Aortic Distensibility Independently Affects Exercise Tolerance in Patients With Dilated Cardiomyopathy

Stefano Bonapace, MD; Andrea Rossi, MD; Mariantonietta Cicoira, MD; Lorenzo Franceschini, MD; Giorgio Golia, MD; Luisa Zanolla, MD; Paolo Marino, MD; Piero Zardini, MD

**Background**—Peak exercise oxygen consumption (\(\dot{V}O_2\)) is crucial for the prognostic stratification of patients with congestive heart failure, but its hemodynamic determinants are still not completely understood. Aortic wall elasticity modulates left ventricular function and coronary blood flow. Whether an increased aortic pulse-wave velocity (PWV), a known marker of arterial stiffness, may predict peak \(\dot{V}O_2\) in patients with dilated cardiomyopathy (DCM) has to be clarified.

**Methods and Results**—A total of 78 patients with clinical diagnosis of DCM (aged 62\(\pm\)11 years; female 29%; mean ejection fraction 34\(\pm\)9%) were selected. All patients underwent a complete echocardiographic-Doppler evaluation. Aortic PWV was measured by Doppler ultrasonography immediately before the exercise. A bicycle exercise test with expiratory gas exchange monitoring was performed to determine \(\dot{V}O_2\). Plasma concentration of the amino-terminal propeptide of type III procollagen (PIIINP), a marker of extracellular matrix turnover, was determined. Mean PWV was 2.2\(\pm\)0.5 m/s, and \(\dot{V}O_2\) was 16.5\(\pm\)5.4 mL \cdot kg\(^{-1}\) \cdot min\(^{-1}\). The hemodynamic variables correlated with \(\dot{V}O_2\) were PWV (\(r=-0.39, P=0.0007\)) and stroke volume (\(r=0.38, P=0.002\)). In a multivariate analysis, PWV (\(P=0.04\)) and stroke volume (\(P=0.05\)) were independently correlated with \(\dot{V}O_2\), accounting for 34% of its variance. PIIINP levels correlated with PWV (\(r=0.35, P=0.002\)) and a more restrictive diastolic filling pattern (\(r=0.40, P=0.02\)).

**Conclusions**—Increased aortic stiffness measured by PWV is an independent predictor of peak \(\dot{V}O_2\) and could partially explain exercise intolerance in patients with DCM. (*Circulation. 2003;107:1603-1608.*)

Key Words: heart failure ■ cardiomyopathy ■ aorta ■ exercise

Patients with chronic heart failure (CHF) due to dilated cardiomyopathy (DCM) are characterized by reduced exercise tolerance, which is measured by oxygen consumption at peak exercise (\(\dot{V}O_2\)).\(^1\) \(\dot{V}O_2\) is a crucial parameter for prognostic stratification\(^2\) and for optimal selection of patients who might benefit from cardiac transplantation.\(^3\) Therefore, full comprehension of the determinants of this parameter is needed. Apart from nonhemodynamic factors that affect \(\dot{V}O_2\), such as age, sex, and skeletal muscle properties,\(^4\) the role of central and peripheral hemodynamic variables in \(\dot{V}O_2\) is still incompletely understood.\(^5\) The failing heart is particularly sensitive to afterload conditions during ejection. Most of the experimental work on the vascular system in CHF patients has been done on the small muscular arteries responsible for mean arterial pressure, the steady component of left ventricular (LV) afterload. The aorta is an elastic chamber that buffers the flow and pressure variation generated by the intermittent LV activity that modulates LV function\(^6\)–\(^9\) and coronary blood flow.\(^10\) Nevertheless, its influence on exercise performance in patients with DCM has not been studied in great detail. This is important, because experimental and clinical studies have documented progressive alteration of large-artery function with the increasing severity of heart failure.\(^11\)–\(^13\) In addition, healthy subjects with a stiffer aorta showed a lower \(\dot{V}O_2\) and hence a reduced exercise tolerance.\(^14\)–\(^16\) Recent studies in older people with diastolic heart failure showed that a low \(\dot{V}O_2\) was associated with increased stiffness of the thoracic aorta.\(^17\) This study was undertaken to assess the possible relationship between resting aortic stiffness, measured noninvasively as aortic pulse-wave velocity (PWV), and exercise tolerance, expressed as \(\dot{V}O_2\), in patients with DCM.

