Left Atrial Function Preserves Pulmonary Circulatory Pressure During Pacing-Tachycardia and Contributes to Exercise Capacity in Patients With Idiopathic Dilated Cardiomyopathy in Sinus Rhythm, Whose Exercise is Limited by Dyspnea

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The aim of this study was to determine whether left atrial (LA) function contributes to pulmonary circulatory pressure during pacing-tachycardia and exercise capacity in patients with idiopathic dilated cardiomyopathy (DCM). Thirty-two patients with DCM and in sinus rhythm had limited exercise capacity because of dyspnea. The correlation between peak oxygen consumption (V\textsubscript{\textcircled{O}}\textsubscript{2}) and the variables of cardiac function by cardiac catheterization and 2-dimensional, Doppler echocardiography, and plasma neurohumoral factor levels was tested, as was the correlation between non-invasive LA functional parameters and pulmonary circulatory pressure during pacing-tachycardia. A significant correlation was observed between V\textsubscript{\textcircled{O}}\textsubscript{2} and LA dimension (r=–0.45, p<0.01), the peak velocities of LA appendage empty flow during atrial systole (r=0.63, p<0.0001) and the pulmonary venous forward flow in early ventricular systole (PVS1; r=0.74, p<0.0001), as well as plasma brain natriuretic peptide (BNP) concentrations. The predictable equation to V\textsubscript{\textcircled{O}}\textsubscript{2} with the multiple regression analysis was: V\textsubscript{\textcircled{O}}\textsubscript{2} = –0.01 BNP + 0.21 PVS1 + 15.4 (r=0.81, p<0.0001). Furthermore, LA functional variables derived from pulmonary venous flow, especially PVS1, but not plasma BNP concentration, were useful for predicting the degree of the increase in pulmonary circulatory pressure during pacing-tachycardia. Therefore, it is suggested that LA function contributes to exercise capacity through its influence on pulmonary hemodynamic reserve in patients with DCM in sinus rhythm whose exercise is limited by dyspnea. (Circ J 2002; 66: 937–942)

**Key Words:** Exercise capacity; Idiopathic dilated cardiomyopathy; Left atrium; Pulmonary venous flow

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hronic left heart failure is characterized by left ventricular (LV) dysfunction and impaired exercise capacity. The degree of the latter is classified by the peak oxygen consumption (V\textsubscript{\textcircled{O}}\textsubscript{2}) measured in an exercise tolerance test. Neither the common hemodynamic parameters nor those of LV systolic function at rest, however, allow precise prediction of the exercise capacity of patients with chronic left heart failure.\cite{1, 2} Pulmonary hypertension,\cite{3} residual peripheral dysfunction, such as vasodilatory dysfunction or intrinsic muscle dysfunction,\cite{4–7} have been reported to limit the exercise capacity of patients with chronic left heart failure. Recently, it has been shown that LV diastolic function contributes to exercise capacity;\cite{8–11} impaired LV diastolic function leads to an elevation of the LV end-diastolic pressure during tachycardia, resulting in pulmonary circulatory congestion, which is in turn closely related to exercise-induced dyspnea.\cite{12}

The significance of left atrial (LA) function in relation to exercise capacity has been reported in patients with recent myocardial infarction\cite{13} and in those with hypertrophic cardiomyopathy.\cite{14} It has been reported that LA dysfunction is present in patients with LV diastolic dysfunction\cite{15} or idiopathic dilated cardiomyopathy (DCM)\cite{16, 17} and the relation between LA systolic function and exercise capacity has been demonstrated in patients with DCM. However, it was not reported which function of the LA, active relaxation, conduit, booster pump or reservoir, relates to exercise capacity in patients with DCM. The aim of this study was to determine whether LA diastolic function contributes to exercise capacity and to assess the importance of LA function in preserving pulmonary circulatory pressure during tachycardia in patients with DCM.

