

Plasma Carnitine Concentrations in Patients Undergoing Open Heart Surgery

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Carnitine is an essential cofactor for fatty acid (FA) metabolism, the predominant source of ATP in the normal aerobic heart. During myocardial ischemia, FA metabolism is impaired and tissue carnitine levels are depleted. Since the heart cannot synthesize carnitine, plasma carnitine could play an important role in maintaining myocardial carnitine levels during reperfusion. The purpose of this study was to determine the incidence of abnormal plasma carnitine concentrations in open heart surgery. Blood samples were obtained from eleven patients before, immediately after, and two hours after cardiopulmonary bypass (CPB). Total and free carnitine levels were significantly reduced immediately after CPB ($p < 0.01$) and remained depressed until two hours after CPB ($p < 0.01$ vs. pre CPB), while acyl carnitine levels were unchanged over the course of this study. These depressed free carnitine levels might affect cardiac metabolism in the heart after open heart surgery. Carnitine supplement might be a useful adjunct in the therapy after open heart surgery. (Ann Thorac Cardiovasc Surg 2004; 10: 19–22)

Key words: cardiac metabolism, carnitine, open heart surgery, cardiopulmonary bypass

Introduction

Long-chain fatty acids (FA) are the preferred substrate for oxidative metabolism in the normal aerobic heart. Carnitine is the requisite carrier for transport of activated FA across the mitochondrial membrane for β -oxidation.¹⁾ In the absence of carnitine, β -oxidation ceases, lipid accumulates, and organ dysfunction results. In some specific conditions, such as myocardial ischemia,²⁾ cardiac hypertrophy,³⁾ and hemodialysis,⁴⁾ secondary myocardial carnitine deficiency has been observed. Since the heart cannot synthesize carnitine, the post-ischemic myocardium cannot resume normal FA metabolism without prior restoration of adequate plasma free carnitine levels. It is reported that FA metabolism was significantly depressed after cardioplegic arrest in coronary bypass surgery.⁵⁾ Although the precise mechanisms of the impaired FA metabolism is unclear, the carnitine deficiency also might

have an important role in this abnormal metabolism after open heart surgery. To determine the incidence of abnormal plasma carnitine concentrations in open heart surgery, we assayed plasma carnitine levels perioperatively.

Methods

Eleven patients undergoing elective open heart surgery, age ranging 28 to 75 years (mean \pm SD, 55.5 \pm 14.3) and six females and five males, were entered in this study. The preoperative diagnosis was 4 mitral stenosis, 1 mitral regurgitation, 2 bioprosthetic valve malfunction, 1 aortic stenosis, 1 prosthetic valve endocarditis, and 2 coronary artery disease with previous myocardial infarction. No patient had severe congestive cases of heart failure requiring inotropic support. There were no diabetes mellitus, hyperlipidemia, or any other metabolic disorder. All operations were performed using tepid blood-cardioplegic arrest during cardiopulmonary bypass (CPB) without transfusion of banked homologous blood. Autologous blood was concentrated and transfused back to the patients in two hours after discontinuation of CPB.

Arterial plasma samples were obtained before, immediately after, and two hours after CPB, and were frozen

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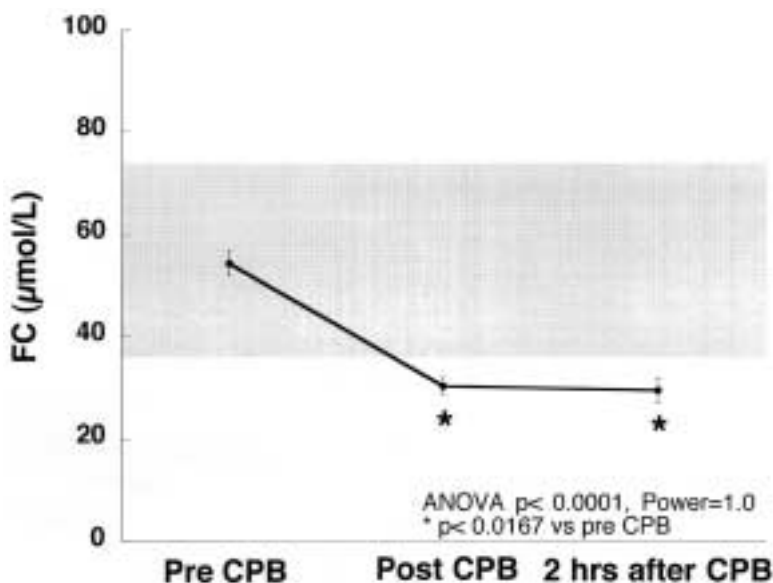


Fig. 1. Plasma free carnitine (FC) concentration. FC concentration decreased significantly and were below the normal values immediately after CPB. Moreover, it did not change significantly and remained less than the normal range two hours after CPB when all of the autologous blood was transfused back to the patients. Normal range for FC is indicated by dotted area. Error bar shows mean ± standard error (SE).

