Relation Between Depressed Cardiac Response to Exercise and Autonomic Nervous Activity in Mildly Symptomatic Patients With Idiopathic Dilated Cardiomyopathy*

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We investigated whether the depressed cardiac response to adrenergic stimulation is accompanied with impaired autonomic function in mildly symptomatic patients with idiopathic dilated cardiomyopathy (DCM). Twenty-seven patients with DCM (New York Heart Association class I or II) and 7 normal control subjects underwent exercise radionuclide ventriculography and 24-h ambulatory ECG. The following frequency components of heart rate variability were calculated: the areas under the low (low frequency component [LF], 0.04 to 0.15 Hz), high (high frequency component [HF], 0.15 to 0.40 Hz), and total frequency portions of the spectrum. HF and HF% (the ratio of HF to total power) were calculated as indexes of specific vagal influences, and LF% (the ratio of LF to total power) and the ratio of LF to HF were of sympathetic tone. The left ventricular ejection fraction (LVEF) increased by more than 5% in all normal control subjects during exercise, whereas 17 (63%) of patients failed to show more than a 5% increase in LVEF. The profile of the mean hourly HF% and LF/HF showed circadian variations in normal control subjects but not in patients. The HF and HF% during sleep were significantly lower and the LF/HF during sleep was higher in patients than in normal control subjects.

In patients, the LVEF during exercise minus LVEF at rest was significantly correlated with HF, LF%, and LF/HF during sleep, and with the ratios of the mean values during early morning to the mean daytime values for those spectral indexes. Our results demonstrated that mildly symptomatic patients with DCM showed an attenuated cardiac response to exercise and altered autonomic function, and their close relationship, suggesting that autonomic nervous activity contributes to cardiac desensitization in DCM.

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DCM=idiopathic dilated cardiomyopathy; HF=high-frequency component (0.15 to 0.40 Hz); HF%=the ratio of HF to total power; LF=low-frequency component (0.04 to 0.15 Hz); LF%=the ratio of LF to total power; LF/HF=the ratio of LF to HF; LVEF=left ventricular ejection fraction; ALVEF=left ventricular ejection fraction during exercise minus left ventricular ejection fraction at rest; NYHA=New York Heart Association; NU=normalized units

Key words: heart rate variability; idiopathic dilated cardiomyopathy; myocardial contractile reserve; power spectral analysis; radionuclide ventriculography

The contractile response to β-adrenergic stimulation is reduced or blunted in the failing human myocardium.1,2 The contractile response is also a prognostic factor in patients with heart failure.3-5 Proposed mechanisms of reduced contractile response include β-receptor down-regulation induced by an elevated plasma concentration of catecholamine6,7 and depletion of myocardial norepinephrine.8 Although these factors may be partially responsible for the depressed cardiac contractile reserve, the exact mechanism remains unknown. It is not clear if mildly symptomatic patients with idiopathic dilated cardiomyopathy (DCM) show a depressed cardiac response to sympathetic stimulation, and it has not been determined if the resting clinical and hemodynamic characteristics are accurate predictors of this response.

Spectral analysis of heart rate variability has been proposed as a noninvasive means of evaluating autonomic activity in the heart.9-13 Spectral analysis has identified a sympathovagal imbalance in patients with severe heart failure.14,15 However, data on autonomic function in patients with DCM with mild symptoms are limited.

We investigated the cardiac response to exercise in mildly symptomatic patients with DCM (New York Heart Association [NYHA] functional class I or II) and...
examined the correlation between the cardiac response and measures of clinical and hemodynamic status, and indexes of autonomic nervous activity derived from spectral analysis of heart rate variability.

**Materials and Methods**

**Subjects**

We studied 27 mildly symptomatic patients with DCM (14 men, 13 women; 58±10 years of age) and 7 normal control subjects (4 men, 3 women; 60±6 years). Normal control subjects had no history, symptoms, or signs of cardiovascular disease and had normal 12-lead ECGs at rest and during exercise and normal M-mode, two-dimensional, and Doppler echocardiograms at rest. None of the control subjects had a history of hypertension, diabetes mellitus, or hyperlipidemia. In the group with DCM, 10 patients were in NYHA class I and 17 were in class II. Patients with DCM who had severe symptoms (NYHA class III or IV) were excluded from the study. Medications included angiotensin-converting enzyme inhibitors in 17 patients, digitalis in 10 patients, and diuretics in all 27 patients. No patients were receiving β-receptor-blocking agents. Patients with atrial fibrillation were excluded because multigated ventriculography cannot be performed in these patients because of the presence of irregular RR-time intervals.

