Limitation of Exercise Tolerance in Chronic Heart Failure: Distinct Effects of Left Bundle-Branch Block and Coronary Artery Disease

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OBJECTIVES
The aim of this study was to identify resting measurements of left ventricular (LV) function that predict exercise capacity in dilated cardiomyopathy (DCM); in particular, the effects of left bundle branch block (LBBB), coronary artery disease (CAD), and total isovolumic time (t-IVT).

BACKGROUND
The t-IVT is a major determinant of cardiac output during dobutamine stress in DCM, and is itself determined by the presence or absence of LBBB and CAD.

METHODS
A total of 111 patients with DCM, 51 with CAD (29 LBBB), and 60 without CAD (30 LBBB) were studied with echocardiography and cardiopulmonary exercise testing. The t-IVT (in s/min) was measured by Doppler echocardiography, and maximal oxygen consumption (peak VO$_2$) and percentage of the normal predicted peak VO$_2$ (%predicted peak VO$_2$) were obtained from exercise testing.

RESULTS
Left bundle branch block reduced peak VO$_2$ (by 10.5 ml·kg$^{-1}$·min$^{-1}$) and %predicted peak VO$_2$ (by 33%, both $p<0.001$) compared with patients without LBBB. Coronary artery disease reduced peak VO$_2$ (by 5.5 ml·kg$^{-1}$·min$^{-1}$, $p<0.001$) and %predicted peak VO$_2$ (by 14%, $p<0.01$) compared with those without CAD ($p<0.01$). The t-IVT, CAD, LBBB, and QRS duration were univariate predictors of exercise tolerance, but only t-IVT and CAD were independent predictors. The t-IVT at rest correlated with peak VO$_2$ ($r=-0.68$) and %predicted peak VO$_2$ ($r=-0.74$, both $p<0.001$). The combination of t-IVT and CAD explained 57% ($r=0.75$, $p<0.001$) of the total variance in exercise capacity.

CONCLUSIONS
Resting t-IVT and less prominently, CAD, are major determinants of exercise tolerance in DCM. Left bundle branch block significantly determines resting t-IVT and thus peak VO$_2$. Prediction of maximum exercise capacity in DCM is therefore possible from time-domain analysis of LV function at rest. (J Am Coll Cardiol 2004;43:1524–31) © 2004 by the American College of Cardiology Foundation

The clinical syndrome of heart failure is associated with impaired exercise tolerance (1), though the factors limiting exercise capacity remain a matter of debate (2); in particular, ejection fraction (EF), the conventional measurement of resting left ventricular (LV) function, does not predict exercise tolerance (assessed by peak exercise capacity [peak VO$_2$]) in patients with dilated cardiomyopathy (DCM) (3,4).

See page 1532

METHODS

Patients. We analyzed data from 111 patients with systolic heart failure who had undergone clinically indicated cardiopulmonary exercise testing in the period 1999 to 2002 at the Royal Brompton Hospital. All had undergone routine resting echocardiography within two months of exercise testing. Systolic heart failure was diagnosed on the basis of a history of limitation of exercise tolerance by fatigue or breathlessness and evidence of LV systolic dysfunction on echocardiography (defined as LV end-diastolic dimension >56 mm and end-systolic dimension >40 mm on an M-mode echocardiogram, and an EF <40%). Significant CAD was demonstrated by at least two-vessel disease (>70% stenosis) at coronary angiography, and LBBB was diagnosed on the basis of a QRS duration >120 ms, absent...
Q waves and wide slurred R waves in V₁ and V₆, and monophasic QS or rS waves in V₁ and V₂. Predetermined criteria for exclusion were patients with atrial fibrillation, structural valve disease, or more than mild functional mitral regurgitation. The patients were closely monitored by a heart failure research nurse, and those who developed significant deterioration in clinical status, change in therapy or electrocardiogram between exercise testing and echocardiography were excluded from the study. For reference, 15 age-matched control subjects were also included, none of whom had symptoms or signs of heart failure or evidence of LV dysfunction on echocardiography.

