P < 0.02 vs. DCM and N; interaction P = 0.02). Cold pressor testing increased MSNA and decreased FVC in ICM (n = 4). Thus paradoxical forearm vasodilator responses to LBNP in HF are not mediated by reflex sympathetic withdrawal. ICM and DCM patients differ qualitatively in their vascular responses to hypotensive LBNP.

etiology; microneurography; muscle sympathetic nerve activity; vascular conductance

Before the development of assays for quantifying plasma catecholamines, or the introduction of direct microneurographic recordings of muscle sympathetic nerve activity (MSNA), the contribution of the sympathetic nervous system to cardiovascular regulation in conscious humans often was assessed indirectly by evaluating responses mediated by reflex sympathetic activation, such as changes in forearm vascular conductance (FVC), in response to acute displacement of blood volume into the legs. Although orthostatic stimuli, such as tilt, or graded lower body negative pressure (LBNP) elicited, consistently, forearm vasoconstriction in healthy subjects (9, 34, 36, 38), this response was not augmented, as had been anticipated, in patients with heart failure (HF) due to ventricular systolic dysfunction (8, 14, 22, 25–27, 37). Rather, many investigators observed either marked attenuation of forearm vasoconstriction, or paradoxical forearm vasodilation (14, 26, 27). Such findings were attributed to either altered cardiopulmonary baroreflex regulation of vascular resistance, resulting in attenuated reflex sympathetic vasoconstriction, or, in some instances, a paradoxical reflex sympathetic withdrawal (10, 11, 26), or to release of epinephrine as a cotransmitter with norepinephrine in HF (12, 21) with subsequent β₂-adrenoceptor-related vasodilation (23).

Sympathetic activation in HF arises from loss of inhibitory, and activation of excitatory, baroreflex- and nonbaroreflex-mediated regulatory mechanisms (16, 17). In humans, the main defect in baroreceptor regulation of the sympathetic nervous system appears to arise from reflexes originating in mechanoreceptors situated within the heart and pulmonary vasculature (3, 11). However, whether such impairment results in muscle sympathetic withdrawal and, as a consequence, paradoxical forearm vasodilation has not been evaluated by simultaneous measurement of these variables. Moreover, the previous literature investigation of this theme has comprised, almost exclusively, patients whose systolic dysfunction was of ischemic origin (8, 10, 14, 22, 23, 25, 26). Also, such observations often arose from experiments in untreated HF patients, or in patients studied before the introduction of contemporary treatment for HF. Whereas, in the past, sympathetic neural activation was considered a hallmark of chronic HF due to systolic dysfunction, it is now appreciated that, in current practice, many such patients do not exhibit sympathetic activation, but, once this develops, its consequences include increasing congestion, symptoms such as diminished exercise capacity, and increased probability of premature mortality due to accelerated disease progression or sudden death (4, 7, 16, 28).

Recently, we reported higher MSNA at rest in HF patients with coronary artery disease than in patients matched for ejection fraction but without coronary artery disease (30). Patients with HF of ischemic [ischemic cardiomyopathy (ICM)] and nonischemic or dilated [dilated cardiomyopathy (DCM)] etiology may differ autonomically in other respects, such as in their reflex sympathetic responses to ventricular mechanoreceptor unloading.

We conducted the present experiments to test two specific hypotheses: 1) attenuated vasoconstriction and/or paradoxical vasodilation in response to LBNP in HF patients results from...
Table 1. Physical characteristics and resting data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Subjects</th>
<th>Heart Failure Patients</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>48.4±2.5</td>
<td>55.3±3.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177.8±16</td>
<td>175.0±2.5</td>
<td>0.34</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>85.4±4.2</td>
<td>86.1±4.6</td>
<td>0.91</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>24.5±2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>64.1±3.0</td>
<td>64.8±3.8</td>
<td>0.89</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>130.0±5.3</td>
<td>118.4±3.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>70.2±2.0</td>
<td>70.5±2.0</td>
<td>0.89</td>
</tr>
<tr>
<td>FBF, ml·min⁻¹·100 g⁻¹</td>
<td>2.7±0.2</td>
<td>2.8±0.3</td>
<td>0.81</td>
</tr>
<tr>
<td>FVR, units</td>
<td>35.0±2.3</td>
<td>36.0±4.8</td>
<td>0.85</td>
</tr>
<tr>
<td>FVC, units</td>
<td>30.2±2.6</td>
<td>32.0±3.0</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. LV, left ventricular; FBF, forearm blood flow; FVR, forearm vascular resistance; FVC, forearm vascular conductance; MSNA, muscle sympathetic nerve activity; PNE, plasma norepinephrine; VO₂peak, peak oxygen uptake. *Statistical difference: normal subjects vs. heart failure patients. †n = 9 and n = 11, respectively.

