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)

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-
sors. She was also using bicarbonate dialysate (Kindaly AF-2E; Fuso, Osaka, Japan) at a dialysate flow rate of 500 mL/min and a polysulfon dialyzer (APS-18SA; Asahi Kasei Medical, Tokyo, Japan). Her dry weight was 62.5 kg before L-carnitine treatment, and the quantity of removed water per HD session was around 5% of her dry weight. She had been treated for hypertension since her 30’s but had no history of diabetes mellitus or ischemic heart disease. She did not present with an apparent slow walking speed, low physical performance or episodes of malnutrition indicating frailty (6) or sarcopenia (7) before symptoms of cardiac failure appeared.

A physical examination revealed a height of 153 cm, body mass index of 26.7 kg/m², body temperature of 36.8°C, pulse rate of 80 beats/min and blood pressure of 170/80 mmHg.

Laboratory studies at the beginning of the first dialysis session of the week following a 2-day interval revealed a white blood cell count of 6,300/mm³, 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 4.8 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 13.2 and 7.1 μmol/L, respectively (normal range: 10-60 μmol/L). The thyroid function was normal. The BNP concentration was extremely elevated at 8,257 pg/mL.

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 dysfunction (1, 2, 14). Kudoh et al. (15) proposed that carnitine deficiency was involved in the pathogenesis of cardiomegaly in HD patients.

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, 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/m²) (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).

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).

Discussion

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

|                                | Before  | After  |
|--------------------------------|---------|--------|
| Left ventricular ejection fraction, % | 50.6    | 71.2   |
| Left ventricular dimension in diastole, mm   | 54.6    | 40.4   |
| Left ventricular dimension in systole, mm    | 38.1    | 24.2   |
| Interventricular septum thickness, mm        | 13.1    | 12.0   |
| Left ventricular posterior wall thickness, mm| 15.0    | 13.3   |
| Left atrial dimension, mm                   | 45.5    | 40.2   |
| E/E’ ratio                                   | 34.5    | 11.8   |
| Left ventricular mass index, g/m²            | 214     | 144    |
| Valvular diseases                            | MR II°, TR I° | None |

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the cytoplasm to the mitochondrial matrix for acid metabolism by transporting long-chain fatty acids from proves cardiac dysfunction remains unclear. ever, the precise mechanism underlying how L-carnitine improves cardiac function or left ventricular hypertrophy (4, 5). How-ever, the cause of the carnitine deficiency in our case may have been caused by other mechanisms, such as the 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.

The authors state that they have no Conflict of Interest (COI).
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