**Echocardiography.** Transthoracic echocardiography was performed using a Phillips Sonos 5500 echocardiograph (Andover, Massachusetts) and a multifrequency transducer. Resting cross-sectional, two-dimensional guided M-mode recordings of the LV minor axis were performed using the left parasternal long-axis view with the cursor at the tips of the mitral valve leaflets. The LV minor axis dimensions were taken at end-diastole (the onset of the QRS complex) and at end-systole (at the first high-frequency vibration of the aortic component of the second heart sound on the phonocardiogram, A2) using leading edge methodology. A2 was confirmed as being synchronous with the onset of the closure artifact on the aortic Doppler record. The left ventricular ejection fraction (LVEF) was obtained using biplane Simpson’s methodology (8). Fractional shortening was calculated as the percentage fall in LV cavity dimension during systole with respect to that in diastole. Mean velocity of circumferential fiber shortening rate (Vcf) was calculated (s⁻¹) as the ratio of fractional shortening to LV ejection time.

Transaortic flow velocity was obtained from the apical five-chamber view. The LV ejection time was measured as the interval between the onset of forward aortic flow to the onset of the aortic valve closure artifact. Transmitral Doppler flow velocities were recorded from the apical four-chamber view, and peak E (early diastolic) and A (atrial) velocities were measured. Filling time was measured from the onset of the E wave to the end of the A wave. Total LV ejection and filling periods were derived as the product of the corresponding time interval and heart rate, expressed in s/min. Total LV ejection and filling periods were derived as the product of the corresponding time interval and heart rate, expressed in s/min. The t-IVT is then calculated as [60 – (total ejection time + total filling time)] (Fig. 1). These values are independent of resting heart rate (9). The Tei index was calculated as the sum per beat of isovolumic contraction and isovolumic relaxation times, divided by ejection time (5). Potential mitral regurgitation was graded using standard criteria: mild, moderate, or severe, according to the distance from the valve orifice that the regurgitant jet remained detectable on the color flow Doppler recording (10). All tracings were acquired at a paper speed of 100 mm/s, with an electrocardiogram (lead II) and a phonocardiogram superimposed.

**Cardiopulmonary exercise testing.** All patients underwent symptom-limited cardiopulmonary exercise testing (modified Bruce protocol) with assessment of minute ventilation (VE), oxygen consumption (VO₂), and carbon dioxide production (VCO₂) every 10 s by mass spectrometer (Amis 2000, Innovision; MedGraphics Cardio O₂ System, Odense, Denmark). Patients were encouraged to exercise to exhaustion (VCO₂/VO₂ > 1.05). Continuous 12-lead electrocardiographic monitoring was used. All participants stopped exercise because of breathlessness and/or fatigue. None experienced chest pain or developed ST segment shift. Predicted peak VO₂ was calculated on the basis of gender,
Table 1. Echocardiographic Variables at Rest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 15)</th>
<th>No CAD, No LBBB (n = 30)</th>
<th>CAD, No LBBB (n = 22)</th>
<th>No CAD, LBBB (n = 30)</th>
<th>CAD and LBBB (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDD (mm)</td>
<td>48 ± 4</td>
<td>66 ± 7</td>
<td>67 ± 6</td>
<td>70 ± 9</td>
<td>71 ± 9</td>
</tr>
<tr>
<td>ESD (mm)</td>
<td>29 ± 5</td>
<td>53 ± 9</td>
<td>55 ± 7</td>
<td>59 ± 11</td>
<td>59 ± 10</td>
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<tr>
<td>EF (%)</td>
<td>75 ± 8</td>
<td>31 ± 4</td>
<td>33 ± 5</td>
<td>31 ± 5</td>
<td>31 ± 6</td>
</tr>
<tr>
<td>Vcf (circ/s)</td>
<td>1.44 ± 3.9</td>
<td>0.8 ± 0.3</td>
<td>0.7 ± 0.2</td>
<td>0.7 ± 0.3</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.0 ± 0.3</td>
<td>1.8 ± 1.5</td>
<td>1.9 ± 1.6</td>
<td>2.6 ± 1.0</td>
<td>1.9 ± 1.3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>76 ± 12</td>
<td>76 ± 17</td>
<td>73 ± 13</td>
<td>83 ± 16</td>
<td>73 ± 13</td>
</tr>
<tr>
<td>t-ET (s/min)</td>
<td>20 ± 2</td>
<td>19 ± 3</td>
<td>19 ± 2</td>
<td>19 ± 3</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>t-FT (s/min)</td>
<td>28 ± 3</td>
<td>30 ± 3</td>
<td>28 ± 3</td>
<td>20 ± 3*</td>
<td>21 ± 3*</td>
</tr>
<tr>
<td>t-IVT (s/min)</td>
<td>12 ± 2</td>
<td>11 ± 2</td>
<td>13 ± 2</td>
<td>21 ± 3*</td>
<td>20 ± 4†</td>
</tr>
<tr>
<td>Tei index</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>1.2 ± 0.3*</td>
<td>1.2 ± 0.3†</td>
</tr>
</tbody>
</table>