Methods

**Subjects**

We studied 32 patients with chronically stable heart failure and DCM in sinus rhythm who had (1) dyspnea or fatigue on exercise, (2) a dilated LV with an LV end-diastolic volume index (LVEDVI) of >90 ml/m\textsuperscript{2} and mild or no mitral regurgitation on diagnostic left ventriculography, (3) LV ejection fraction <50 % on echocardiography, and (4)
no evident lung disease. There were 23 men and 9 women aged 54.0±10.7 years (range, 23–73 years), and of them, 24 were in New York Heart Association classification II, and 8 were in classification III. In all patients, the exercise tolerance test, described later, was limited by dyspnea.

Background medications, including angiotensin-converting enzyme inhibitor (enalapril, 5–7.5 mg/day), diuretic (furosemide, 20–40 mg/day) and digitalis (digoxin, 0.125–0.25 mg/day), had been withheld for at least 3 months before the study. No other cardiovascular medications, other than antiarrhythmic agents and nitrates, were given. Treatment with all medications was discontinued for at least 12 h before the study. The study protocol was approved by the Committee on Human Subjects and Research of the National Cardiovascular Center, and all patients gave their written informed consent to participate in the study.

Study Protocol and Measurements

We tested the correlation between VO2 and the variables of cardiac function by cardiac catheterization and 2-dimensional (D) Doppler echocardiography, and plasma neurohumoral factor concentrations. Furthermore, we tested the correlation between LA functional parameters by 2-D Doppler echocardiography and pulmonary circulatory pressure during pacing-tachycardia.

All patients underwent transthoracic and transesophageal Doppler echocardiography and blood sampling followed by combined diagnostic right and left heart catheterization on the same day. The interval between these procedures and the exercise tolerance test was less than 1 week (3.2±0.8 days).

The LA dimension (mm), the LV end-diastolic dimension (LVDd; mm), the peak velocities of the E and A waves in the transmural flow, the isovolumic relaxation time (IRT; ms) and the deceleration time of the early dias-
tolic filling (DcT; ms) were measured by transthoracic Doppler echocardiography using a commercially available Toshiba SSH 160A (Toshiba Corp, Tokyo, Japan) ultrasound diagnostic system provided with a 5-MHz biplane probe.19,20 and the E/A ratio was calculated. The peak velocities of the E and A waves during atrial systole (PEA, peak PV back flow in ventricular end-diastole; PVC, peak PV back flow in early ventricular systole) were obtained by transesophageal Doppler echocardiography using a commercially available Aloka SSD 870 (Aloka Co, Ltd, Tokyo, Japan) ultrasound diagnostic system provided with a 5.5-MHz biplane probe.

Blood samples were drawn by venipuncture after allowing the patients to rest for at least 30 min in the supine position; samples were immediately placed on ice and centrifuged at 3,000 rpm for 10 min. Plasma concentrations of norepinephrine (NE; pg/ml) was measured by high-performance liquid chromatography using electrochemical detection, and that of brain natriuretic peptide (BNP; pg/ml) with Shiono BNP radioimmunoassay kits (Shionogi Co, Osaka, Japan).21

The mean blood pressure was measured at the descending thoracic aorta; then, the LV end-diastolic pressure (LVEDP; mmHg) was measured and the LV ejection fraction (LVEF; %) and the LVEDVI (ml/m²) were calculated from a left ventriculogram using a 5F pig-tail catheter.22

Hemodynamic variables such as the mean pulmonary capillary wedge pressure (PCWP; mmHg), the mean pulmonary artery pressure (PAP; mmHg), the mean right atrial pressure (RAP; mmHg) and the cardiac index (CI; L·min⁻¹·m⁻²) were measured using a 7F balloon-tipped thermodilution catheter. We next performed pacing-tachycardia at the right ventricular apex for 15 min at 140 beats/min. The hemodynamic variables described before were measured just before terminating the pacing and were denoted as ‘p’. The degree of change in the variables from the baseline was denoted as Δ.