**Methods**

**Study Population**

We assessed for eligibility 90 consecutive patients of stable clinical status who were followed up at our Outpatient Heart Failure Clinic. All subjects gave informed consent for participation in the study, which was approved by the Ethics Committee of the Ospedale Civile Maggiore of Verona. All patients had an LV ejection fraction <45% and a duration of heart failure of at least 6 months, were taking standard therapy for heart failure, and were taking an optimal dose of diuretics. Criteria of exclusion were as follows: (1) intermittent claudication, significant pulmonary disease, inducible ischemia, or disorders other than cardiac disease that limited exercise performance; (2) presence of atrial fibrillation; (3) more than mild aortic...
regurgitation as assessed by color Doppler; and (4) renal failure (serum creatinine >150 μmol/L). A total of 78 patients were enrolled in the study; 3 patients were excluded for renal failure, 7 for atrial fibrillation, and 2 for inducible ischemia.

**Echocardiography**

A complete echocardiographic-Doppler examination was performed immediately before the exercise test. LV end-diastolic and end-systolic volumes (area-length method; monoplane 4-chamber view) and LV ejection fraction were measured. Mitral E-wave (Emax) and A-wave (Amax) velocities, E/A ratio, and E-wave deceleration time were measured at the mitral flow Doppler examination, with the pulsed Doppler sample volume placed at the tip of the mitral leaflets. Restrictive mitral filling pattern was defined as E/A >2 or E/A >1 and E-wave deceleration time <140 ms. Stroke volume (SV) was measured as the product of the LV outflow tract annulus area and time-velocity integral measured at the same level by pulsed-wave Doppler. Mitral regurgitant volume was calculated as the difference between LV end-diastolic and LV end-systolic volumes minus LV outflow tract annulus SV.

**Pulse-Wave Velocity**

PWV is considered a good surrogate for arterial distensibility, being correlated with direct measurement of arterial stiffness. As stated by the Moens Koerteweg equation, PWV, which is proportional to the square root of Young’s elastic modulus, travels faster in stiffer arteries. Pulsed Doppler was used to measure the time taken by the pulse wave to travel along the thoracic aorta. To measure the flow at the aortic arch, the transducer was placed at the suprasternal notch, and the sample volume was placed distally to the origin of the left subclavian artery. The distance (d1) between the transducer and the sample volume was then measured in a 2D frame. The flow in the abdominal aorta was determined from the subcostal approach. The distance (d2) from the suprasternal notch to the position of the probe in the abdomen was then measured with a tape measure. The distance (d) between the 2 sample volumes was calculated as d1−d2. The R wave of the QRS complex of a simultaneously recorded ECG was used as a fixed reference time point. The time (t) between the R wave on the ECG and the foot of each flow wave was subtracted to calculate the transit time, and PWV was then calculated as the distance traveled by the pulse wave divided by the time required, PWV (m/s)=dt/d.

**Cardiopulmonary Exercise Testing**

All patients underwent a symptom-limited bicycle ergometer exercise test at a constant cadence of 60 rpm. A continuous ramp protocol was used in which work rate was increased by 10 W/min. Gas exchange was monitored during the exercise test with a computerized metabolic cart (SensorMedics, Vmax 229). Oxygen uptake (V02), carbon dioxide production, minute ventilation (VE), and respiratory exchange ratio were measured online every 10 seconds by a standard inert gas dilution technique. VO2 was defined as the highest VO2 achieved during exercise and was expressed in mL·kg⁻¹·min⁻¹. The slope of the relation between ventilation and carbon dioxide production (VE/VO2) was calculated from the exercise data and taken as an index of the ventilatory response to exercise.

