Cardiac autonomic responses to volume overload in normal subjects and in patients with dilated cardiomyopathy

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1Institute of Internal Medicine, Cardiology and Heart Surgery, University of Naples Federico II, 80131 Naples; 2Institute of Cybernetics, National Research Council, 80072 Naples; and 3Department of Experimental Medicine and Pathology, University of Rome “La Sapienza,” 00161 Rome, and Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Neurologico Mediterraneo, 86077 Pozzilli, Italy

Spinelli, L., M. Petretta, F. Marciano, G. Testa, M. A. E. Rao, M. Volpe, and D. Bonaduce. Cardiac autonomic responses to volume overload in normal subjects and in patients with dilated cardiomyopathy. Am. J. Physiol. 277 (Heart Circ. Physiol. 46): H1361–H1368, 1999.—This study evaluated the effects of acute isotonic volume expansion on heart rate variability (HRV) in 10 patients with dilated cardiomyopathy (DCM) and in 10 age- and sex-matched normal volunteers. Echocardiographic left ventricular volumes and HRV measurements by continuous Holter recording were assessed at baseline, at 60 and 120 min during intravenous saline load (0.9% NaCl, 0.25 ml·kg⁻¹·min⁻¹), and 60 min after infusion was terminated. Data analysis was performed by repeated-measures ANOVA. After volume expansion, left ventricular ejection fraction increased (F = 9.8; P < 0.001) in normal subjects and decreased (F = 8.7; P < 0.001) in DCM patients. During volume expansion a significant difference was also detectable between the two groups in root-mean-square successive difference (F = 25.2; P < 0.001), percentage of differences between successive normal R-R intervals >50 ms (F = 97.6; P < 0.001), high-frequency power (F = 50.1; P < 0.001), and low-frequency power (F = 41.6; P < 0.001), all of which reflect parasympathetic modulation of heart rate; in fact, these measurements increased in normal subjects and decreased in DCM patients. In normal subjects, the increase in HRV measurements during volume expansion suggests a parasympathetic activation, mediated by stimulation of cardiopulmonary and arterial mechanoreceptors. On the contrary, in DCM patients the parasympathetic withdrawal, already detectable at baseline, increases during volume expansion.

heart rate variability; isotonic volume expansion; left ventricular dysfunction

ACUTE ISOTONIC VOLUME EXPANSION has been utilized to unmask abnormalities of cardiovascular and renal responses in patients with idiopathic dilated cardiomyopathy (DCM) and asymptomatic to mildly symptomatic heart failure (28, 29). In particular, it has been reported that in DCM patients volume expansion is followed by a reduction in ejection fraction with a paradoxical increase in forearm vascular resistance even in patients with basal hemodynamic, hormonal, and renal profiles still in the normal range (28, 29). An abnormal reflex control of the cardiovascular system with a neurohumoral excitation is currently considered responsible for this paradoxical hemodynamic response (11). Heart rate variability (HRV) has proven a valid noninvasive technique for assessing cardiac autonomic control (3, 24). Furthermore, changes in HRV have recently been found in patients with chronic heart failure and have been reported to be associated with the progression from mild to moderate heart failure (19). The aim of the present investigation was to evaluate cardiac autonomic control in DCM patients with mild heart failure symptoms during isotonic water loading. The results could help to clarify the mechanisms of neurohumoral excitation and of parasympathetic withdrawal commonly observed in the early stage of heart failure.

