Original article

Improvement effect on endothelial function in patients with congestive heart failure treated with cardiac resynchronization therapy

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KEYWORDS
Heart failure; Treatment; Cardiomyopathies; Dilated; Endothelium; Cardiac output

Summary
Background and purpose: Cardiac resynchronization therapy (CRT) is a beneficial strategy to improve severe cardiac dysfunction in patients with congestive heart failure (CHF). The improvement of endothelial function in CHF patients treated with CRT is reflected in the mortality risk reduction. However the precise mechanisms of the relationship between CRT and vascular endothelial function have not been well discussed.

Methods and subjects: Twenty-two severe consecutive CHF patients associated with dilated cardiomyopathy [New York Heart Association (NYHA) class 3.3±0.5, left ventricular ejection fraction (LVEF) 24.4±5.9%] were included in this study. We evaluated endothelial function, measured by reactive hyperemia peripheral arterial tonometry (RH-PAT), between optimal medical therapy alone group (medical therapy group: n=10) and CRT group (n=12) at the study enrolment and 12 weeks later. Furthermore we analyzed the association between the RH-PAT and cardiac function.

Essential results: Both therapies significantly and equally improved NYHA class, LVEF, end-diastolic left ventricular dimension and plasma levels of brain natriuretic peptide (BNP). CRT significantly increased RH-PAT index (medical therapy group: 1.5±0.2 to 1.5±0.3, p=0.824; CRT group: 1.4±0.2 to 1.7±0.4, p=0.003) and cardiac output (medical therapy group: 3.3±1.1 to 3.5±1.0, p=0.600; CRT group: 2.7±0.6 to 4.3±1.5, p=0.001), compared to the medical therapy group. There was significant positive correlation between the change in RH-PAT index and cardiac output (r=0.600, p=0.003).

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Introduction

Impaired vascular endothelial function has been shown to be associated with an increase in mortality risk in patients with congestive heart failure (CHF) [1,2], since endothelial function was thought to play a key role in coordinating tissue perfusion and modulating arterial compliance. Cardiac resynchronization therapy (CRT) has emerged as an effective treatment for congestive heart failure in the era of optimal medical treatment [3–5]. CRT in patients with heart failure improves endothelial function, and this improvement is reflected in the mortality risk reduction [2,6].

Endothelial function in peripheral arteries is currently assessed by forearm flow mediated vasodilation [7,8]. However, the results of forearm flow mediated vasodilation could vary due to technical problems encountered during measurement. Thus, forearm flow mediated vasodilation is not standardized among institutions [9,10]. Recent studies reported that the measurement of digital hyperemic response by reactive hyperemia peripheral arterial tonometry (RH-PAT) is a noninvasive, automatic and beneficial objective clinical test for evaluating endothelial function [11,12]. In the present study, we examined endothelial function using RH-PAT in CHF patients associated with dilated cardiomyopathy to evaluate the difference in the improvement of endothelial dysfunction between patients treated with medical therapy alone and medical treatment.

Methods

Twenty-two consecutive patients with left ventricular dysfunction who were admitted with CHF associated with dilated cardiomyopathy were included in this study. The medical therapy group consisted of 10 patients who were treated with optimal medical therapy. The CRT group consisted of 12 patients who were treated with both optimal medical therapy and CRT. The inclusion criteria were: New York Heart Association (NYHA) class III or IV, left ventricular ejection fraction (LVEF) <40% at admission. Written informed consent was obtained from each patient. The protocol was approved by the hospital human research committee.

Reactive hyperemia peripheral arterial tonometry

Digital pulse amplitude was measured in the fasting state with a peripheral arterial tonometry (PAT) device placed on the tip of each index finger (Endo-PAT2000; Itamar Medical, Caesarea, Israel). The principle of PAT has been described previously [13]. Briefly, a blood pressure cuff was placed on one upper arm (study arm), while the contralateral arm served as a control (control arm). Peripheral arterial tonometry probes were placed on one finger of each hand for continuous recording of the PAT signal. After a 5 min equilibration period, the cuff was inflated to 60 mm Hg above systolic pressure or 200 mm Hg for 5 min, and then deflated to induce reactive hyperemia, whereas PAT recording was continued for 10 min.

