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Original Article

L-Carnitine supplementation for the prevention of postoperative atrial fibrillation in aortic valve surgery

Running head: Prevention of POAF by L-Carnitine

Yasushige Shingu[1], PhD, Nobuyasu Katoh[1], PhD, Tomonori Ooka[1], PhD, Hiroki Katoh[2], PhD, Satoru Wakasa[1], PhD

[1]Department of Cardiovascular and Thoracic Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

[2]Emergency and Critical Care Center, Hokkaido University Hospital, Sapporo, Japan

Address reprint requests to Dr. Satoru Wakasa, MD, PhD

Department of Cardiovascular and Thoracic Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University

Kita-15, Nishi-7, Kita-Ku, Sapporo 060-8638, Japan

Tel: +81-11-706-6042; Fax: +81-11-706-7612; Email: wakasa@med.hokudai.ac.jp

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Abstract

Objectives: L-carnitine, a quaternary amine, improves fatty acid metabolism in the heart and has anti-inflammatory effects. Several studies have reported the efficacy of L-carnitine for the prophylaxis of arrhythmia. We assessed the clinical effectiveness of L-carnitine in preventing postoperative atrial fibrillation (POAF) in aortic valve surgery.

Methods: Thirty patients who underwent aortic valve surgery were included. Fifteen patients had no prophylaxis other than conventional measures (control), while 15 patients received oral L-carnitine for nine days (daily dose of 3 g). The incidence of POAF during one week after surgery was compared between the two groups. The multivariable logistic regression analysis for POAF was performed using the pre- and intraoperative parameters.

Results: Preoperative characteristics and operative data were comparable between the groups. The POAF rate was significantly lower in the L-carnitine group than in the control (20% and 60%, respectively; P=0.025). L-carnitine use was an independently negative predictor for POAF (odds ratio, 0.067; 95% confidence interval, 0.006-0.768).

Conclusions: L-carnitine administration may have potential for the prevention of POAF in aortic valve surgery.

Introduction

New-onset postoperative atrial fibrillation (POAF) is still one of the major complications of cardiothoracic surgery, even with improvements in surgical techniques and anesthesia. The incidence of POAF has been 30–65% for the past 20 years (1, 2). POAF may induce thromboembolic events and heart failure (3), and the length of hospital stay of POAF patients is approximately 4 days longer than patients without POAF (4). Hence, the POAF patient subgroup has higher medical costs during the initial hospitalization than the non-POAF patient subgroup (mean cost difference of $13,993) (4).

We recently conducted a study examining atrial gene expression associated with metabolism of fatty acids, which accounts for 70% of the energy production in the normal working heart. The gene expression of fatty acid binding protein 3 (*FABP3*), which is involved in the cells' fatty acid uptake and intracellular fatty acid transport, was significantly lower in the POAF group than in the non-POAF group regardless of age and left atrial diameter (5). L-carnitine, a quaternary amine, improves fatty acid metabolism, and its administration can reverse reduced *FABP3* (6). In a meta-analysis, the administration of L-carnitine was associated with a 65% reduction in arrhythmia after myocardial infarction (7). However, it has not been used for the prevention of POAF in valve surgery, although it is potentially considered as a prophylactic therapy. We hypothesized that L-carnitine supplementation may be effective for the prevention of POAF in heart valve surgery. This study aimed to compare the incidence of POAF between this interventional group by L-carnitine and our historical control.

Methods

Subjects

The study was a partly interventional study including 30 patients: 15 patients who underwent aortic valve surgery from 2017 to 2019 (L-carnitine group) and age-matched 15 patients from 2013 to 2015 (historical control). We included the patients from our previous prospective study for the control group: the same detection methods for POAF was used in the study (5). The number of patients in interventional group was calculated based on a sample size analysis using 53% and 65% as a threshold and the expected reduction rate of POAF (7-9). Patients were excluded from the study if they met the any of the following: (i) a history of atrial fibrillation before surgery; (ii) underwent emergent surgery, aortic surgery using deep hypothermia, CABG or mitral repair as the main procedure; (iii) had renal failure (serum creatinine > 1.5 mg/dl) because L-carnitine is cleared in urine; and (iv) were taking any supplements such as vitamins C and E, and polyunsaturated fatty acids (PUFAs) before surgery. However, patients taking preoperative medications such as beta-blockers and statins were not excluded. The Ethics Review Committee of Hokkaido University Hospital approved the study protocol (No: 016-0358). All patients provided informed consent for inclusion in the study. The study was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry: UMIN000025737.

