Effect of carvedilol on coronary flow reserve in patients with hypertensive left-ventricular hypertrophy

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Abstract

Objective. Patients with hypertensive left-ventricular hypertrophy (LVH) have lower coronary flow reserve (CFR). Whether carvedilol can improve CFR of patients with hypertensive LVH is unknown. We aimed to investigate the effects of carvedilol on CFR in patients with hypertensive LVH. Methods. Sixty-three patients were randomly divided into two groups for treatment with carvedilol or metoprolol. The peak diastolic coronary flow velocity in the left anterior descending coronary artery at rest and at maximal vasodilation with dipyridamole infusion was recorded by transesophageal echocardiography (TEE), then CFR was calculated at baseline and at the end of 6 months of therapy. Left-ventricular mass index (LVMI) was calculated by 2-D echocardiography. Endothelium-dependent and -independent reactivity of the brachial artery was measured. Levels of plasma endothelin-1 (ET-1), nitric oxide (NO) and other metabolites were monitored and analyzed before and after 6-month therapy. Results. Both blood pressure and heart rate decreased significantly in the two treatment groups after therapy ($p<0.05$). With carvedilol treatment, LVMI was lower ($p<0.05$), endothelium function of the brachial artery was higher ($p<0.05$), and peak diastolic coronary flow velocity at rest and at maximal vasodilation after dipyridamole infusion was significantly higher ($p<0.05$) than with metoprolol treatment, which led to a significantly higher CFR ($p<0.05$). Changes in CFR and LVMI with carvedilol treatment were inversely correlated ($R^2=0.474$, $p=0.036$). With carvedilol treatment, plasma level of ET-1 was lower, but that of NO was significantly higher than with metoprolol treatment (both $p<0.05$). Conclusions. The CFR of patients with hypertensive LVH but not coronary artery disease could increase with 6-month carvedilol therapy.

Key Words: Endothelin-1, endothelium-dependent and -independent vasodilation, left-ventricular mass index, transesophageal echocardiography

Introduction

Most patients with hypertensive left-ventricular hypertrophy (LVH) show symptoms of angina, which is difficult to distinguish from atherosclerotic heart disease. The myocardium in hypertensive LVH may have undergone ischemia.

Many studies have reported lower coronary flow reserve (CFR) in patients with hypertensive LVH than in patients without hypertensive LVH (1–3).

Carvedilol, a third-generation beta-blocker, is a multiple-acting compound with non-selective beta-adrenoceptor and selective alpha-1-adrenoceptor blocking activity in the calcium channel. Carvedilol has many other properties distinct from second-generation beta-adrenoreceptor blockers, such as anti-oxidation (4,5), anti-proliferation of smooth muscle cells (6,7), alleviation of endothelium dysfunction (8) and radical free-oxygen scavenging and iron chelating (9). In addition, carvedilol has more pronounced antioxidative effects and inhibitory effects than the second-generation beta-adrenoreceptor blockers on the sympathetic nervous system. It has related blood viscosity in patients after acute myocardial infarction (10,11). The recently published large-scale carvedilol or metoprolol European trial (COMET) demonstrated that carvedilol reduces total mortality to a greater extent than does metoprolol (12). Furthermore, carvedilol could improve the CFR of
Carvedilol could increase CFR of patients with hypertensive LVH

Materials and methods

Study population

We studied 63 patients with hypertensive LVH (35 men; mean age 61.2 ± 12.6 years) who were admitted to the Department of Cardiovascular Medicine, Shandong University Qilu Hospital, China.

Inclusion and exclusion criteria

The patients satisfied the following inclusion criteria: (i) systolic blood pressure (BP) 140–160 mmHg or diastolic BP 90–100 mmHg; (ii) hypertensive LVH (Devereux criteria: left-ventricular mass index (LVMI) ≥ 134 g/m² for men and ≥ 110 g/m² for women) (14); (iii) subjective or objective signs of ischemia during exercise stress (19 patients with symptoms of angina and 44 with descended ST segment); and (iv) no evidence of coronary artery disease after coronary angiography. Patients with secondary hypertension, diabetes mellitus, or esophageal, liver or kidney disease were excluded. Patients with a heart rate (HR) < 50 beats/min, significant brady-arrhythmia, atrio-ventricular block, presence of stenotic valvular heart disease, hypertrophic obstructive cardiomyopathy, and active myocarditis were also excluded.