RH-PAT data were automatically analyzed on-line in an operator-independent manner (Endo-PAT2000 software Ver: 3.0.4). Reactive hyperemia was represented by the RH-PAT index, which was calculated as the ratio of the average amplitude of PAT signal over 1 min starting 1.5 min after cuff deflation (control arm: A; occluded arm: C) divided by the average amplitude of the PAT signal for 2.5 min before cuff inflation (baseline) (control arm: B; occluded arm: D). The RH-PAT index values computed for the test arm were normalized to the control arm to compensate for potential systemic changes:

\[
\text{RH-PAT index} = \frac{(C/D)}{(A/B)}
\]

Statistical analysis

Hazard ratios, 95% confidence intervals (95% CI), and levels of statistical significance (p-value) were calculated. Values are expressed as the mean ± standard deviation (SD). A value of \( p < 0.05 \) was considered significant. All statistical analyses were carried out using SPSS, version 11.0J (SPSS Inc., Chicago, IL, USA).

To compare the baseline characteristics of the two groups, data were analyzed by Student’s t-test for unpaired data and \( \chi^2 \)-test (or Fisher’s exact test for \( n < 5 \)) for categorical data. A paired Student’s t-test was performed to analyze the effect of 12 weeks of treatment. The relationship between RH-PAT index and cardiac parameters was assessed using Pearson’s correlation coefficient.

Results

Baseline characteristics

Among the 22 CHF patients (age, 65 ± 10 years, 64% males, LVEF 24.4 ± 5.9%, NYHA class 3.3 ± 0.5) included in this study, there was no significant difference in sex, age, body mass index, risk factors associated with the endothelial dysfunction and medical therapy between the two groups (Table 1). The baseline blood pressure, NYHA class, plasma levels of brain natriuretic peptide (BNP), cardiac echo parameters and RH-PAT index in the two groups were not significantly different (Table 2).
### Comparison of cardiac echo parameters

The change in cardiac evaluations between the two groups is shown in Table 2. Both therapies significantly and equally improved NYHA class, plasma BNP levels, LVEF, and end-diastolic left ventricular dimension (LVDd). CRT significantly increased cardiac output (CO) but not in the medical therapy group (Table 2). The increment of CO in the CRT group was significantly higher than that in the medical therapy group (CRT group; +1.6 ± 1.3 L/min vs. medical therapy group; +0.2 ± 1.3 L/min, \( p = 0.019 \)).

### Correlation between endothelial function and cardiac parameters

CRT significantly increased the RH-PAT index but not medical therapy alone (Table 2). The increment of RH-PAT index in the CRT group was significantly higher than that in the medical therapy group (CRT group; +0.4 ± 0.3 vs. medical therapy group; 0.0 ± 0.3, \( p = 0.007 \)). The change in the RH-PAT index significantly and positively correlated with the change in CO (\( r = 0.600, p = 0.003 \)), but not with the change in blood pressure, NYHA class, BNP levels, LVEF, and LVDd.

### Discussion

The improvement in endothelial function was observed only in the CRT group although plasma BNP levels, LVEF, LVDd, and NYHA class were similarly ameliorated in both medical therapy and CRT groups. In the present study, for the first time, we found that CRT has a great advantage for the improvement in endothelial dysfunction through the improvement in CO compared to medical therapy alone in patients with CHF associated with dilated cardiomyopathy.

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**Table 1** Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Medical therapy group (n = 10)</th>
<th>CRT group (n = 12)</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>64.8 ± 9.6</td>
<td>66.2 ± 11.0</td>
<td>0.595</td>
</tr>
<tr>
<td><strong>Male (n)</strong></td>
<td>7 (70.0%)</td>
<td>6 (50.0%)</td>
<td>0.590</td>
</tr>
<tr>
<td><strong>Body height (cm)</strong></td>
<td>160 ± 10</td>
<td>158 ± 10</td>
<td>0.669</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>23.4 ± 3.4</td>
<td>22.1 ± 2.9</td>
<td>0.350</td>
</tr>
<tr>
<td><strong>Risk factor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>4 (40%)</td>
<td>4 (33%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>3 (30%)</td>
<td>2 (17%)</td>
<td>0.624</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>4 (40%)</td>
<td>5 (42%)</td>
<td>0.691</td>
</tr>
<tr>
<td><strong>CKD</strong></td>
<td>5 (50%)</td>
<td>4 (33%)</td>
<td>0.666</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>5 (50%)</td>
<td>5 (42%)</td>
<td>0.696</td>
</tr>
<tr>
<td><strong>Medical therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ACE-I/ARB</strong></td>
<td>9 (90%)</td>
<td>12 (100%)</td>
<td>0.455</td>
</tr>
<tr>
<td><strong>Beta-blocker</strong></td>
<td>10 (100%)</td>
<td>12 (100%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>CCB</strong></td>
<td>1 (10%)</td>
<td>3 (25%)</td>
<td>0.594</td>
</tr>
<tr>
<td><strong>Digitalis</strong></td>
<td>1 (10%)</td>
<td>0 (0%)</td>
<td>0.455</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>9 (90%)</td>
<td>11 (92%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td>5 (50%)</td>
<td>8 (67%)</td>
<td>0.378</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, Ca-channel blocker; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy.