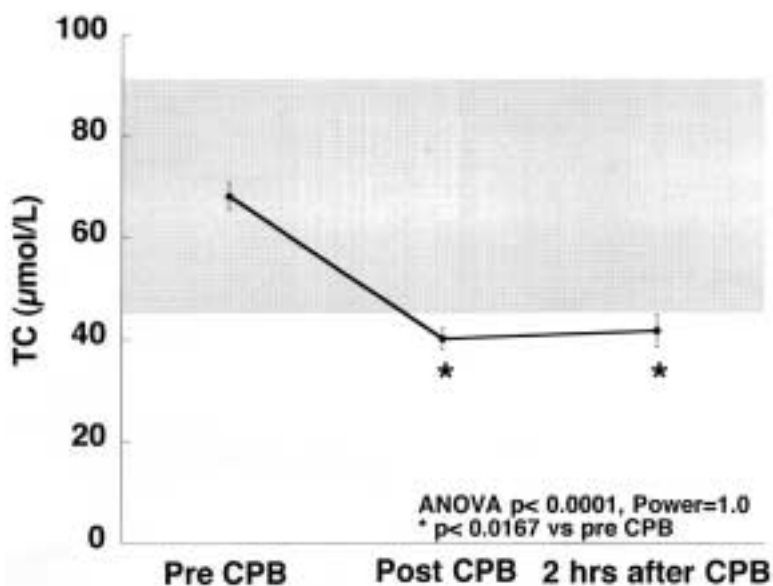


Fig. 2. Plasma total carnitine (TC) concentration. TC levels decreased parallel with FC concentration. Normal range for TC is indicated by dotted area. Error bar shows mean ± SE.

until assay. Plasma carnitine profiles [free carnitine (FC), acyl carnitine (AC), and total carnitine (TC)] were determined by a spectrophotometric method using Cobas Bio centrifugal analyzer (Hoffmann-La Roche Inc., Nutley, NJ).^{6,7} Normal values for the laboratory are as follows; TC: 45-91 μM/L, FC: 36-74 μM/L, and AC: 6-12 μM/L. This protocol was approved by the review committee of Seirei Hamamatsu General Hospital and informed consent was obtained from each patient.

All values were expressed as mean ± standard error (SE) and analyzed by a statistical analysis system (Stat View ver. 5.0, SAS Institute Inc., Cary, NC). Comparisons made regarding given parameters over the course of this study represented multiple repeated comparisons.

Therefore, we used one-way analysis of variance (ANOVA) to test statistical differences followed by a Student-Newman-Keuls test if ANOVA testing demonstrated that difference were present. A p<0.05 was considered statistically significant.

Results

Figures 1 and 2 demonstrate plasma FC and TC levels, respectively. The two concentrations decreased significantly and were below the normal values immediately after CPB. Moreover, they did not change significantly and remained less than the normal ranges two hours after CPB when all of the autologous blood was transfused

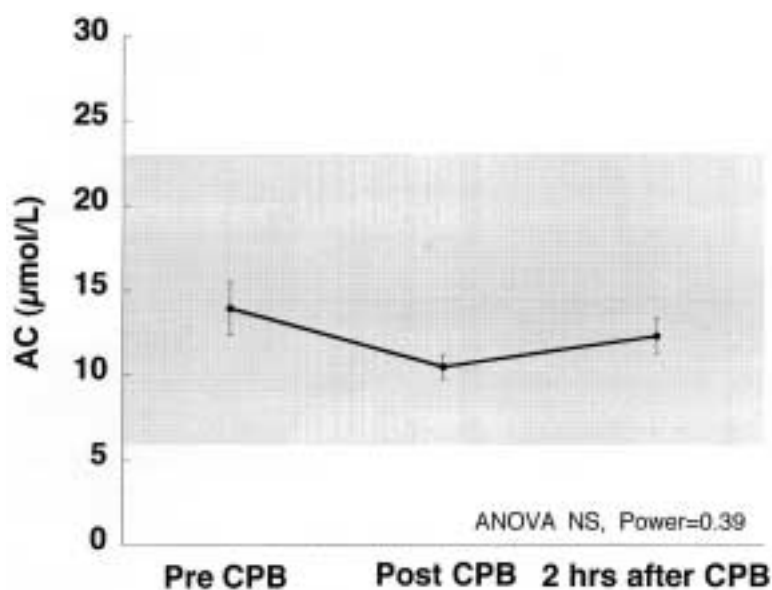


Fig. 3. Plasma acyl carnitine (AC) concentration. AC did not vary significantly over the course of this study and was always within the normal range. Normal range for AC is indicated by dotted area. Error bar shows mean \pm SE.

