

Left ventricular chamber stiffness at rest as a determinant of exercise capacity in heart failure subjects with decreased ejection fraction

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Meyer, Timothy E., Mustafa Karamanoglu, Ali A. Ehsani, and Sándor J. Kovács. Left ventricular chamber stiffness at rest as a determinant of exercise capacity in heart failure subjects with decreased ejection fraction. *J Appl Physiol* 97: 1667–1672, 2004. First published June 18, 2004; doi:10.1152/jappphysiol.00078.2004.—Impaired exercise tolerance, determined by peak oxygen consumption ($\dot{V}O_{2\text{ peak}}$), is predictive of mortality and the necessity for cardiac transplantation in patients with chronic heart failure (HF). However, the role of left ventricular (LV) diastolic function at rest, reflected by chamber stiffness assessed echocardiographically, as a determinant of exercise tolerance is unknown. Increased LV chamber stiffness and limitation of $\dot{V}O_{2\text{ peak}}$ are known correlates of HF. Yet, the relationship between chamber stiffness and $\dot{V}O_{2\text{ peak}}$ in subjects with HF has not been fully determined. Forty-one patients with HF New York Heart Association [(NYHA) class 2.4 \pm 0.8, mean \pm SD] had echocardiographic studies and $\dot{V}O_{2\text{ peak}}$ measurements. Transmittal Doppler E waves were analyzed using a previously validated method to determine k , the LV chamber stiffness parameter. Multiple linear regression analysis of $\dot{V}O_{2\text{ peak}}$ variance indicated that LV chamber stiffness k ($r^2 = 0.55$) and NYHA classification ($r^2 = 0.43$) were its best independent predictors and when taken together account for 59% of the variability in $\dot{V}O_{2\text{ peak}}$. We conclude that diastolic function at rest, as manifested by chamber stiffness, is a major determinant of maximal exercise capacity in HF.

diastole; echocardiography; oxygen consumption

CHRONIC HEART FAILURE (HF) is a major health problem that carries a high mortality rate despite continued significant advances in medical therapy. With \sim 400,000 new cases of HF diagnosed each year, 4.7 million Americans suffer from this debilitating disease (1). It has been established that patients with HF have impaired exercise tolerance that is predictive of mortality and the need for cardiac transplantation (10). Characteristically, the failing heart demonstrates an inability to maintain an adequate cardiac output, first during effort and later also at rest. Cardiac decompensation ultimately leads to impaired exercise capacity, fatigue, and exertional dyspnea. Patients with HF thus may have a decreased left ventricular (LV) ejection fraction (LVEF), large end-diastolic volume, and impaired contractile reserve (33, 34). Ventricular dysfunction as quantitated by a decreased LVEF is the main manifestation of HF that ultimately results in circulatory failure. Advanced LV dysfunction is associated with a variety of neurohumoral, peripheral circulatory, skeletal muscle, and respiratory adapta-

tions that determine the syndrome's overall clinical presentation and prognosis (33, 34). The known mechanisms that lead to HF are highly complex, involving chamber enlargement and remodeling and decreased LV contractile reserve (10). The factor common to all types of HF regardless of etiology is increased LV end-diastolic pressure (LVEDP), which compromises LV filling, diminishes stroke volume and cardiac output, and is one of the earliest clinical signs of HF when, due to elevation of the alveolar-arterial (A-a) gradient, it manifests as dyspnea.

The best marker of exercise capacity is oxygen consumption ($\dot{V}O_2$) at peak exercise ($\dot{V}O_{2\text{ peak}}$) (22). Changes in $\dot{V}O_{2\text{ peak}}$ are mediated by cardiac output and/or oxygen extraction from exercising skeletal muscles. LV diastolic function can modulate cardiac output by determining filling via chamber stiffness and LVEDP. Therefore, it is plausible that impaired LV diastolic function at rest, manifesting as increased chamber stiffness, resulting in increased LVEDP and associated increase in A-a gradient, can limit aerobic power in HF. Kitzman et al. (14) demonstrated that reduced $\dot{V}O_{2\text{ peak}}$ in patients with HF and normal ejection fraction was primarily due to abnormalities of diastolic function that limited LV filling and consequently reduced the stroke volume response to exercise. Moreover, LV systolic performance has not been shown to be highly correlated with exercise tolerance in patients with HF (21, 24). However, the relationship between resting diastolic function expressed in terms of chamber stiffness determined noninvasively and exercise capacity in patients with HF is unclear. As motivation for the present study, we hypothesized that LV chamber stiffness could be the diastolic abnormality that is a significant determinant of aerobic capacity in patients with HF and systolic dysfunction. By using a validated kinematic model to analyze the filling process, applied to different New York Heart Association (NYHA) class patients, we determined $\dot{V}O_{2\text{ peak}}$ and diastolic function at rest as reflected by LV chamber stiffness (16).