Values are mean ± SD. CAD (no LBBB) versus no CAD (no LBBB): all p = NS. *p < 0.001, no CAD (LBBB) versus no CAD (no LBBB). †p < 0.001, CAD (LBBB) versus CAD (no LBBB). 

CAD = coronary artery disease; E/A ratio = ratio of early transmitral flow velocity to atrial flow velocity; EDD = end-diastolic dimension; EF = ejection fraction; ESD = end-systolic dimension; HR = heart rate; LBBB = left bundle branch block; t-ET = total ejection time; t-FT = total filling time; t-IVT = total isovolumic time; Vcf = mean velocity of circumferential fiber shortening.

Limitation of Exercise Tolerance in Heart Failure

age, and weight. Peak VO₂ was expressed in milliliters per kilogram per minute and also as a percentage of the normal predicted peak VO₂ (%predicted peak VO₂) (11). The slope of the relationship between VE and VCO₂ (VE/VCO₂) was calculated as the index of ventilatory response to exercise (12).

Data analysis. Statistical calculations were performed using the Statview 4.5 package (Abacus Concepts, Berkeley, California). Numerical values are expressed as mean ± SD. An unpaired Student t test was used to compare values between subgroups of patients with DCM. A two-way analysis of variance, which considered all the patients as a single group, was used to identify the individual contributions of CAD and LBBB to resting echo values and to exercise variables. The incremental value of CAD, LBBB (both either present or absent), QRS duration, t-IVT, and Tei index were tested using a multiple regression analysis, using a variance ratio (F) >6 as the criterion for entry into the multivariate analysis. Correlation was performed by linear regression analysis. In view of multiple statistical tests, a significant difference was taken as p < 0.01.

Reproducibility. Interobserver variability was assessed by two investigators, both unaware of the original diagnosis and of the other’s finding. Duplicate measurements of total ejection and total filling times in 20 patients were obtained from the same original records. Reproducibility was expressed as the root mean square (RMS) difference between duplicate values and as a coefficient of variation (CV). The interobserver RMS difference for total ejection time was 0.8 s/min (CV 4.2%) and 1.9 s/min for total filling time (CV 6.4%). To exclude any significant beat-to-beat variation in heart rate between recordings of mitral inflow and LV outflow in determining t-IVT, the reproducibility of RR interval at the time of measuring LV filling and ejection times was assessed, again in 20 patients. The interobserver RMS difference for RR interval was 20 ms (CV 2.4%). Reproducibility of peak VO₂ in a similar group of patients has previously been reported from this institution (difference between 2 tests: 0.93 ml/kg·min⁻¹; SD of the difference: 3.07 ml/kg·min⁻¹; coefficient of variability: 17.5%) (13).

