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【 CASE REPORT 】

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

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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 ^{123}I-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), ^{123}I-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 ^{123}I-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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Table. Findings of Cardiac Ultrasonography before and after L-carnitine Treatment.

	L-carinitine 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/m^2	214	144
Valvular diseases	MR II°, TR I°	None

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/m^2, body temperature of 36.8℃, 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/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: 45-91 and 36-74 μmol/L, respectively), although acylcarnitine concentration was normal at 16.4 μmol/L (normal range 6-23 μmol/L). The thyroid function was normal. The BNP concentration was extremely elevated at 8,257 pg/mL (normal range: <20 pg/mL).

Cardiac ultrasonography revealed mild to moderate hypokinesis of diffuse left ventricular wall motion without asynergy, a low LVEF of 50.6% (normal range: 55-85), extreme left ventricular hypertrophy with an increased LVMI of 214.0 g/m^2 (normal range: <95 g/m^2 in women) (8) and no severe valvular abnormalities (Table). Electrocardiogram (ECG) revealed no evidence of ischemic heart disease.

The patient also had her myocardial fatty acid metabolism examined using ^{123}I-labeled BMIPP SPECT (Nihon Medi-Physics, 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, 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).

Discussion

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

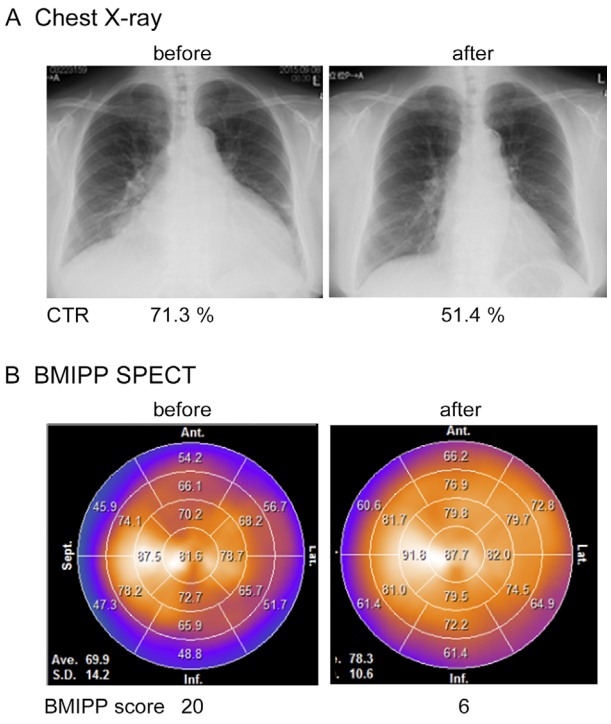

Figure 1. Images of chest X-ray (A) and BMIPP SPECT (B) before and after L-carnitine administration. (A) L-carnitine administration resulted in a decrease in the CTR from 71.3% to 51.4%. (B) The administration also resulted in the decrease of BMIPP summed scores from 20 to 6, indicating that the myocardial 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

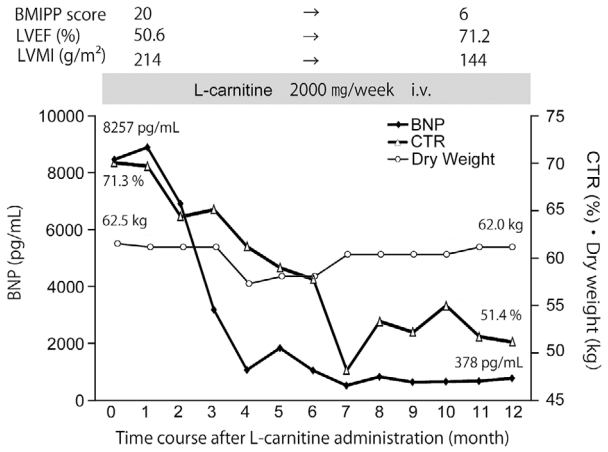

Figure 2. The clinical course before and after L-carnitine treatment. BMIPP: β-methyl-*p*-iodophenyl-pentadecanoic acid, BNP: brain natriuretic peptide, CTR: cardiothoracic ratio, LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index

adult patients on HD. There have been several reports regarding the improvement of the cardiac function following L-carnitine treatment, particularly in patients with a reduced cardiac function or left ventricular hypertrophy (4, 5). However, the precise mechanism underlying how L-carnitine improves cardiac dysfunction remains unclear.

