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1 *Original*

2 **Incidence of atrial fibrillation after esophageal cancer surgery with L-carnitine**
3 **use: A preliminary single-group interventional study**

4

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22

23 **Key words:** Postoperative atrial fibrillation, Esophagus, Cardiovascular

24

25 **Abstract**

26 **Purpose:** We aimed to investigate the POAF rate and blood FABP4 levels after perioperative L-
27 carnitine administration in patients with esophageal cancer.

28 **Methods:** L-carnitine (3 g in three divided doses) was administered to 15 patients for two days
29 before and three days after surgery. POAF during the study period and blood FABP4 levels
30 (ELISA) before and after L-carnitine administration were evaluated. Accurate 95% confidence
31 intervals (CI) for POAF incidence and changes in blood FABP4 levels were calculated. The
32 preoperative predicted POAF rate was calculated using an application for esophageal cancer. The
33 correlation between FABP4 levels and predicted POAF rate was analyzed using Pearson's
34 coefficient (r).

35 **Results:** Thirteen patients completed the study. The predicted POAF rate was 24% (17%, 34%)
36 (median; interquartile range). The actual incidence of POAF was 7.7% (95% CI: 0.2%–36%).
37 Blood FABP4 levels changed from 10.3 to 7.0 ng/mL; the average change was –3.3 (95% CI: –6.6
38 to –0.1). A positive correlation was found between the preoperative FABP4 levels and predicted
39 POAF rates ($r = 0.564$).

40 **Conclusions:** The POAF rate after esophageal surgery was 7.7% with L-carnitine. L-carnitine may
41 reduce blood FABP4 levels. This preliminary study will contribute to the planning of sample size in
42 future randomized trials.

43

44 **Introduction**

45 Postoperative atrial fibrillation (POAF) occurs in 9%–46% of patients undergoing esophageal
46 resection [1], which can lead to an increase in complications (e.g., hypotension, heart failure, stroke,
47 and systemic embolization). In addition to prolonging hospital stay and increasing medical costs for
48 anti-arrhythmic drugs, POAF might affect the long-term prognosis in patients with esophageal
49 cancer. [2]. β -blockers and amiodarone (group III antiarrhythmic drug) are reportedly effective in
50 preventing POAF in patients with esophageal cancer [1, 3]. However, they are not commonly used;
51 in some cases, they cause side effects such as bradycardia and hypotension. Therefore, there is a
52 need for an effective method for POAF prevention with fewer side effects.

53 POAF occurs most frequently within 2 days of surgery, suggesting an association with
54 inflammation [4]. However, the mechanism of POAF in esophageal surgery remains unclear. It has
55 been recently reported that adipokines (e.g., fatty acid-binding protein 4 [FABP4]) secreted from
56 adipose tissue are important for the progression and metastasis of malignant tumors [5]. Adipokines
57 are also increased in patients with atrial fibrillation (AF) and are suspected to be the reason for AF
58 in patients with malignant tumors [6]. Although the relationship between POAF and adipokines in
59 patients with malignant tumors is unknown, a similar mechanism is highly suspected. FABP4 is
60 reportedly a new biomarker for congestive heart failure [7] and AF recurrence after catheter
61 ablation [8].

62 L-carnitine, an amino acid derivative, reportedly reduces the serum levels of toxic
63 adipokines [9]. While L-carnitine is indicated in carnitine deficiency, it has recently been reported
64 to be effective in suppressing ventricular arrhythmias after myocardial infarction [10] and POAF
65 after coronary artery bypass surgery (CABG) [11]. It is well tolerated, with no reports of serious
66 side effects, and can be administered safely in the perioperative period [12]. Till date, there have
67 been no reports of L-carnitine administration for POAF prevention after esophageal cancer surgery.

68 Thus, this exploratory single-group interventional study was designed to obtain a 95% confidence
69 interval (CI) of POAF incidence with L-carnitine administration, and thus provide basic data for
70 future randomized controlled trials. Therefore, in this study, we did not assess the effect of L-
71 carnitine administration by comparing to those without the administration as control. Furthermore,
72 we examined changes in blood levels of FABP4.

