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Ambulatory Monitoring of Left Ventricular Function: Walk and Bicycle Exercise in Congestive Heart Failure

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The aim of this study was to assess changes in left ventricular (LV) function during 6-min walk test and cardiopulmonary exercise by continuous radionuclide monitoring in patients with congestive heart failure (CHF). **Methods:** Seventeen patients with CHF and 10 normal subjects underwent monitoring of LV function (Vest) during 6-min walk test and during bicycle exercise with combined analysis of pulmonary gas exchange. During cardiopulmonary exercise, all parameters of LV function were measured at rest, at the anaerobic threshold (AT) and at peak oxygen uptake (peak VO_2). **Results:** In the normal subjects, during the walk test, heart rate (HR), ejection fraction (EF), end-diastolic volume (EDV), cardiac output (CO) and stroke volume (SV) significantly increased from rest to peak (all $p < 0.001$), while end-systolic volume (ESV) significantly decreased from rest to peak ($p < 0.001$). In patients with CHF, during the walk test, HR, EDV, ESV and CO significantly increased from rest to peak ($p < 0.001$), EF significantly decreased from rest to peak ($p < 0.001$) and SV did not show significant change. During cardiopulmonary exercise, normal subjects showed a significant increase in HR and CO, from rest to AT and from AT to the peak VO_2 ($p < 0.001$). EF, EDV and SV significantly increased from rest to AT ($p < 0.001$), with no significant change from AT to peak VO_2 . ESV decreased from rest to AT ($p < 0.001$), showing no significant change from AT to peak VO_2 . In patients with CHF, HR, CO, ESV and EDV increased significantly

from rest to AT ($p < 0.001$) and from AT to peak VO_2 ($p < 0.001$). EF and SV did not show significant changes from rest to AT, showing a significant decrease from AT to peak VO_2 ($p < 0.001$). **Conclusion:** Vest can be used to evaluate cardiac responses during 6-min walk test and cardiopulmonary exercise in patients with CHF. In such patients, significant impairment of LV function is already present during submaximal physical exercise becoming more evident during the anaerobic phases of bicycle exercise.

Key Words: Vest; physical exercise; left ventricular dysfunction; congestive heart failure

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Congestive heart failure (CHF) is a major health problem. In the U.S. CHF is responsible for more than 900,000 hospitalizations a year and 37,000 deaths a year (1). Functional capacity in patients with CHF has been measured using the New York Heart Association (NYHA) criteria (2). However, this approach provides a subjective and semiquantitative evaluation of these patients. Therefore, objective and reliable techniques allowed to assess the severity of left ventricular (LV) dysfunction and the response to the therapy are essential for the optimal clinical management of patients with CHF. The 6-min walk test has been widely used in the evaluation and serial assessment of patients with chronic respiratory disorders (3). However, experience in patients with CHF is more limited (4,5). Although this

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test seems well accepted by patients and easily implemented in an outpatient setting, it remains unclear whether this submaximal exercise is clinically useful in the evaluation of patients with CHF. Ambulatory monitoring of LV function is a noninvasive radionuclide technique for measuring cardiac performance at rest and during physical exercise in normal subjects and in patients with CHF (6–10). Such an approach may provide insight into ventricular performance on a sequential basis and hence noninvasive detection of transient adaptations of LV function as they may occur during physical activities.

The aim of this study was to assess changes in LV function during submaximal physical exercise (6-min walk test) and during cardiopulmonary bicycle exercise in patients with CHF using an ambulatory radionuclide system. We also studied the change in systolic performance during the aerobic and anaerobic phases of bicycle exercise to assess whether the development of anaerobic metabolism is associated with altered LV function response to exercise.

MATERIALS AND METHODS

Study Population

Two groups of subjects were studied. The first group included 10 asymptomatic healthy normal volunteers (8 men, 2 women, mean age 55 ± 3 yr). This group represents a series of healthy subjects who volunteered for the investigational protocol after informed consent was obtained. No subjects were referred for radionuclide study for clinical purposes. These subjects had no evidence of underlying cardiovascular disease by medical history, physical examination and exercise electrocardiography.