MATERIALS AND METHODS

Subjects and study population. All patients gave informed consent for participation in the study as mandated by the Washington University School of Medicine Human Studies Committee guidelines. Forty-one patients (age 54.4 ± 9.3 yr) with HF were studied consecutively. No subject had significant mitral regurgitation. Patients were classified according to NYHA functional class I–IV before $\dot{V}O_{2\text{ peak}}$ deter-

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mination (11). All patients received standard therapy for HF. Patients had taken their medications, including angiotensin-converting enzyme inhibitors and β -blockers, before the $\dot{V}O_{2\text{ peak}}$ evaluation. Ninety-eight percent of patients were on β -blockers, 88% on an angiotensin-converting enzyme inhibitor, and 66% on digoxin. Because our study sought the physiological relationship between diastolic function and $\dot{V}O_{2\text{ peak}}$ in HF patients as encountered in clinical practice, we made no attempts to control or modify patients' medications in this cohort.

Echocardiography. A standard two-dimensional Doppler echocardiography examination was performed immediately before the $\dot{V}O_{2\text{ peak}}$ test. Specifically, the examination was performed with the patient supine or in the left lateral position. Transmitral Doppler flow velocity images (E waves) were acquired in the four-chamber view according to standard American Society of Echocardiography criteria using a commercial echocardiographic imaging system (model SONOS 5500, Hewlett-Packard, Andover, MA) equipped with a 1- to 3-MHz transducer (29).

Determination of peak aerobic power. A maximal treadmill exercise test was performed using the following protocol: after a warm-up during which the patients walked on a treadmill at 0% grade for 3–4 min at speeds ranging from 0.5 to 1.2 miles/h, speed was kept constant, and the grade was increased 1 or 2% every 1 or 2 min until the patients could no longer continue to exercise either because of exhaustion or cardiac symptoms or because they showed ECG changes or a drop in systolic blood pressure (≥ 10 mmHg) that justified cessation of exercise. $\dot{V}O_{2\text{ peak}}$ was measured continuously with open-circuit spirometry, as previously described (15). Maximal $\dot{V}O_2$ ($\dot{V}O_{2\text{ max}}$) was defined using the following criteria: 1) an attainment of plateau of $\dot{V}O_2$ despite increasing exercise intensity, 2) a respiratory exchange ratio ≥ 1.1 , and 3) measured $\dot{V}O_2$ lower than predicted for the work rate (15). Because some patients did not meet the technical criteria for $\dot{V}O_{2\text{ max}}$, the highest $\dot{V}O_2$ attained was designated as $\dot{V}O_{2\text{ peak}}$.

Data analysis. Chamber stiffness was determined using a kinematic model of filling that has been previously validated via simultaneous cardiac catheterization and echocardiography in a large subject sample (12, 16, 17, 19). Briefly, the model treats E-wave generation as being initiated by mechanical suction, i.e., the release of elastic strain stored during systole (12, 16, 17). Three mathematically independent model parameters (x_0 , c , k) are determined from the clinical Doppler E wave by model-based image processing (MBIP). The parameters account for the amplitude, width, and rate of decay of the E-wave

contour, respectively (Fig. 1) (16). The model parameter k reflects average chamber stiffness (ratio of change in pressure to change in volume) as determined during simultaneous catheterization and echocardiography (17, 19).

