Improvement in Cardiac Function and Free Fatty Acid Metabolism in a Case of Dilated Cardiomyopathy With CD36 Deficiency

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A 27-year-old man diagnosed as having dilated cardiomyopathy (DCM) without myocardial accumulation of 123I-3,3'-methyl-iodophenylpentadecanoic acid, and he was found to have type I CD36 deficiency. This abnormality of cardiac free fatty acid metabolism was also confirmed by other methods: 18F-fluoro-2-deoxyglucose positron emission tomography, measurements of myocardial respiratory quotient and cardiac fatty acid uptake. Although the type I CD36 deficiency was reconfirmed after 3 months, the abnormal free fatty acid metabolism improved after carvedilol therapy and was accompanied by improved cardiac function. Apart from a cause-and-effect relationship, carvedilol can improve cardiac function and increase free fatty acid metabolism in patients with both DCM and CD36 deficiency. (Jpn Circ J 2000; 64: 731–735)

Key Words: Carvedilol; Idiopathic dilated cardiomyopathy; Myocardial substrate utilization; Type I CD36 deficiency

CD36 has been proposed as a transporter for long-chain free fatty acids in humans! Patients with CD36 deficiency are, therefore, expected to show an abnormality of cardiac free fatty acid metabolism and it has been revealed that such patients, in whom neither platelets nor monocytes/macrophages express CD36, classified as type I CD36 deficiency, show absolutely no accumulation of 123I-3,3'-methyl-iodophenylpentadecanoic acid (BMIPP)2-3 Therefore, these patients can be identified in the clinical settings by the lack of cardiac BMIPP accumulation, and the CD36 deficiency can be confirmed from blood samples. The clinical phenotype of CD36 deficiency is not uniform and although CD36 deficiency is often reported in patients with hypertrophic cardiomyopathy (HCM), it is also reported in dilated cardiomyopathy (DCM); which implies an independence between long-chain free fatty acid metabolism and cardiac function.

We report a patient with both DCM and CD36 deficiency in whom we investigated whether carvedilol therapy could improve cardiac performance, as well as in patients with DCM without CD36 deficiency2-5 and whether it can alter cardiac energy substrate utilization.

Case Report

A 27-year-old asymptomatic man was referred to us for investigation of cardiomegaly and an abnormal electrocardiogram (ECG). His own and his family history were both otherwise unremarkable. His height was 165 cm, body weight was 76 kg, and blood pressure was 140/100 mmHg. His physical examination was unremarkable. The cardio-thoracic ratio calculated from the chest X-ray was 53% (Fig 1a). An ECG revealed regular sinus rhythm at a rate of 92 beats/min and left ventricular hypertrophy with depressed S4 segment and inverted T wave (Fig 1b). Initial transthoracic echocardiography also revealed left ventricular (LV) dilatation and reduced systolic and diastolic function with a preserved wall thickness of 11 mm (Table I). Left cardiac catheterization showed a LV end-diastolic volume index of 87 ml/m2, ejection fraction of 27%, and LV end-diastolic pressure of 26 mmHg. Coronary arteriography did not reveal any significant stenosis. Right cardiac catheterization revealed no pulmonary hypertension. Light microscopic examination of hematoxylin-eosin stained sections from the right ventricular endocardium showed marked disparity and vacuolar degeneration of myocytes. Furthermore, moderate interstitial fibrosis and fatty infiltration were observed with Masson-trichrome stain. He was thus diagnosed as DCM, and further evaluation for cardiac metabolism was performed, using BMIPP scintigraphy for free fatty acid metabolism and 18F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) for glucose metabolism, after written consent was obtained from the patient. No cardiac accumulation of BMIPP was observed (Fig 2a). In the FDG-PET imaging, myocardial glucose uptake was assessed by the ratio of the mean count density for each myocardial region of interest (ROI) to blood pool (R/B ratio)6 In our laboratory the region in which the R/B ratio is above 1.5 is regarded as the region of enhanced glucose uptake. The R/B ratio of 7.4 averaged for every ROI before carvedilol treatment was high, representing dominant glucose use (Fig 3a). Written informed consent was obtained for cardiac catheterization and FDG-PET imaging.

