SCIENTIFIC LETTER

Carvedilol improves endothelium-dependent vasodilation in patients with dilated cardiomyopathy

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Recently, large clinical trials have clearly shown that the third-generation β -blocker carvedilol reduces the risk of hospitalisation and death in patients with mild-to-moderate and severe heart failure.^{1,2} The possibility that endothelial dysfunction per se contributes to the pathogenesis of heart failure has been postulated. It has also been reported that carvedilol stimulates nitric oxide (NO) release from endothelial cells.³ There is no information regarding the role of carvedilol in vascular function in patients with heart failure, but we hypothesised that treatment with carvedilol improves not only cardiac function but also endothelial function in patients with dilated cardiomyopathy (DCM).

METHODS

Sixteen male patients with stable DCM (mean age 53 ± 17 years) who were admitted to Hiroshima University Hospital were enrolled in this study. The patients were divided randomly into a carvedilol group (carvedilol group; $n = 8$) and a conventional therapy group (control group; $n = 8$). Medical treatment consisted of administration of diuretics ($n = 16$), digitalis ($n = 12$), nitrate ($n = 12$), and angiotensin converting enzyme inhibitor ($n = 9$). Patients had received conventional therapy for 17 ± 7 months (8–26 months) before enrolment in this study. The study protocol was approved by the ethics committees of Hiroshima University Graduate School of Biomedical Sciences and informed consent for participation was obtained from all subjects.

Carvedilol treatment was started after measurement of forearm blood flow (FBF) at a dose of 2.5 mg/day in all patients with stable DCM. The mean dose of carvedilol after 4 weeks was 22 ± 5 mg/day. FBF was measured before and after 4 weeks of follow-up with a mercury-filled Silastic strain-gauge plethysmography (EC-5R, D.E. Hokanson, Bellevue, WA) as previously described.⁴ The effects of infusion of acetylcholine (ACh; Daiichi Pharmaceutical, Tokyo, Japan) and sodium nitroprusside (SNP; Maruishi Pharmaceutical, Osaka, Japan) on FBF were also measured. ACh infusion was intra-arterially administered at a dose of 3.75, 7.5 and 15 μ g/min, and SNP infusion was intra-arterially administered at a dose of 0.75, 1.5 and 3.0 μ g/min for 5 min at each dose. Infusions of ACh or SNP were carried out in a randomised fashion. Each study proceeded after FBF had returned to baseline. After a 30-min rest period, N^G -monomethyl-L-arginine (L-NMMA; CLINALFA, Laeufelfingen, Switzerland), an inhibitor of NO synthase, was infused intra-arterially at a dose of 8 μ g/min for 5 min while baseline FBF and arterial blood pressure were recorded, and ACh was administered before and after a 4-week follow-up period. Results are presented as the mean $\pm$ standard deviation (SD). Values of $p < 0.05$ were considered significant.

RESULTS

Treatment with carvedilol decreased systolic blood pressure from 124.2 ± 19.9 to 107.5 ± 13.2 mm Hg, heart rate from

89.6 ± 11.5 to 79.2 ± 11.4 bpm, New York Heart Association functional class from 2.1 ± 0.6 to 1.7 ± 0.5 , and left ventricular end-diastolic diameter from 64.0 ± 3.6 to 62.0 ± 3.5 mm, and it increased % fractional shortening from $16.7 \pm 2.4\%$ to $18.5 \pm 4.2\%$ and FBF from 3.4 ± 1.3 to 4.4 ± 1.2 ml/min/100 ml tissue ($p < 0.05$, respectively). In the control group, there was no significant difference between parameters before and after the 4-week follow-up period. Carvedilol augmented FBF response to ACh in the carvedilol group, while ACh-stimulated vasodilation before and after the 4-week follow-up period was similar in the control group (fig 1, left). The SNP-stimulated vasodilation before and after the 4-week follow-up period was similar in both groups (fig 1, right). No significant change was observed in arterial blood pressure or heart rate after intra-arterial infusion of either ACh or SNP in all subjects. Intra-arterial infusion of the endothelial NO synthase inhibitor L-NMMA significantly decreased basal FBF from 3.8 ± 1.3 to 2.9 ± 1.3 ml/min/100 ml tissue ($p < 0.01$) in the carvedilol group and from 3.5 ± 1.4 to 2.7 ± 1.5 ml/min/100 ml tissue ($p < 0.01$) in the control group. The administration of L-NMMA completely abolished the carvedilol-induced augmentation of FBF response to ACh (fig 1, left). No significant change in arterial blood pressure or heart rate was detected during the infusion of L-NMMA in all subjects.

DISCUSSION

In the present study, enhanced response of forearm vasculature to ACh in DCM patients treated with carvedilol was substantially inhibited by the NO synthase inhibitor L-NMMA, suggesting that augmentation of NO production is involved in carvedilol-enhanced endothelium-dependent vasorelaxation. It is thought that treatment with carvedilol increases shear stress in peripheral vessels through improvement in cardiac function. Indeed, in the present study, carvedilol increased basal FBF in patients with DCM. Carvedilol increases peripheral blood flow through improvement in cardiac function, resulting in activation of the phosphatidylinositol-3-kinase-Akt pathway, which causes intracellular calcium-independent eNOS phosphorylation and activation.

Carvedilol inhibits the generation of reactive oxygen species (ROS) in the endothelial cells.⁵ In a preliminary study, we did not find significant changes in oxidative markers such as urinary excretion of 8-hydroxy-2'-deoxyguanosine (from 15.8 ± 7.8 to 14.9 ± 8.1 ng/mg of creatinine) or serum malondialdehyde low-density lipoprotein concentration (from 86.7 ± 30.6 to 79.9 ± 28.6 U/l) in nine patients with DCM after 4 weeks of treatment with carvedilol. However, we do not deny the possibility that oxidative stress increases in patients with

Abbreviations: ACh, acetylcholine; DCM, dilated cardiomyopathy; FBF, forearm blood flow; L-NMMA, N^G -monomethyl-L-arginine; NO, nitric oxide; ROS, reactive oxygen species; SNP, sodium nitroprusside

Figure 1 Comparison of the forearm blood flow response to acetylcholine (left) or sodium nitroprusside (right) administration in the carvedilol group (top) and the control group (bottom). Comparison of the forearm blood flow response to acetylcholine administration after the infusion of L-NMMA in the carvedilol group (left top) and the control group (left bottom).

DCM and that carvedilol decreases oxidative stress. Unfortunately, we do not have a sensitive and specific marker of oxidative stress at present. Additional experiments using a sensitive and specific marker of oxidative stress would enable more specific conclusions concerning the role of carvedilol in decreasing oxidative stress, resulting in improvement in endothelial function in patients with DCM, to be drawn.

Study limitations

Although our results showed that carvedilol improved endothelial function in patients with DCM, the number of subjects in this study was small. The use of nitrates, exogenous NO donors and ACE inhibitors in some of the patients may be confounding for assessing endothelial function in these patients. Our data should be confirmed by further large-scale studies. In addition, the precise mechanisms by which carvedilol improved endothelial function were not evaluated in the present study.

In conclusion, the beneficial effects of carvedilol, such as increase in shear stress and decrease in vasoconstrictors and oxidative stress, may independently or interdependently contribute to improvement in endothelial function through an increase in NO release and/or inhibition of NO degradation. From a clinical perspective, it is important to select appropriate drugs that also have beneficial effects on peripheral arterial function in patients with DCM.

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