**Table 2** Cardiac parameters and endothelial function.

<table>
<thead>
<tr>
<th></th>
<th>Medical therapy group (n = 10)</th>
<th>CRT group (n = 12)</th>
<th>All (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP (mm Hg)</strong></td>
<td>106 ± 25</td>
<td>107 ± 21</td>
<td>109 ± 21</td>
</tr>
<tr>
<td><strong>DBP (mm Hg)</strong></td>
<td>66 ± 15</td>
<td>66 ± 11</td>
<td>67 ± 10</td>
</tr>
<tr>
<td><strong>NYHA</strong></td>
<td>3.4 ± 0.5</td>
<td>3.3 ± 0.5</td>
<td>3.3 ± 0.5</td>
</tr>
<tr>
<td><strong>BNP (pg/mL)</strong></td>
<td>943 ± 551</td>
<td>445 ± 467</td>
<td>739 ± 542</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>25.7 ± 6.9</td>
<td>23.2 ± 5.0</td>
<td>24.4 ± 5.9</td>
</tr>
<tr>
<td><strong>LVDd (mm)</strong></td>
<td>62.5 ± 8.1</td>
<td>65.7 ± 5.6</td>
<td>64.2 ± 6.9</td>
</tr>
<tr>
<td><strong>CO (L/min)</strong></td>
<td>3.3 ± 1.1</td>
<td>2.7 ± 0.6</td>
<td>3.0 ± 0.9</td>
</tr>
<tr>
<td><strong>RH-PAT</strong></td>
<td>1.5 ± 0.2</td>
<td>1.4 ± 0.2</td>
<td>1.4 ± 0.2</td>
</tr>
</tbody>
</table>

BNP, brain natriuretic polypeptide; CO, cardiac output; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LVDd, left ventricular diastolic dimension; NYHA, New York Heart Association; RH-PAT, reactive hyperemia peripheral arterial tonometry; SBP, systolic blood pressure.

\( p < 0.05 \)

\( p < 0.01 \), compared with the respective baseline value.
A previous randomized trial (MIRACLE) demonstrated that CRT showed a significant improvement in the heart failure clinical status compared to medical therapy alone [4]. Also, CRT decreased the risk of heart failure events in relatively asymptomatic patients with a low ejection fraction [5]. Katz et al. have reported that endothelial dysfunction in CHF is associated with an increased mortality risk in subjects with either ischemic or non-ischemic CHF [1]. CRT for patients with heart failure improves endothelial function [6] and this is reflected in the mortality risk reduction [2]. However, the mechanism of improvement of endothelial dysfunction by CRT has not been clarified. Our study might explain one of its mechanisms.

Regarding the improvement effect of endothelial dysfunction in CHF patients, several mechanisms have been proposed. Decreased nitric oxide production associated with endothelial nitric oxide synthase expression and increased nitric oxide degradation by oxidative stress have been proposed as the mechanisms of endothelial dysfunction [14–17]. A decrease in CO decreases shear stress, thereby decreasing the vascular nitric oxide bioavailability [18]. In the present study, the CO evaluated by echocardiography significantly increased in the CRT group, but not in the group on medical therapy alone. Indeed, there was a significant positive correlation between the RH-PAT and CO. These improvements in CO might increase nitric oxide production through an increase in shear stress and thus result in improved endothelial function.

It is already known that many conventional medications such as angiotensin-converting enzyme inhibitors ameliorate vascular endothelial dysfunction. However, several studies have reported that optimal medical therapy including angiotensin-converting enzyme inhibitors did not improve endothelial dysfunction in heart failure patients [19, 20]. These findings explain the absence of improvement in endothelial function in the medical therapy group in the present study.

Conclusion

Cardiac resynchronization therapy prominently improves endothelial function through the improvement in CO in patients with severe CHF associated with dilated cardiomyopathy. It could be an effective clinical strategy to reduce the risk of mortality in severe heart failure status.

Disclosures

None.

Acknowledgment

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References