METHODS

Study patients. The overall study population included 10 patients with idiopathic DCM and chronic, stable, mild heart failure and 10 age- and sex-matched normal volunteers. The investigation conforms with the recommendations of the Declaration of Helsinki, and the study protocol was approved by the ethical committee of our institution. All subjects gave written, informed consent before entering the study. The patients, 7 men and 3 women ranging in age from 36 to 56 yr (mean ± SD: 49 ± 6 yr) were recruited by selection of consecutive patients in the outpatient clinic of cardiovascular diseases of our institution. Exclusion criteria included any other major disease: ischemic heart disease; hypertension; diabetes; atrial fibrillation or severe ventricular arrhythmia; renal failure; recent acute cardiac decompensation, as defined by the sudden accumulation of pulmonary congestion or peripheral edema; valvular disease or significant mitral regurgitation; and cardiopulmonary anatomy not allowing satisfactory and reproducible echocardiographic recordings. The diagnosis of DCM was based on the exclusion of any obvious underlying cause of heart failure during routine evaluation. In particular, no patient had a history of angina or myocardial infarction, and all patients had undergone coronary angiography showing normal coronary arteries. The definition of mild heart failure was based on the following criteria: no reduction (2 patients) or mild reduction (8 patients) in functional capacity according to the New York Heart Association classification (class I or II); mild to moderate limitation of exercise capacity, as determined by cardiopulmonary exercise testing using a standard protocol (upright bicycling with a stepwise increase of 10 W/min) (mean exercise duration in patients was 9.7 ± 0.5 min; peak oxygen consumption averaged 18 ± 0.8 ml·kg⁻¹·min⁻¹; echocardiographic end-diastolic left ventricular diameter ≥56 mm; and left ventricular ejection fraction, as determined by equilibrium radionuclide angiography, <45% on at least one measurement within 3 mo before the study. At the time of their first visit to the outpatient...
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Clinic, seven patients were undergoing treatment with angiotensin-convertase enzyme (ACE) inhibitors, whereas digitalis and diuretics were being given to four and five patients, respectively.

Experimental protocol. All drug therapy was discontinued at least 1 wk, and ACE inhibitor at least 2 wk, before the study. Alcohol, caffeine, cigarettes, and physical exercise were all prohibited within 24 h of the study. After being admitted to the clinic ward, all subjects were maintained on a daily diet containing 100 meq of sodium, 50 meq of potassium, and 1,500 ml of water. Daily 24-h urine collections were analyzed for sodium, potassium, and creatinine excretion. When a satisfactory equilibrium between sodium and water excretion was achieved, the patients underwent the study protocol on two consecutive days, as previously described (28). On the first day, patients underwent 24-h Holter recording. The recording started between 8:00 and 10:00 AM, and patients were asked to record the time they went to sleep and the time they awakened. All patients reported sleeping normally during the night they were monitored. When this 24-h monitoring was terminated, a second Holter recording was started; after voiding, the patient assumed a comfortable lying position. After 60 min, an intravenous isotonic saline load (0.9% NaCl, 0.25 ml·kg⁻¹·min⁻¹) was started and maintained at a constant rate for 2 h. Arterial blood pressure was measured at 10-min intervals by a standard sphygmomanometric technique. Heart rate was continuously monitored by electrocardiogram (ECG) lead II. M- and B-mode echocardiograms were recorded for measurements of cardiac dimensions, calculation of left ventricular ejection fraction, and estimation of stroke volume and the derived parameters before the isotonic saline load was started, at 60-min intervals during the saline load, and 60 min after its termination. At the same time, urine output was measured. Thereafter, the Holter recording was interrupted and the study session terminated. The same study protocol was performed in control subjects.

Echocardiographic measurements. Wide-angle, two-dimensional echocardiograms were recorded with a phased-array sector scanner (V77020 AC, Hewlett-Packard, Andover, MA). All studies were videotaped on ¾-in. tape with the use of a wide-angle, two-dimensional echo module, which allows frame-by-frame bi-directional playback. The video frame rate of the system was ~60 frames/s. All patients were studied while in a comfortable lying position with multiple views through the apical window. Two views were selected for measurements: an apical four-chamber view and an apical two-chamber view. The left ventricular long axis (Lmax) was measured at end diastole as the longest major axis in either of the two apical views. The measurements of Lmax were rounded off to the closest whole number to ensure reproducibility. Left ventricular end-diastolic area was measured by using the largest of all the left ventricular minor axes measured. Left ventricular end-diastolic volume (in ml) was calculated according to the single-plane ellipse method as EDV = ½(EDA²)(πLmax), where EDA is end-diastolic area (13). The same measurements were undertaken in end systole to calculate end-systolic volume. Ejection fraction was measured using the averages of all the end-diastolic and end-systolic volumes (13). All studies were performed by the same investigator and read independently by two experts unaware of the protocol. The readings that were obtained showed correlation for both Lmax (r = 0.96; P < 0.001) and end-diastolic area (r = 0.95, P < 0.001). Excellent correlations between the two observers were also obtained for the measurements of end-diastolic (r = 0.96, P < 0.001) and end-systolic volume (r = 0.95, P < 0.001).