**Neurohormonal Activation**

Venous blood samples were drawn on the day of the study after a 30-minute supine rest in a fasting state between 8 and 9 AM. Renin and aldosterone were determined by a sandwich radioimmunoassay (Biochem Immuno System). Intra-assay and interassay coefficients of variation for renin were 5% and 6%, respectively, and for aldosterone, they were 7% and 8%. Plasma epinephrine and norepinephrine levels were measured by high-performance liquid chromatography with electrochemical detection. Intra-days and interdays coefficients of variation for epinephrine were 7% and 8.5%, respectively, and for norepinephrine, they were 4.5% and 5%. Plasma concentrations of the amino-terminal propeptide of type III procollagen (PIIINP) were measured by radioimmunoassay (Orion Diagnostica) with intra-assay and interassay coefficients of variation of 5% and 8%, respectively.

**Statistical Analysis**

All data are given as mean±SD. Univariate correlations between VO2, PWV, and other clinical and hemodynamic variables were calculated. Correlations between normally distributed data were analyzed with the nonparametric Spearman test. To assess whether the association between PWV and peak VO2 was independent of other clinical and hemodynamic variables, several bivariate models were performed. A multivariate model was constructed using those hemodynamic variables significantly related to VO2 in the univariate analysis. Comparison between ischemic and nonischemic pathogenesis was made with a 2-tailed unpaired Student’s t test. Statistical significance was established at a level of P<0.05. A commercially available statistical software package was used (StatView 4.5, Abacus Concept Inc).

**RESULTS**

The characteristics of the population are shown in Table 1. Ninety-two percent of the patients were treated with ACE inhibitors (captopril, enalapril, or ramipril), 68% with β-blockers (metoprolol or carvedilol), and 90% with diuretics.
The mean PWV was 5.7 m/s, and a wide range of measurement was observed (2.5 to 12.8 m/s). The variables associated with PWV are described in Table 2. PWV was significantly related to increasing severity of CHF, expressed by New York Heart Association class, and increasing age of patients. A higher PWV was associated with lower SV and a more restrictive mitral filling pattern. Lower diastolic blood pressure (DBP) at rest and during exercise was associated with a higher PWV, whereas systolic blood pressure (SBP) during exercise tended to decrease in those with a stiffer aorta, although this did not reach statistical significance. The diameter of the aorta taken from the subcostal view over the region in which PWV was measured did not relate to PWV, which suggests that structural and functional aortic wall properties rather than the diameter were the major determinants of elasticity. There were no significant relations between PWV and plasma venous norepinephrine, epinephrine, renin, or aldosterone. A significant relation was found between plasma PIIINP concentration, PWV, and a more restrictive mitral filling pattern (Table 3).

PWV and Exercise Tolerance

Univariate predictors of VO2 are reported in Table 4. PWV showed significant correlation with both peak VO2 (r = −0.39; P = 0.0007) and the duration of exercise (r = −0.44; P = 0.0002; Figure). PWV correlated with peak VO2 independently of both clinical and hemodynamic variables, as shown by bivariate models (Table 5). A multivariate model that included hemodynamic variables, from among those significantly related to peak VO2 on univariate analysis, was able to predict 34% of the variability of VO2 (aortic SV, P = 0.05; LV ejection fraction, P = 0.4; PWV = 0.04; Emax, P = 0.1).

There were no differences between ischemic and nonischemic causes of DCM in age (63 ± 9 versus 61 ± 9 years, P = 0.35), peak VO2 (16.3 ± 4.9 versus 16.9 ± 3.7 mL · kg−1 · min−1, P = 0.58), or PWV (5.7 ± 0.2 versus 5.5 ± 0.23 m/s, P = 0.6). The association between PWV and VO2 was confirmed in both groups (ischemic, r = −0.33, P = 0.02; nonischemic, r = −0.55, P = 0.005).