Table 2. Hemdynamic and neurohumoral response to LBNP in HF and normal subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>LBNP-5</th>
<th>LBNP-10</th>
<th>LBNP-20</th>
<th>LBNP-40</th>
<th>Main Effects</th>
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<td><strong>Hemodynamics</strong></td>
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<tr>
<td>Heart rate, beats/min</td>
<td>64.8±3.8</td>
<td>67.3±4.0</td>
<td>67.3±3.7</td>
<td>69.2±4.0*</td>
<td>72.5±3.7*</td>
<td>LBNP P &lt; 0.001</td>
</tr>
<tr>
<td>HF</td>
<td>64.1±3.0</td>
<td>63.0±3.0</td>
<td>63.4±2.8</td>
<td>66.4±3.0</td>
<td>75.7±2.5*</td>
<td>Interaction P &lt; 0.001</td>
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<tr>
<td>Normal</td>
<td>118.4±3.4</td>
<td>117.2±3.3</td>
<td>116.1±3.9</td>
<td>113.0±3.0</td>
<td>112.6±4.5</td>
<td>LBNP P = 0.009</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>130.0±5.3</td>
<td>125.6±6.0</td>
<td>130.0±5.6</td>
<td>129.0±6.0</td>
<td>123.7±6.3</td>
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</tr>
<tr>
<td>HF</td>
<td>70.5±2.0</td>
<td>68.2±1.6</td>
<td>68.6±2.5</td>
<td>71.2±2.3</td>
<td>68.3±2.5</td>
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</tr>
<tr>
<td>Normal</td>
<td>70.1±2.0</td>
<td>68.5±2.6</td>
<td>67.8±2.0</td>
<td>67.0±2.5</td>
<td>71.7±2.8</td>
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</tr>
<tr>
<td>MAP, mmHg</td>
<td>86.3±2.1</td>
<td>84.4±2.0</td>
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<td>85.0±2.3</td>
<td>83.0±3.0</td>
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<td>HF</td>
<td>89.9±2.7</td>
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<tr>
<td><strong>Neurohumoral</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>46.2±3.0</td>
<td>49.7±3.1</td>
<td>50.0±3.4</td>
<td>52.3±3.3</td>
<td>57.6±3.3*</td>
<td>LBNP P &lt; 0.001</td>
</tr>
<tr>
<td>HF</td>
<td>29.8±2.3</td>
<td>31.5±2.1</td>
<td>36.0±2.1*</td>
<td>37.2±2.4*</td>
<td>43.7±2.5*</td>
<td>Group P &lt; 0.001</td>
</tr>
<tr>
<td>Normal</td>
<td>71.3±2.6</td>
<td>74.6±3.6</td>
<td>74.4±3.4</td>
<td>76.0±3.3</td>
<td>80.2±4.0*</td>
<td>LBNP P &lt; 0.001</td>
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<tr>
<td>MSNA, bursts/100 heartbeats</td>
<td>47.4±3.5</td>
<td>50.6±3.3</td>
<td>56.9±2.5*</td>
<td>56.7±3.8*</td>
<td>58.2±3.6*</td>
<td>Group P &lt; 0.001</td>
</tr>
<tr>
<td>HF</td>
<td>1.68±0.24</td>
<td>2.02±0.22</td>
<td>1.90±0.24</td>
<td>2.25±0.27*</td>
<td>2.54±0.29*</td>
<td>LBNP P &lt; 0.001</td>
</tr>
<tr>
<td>Normal</td>
<td>0.84±0.12</td>
<td>1.04±0.12</td>
<td>0.99±0.11</td>
<td>1.26±0.10*</td>
<td>1.61±0.23*</td>
<td>Group P = 0.005</td>
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<tr>
<td>PNE, nmol/l</td>
<td>0.21±0.10</td>
<td>0.23±0.10</td>
<td>0.12±0.02</td>
<td>0.22±0.05</td>
<td>0.13±0.03</td>
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</tr>
<tr>
<td>HF (n = 11)</td>
<td>0.12±0.02</td>
<td>0.10±0.01</td>
<td>0.12±0.02</td>
<td>0.11±0.01</td>
<td>0.15±0.02</td>
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<tr>
<td>Normal (n = 9)</td>
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</table>

