Randomized Trial of Carnitine for the Prevention of Perioperative Atrial Fibrillation

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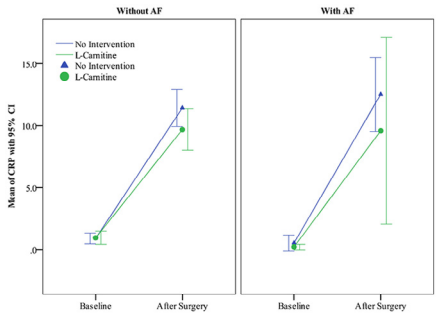
Atrial fibrillation (AF) is one of the most common complications in patients who undergo coronary artery bypass graft surgery (CABG). The aim of this study was to evaluate the effect of L-carnitine administration on postoperative AF and the levels of C-reactive protein (CRP) following CABG. The effects of L-carnitine on the incidence of acute kidney injury after CABG were also assessed. One hundred thirty-four patients undergoing elective CABG, without a history of AF or previous L-carnitine treatment, were randomly assigned to an L-carnitine group (3000 mg/d L-carnitine) or a control group. CRP levels, as a biomarker of inflammation, were assessed in all the patients before surgery as baseline levels and 48 hours postoperatively. Neutrophil gelatinase-associated lipocalin, as a kidney biomarker, was also measured in the patients before surgery and 2 hours thereafter. The incidence of AF was 13.4% in our population. The incidence of AF was decreased in the L-carnitine group (7.5% in the L-carnitine group vs 19.4% in the control group; $P = 0.043$) and the postoperative CRP level (8.79 ± 6.9 in the L-carnitine group, and 10.83 ± 5.7 in the control group; $P = 0.021$). The postoperative neutrophil gelatinase-associated lipocalin concentration demonstrated no significant rise after surgery compared with the preoperative concentration (72.54 ± 20.30 in the L-carnitine group vs 67.68 ± 22.71 in the placebo group; $P = 0.19$). Our study showed that L-carnitine administration before CABG might inhibit and reduce the incidence of AF after CABG. It seems that a rise in the CRP level, as an inflammation marker, may be associated with the incidence of AF. Inflammation as measured by CRP was also reduced in the carnitine group, compared with the control group.

Semin Thoracic Surg ■■:■■–■■ © 2017 Elsevier Inc. All rights reserved.

Keywords: L-carnitine, atrial fibrillation, coronary artery bypass grafting



The changes in hs-CRP levels and incidence of AF between groups.

Central Message

L-Carnitine administration before coronary artery bypass graft surgery reduces the incidence of postoperative atrial fibrillation.

Perspective Statement

Atrial fibrillation is one of the most common complications in patients who undergo coronary artery bypass graft surgery and has been associated with a prolonged length of hospital stay, intensive care unit readmission, and a greater need for reintubation. The aim of this study was to evaluate the effect of L-carnitine administration on postoperative AF following CABG.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia following coronary artery bypass graft (CABG) surgery.[1] The reported incidence of postoperative AF ranges from 25% to 40% post CABG, and up to 62% after a combined CABG and valve procedure.[1,2] The occurrence of postoperative AF has been associated with a prolonged length of hospital stay, intensive care unit readmission, and a greater need for reintubation.[3,4] AF can also cause atrial pump dysfunction and ventricular filling impairment with an increase in the incidence of heart failure and development of stroke, contributing to a rise in post-CABG disability and mortality.[5,6] Thus, it is crucial to prevent the occurrence of AF following CABG. Carnitine (3-hydroxy-4-N-trimethylaminobutyric acid) is an essential amino acid that is necessary for the transport of long-chain fatty acids from the cytoplasm of cells to the mitochondrial matrix facilitating energy production. Carnitine deficiency is associated with the accumulation of excess acyl-CoA esters and the disruption of intermediary metabolism. Its supplementation increases carnitine plasma concentrations. The use of carnitine reduced ischemia or reperfusion-induced injury in the myocardium in a number of experimental models. There are also no reports of toxicity from