The second group consisted of 17 patients with CHF (17 men, mean age 53 ± 2 yr). In all patients, the cause of CHF was coronary artery disease. Patients were eligible for enrollment if they had a resting LV ejection fraction $< 45\%$ (by radionuclide angiography) in association with radiological evidence of CHF (one or more of the following: pulmonary venous redistribution, basal or peripheral vascular blurring, alveolar or pulmonary edema, Kerley's B lines or pleural effusions). In all patients, the NYHA criteria were defined at the time of the admission. Five of the patients were in NYHA Class I, six in NYHA Class II, five in NYHA Class III and one patient in NYHA Class IV. The individual characteristics of these patients with CHF are listed in Table 1. Patients were excluded from the study if they had the following disorders: valvular disease, active myocarditis, hypertrophic or restrictive cardiomyopathy, recent acute cardiac decompensation, primary pulmonary disease, myocardial infarction within the previous 8 mo, stable or unstable angina, systolic blood pressure ≥ 160 mm Hg or ≤ 90 mm Hg, diastolic blood pressure ≥ 95 mm Hg, claudication, stroke within the past 12 mo or renal, hepatic or endocrine disorders. In all patients with CHF, exercise-induced ischemia was excluded by stress-redistribution ^{201}Tl perfusion tomographic imaging. The protocol was approved by the institutional ethic review committee at our university, and all patients gave written informed consent before entering the study.

Study Protocol

All drug therapy was discontinued at least 2 wk before the patients entered the study. Equilibrium radionuclide ventriculography was performed immediately before the Vest study. All subjects underwent continuous ambulatory monitoring of LV function by Vest for at least 1 hr. Baseline measurements were made while subjects sat quietly for > 10 min. Thereafter, they stood in place for 2 min and walked in the hospital corridor for 6 min.

At the end of the 6-min walk test, all subjects underwent upright bicycle exercise with combined analysis of pulmonary gas exchange. During cardiopulmonary exercise testing, all parameters of

TABLE 1
Individual Characteristics of the Patients With Congestive Heart Failure

Patient no.	Age (yr)	LVEF (%)	6-min distance (m)	NYHA Class
1	52	42	630	I
2	55	36	602	II
3	54	30	450	III
4	62	40	605	II
5	62	37	612	II
6	55	37	550	III
7	50	42	640	I
8	64	26	520	III
9	54	25	216	IV
10	50	25	464	III
11	48	26	414	III
12	43	34	600	II
13	50	44	620	I
14	50	44	604	I
15	50	40	610	I
16	49	30	540	II
17	49	38	585	II
Mean \pm s.e.m.	53 ± 2	35 ± 2	545 ± 26	

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

LV function were measured under control conditions at rest, at the anaerobic threshold (point of nonlinear increase in ventilation relative to oxygen uptake), at peak oxygen uptake (peak VO_2) and after 3 min of recovery. During these activities, subjects were accompanied by a physician, and blood pressure was recorded by sphygmomanometry.

Equilibrium Radionuclide Angiography

In vivo labeling of red blood cells was performed with 555 MBq $^{99\text{m}}\text{Tc}$. Equilibrium radionuclide angiography was performed at rest in the 45° left anterior projection with a 15° craniocaudal tilt with the patient in supine position. A small field of view gamma camera equipped with a low-energy, all-purpose collimator was used. Data were recorded at a frame rate of 30 frames/cardiac cycle on a dedicated computer system. At least 200,000 counts/frame were acquired.

Ambulatory Monitoring of LV Function

The ambulatory ventricular function monitor has been described previously in detail (11,12). At the conclusion of equilibrium radionuclide ventriculography, all subjects wore the Vest, and the radionuclide detector was positioned over the LV. The position of the detector was confirmed by acquiring 30-sec static image with the gamma camera (11,12). Each patient wore the Vest during the 6-min walk test and during cardiopulmonary exercise testing. At the conclusion of the Vest study, a second 30-sec static image was obtained to confirm that the detector did not move during recording.

Walk Test

The 6-min walk test was conducted as described previously (4). In a corridor, a 30.5 m course was marked, and a chair was placed at each end. Patients were instructed to walk from end to end at their own pace while attempting to cover as much ground as possible in the allotted period of 6 min. A nurse timed the walk test, called out the time every 2 min and encouraged the patient every 30 sec in a standardized fashion (while facing the patient and using one of the two phrases "You are doing well" or "Keep up the good work"). Patients were allowed to stop and rest during the test but were instructed to resume walking as soon as they felt they were

able to do so. After 6 min had elapsed, the patients were instructed to stop walking and the total distance walked was measured. Symptoms experienced during the walk were recorded.