back to the patients. Figure 3 demonstrates that AC did not vary significantly over the course of this study and was always within the normal range.

Discussion

Two possible mechanisms might be considered to explain the decrease in plasma FC concentration in open heart surgery. First, during CPB, plasma carnitine could be excreted through extracorporeal ultrafiltration method (ECUM), which is routinely used for blood conservation in modern open heart surgery.⁸⁾ Although we did not measure carnitine concentrations in the filtrated water, this is supported by the fact that hemodialyzed patients exhibit a constant loss of plasma carnitine through filtration.⁴⁾ Moreover, a previous study has demonstrated positive effects of carnitine supplementation on skeletal muscular symptoms in hemodialyzed patients.⁹⁾ Second, endogenous carnitine biosynthesis might not be sufficient to restore plasma and myocardial carnitine to basal levels. Since the myocardium can not synthesize carnitine, carnitine is synthesized in the liver and kidney and transported to cardiac muscle. Substrate supply for carnitine synthesis could be reduced perioperatively due to ultrafiltration¹⁰⁾ and lack of oral intake. Furthermore, the synthesis in the liver might be damaged during CPB. Further studies measuring levels of 6-N-trimethyllysine, the precursor of carnitine in plasma and filtrated water will be necessary to elucidate the possible down regulation of the synthetic process.

On the other hand, AC concentration did not vary after

CPB despite using ECUM. It is reported that hypoxic and ischemic hearts have a rapid drop in FC with a coincident rise in AC, and carnitine was leaked.²⁾ AC could be released continuously from damaged skeletal and cardiac tissue due to physiologically abnormal perfusion and ischemia, respectively. Since development of AC inhibits adenylate translocase, which is responsible for transferring adenosin triphosphate (ATP) from mitochondria to the cytosol for its specific activity,¹¹⁾ it might be beneficial to the damaged myocardium after reperfusion to maintain AC levels within the normal range in the perioperative period, as seen in this study.

Although we did not examine carnitine levels in cardiac and skeletal tissue in this study, we believe that cardiac carnitine levels should decrease in reperfusion after cardioplegic arrest and decreased myocardial carnitine level might affect β -oxidation in FA metabolism. This speculation is supported by the fact that the tissue free carnitine level is decreased in the ischemic heart in the rat global no-flow model and that tissue carnitine is maintained mostly by a saturable carrier-mediated transport activated maximally at physiological concentration of extracellular FC.¹²⁾ Thus, the low plasma FC concentration noted in this study might not be adequate to activate this uptake mechanism.

Previous studies reported the beneficial effects of carnitine supplement on cardiac function in ischemia-reperfusion.¹³⁻¹⁵⁾ However, precise mechanisms of the beneficial effects of carnitine supplement still need to be elucidated. Carnitine supplement at physiological concentration (40 μ M/L) during reperfusion, not in cardiople-

gia, after cold cardioplegic arrest restored FA metabolism in an *ex vivo* blood perfused rabbit heart model.¹⁶⁾ On the other hand, interestingly, when carnitine was supplemented at 100 times physiologic dose (5 mM/L) during the reperfusion, the FA metabolism remained depressed but cardiac function and coronary blood flow significantly improved.^{15,16)} This might suggest that the high dose of carnitine supplement during reperfusion stimulates carbohydrate utilization rather than FA metabolism.^{16,17)} In addition, it has been reported that carnitine supplement suppressed the generation of free radical oxygen species¹⁸⁾ and preserved phospholipids¹⁹⁾ against ischemia-reperfusion injury. These beneficial effects of a carnitine supplement other than on metabolism could maintain the membrane stability in cardiac myocytes and coronary endothelial cells. Taken together our findings in this study and previous studies, carnitine supplement could be an effective therapeutic approach to abnormal cardiac metabolism and cardiac dysfunction after open heart surgery.

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