Statistical analysis. On the basis of previously published correlates of $\dot{V}O_{2\text{ peak}}$, our list of dependent parameters consisted of NYHA class, ratio of peak early transmitral flow velocity to peak atrial flow velocity (E/A ratio), peak E-wave velocity, peak A-wave velocity, maximal heart rate, LVEF, age, acceleration time, body mass index, diastolic duration, deceleration time, E-wave duration, resting heart rate, resting systolic blood pressure, and the MBIP-determined parameters x_0 , c , and k . For each of the 17 selected dependent parameters, univariate regression was initially performed. A stepwise multiple regression analysis was subsequently performed on the most relevant five variables that correlated with $\dot{V}O_{2\text{ peak}}$. At each step in the analysis, variables were entered until no further improvement in the value of the generalized r^2 was seen. In accordance with convention that the ratio of subjects ($n = 41$) to the nine independent predictors be in the 6–10 range, a final set of five independent predictors was used (see Table 2). The variables with a high degree of multicollinearity, quantified as a variance inflation factor of >2.0 , were excluded (31). Analyses were performed using a commercially available statistical package (SPSS for Windows version 10.0, SPSS). Data are expressed as means \pm SD. P values of <0.05 were considered statistically significant.

RESULTS

Descriptive characteristics for the entire subject sample are summarized in Table 1. The etiology of HF in all subjects was as follows: ischemic cardiomyopathy in 20 (49%), idiopathic dilated cardiomyopathy in 17 (41%), and 4 patients (10%) lacked classification. Five patients were in NYHA class I (12%), 16 (39%) in class II, 14 (34%) in class III, and 6 (15%) in class IV. Overall, NYHA class IV patients demonstrated a lower maximal heart rate, ventilation rate, $\dot{V}O_{2\text{ peak}}$, and resting ejection fraction and a higher resting heart rate than other NYHA classes. Moreover, these individuals differed also in E-wave characteristics: increased E_{peak} (peak of the E wave), decreased acceleration time, and decreased deceleration time. These findings are in agreement with other studies and are

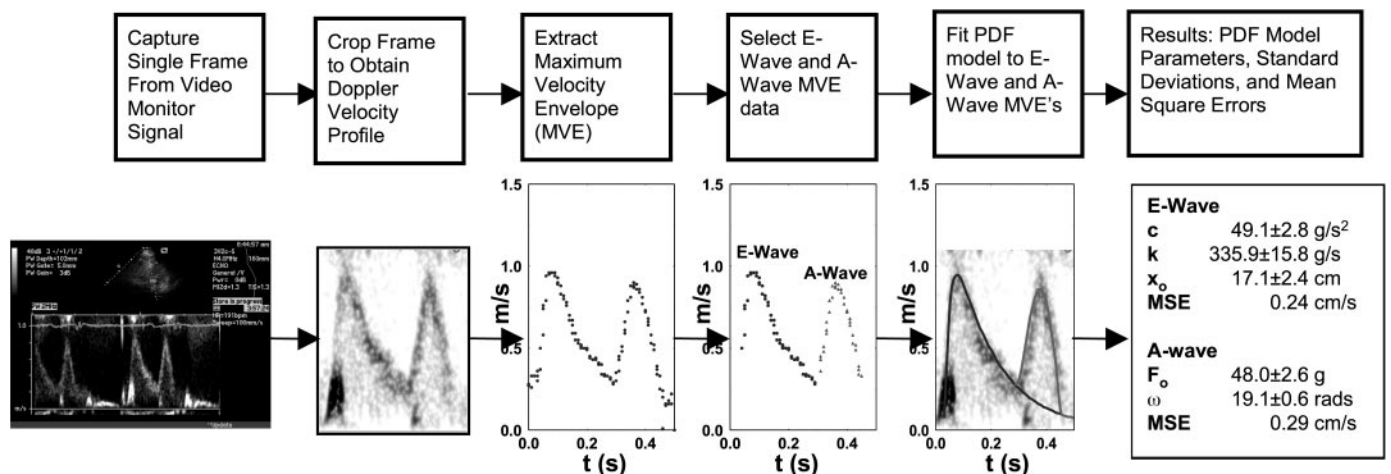


Fig. 1. Overview of the model-based image-processing (MBIP) method of model fitting and parameter determination with the Doppler image as input. Sequence of steps is as follows: acquire digital transmitral Doppler image, select diastolic interval of interest, determine maximum velocity envelope to be used as input for MBIP, and perform fit using Levenburg-Marquardt method. Results, i.e., parameter values and standard deviations, including mean square error (MSE) as a measure of goodness of fit, are indicated in the last box. x_0 , Initial displacement; c , damping constant; k , spring constant; F_0 , magnitude (dyn); ω , angular velocity; t , time.