Cardiopulmonary Exercise Testing

All subjects underwent upright bicycle exercise in the morning. Patients were connected with a 2001 instrument to analyze breathing patterns and measure oxygen uptake (VO_2), carbon dioxide release and ventilation. Reproducibility of this system in our laboratory was documented by the techniques described by Jones (13). The variability was less than 10% of the gas exchange with a variable obtained in four subjects over 6 mo. The electrocardiogram was continuously monitored and blood pressure serially measured by the auscultatory method. All subjects exercised at constant speed (60 rpm) for 3 min; the workload was then increased by 1 W every 3 sec (ramp protocol) according to the previously established exercise tolerance until exhaustion. No test was interrupted for angina, ST depression, arrhythmias or hypotension. Maximal VO_2 was considered as the 30-sec averaged peak exercise value at the point when oxygen uptake did not increase despite increase in workload (peak VO_2). Peak VO_2 was considered as an index of functional capacity. The anaerobic threshold (AT) was determined by the gas exchange criteria as the point of nonlinear increase in the ventilatory equivalent for oxygen, which has been previously associated with elevations in simultaneously obtained arterial lactate samples without a simultaneous increase in ventilatory equivalent for CO_2 (13). Heart rate, blood pressure, workload, VO_2 at rest, AT and peak exercise were noted.

Data Analysis

Equilibrium radionuclide ventriculography was analyzed using standard commercial software as described previously (11,12). Briefly, LV region of interest (ROIs) were automatically drawn for each frame. A background ROI was also computer-delineated on the end-systolic frame. After background correction, a LV time-activity curve was generated. Ejection fraction was computed on the raw time-activity curve. Vest studies were analyzed as described previously (11,12). Briefly, at the end of the Vest study, data were reviewed for technical adequacy. The decay-corrected average counting rate of the entire recording was displayed. The Vest study was considered technically adequate if the decay-corrected curve had less than 10% deviation from a straight line. Sudden shifts in the slope of the line were indicative of detector movement or instrument malfunction. The radionuclide and ECG data were summed for 30-sec intervals. Ejection fraction was computed as the stroke counts divided by the background-corrected end-diastolic counts. Background was determined by matching the initial resting Vest ejection fraction value to that obtained by a gamma camera. These background values ranged from 70%–82%. Relative end-diastolic volume were expressed as 100% at the beginning of the study, end systolic volume were expressed relative to end-diastolic volume and cardiac output was calculated as relative stroke volume multiplied by heart rate.

Statistical Analysis

Data were expressed as mean \pm s.e.m. Comparisons of LV function obtained at rest and during cardiopulmonary exercise were made by analysis of variance for repeated measures. When the F-test was significant, individual comparison of resting values and those of each work level were made by Duncan's multiple range test. A paired Student's t-test was used to evaluate the variations in LV function during the 6-min walking test in comparison with resting conditions and between anaerobic threshold and peak exercise during cardiopulmonary exercise testing. A p value $<$ 0.05 was considered statistically significant.

TABLE 2
Demographic and Clinical Characteristics of the Study Groups

	Normal subjects (n = 10)	Patients with CHF (n = 17)
Age (yr)	55 \pm 3	53 \pm 2
Sex (M/W)	9/1	17/0
SBP (mmHg)	120 \pm 4	124 \pm 4
DBP (mmHg)	81 \pm 2	80 \pm 3
Weight (Kg)	69 \pm 3	72 \pm 2
Height (cm)	166 \pm 2	164 \pm 3

CHF = congestive heart failure; SBP = systolic blood pressure; DBP = diastolic blood pressure.

RESULTS

Study Group Characteristics

The experimental study groups (patients with CHF and healthy subjects) were comparable with regard to demographic and clinical characteristics (Table 2).

LV Function During 6-Min Walk Test

All normal subjects were able to complete the test without breaks in continuity, and as expected they walked further than patients with CHF (670 \pm 10 m versus 545 \pm 26 m, respectively, $p <$ 0.001). The group of normal subjects did not develop any symptoms during the test. Conversely, in the group of patients with CHF, nine patients complained of dyspnea and eight of fatigue. Among the patients with CHF, those with worse NYHA functional class generally walked shorter distances than individuals with better NYHA class (Table 1).