The variability of multiple measurements of volumes over a period of 2 h did not exceed 3.5%. Stroke volume was derived as the difference between end-diastolic volume and end-systolic volume, and cardiac output and total peripheral resistance were estimated by using standard formulas. In our laboratory, the echocardiographic measurements of stroke volume were significantly correlated with the measurements obtained using the thermodilution technique (r = 0.88, P < 0.01).

Processing 24-h Holter recordings. All 24-h Holter recordings were analyzed at the National Research Council cybernetics laboratory, as previously described (5). The two electrocardiographic analogic channels were read via a modified Teac-Tascam 234 Syncaset tape deck (Teac, Tokyo, Japan) and digitized at 330 samples/s. In addition to evaluation of the usual electrocardiographic parameters, including the identification of QRS widths and shapes and R-R interval abnormalities, all R-R interval sequences were stored, and each was labeled with a code number identifying its normality or its class of abnormality. Premature complexes and their adjacent R-R intervals, used only for timekeeping purposes, were rejected by the software, as were electrical noise and other aberrant electrocardiographic signals. To be eligible for the present study, Holter recordings were those per tape due to persistent rhythm anomalies and artifacts could not exceed 10% of the entire recording or of daytime (7:30 AM to 9:30 PM) or nighttime recordings (12:00 AM to 5:00 AM). The sequence of normal R-R (NN) intervals was analyzed to compute time- and frequency-domain measurements of HRV (3, 24).

Time-domain measurements of HRV. From the time series of NN intervals we calculated the time-domain variables defined in Table 1. The standard deviation of the NN intervals (SDNN) calculated over a 24-h period encompasses short-term as well as long-term NN-interval variations. The standard deviation of the average NN intervals for all 5-min segments of the entire 24-h ECG recording (SDANN index) also evaluates short-term R-R variations, whereas the mean of the standard deviations of NN intervals for all 5-min segments of the entire 24-h ECG recording (SDNN index) depends on short-term R-R variations. On the other hand, the root-mean-square successive difference (r-MSSD) of all NN intervals and the percentage of differences between adjacent NN intervals exceeding 50 ms (pNN50) for the entire 24-h recording.

Frequency-domain measurements of HRV. The 24-h heart rate power spectrum was computed by means of the fast Fourier transform algorithm, as previously described (5). A smooth shape for fast Fourier transform estimates, reducing side-lobe leakage, was obtained by cosine tapering the original time series at each end over one-tenth of the window (2). An R-R interval function of time was obtained from the sequence of R-R intervals as follows: from the sequence of NN values, the sequence [NN₁, NN₂, ..., NN₁₉₉] was evaluated, and from this the temporal sequence [NN₁, NN₂, ..., NN₁₉₉] = f(t), where i = 100, 200, 300 ms... was computed by linear interpolation with a time step of 100 ms; this is a low-pass filtering operation that attenuates any variability above the chosen value of the sampling frequency. The final average spectrum provided total power and average power per band in square millisecond. The frequency bands explored are reported in Table 1; the ratio of low- to high-frequency power was calculated from the absolute values of these two components. An epoch of 300 s and a sampling period of 293 ms...
and "time" as well as the "time-group" interaction. dent variables "group" (normal subjects vs. DCM patients) repeated measures considering the main effects of the indepen-
within the same group. Between-group comparisons of the performed to detect changes over time during saline load
multiple comparisons with the Bonferroni correction was
significant. Repeated-measures ANOVA followed by post hoc

Time- and frequency-domain measurements of heart rate variability obtained by 24-h Holter recording

RESULTS

HRV analysis of 24-h Holter recording. The results of HRV analysis by 24-h Holter recordings are reported in Table 2. Average NN values were lower in patients with DCM than in controls. Moreover, DCM patients had lower values of time-domain measurements of HRV. Frequency-domain measurements were also lower in DCM patients than in controls, whereas the ratio of low- to high-frequency power was comparable between the two groups.