We randomly assigned the 63 patients into two groups for treatment with carvedilol or metoprolol. After a 2-week drug washout, patients received oral doses twice daily of 10 mg carvedilol tartrate (Astra Zeneca, China) or 50 mg metoprolol (Qilu Pharmaceutical Co, Jinan ShanDong P.R China). Patients with side-effects were dropped from the study. At the end of 6-month therapy, 28 patients remained in the carvedilol group and 29 in the metoprolol group. The research was a single-centre, randomized, open, endpoint-blinded, parallel-group study. All recruited patients received endpoint-blinded treatment.

Each subject gave their written informed consent to be in the study, which was approved by the Ethics Committee of Shandong University Qilu Hospital.

Patients visited physicians every 2 weeks for BP and HR monitoring during the study. Before and after treatment with carvedilol or metoprolol, patients underwent TEE, assessment of endothelium function of the brachial artery and transthoracic echocardiography. Blood samples were drawn for monitoring levels of endothelin-1 (ET-1), nitric oxide (NO), fasting glucose (Gs), total cholesterol (TC), total triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). In addition, the plasma concentration of ET-1 was determined by use of a radioimmunoassay kit (Dongya Immuno-technology Institute, Beijing, China). Plasma level of NO was tested by the enzymic method (Jingmei Biotech Co. Ltd. Shenzhen, China).

Echocardiography

Echocardiography involved use of a SONOS-5500 (Philips Medical Systems. The Netherlands) equipped for transthoracic examination (2–4 MHz), TEE (5–7 MHz) and peripheral vessel examination (7–12 MHz). Imaging depth was adjusted for each patient to obtain the echocardiographic image that included the whole left ventricle. Harmonic imaging was used with optimal adjustment of gain to ensure the best-quality images and adequate delineation of endocardial borders. Images were stored on magneto-optical disks for off-line analysis.

2-D Echocardiography

2-D echocardiography was used to measure the thickness of the interventricular septum (IVS), posterior left ventricular wall (LVPW) and left ventricular end-diastolic diameter (LVEDD) as described (14). LVMI was calculated as follows (15):

\[
LVM = 1.04[(IVS + LVEDD + LVPW) - (LVEDD)] - 13.6 \text{ g;}
\]

\[
LVMI = LVM / \text{body surface area (BSA)};
\]

\[
\text{BSA (m}^2) = 0.061 \times \text{height (cm)} + 0.0128 \times \text{weight (kg)} - 0.1529.
\]

Transesophageal echocardiography

Each patient underwent TEE after 6-h fasting, with the throat anesthetized by use of 2% tetracaine. The coronary artery was visualized by use of a transducer just above the aortic leaflets. The ultrasound probe was placed at the aortic root to show the cut section of the aortic valve after turning the probe wafer to 30°. At the same time, the probe was turned slowly to show the Y-shaped bifurcation of the left coronary artery, the circumflex branch and the left anterior descending branch. The blood velocity of the initial part of left anterior descending coronary artery was measured by pulsed-wave Doppler at rest and at hyperemia after dipyridamole injection (0.56 mg/kg intravenously for 5 min). Peak diastolic velocity (PDV), and mean diastolic velocity were evaluated by tracing the contour of the Doppler pattern in five to seven consecutive cardiac cycles. CFR was calculated as follows: 

\[
\text{CFR} = PDVh / PDVa,
\]

where PDVh is mean hyperemic diastole coronary blood flow velocity after dipyridamole injection and PDVa...
All procedures were well tolerated, apart from the common side-effects found with beta-receptor blockers. In the carvedilol group, data for four patients were dropped from analysis because of headache (1), vertigo (1) and poor compliance (2). In the metoprolol group, data for two patients were dropped from analysis because of vertigo (1) and poor compliance (1). Data for the remaining 57 patients (28 in carvedilol group and 29 in metoprolol group) were analyzed.