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Registration number in IRCT: 2013010286987

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https://doi.org/10.1053/j.semtcvs.2017.08.006

an overdose of L-carnitine.[7] Recent studies have claimed that AF after CABG may be related to the inflammatory response, and that L-carnitine, as an inflammatory inhibitor, may diminish the incidence of AF after CABG.[8] However, because AF has significant interpatient differences and the efficacy of the drugs can be diverse among patients, investigating the effects of L-carnitine on post-CABG AF is of great clinical significance. Some studies have revealed that the time-dependent C-reactive protein (CRP) level, as a biomarker of inflammation, tends to significantly rise after surgery as a biomarker of inflammation.[6]

Acute kidney injury (AKI) is another serious complication of CABG that causes a postoperative increase in serum creatinine; it is detected in 5%-20% of patients.[9] Moreover, AKI necessitates dialysis in 1% of patients and is associated with extreme in-hospital morbidity and mortality.[9] Postsurgery AKI has been shown to be associated with the systemic inflammatory response during surgery and ischemia or reperfusion injury. L-Carnitine, as an antiinflammatory agent, may reduce the systemic inflammatory response and consequently improve the kidney function.[7]

In this randomized controlled trial, we assessed whether the administration of L-carnitine (3 g/d), commenced 2 days before selective CABG and continued for 2 days postoperatively, could prevent postoperative AF as compared with a control group. We also evaluated the effects of L-carnitine on the prevention of AKI following CABG as another end point by using neutrophil gelatinase-associated lipocalin (NGAL) as a kidney biomarker.

METHODS

This study was registered at the Iranian Registry of Clinical Trials (registration # 201301028698N7) and was approved by the Ethics Committee of Tehran Heart Center, a referral hospital. From April to December 2013, a total of 195 consecutive patients, who were scheduled to undergo CABG at Tehran Heart Center, were enrolled. The exclusion criteria comprised history of any preoperative supraventricular arrhythmias, concomitant valve surgery, history of the use of antiarrhythmic drugs except for beta-blockers and calcium-channel blockers, history of seizure or epilepsy, history of hypersensitivity to L-carnitine, chronic liver insufficiency (liver enzyme levels > 3 times the upper limit of normal), chronic kidney disease (stages IV and V), history of the use of antiinflammatory medications except for aspirin for at least 2 weeks before admission, hypothyroidism, and consumption of magnesium before CABG. To detect an effect size of at least 0.51 (30 mg/L difference of C_{max} [CRP kinetic parameter] levels) between groups with standard deviation of 58.5 mg/L,[10] with 80% power and 5% type I error, we needed 61 samples in each group. Considering 10% probability of sample loss increased the sample size to 67 in each group). Thus, 180 patients were included in the study population and randomly assigned to an L-carnitine group (3000 mg/d of L-carnitine, n = 90) or a control group (n = 90) via the permuted block randomization method, as is described in the Consolidated Standards of Reporting Trials (CONSORT) flowchart (Figure). The whole study population underwent on-pump cardiopulmonary bypass surgery.

All the patients underwent preoperative electrocardiography (ECG), chest X-ray, echocardiography, and selective coronary angiography. They also signed a consent form before surgery. Finally, 134 patients met the selection criteria for the randomized trial, with 67 patients assigned to receive L-carnitine and 67 to be included in the control group. An oral solution (1 g, 3 times a day) of L-carnitine (So.Se.PHARM, Italy) was administered to the 67 patients in the L-carnitine group from 2 days before the scheduled surgery to 2 days afterward, whereas those in the control group did not receive L-carnitine or a placebo. The assessors were blinded to the intervention groups. Continuous ECG monitoring was carried out for at least 7 days for all the patients. Optimization of magnesium serum levels and beta-blockers are considered for all patients undergoing CABG without contraindication. We continued b-blockers for those patients taking these medications preoperatively to avoid b-blockade withdrawal. Atorvastatin was also considered by some cardiologists to prevent POAF for statin-naive patients. AF was defined as the occurrence of at least 1 episode of AF (with or without symptoms) lasting for over 5 minutes and confirmed by ECG. The time of the onset of AF and its duration were observed and recorded. The adverse reactions associated with L-carnitine, as well as the complications, were followed up in both groups. The primary end point of the trial was the occurrence of postoperative AF.