Table 1. Characteristics of patients

Category	Mean \pm SD
Clinical characteristics	
Age, yr	54.4 \pm 9.3
Gender	36 M, 5 F
BMI, kg/m ²	30.3 \pm 5.9
NYHA class	2.4 \pm 0.8
Resting hemodynamics	
SBP, mmHg	117.4 \pm 14.2
DBP, mmHg	75.6 \pm 9.4
HR _{seated} , beats/min	68.7 \pm 10.7
LVEF, %	27.9 \pm 8.1
Peak exercise	
HR _{peak} , beats/min	129.2 \pm 23.2
$\dot{V}O_{2\text{ peak}}$, ml·kg ⁻¹ ·min ⁻¹	16.8 \pm 4.7
E-wave parameters	
E _{peak} , cm/s	78.8 \pm 27.2
A _{peak} , cm/s	52.5 \pm 17.3
AT, ms	88.8 \pm 26.0
DT, ms	162.2 \pm 58.7
E/A ratio	1.7 \pm 1.0
k, g/s ²	237.1 \pm 61.1

M, male; F, female; A_{peak}, peak A-wave velocity; AT, E-wave acceleration time; BMI, body mass index; DBP, resting diastolic blood pressure; DT, E-wave deceleration time; E/A ratio, ratio of early transmitral flow velocity to atrial flow velocity; E_{peak}, peak E-wave velocity; HR, resting heart rate; HR_{peak}, maximal heart rate at peak exercise; k, left ventricular chamber stiffness parameter; LVEF, left ventricular ejection fraction; SBP, resting systolic blood pressure; $\dot{V}O_{2\text{ peak}}$, peak oxygen consumption.

consistent with the “constrictive-restrictive” (tall-narrow) E-wave pattern encountered in significant HF (2, 18, 25, 32). The trend in the magnitude of *k* in our subjects reflects the fact that as NYHA class increases so does LV chamber stiffness (class I, *k* = 167.8; class II, *k* = 216.2; class III, *k* = 253.8; and class IV, *k* = 307.9).

To identify the potentially independent determinants of $\dot{V}O_{2\text{ peak}}$, all clinical, hemodynamic, exercise, and Doppler echocardiographic data were proposed for multiple regression model inclusion. Our statistical approach is commonly used in the literature to analyze similar physiological relationships. Specifically, it is similar to the analysis used by Lapu-Bula et al. (18) in their study assessing the relation of exercise capacity to LV systolic function and diastolic filling in idiopathic or ischemic dilated cardiomyopathy. Univariate predictors of $\dot{V}O_{2\text{ peak}}$ are reported in Table 2. Age, seated heart rate, diastolic duration, *x*₀, *c*, gender, body mass index, acceleration time, and deceleration time were not predictors of $\dot{V}O_{2\text{ peak}}$. The parameter *k* and NYHA classification were the two best predictors of $\dot{V}O_{2\text{ peak}}$, and they were both inversely correlated with $\dot{V}O_{2\text{ peak}}$. Although complete characterization of the Doppler E wave according to the model includes determination of *x*₀ (reflecting E-wave amplitude), *c* (reflecting chamber viscosity and/or relaxation), and *k* (reflecting chamber stiffness), only *k* accounted for the majority of variance.

As expected, $\dot{V}O_{2\text{ peak}}$ is strongly correlated with NYHA classification in all subjects (*P* < 0.001) (Fig. 2), but it did not predict NYHA classification as well as did *k* (*P* < 0.001) (Fig. 3).

