L-carnitine Improved the Cardiac Function via the Effect on Myocardial Fatty Acid Metabolism in a Hemodialysis Patient

Mai Kaneko, Hirotaka Fukasawa, Kento Ishibuchi, Hiroki Niwa, Hideo Yasuda and Ryuichi Furuya

Abstract:
Patients on hemodialysis often have carnitine deficiency. We herein report a woman who experienced the dramatic improvement of cardiac dysfunction after intravenous L-carnitine administration. We also investigated the myocardial fatty acid metabolism using 123I-labeled β-methyl-p-iodophenyl-pentadecanoic acid (BMIPP) single-photon emission computed tomography (SPECT) before and after L-carnitine therapy, and the impaired metabolism was ameliorated. Taken together, these findings indicate that L-carnitine therapy improved cardiac dysfunction via the amelioration of the abnormal myocardial fatty acid metabolism, at least in part.

Key words: carnitine, fatty acid metabolism, hemodialysis (HD), 123I-labeled β-methyl-p-iodophenyl-pentadecanoic acid (BMIPP), single-photon emission computed tomography (SPECT)

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Introduction
Patients undergoing maintenance hemodialysis (HD) often have carnitine deficiency, which may contribute to clinical disorders, including erythropoiesis-stimulating agent (ESA)-resistant anemia, insulin resistance, endothelial dysfunction and muscle cramps (1, 2). Furthermore, carnitine deficiency is known to cause cardiac dysfunction (3, 4).

Recently, Higuchi et al. (5) reported that one-year L-carnitine administration improved cardiac dysfunction (an increased left ventricular ejection fraction [LVEF] and a decreased left ventricular mass index [LVMI] and N-terminal pro brain natriuretic peptide [BNP]) in HD patients, particularly those with left ventricular hypertrophy. However, the precise mechanism underlying how L-carnitine therapy improved the cardiac dysfunction remains unclear.

We herein report a case of dramatic improvement of cardiac dysfunction after L-carnitine administration. We also investigated the myocardial fatty acid metabolism using 123I-labeled β-methyl-p-iodophenyl-pentadecanoic acid (BMIPP) single-photon emission computed tomography (SPECT) before and after the administration and found that the impaired metabolism was ameliorated. Taken together, the findings in this hemodialysis case suggest that treatment with L-carnitine improved the cardiac dysfunction by ameliorating the myocardial fatty acid metabolism.

Case Report
A 51-year-old woman had been suffering from sustained dyspnea (New York Heart Association [NYHA] functional classification, class III) for several months, and the gradual enlargement of the cardiothoracic ratio (CTR, 72.3%) was observed on chest X-ray. She had been on HD since 48 years of age due to end-stage renal disease (chronic glomerulonephritis suspected). She was subjected to regular HD for 4 hours three session times per week at a blood flow rate of 200 mL/min via the brachiocephalic arteriovenous fistula of her left arm without the use of vasopres-

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white blood cell count of 6,300/mm$^3$. A physical examination revealed a height of 153 cm, body mass index of 26.7 kg/m$^2$. Laboratory studies at the beginning of the first dialysis session revealed a white blood cell count of 6,300/mm$^3$, hemoglobin of 10.6 g/dL, hematocrit of 34.6%, serum albumin of 3.8 g/dL, blood urea nitrogen (BUN) of 54 mg/dL, serum creatinine of 7.93 mg/dL, sodium of 140 mEq/L, potassium of 5.9 mEq/L, corrected calcium of 9.7 mg/dL, phosphate of 3.9 mg/dL, magnesium of 2.4 mg/dL, and C-reactive protein (CRP) of 0.01 mg/dL. The total and free carnitine concentrations were low at 33.9 and 17.5 μmol/L, respectively (normal range: 60-68 μmol/L as well as the BMIPP summed scores (from 20 [severely impaired] to 6 [mildly impaired]) (Fig. 1, 2). During L-carnitine treatment, no β-blockers, renin-angiotensin system inhibitors, diuretics, digitalis, anti-platelet agent or statins were added, and the conditions for the HD procedure were not changed, as we planned to evaluate the actual effects of L-carnitine administration on the cardiac function. In addition, the dose of phosphate binders was not changed, and her blood pressure and dry weight were almost constant during L-carnitine treatment (Fig. 2).

Cardiovascular disease (CVD) is a significant cause of morbidity and mortality in patients undergoing HD (11). The rate of mortality caused by CVD in such patients is 10- to 40-fold higher than that in the general population (12). Therefore, the assessment and treatment of CVD are major concerns for managing such patients. Traditional CVD risk factors, such as an older age, male sex, smoking, diabetes mellitus, hypertension and dyslipidemia, are highly prevalent in patients on HD. There are also predisposing factors that relate specifically to the uremic milieu on HD, including myocardial stress, such as recurrent volume expansion, the accumulation of advanced glycation end products and a deficit of certain substances essential for the metabolism of myocardial cells (13).