Circulatory response to volume expansion. Figure 1 shows the responses of systemic and cardiac hemodynamics to saline load in the two groups. Systolic and diastolic arterial pressure did not change during saline load, and no difference between the two groups was detectable. In normal subjects left ventricular end-diastolic volume (F = 21.8; P < 0.001), left ventricular ejection fraction (F = 9.8; P < 0.001), stroke volume (F = 17.4; P < 0.001), and cardiac output (F = 9.38; P < 0.001) increased during saline load, whereas left ventricular end-systolic volume did not change. In contrast, in heart failure patients both left ventricular

<table>
<thead>
<tr>
<th>Variables</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Average NN interval, ms</td>
<td>Average of all normal R-R intervals over entire 24-h ECG recording</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>Standard deviation of all normal R-R intervals over entire 24-h ECG recording</td>
</tr>
<tr>
<td>SDANN index, ms</td>
<td>Standard deviation of average normal R-R intervals for all 5-min segments of entire 24-h ECG recording</td>
</tr>
<tr>
<td>SDNN index, ms</td>
<td>Mean of standard deviations of all normal R-R intervals for all 5-min segments of entire 24-h ECG recording</td>
</tr>
<tr>
<td>r-MSSD, ms</td>
<td>Root-mean-square successive difference (square root of mean of squared differences between adjacent normal R-R intervals over entire 24-h ECG recording)</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>Percentage of differences between successive normal R-R intervals that are &gt;50 ms computed over entire 24-h ECG recording</td>
</tr>
<tr>
<td>Frequency domain</td>
<td></td>
</tr>
<tr>
<td>Very-low-frequency power, ms²</td>
<td>Energy in heart rate power spectrum &lt;0.04 Hz</td>
</tr>
<tr>
<td>Low-frequency power, ms²</td>
<td>Energy in heart rate power spectrum between 0.04 and 0.15 Hz</td>
</tr>
<tr>
<td>High-frequency power, ms²</td>
<td>Energy in heart rate power spectrum between 0.15 and 0.40 Hz</td>
</tr>
<tr>
<td>Low- to high-frequency ratio, absolute units</td>
<td>Ratio of low-frequency power to high-frequency power</td>
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</tbody>
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ECG, electrocardiogram.

The results of

<table>
<thead>
<tr>
<th>Normal Subjects</th>
<th>DCM Patients</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Time-domain measurements</td>
<td></td>
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</tr>
<tr>
<td>Average NN, ms</td>
<td>918 ± 41</td>
<td>816 ± 88</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>151 ± 25</td>
<td>114 ± 25</td>
</tr>
<tr>
<td>SDANN index, ms</td>
<td>132 ± 23</td>
<td>95 ± 31</td>
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<tr>
<td>SDNN index, ms</td>
<td>68 ± 10</td>
<td>57 ± 11</td>
</tr>
<tr>
<td>r-MSSD, ms</td>
<td>55 ± 9</td>
<td>41 ± 13</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>20 ± 9</td>
<td>10 ± 9</td>
</tr>
<tr>
<td>Frequency domain measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total power, ms²</td>
<td>3,416 ± 770</td>
<td>2,259 ± 647</td>
</tr>
<tr>
<td>In total power</td>
<td>8.10 ± 0.28</td>
<td>7.68 ± 0.27</td>
</tr>
<tr>
<td>VLF power, ms²</td>
<td>2,077 ± 605</td>
<td>1,441 ± 378</td>
</tr>
<tr>
<td>In VLF power</td>
<td>7.60 ± 0.28</td>
<td>7.24 ± 0.26</td>
</tr>
<tr>
<td>LF power, ms²</td>
<td>1,030 ± 171</td>
<td>649 ± 78</td>
</tr>
<tr>
<td>In LF power</td>
<td>6.92 ± 0.18</td>
<td>6.46 ± 0.25</td>
</tr>
<tr>
<td>HF power, ms²</td>
<td>535 ± 109</td>
<td>308 ± 171</td>
</tr>
<tr>
<td>In HF power</td>
<td>6.26 ± 0.20</td>
<td>5.63 ± 0.43</td>
</tr>
<tr>
<td>LFH power</td>
<td>1.97 ± 0.39</td>
<td>2.43 ± 0.73</td>
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Values are means ± SD. DCM, dilated cardiomyopathy; In, logarithmic units; VLF, very low frequency; LF, low frequency; HF, high frequency; NS, not significant.
end-diastolic (F = 9.8; P < 0.001) and end-systolic volume (F = 13.6; P < 0.001) increased, whereas left ventricular ejection fraction, stroke volume, and cardiac output remained unchanged. Two-factor repeated-measures ANOVA showed a significant (P < 0.001) between-group difference for all the echocardiographically derived parameters; moreover, the time-group interaction was significant for end-systolic volume (F = 14.3; P < 0.001), left ventricular ejection fraction (F = 8.7; P < 0.001), and stroke volume (F = 4.7; P < 0.005).