Intervention protocol

The patients in the L-carnitine group were administered with L-carnitine before and after surgery for nine days perioperatively (**Fig. 1**). A 10% L-carnitine (L-Cartin® FF oral solution, Otsuka Pharmaceutical Co., Ltd., Tokyo) (3 g/day) was administered

daily to the patients in three oral doses of 1 g each for two days immediately before surgery. Similar doses were administered to the patients from postoperative days 1 to 7. This dose was determined according to the previously reported meta-analysis (7), where 2 g/day is the minimally effective dosage for prevention of arrhythmia after myocardial infarction, and the product information of L-Cartin® that stated 3 g/day as a maximum dose. The period of two days before surgery was set according to a previous study using L-carnitine for CABG (10). The selection of seven days after surgery was based on the fact that POAF usually occurs within seven days postoperatively (11).

Detection of postoperative atrial fibrillation and biomarkers for inflammation and myocardial damage

POAF was defined as postoperative AF lasting at least 30 seconds. Electrocardiographic monitoring of all patients was conducted for 24 h a day using a telemetry system (FUKUDA DENSHI, Tokyo, Japan). Our therapeutic strategy for POAF was anticoagulation, normalization of serum potassium, and administration of class I antiarrhythmic agents. Cardioversion was performed when hemodynamic compromise was evident. Amiodarone was administered for refractory POAF. Postoperative maximum C-reactive protein (CRP), creatine kinase MB (CK-MB), and creatinine were also assessed during the 7-day postoperative period.

Statistical analyses

Summary statistics of patients' characteristics were presented as mean ± standard deviation or median (interquartile range). The continuous values with normal distributions were compared by the *t* test and those with non-normal distributions by

the Mann-Whitney *U* test. The incidence of POAF and other categories in the two groups were compared using the chi-square or Fisher's exact test as appropriate. A two-sided P value less than 0.05 was considered statistically significant. The factors for multivariable analysis of POAF were selected by forward selection method using the pre- and intraoperative parameters with P value < 0.05 in the univariate analysis. Firth procedure which can be used with small datasets was finally adopted for the multivariable analysis. Data were analyzed using SPSS (SPSS Inc. Chicago, IL) and SAS (SAS Institute Inc. Cary, NC)

Results

Preoperative and operative data

Table 1 shows the patient characteristics and preoperative echocardiographic parameters in the control and L-carnitine groups. All the preoperative characteristics including age, blood pressure, and the rate of statins and β-blockers were comparable between the groups. The parameters of electrocardiogram were comparable between the groups. No difference existed in the cardiac functional parameters including left ventricular dimensions, ejection fraction, left atrial volume index, and the degree of valve disease.

Table 2 shows operative data in the control and L-carnitine groups. All the patients underwent aortic valve replacement or valve-sparing aortic root replacement. Concomitant procedures, aortic cross clamp times, cardiopulmonary bypass times, and amount of transfusion were comparable between the groups.

Postoperative data

No patients presented with any side effects of L-carnitine; all completed the protocol. **Table 3** shows the postoperative data in the control and L-carnitine groups. The POAF rate was significantly lower in the L-carnitine group than in the control (20% and 60%, respectively; P=0.025). Postoperative maximum CRP tended to be lower in the L-carnitine group than in the control. No significant difference existed in postoperative maximum CK-MB and creatinine, duration of hospital stay. The parameters of electrocardiogram before discharge were comparable between the groups.

Multivariable analysis for POAF

In the univariate analysis for POAF, age, the preoperative level of brain natriuretic peptide, left atrial volume index, L-carnitine use, aortic cross clamp time, and postoperative maximum CRP were significantly different between the POAF (n=12) and non-POAF groups (n=18). In the multivariable analysis for POAF using the pre- and intraoperative parameters, age and L-carnitine use were the independent predictors for POAF (**Table 4**). The distribution of age in POAF and non-POAF groups was shown in **Fig. 2**. The patients with POAF were significantly older than those without POAF; the distribution of age was comparable between control and L-carnitine groups.

Discussion

We demonstrated that the incidence of POAF was lower in the L-carnitine group than in the control group. L-carnitine use was an independently negative predictor for POAF.