RESULTS

Subjects. Of 111 patients studied, 94 were male (age 57 ± 13 years). Fifty-one patients had significant CAD, 22 with normal activation (QRS duration 97 ± 9 ms) and 29 with LBBB (QRS 160 ± 24 ms). Coronary angiography was normal in 60 patients, 30 with normal activation (QRS duration 97 ± 10 ms) and 30 with LBBB (QRS duration 146 ± 27 ms, p = NS compared with those with CAD). There were no significant differences in medical therapy between patient groups. In those with no CAD, 25 of 60 were receiving a beta-blocking agent, 56 an angiotensin-converting enzyme inhibitor, and 58 a diuretic. In patients with CAD, 28 of 51 patients were receiving a beta-blocking agent, 51 an angiotensin-converting enzyme inhibitor, and 47 a diuretic. The median time interval between resting echocardiography and cardiopulmonary exercise testing, calculated irrespective of which test was performed first, was two days (interquartile range 0 to 21 days).

Echocardiographic data at rest in DCM. In patients, end-diastolic dimension was 69 ± 9 mm, end-systolic dimension 57 ± 10 mm, EF 34 ± 5%, and Vcf 7.2 ± 2.5 s⁻¹ (all p < 0.001 compared with control subjects). There was no difference in the severity of LV dysfunction within patient subgroups in terms of LV cavity dimensions, LVEF, Vcf, or the ratio of early transmitral flow velocity to atrial flow velocity (E/A ratio) (Table 1), nor in terms of mitral regurgitation (mild mitral regurgitation was present in 21 patients with no CAD nor LBBB, 14 with CAD alone, 26 with LBBB alone, and 23 patients with both CAD and LBBB). There was also no difference in resting t-IVT between patients with or without CAD compared with control subjects, provided activation was normal. However, t-IVT at rest was significantly prolonged in patients with...
LBBB compared with those with normal activation (by 9 s/min, \(F = 208, p < 0.001\)), whether or not CAD was present (Table 1), primarily as a result of shortening of total filling time (by 8 s/min, \(F = 101, p < 0.001\)). Similarly, Tei index was normal in patients with or without CAD provided activation was normal, but was increased in patients with LBBB (by 0.52, \(F = 112, p < 0.001\)), irrespective of whether CAD was present or absent.

**Cardiopulmonary exercise testing.** There were significant differences in exercise tolerance within patient subgroups (Table 2).

**Patients with neither CAD nor LBBB.** These patients had the highest values for peak VO\(_2\) and %predicted peak VO\(_2\) compared with other patient subgroups (Fig. 2), although the values were less than normal in each case (by 12.7 ml·kg\(^{-1}\)·min\(^{-1}\) and by 30%, both \(p < 0.001\) compared with control subjects).

**CAD, no LBBB.** Peak VO\(_2\) and %predicted peak VO\(_2\) were lower in patients with CAD compared with those with no CAD (by 5.5 ml·kg\(^{-1}\)·min\(^{-1}\), \(p < 0.001\), and by 14%, \(p < 0.01\), respectively).

**LBBB, no CAD.** Peak VO\(_2\) and %predicted peak VO\(_2\) were significantly lower (by 10.5 ml·kg\(^{-1}\)·min\(^{-1}\) and by 33%), and VE/VCO\(_2\) slope was increased (by 13.4, all \(p < 0.001\)) in patients with LBBB compared with those with normal activation.

**CAD and LBBB.** Peak VO\(_2\) and %predicted peak VO\(_2\) were reduced (Fig. 2), and VE/VCO\(_2\) slope was increased, in patients with both CAD and LBBB compared with CAD alone (by 6.2 ml·kg\(^{-1}\)·min\(^{-1}\), 21%, and 8.8, respectively, all \(p < 0.001\)). There was no significant difference in any exercise variable between patients with CAD and LBBB compared with CAD alone.