As some other studies have revealed that the time-dependent CRP level tends to significantly rise after surgery and reach a peak within 48-72 hours ($P < 0.001$),[6,11] we assessed the CRP levels in all the selected patients before surgery and 48 hours postoperatively. High-sensitivity C-reactive protein (hs-CRP) was measured via the KRIPTOR ultrasensitive immunofluorescent assay (Brahms, Hennigsdorf/Berlin, Germany) with a detection limit of 0.06 mg/mL. Additionally, NGAL, as an emerging kidney biomarker, was measured in the patients before surgery as baseline levels and 2 hours after surgery to evaluate the effects of L-carnitine on the incidence of post-CABG AKI (defined as ≥ 50% or 0.3 mg/dL increase in serum creatinine during a 48-hour period according to the Acute Kidney Injury Network criteria) based on preclinical studies in animal models. In these studies, NGAL was identified as one of the most upregulated genes and proteins in the kidney very early in the course of AKI, especially within 2 hours of CABG.[12] The patients' serum creatinine levels before and then after surgery were also evaluated in the 2 groups until discharge from the hospital. Twenty-four hours' urine specimens were collected, and creatinine clearance was estimated using both Cockcroft-Gault and Modification of Diet in Renal Disease-7 formulas.

Statistical Analysis

The continuous data are described as means and standard deviations or medians with 25th and 75th percentiles when the data had a skewed distribution, and they were compared between the intervention and the control groups using the Student *t* or the Mann-Whitney *U* tests. The categorical variables are expressed as frequencies and percentages, and they were compared between the treatment and the control groups using the chi-square or the Fisher exact test. To adjust the effect of intervention on AF for sex, we

applied the Cochran-Mantel-Haenszel test and reported the adjusted results through common odds ratio with 95% confidence intervals. Additionally, we assessed the correlation between the CRP level change and the AF occurrence. All the statistical analyses were conducted using IBM SPSS Statistics 20.0 (IBM Corp, Armonk, NY). All *P* values equal to or less than 0.05 were considered statistically significant.

The authors are solely responsible for the design and conduct of this study, as well as for all the analyses and the drafting and editing of the paper. This study was awarded a grant by Tehran University of Medical Sciences as a residency research.

RESULTS

The patients' demographic data are described in Table 1. There were no significant differences in age, body mass index, history of myocardial infarction, ejection fraction, concomitant diseases (diabetes, hypertension, hyperlipidemia, and cerebrovascular accident), preoperative medications, number of involved vessels (as most of the patients had 3-vessel disease), baseline clearance of creatinine, and resumption of postoperative medications. All the patients showed good compliance with L-carnitine, except for 3 patients, who experienced nausea following the ingestion of the medication.

There were no significant differences in the average number of grafts, with the left internal mammary artery and saphenous vein graft being the ones most frequently used. The aortic cross-clamping

Table 1. Comparisons of the Patients' General Characteristics Between the Groups

Variable	L-Carnitine Group (n = 67)	Control Group (n = 67)	*P*
Age (y)	60.0 ± 9.2	59.9 ± 8.0	0.93
Sex (male)	54 (80.6%)	45 (67.2%)	0.08
BMI (kg/m^2)	28.2 ± 4.5	27.1 ± 4.1	0.16
Diabetes	23 (34.3%)	28 (41.8%)	0.37
Hypertension	42 (62.7%)	40 (59.7%)	0.72
MI	12 (18.2%)	15 (22.4%)	0.55
Hyperlipidemia	35 (52.2%)	32 (47.8%)	0.60
Smoking history	6 (9%)	4 (6%)	0.74
CVA	6 (9%)	2 (3%)	0.15
LVEF (%)	45.4 ± 8.8	42.8 ± 10.2	0.18
EF < 30	2 (3%)	5 (7.5%)	0.44
3VD	51 (76.1%)	54 (81.8%)	0.35
Beta-blocker	66 (98.5%)	66 (98.5%)	1.00
Ca^{2+} channel blocker	10 (14.9%)	7 (10.6%)	0.46
ACEI/ARB	53 (79.1%)	54 (80.6%)	0.83
Aldosterone antagonist	3 (4.5%)	8 (11.9%)	0.12
Nitrate	57 (85.1%)	55 (82.1%)	0.64
Statin	67 (100%)	67 (100%)	1.00
Postoperative beta-blocker	67 (100%)	64 (95.5%)	0.24
Postoperative ACEI/ARB	37 (55.2%)	42 (62.7%)	0.38