The exercise capacity of each patient was examined by symptom-limited exercise testing on an upright bicycle ergometer (Aerobike 232C; Combi, Tokyo, Japan). Exercise workload was increased according to a ramp incremental protocol of 15 W/min after 1-min warm-up at 0 W. Exercise was continued until the patients complained of symptomatic limits of dyspnea (ie, 19–20 on the Borg scale)23 During the exercise tolerance test, heart rate was

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Table 1  Correlation Between VO2 Patients Characteristics and Hemodynamic, Doppler-Echocardiographic and Neurohumoral Variables

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Mean±SD</th>
<th>R</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.0±10.7</td>
<td>-0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.7±0.2</td>
<td>0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Heat rate (beats/min)</td>
<td>78.2±12.4</td>
<td>0.06</td>
<td>NS</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>84.3±6.9</td>
<td>0.23</td>
<td>NS</td>
</tr>
<tr>
<td>LV functional variables</td>
<td></td>
<td></td>
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<tr>
<td>LVEF (%)</td>
<td>38.0±10.9</td>
<td>0.29</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDVI (ml/m²)</td>
<td>111.8±22.5</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>10.0±2.6</td>
<td>-0.24</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDVI (mm)</td>
<td>61.0±8.5</td>
<td>-0.20</td>
<td>NS</td>
</tr>
<tr>
<td>Transmitial flow parameters</td>
<td></td>
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<tr>
<td>E (cm/s)</td>
<td>56.7±22.2</td>
<td>-0.10</td>
<td>NS</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>42.9±24.1</td>
<td>-0.08</td>
<td>NS</td>
</tr>
<tr>
<td>IRT (ms)</td>
<td>163.0±42.9</td>
<td>0.15</td>
<td>NS</td>
</tr>
<tr>
<td>DcT (ms)</td>
<td>90.2±16.2</td>
<td>-0.39</td>
<td>&lt;0.05</td>
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<tr>
<td>Atrial functional variables</td>
<td></td>
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<tr>
<td>LAD (mm)</td>
<td>37.5±6.5</td>
<td>-0.45</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LAAC (cm/s)</td>
<td>49.6±20.7</td>
<td>0.63</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>PVSI (cm/s)</td>
<td>31.8±12.8</td>
<td>0.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVDI (cm/s)</td>
<td>44.3±11.4</td>
<td>0.33</td>
<td>NS</td>
</tr>
<tr>
<td>PVC (n=16) (cm/s)</td>
<td>7.2±6.1</td>
<td>0.10</td>
<td>NS</td>
</tr>
<tr>
<td>PVA (cm/s)</td>
<td>19.4±3.4</td>
<td>0.29</td>
<td>NS</td>
</tr>
<tr>
<td>Hemodynamic parameters</td>
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<tr>
<td>PCWP (mmHg)</td>
<td>8.2±8</td>
<td>-0.44</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>15.2±7.1</td>
<td>-0.36</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>3.1±1.5</td>
<td>0.08</td>
<td>NS</td>
</tr>
<tr>
<td>CI (L·min⁻¹·m⁻²)</td>
<td>3.5±0.7</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Neurohumoral factors</td>
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</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>112.3±121</td>
<td>-0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NE (pg/ml)</td>
<td>464.3±294.3</td>
<td>0.09</td>
<td>NS</td>
</tr>
</tbody>
</table>

BNP, brain natriuretic peptide; SBP, systolic blood pressure; CI, cardiac index; DcT, deceleration time of the early diastolic filling; IRT, isovolumic relaxation time; LAAF, peak left atrial appendage empty flow velocity during atrial systole; LAD, left atrial dimension; LVEDP, left ventricular end-diastolic pressure; LVEDVI, left ventricular end-diastolic volume index; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NE, norepinephrine, PAP, the mean pulmonary artery pressure; PCWP, the mean pulmonary capillary wedge pressure; PVC, peak PV back flow in ventricular end-diastole; PVDC, peak PV back flow on closure of mitral valve; PVD, peak PV forward flow in ventricular diastole; PVPSI, peak PV forward flow in early ventricular systole; PV, peak PV forward flow in mid to late ventricular systole; RAP, mean right atrial pressure.
continuously monitored, and blood pressure was measured every minute. Expired gases were measured on a breath-by-breath basis during the test using a respirometer (Aero Monitor AE-280; Minato Medical Science, Osaka, Japan) connected to a personal computer with analyzing software.