Previous studies of preventive measures for POAF

The recommended first-line prophylaxis is preoperative administration of beta-blockers (12). In a recent meta-analysis including 497 CABG cases, carvedilol was reported to be more effective than metoprolol for the prevention of POAF (13). However, beta-blockers would not be applied to those with bradycardia and hypotension after surgery. While the main effects of beta-blockers would be the suppression of sinus and sympathetic activation, anti-oxidative or anti-inflammatory properties would be additional. Other anti-arrhythmic agents, e.g., amiodarone, sotalol, and non-dihydropyridine calcium channel blockers are not the first-line agents because of negative inotropic effect, QT interval prolongation, and extra-cardiac side effects.

Antioxidants have been also candidates for POAF prevention. Reactive oxygen species in the atrium has been reported to be a key determinant of myocardial redox balance and associated with POAF (14). In a meta-analysis of five randomized controlled trials with 567 patients, prophylactic use of vitamins C and E was reported to significantly reduce the incidence of POAF. However, there was no significant effect on POAF in a subgroup analysis of those receiving vitamin C only (15). Omega-3 PUFAs (n-3 PUFAs), with their anti-inflammatory properties and antiarrhythmic effects, may prevent POAF after open-heart surgery. Although a significant effect of n-3 PUFAs was reported in patients undergoing CABG in a

meta-analysis (16), the effect was invalidated by a large multinational randomized controlled trial (17).

In a recent study which tried to identify specific gene transcripts of the atrium, POAF patients had preoperative left atrial tissue profiles suggestive of more inflammation and worse inflammatory handling (18). A meta-analysis suggested that steroid prophylaxis may reduce POAF (19). However, the risk of infection would be the major concern for the use of steroid.

Atrial pacing appears to reduce the incidence of POAF (20). Biatrial pacing would be the most efficacious, while right atrial pacing alone may reduce the incidence of POAF. Left atrial pacing alone does not reduce the incidence of POAF.

The management of postoperative electrolyte concentrations would be also important for the prevention of POAF. In a recent large observational study, serum potassium concentration < 4.5 mmol/L was associated with an increased risk of POAF (21). On the other hand, there is a report suggesting that potassium supplementation is not protective against POAF (22). Further studies would be necessary to examine whether potassium supplementation can prevent POAF.

Taken together, there is currently no standard prophylactic strategy that eliminates POAF after CABG. Furthermore, reports regarding the incidence and prevention of POAF in valvular surgery are scarce.

Implications of the use of L-carnitine for POAF prevention in valve surgery

The L-Cartin® FF oral solution 10% is indicated only for primary or secondary carnitine deficiency. As an off-label use, an effect of L-carnitine in prevention of arrhythmia was reported in a meta-analysis of myocardial infarction (7). Furthermore,

Dastan et al. have recently reported that L-carnitine was effective for POAF prevention after CABG in a randomized trial (10). They also suggested that L-carnitine has anti-inflammatory effects, because the levels of CRP 48-h after surgery were significantly lower in the L-carnitine group than in controls. In the present study, the postoperative maximum CRP was significantly higher in POAF group than in non-POAF group (data not shown), while maximum CRP was comparable between control and L-carnitine groups.

In a heart failure animal model, L-carnitine has been reported to increase *FABP3* (6), which was reduced in POAF patients in our previous study (5). During cardiac surgery using high-dose heparin, serum-free fatty acid levels can increase to a harmful level (lipotoxicity) (23). We speculate that L-carnitine may prevent perioperative lipotoxicity by enhancing fatty acid metabolism and reducing lipid droplets in the myocytes, although it is difficult to confirm this mechanism in humans.

Limitations

The study has several limitations. First, this was a single institutional study in a small group of patients. We are planning a randomized trial with more patients based on the present preliminary study. Second, the study period was different between the groups; however, the strategies for myocardial protection and temperature during surgery, as well as hemodynamic and glycemic control in the intensive care unit, were not changed in the study period. Third, the POAF rate in the control group was relatively high (60%). We speculate that the reasons are the difference of detection method of POAF and relatively large left atrial volume of the patients in the present study. The incidence of POAF after valve surgery has been reported to be from 34% to 49% (1).

However, the detection methods of POAF are various: 24-h telemetry, electrocardiogram at symptom presentation, and any interventions for POAF. The rate of POAF with any intervention was 47% in the present study. In another study of aortic valve surgery (2), the POAF rate was 65% in patients with enlarged left atrium. The preoperative values of LAVI (48 and 44 ml/m^2, in control and L-carnitine, respectively) were over twice as large as the normal value (22 ml/m^2).

Conclusion

The POAF rate was significantly lower in the L-carnitine group than in the control. L-carnitine administration may have potential for the prevention of POAF in aortic valve surgery.