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 β-oxidation in various tissues (16). The presence of adequate carnitine concentrations in the intracellular compartment is essential for the normal fatty acid metabolism in humans, particularly in myocardial cells, which preferentially use fatty acids as primary energy sources rather than glucose (17). Accordingly, the treatment with L-carnitine positively affecting the cardiac function via the improvement of impaired myocardial fatty acid metabolism, as was observed in our case, might be reasonable.

Sakurabayashi et al. (18) reported that the oral administration of L-carnitine to HD patients did not affect the myocardial accumulation on BMIPP scintigraphy, although it increased the washout rate. Recently, Nishimura et al. (19) reported that the BMIPP summed scores with SPECT after the intravenous administration of L-carnitine did not differ markedly from those before it, although they also suggested that the cardiac function was improved in the subgroup of patients with reduced BMIPP summed scores after the administration. Taken thogether, these findings failed to clarify the actual effect of L-carnitine administration on the myocardial fatty acid metabolism and the cardiac function, as reported previously (4, 5).

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.

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

References

1. Bohmer T, Bergrem H, Eiklid K. Carnitine deficiency induced during intermittent haemodialysis for renal failure. Lancet **1**: 126-128, 1978.
2. Ahmad S. L-carnitine in dialysis patients. Semin Dial **14**: 209-217, 2001.
3. Hart ZH, Chang CH, Di Mauro S, Farooki Q, Ayyar R. Muscle carnitine deficiency and fatal cardiomyopathy. Neurology **28**: 147-151, 1978.
4. van Es A, Henny FC, Kooistra MP, Lobatto S, Scholte HR. Amelioration of cardiac function by L-carnitine administration in patients on haemodialysis. Contrib Nephrol **98**: 28-35, 1992.
5. Higuchi T, Abe M, Yamazaki T, et al. Levocarnitine improves cardiac function in hemodialysis patients with left ventricular hypertrophy: a randomized controlled trial. Am J Kidney Dis **67**: 260-270, 2016.
6. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci **56**: M146-M156, 2001.
7. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. Age Ageing **39**: 412-423, 2010.
8. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol **57**: 450-458, 1986.
9. Nishimura M, Tsukamoto K, Hasebe N, Tamaki N, Kikuchi K, Ono T. Prediction of cardiac death in hemodialysis patients by myocardial fatty acid imaging. J Am Coll Cardiol **51**: 139-145, 2008.
10. Moroi M, Tamaki N, Nishimura M, et al. Association between abnormal myocardial fatty acid metabolism and cardiac-derived death among patients undergoing hemodialysis: results from a cohort study in Japan. Am J Kidney Dis **61**: 466-475, 2013.
11. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis **32**: S112-S119, 1998.
12. Sarnak MJ. Cardiovascular complications in chronic kidney disease. Am J Kidney Dis **41**: 11-17, 2003.
13. Li YM, Steffes M, Donnelly T, et al. Prevention of cardiovascular and renal pathology of aging by the advanced glycation inhibitor aminoguanidine. Proc Natl Acad Sci U S A **93**: 3902-3907, 1996.
14. Evans AM, Faull RJ, Nation RL, et al. Impact of hemodialysis on endogenous plasma and muscle carnitine levels in patients with end-stage renal disease. Kidney Int **66**: 1527-1534, 2004.
15. Kudoh Y, Shoji T, Oimatsu H, Yoshida S, Kikuchi K, Iimura O. The role of L-carnitine in the pathogenesis of cardiomegaly in patients with chronic hemodialysis. Jpn Circ J **47**: 1391-1397, 1983.
16. Fritz IB. Carnitine and its role in fatty acid metabolism. Adv Lipid Res **1**: 285-334, 1963.
17. Neely JR, Rovetto MJ, Oram JF. Myocardial utilization of carbohydrate and lipids. Prog Cardiovasc Dis **15**: 289-329, 1972.
18. Sakurabayashi T, Takaesu Y, Haginoshita S, et al. Improvement of myocardial fatty acid metabolism through L-carnitine administration to chronic hemodialysis patients. Am J Nephrol **19**: 480-484, 1999.
19. Nishimura M, Tokoro T, Takatani T, et al. Effects of intravenous l-carnitine on myocardial fatty acid imaging in hemodialysis patients: responders or non-responders to l-carnitine. Springerplus **4**: 353, 2015.