Values are means ± SE; n, no. of subjects. LBNP-5, LBNP-10, LBNP-20, LBNP-40: lower body negative pressure at 5, 10, 20, and 40 mmHg, respectively; HF, heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; PE, plasma epinephrine. *P < 0.05 vs. baseline within groups.
min. Forearm vascular resistance (FVR) was calculated as follows: the mean of four to eight measurements made at 15-s intervals over 2 reciprocal of FVR. in random order, with each maneuver separated by 10 min blocks. the following three interventions and four LBNP levels were imposed baseline recording, including 2 min of FBF, was acquired. Thereafter, Protocol sion, stored in a personal computer for subsequent analysis. Ment Systems, Madison, WI) and, following analog-to-digital conver- the electrocardiogram. Mean arterial pressure was calculated as one- monitored every minute by an automated device (Dinamap Pro 100; Critikon LLC, Tampa, FL), and heart rate was derived from lead II of the electrocardiogram. Mean arterial pressure was calculated as one-third pulse pressure + diastolic BP. Multiunit recordings of postganglionic MSNA were obtained with a unipolar tungsten electrode inserted selectively into a muscle-nerve fascicle of the right or left peroneal (fibular) nerve, posterior to the fibular head, as described previously (28, 29). Sympathetic nerve bursts were counted using customized computer analysis (LabVIEW software, National Instruments, Austin, TX) and expressed as burst frequency (bursts/min) and burst incidence (bursts/100 heart beats). Forearm blood flow (FBF) was measured by plethysmography with a mercury-in-Silastic strain-gauge apparatus (model 270A, Parks Electronics Laboratory, Beaverton, OR, or EC6 plethysmograph, or D. E. Holkanson Bellevue, WA) (40). The strain gauge was placed ~5 cm below the antecubital crease of the nondominant arm. The arm was elevated and supported so that the proximal forearm was ~10 cm above the anterior chest wall. Circulation to the hand was arrested by inflation of the wrist cuff to 180–200 mmHg during measurement of blood flow. The pressure in the venous occlusion cuff on the upper arm was 40 mmHg. FBF (in ml·100 g⁻¹·min⁻¹) was calculated from the mean of four to eight measurements made at 15-s intervals over 2 min. Forearm vascular resistance (FVR) was calculated as follows: FVR = mean arterial pressure/ FB FVC was calculated as the reciprocal of FVR. Signals were output to a recorder (Gould Viper-TA, Gould Instrument Systems, Madison, WI) and, following analog-to-digital conversion, stored in a personal computer for subsequent analysis. Protocol After this setup and following a stabilization period, a 7-min baseline recording, including 2 min of FBF, was acquired. Thereafter, the following three interventions and four LBNP levels were imposed in random order, with each maneuver separated by 10 min blocks. LBNP. Four minutes each of intermittent LBNP at −5, −10, −20, and −40 mmHg were applied. Responses over the last 2 min of each level were averaged. 

Cold pressor test. The right hand was immersed in ice water for 90 s, in a subgroup of nine HF and six healthy subjects, to ensure that sympathetically mediated vasoconstriction elicited by a nonbaroreceptor reflex stimulus to neural norepinephrine release did not differ between groups.

 Reactive hyperemia. To ensure that vasodilator capacity did not differ between groups, the immediate vascular response to hyperemia was assessed in nine HF and seven of the control subjects. An upper arm cuff was inflated to suprasystolic levels (<200 mmHg) for 5 min to provide an ischemic stimulus. The vasodilator reserve was determined by calculating FVC over the first 15-s sequence acquired immediately after release of the cuff (31).