Figure 1 shows the mean values of the hemodynamic parameters recorded under control conditions and at peak exercise during the 6-min walk test in the group of normal subjects and in the group of patients with CHF. In the normal subjects, heart rate was characterized by a significant increase from resting conditions (85 \pm 4 bpm) to peak exercise (95 \pm 4 bpm) ($p <$ 0.001). Ejection fraction significantly increased from resting conditions (62% \pm 2%) to peak exercise (68% \pm 2%) ($p <$ 0.001). End-diastolic volume significantly increased from resting conditions (96% \pm 2%) to peak exercise (99% \pm 2%) ($p <$ 0.001). End-systolic volume significantly decreased from resting conditions (37% \pm 4%) to peak exercise (28% \pm 2%) ($p <$ 0.001). The response pattern of stroke volume and cardiac output was similar to ejection fraction. In particular, stroke volume significantly increased from resting conditions (60% \pm 3%) to peak exercise (68% \pm 3%) ($p <$ 0.001), and cardiac output significantly increased from resting conditions (52% \pm 4% end-diastolic volume/min) to peak exercise (66% \pm 4% end-diastolic volume/min) ($p <$ 0.001).

In patients with CHF (Fig. 1), heart rate was characterized by a significant increase from resting conditions (76 \pm 4 bpm) to peak exercise (88 \pm 3 bpm) ($p <$ 0.001). Ejection fraction significantly decreased from resting conditions (35% \pm 2%) to peak exercise (31% \pm 2%) ($p <$ 0.001). End-diastolic volume significantly increased from resting conditions (96% \pm 2%) to peak exercise (99% \pm 1%) ($p <$ 0.001). End-systolic volume significantly increased from resting conditions (61% \pm 3%) to peak exercise (67% \pm 3%) ($p <$ 0.001). Stroke volume did not show any significant change from resting conditions (34% \pm 3%) to peak exercise (35% \pm 2%). Finally, cardiac output significantly increased from resting conditions (26% \pm 3% end-diastolic volume/min) to peak exercise (36% \pm 3% end-diastolic volume/min) ($p <$ 0.001).