Respiratory gases were analyzed as the value of averaged data every 15 s. In all patients the gas exchange anaerobic threshold was reached (the point at which CO₂ production increases disproportionately in relation to O₂ consumption). Peak oxygen consumption (\( V_{\text{O2}} \); ml·kg⁻¹·min⁻¹) was defined as the value of averaged data in the final 15 s of exercise.

Statistical Analyses

All results were expressed as mean values ± standard deviation (SD). Linear regression analysis was used to check the correlation between variables. Similar regression analysis was performed on the results of numerical modeling to correlate the different parameters shown in Table 1 to \( V_{\text{O2}} \). Stepwise and multivariate regression analyses were used to generate multivariate equations to predict \( V_{\text{O2}} \). To evaluate the agreement between the multivariate equations and the measured \( V_{\text{O2}} \), data were processed by the Bland and Altman methods. The 95% limits of agreement are expressed as an absolute value. The sensitivity, specificity, and positive and negative predictive value were calculated using standard formula. A probability value of less than 0.05 was regarded as statistically significant.

Results

Correlation Between \( V_{\text{O2}} \) and Variables at Rest

Among the 26 variables shown in Table 1, PVS1 (Fig 1A), LAAF (Fig 1B) and plasma BNP concentration closely correlated with \( V_{\text{O2}} \), whereas IRT, LAD (Fig 1C), PCWP and PAP were roughly correlated. However, neither patients’ characteristics nor the LV functional variables shown in Table 1 correlated with the atrial functional variables and \( V_{\text{O2}} \), except for the rough correlation between PVD and LVEDP \((r=0.42, p<0.05)\), between PVS2 and LVEDP \((r=0.45, p<0.05)\), between LAHF and LVDd \((r=0.45, p<0.05)\), and between IRT and \( V_{\text{O2}} \) (Table 1). Furthermore, transmitral flow parameters also did not correlate with the atrial functional variables, except for the close correlation between PVD and peak E velocity \((r=0.52, p<0.005)\), and the E/A ratio \((r=0.59, p<0.0005)\).

Estimation of \( V_{\text{O2}} \)

Among the 7 variables that correlated with \( V_{\text{O2}} \) (Table 1), forward stepwise regression analysis led to a multilinear equation that included BNP and PVS1 for predicting \( V_{\text{O2}} \). The predictable equation to \( V_{\text{O2}} \) was

\[
V_{\text{O2}} = -0.01 \text{BNP} + 0.21 \text{PVS1} + 15.4 \quad (r=0.81, p<0.0001)
\]

Equation 1.

There was a good linear relationship between the measured \( V_{\text{O2}} \) and estimated \( V_{\text{O2}} \) by Equation 1 \((y=1.08x-2.25, r=0.81, p<0.0001; \text{Fig 2A})\). The sensitivity, specificity, and positive and negative predictive values were calculated using standard formula. A probability value of less than 0.05 was regarded as statistically significant.
mate \( \dot{V}O_2 \) was
\[
\dot{V}O_2 = -0.02 \text{BNP} - 0.30 \text{LAD} + 34.06 \quad (r=0.71, \ p<0.0001)
\] Equation 2.

Therefore, in the present study subjects we could estimate \( \dot{V}O_2 \) with PV flow derived LA functional variables, or from the results of routine 2-D echocardiography, together with serum BNP concentration.