**Radionuclide Ventriculography**

Fasting patients and normal control subjects underwent radionuclide ventriculography at rest and during exercise in the supine position. RBCs were labeled in vivo by injection of 2.0 mg of stannous pyrophosphate, followed by injection of 1.11 GBq (30 mCi) of 99mTc pertechnetate. Electrocardiographic multigated ventriculography was performed using a mobile gamma camera (LFOV; Siemens-Elena; Solna, Sweden) equipped with a parallel-hole, high-resolution collimator that interfaced with a computer system (SCINTIPAC 2400 Medical Data System Computer, Shimadzu, Kyoto, Japan). Images were obtained in the left anterior oblique projection, which optimized separation of the left ventricle from the right ventricle. Images were acquired for 300 beats at 40 to 50 ms per frame at rest and for 120 at 20 to 30 ms per frame during exercise. Threshold and second derivative edge detection techniques were applied to a variable region of interest to define the left ventricle. A ventricular time-activity curve was constructed by measuring the background-corrected left ventricular counts in each frame and by plotting these counts against time following the ECG R wave. End-diastolic counts and end-systolic counts were obtained from the time-activity curve, and the left ventricular ejection fraction (LVEF) and ΔLVEF were determined as follows: LVEF=end-diastolic count-end-systolic count/end-diastolic counts; ΔLVEF=LVEF at peak exercise−LVEF at rest.

Subjects performed a multistage exercise test in which the exercise load was increased in 25-W increments at 3-min intervals until signs of exhaustion (shortness of breath, dyspnea, and leg fatigue) appeared. This symptom-limited exercise test was performed in the supine position using an electromagnetically braked bicycle ergometer (Siemens). ECGs, cuff BP, and heart rate were recorded at baseline and every minute during exercise and the recovery period.

**Heart Rate Variability**

Continuous 24-h ambulatory ECGs were recorded. Holter recordings were evaluated semiautomatically on a system (Marquette 8000 System; Marquette Electronics, Inc; Milwaukee). The following hourly data were computed and tabulated on printouts: heart rate, the total number of ventricular premature beats, the number of couplets, ventricular tachycardia runs, and ventricular tachycardia beats. After arrhythmia analysis, the data files of the 24-h recordings were reviewed and edited by experienced cardiol-

| Table 1—Exercise Stress Radionuclide Ventriculography* |
|---------------------------------|--------------------|--------------------|
|                                  | Normal Control     | Patients With      |
|                                  | Subjects (n=7)     | Mild DCM (n=27)    |
| Age, yr                         | 60±6              | 58±10              |
| Sex, M/F                        | 4/3               | 14/13              |
| LVEF at rest, %                 | 66.9±7.6          | 35.6±17.6*        |
| Systolic BP at rest, mm Hg      | 124±10            | 117±17             |
| Heart rate at rest, beats/min   | 71±11             | 69±12              |
| Systolic BP during exercise, mm Hg | 176±11          | 158±29             |
| Heart rate during exercise, beats/min | 137±13             | 124±17*          |
| Maximum workload, W             | 128±11            | 64±24*             |
| ΔLVEF, %                        | 8.2±2.5           | 3.6±7.0*          |

*Data are the mean±SD.

1p<0.01 vs normal control subjects.

1p<0.05 vs normal control subjects.

ogists; the ECG templates were studied and relabeled as normal or abnormal as appropriate. Incorrectly labeled segments and sections with bradyarrhythmias and tachyarrhythmias (including ectopic beats) were removed before computing differences between successive normal RR intervals. The algorithm excludes postectopic segments by holding the previous normal coupling interval constant throughout the aberrant section.