We also measured the myocardial free fatty acid uptake ratio and myocardial respiratory quotient (mRQ), a reflection of myocardial substrate utilization during cardiac
### Table 1  Treatment Course

<table>
<thead>
<tr>
<th></th>
<th>Before carvedilol</th>
<th>After 3 months’ carvedilol</th>
<th>After 1 year</th>
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</thead>
<tbody>
<tr>
<td><strong>UCG</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dd (mm)</td>
<td>68</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>FS (%)</td>
<td>17</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>DcT (ms)</td>
<td>120</td>
<td>230</td>
<td>200</td>
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<tr>
<td><strong>Fatty acid metabolism</strong></td>
<td></td>
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<tr>
<td>Plasma FFA (mEq/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before heparin</td>
<td>1819</td>
<td>1380</td>
<td>ND</td>
</tr>
<tr>
<td>After heparin</td>
<td>4115</td>
<td>3752</td>
<td>ND</td>
</tr>
<tr>
<td>FUR (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Before heparin</td>
<td>6.8</td>
<td>17.5</td>
<td>ND</td>
</tr>
<tr>
<td>After heparin</td>
<td>3.5</td>
<td>7.5</td>
<td>ND</td>
</tr>
<tr>
<td>mRQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before heparin</td>
<td>0.91</td>
<td>0.78</td>
<td>ND</td>
</tr>
<tr>
<td>After heparin</td>
<td>0.94</td>
<td>0.64</td>
<td>ND</td>
</tr>
<tr>
<td><strong>FDG-PET</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R/B ratio</td>
<td>7.4</td>
<td>4.0</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: not done; DcT, deceleration time of E wave; Dd, end-diastolic diameter; FDG-PET, 18F-fluoro-2-deoxyglucose positron emission tomography; FFA, free fatty acid; FS, fractional shortening; FUR, fatty acid uptake rate; UCG, ultrasound cardiography; mRQ, myocardial respiratory quotient; R/B ratio, every myocardial region of interest to blood pool.

**Fig. 1.** (a) Chest X-ray on admission. (b) Electrocardiogram on admission.

**Fig. 2.** BMIPP imaging. Anterior planar image reveals no myocardial uptake of BMIPP. (a) Before treatment, (b) after 3 months of carvedilol therapy.
catheterization. Free fatty acid uptake ratio and mRQ were determined by blood samples taken from the femoral artery and great cardiac veins. Because myocardial substrate uptake and utilization depend on blood substrate availability, we measured these values in both the fasting state and after administration of 50 units/kg of heparin, which is reported to increase plasma free fatty acid level by activating lipoprotein lipase. The free fatty acid uptake ratio and mRQ were calculated as follows:

\[ \text{FUR} = \frac{\text{FFA}_{Ar} - \text{FFA}_{GCV}}{\text{FFA}_{Ar} \times 100} (\%) \]

where FUR is free fatty acid uptake ratio, and FFA	extsubscript{Ar} and FFA	extsubscript{GCV} are arterial and great cardiac venous free fatty acid content, respectively, and

\[ \text{mRQ} = \frac{\text{CO}_{2GCV} - \text{CO}_{2Ar}}{(\text{O}_{2Ar} - \text{O}_{2GCV})} \]

where CO	extsubscript{2Ar}, O	extsubscript{2Ar}, CO	extsubscript{2GCV} and O	extsubscript{2GCV} are arterial and great cardiac vein carbon dioxide and oxygen contents, respectively. The carbon dioxide content of the blood specimen was calculated by the Douglas' equation.\textsuperscript{10}

Flow cytometry revealed that the surface expression of CD36 on both platelets and monocytes was absent (Fig 4). The concentration of serum carnitine was normal.

