Relation of changes over time in ventricular size and function to those in exercise capacity in patients with chronic heart failure

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Background We studied the direction and magnitude of changes in left ventricular (LV) cavity size and mass over time and whether these changes were related to those in exercise performance in patients with chronic heart failure (CHF).

Methods and Results The study group was composed of 59 patients (55 men aged 58 ± 10 years) with CHF and LV end-diastolic diameter (EDD) >55 mm. All underwent echocardiography and a treadmill cardiopulmonary exercise test within a 4-week interval (baseline) and again after a period of ≥4 months (median of 14 months). At baseline, the group as a whole had moderate to severe LV dysfunction with an EDD of 70 ± 9 mm, end-systolic diameter (ESD) of 60 ± 11 mm, and LV mass of 500 ± 200 g. The mean peak oxygen consumption (\(\dot{V}O_2\), 18 ± 6 mL/kg per minute) was unrelated to LV cavity size or mass. EDD increased in 37 (63%) of the patients and fell in 22 (37%) patients from the initial to the second test. The absolute magnitude of changes over time averaged 7 mm for EDD, 125 g for mass, and 6 mL/kg per minute for peak \(\dot{V}O_2\). Changes in LV size and mass per year were significantly related to those in peak \(\dot{V}O_2\) (\(r = -0.49\) for EDD, \(r = -0.56\) for ESD, and \(r = -0.44\) for LV mass, respectively, all \(P < .001\)) and ventilatory response to exercise (\(r = 0.60\), \(r = 0.58\), and \(r = 0.72\) for EDD, ESD, and LV mass, respectively, all \(P < .001\)).

Conclusions Changes over time in objective measures of LV dimensions and mass, in patients with CHF are significantly related to those in exercise capacity and respiratory efficiency. (Am Heart J 2000;139:913-7.)
by coronary arteriography or documented myocardial infarction. Patients were classified as having dilated cardiomyopathy if normal coronary arteries had been demonstrated on coronary angiography. The medical regimens of all the enrolled patients were optimized, and all were symptomatically stable. None of patients underwent myocardial revascularization or exercise rehabilitation during the study period. The medical treatment included angiotensin-converting enzyme inhibitors (91%), diuretics (96%), nitrates (25%), digitals (30%), and warfarin (24%) in varying combinations. All patients were limited by fatigue or dyspnea on exercise testing rather than electrocardiographic evidence of myocardial ischemia or chest pain, and none had clinical evidence of primary lung disease.

Exercise protocol

A standard Bruce protocol was used with the addition of a stage 0, consisting of 3 minutes at a speed of 1 mile per hour with a 5% gradient. Minute ventilation, oxygen consumption, and carbon dioxide production were calculated on-line every 10 seconds with the use of a standard inert gas dilution technique (Amis 2000, Odense, Denmark). Peak VO₂ and the VE/VCO₂ were recorded. Patients were encouraged to exercise to exhaustion. The reproducibility (coefficient of variance of repeated measurements) has been found to be 12% for peak VO₂ and 7% for VE/VCO₂ in patients with heart failure who were studied in our laboratory. All exercise tests were performed on the patients while on a stable medical regimen.

Echocardiography

Overall left ventricular function was studied on the 2D display from parasternal long and short axes and apical 4- and 2-chamber views. If significant regional abnormalities were absent, standard resting left ventricular minor axis recordings were then obtained from the left parasternal long-axis view with the patient in semilateral position and the cursor by the tips of mitral valve leaflets. Left ventricular dimensions were taken at end-diastole (onset of the Q wave of the electrocardiogram) and end-systole (first high-frequency vibration of the aortic component of the second heart sound [A₂] on a superimposed phonocardiogram). Left ventricular fractional shortening was calculated as the percentage systolic fall in left ventricular dimension with respect to end-diastole. Left ventricular mass was calculated according to the Penn convention:

\[ \text{Left ventricular mass} = 1.04 \times (\text{EDD}^3 - \text{ESD}^3 - 13.6) \]

where PWTD is the posterior wall thickness in diastole and IVSTD is the interventricular septal thickness in diastole (EDD is end-diastolic diameter). From the pulsed Doppler traces of the transmural forward flow velocity, we measured peak early and late diastolic filling velocities—both from the baseline—and hence calculated E/A ratio. We also measured transmural E-wave deceleration time interval from the peak of the E wave to its end. The reproducibility of the echocardiographic overall left ventricular performance in our laboratory has been previously described.