In normal subjects during saline load, urinary volume increased from 2.15 ± 0.14 to 2.94 ± 0.55 ml/min at 60 min to 4.14 ± 0.69 ml/min at 120 min and 3.72 ± 0.52 ml/min at 180 min. In heart failure patients the response of urinary volume (1.81 ± 0.10 ml/min at baseline, 1.95 ± 0.33 ml/min at 60 min, 2.05 ± 0.28 ml/min at 120 min, and 1.81 ± 0.19 ml/min at 180 min) did not achieve statistical significance.

HRV measurements and volume expansion. Figure 2 shows the responses of heart rate and time-domain measurements of HRV during volume expansion in the two groups. The response to saline load in normal subjects was different from that in DCM patients. In normal subjects average NN remained unchanged during saline load, whereas r-MSSD (F = 9.4; P < 0.001), pNN50 (F = 4.1; P < 0.05), and SDNN index (F = 7.3; P < 0.001) increased significantly. In contrast, in DCM patients average NN decreased during saline load (F = 5.1; P < 0.01), whereas r-MSSD, pNN50, and SDNN index remained unchanged. Two-factor repeated-measures ANOVA showed a significant between-group difference in average NN (F = 6.1; P < 0.05), r-MSSD (F = 25.2; P < 0.001), pNN50 (F = 97.6; P < 0.001), and SDNN index (F = 28.7; P < 0.001). Also, the time-group interaction showed a significant difference for average NN (F = 3.2; P < 0.05), r-MSSD (F = 5.4; P < 0.005), pNN50 (F = 3.3; P < 0.05), and SDNN index (F = 3.9; P < 0.05). The effect of saline load on frequency-domain measurements is shown in Fig. 3. In normal subjects saline load induced an increase in very low-frequency (F = 32.4; P < 0.001), low-frequency (F = 12.7; P < 0.001), and high-frequency power (F = 30.1; P < 0.001). In DCM patients frequency-domain measurements did not change. The ratio of low- to high-frequency power
remained unchanged during saline load in the two groups. When the changes in frequency-domain measurements were analyzed by two-factor ANOVA with group as the main effect, a significant difference was detectable between the two groups in very low-frequency \( (F = 6.1; P < 0.05) \), low-frequency \( (F = 41.6; P < 0.001) \), and high-frequency power \( (F = 50.1; P < 0.001) \), and the time-group interaction was significant for very low-frequency \( (F = 3.8; P < 0.01) \), low-frequency \( (F = 5.7; P < 0.005) \), and high-frequency power \( (F = 6.6; P < 0.001) \), confirming the different responses of HRV to saline load between the two groups. Mean respiratory rate, measured from the ECG-derived respiratory signal, was higher at baseline in DCM patients than in normal subjects \((0.31 \pm 0.03 \text{ vs. } 0.25 \pm 0.04 \text{ Hz}; P < 0.001)\) and remained unchanged in normal subjects, whereas it increased in DCM patients \((F = 12.7; P < 0.001)\) and was \(0.32 \pm 0.03 \text{ Hz}\).
at 60 min, 0.33 ± 0.04 Hz at 120 min, and 0.32 ± 0.03 Hz at 180 min. Thus, when the two groups were compared by two-factor ANOVA, a significant between-group difference (F = 99.2; P < 0.001) as well as a significant time-group interaction (F = 3.9; P < 0.05) was detectable.