Spectral plots were computed in 2-min segments using a 256-point fast Fourier transformation algorithm with a frequency resolution of 1/120 (0.0083 Hz). A Hanning windowing function was applied to minimize spectral leakage between segments without diminishing frequency resolution. Power spectra from sequential windowed segments were averaged over each hour and over the entire 24 h and quantified by measuring the area in the total band (total power), in the low-frequency band (0.04 to 0.15 Hz, LF), and in the high-frequency band (0.15 to 0.40 Hz, HF). The low- and high-frequency areas were regarded as indexes of the general autonomic and specific vagal components of heart rate variability, respectively, although it is recognized that the low-frequency component contains an input from the parasympathetic nervous system. To simplify comparison between spectra, we also considered the relative percentage of each spectral component compared with the total oscillatory power and expressed it as normalized units (NU).16 HF and HF% (the ratio of HF to total power) were used as indexes of specific vagal tone, and LF% (the ratio of LF to total power) and LF/HF were used as indexes of sympathetic activity, as described in previous reports.16,17 Based on activity records kept by the subjects, all subjects slept from 2 AM to 4 AM. Therefore, we assessed the spectral indexes during sleep (from 2 AM to 4 AM) to minimize any artificial interference related to differences in the subjects' daytime activity.

**Statistics**

Results are expressed as the mean±SD. Analysis of variance followed by t test (paired or unpaired) was used for normally distributed parameters, and the nonparametric method (Mann-Whitney U test or Wilcoxon signed rank test) was used for nonnormally distributed parameters. A p value <0.05 was defined as indicating significance. Linear regression analysis was used to assess the relation between the ΔLVEF to clinical and hemodynamic measurements and indexes of heart rate variability.
RESULTS

Hemodynamic Measurements at Rest and During Exercise

The resting systolic BP and the resting heart rate were similar in both groups (Table 1). The systolic BP during exercise was also similar in both groups, but the heart rate during exercise was significantly lower in patients than in normal control subjects (p<0.05). The maximum workload was significantly lower in patients than in normal control subjects. LVEF increased during exercise by more than 5% in normal control subjects, but 17 (63%) of 27 patients failed to show a greater than 5% increase in LVEF during exercise. The ΔLVEF was significantly lower in patients than in normal control subjects (p<0.05). There was no significant correlation between the ΔLVEF and the LVEF (r=0.289, p=0.151; Fig 1) or other resting parameters. The ΔLVEF showed a significant positive correlation with the maximum workload in patients (r=0.506, p<0.01), although the resting LVEF was not significantly correlated with the maximum workload (r=0.226, p=0.27).

24-h Spectral Indexes of Heart Rate Variability

The 24-h HF curves in patients and normal control subjects showed little variation (Fig 2). The 24-h HF% profile was characterized by significantly higher values during the evening to early morning compared with daytime values in normal control subjects: 19.9±11.6 NU (2 AM to 5 AM) vs 11.0±3.0 NU (10 AM to 1 PM), (p<0.05). The 24-h HF% profile showed little variation in the patient group. The 24-h LF% profiles showed marked variations, with lower values during the evening to early morning hours and higher values in the daytime, in both normal control subjects and patients. This variation was more pronounced in normal control subjects compared with patients (analysis of variance, p<0.01 vs p<0.05, respectively). The variation in the 24-h LF/HF was similar to that of the LF% curve in normal control subjects. Little variation was observed in the 24-h LF/HF in patients.

We investigated the circadian variation in spectral indexes of heart rate variability by determining the ratio of the mean indexes during early morning (2 AM to 5 AM) to the mean daytime indexes (10 AM to 1 PM) for individual patients. The ratios for HF, LF%, and LF/HF were significantly correlated with the ΔLVEF, and the ratio for HF% tended to increase as the ΔLVEF increased (Fig 3). These ratios of the spectral indexes of heart rate variability were not significantly correlated with the resting LVEF or other hemodynamic measurements at rest.

Spectral Indexes During Sleep

HF and HF% during sleep were significantly lower in patients than in normal control subjects (Fig 4). The LF/HF during sleep was significantly higher in patients than in normal control subjects, although LF% was similar in both groups.

HF was significantly correlated with the ΔLVEF (Fig 5). LF% and LF/HF were also significantly correlated with the ΔLVEF. HF% tended to increase as the ΔLVEF increased. None of these spectral indexes during sleep was correlated with the resting LVEF or other resting variables.