3VD, 3-vessel disease; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

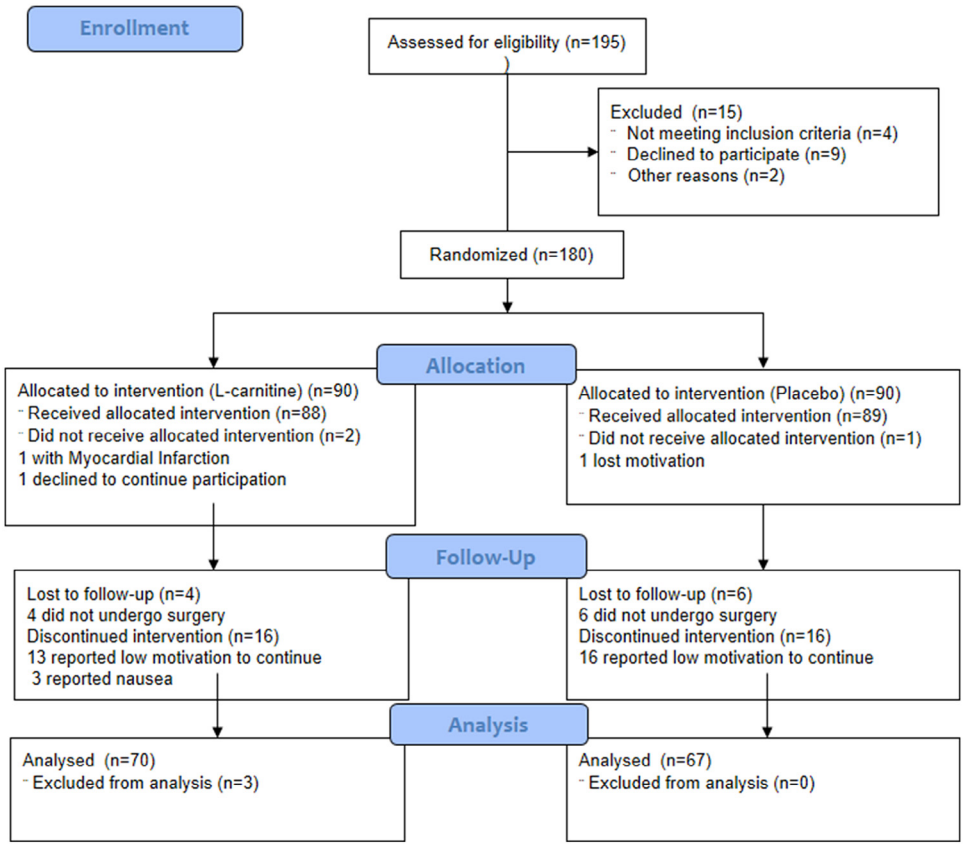

Figure. Consort flowchart. (Color version of figure is available online.)

time was lower in the L-carnitine group; the difference, however, constituted no statistically significant difference between the 2 groups ($P = 0.11$).