**Exercise Capacity and Pulmonary Circulatory Pressure During Pacing-Tachycardia (Table 2, Fig 3)**

We tested the correlation between \( \dot{V}O_2 \) and hemodynamic variables during pacing-tachycardia. \( \dot{V}O_2 \) closely correlated with the pPCWP, pPAP, \( \Delta \text{PCWP} \) and \( \Delta \text{PAP} \), although it did not correlate with the pCI or \( \Delta \text{CI} \). Among the 6 catheter-derived hemodynamic variables that correlated with \( \dot{V}O_2 \) (Tables 1,3), forward stepwise regression analysis led to a multilinear equation that included pPCWP and \( \Delta \text{PCWP} \) for predicting \( \dot{V}O_2 \):
\[
\dot{V}O_2 = -0.60 \text{pPCWP} - 0.58 \Delta \text{PCWP} + 35.06 \quad (r=0.77, \ p<0.0001)
\] Equation 3.

Therefore, \( \dot{V}O_2 \) was related to pulmonary hemodynamics during pacing-tachycardia, especially with pPCWP and \( \Delta \text{PCWP} \).

**Correlation Between Parameters of Atrial Function, Plasma BNP Concentration and the Hemodynamic Parameters During Pacing-tachycardia (Table 2)**

The pPCWP closely correlated with plasma BNP concentration, PVS1 (Fig 3A), PVS2 and LAAF, and roughly with LA dimension. The pPAP correlated with plasma BNP levels and LAAF and PVS1 (Fig 3B), and PVS2. On the other hands, the \( \Delta \text{PCWP} \) closely correlated with PVS1 (Fig 3A), and roughly with LAAF, but not with plasma BNP levels. The \( \Delta \text{PAP} \) closely correlated with PVS1 (Fig 3B) and LAAF, but not with plasma BNP concentration. The pCI and \( \Delta \text{CI} \), however, did not correlate with the atrial functional parameters or with plasma BNP concentration. In addition, no hemodynamic parameters during pacing-tachycardia correlated with LV functional

<table>
<thead>
<tr>
<th>Parameter</th>
<th>pPCWP</th>
<th>pPAP</th>
<th>pCI</th>
<th>( \Delta \text{PCWP} )</th>
<th>( \Delta \text{PAP} )</th>
<th>( \Delta \text{CI} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \dot{V}O_2 )</td>
<td>0.65</td>
<td>-0.57</td>
<td>NS</td>
<td>-0.54</td>
<td>-0.50</td>
<td>NS</td>
</tr>
<tr>
<td>BNP</td>
<td>0.81</td>
<td>0.78</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LAD</td>
<td>-0.45</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PVS1</td>
<td>-0.62</td>
<td>-0.47</td>
<td>NS</td>
<td>-0.67</td>
<td>-0.60</td>
<td>NS</td>
</tr>
<tr>
<td>PVS2</td>
<td>-0.52</td>
<td>-0.46</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PVD</td>
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<td>NS</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PVC</td>
<td>NS</td>
<td>NS</td>
<td>-0.48</td>
<td>NS</td>
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</tr>
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<td>PVA</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.50</td>
</tr>
<tr>
<td>LAAF</td>
<td>-0.70</td>
<td>-0.52</td>
<td>0.38</td>
<td>-0.42</td>
<td>-0.46</td>
<td>NS</td>
</tr>
</tbody>
</table>

BNP, brain natriuretic peptide (pg/ml); CI, cardiac index (L·min\(^{-1}\)·m\(^{-2}\)); LAAF, peak left atrial appendage empty flow velocity during atrial systole (cm/s); LAD, left atrial dimension (mm); PAP, the mean pulmonary artery pressure (mmHg); PCWP, the mean pulmonary capillary wedge pressure (mmHg); \( \dot{V}O_2 \), peak oxygen consumption (ml·kg\(^{-1}\)·min\(^{-1}\)); PVA, peak PV back flow in ventricular end-diastole (cm/s); PVC, peak PV back flow on closure of mitral valve (cm/s); PVD, peak PV forward flow in ventricular diastole (cm/s); PVS1, peak PV forward flow in early ventricular systole (cm/s); PVS2, peak PV forward flow in mid to late ventricular systole (cm/s); ‘p’ indicates the value during pacing-tachycardia, and ‘\( \Delta \)’ indicates the value during pacing minus that at baseline. Values are correlation coefficients with p values in parentheses [ ].