In the multivariate stepwise regression model (Table 2), *k* and NYHA classification were the only remaining non-exercise-related predictive correlates of $\dot{V}O_{2\text{ peak}}$. In this

Table 2. Univariate predictors of $\dot{V}O_{2\text{ peak}}$

Parameter	Partial <i>r</i>	<i>P</i>
<i>k</i>	-0.75	<0.001
NYHA Class	-0.67	<0.001
E/A ratio	-0.56	<0.001
E _{peak}	-0.48	<0.001
A _{peak}	0.50	<0.01
HR _{peak}	0.47	<0.01
LVEF	0.44	<0.01
Resting SBP	0.30	<0.05
E-wave duration	0.28	<0.05
DT	0.25	0.06
Age	0.22	0.08
HR _{seated}	0.17	0.15
DD	0.11	0.25
BMI	0.11	0.25
AT	0.10	0.27
<i>x</i> ₀	0.08	0.31
<i>c</i>	0.02	0.44
<i>Multivariate analysis</i>		
Independent nonexercise predictors	Multiple <i>r</i> ²	<i>P</i>
<i>k</i>	0.55	<0.0001
NYHA Class	0.59	<0.0001

NYHA, New York Heart Association; DD, diastolic duration; *x*₀, initial displacement; *c*, clamping constant.

model, *k* (multiple *r*² = 0.55, *P* < 0.0001) and NYHA classification (multiple *r*² = 0.59, *P* < 0.0001) together predicted 59% of the variability in $\dot{V}O_{2\text{ peak}}$ with NYHA classification contributing 4%.

DISCUSSION

In this study in patients with HF, we tested the hypothesis that LV chamber stiffness could be the diastolic abnormality that is a key determinant of aerobic capacity in patients with HF and systolic dysfunction. We therefore determined whether diastolic function, as reflected by LV chamber stiffness obtained at rest, correlated with measures of aerobic capacity obtained during exercise and NYHA classification. Although all patients had known systolic dysfunction in this study, as reflected by decreased LVEF, the degree of diastolic dysfunction worsened with worsening $\dot{V}O_{2\text{ peak}}$. We found strong correlations between *k*, $\dot{V}O_{2\text{ peak}}$, and NYHA classification. We also found that *k* appears to be a

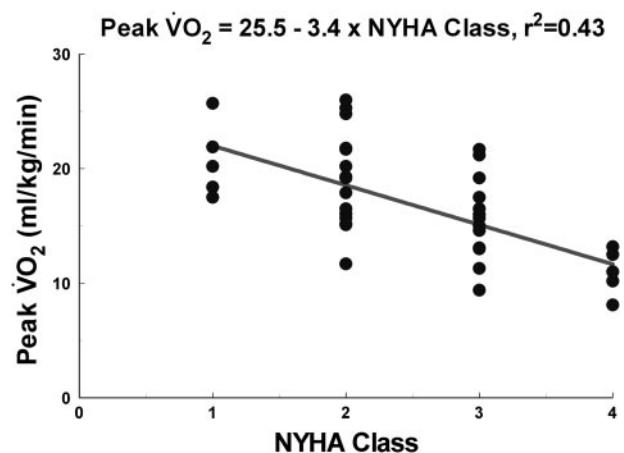


Fig. 2. Linear regression analysis of New York Heart Association (NYHA) class and peak oxygen consumption ($\dot{V}O_{2}$).

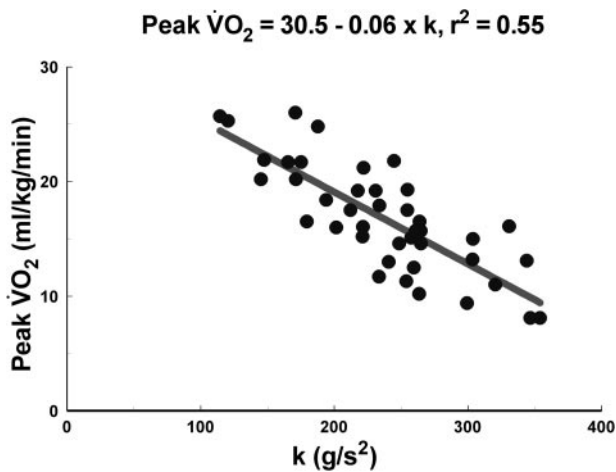


Fig. 3. Linear regression analysis of k and peak $\dot{V}O_2$.