DISCUSSION

The present study demonstrates that changes in HRV measurements after acute volume expansion differ in patients with DCM from those observed in normal subjects. In fact, cardiac vagal control decreased in patients with DCM during saline load but increased in normal subjects. Moreover, the response of urinary volume to saline load was significantly depressed in DCM patients compared with normal subjects. These findings extend previous observations (28, 29) that demonstrate the presence of abnormal hemodynamic, hormonal, and renal adaptation to volume loading in mild heart failure patients.

HRV and chronic heart failure. In our study, time- and frequency-domain measurements obtained from 24-h Holter recordings were lower in DCM patients than in normal subjects. A clear reduction in total power of the heart rate power spectrum and in each of its components has recently been demonstrated in patients with chronic heart failure (10). High-frequency power reflects the modulation of cardiac autonomic control by respiratory frequency and depth and is considered a pure measurement of cardiac vagal control (3, 24). Therefore, the decrease in high-frequency power that we observed in DCM patients reflects the parasympathetic withdrawal that is an integral component of the autonomic dysfunction detectable in patients with asymptomatic to mildly symptomatic heart failure (4). The decrease in low-frequency power is also commonly observed in patients with chronic heart failure, and different hypotheses have been proposed to connect the decrease in this frequency band with the known sympathovagal characteristics of patients with heart failure. Saturation of the sinus node with sympathetic traffic has been shown to prohibit the superimposition of any variability on a heart rate pattern (16). Accordingly, the progressive sympathetic activation that occurs in chronic heart failure may be accompanied by a reduction in the power of the low-frequency band. The progressive down-regulation of myocardial β-adrenergic receptors and the reduction of myocardial catecholamine stores may also produce a reduction in end-organ responsiveness to sympathetic stimulation (9). Recently, van de Borne et al. (27) performed the spectral analysis of simultaneous recordings of resting muscle sympathetic nerve activity and R-R interval in patients with chronic heart failure and in age-matched control subjects. Despite the increase in muscle sympathetic nerve activity, the low-frequency components of R-R interval and nerve activity were lower in heart failure patients than in control subjects. These authors hypothesized that the reduction in low-frequency components in heart failure patients reflects a disturbance of rhythmic oscillations of autonomic outflow due to a central autonomic impairment (27).

Finally, it is well established that the parasympathetic arm of the autonomic nervous system contributes to low-frequency power (8, 24). Therefore, a reduction in the parasympathetic modulation of heart rate could compound the reduction of low-frequency power, which is detectable with the progression of left ventricular dysfunction. Interestingly, it has been demonstrated that in heart failure patients the degree of autonomic dysfunction as represented by impaired HRV is an independent predictor of mortality that is able to add prognostic information to that of left ventricular ejection fraction (20).

Volume overload and cardiac adaptations. Hemodynamic, hormonal, and renal adaptations to volume loading have been widely evaluated to define the time of onset of the hormonal and cardio-renal abnormalities in patients with mild to moderate heart failure. Volpe et al. (28, 29) found that in DCM patients with chronic, stable, mild heart failure, ejection fraction and stroke volume decrease progressively during volume expansion, whereas forearm vascular and calculated total peripheral resistances paradoxically increase. In contrast, in normal subjects ejection fraction increases and peripheral resistances decrease.