Fig 3. Correlation between peak PV forward flow in early ventricular systole (PVS1) and pulmonary circulatory pressure during pacing-tachycardia. PAP, mean pulmonary artery pressure; PCWP, mean pulmonary capillary wedge pressure. The ‘p’ (˔) indicates the value during pacing-tachycardia, and the ‘\( \Delta \)’ (˓) indicates the value during pacing minus baseline.
parameters or transmitral flow parameters including IRT, an LV diastolic functional parameter among the 7 parameters that correlated with VO2.

Discussion

Contribution of LA Function to Exercise Capacity

We demonstrated that LA function correlated with exercise capacity in patients with DCM in sinus rhythm. Jikuhara et al demonstrated in patients with recent myocardial infarction that LA fractional shortening at rest reflected LV diastolic filling during exercise and therefore predicted exercise capacity. However, because the bicycle exercise test in their subjects was limited by exercising muscle fatigue, not by dyspnea, it was not elucidated whether LA function contributes to exercise-induced dyspnea. Furthermore, because LA fractional shortening represents a global LA function, it was not clear which LA systolic or diastolic dysfunction was more important in limiting exercise capacity. Tripodi et al demonstrated that LA size and systolic function in patients with DCM correlated with exercise capacity, but did not evaluate the significance of LA diastolic function with regard to exercise capacity.

PV flow parameters in transesophageal Doppler echocardiography consist of 2 antegrade flows (the PVS wave during ventricular systole and the PVD wave during ventricular diastole) and 2 backward flows (the PVC wave seen at closing of the mitral valve and PVA at the same time of the A wave in transmitral flow). PVD relates to LA conduit function and PVA relates to LA booster pump function, and the PVS flow seen at the late systolic phase (PVS2) relates to LA reservoir function. The PVS flow seen at the early systolic phase (PVS1) has been attributed to a net retrograde wave secondary to a fall in atrial pressure and to represent LA active relaxation. We demonstrated in patients whose exercise was limited by dyspnea that the function of LA active relaxation evaluated by PVS1, but not the LA functions of conduit, booster pump or reservoir, closely correlated with exercise capacity (Table 1) and that VO2 was estimated with PVS1 together with plasma BNP concentration (Equation 1).

LA Diastolic Function and Pulmonary Circulatory Pressure During Pacing-Tachycardia

Impaired LA diastolic function limits the influx of blood from the pulmonary vein to the LA, resulting in pulmonary circulatory congestion. This mechanism occurs easily when the LVEDP is elevated during exercise or tachycardia, when LV filling is restricted. Consequently, impaired LA diastolic function may lead to impairment of percent fractional LA relaxation followed by an increase in PCWP during pacing-tachycardia. Actually, patients with chronic heart failure and atrial fibrillation in whom LA diastolic function is seriously impaired, have lower exercise capacity than those with sinus rhythm. In the present study, neither LV functional parameters nor transmitral flow parameters, shown in Table 1, correlated with the hemodynamic parameters during pacing-tachycardia, although IRT, one of the LV diastolic functional parameters, roughly correlated with exercise capacity. On the other hand, PVS1, but not PVS2, PVD or PVA, correlated with the degree of elevation in pulmonary circulatory pressure during pacing-tachycardia (Table 2). This result leads to the hypothesis that LA active relaxation contributes to the preservation of pulmonary hemodynamics during pacing-tachycardia, and that the PVS1 wave is a good predictor of the pulmonary circulatory reserve during pacing-tachycardia.