Discussion

In this study, we found that aortic stiffness was an independent predictor of VO2 and hence of exercise tolerance in patients with CHF due to DCM. A stiffer aorta might influence VO2 through various hemodynamic mechanisms. First, the reduction in SV in those subjects with a stiffer aorta suggests that a less distensible proximal vasculature might influence exercise tolerance, thereby modulating LV systolic function. Previous studies have shown that a less compliant aorta may affect both LV systolic energetics and mechanics. When the aorta was experimentally stiffened, an increase in cardiac energetic cost for a given SV was found.21 Moreover, in isolated prepared hearts and in dogs, SV varied inversely

The clinical and hemodynamic predictors of PWV are described in Table 2. PWV and markers of diastolic function are described in Table 3. The linear regression analysis (univariate analysis) of clinical and hemodynamic predictors of VO2 is shown in Table 4. The abbreviations as in Table 1.
with aortic stiffness. In addition, a stiffer aorta with higher PWV may have a detrimental effect on systolic function of an already depressed LV through changes in the reflected waves that arise from the periphery. Although we did not measure the contribution of reflections, previous studies in CHF found an earlier return of the backward wave to the aorta either at rest or during exercise. The earlier reflected wave has an impact on the forward wave during systole, increasing LV systolic stress and imposing an additional systolic load. Nitroprusside infusion improved hemodynamic performance by lowering aortic PWV and reducing wave reflection, which later returned to the proximal aorta with a concomitant increase in SV.

Second, stiffer central vessels may also affect V̇O₂, influencing LV relaxation. The association between a higher PWV and a more restrictive mitral filling pattern is consistent with this. A link between greater aortic stiffness and a restrictive mitral filling pattern could occur as a result of cardiac hypertrophy, changing the properties of both the myocytes and the interstitium, which is known to be a factor that influences LV diastolic filling. The raised LV end-diastolic pressure secondary to increased ventricular volumes or myocardial stiffness might further reduce the preload reserve, with an earlier onset of exercise-limiting symptoms.

Third, a reduction in aortic distensibility may worsen the burden of a weakened heart through changes in blood pressure. The consequences of aortic stiffening during the aging process with preserved LV systolic function are higher SBP and lower DBP. In subjects in the present study, lower DBP at rest and during exercise was associated with a stiffer aorta. A possible explanation could be in the earlier reflections merging with the incoming wave during systole instead of diastole, thus decreasing aortic diastolic pressure, which might affect impairment of coronary perfusion by exercise tolerance. In experimental models, greater aortic stiffness was associated with subendocardial ischemia through a reduction in DBP. In the present study population, SBP tended to decrease with the increase in aortic stiffness during exercise. This might be explained by decreasing inotropic reserve with increasing severity of systolic heart failure, therefore blunting the SBP response during exercise. Recently, an increased pulse pressure in CHF was associated with DBP reduction rather than SBP increase. Because pulse pressure results from both cardiac and arterial factors, we speculate that the absence of a significant relation between aortic stiffness and pulse pressure in the present study population might be a consequence of the LV ejection impairment. As reported in more severe end-stage renal disease and in patients in the present study, mean blood pressure did not relate to aortic PWV. The fact that PWV is at least partially independent of blood pressure suggests that this index of arterial stiffness is probably not merely a surrogate of blood pressure and might reflect the consequences of disease-induced structural changes of the arterial wall. In both nonsystolic and systolic CHF, a reduced distensibility of the thoracic and abdominal aorta was associated with increased wall thickness, which suggests possible structural changes of these large-artery segments. We speculate that the raised activity of the renin-angiotensin-aldosterone system that characterizes heart failure might be involved in increased collagen turnover not only in the LV but also in the aorta. In fact, aortic collagen accumula-

Table 5. Linear Regression Analysis (Bivariate Models): Clinical and Hemodynamic Predictors of V̇O₂