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Conflict of interest: None.

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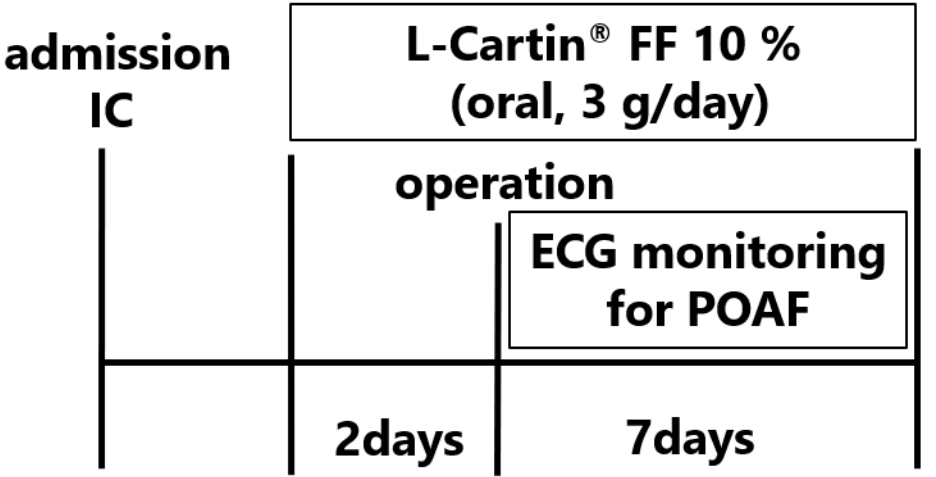
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Figure legends

Figure 1. Intervention protocol in L-carnitine group. ECG, electrocardiogram; FF, free form; IC, informed consent; POAF, postoperative atrial fibrillation.

Figure 2. Distribution of age in POAF and non-POAF groups. POAF, postoperative atrial fibrillation.


admission
IC
L-Cartin® FF 10 %
(oral, 3 g/day)
operation
ECG monitoring
for POAF
2days
7days