The incidence of postoperative AF in the 2 groups was evaluated: AF occurred in 18 (13.4%) patients. The incidence of AF following CABG in the L-carnitine group was significantly lower than that in the control group (7.5% vs 19.4%, respectively; $P = 0.043$). The fastest heart rate recorded in the L-carnitine group was 117 ± 11 bpm, which was significantly lower than that in the control group (133 ± 8 bpm) ($P < 0.0001$). The duration of AF in the L-carnitine group was remarkably shorter than that in the control group (3.9 ± 0.5 hours vs 6.4 ± 1.2 hours; $P < 0.001$). Time to AF in the control group was 2 (1-4) days, as compared with 2 (0.5-3) days in the intervention group ($P = 0.443$).

Given the significant difference in terms of gender between the 2 groups, the Cochran-Mantel-Haenszel test was used to evaluate the effect of carnitine on AF, adjusting for the gender imbalance (odds ratio: 0.34, 95% confidence interval: 0.11 to 1.04; $P = 0.052$).

The serum CRP levels in both groups were assessed via the hs-CRP assay (Table 2). The baseline CRP level (before surgery) showed no significant differences between the 2 groups (0.87 ± 1.98 mg/L in the L-carnitine group vs 0.81 ± 1.5 mg/L in the control group; $P = 0.8$). The CRP levels increased notably after surgery. The CRP levels, measured 48 hours following CABG, were significantly lower in the L-carnitine group than in the control group (9.67 ± 6.34 mg/L in the L-carnitine group vs 11.65 ± 5.31 mg/L in the control group; $P = 0.018$). The CRP change was also evaluated in both groups. The statistical analyses revealed a significantly higher increase in the levels of this biomarker in the control group than in the L-carnitine group (10.72 [7.21-13.87] mg/L vs 7.51 [4.17-13.28], respectively; $P = 0.021$). Although the association between hs-CRP and AF was not statistically significant, a trend was seen insofar as in the patients with AF a change in hs-CRP was more pronounced (10.7 [7.3-16.4] mg/L in those with AF vs 8.9 [5.4-13.7] mg/L in those without AF; $P = 0.307$). The power achieved was 20%.

In another part of our study, where we evaluated the impact of L-carnitine on post-CABG AKI, the postoperative NGAL concentration demonstrated no significant rise 2 hours after surgery compared with the concentration before CABG. The NGAL concentration change also showed no significant difference in both groups. The other data are depicted in Table 3.

Table 2. C-Reactive Protein Levels as the Primary Outcome

	L-Carnitine Group	Control Group	*P*
Incidence of AF (n = 18, 13.4%)	7.5% (n = 5)	19.4% (n = 13)	0.04
Duration of AF (h)	3.9 ± 0.5	6.4 ± 1.2	0.00
Baseline hs-CRP level (mg/L)	0.9 ± 2.0	0.8 ± 1.5	0.8
Post-CABG hs-CRP level (mg/L)	9.7 ± 6.3	11.6 ± 5.3	0.02
Hs-CRP Change	8.79 ± 6.9	10.8 ± 5.7	0.02

AF, atrial fibrillation; CABG, coronary artery bypass graft surgery; hs-CRP, high-sensitivity C- reactive protein.

Table 3. Comparison of the Patients' Kidney Function Characteristics Between the Groups

Variable	L-Carnitine Group (n = 67)	Control Group (n = 67)	*P*
Baseline NGAL (ng/mL)	43.7 ± 26.1	42.2 ± 21.7	0.88
Post-CABG NGAL (ng/mL)	72.5 ± 20.3	67.7 ± 22.7	0.19
NGAL change (ng/mL)	28.9 ± 30.1	25.5 ± 31.0	0.61
Baseline SCr (mg/dL)	0.8 ± 0.3	0.8 ± 0.2	0.41
Peak post-CABG SCr (mg/dL)	1.0 ± 0.4	1.1 ± 0.6	0.74
SCr change (mg/dL)	0.2 ± 0.2	0.3 ± 0.5	0.44
Baseline CL (mL/min)	88.9 ± 30.3	96.1 ± 44.4	0.55
Post-CABG CL (mL/min)	71.7 ± 22.2	73.1 ± 28.6	0.83
CL change (mL/min)	–17.2 ± 21.3	–23.0 ± 31.9	0.26

CABG, coronary artery bypass grafting; CL, creatinine clearance; NGAL, neutrophil gelatinase-associated lipocalin; SCr, serum creatinine.