DISCUSSION

The cardiac response to exercise was attenuated in patients with DCM with mild symptoms. Resting clinical and hemodynamic parameters did not appear to be associated with the residual myocardial contractile reserve. Autonomic function was significantly different in the two groups, as indicated by a blunted circadian rhythm, and accelerated sympathetic activity and reduced vagal tone during sleep in patients with DCM with mild symptoms. The left ventricular response to exercise, which reflects the residual myocardial contractile reserve, was significantly correlated with autonomic nervous activity in patients.

Depressed Cardiac Response to Exercise

A normal exercise response is defined as an increase of 5% or more (in absolute terms) in the global ejection fractions of both the right and left ventricles. Normal control subjects showed a uniform increase (>5%) in LVEF during exercise. Previous studies have shown that patients with severe heart failure show a reduced cardiac response to sympathetic stimulation. This abnormal response may be related to the patients’ clinical outcome. However, other studies have shown that patients with markedly de-
pressed resting cardiac performance exhibited a favorable increase in LVEF in response to exercise-induced sympathetic stimulation. In the present study, 63% of patients with DCM, who had a depressed LVEF at rest (resting LVEF, 36±18%) but did not have severe symptoms (NYHA class I or II), showed a reduced cardiac response to exercise. Resting clinical and hemodynamic indexes, failed to adequately predict individual left ventricular performance during exercise in the present study. Patients with a relatively well-preserved resting LVEF, for example, did not always show a favorable left ventricular response to exercise, indicating that left ventricular contractility at rest does not accurately reflect the cardiac pumping reserve. These findings are consistent with the results of a study by Franciosa et al 21 who found that the cardiac pumping reserve was not necessarily correlated with the resting LVEF or with resting cardiac hemodynamic measurements in patients with severe heart failure.

Heart Rate Variability in Normal Control Subjects and Mildly Symptomatic Patients With Idiopathic Dilated Cardiomyopathy

Heart rate variability was well preserved, and autonomic nervous activity showed significant circadian variation in control subjects in the present study, which is consistent with previous findings.14,15 Parasympathetic activity was accelerated during the evening and early morning hours and was diminished in the daytime. Sympathetic tone showed the opposite pattern.

To our knowledge, autonomic modulation assessed by spectral analysis of heart rate variability in mildly symptomatic patients with DCM has not been previously described. We found that autonomic nervous activity was markedly altered and that its circadian rhythm was blunted in our patients, which is consistent with previous findings in patients with more severe symptoms (NYHA class III and/or IV).14,15 These findings suggest that changes in autonomic function, which may occur as a compensatory mechanism and also be part of an underlying disease process, may precede the progression of symptoms in patients with DCM.

Mechanisms of the Reduced Cardiac Response to Exercise

Reduced myocardial contractile reserve in the failing myocardium has been attributed to a number of mechanisms, including β-adrenergic pathway abnormalities such as downregulation of myocardial β-adrenoceptors,6,7 a defect in receptor-adenylate cyclase coupling,22 and impaired exercise-induced physiologic upregulation of β-adrenoceptors,4 and depletion of myocardial norepinephrine.8 Limitation of the coronary flow reserve23,24 and an inappropriate elevation in myocardial wall stress in response to exercise25 have also been implicated. These mechanisms may contribute in part to the myocardial contractile reserve. However, the close relationship between myocardial contractile reserve and autonomic function observed in the present study suggests another possible mechanism. When sympathetic nervous activity is markedly accelerated and vagal tone is reduced even in the resting condition, resulting in a blunted circadian rhythm, the heart may no longer react to sympathetic stimulation. In patients with preserved autonomic function, however, the heart may still respond to such stress. Previous studies using the plasma level of norepinephrine as an index of sympathetic nervous activity found a negative relationship between the resting plasma level of norepinephrine and the myo-
Figure 3. The relation between ΔLVEF and the ratio of the mean indexes of heart rate variability during early morning to the mean daytime indexes in mildly symptomatic patients with idiopathic dilated cardiomyopathy.