Carnitine deficiency in HD patients is common as a result of the loss of carnitine during the dialysis procedure, possible reductions in dietary intake and endogenous synthesis and can cause several clinical disorders, including ESA-resistant anemia, insulin resistance, endothelial dysfunction, dyslipidemia, muscle weakness and cardiac dysfunc-

### Table. Findings of Cardiac Ultrasonography before and after L-carnitine Treatment.

<table>
<thead>
<tr>
<th>L-carnitine treatment</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>50.6</td>
<td>71.2</td>
</tr>
<tr>
<td>Left ventricular dimension in diastole, mm</td>
<td>54.6</td>
<td>40.4</td>
</tr>
<tr>
<td>Left ventricular dimension in systole, mm</td>
<td>38.1</td>
<td>24.2</td>
</tr>
<tr>
<td>Interventricular septum thickness, mm</td>
<td>13.1</td>
<td>12.0</td>
</tr>
<tr>
<td>Left ventricular posterior wall thickness, mm</td>
<td>15.0</td>
<td>13.3</td>
</tr>
<tr>
<td>Left atrial dimension, mm</td>
<td>45.5</td>
<td>40.2</td>
</tr>
<tr>
<td>E/E' ratio</td>
<td>34.5</td>
<td>11.8</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m$^2$</td>
<td>214</td>
<td>144</td>
</tr>
</tbody>
</table>

Valvular diseases MR II°, TR I° None

Discussion

The patient also had her myocardial fatty acid metabolism examined using $^{123}$I-labeled BMIPP SPECT (Nihon Medi-Physics Co. Ltd., Tokyo, Japan) in accordance with the methods reported previously (9, 10). In brief, the images were divided into 17 segments for analyses. The amount of radioactivity in each segment was graded visually and assigned scores from 0-4 (0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; 4, no uptake). The BMIPP SPECT scores for 17 segments were designated as the summed BMIPP. The range of BMIPP summed scores was 0-68. In this patient, the BMIPP summed score was 20 (severely impaired) before L-carnitine administration.

We tried to remove the excess fluid by the lowering her dry weight during HD to improve her symptoms, but this failed due to a decrease in her blood pressure. Therefore, the patient was started on treatment with intravenous L-carnitine (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) at 2,000 mg/week (1,000 mg, twice a week) at the end of HD session. After several months, her symptom of dyspnea gradually improved. In addition, 1-year L-carnitine treatment increased her LVEF (from 50.6% to 71.2%) and decreased her LVMI (from 214.0 to 144.0 g/m$^2$) (Table), CTR (from 71.3% to 51.4%) and BNP concentrations (8,257 to 378 pg/mL) as well as the BMIPP summed scores (from 20 [severely impaired] to 6 [mildly impaired]) (Fig. 1, 2). During L-carnitine treatment, no β-blockers, renin-angiotensin system inhibitors, diuretics, digitalis, anti-platelet agent or statins were added, and the conditions for the HD procedure were not changed, as we planned to evaluate the actual effects of L-carnitine administration on the cardiac function. In addition, the dose of phosphate binders was not changed, and her blood pressure and dry weight were almost constant during L-carnitine treatment (Fig. 2).
Carnitine plays an important role in the myocardial fatty acid metabolism by transporting long-chain fatty acids from the cytoplasm to the mitochondrial matrix for acid metabolism. The administration of L-carnitine was associated with the improvement of impaired myocardial fatty acid metabolism, as was observed in our case, at least in part. However, we cannot rule out other possibilities, such as the theoretical mechanism described above, we believe that the actual effect of L-carnitine administration on the myocardial fatty acid metabolism and the cardiac function, as reported previously.

On this point, our case provides new knowledge, as we observed changes in both the cardiac function and the myocardial fatty acid metabolism with BMIPP SPECT before and after L-carnitine treatment. Based on those changes and the theoretical mechanism described above, we believe that the effects of L-carnitine on the myocardial fatty acid metabolism contributed to the improvement of cardiac dysfunction in our case, at least in part. However, we cannot rule out the possibility that those effects on the cardiac function may have been caused by other mechanisms, such as the improvement of the insulin resistance or endothelial dysfunction. We also cannot rule out other possibilities, such as transient cardiomyopathy, ischemic heart disease, afterload mismatch, unrecognized arrhythmia or the coincidental improvement of overhydration by re-setting the dry weight. In addition, the cause of the carnitine deficiency in our case was unknown.

In summary, we herein described a woman on HD whose cardiac dysfunction and myocardial fatty acid imaging findings with BMIPP SPECT dramatically improved after intravenous L-carnitine administration. These findings suggest that L-carnitine treatment affected the cardiac function via the improvement of the abnormal myocardial fatty acid metabolism, suggesting that such treatment may be an option for HD patients with cardiac dysfunction of unknown cause.

**Figure 1.** Images of chest X-ray (A) and BMIPP SPECT (B) before and after L-carnitine administration. (A) L-carnitine administration resulted in a decrease in the CTR from 71.3% to 51.4%. (B) The administration also resulted in the decrease of BMIPP summed scores from 20 to 6, indicating that the myocardial fatty acid metabolism was improved. The BMIPP summed scores were calculated using a 17-segment 5-point system (normal, 0; absent, 4). The range of BMIPP summed scores was 0-68. BMIPP: β-methyl-p-iodophenyl-pentadecanoic acid, CTR: cardiothoracic ratio, SPECT: single-photon emission computed tomography.

**Figure 2.** The clinical course before and after L-carnitine treatment. BMIPP: β-methyl-p-iodophenyl-pentadecanoic acid, BNP: brain natriuretic peptide, CTR: cardiothoracic ratio, LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index.
The authors state that they have no Conflict of Interest (COI).

References


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