Table 4. Comparison of the Patients' Postoperative Characteristics* and Clinical Outcomes

	L-Carnitine Group (n = 67)	Control Group (n = 67)	*P*
CPB time (min)	42.1 ± 21.2	38.2 ± 20.2	0.43
ACC time (min)	20.6 ± 15.6	22.1 ± 17.4	0.11
Prolonged mechanical ventilation	0	2 (3.0)	0.50
Inotrope usage	8 (12.5)	8 (12.5)	0.95
Blood product usage	10 (15.6)	17 (27.4)	0.11
Cardiac tamponade	2 (3.1)	0	0.65
ICU blood transfusion	24 (37.5)	27 (43.5)	0.49
Stroke	0	1 (1.5)	0.43

ACC, aortic cross-clamping; CPB, cardiopulmonary bypass; ICU, intensive care unit.
*Data are presented as mean ± SD or n (%).

We also assessed the post-CABG characteristics of the groups (Table 4). Renal failure, cardiac arrest, myocardial infarction, aortic dissection, and liver function impairment were not observed. Redo for bleeding was not performed. Stroke and coma was reported in 1 patient, and prolonged ventilation (>21 days) was observed in 2 patients—both in the control group. Two cases of cardiac tamponade and 1 case of cerebrovascular accident were detected in the L-carnitine group. Mortality was not seen during the follow-up period in both groups. There was also no significant difference between the 2 groups in terms of receiving inotropes following surgery ($P = 0.52$).

DISCUSSION

AF after cardiac surgery is a highly frequent complication that increases the risk of mortality and morbidity, predisposes patients to a considerably higher risk of thromboembolism and stroke, often needs supplementary treatment, and largely increases the costs

of postoperative care.[2,13] It is, therefore, clinically significant that post-CABG AF be prevented.

Among our study population, AF occurred in 18 (13.4%) patients. Although the incidence of AF in our study is considerably low compared with that in previous reports, it can be justified by some studies.[14-16] Mariscalco et al[14] used a bedside tool to predict postoperative AF and succeeded in presenting a prediction model that included such variables as chronic obstructive pulmonary disease, valve surgery, need for emergency surgery, and renal failure. We excluded all these risk factors in our study, hence our comparatively low incidence rate of postoperative AF.

Our findings also showed that the incidence of AF following CABG in the L-carnitine group was significantly lower than that in the control group (7.5% vs 19.4%; $P = 0.043$), indicating that L-carnitine was able to reduce the risk of post-CABG AF.

Carnitine is a natural amino acid that is necessary for the transport of long-chain fatty acids from the cell cytoplasm to the mitochondrial matrix, where β-oxidation of fatty acids and, thus, adenosine triphosphate (ATP) production occur.[7,17] Carnitine is also reported to be an essential cofactor that can reduce ischemia or reperfusion injury in the myocardium. Recent studies have indicated its effectiveness in the recovery of post-ischemic cardiac function, as confirmed by an experimental model of myocardial ischemia or reperfusion. These studies have demonstrated that carnitine can significantly reverse mechanical dysfunction during both myocardial ischemia and reperfusion.[18] Carnitine deficiency is the major cause of impaired metabolism, which principally results in cardiomyopathy.[19] Accordingly, the notion of carnitine administration as a treatment for the deficiency is supported by a substantial amount of evidence.[18,19] Moreover, carnitine in the myocardium prevents fatty acid accumulation and lactic acid production and augments the myocardial function.[18] A recent meta-analysis assessed 94 trials on the prevention of postoperative AF. All the 5 common interventions—namely beta-blockers, sotalol, amiodarone, magnesium, and atrial pacing—were shown to be effective in preventing AF. Nonetheless, they also exhibited potential cardiovascular side effects such as hypotension, bradycardia, and torsades de pointes.[20,21]