Exercise tolerance test. Exercise capacity was assessed on a separate day by a graded exercise test performed on a bicycle ergometer with ramped increments of 17 W/min until pedal speed could no longer be maintained and the respiratory exchange ratio (CO₂ production/O₂ consumption) exceeded 1.1. Oxygen consumption at peak exercise (VO2peak) was obtained by open circuit spirometry (Horizon MMC System or Vmax Series 229, Sensormedics, CA). VO2peak was expressed both as liters per minute, milliliters per kilogram per minute, and as percentage of predicted VO2peak, to account for age, sex, body weight, and height.
Statistical Analysis

Data are presented as means ± SE. Unpaired t-tests were performed to test for differences between group means for dependent variables measured at rest. A repeated-measures two-way ANOVA was used to examine the main effects of group (HF, N) and LBNP (−5, −10, −20, −40 mmHg) or cold pressor test (CPT) (SigmaStat for Windows, version 1.0, Jandel Scientific, San Rafael, CA) on dependent variables. A similar analysis was applied to assess differences in response between HF etiology groups (ischemic, nonischemic) and N subjects. Prespecified hypotheses were then assessed by the post hoc Student Newman-Keuls test.

RESULTS

Descriptive and Resting Data

See Table 1. Cohorts were well matched for age, body weight, and height. Both absolute and normalized VO₂peak were significantly reduced in the HF patients (P < 0.001), with a mean VO₂peak in patients at 63% of predicted vs. 95% of predicted in N subjects. Resting heart rate, BP, FBF, and calculated FVR and FVC were similar in the two groups. As anticipated, HF patients exhibited significantly higher MSNA (burst frequency and incidence) (P < 0.001) and plasma norepinephrine (P = 0.009). Venous pressure in six HF subjects with indwelling central catheters was 4.8 ± 0.7 mmHg.

Response to LBNP

See Table 2. Graded LBNP produced an incremental decline in central venous pressure (Fig. 1). Heart rate rose significantly in both groups (main effect, P < 0.001). There was a significant increase in heart rate from baseline at an LBNP of −40 mmHg in N subjects and at both −20 and −40 mmHg in the HF group (interaction of group and LBNP, P < 0.001) (Table 2).

BP was stable throughout LBNP in all subjects until LBNP −40 mmHg, which elicited a slight but significant drop in systolic BP in both groups (main effect, P = 0.009). MSNA burst frequency and incidence were higher in the HF patients at all LBNP levels (main effect of group, P < 0.001). Importantly, the two subject groups had similar increases in MSNA with LBNP, whether expressed as absolute change in burst frequency from baseline (main effect of LBNP, P < 0.001; no group effect or interaction) (Fig. 2), or as the absolute change in burst incidence (P = 0.004, data not shown).

LBNP lowered FBF and FVC significantly in both groups (main effect, LBNP, P = 0.003 and 0.01, respectively, no group effect), but the absolute decrease in FVC was greater in the N subjects. There was virtually no change in FVC in the HF group (interaction, P = 0.03, P = 0.01, HF vs. N at LBNP −40 mmHg) (Fig. 2). Thus the principal difference between HF and control subjects was this dissociation between the effect of LBNP on sympathetic vasoconstrictor tone and FVC in the HF group.

HF Etiology

When the FVC response to LBNP −40 mmHg was examined in individual patients, two distinct patterns emerged: vasoconstriction similar to that in healthy controls in six of the HF patients, but, in the other six, either no change or an increase in FBF and FVC. Vasodilation in these individuals occurred, despite a simultaneous increase in sympathetic vasoconstrictor burst frequency. Figure 3 illustrates this finding in one HF patient. Importantly, this dissociation was only present in the six patients with HF and coronary artery disease.

LBNP elicited similar increases in MSNA burst frequency in HF patients, with or without initial coronary artery disease, and in age-matched N subjects (main effect LBNP, P < 0.001, no group effect). FVC decreased in the six patients without coronary artery disease and increased only in the six patients with HF and coronary artery disease (interaction P = 0.02). The response to LBNP −40 mmHg was significantly greater in the latter group than in either patients with nonischemic cardiomyopathy (P = 0.002) or N subjects (P = 0.02) (Fig. 4).