**Effect of carvedilol and metoprolol on BP, HR and metabolic parameters**

HR and BP decreased significantly after 6-month therapy in both metoprolol and carvedilol groups as compared with at baseline \( (p<0.05) \), with no significant difference between the two groups (Figure 1). Plasma levels of TC, HDL-C, LDL-C, TGs or FGs did not change before or after carvedilol or metoprolol treatment \( (p=NS) \). However, in the carvedilol group, the plasma level of ET-1 significantly decreased, from 79.11 ± 11.02 to 50.04 ± 10.09 pg/ml \( (p<0.05) \). NO level significantly increased after carvedilol therapy, from 62.69 ± 10.42 to 85.78 ± 11.23 μmol/l \( (p<0.05) \). Conversely, in the metoprolol group, the plasma levels of ET-1 and NO did not significantly change from baseline after 6-month treatment (Table II).

**Statistical analysis**

Data are expressed as mean ± SE. Statistical analysis involved use of SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Comparison of variables involved use of analysis of variance (ANOVA). Comparisons between the two treatment groups at the end of 6 months were analyzed by two-way repeat-measures ANOVA, as appropriate. A \( p<0.05 \) was considered statistically significant. The correlation between changes in CRF and LVMI before and after treatment in the two groups was analyzed by Pearson correlation coefficient.

**Results**

The characteristics of patients are in Table I. The two treatment groups did not differ in age, sex, etiology of hypertrophic ventricle or BP.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Carvedilol (n=28)</th>
<th>Metoprolol (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.2 ± 11.6</td>
<td>62.1 ± 13.8</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>18/10</td>
<td>17/12</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>89 ± 4</td>
<td>90 ± 2</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>156 ± 7</td>
<td>158 ± 4</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>90 ± 2</td>
<td>89 ± 3</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>8%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Data are mean ± SD unless indicated. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Figure 1. Changes in systolic and diastolic blood pressure and heart rate during treatment with carvedilol and metoprolol for 26 weeks. Comparison of systolic blood pressure (SBP) and diastolic blood pressure (DBP) and heart rate (HR) between baseline and 6-month treatment with carvedilol and metoprolol monitored every 2 weeks.
Table II. Effect of 6-month carvedilol and metoprolol treatment on metabolic variables in patients with hypertensive LVH (n=57).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Carvedilol (n=28)</th>
<th>Metoprolol (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After treatment</td>
</tr>
<tr>
<td>GS (mmol/l)</td>
<td>5.1±1.3</td>
<td>5.7±1.2</td>
</tr>
<tr>
<td>UA (μmol/l)</td>
<td>290±97</td>
<td>269±102</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>185±43</td>
<td>182±31</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>104±13</td>
<td>112±10</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>52±3</td>
<td>48±2</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>112±12</td>
<td>107±11</td>
</tr>
<tr>
<td>GPT (IU/l)</td>
<td>20.68±7.11</td>
<td>25.71±5.09</td>
</tr>
<tr>
<td>BUN (mmol/l)</td>
<td>6.4±1.0</td>
<td>7.6±1.7</td>
</tr>
<tr>
<td>SCr (µmol/l)</td>
<td>78±11</td>
<td>83±23</td>
</tr>
<tr>
<td>EF-1 (pg/µl)</td>
<td>79.11±11.02</td>
<td>50.04±10.09,∗∗</td>
</tr>
<tr>
<td>NO (µmol/l)</td>
<td>62.69±10.42</td>
<td>85.78±11.23,∗∗</td>
</tr>
</tbody>
</table>

GS, glucose; UA, uric acid; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-C; LDL-C, low-density lipoprotein-C; GPT, glutamate-pyruvate transaminase; BUN, blood urea nitrogen; SCr, serum creatinine; EF-1, endothelin-1; NO, nitric oxide; NS, not significant. ∗p<0.05 vs baseline; ∗∗p<0.05 vs after metoprolol therapy.

Effect of carvedilol and metoprolol on CFR

In the carvedilol group, the PDV of the anterior descending coronary artery at rest was significantly higher post-treatment than at baseline (p<0.05), and the peak hyperemic diastolic blood flow velocity after dipyridamole treatment was higher (p<0.05) (Figures 2 and 3). However, in the metoprolol group, both PDV at rest and after dipyridamole treatment decreased significantly after therapy (p<0.05).

CFR was significantly higher after carvedilol therapy than at baseline (2.31±0.31 vs 3.16±0.67, p=0.039); in the metoprolol group, CFR showed no significant change from baseline (Figure 4). The two treatment groups significantly differed in CFR at 6 months (3.16±0.67 vs 2.46±0.58, p<0.05).