Our study showed that the incidence of AF following CABG in the L-carnitine group was significantly lower than that in the control group (7.5% vs 19.4%; $P = 0.043$), indicating that L-carnitine was able to reduce the risk of post-CABG AF. The duration of AF in the L-carnitine group was also significantly shorter than that in the control group (3.9 ± 0.5 hours vs 6.4 ± 1.2 hours; $P < 0.001$). In addition, the fastest ventricular rate was remarkably lower in the L-carnitine group. These results are similar to those reported by Cacciatore et al,[22] who showed that L-carnitine therapy in angina pectoris was correlated with a remarkable decrease in the frequency of ventricular arrhythmia. Di Biase et al[23] demonstrated that the cycle duration in the sinus node after carnitine administration was shortened by 5%. Our results also are consistent with those in another study, which reported that L-carnitine was able to reduce the incidence of ventricular and supraventricular arrhythmia in patients on hemodialysis.[23] The results of our study confirmed L-carnitine as an effective agent capable of preventing AF following CABG. This positive effect can be described by the following hypotheses.

Recent studies have demonstrated that during CABG, the myocardium needs extensive energy, which is provided by ATP production through fatty acid metabolism.[24] L-carnitine facilitates this process by the transport of free fatty acids across the inner mitochondrial membrane, leading to ATP production. Carnitine therapy (1 g) for 2 days before CABG surgery was associated with a higher ATP production in the myocardium.[25] In patients after CABG, L-carnitine has been demonstrated to increase the uptake of free fatty acids by the myocardium.[25] Research on dogs treated with L-carnitine in doses of 40-80 mg/kg/min revealed a decrease in the heart rate by about 17%-30%, respectively.[26] Heart electrophysiology after carnitine administration (30 mg/kg over 3 minutes) did not show any changes either in the conductivity time or in the refraction period.[23] Rizzon et al[27] observed a statistically significant drop in the frequency of ventricular arrhythmia in a group of patients with acute myocardial infarction, who had been given 100 mg of carnitine per kilogram of body weight. We chose the dosage of 3 g daily for 4 days based on such evidence and also the pharmacokinetics data in the existing literature. The oral bioavailability of L-carnitine is 10%-20% and its half-life elimination is 17.4 hours; consequently, this dosage seems to compensate carnitine deficiency for ATP production during surgery.

In our study, L-carnitine administration exerted a significant effect on the occurrence of AF after CABG. L-carnitine also delayed the onset of post-CABG AF and reduced its duration.

Another mechanism that supports the efficacy of L-carnitine in the prevention of post-CABG AF is its antiinflammatory effects as it is a well-known free radical scavenger.[7] CRP can be used to assess the systemic inflammation in a clinical setting; accordingly, we drew on this biomarker to evaluate the antiinflammatory effects of L-carnitine in light of the reports that L-carnitine is capable of reducing CRP levels.[28,29] In another study, which assessed the role of the preoperative administration of atorvastatin in the prevention of AF following CABG, CRP was also used.[6]

Our statistical analyses revealed that the time-dependent change in the CRP levels was significantly different between the L-carnitine and the control groups; this finding is similar to those reported by the following studies. In 1 study, which evaluated the effects of L-carnitine on plasma coagulation and anticoagulation factors in patients on hemodialysis, the CRP levels decreased significantly in the L-carnitine group (41%; $P < 0.01$) at the end of a 12-week period compared with the baseline.[30] In another study, which assessed the effects of L-carnitine on serum inflammatory cytokines in patients on hemodialysis with Lp (a) hyperlipoproteinemia, the serum CRP levels showed a significant decrease of 29% ($P < 0.05$) in the L-carnitine group.[31]

Because post-CABG AF often takes place within 2-4 days after the procedure, with a peak incidence on the second postoperative day, we measured the hs-CRP levels 48 hours after surgery in addition to the baseline levels.[14] Although the preoperative CRP levels were not significantly different between our 2 groups, the CRP levels obtained 48 hours postoperatively were significantly lower in the L-carnitine group. The CRP change in the patients

with AF was not statistically significantly different from that in those with normal sinus rhythm. This could be attributed to our small sample size as shown by the achieved power of 20%. However, a trend was clearly seen. The analysis showed that high postoperative CRP levels, as a biomarker of inflammation, might be associated with an increased risk of post-CABG AF.