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**Table 2. Cardiopulmonary Exercise Testing**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 15)</th>
<th>No CAD, No LBBB (n = 30)</th>
<th>CAD, No LBBB (n = 22)</th>
<th>No CAD, LBBB (n = 30)</th>
<th>CAD and LBBB (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO(_2) (ml·kg(^{-1})·min(^{-1}))</td>
<td>38.4 ± 8.4</td>
<td>26.2 ± 5.9*</td>
<td>20.7 ± 4.7‡</td>
<td>15.6 ± 4.8§</td>
<td>14.4 ± 3.5¶</td>
</tr>
<tr>
<td>% predicted peak VO(_2)</td>
<td>115 ± 13</td>
<td>85 ± 15*</td>
<td>71 ± 17†</td>
<td>52 ± 16§</td>
<td>50 ± 13¶</td>
</tr>
<tr>
<td>RER (V(<em>{CO2})/V(</em>{O2}))</td>
<td>1.09 ± 0.76</td>
<td>1.13 ± 0.12*</td>
<td>1.06 ± 0.10</td>
<td>1.08 ± 0.11</td>
<td>1.08 ± 0.13</td>
</tr>
<tr>
<td>VE/VCO(_2) slope</td>
<td>24.9 ± 3.4</td>
<td>29.2 ± 6.8</td>
<td>34.2 ± 8.8</td>
<td>42.6 ± 14.3§</td>
<td>42.9 ± 13.2¶</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *\(p < 0.001\), no CAD (no LBBB) versus control subjects. †\(p < 0.01\); ‡\(p < 0.001\), CAD (no LBBB) versus no CAD (no LBBB). §\(p < 0.001\), no CAD (LBBB) versus no CAD (no LBBB). ¶\(p < 0.001\), CAD (LBBB) versus CAD (no LBBB). CAD = coronary artery disease; LBBB = left bundle branch block; RER = respiratory exchange ratio at peak exercise; V\(_{CO2}\) = carbon dioxide production; V\(_E\) = minute ventilation; peak VO\(_2\) = peak oxygen uptake.

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**Figure 2.** Percentage predicted peak exercise capacity (VO\(_2\)) in individual patients with dilated cardiomyopathy. Patients with neither coronary artery disease (CAD) nor left bundle branch block (LBBB) had the highest values for %peak VO\(_2\). Coronary artery disease reduced %predicted peak VO\(_2\), but patients with LBBB had the lowest values of all, irrespective of whether CAD was present.
OVERALL EFFECT OF CAD IN DCM. Coronary artery disease reduced both peak VO₂ (by 3.8 ml·kg⁻¹·min⁻¹, F = 13, p < 0.001) and %predicted peak VO₂ (by 10%, F = 8, p < 0.01) compared with patients with no CAD, irrespective of whether LBBB was present or not, but had no significant effect on Ve/VCO₂ slope (F = 0.2, p = NS).

OVERALL EFFECT OF LBBB IN DCM. Left bundle branch block reduced peak VO₂ (by 8.8 ml·kg⁻¹·min⁻¹, F = 82) and %predicted peak VO₂ (by 28%, F = 83) compared with patients with no LBBB, irrespective of whether CAD was present or absent, and increased the Ve/VCO₂ slope (by 11.4, F = 25, all p < 0.001). There was no interaction between CAD and LBBB.

Relationship between t-IVT, Tei index, and exercise capacity. There were significant correlations between resting t-IVT and peak VO₂ (r = −0.68) and resting t-IVT and %predicted peak VO₂ (r = −0.74, Fig. 3, both p < 0.001) in patients with DCM. There was a similar correlation with Tei index at rest (r = −0.70, p < 0.001), but ejection time at rest showed no correlation with %predicted peak VO₂ (r = 0.22, p = NS).

Independent predictors of exercise capacity in patients with DCM. The t-IVT, CAD, LBBB, Tei index, and QRS duration were all univariate predictors of %predicted peak VO₂ in patients with DCM (Table 3), but in a multivariate analysis only t-IVT and CAD were independent predictors of exercise capacity (LBBB, QRS duration, and Tei index were all subsumed by t-IVT). The combination of t-IVT and CAD explained 57% (r = 0.75) of the total variance in %predicted peak VO₂ in the overall patient group. There was no correlation between %predicted peak VO₂ and LVEF (Fig. 3), Vcf, E/A ratio, or the presence of mild mitral regurgitation (Table 3).