The patient was administered carvedilol, which was increased gradually up to 20 mg/day. His cardiac performance improved after 3 months of therapy, and continued at least for 1 year (Table 1). The lack of cardiac BMIPP accumulation (Fig 2b) and CD36 deficiency was confirmed after 3 months, but carvedilol therapy increased myocardial free fatty acid: namely, free fatty acid uptake rate increased from 6.8 to 17.5% before and from 3.5 to 7.5% after heparin administration, and mRQ decreased from 0.91 to 0.78 before and from 0.84 to 0.64 after heparin administration. Myocardial glucose uptake and utilization, expressed by the R/B ratio, decreased reciprocally from 7.4 to 4.0 (Fig 3b, Table 1).

**Discussion**

We have described a patient clinically diagnosed as DCM with type I CD36 deficiency. The decreased cardiac free fatty acid uptake and utilization improved, accompanied by improved cardiac function, after carvedilol therapy.

Although in the past it was thought that fatty acids are taken passively into the myocyte,\textsuperscript{11} a carrier protein has been recently revealed and named CD36.\textsuperscript{1,3,12} Whether CD36 deficiency is accompanied by or leads to specific diseases such as HCM or DCM is unknown. Tanaka et al demonstrated a correlation between impaired cardiac BMIPP uptake and CD36 deficiency in 11 patients with HCM and 1 patient with DCM; although one patient with DCM had type II CD36 deficiency. Furthermore, it has been reported that the chemical inhibition of CD36 expression induced cardiac hypertrophy in rats.\textsuperscript{13} To our knowledge, the coexistence of DCM and type I CD36 deficiency has not been reported, although these 2 conditions may have occurred together by chance.

Patients with CD36 deficiency can not take free fatty acid into myocytes, and in the current patient decreased free fatty acid uptake and utilization was reflected by a complete lack of BMIPP uptake, decreased myocardial free fatty acid uptake, reciprocally increased FDG uptake, and
increased mRQ. It is quite intriguing that free fatty acid utilization improved, even though the CD36 deficiency remained unchanged, after carvedilol therapy.

The free fatty acid uptake ratio of the present patient was extremely low in comparison with that of 13 other DCM patients with BMIPP accumulation (probably without CD36 deficiency), but after 3 months’ carvedilol treatment, his free fatty acid uptake ratio increased to the average level of the other DCM patients both before and after heparin injection (Fig 5) (unpublished data). Because CD36 is a carrier protein for long-chain free fatty acids, overall improvement in free fatty acid uptake or utilization may reflect improvement in medium or short-chain free fatty acid transport as well.

On the other hand, several meta-analyses have provided evidence supporting the favorable effects of β-blockade on left ventricular ejection fraction and the combined risk of death and hospitalization for heart failure. Carvedilol is a third-generation β-blocker that combines nonselective β-blockade (β1 and β2), a-blockade, and antioxidant effects. Carvedilol increases the free fatty acid uptake ratio and decreases mRQ after 1 month of therapy in patients with DCM (unpublished data) and this improvement in free fatty acid uptake was also recognized in the present patient with CD36 deficiency, which is inconsistent with a previous report that metoprolol promotes glucose uptake and utilization. Eichhorn et al reported that the concentration ofnorepinephrine in the coronary sinus deteriorated and the mRQ increased in patients with DCM who were administrated metoprolol for 3 months. In the early heart failure phase, the activated sympathetic nervous system increases the activity of lipoprotein lipase and hormone sensitive lipase and so the availability of free fatty acid increases. The additional actions of carvedilol, such as nonselective β-blockade, a-blockade, and antioxidant effects, may provide further clinical benefit for heart failure patients. Further examination of the differences between carvedilol and metoprolol on glucose uptake and utilization is required.

Apart from a cause-and-effect relationship, carvedilol can improve cardiac function and increase free fatty acid use in patients with both DCM and CD36 deficiency.

Acknowledgment

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