better predictor of $\dot{V}O_{2\text{ peak}}$ than NYHA classification or LVEF most likely because the former is a better surrogate of exercise capacity than the latter two. Patients with HF have a limited ability to perform physical exercise, and this study sheds light on the role of diastolic function as part of that limitation. The recent study by Zile et al. (37) supports our observation that subjects with HF have abnormal diastolic function. More specifically, they concluded that abnormal relaxation and increased passive stiffness are key determinants of diastolic HF (37). Although our patients had systolic dysfunction in addition, the presence of diastolic dysfunction as indicated by the noninvasively derived k accentuates the pathophysiological HF scenario. As a consequence of the demand for increased cardiac output in response to exercise, heart rate increase, diastolic duration shortens, and the associated increase in chamber stiffness (k) mandates development of elevated LVEDP, resulting in dyspnea and compromised oxygenation due to an increase in the A-a gradient with concomitant limitation of cardiac output. This physiological scenario may account in part for the observation that LV chamber stiffness determined by the same method was the strongest independent predictor of 1-yr mortality in elderly subjects hospitalized with HF (27). Furthermore, Doppler tissue imaging has shown that the Doppler E-wave maximum-to-mitral annular velocity maximum ratio and exercise capacity demonstrate a strong negative correlation. The Doppler E-wave maximum-to-mitral annular velocity maximum ratio has not only been observed to be highly correlated with LVEDP or pulmonary capillary wedge pressure but also has been shown to be a causal determinant of LVEDP as a consequence of the “constant-volume” property of the two-chambered heart (20, 25, 30).

Exercise intolerance in HF patients is a poorly understood multifactorial pathological entity and is mediated by numerous mechanisms encompassing central limitations (i.e., cardiac limitations) peripheral limitations that are predominantly muscular and metabolic in origin, or a combination of both (18). Apart from age, gender, and habitual physical activity that affect $\dot{V}O_{2\text{ peak}}$, the relative contribution of central and peripheral factors to the modulation in $\dot{V}O_{2\text{ peak}}$ continues to be investigated (6). Central components include cardiac output, heart rate, mean arterial pressure, stroke volume, LV end-diastolic and end-systolic volumes, LVEF, and the Doppler echo-determined E/A ratio. Miyashita et al. (24) recently reported that LV diastolic function, but not systolic function

during exercise, determined exercise capacity in patients with HF, indicating that adequate LV filling appears to be more important than LV emptying to provide an adequate stroke volume needed during exercise. In a review by Little et al. (21), it was noted that cardiac output during exercise depended on the capacity of the LV to increase its ability to fill without an abnormal increase in left atrial pressure. However, in patients with HF, the ability to enhance cardiac output and LV filling without a concomitant increase in LV filling pressure during exercise was lost. Because central hemodynamic factors by themselves may not be sufficient to explain the limitation of exercise in patients with HF, interest in determining the extent to which peripheral factors also play a role continues to evolve.

Peripheral factors that may contribute to exercise intolerance include abnormalities in skeletal muscle blood flow and early anaerobic metabolism. Our finding contrasts with previous studies that found selected peripheral components rather than central hemodynamic parameters to be better predictors of $\dot{V}O_{2\text{ peak}}$ in HF (5, 8, 9, 13, 23). For example, Cicoira et al. (5) demonstrated that skeletal muscle is an important determinant of exercise capacity independent of central hemodynamics in noncachectic patients with HF. Leg muscle cross-sectional area has also been shown to be significantly correlated with and serve as an independent predictor of $\dot{V}O_{2\text{ peak}}$ in male patients with HF (13). Furthermore, exercise capacity is limited in part by the fixed delivery of blood to the periphery, especially in subjects with small muscle mass where local metabolic factors dominate (23). Thus there are data to support the view that both central and peripheral responses are involved in limiting exercise capacity in patients with HF.