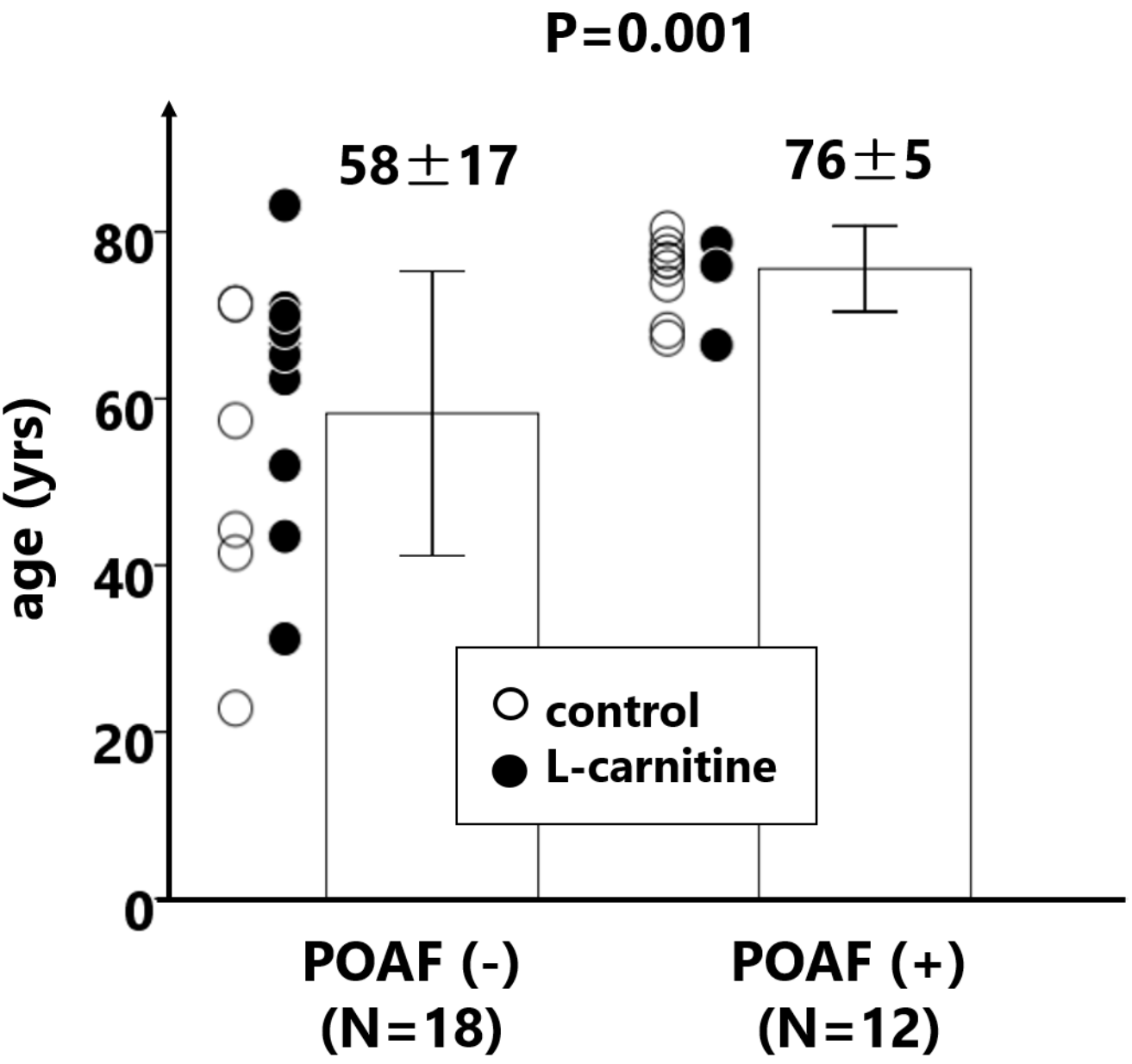

P=0.001
58±17
76±5
80
60
40
20
0
age (yrs)
control
L-carnitine
POAF (-)
(N=18)
POAF (+)
(N=12)

Table 1. Patient characteristics and preoperative echocardiographic parameters

Variables	Control (n=15)	L-carnitine (n=15)	P values
Male, n	6	7	0.71
Age, yrs	72 (57-78)	68 (62-71)	0.24
Body mass index, kg/m^2	23 ± 3	22 ±2	0.35
Heart rate, bpm	70 ± 8	72 ± 10	0.93
Systolic blood pressure, mm Hg	120 ± 16	124 ± 15	0.44
Diastolic blood pressure, mm Hg	59 ± 11	64 ± 14	0.26
Diabetes mellitus, n	2	2	1.00
Coronary artery disease, n	2	1	1.00
Medications			

Table 2. Operative data in control and L-carnitine groups

Variables	control (n=15)	L-carnitine (n=15)	P values
Aortic valve replacement, n	13	14	1.00
Aortic root replacement, n	2	1	1.00
Mitral valve repair, n	1	1	1.00
CABG, n	1	1	1.00
Aortic cross clamp time, min	101 (79-159)	89 (79-111)	0.33
Cardiopulmonary bypass time, min	141 (130-214)	138 (117-163)	0.44
Transfusion			
Red cells concentrates, unit	4 (0-12)	2 (0-4)	0.43
Fresh frozen plasma, unit	8 (0-22)	6 (0-10)	0.60
Platelet concentrates, unit	10 (0-20)	0 (0-10)	0.15

Values are median (interquartile range). CABG, coronary artery bypass grafting

Table 3. Postoperative data in control and L-carnitine groups

Variables	control (n=15)	L-carnitine (n=15)	P values
POAF, n	9	3	0.025
Maximum CRP, mg/dL	8.5 ± 2.3	6.8 ± 2.3	0.055
Maximum CK-MB, IU/L	42 ± 14	45 ± 20	0.68
Maximum creatinine, mg/dL	0.93 ± 0.36	1.03 ± 0.35	0.44
Hospital stay, d	15 (13-43)	16 (12-21)	0.51
Electrocardiogram before discharge			
Heart rate, bpm	88 ± 13	87 ± 17	0.89
PQ interval, ms	168 ± 22	159 ± 35	0.42
QRS duration, ms	113 ± 22	107 ± 20	0.56
Complete atrioventricular block, n	1	0	1.00
Left bundle branch block, n	1	0	1.00
Right bundle branch block, n	2	2	1.00

Values are mean ± standard deviation or median (interquartile range). CK, creatine kinase; CRP, C-reactive protein; POAF, postoperative atrial fibrillation

Table 4. Multivariable analysis for the incidence of POAF

Variables	odds ratio	95% CI	P values
Age	1.140	1.011-1.285	0.032
Carnitine supplementation	0.067	0.006-0.768	0.049
Aortic cross clamp time	0.967	0.930-1.005	0.085

CI, confidence interval; POAF, postoperative atrial fibrillation.