CPT

In response to the CPT, MSNA increased to a similar extent in HF and N subjects (HF: 47 ± 4.8 bursts/min at rest to 55 ± 5.9 bursts/min during 1.5 min of hand immersion in cold water vs. N: 32 ± 2.2 to 42 ± 5.2 bursts/min; means ± SE, no group main effect), indicating similar capacity of a nonbaroreflex stimulus to increase sympathetic outflow to the peripheral vasculature. However, patients with HF and coronary artery...
After ischemia vs. DCM 2.9 ± 0.6 to 13.2 ± 1.6 ml·100 g⁻¹·min⁻¹; means ± SE, \( P = 0.01 \).

**DISCUSSION**

The present study confirms previous reports of an attenuated forearm vasoconstrictor response to LBNP in patients with HF (2, 8, 14, 25–27, 37) and presents two novel findings concerning its interpretation: 1) it cannot be attributed to blunted reflex sympathetic vasoconstriction, refuting previous assumptions; and 2) HF patients with coronary artery disease and HF without coronary artery disease differ qualitatively in their forearm vascular response to this stimulus.

**Response to LBNP**

In healthy subjects, reduction in central venous pressure caused by graded LBNP elicits reflex increases in MSNA burst frequency in both arm and leg, total body norepinephrine spillover (3, 9, 17, 36, 38), and FVR (34, 41). These responses are affected by increased age (9, 34) and deconditioning (35), which are common features of HF patients.

Previous investigations using changes in plasma norepinephrine concentrations as a surrogate for neurogenic vasoconstriction have attributed the attenuated vascular response to LBNP in HF to less reflex sympatheic activation, or even sympathetic inhibition (10, 24, 26, 27). However, because variations in norepinephrine concentrations are a function of changes in regional norepinephrine release, its reappearance, and its clearance (18), reflex increases in cardiac output augmenting clearance could also decrease plasma norepinephrine concentration in HF patients. A normal increase in MSNA during LBNP (Fig. 2), even in those patients exhibiting paradoxical vasodilation (Figs. 3 and 4) argues against sympathoinhibition as an explanation for impaired reflex vasoconstriction. Any differences between healthy and HF patients in either central or left ventricular reflex-related sympathetic inhibition during volume unloading (39), or in stimulation of vagally mediated left ventricular mechanoreceptors by a shift in the left ventricular pressure-volume curve (2, 14), should elicit comparable responses in groups of directly measured sympathetic nerve traffic, but this was not found. In the present series, muscle sympathetic nerve firing rate rose to a similar extent in both HF and control subjects, yet the reflex forearm vasoconstriction response to LBNP was attenuated markedly in the former group.

Within the HF group, responses were bimodal. Our previously reported finding of higher MSNA at rest in ICM patients (30) suggested that this distribution might be a function of HF etiology. Despite an increase in MSNA during LBNP (Fig. 2), even in those patients exhibiting paradoxical vasodilation, the reflex forearm vasoconstriction response to LBNP was attenuated markedly in the former group.

**Reactive Hyperemic Response**

HF and N subjects exhibited similar increases in maximal FBF following 5 min of ischemia (HF: 2.7 ± 0.3 ml·100 g⁻¹·min⁻¹ at rest to 18.6 ± 3.5 ml·100 g⁻¹·min⁻¹ after ischemia vs. N: 2.9 ± 0.2 to 17.4 ± 2.2 ml·100 g⁻¹·min⁻¹; means ± SE, no group main effect). However, the patients with HF with ischemic etiology had a significantly greater hyperemic response than those patients without (ICM: 2.5 ± 0.3 ml·100 g⁻¹·min⁻¹ at rest to 23.9 ± 4.6 ml·100 g⁻¹·min⁻¹ after ischemia vs. DCM: 42.2 ± 4.0 to 48.0 ± 4.4 bursts/min; means ± SE, \( P = 0.02 \)).

*Fig. 4. A: individual MSNA burst frequency at rest and LBNP –40 mmHg. B: individual FVC at rest and LBNP –40 mmHg in HF with ischemic etiology [ischemic cardiomyopathy (ICM); solid lines] and HF with nonischemic etiology [dilated cardiomyopathy (DCM); dashed lines], with mean data summary for ICM, DCM, and healthy N subjects shown on the right in A and B. All groups have similar increase in MSNA burst frequency (main effect LBNP, \( P < 0.001 \)), but ICM have an increase in FVC during LBNP, suggesting paradoxical vasodilation compared with DCM and N, in whom FVC is decreased during LBNP (interaction, \( P = 0.02 \)). *\( P < 0.02 \), ICM vs. DCM and N.*
or tilt has been reported in subgroups of patients only when the HF cohort included ICM patients (5, 14, 26, 27). Importantly, no previous study has compared such responses in patients with and without coronary artery disease.