PVS2, a parameter of LA reservoir function, did not correlate with pulmonary hemodynamic reserve during pacing-tachycardia, in the present study, although LA reservoir function itself might correlate. The probable reason is that PVS2 is influenced by not only LA relaxation, but also by other factors such as LA elasticity and LV contractility. Also, it was not determined whether LA systolic function could relate to pulmonary hemodynamic reserve during pacing-tachycardia because LA AF not only reflects LA systolic function, but it is also influenced by other hemodynamic conditions. However, LA systolic function evaluated by LAAF roughly correlated with the pulmonary hemodynamic reserve during pacing-tachycardia because LAAF not only reflects LA systolic function, but it is also influenced by other hemodynamic conditions. Therefore, this may be that there are no parameters that can precisely detect LV diastolic function; plasma BNP concentration, E/A, DcT and IRT could not independently detect LV diastolic function.

DCM is characterized by degeneration of the myocardium from unknown causes. Because the degeneration probably spreads into the atrial myocardium as well as the ventricular tissue, the cause of impaired LA myocardium in patients with DCM could be (1) secondary LA myocardial damage, because elevated LVEDP results in mismatch of the LA afterload, and/or (2) primary LA myocardial damage. In our study, LA functional variables did not correlate with LV functional variables, except for the rough correlation between PVS1 and LVEDP, between PVS2 and LVEDP, and between LAAF and LVDd. Therefore, although we could not clarify which of the mechanisms was the main cause of impaired LA function in our patients, the latter would appear to be involved.

Clinical Significance of Predicting Exercise Capacity

An exercise test is an important evaluation of exercise capacity in patients with chronic heart failure but requires equipment, such as an upright bicycle ergometer, and expiratory gas analyses, and the evaluation of VO2 is complex. Therefore, it is clinically convenient if exercise capacity can be easily and non-invasively predicted. Equation 1 demonstrates that the measurement of PVS1 together with plasma BNP concentration can predict with a good degree of precision the level of exercise-induced dyspnea. Equation 2 shows that transthoracic echocardiography instead of transesophageal Doppler echocardiography is also useful for this purpose. Therefore, we can non-invasively evaluate the level of exercise-induced dyspnea in patients with DCM and sinus rhythm, using different parameters according to the equipment available in the institution.

Study Limitations

Because we did not assess LA function during pacing-tachycardia, it is not clear whether the pulmonary circulatory reserve during pacing-tachycardia depends on the LA functional reserve by itself, especially the LA diastolic reserve. Furthermore, because we did not demonstrate that correction of LA dysfunction enhanced VO2 in our subjects, it is not clear whether LA dysfunction directly results in impaired exercise capacity. Furthermore, although it is conceivable that LA appendage (LAA) function may be
dissociated from global LA function.\textsuperscript{31} We did not assess LAA function except for the peak velocities of LAA empty flow during atrial systole, and did not evaluate the significance of LAA function in relation to exercise capacity. Further studies are needed to clarify these points.

Because the pacing-tachycardia in our study was not physiological, and fixed at 140 beats/min despite the variety of maximum heart rates reached during physiological exercise, the degree of contribution of LA function on the mechanism of dyspnea during physiological exercise in patients with chronic heart failure is not clear. Also, whether our results can be extrapolated to patients with chronic heart failure of any etiology, or those with moderate to severe mitral regurgitation, or those whose exercise is limited by leg fatigue rather than dyspnea is not clear. Further physiological studies are needed to clarify these points.

Conclusions

The LA diastolic function, especially the function of LA active relaxation, contributes to exercise capacity by its influence on pulmonary hemodynamic reserve during pacing-tachycardia in patients with DCM in sinus rhythm whose exercise is limited by dyspnea. Further physiological studies are needed to confirm the significance of LA active relaxation in limiting exercise capacity in patients with chronic heart failure of different etiologies.

References