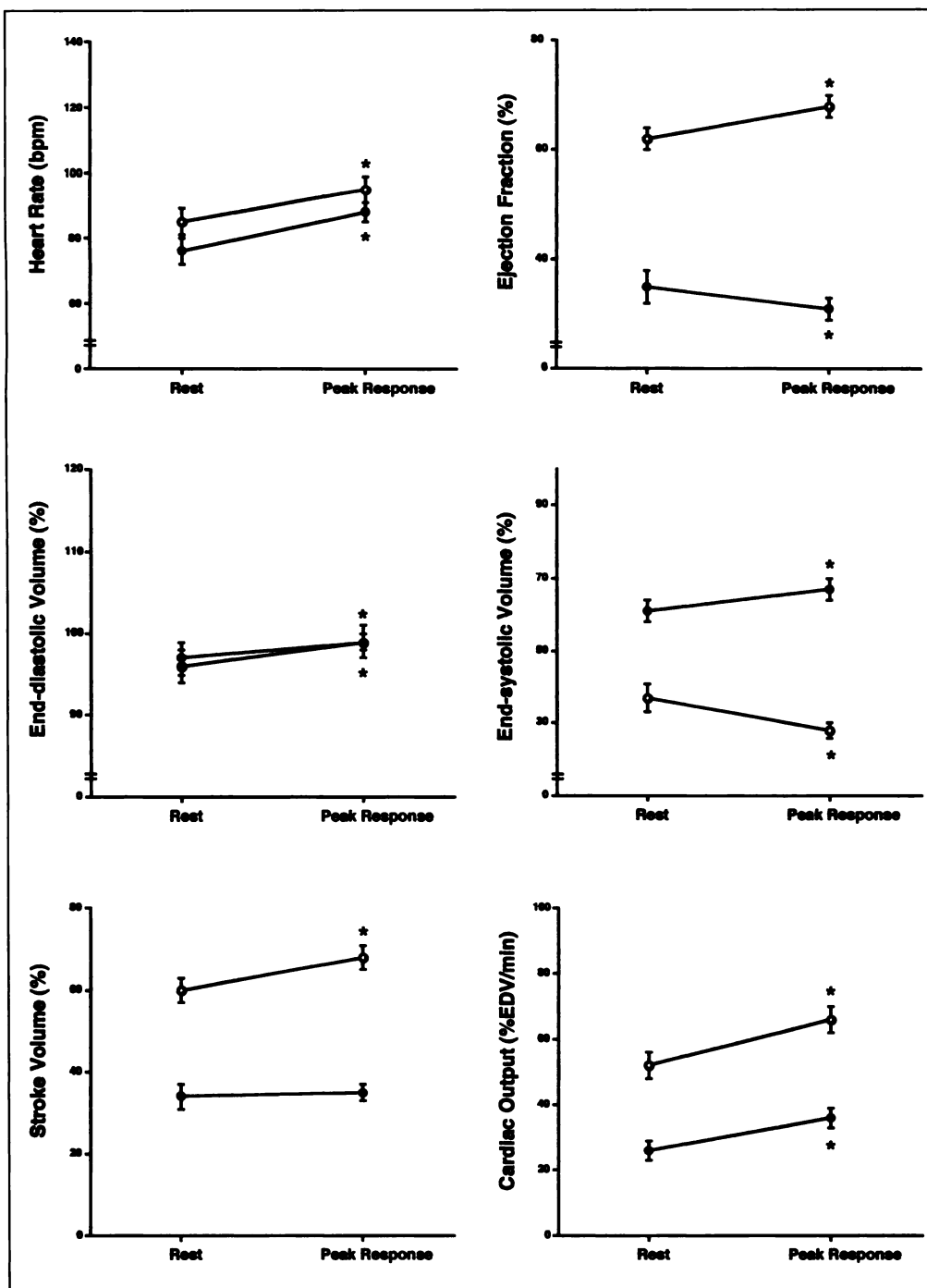


FIGURE 1. Mean value of hemodynamic parameters recorded under control conditions (rest) and at peak exercise during the 6-min walk test in normal subjects (open circles) and in patients with congestive heart failure (closed circles). * $p < 0.001$ versus rest.

LV Function During Cardiopulmonary Exercise Test

In normal subjects, mean exercise duration time during cardiopulmonary exercise test was 12 ± 2 min, and mean exercise workload was 123 ± 18 W. In patients with CHF, mean exercise duration during cardiopulmonary exercise testing was 7 ± 3 min, and mean exercise workload was 75 ± 14 W.

Figure 2 shows the mean values of the hemodynamic parameters recorded under control conditions, at AT and at peak VO_2 in the group of normal subjects and in the group of patients with CHF. In normal subjects, LV and chronotropic responses to exercise were characterized by a progressive increase in heart rate, which significantly increased from resting conditions (85 ± 4 bpm) to AT (123 ± 4 bpm) ($p < 0.001$) and from AT to peak VO_2 (150 ± 4 bpm) ($p < 0.001$). Ejection fraction significantly increased from resting conditions ($62\% \pm 2\%$) to AT ($69\% \pm 2\%$) ($p < 0.001$) showing no significant change

from AT to peak VO_2 ($66\% \pm 4\%$). End-diastolic volume significantly increased from resting conditions ($96\% \pm 2\%$) to AT ($102\% \pm 3\%$) ($p < 0.001$) showing no significant change from AT to peak VO_2 ($104\% \pm 3\%$). End-systolic volume significantly decreased from resting conditions ($37\% \pm 4\%$) to the AT ($31\% \pm 5\%$) ($p < 0.001$) showing no significant change from AT to peak VO_2 ($34\% \pm 5\%$). Stroke volume significantly increased from resting conditions ($60\% \pm 3\%$) to AT ($69\% \pm 4\%$) ($p < 0.001$) showing no significant change from AT to peak VO_2 ($68\% \pm 6\%$). Finally, cardiac output significantly increased from resting conditions ($52\% \pm 4\%$ end-diastolic volume/min) to AT ($76\% \pm 5\%$ end-diastolic volume/min) ($p < 0.001$) and from AT to peak VO_2 ($88\% \pm 6\%$ end-diastolic volume/min) ($p < 0.001$).

In patients with CHF (Fig. 2), LV and chronotropic responses to exercise were characterized by a progressive increase in heart