If not reflex sympathoinhibition, what then could account for the observed paradoxical vasodilation specific to these HF patients with concomitant coronary artery disease? Mohanty et al. (26) reported paradoxical vasodilation in 8 of 29 patients during LBNP. These were characterized by more severe HF and higher cardiac filling pressures. Similarly, Nishian et al. (27) observed a significantly higher pulmonary wedge pressure in those HF patients who exhibited paradoxical vasodilation during LBNP at −20 mmHg compared with those who vasconstricted. An increase in left ventricular stroke volume and cardiac output could improve FVC, particularly if the end-diastolic volume of the left ventricle at rest is reduced because cardiac output could improve FVC, particularly if the end-diastolic volume of the left ventricle at rest is reduced because of biventricular dilation and pericardial constraint (1, 2). This particular mechanism may be more active in patients with elevated filling pressures (14, 24, 27). Edema was absent in our HF cohort, and central venous pressure was not elevated (Fig. 1).

CPT and Reactive Hyperemia

HF patients with coronary artery disease had a greater increase in MSNA and a higher mean arterial pressure during the CPT than those without coronary artery disease and did not develop paradoxical vasodilation during this nonbaroreflex-mediated sympathoexcitatory stimulus; FVC decreased in all four patients who underwent this test. Thus the present findings indicate that paradoxical reflex vasodilation in HF is not caused by neuroeffector dysfunction, a conclusion consistent with that of previous reports (8, 14, 27).

A nonneurally mediated sympathetic vascular dissociation during adrenergic stimulation can be elicited in healthy subjects; this discordance has been attributed to the local actions of epinephrine and nitric oxide (19, 33). In the present series, the magnitude of reactive hyperemia following forearm ischemia was also greater in the HF patients with coronary artery disease, which suggests that such patients may be particularly sensitive to any endogenous local vasodilators that might be released by LBNP. If one such dilator was epinephrine, neurally released from sympathetic nerve endings (21), and acting on postjunctional β2-adrenoceptors to effect vasodilation, similar responses to CPT should have been anticipated, but were not observed.

Limitations

We measured sympathetic activity in the leg and vascular responses to LBNP in the forearm. Although no one has published measurement of MSNA obtained concurrently in the arm and leg in HF patients under similar conditions, prior studies, such as those by Rea et al. (32) involving LBNP, as well as more recent observations during mental stress by Carter et al. (6), demonstrate highly correlated values for MSNA measured simultaneously in the radial and peroneal nerves in healthy subjects. This latter concordance is of particular interest, because mental stress can elicit a different vascular response in the two limbs. Parallel increases in MSNA in the peroneal and median nerve (3, 9, 36, 38) and vascular responses in the calf and forearm (20) during LBNP have also been observed. On the basis of these facts, we consider that LBNP should elicit similar increases in sympathetic outflow to the arm and the leg in patients with ICM.

Our subject number was relatively small yet sufficient to detect a difference in response between HF and N subjects and also to distinguish vascular and neural responses to LBNP between HF patients with and without coronary artery disease. We avoided the confounding effects of drug withdrawal by studying patients while on medical treatment for HF. The distribution of medications was similar in the two HF populations, with the exception of a higher proportion taking digitalis (4 of 6 vs. 2 of 6) in the nonischemic vs. ICM group.

Summary

Sympathoinhibition does not account for the paradoxical vasodilation response during postural stress with LBNP in some patients with HF. Patients with nonischemic cardiomyopathy had decreases in FVC during LBNP, which were similar to those of age-matched, healthy control subjects, whereas those patients with HF due to coronary artery disease exhibited dissociated sympathetic neural and vascular responses, most evident at the highest level of LBNP. Why such paradoxical vasodilation should occur only in HF patients with coronary artery disease is not clear and warrants further targeted investigation.

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H1766 DISCORDANT SYMPATHETIC AND VASCULAR RESPONSES TO LBNP

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