Comparison with normal control subjects. In the patient group as a whole, peak VO₂ and %predicted peak VO₂ were reduced compared with control subjects (19.2 ± 6.7 ml·kg⁻¹·min⁻¹ vs. 38.4 ± 8.4 ml·kg⁻¹·min⁻¹, and 64 ± 21% vs. 115 ± 13%, both p < 0.001). A multivariate analysis was repeated to include normal control subjects. The total variance in %predicted peak VO₂ increased from 57% to 72% (r² = 0.85, p < 0.001) when DCM was included with t-IVT and CAD. Left bundle branch block, Tei index, and QRS duration were again subsumed by t-IVT.

DISCUSSION

Exercise tolerance is frequently limited in patients with congestive heart failure, but resting ventricular function as assessed by EF does not predict maximum exercise capacity (3,4). This has been taken as evidence that LV function is not a primary determinant of peak VO₂ in stable chronic heart failure (2), so that recent attention has been diverted to extra-cardiac abnormalities, such as disturbances in peripheral blood flow, endothelial function, skeletal muscle, and lung function (14–17). Indeed, higher correlations with exercise tolerance have been found with these peripheral abnormalities than with EF (18). Nevertheless, on an intuitive basis, it still seems that LV function appropriately assessed might be a major determinant of maximum exercise capacity in patients with primary LV disease.

Our results confirm previous studies in demonstrating that variability in exercise tolerance in patients with DCM cannot be explained on the basis of either systolic (EF and Vcf) or diastolic (E/A ratio) LV function. Rather, we found that both absolute and percentage predicted values of peak VO₂ were strikingly reduced in patients with LBBB compared with those without, and to a lesser extent by CAD (19), even when exercise tolerance was not limited by acute ischemia. Patients with neither LBBB nor CAD thus had the highest absolute and percentage predicted values of peak VO₂, whereas those with LBBB had the lowest values of all, irrespective of whether CAD was present or not. Even when LBBB and CAD were allowed for, resting t-IVT, a simple echo-derived measurement, had additional predictive value. QRS duration varied over a wide range, but provided no information additional to that derived from the simple presence or absence of LBBB. The Tei index predicted exercise tolerance, but only because it included t-IVT in its derivation. Ejection time, the second component of the Tei index, was of no predictive value on its own; its inclusion did not increase the predictive value of the Tei index above that of t-IVT alone, and it was eliminated by t-IVT in multivariate analysis as an independent predictor of peak VO₂.

Mechanisms. Prolongation of t-IVT proved a major determinant of exercise capacity. It is likely that this prolongation was due to ventricular asynchrony, which in LBBB is the result of abnormal activation causing dispersion in the timing of local systole and diastole (20). However, despite the overwhelming effect of LBBB on resting t-IVT, the presence of CAD still remained a highly significant determinant of peak VO₂. The reason for this was not clear, because CAD was without significant effect on resting t-IVT. Although its effect during exercise may be the result of some other mechanism, the association is compatible with the idea that CAD prolongs t-IVT on exercise though not at rest.

The present results have many features in common to those recorded during pharmacologic stress with dobutamine. In both circumstances, t-IVT was a major determinant of peak cardiac output, and was itself determined by both LBBB and CAD, though the effect of the latter was apparent only during stress (6). If CAD showed similar divergence in its effects between rest and muscular exercise, it would explain how it might remain independent of resting t-IVT in predicting peak VO₂, as in our present findings. However, there are significant differences between cardiopulmonary exercise testing and dobutamine stress. It was only peak stress t-IVT, not resting t-IVT, that predicted peak cardiac output during stress. In addition, the effects of CAD and LBBB appeared to be independent during dobutamine stress, so that when both were present, peak stress cardiac output was lower than with either alone.
These findings underline that although erect muscular exercise and pharmacologic stress have similar effects on cardiac function, they are not identical, and findings from one cannot always be extrapolated directly to the other.