Effect of carvedilol and metoprolol on LVMI

LVMI was attenuated significantly after therapy as compared with at baseline only in the carvedilol group (144.41±43.21 g/m² vs 128.7±21.14 g/m², p=0.043), with significant differences between the groups after therapy (p<0.05) (Figure 5). In the carvedilol group, increases in CFR and LVMI were inversely correlated (R²=0.474, p=0.036).

Effect of carvedilol and metoprolol on brachial arterial dilation

For both treatment groups, brachial artery diameter did not significantly change after therapy. In the carvedilol group, flow-mediated arterial dilation increased significantly, from 7.21±2.90% to 9.81±2.79% (p<0.05), as did glyceryl trinitrate-induced dilation, from 20.50±7.21% to 23.87±6.78% (p<0.05) (Figure 6). The metoprolol group showed no significant changes in endothelium-dependent and -independent arterial dilation (p=NS). Changes in brachial arterial dilation in the two groups were significant (p<0.05).

Discussion

In this study, we used TEE to determine whether carvedilol could improve CFR in patients with hypertensive LVH. The flow velocity of the left anterior descending coronary artery after dipyridamole injection was increased only by 2.31-fold at baseline in the patients, which is much lower than normal. Therefore, the CFR of patients with hypertensive LVH was lower than normal, as was reported previously (17). Both carvedilol and metoprolol significantly reduced the BP and HR of patients with hypertensive LVH. The effects seem to be attributed to the beta-receptor blockade effect of carvedilol and metoprolol, which may be explained by negative inotropy and negative conduction of beta-receptor blockade. Interestingly, despite similar lowered BP and HR by the two beta-blockers, carvedilol additionally increased CFR, attenuated LVMI, improved endothelium function and regulated ET-1 and NO levels.

CFR is defined as the ratio of hyperemic to basal average peak coronary flow velocity (17). In the carvedilol group, the mean PDV of maximal hyperemia after administration of dipyridamole increased more significantly than that of the baseline state after treatment, which led to a significantly higher CFR. However, in the metoprolol group, both PDV at maximal hyperemia after administration of dipyridamole and that of the baseline state decreased. So CFR in the metoprolol group did not significantly change with treatment. The different effects of carvedilol and metoprolol on CFR must be attributed to the different properties of the two beta-adrenoceptor blockers.

Carvedilol, a third-generation beta-adrenoceptor blocker, is a multiple-acting compound with non-selective beta-adrenoceptor and selective alpha-1-adrenoceptor blocking activity, calcium channel blocking; it has many other properties distinct from
myocardial microcirculation, which lead to lower CFR (20–22). First, impaired endothelium-dependent vascular dilation (23) may induce microcirculation coronary dysfunction, thus leading to myocardial ischemia. Our study demonstrated that the plasma levels of ET-1 and NO of patients with hypertensive other second-generation beta-adrenoreceptor blockers such as metoprolol. The distinctive properties are anti-oxidation, anti-proliferation of smooth muscle cells, alleviating endothelium dysfunction, radical free-oxygen scavenging and iron chelating.

In the absence of epicardial artery stenosis, the CFR of the distal anterior descending coronary artery is a reliable marker of microvascular function (18). Many reported pathological changes (19) of hypertension with LVH could result in disturbances of myocardial microcirculation, which lead to lower CFR (20–22). First, impaired endothelium-dependent vascular dilation (23) may induce microcirculation coronary dysfunction, thus leading to myocardial ischemia. Our study demonstrated that the plasma levels of ET-1 and NO of patients with hypertensive

Figure 2. Changes in coronary artery flow velocity in patients with hypertensive left-ventricular hypertrophy during treatment with carvedilol for 26 weeks. At baseline, the peak diastolic and systolic blood flow velocity of the anterior descending coronary artery was 55 and 25 cm/s, respectively (A), and increased to 125 and 60 cm/s, respectively, during maximal hyperemia with intravenous dipyridamole treatment (B). After carvedilol treatment, at baseline the peak diastolic and systolic blood flow velocity was 52 and 20 cm/s, respectively (C), and increased to 160 and 60 cm/s with dipyridamole injection (D). After carvedilol treatment, the ratio of the systolic peak hyperemic flow velocity to baseline flow velocity increased from 2.27 to 2.67 and the ratio of the diastolic peak hyperemic flow velocity to baseline flow velocity increased from 2.4 to 3.0.