### Statistical analysis

Data were first examined with the Kolmogorov-Smirnov test to ensure normal distribution. All results are therefore presented as mean ± SD. The number of individual values outside the 95% confidence limits of respective mean values was appropriate, and no significant outliers were identified. To analyze relations between variables, univariate and multivariate linear regression analyses were performed. To take account of multiple analyses, a value of P < .01 was considered statistically significant. Changes over time in studied measurements were assessed by multivariate repeated-measures analysis of variance. Differences were considered significant at a value of P < .05. The paired t test was used to compare the results of initial and final assessments. Statistical analysis was performed with the use of a standard statistical program (StatView, version 4.5; Abacus Concepts).

### Results

Table I summarizes the main left ventricular dimensions and function and exercise data for all 59 patients with CHF at the initial and second examinations. By definition, at the initial examination, the left ventricle was dilated in all patients (as indicated by EDD of 70 ± 9 mm and end-systolic diameter of 60 ± 11 mm). The left ventricular fractional shortening at that evaluation was decreased (15% ± 8%) and the left ventricular mass was increased (500 ± 200 g). The mean value of peak VO₂ was 18 ± 6 mL/kg per minute, and that of VE/VCO₂ slope was 38 ± 11 (upper limit of normal in our laboratory).

Although there was no consistent change in left ventricular dimensions in the patient population as a whole, left ventricular EDD increased in 37 (63%) of the patients and fell in 22 (37%) patients from the initial to the second test. The absolute magnitude of changes over time averaged 7 mm for EDD and 125 g for left ventricular mass. Mean values of exercise performance also did not change significantly from the initial to the second examinations in the patient population as a whole; peak VO₂ increased in 28 (47%) of the patients and fell...
in 31 (53%) patients, the absolute magnitude of changes averaging 6 mL/kg per minute. The mean respiratory quotient of the initial and follow-up exercise tests did not differ significantly (1.145 ± 0.148 vs 1.149 ± 0.173 for initial and final respiratory quotient, respectively), indicating similar exercise end points.

Neither at baseline nor at the second study did any measurements of left ventricular structure or function correlate with peak VO₂ or VE/VCO₂ slope. However, significant correlations were found between changes in exercise capacity and changes in left ventricular measurements over time (Table II). The correlation between changes in peak VO₂ per year and changes in left ventricular end-systolic diameter per year was –0.56 (P < .001, standard error of estimate (SEE) = 1.0). The regression relation had a slope of –4.1 ± 0.8 mL/kg per minute per centimeter and intercept of –0.5 ± 1.1 mL/kg per minute per year. Changes in left ventricular mass correlated with those in peak VO₂: we found a correlation coefficient of –0.44, P < .001, SEE = 1.1; the slope was –0.02 ± 0.01 mL/kg per minute per gram and the intercept was 0.5 ± 1.1 mL/kg per minute per year.

Stronger relations were found between changes in the VE/VCO₂ slope per year and those in left ventricular dimensions and mass (Table II). The correlation for changes in end-systolic diameter consisted of r = 0.58, P < .001, SEE = 2.8; the regression slope being 11.1 ± 2.2 mL/kg per minute per centimeter and the intercept of 6.7 ± 2.9 mL/kg per minute per year. Changes in the VE/VCO₂ slope were even more closely related to those in left ventricular mass: r = 0.72, P < .001, SEE = 2.4. The regression slope was 0.10 ± 0.01 mL/kg per minute per gram and the intercept was 3.7 ± 2.4 mL/kg per minute per year.

**Discussion**

Our results are consistent with previous studies in showing that in a group of stable patients with the clinical syndrome of heart failure, there was no significant relation between the extent of cavity enlargement and exercise tolerance in a cross-sectional study.15 However, when these patients were followed for up to 42 months, changes in transverse cavity diameter and ventricular mass were observed, which were related to exercise tolerance and respiratory efficiency. The magnitudes of changes were relatively small: That of peak VO₂ averaged 6 mL/kg per minute, in cavity diameter 7 mm, and in left ventricular mass 125 g. They were not consistent in direction, so that in the group of patients as a whole, the mean of the change in each measurement was not significantly different from zero. However, in individuals, when cavity size or ventricular mass fell, there was likely to be an increase in exercise tolerance, strongly suggesting that neither change was simply random or caused by measurement error but rather that such continuous evolution should be considered as part of the natural history of the disease.