Postoperative AKI, defined as a minimum 50% increase in serum creatinine (according to the Acute Kidney Injury Network criteria),[32] is an important complication and is accompanied by increased morbidity and mortality.[33] The glomerular filtration rate in all the patients undergoing CABG included in the current study declined postoperatively. This reduction was more prominent in the control group than in the L-carnitine group, although the difference was not statistically significant. The NGAL concentration also increased further in the control group than in the L-carnitine group, even though it was not significant. Suggested as an early indicator of impaired renal function, NGAL may be superior to serum creatinine in terms of diagnostic accuracy for reduced creatinine clearance. In addition, it is reported to be a more sensitive marker of changes in creatinine clearance than serum creatinine.[32] NGAL is detected in the urine and serum within 3 hours of ischemic injury in both mouse and rat models of renal failure.[34] It is critical that the currently promising biomarkers go through several clinical validation processes of both their assay performance and their diagnostic utility. It is hoped that clinical trials will yield new therapies that can be introduced earlier in the course of the disease to reverse this fundamentally reversible condition. Because other biomarkers such as cystatin-C, as an early marker of changes in the glomerular filtration rate after CABG, have been assessed in previous studies,[35] we chose NGAL as another novel biomarker. In prospective studies of children who underwent elective cardiac surgery, AKI occurred 2-3 days after surgery. In contrast, NGAL levels in urine and plasma—measured with the enzyme-linked immunosorbent assay—revealed a dramatic increase within 2 hours of the surgery in those who subsequently developed AKI. Both urine and plasma NGAL levels were excellent independent predictors of AKI, with a receiver operating characteristic curve of more than 0.9 for the measurements made between 2 and 6 hours.[15,36] These findings have now been confirmed and published in several additional prospective studies of adult and children who developed AKI after such defined clinical events as cardiac surgery. A recent study showed that in subjects undergoing cardiac surgery, the 2-hour postoperative plasma NGAL levels were strongly correlated with the duration and severity of AKI as well as the length of hospital stay and that the 12-hour plasma NGAL level was strongly correlated with mortality.[34] Nevertheless, AKI occurrence may be associated with post-CABG NGAL concentration levels at a different time point (ranging between 2 and 6 hours after surgery), as was shown in a study conducted by Mishra et al.[12] This may be one of the reasons why the rise in the NGAL concentration was not significant in both groups in our study.

Our results may be explained by several factors and limitations. Some patients at the highest risk of ischemia or reperfusion injury during CABG surgery (eg, those with acute myocardial infarction, shock, or emergency surgery; those undergoing concomitant valve surgery; and those with advanced renal disease) were not included in this study. The effects of L-carnitine in other populations, particularly those at higher risk of ischemia or reperfusion injury, might be different. The sample size was calculated based on the changes of CRP after CABG based on previous studies as the incidence of AF was various significantly among them. There was also a large decrease from the randomized to the analyzed population as another limitation of the study. Further, we applied a specific dosing regimen of L-carnitine (3 g/d) based on the similar studies and the oral bioavailability of L-carnitine. Although the absorption and plasma half-life of L-carnitine suggests that adequate levels were achieved, the intracellular kinetics of L-carnitine are not well understood, and it is possible that a different dose, dosing strategy, and duration would yield dissimilar results. Moreover, the control group did not receive a placebo and was not blinded to treatment allocation. We would strongly recommend serial measurements of hs-CRP levels with a view to establishing whether there is a definite correlation between the incidence of AF and the level of hs-CRP.

Overall, the findings of the present study showed that L-carnitine administration before CABG might lessen the incidence of AF following CABG.

SUPPLEMENTARY MATERIAL

Supplementary materials associated with this article can be found in the online version at https://doi.org/10.1053/j.semtcvs.2017.08.006.

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