The exertional fatigue exhibited in patients with HF has been attributed to underperfusion of skeletal muscle because patients with HF on average demonstrate reduced cardiac output and leg blood flow responses to exercise (23, 27–29, 31–36). Patients with HF and exertional fatigue were, however, shown to be limited by skeletal muscle abnormalities rather than by skeletal muscle underperfusion (35). Moreover, other more recent studies indicate that early skeletal muscle anaerobic metabolism is the primary factor limiting exercise performance in patients with HF (3). Hence, uncertainty remains in characterizing exercise intolerance pathophysiologically. Even though cardiac pump function and peripheral abnormalities may exacerbate the other, the question of which is the primary cause remains ambiguous. In an attempt to find an answer, Florea et al. (7) found that, in patients with severe HF, aerobic performance was primarily determined by peripheral hemodynamic factors, whereas, in patients with mild to moderate HF, exercise tolerance was predominantly mediated by central hemodynamic factors. Thus the novel finding in this study is that increased chamber stiffness determined at rest is the measure of diastolic dysfunction that predicts exercise capacity in subjects with systolic dysfunction. Our results support the perspective that central factors may be dominant in determining values of $\dot{V}O_{2\text{ peak}}$.

Limitations. In light of previous work relating peripheral factors to exercise limitation, we did not specifically measure peripheral factors. Accordingly, our findings that LV chamber stiffness explained the major portion of the variance in $\dot{V}O_{2\text{ peak}}$ as a measure of exercise tolerance in HF subjects with decreased LVEF should be viewed as complementary to previous

studies demonstrating the role of peripheral factors in exercise limitation in HF patients.

Although we found a strong linear relationship between $\dot{V}O_{2\text{ peak}}$ and k in subjects from all four NYHA classes, several additional limitations remain.

We examined a modest number of patients who were on heterogeneous therapy at different stages in their disease process, and the vast majority of patients were treated with angiotensin-converting enzyme inhibitors and β -blockers. The medications, the underlying cause of HF, local hormonal changes, and the variability among the NYHA classes among the patients may have an effect on the observed relationship.

We did not measure LV diastolic stiffness during exercise but determined it at rest. It is known that increased LV diastolic stiffness as manifested via increased LVEDP is disadvantageous during exercise and that it represents an unfavorable hemodynamic condition for exercise by sharply compromising LV filling. Although we observed a high correlation between $\dot{V}O_{2\text{ peak}}$ and k , it is possible that a slightly different correlation would be obtained if k were measured during exercise.

Because of respiratory and heart rate variation, there exists a slight beat-to-beat variability of E-wave amplitudes, whereas the variation in E-wave duration is minimal. It is known that the amplitude (peak) of the E wave is preload dependent (3, 4). However, the MBIP method used to estimate k accounts for preload (i.e., E-wave amplitude) effects through the (mathematically) independent model parameter x_o , which was found to be an insignificant predictor of $\dot{V}O_{2\text{ peak}}$ (12, 16, 17).

The mean age of the patients in this study is somewhat young for a HF population, although it reflects the population in the HF clinic at our institution. The MBIP method of chamber stiffness determination used in this study is a well-established (noncommercial) research tool for which an approximate conventional surrogate in the form of transmitral flow-based deceleration time has also been shown to correlate with poor outcome in patients with HF (2). The strength of MBIP resides in its ability to causally characterize the determinants of the entire Doppler contour. In contrast, current methods utilize only one or two points from the entire contour and cannot distinguish between differently shaped E-wave contours that may have the same peak and deceleration time.

Although we have not yet completed determination of normal gender- and age-related values for k , the trend our study reveals is meaningful, in that HF subjects with stiffer ventricles tend to have worse $\dot{V}O_{2\text{ peak}}$.

Conclusion. This study shows that HF patients with increased ventricular chamber stiffness determined at rest have worse exercise tolerance. The chamber stiffness determined at rest accounts for a majority of the statistical variance in $\dot{V}O_{2\text{ peak}}$ and suggests that it is a major factor contributing to limitation of functional capacity of patients with HF. Moreover, because this index can be obtained noninvasively, it may be a helpful adjunct to exercise testing to assess exercise capacity in clinical practice. Further studies in larger groups of patients with specific etiologies of HF should be undertaken.

GRANTS

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