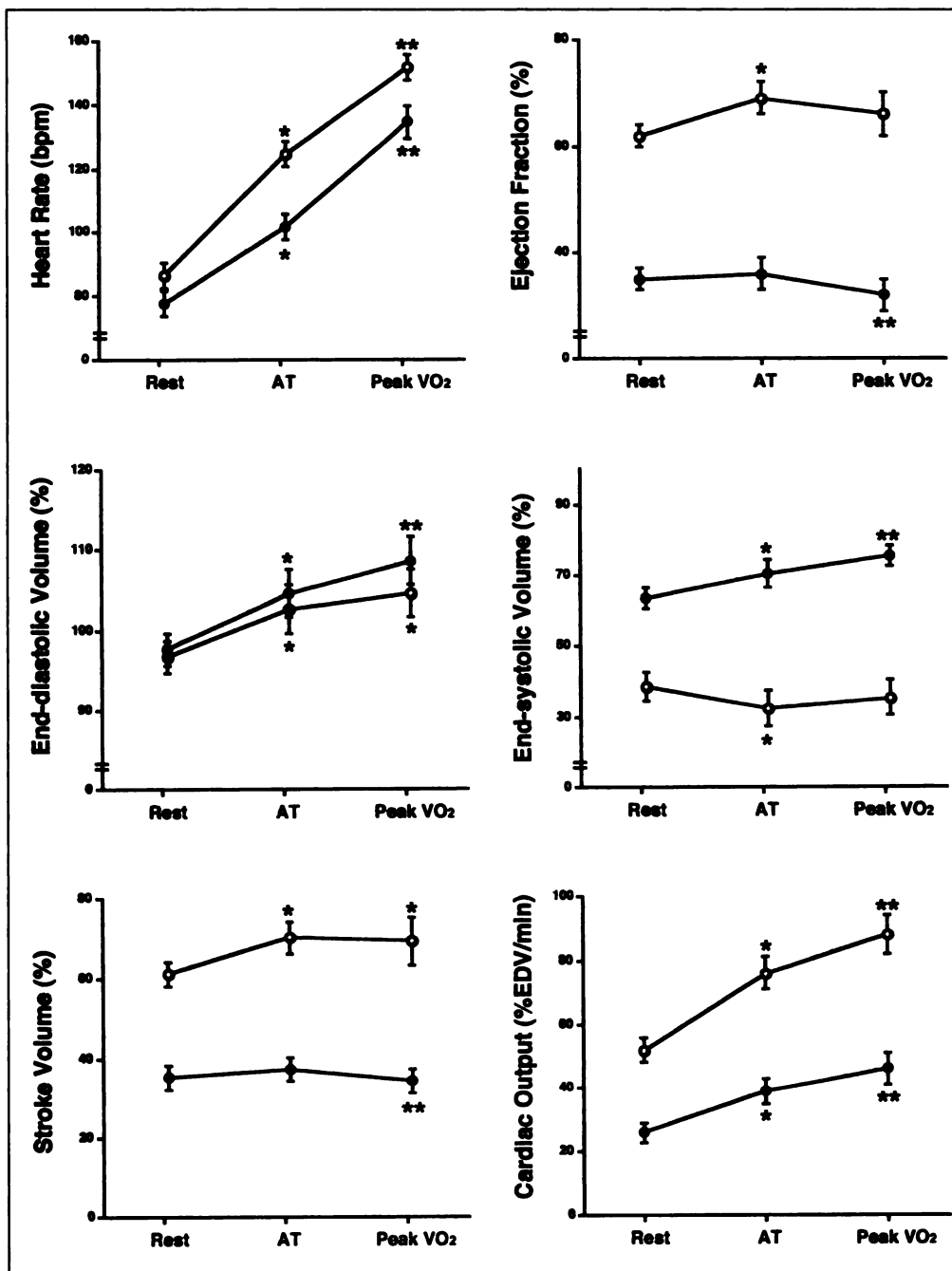


FIGURE 2. Mean value of hemodynamic parameters recorded under control conditions (rest), at AT and at peak oxygen uptake (Peak VO₂) during cardiopulmonary exercise testing, in normal subjects (open circles) and in patients with congestive heart failure (closed circles). *p < 0.001 versus rest. **p < 0.001 versus AT and rest.

rate, which significantly increased from resting conditions (76 ± 4 bpm) to AT (100 ± 4 bpm) (p < 0.001) and from AT to peak VO₂ (133 ± 5 bpm) (p < 0.001). Ejection fraction did not show any significant change from resting conditions (35% ± 2%) to AT (36% ± 3%) showing a significant decrease from AT to peak VO₂ (32% ± 3%) (p < 0.001). End-diastolic volume significantly increased from resting conditions (96% ± 2%) to AT (104% ± 2%) (p < 0.001) and from AT to peak VO₂ (108% ± 3%) (p < 0.001). End-systolic volume significantly increased from resting conditions (61% ± 3%) to AT (69% ± 3%) (p < 0.001) and from AT to peak VO₂ (74% ± 3%) (p < 0.001). Stroke volume did not show any significant change from resting conditions (34% ± 3%) to AT (36% ± 3%) showing a significant decrease from AT to peak VO₂ (33% ± 3%) (p < 0.001). Finally, cardiac output significantly increased from resting conditions (26% ± 3% end-diastolic volume/min) to AT (39% ± 4%) (p < 0.001) and from AT to peak VO₂ (46% ± 5% end-diastolic volume/min) (p < 0.001).