<table>
<thead>
<tr>
<th>Model/Variables</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>PWV, m/s 0.007</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 2</td>
<td>PWV, m/s 0.005</td>
</tr>
<tr>
<td>Sex</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 3</td>
<td>PWV, m/s 0.006</td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.0005</td>
</tr>
<tr>
<td>Model 4</td>
<td>PWV, m/s 0.007</td>
</tr>
<tr>
<td>Emax, m/s</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 5</td>
<td>PWV, m/s 0.0009</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>0.8</td>
</tr>
<tr>
<td>Model 6</td>
<td>PWV, m/s 0.003</td>
</tr>
<tr>
<td>SV, mL</td>
<td>0.04</td>
</tr>
<tr>
<td>Model 7</td>
<td>PWV, m/s 0.0001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.03</td>
</tr>
<tr>
<td>Model 8</td>
<td>PWV, m/s 0.001</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
tion through an aldosterone-mediated mechanism was documented. Although we did not perform a structural analysis of the aorta and the LV, the relation between plasma PIIINP, an established marker of collagen turnover in DCM, PWV, and a restrictive mitral filling pattern might reflect a fibrotic process that involves both the LV and the aorta, contributing to the vicious circle and worsening the heart failure.

Age has been documented to be an independent determinant of exercise tolerance and of aortic stiffness. In patients in the present study, aortic stiffness was related to VO2 independently of age, which suggests that factors other than well-known age-linked changes in aortic wall composition might reduce aortic distensibility and hence exercise performance. Analogous changes in arterial distensibility and in exercise tolerance were seen whether the pathogenesis was ischemic or nonischemic, which suggests that factors other than the atherosclerotic process might be involved in stiffening the aorta and impairing physical performance. Earlier studies showed no differences in large-artery distensibility in patients with CHF of different origins.

**Methodological Considerations and Study Limitations**

PWV measurement is a simple and noninvasive method to evaluate arterial stiffness. It allows serial measurements over time to monitor changes in central artery properties that may predict exercise tolerance in patients with a wide spectrum of severity of systolic heart failure. A precise determination of the transit time and the length of the vascular segments are crucial factors. In fact, measurement over the body surface of the aortic length is particularly an approximation, especially in subjects with folded vessels. Furthermore, because the relative proportion of collagen, smooth muscle cells, and elastin that provide the tensile support of the large-artery wall varies along vessels, it remains to be demonstrated that the changes seen at the thoracic aorta would involve other large-artery districts. In addition, subjects in the present study were already taking drugs that influence wall elasticity and neurohormonal levels, and this could explain in part the lack of relationship between neurohormones and aortic stiffness. Because we did not perform a structural analysis of the aorta and the ventricle, we can only suggest a statistical association and not a causal relationship between PIIINP levels and a stiffer vascular-ventricular system. Moreover, aortic stiffness was measured in resting conditions. In patients with idiopathic DCM, it has been reported that arterial-ventricular coupling was altered at peak exercise because of a lack of increase in LV inotropic response and not because of altered arterial elasticity. We do not know whether changes in aortic stiffness occurred during exercise in patients in the present study; however, we believe that increased aortic stiffness at rest represents an unfavorable hemodynamic condition for the LV, which faces a greater load whether or not changes in aortic distensibility occur during exercise.

**Conclusions**

Our data suggest a possible mechanism whereby aortic stiffness may limit exercise tolerance in patients with DCM. A stiffer aorta may interfere with both systolic and diastolic function. Moreover, the combination of a stiffer LV with a stiffer central vasculature can further reduce exercise performance in patients with an already depressed LV function. Changes in aortic stiffness may be a clinically important parameter in predicting exercise response and may become an additional target for therapeutic interventions that aim to improve the ventricular burden of patients with DCM.

**References**

Aortic Distensibility Independently Affects Exercise Tolerance in Patients With Dilated Cardiomyopathy
Stefano Bonapace, Andrea Rossi, Mariantonietta Cicoira, Lorenzo Franceschini, Giorgio Golia, Luisa Zanolla, Paolo Marino and Piero Zardini

_Circulation_. 2003;107:1603-1608; originally published online March 10, 2003;
doi: 10.1161/01.CIR.0000051458.39176.43
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/12/1603

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/