**Mechanism of changes**

A number of possible mechanisms might underlie related changes in left ventricular cavity size or mass and exercise tolerance. These long-term changes in cavity dimensions and ventricular mass differed from those underlying the initial ventricular disease in that they correlated with exercise tolerance and so are likely to arise from a fundamentally different mechanism. Similarly, they could be distinguished from the increase in exercise tolerance associated with physical conditioning, which is not accompanied by any consistent change in cavity size.19,20

There was no relation between alterations in exercise tolerance or cavity size and differences in treatment between patients, nor could they be related to the underlying etiology of the heart disease. Differing loading conditions, particularly left atrial pressure, might conceivably be involved. A fall in stroke work caused by underfilling of the ventricle, mediated by Starling’s Law, possibly as the result of inappropriate diuretic therapy, can be excluded from the inverse rather than parallel relation between ventricular size or mass and exercise tolerance. The reverse mechanism, namely an increase in left atrial pressure causing end-diastolic cavity dilation with a fall in exercise tolerance as the result of pulmonary congestion, might be suggested by an increase in E-wave deceleration time as cavity size falls. However, this was not accompanied by any change in E/A ratio, nor would it explain concomitant changes in left ventricular mass. In addition, no consistent relation between left atrial pressure and exercise capacity has been demonstrated. For the same reason, changes in the severity of functional mitral regurgitation, never more than mild in any case, seem an unlikely cause of alteration in either cavity size or exercise tolerance.

Remodeling of the ventricle is an important mechanism underlying the progression of disease.6,7,21 It is a process that can be delayed or even reversed by appropriate treatment. This is not totally compatible with
present results, in which all patients were receiving medical treatment, yet the chances of deterioration approximated those of improvement. Indeed, this apparent symmetry of outcome seemed to make any simple and uniform explanation unlikely.

An additional finding of this study is that changes over time in the slope relating carbon dioxide output and minute ventilation (VE/VCO2 slope) also correlated with changes in the indexes of left ventricular mass and dimensions. The excessive exercise ventilatory response in patients with CHF can be quantified as a steeper VE/VCO2 slope. A greater minute volume at a given level of carbon dioxide production reflects the severity of the ventilatory abnormality in CHF, strongly correlates with exercise capacity of these patients, and may serve as an independent prognostic marker.

**Limitations**

The study has the disadvantages of being retrospective and noncontrolled and is thus hypothesis generating rather than definitive. The individual measurements made, particularly in left ventricular cavity size and mass, will have been subject to measurement error, a problem compounded when small differences between those made on 2 occasions several months apart were derived. This effect was minimized by using identical equipment and techniques on both occasions. Indeed, random variation in measurements tends to attenuate rather than emphasize relations: The underlying relations between changes in cavity size and exercise tolerance are likely to have been closer than our measurements suggest. The study was based on retrospective data, though all measurements of ventricular cavity size were made in the absence of any knowledge of exercise tolerance. There were no specific patient characteristics that tended to drive clinicians to repeat the echocardiographic and exercise tests. Treatment was individualized and was thus not uniform throughout the group of patients studied, and the majority of observations were made before the introduction of beta-blocking drugs into the treatment of such patients. We do not have direct hemodynamic measurements of left ventricular filling pressure but have relied on noninvasive indexes, which have proved reliable in homogeneous groups of patients like the present one. Finally, measurements in individual patients were made on only 2 occasions, so we cannot say whether these changes remain consistent in the longer term in their direction or magnitude.

**Clinical implications**

Subject to the limitations of the study, we believe that our observations have clinical implications in the long-term understanding of the clinical syndrome of heart failure. Conventionally, ventricular disease in such patients is thought to be the result of the combined effects of an initial stimulus such as a myocardial infarction or an abnormal load on which are superimposed those of remodeling. Our results suggest that in clinically stable, medically treated patients, a fall in left ventricular cavity size or mass associated with an increase in exercise tolerance with time is as likely to occur as is the reverse. Furthermore, changes in exercise tolerance are clinically significant, up to 7 mL/kg per minute, although those in cavity size are proportionately smaller. It may be that the apparently spontaneous regression of dilated cardiomyopathy that occurs in a minority of patients may represent the extreme in one direction of the much commoner but smaller variation that we have observed. We would predict that the extreme in the opposite direction, rapid and unexplained deterioration, might also exist, giving rise to diagnostic uncertainty in the individual patients in whom it occurs. Finally, we believe that these processes are worthy of further investigation because they seem to hint at long-term mechanisms operating in these patients, whose beneficial effects might be selected and deleterious ones blocked. Greater understanding of their nature thus might be coupled with improved therapeutic prospects.

**References**

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