DISCUSSION

The results of this study show that radionuclide ambulatory monitoring of LV function performed during submaximal exercise (i.e., 6-min walk test) and simultaneously with noninvasive measurement of respiratory gas exchange during bicycle exercise provides an objective method for quantitative evaluation of LV functional capacity and cardiac reserve in patients with CHF. The technical approach adopted allowed us to obtain continuous noninvasive monitoring of LV function throughout the experimental period and to assess the sequence of cardiac adaptations in normal subjects as well as their abnormalities in CHF patients.

Limitation of physical activity is the earliest indication of LV dysfunction in patients with CHF. Although difficult to measure, because of the lack of sensitive and reliable methods, and because of the high variability among patients with apparent similar pathophysiology, physical activity levels are important because they provide the clinician baseline information that can

be used to evaluate the efficacy of prescribed pharmacologic or hygienic therapies. Until now, a simple, noninvasive and reproducible method to assess the degree of LV dysfunction during daily physical activities in patients with CHF has not been available. The 6-min walk, a test in which a subject is instructed to cover as much ground as possible in 6 min, has been applied in the past to address this problem (4,5). Previous studies using this test demonstrated that distance covered is a reliable measure for distinguishing patients with severe heart failure, but it is somewhat less effective in assessing patients with milder heart failure (14). In addition, step rate and distance walked measurements, are not always able to discriminate heart failure subjects from the elderly controls (14).

The introduction in nuclear cardiology of a portable scintillation probe (Vest) similar to a miniaturized nuclear stethoscope has proven useful for measuring LV function both at rest and during exercise in several cardiac disorders (11,12). In this study, we have used the Vest system to evaluate LV function responses during the 6-min walk test in a group of patients with CHF and in a control group of normal subjects. Our data demonstrate that there are significant differences between patients with CHF and healthy subjects in the LV responses to submaximal exercise and our data are consistent with the interpretation that impairment of cardiac dynamics limits exercise capacity during daily physical activity in patients with CHF. These findings also suggest that Vest may improve the diagnostic potential of the 6-min walk test providing a better understanding of LV functional responses during conditions of submaximal exercise and extending the diagnostic capabilities of the traditional measures (i.e., step rate and distance covered) already provided by the 6-min walk test.

In this study, we also evaluated the cardiac performance during the aerobic and anaerobic phases of dynamic exercise testing to assess whether the development of anaerobic metabolism is associated with altered LV functional response. Previous studies demonstrated that the AT (the work level at which lactic acid accumulates in the blood due to a shift to anaerobic metabolism in the working muscles) can be used to identify the severity of chronic heart failure, noninvasively (15,16). In particular, it has been suggested that anaerobic metabolism occurs during exercise when oxygen supply to the working muscles cannot be increased sufficiently to maintain aerobic metabolism. Many investigators have used the AT measurement to estimate the degree of cardiovascular impairment and effectiveness of therapy in patients with CHF (15,17). Although there are some reports that contradict the theory of the AT, suggesting that the lactate increase during exercise is unrelated to hemodynamic indexes of LV function, such as cardiac output or LV filling pressure (18), it has been shown that the magnitude of the AT reduction correlates well with the degree of hemodynamic abnormality (19). A previous study from our laboratory showed that LV performance during exercise testing in normal sedentary subjects is limited by the conversion of aerobic to anaerobic metabolism (8). In particular, ejection fraction response to exercise is highly variable after reaching

the AT, and a uniform increase is not necessarily expected even in normal subjects (8). The data of this study demonstrate significant impairment of cardiac dynamics in response to the augmented demand induced by exercise in patients with CHF. The results of this study also support previous observed relations between the AT and the severity of exercise impairment in patients with CHF (20).

CONCLUSION

Vest performed during submaximal exercise (i.e., 6-min walk test) or simultaneously with noninvasive measurement of respiratory gas exchange during bicycle exercise provides an accurate and objective method for quantitative evaluation of LV functional capacity and cardiac reserve in patients with CHF.

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