Figure 3. Changes in peak diastolic blood flow velocity (PDV) of anterior descending coronary artery after carvedilol and metoprolol treatment in hypertensive patients with left-ventricular hypertrophy (LVH). PDV at rest and hyperemia increased significantly after carvedilol treatment.

Figure 4. Changes in coronary flow reserve (CFR) before and after 6-month carvedilol and metoprolol therapy in patients with hypertensive left-ventricular hypertrophy (LVH). CFR increased significantly after carvedilol treatment. NS, not significant; M, month.
Carvedilol could increase CFR of patients with hypertensive LVH

LVH were out of balance. That of ET-1, the most important vascular constricting factor, was increased and that of NO, the most important vascular dilating factor, was decreased. This observation may be related to damaged endothelium-dependent vascular dilatation of patients with hypertensive LVH. Carvedilol could have regulated the levels of ET-1 and NO. Furthermore, it improved endothelium-dependent vasodilatation. All of these results suggest that carvedilol might play a protective role in the endothelium system of patients with hypertensive LVH by regulating the endothelium-derived factors ET-1 and NO. At the same time, reactive oxygen species (ROS), including the superoxide anion, could react with NO and reduce NO bioavailability (24). A decrease in the relative bioavailability of NO impairs endothelium-dependent vasorelaxation of the artery. The anti-oxidation of carvedilol may have had a close relation to improved endothelium-dependent vasodilatation in the study. However, ROS levels were not determined. The potential mechanisms need further study.

Second, coronary artery remodeling and CFR are closely related. The wall of minimal coronary artery, especially the tunica media, becomes thicker gradually in patients with hypertensive LVH (25,26). Smooth-muscle-cell hypertrophy and hyperplasia in the arterioles resulting from prolonged hypertension reduce the caliber of the lumen, with a larger ratio of wall to lumen, thus decreasing CFR. The remodeling decreases coronary arteriolar compliance and plays an important role in affecting the CFR of patients with hypertensive LVH (27–29). So glyceryl trinitrate (GTN)-mediated dilation of the brachial artery of patients with hypertensive LVH is lower than normal. GTN, a donor of NO, acts directly on vascular muscle and not on endothelium (30). We showed that GTN-mediated dilation of the brachial artery was greater in the carvedilol group than in the metoprolol group. Carvedilol might reduce the remodeling of the coronary artery. The reduction may be attributed to anti-proliferation of smooth muscle cells by carvedilol, but arterial intimal-media thickness (IMT) was not detected. A final analytical conclusion is still unclear.

Third, extravascular factors also harm the CRF of patients with hypertensive LVH by perhaps by decreasing expansion of coronary arterioles (31). Myocardial cells in patients with hypertensive LVH show hypertrophy, hyperplasty and disordered myoneme (32,33), so extra-myocardium collagen levels and matrix also increase (34). All of the extravascular factors result in higher stiffness of the myocardium. In our study, carvedilol significantly attenuated LVMI significantly. Carvedilol improved the CFR of patients with hypertensive LVH, possibly through attenuating LVMI, although the negative correlation between changes in CRF and in LWMI was weak. In fact, little is known about the role of carvedilol in reversing the cardiac hypertrophy. Whether the agent can reduce myonemes needs further study.

In summary, this study disclosed that carvedilol could elevate the CFR of patients with hypertensive LVH as compared with metoprolol. The different effect on the CFR of patients with hypertensive LVH was related to the special functions of carvedilol.

Limitations of the study

We did not investigate ROS level and the IMT of arteries, which may have a strong relation to CFR. Further mechanisms of carvedilol affecting CFR need further investigation.

Second, we monitored the endothelial function of the brachial artery, not the coronary artery in this trial. In fact, the two arteries differ in structure, arrangement, development and origin. So the response of the two arteries to altered NO and ET-1 levels must
differ. However, examining the endothelial function of the coronary artery is more difficult than examining that of the brachial artery, so we monitored the endothelial function of the brachial artery instead of coronary artery, which might have increased systematic error.

Third, the research was an open trial. Such a trial is easy and feasible to carry out, but it could have incurred unavoidable bias.

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