**Practical implications.** The results from our study suggest that asynchrony, rather than uniform depression of systolic or diastolic ventricular function, prolongs the total isovolumic period within the cardiac cycle, and that it is this asynchrony that is the significant factor in determining maximum exercise tolerance in patients with DCM and heart failure. Our study thus re-emphasizes that LV function is important in the genesis of the clinical syndrome of heart failure but that indices of LV asynchrony need to be assessed if this relationship is to be demonstrated. Time-domain analysis of LV function is simple and highly reproducible, and should be included in the assessment of

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**Figure 3.** (Top) Correlation between resting total isovolumic time (t-IVT) and percentage predicted peak exercise capacity (\(\text{VO}_2\)). When individual patients were considered as a single group, resting t-IVT correlated closely with %predicted peak \(\text{VO}_2\). Patients with left bundle branch block (LBBB) had the longest t-IVT at rest and the lowest %predicted peak \(\text{VO}_2\), irrespective of whether coronary artery disease (CAD) was present. (Bottom) Lack of correlation between left ventricular ejection fraction and %predicted peak \(\text{VO}_2\).
these patients, along with other well-established measures such as EF, wall stiffness, or rates of change of pressure, which take no account of regional heterogeneity. Furthermore, our results might explain the limited value of positive inotropic agents (21), whose effects may be modified in patients with heterogeneous LV disease. Peak oxygen uptake, VE/VO2 slope, and QRS duration have all been used to predict survival and stratify risk in patients with chronic heart failure (22,23). Future studies may determine whether resting t-IVT can be used in the same way.

Study limitations. This was a retrospective study of patients with a clinical diagnosis of heart failure referred to a tertiary referral center. The time-related variables chosen to predict maximum exercise capacity in patients with DCM were pre-specified from previous studies using dobutamine stress (6), and therefore the present results need not be regarded as a learning set. The time interval of up to two months between exercise testing and echocardiography in a minority of patients may well have introduced additional variability into estimates of t-IVT, but 50% of the patient population underwent both tests within a two-day period, and in all cases, electrocardiographic analysis was synchronous with exercise testing. However, to elucidate the exact relationship between LBBB and exercise capacity will require verification in a prospective investigation that conducts both studies on the same day. In common with previous studies, patients with atrial fibrillation were not included, so its importance in limiting exercise tolerance was not determined. Although there were no significant differences in therapeutic regimes between patient groups, the number of patients receiving beta-blockers appeared relatively low, because determination of exercise tolerance usually preceded their up-titration. In fact, the presence or absence of beta-blockade proved to have no significant effect on resting t-IVT. A subjective component in exercise testing in patients with heart failure is well recognized, but to qualify for inclusion, the respiratory exchange ratio at peak exercise (VECO2/VO2) was >1.05. Finally, we did not investigate extra-cardiac abnormalities, such as those in skeletal muscle blood flow, endothelial and neurohormonal or lung function, so any additional independent contribution they might have remains uncertain.

CONCLUSIONS

Limitation of exercise tolerance remains a major component of the clinical syndrome of heart failure and causes considerable deterioration in quality of life. The possibility of successful treatment in individual patients is likely to be increased by understanding its physiologic basis. Uniform depression of ventricular systolic or diastolic function is not the main limiting factor, explaining the lack of success of treatment modalities designed on this basis. However, our results suggest that the left ventricle, as well as the peripheral circulation or neurohormonal axis, remains an appropriate therapeutic target, provided that asynchrony resulting from LBBB or CAD is addressed. Despite the technical problems, future studies should investigate interrelationships between t-IVT and peak VO2 at the time of peak exercise. They should also investigate how other forms of interventricular conduction delay or biventricular pacing impact on t-IVT and exercise capacity. Altering asynchrony by manipulation of t-IVT, whether by medical, surgical, or electrophysiologic methods, may lead to a useful increase in exercise tolerance in these patients.

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REFERENCES