Therefore, the overall mechanisms of adaptation to increased preload in patients with DCM are quite different from those operating in physiological states. In our study, volume overload in normal subjects was followed, as expected, by an increase in left ventricular ejection fraction, due to an increase in left ventricular end-diastolic volume, without changes in left ventricular end-systolic volume (Fig. 1). In heart failure patients, volume overload induced an increase in both left ventricular end-diastolic and end-systolic volumes with a slight reduction of ejection fraction. These findings confirm the early exhaustion of the preload reserve mechanism even in the early stage of heart failure.

Volume overload and HRV measurements. The major finding of the present study is the difference in cardiac autonomic control during volume expansion, as revealed by HRV analysis, between normal subjects and DCM patients. In fact, in normal subjects we observed that saline loading was followed by a progressive increase of high-frequency power, r-MSSD, and pNN50, measurements considered to reflect the parasympathetic modulation of heart rate. The increase in low-frequency power may also be ascribed to an increase in vagal activity, because this frequency band reflects the mixed modulation by the parasympathetic and sympathetic branches of the autonomic nervous system (8). It is well known that, in normal subjects, a tonic inhibitory influence on sympathetic efferent outflow from the medullary cardiovascular centers is exerted by the activation of arterial and cardiopulmonary mechanoreceptors (14). The left ventricle is the site of many of these cardiac sensory receptors (6), and the principal determinants of their activity are cardiac filling pressure, the inotropic state of the ventricle, and the mechanical deformation of the walls in which they are located (12, 26). During volume expansion, low-pres-
sure mechanoreceptors increase their inhibitor influence on sympathetic efferent outflow and increase their excitatory influence on parasympathetic outflow. This restraint effect on sympathetic efferent outflow is responsible for the reduction of forearm vascular resistance observed in normal subjects when the venous return to the heart is increased, such as after leg rise (1, 17) or saline load (29). However, it has been demonstrated that arterial baroreceptors located in the carotid artery (15) and thoracic aorta (25) are exquisitely sensitive to deformation and may respond to minor volume changes. Therefore, it is conceivable that the changes we observed in HRV measurements during volume loading are, importantly, mediated also by arterial baroreceptors. The increased mechanoreceptor activity is involved in the reflex increase in urine flow and sodium excretion as well as in the decrease in vasopressin release, renin release, and renal sympathetic nerve activity (23, 30).

In DCM patients, but not in controls, we observed a clear reduction in r-MSSD, pNN50, and high-frequency power, measurements that indicate vagal modulation of heart rate. These findings confirm that patients with chronic left ventricular dysfunction have a significant impairment of cardiopulmonary and arterial baroreflex mechanisms and reduced sensitivity of mechanoreceptors with vagal afferent endings. The reduced sensitivity of these receptors with inhibitory influence would produce a net increase in sympathetic activity. Moreover, receptors whose afferent fibers run along cardiac sympathetic nerves have been also described (22). It is conceivable that during volume expansion there is an uncontrolled stimulation of these cardiac receptors with sympathetic afferents, leading to a further decrease in vagal modulation of heart rate (22). Also, breathing frequency influences vagal cardiac nerve traffic, and faster breathing rates reduce noninvasive indexes of cardiac vagal control (7). In our study DCM patients breathed more rapidly than normals at baseline and increased their breathing frequency during volume load. These differences in breathing may have contributed to the differences in responses in HRV measurements reflecting vagal control observed in the two groups.

Thus the response of the autonomic nervous system differs between normal subjects and heart failure patients. In normal subjects, volume expansion is followed by a parasympathetic activation that contributes, along with cardiac and hormonal adaptation, to eliminate promptly the saline load and to regulate vascular volumes. On the contrary, in patients with left ventricular dysfunction, the progressive decrease in HRV measurements demonstrated that the autonomic dysfunction detectable in resting condition is more evident during volume expansion. These abnormalities of reflex control are responsible for peripheral vasoconstriction and consequent reduced blood flow to peripheral tissue, and they contribute to water and salt retention in chronic heart failure.

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Received 29 January 1999; accepted in final form 19 May 1999.