Figure 4. Spectral indexes during sleep. Values represent mean±SD. Asterisk=p<0.05 vs normal control subjects; two asterisks=p<0.01 vs normal control subjects.
cardiac contractile reserve, suggesting that neurohumoral (autonomic) activity may be a mechanism of adrenergic desensitization in the failing myocardium. Our results are consistent with these previous investigations and suggest that a depressed left ventricular response to exercise-induced adrenergic stimulation depends, to some extent, on autonomic nervous activity in mildly symptomatic patients with DCM.

**Limitations**

The LVEF and ΔLVEF are widely used indexes of left ventricular contractility and myocardial contractile reserve, respectively. However, both LVEF and ΔLVEF may be influenced by several factors, including the presence or absence of mitral regurgitation and the degrees of preload and afterload. None of our patients had echocardiographic evidence of valvular disease. Only 3 (11%) of 27 patients had a minor degree of functional mitral regurgitation. We did not measure the left ventricular volume (either end-systolic and end-diastolic) or systemic vascular resistance. Therefore, the effects of preload and afterload were not evaluated.

To exclude artificial effects related to interindividual variations in physical and mental activities, we analyzed parameters during the period of sleep (2 AM to 4 AM). The patients' activity records confirmed that they were sleeping during that period. However, their respiration was unlikely to be similar. The major contribution to heart rate variability may be respiratory sinus arrhythmia. Under physiologic conditions, respiration is controlled by the CNS via the vagal nerve. Thus, our findings may have been influenced by variations in respiration among subjects.

Physical deconditioning commonly accompanies DCM. Abnormal autonomic function in physical deconditioning such as long-term bed rest in normal control subjects is similar to that seen in patients with congestive heart failure. Although the patients in this study did not include those with severe symptoms (NYHA III or IV), they had about half of the maximum work load of normal subjects and, therefore, may have been deconditioned, at least to some degree. Considerable attention should be given to interpret the auto-

![Figure 5. Relations between the ΔLVEF and spectral indexes of heart rate variability in mildly symptomatic patients with DCM.](image_url)
nomic function of patients with DCM because the demonstrating alterations in autonomic function might contain those induced by physical deconditioning alone. However, it could not be predicted how physical deconditioning contributed to the alteration of autonomic function in this study. Physical training may change the autonomic function of chronic heart failure toward normal. The next study will be performed after physical training so that the effect of deconditioning on heart rate variability can, to some extent, be excluded. Also, further studies should allow for conditioning status when assessing autonomic function in heart failure in either cross-sectional or intervention studies.

Medications have also been reported to have some effects on heart rate variability. No subjects were receiving beta-blockers, and subgroup analysis showed no significant differences in the spectral indexes of heart rate variability between patients with and without angiotensin-converting enzyme inhibitors or digoxin in the present study. Why did angiotensin-converting enzyme inhibitors seem unlikely to influence the heart rate variability for this study? Several reasons are considered: (1) 63% of the patients were taking this agent and the remaining 37% did not represent an adequate control group either because their age, gender, and NYHA functional class were slightly different, or digitalis was more prevalent; (2) we studied a comparatively small number of patients; and (3) our subjects did not include patients with overt heart failure, to whom angiotensin-converting enzyme inhibitors may have offered many beneficial effects.

Exercise radionuclide ventriculography and 24-h ECGs were not necessarily recorded on the same day. The mean interval between the two tests was 2.7±2.0 days (maximum, 5 days). Our patients continued taking medication throughout the study, and their clinical status remained unchanged. Therefore, the patients' underlying neurohumoral (autonomic) conditions appeared to have remained constant throughout this study.

Clinical Implications

Our findings showed that mildly symptomatic patients with DCM showed a reduced cardiac response to exercise-induced sympathetic stimulation and altered autonomic function. This cardiac response and autonomic nervous activity were significantly correlated. Exercise radionuclide ventriculography and spectral analysis of heart rate variability provided noninvasive and comparatively simple methods of assessing these alterations. Previous studies have suggested that alterations in the cardiac response to exercise and in autonomic function reflect the patient's clinical status and may predict prognosis in patients with heart failure. Therefore, assessments of cardiac reserve and autonomic function and the determination of the relationship between these parameters may be useful for determining the choice of treatment, evaluating treatment effects, and identifying the subset of patients who may have a poor prognosis, even when symptoms are mild.

References

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