73

74 **Materials and Methods**

75 *Study design and setting*

76 This was a nonblinded, single-group interventional study. Patients who underwent esophagectomy
77 for esophageal cancer between Mar. 2021 and Jun. 2022 at Hokkaido University Hospital were
78 eligible for the study. The disease was staged based on the Japanese Classification of Esophageal
79 Cancer, 11th Edition [13, 14]. The cStage was based on the diagnosis at the time of surgery and
80 included patients who received neoadjuvant therapy. Electrocardiography and transthoracic
81 echocardiography were performed within three months before surgery. Heart rhythm, PQ, and QRS
82 intervals were assessed on electrocardiograms. The left ventricular end-diastolic dimension, ejection
83 fraction, and left atrial volume index were assessed using echocardiography. Exclusion criteria were
84 as follows: history of AF and lethal arrhythmia, unstable angina, acute myocardial infarction, renal
85 failure on hemodialysis, and use of digitalis or group I and III antiarrhythmic drugs. The study
86 protocol was approved by the University's ethics committee (No. 018-046; date of approval: Jan.
87 14th, 2021) and was registered in the Japan Registry of Clinical Trials (No: jRCTs011200020; date
88 of registration: Jan. 27th, 2021). Written informed consent was obtained from all the patients.

89

90 *L-carnitine administration and estimation of blood FABP4 levels*

91 The patients were administered L-carnitine (L-Cartin[®] FF oral solution 10%; Otsuka
92 Pharmaceutical Co., Ltd., Tokyo, Japan) for two days preoperatively and for three days after
93 surgery (**Fig. 1**). L-carnitine was administered daily to the patients at three oral doses of 1 g (1,833
94 JPY:12.4 USD / day). Because oral intake was not applicable to patients after surgery, L-carnitine
95 was administered postoperatively through surgically inserted enteral tubes. The dose was based on a
96 meta-analysis [10], where 2 g/day was the minimally effective dose for arrhythmia. The maximum
97 dose recommended on the product label is 3 g/day.

98 Blood samples (1 mL) were obtained before and after surgery (**Fig. 1**). The first and second
99 blood samples were obtained at 6:00 AM on the first and last days of L-carnitine administration.
100 The serum was separated in a refrigerated centrifuge (4 °C) at 3,500 rpm for 10 min and preserved
101 at -80 °C until further analysis. FABP4 levels were estimated using a Human FABP4/A-FABP
102 ELISA Kit (Catalog Number EH177RB; Thermo Fisher Scientific Inc., Waltham, MA, USA)
103 according to the manufacturer's instructions and expressed as ng/mL.

104

105 ***Definition of POAF and monitoring***

106 The incidence of arrhythmia was monitored using a 24-h electrocardiogram, 3 days after surgery
107 (**Fig. 1**). The observation duration was determined based on the routine monitoring period at our
108 institution and period during which POAF has been reported [4]. POAF was defined as AF that
109 continued for > 30 seconds [15]. POAF was determined when the following conditions were
110 satisfied in leads II, III, or aVF: 1) absence of P-waves, 2) presence of irregular and fine tremors
111 (fibrillation waves) at baseline, and 3) irregular RR intervals. The diagnosis of POAF was made by
112 an investigator (Y.S.) and a cardiac surgeon not involved in the study. Atrial flutter was also noted
113 if the flutter continued for more than 30 s.

114

115 ***Predicted POAF rate***

116 The predicted POAF rate was estimated using an application established by Amar et al. [16]
117 A multivariate logistic regression model used the preoperative brain natriuretic peptide (BNP) levels
118 together with age, body mass index, and history of AF to predict the risk of POAF after
119 esophagectomy. The application was not openly accessible and was kindly provided by the
120 developer. Plasma BNP levels were estimated within one week before surgery.

121

122 ***Statistical analysis***

123 All values are presented as median (interquartile range [IQR]). A sample size of 13 was required to
124 achieve an accurate 95% CI width of $\leq 40\%$. Assuming a dropout rate of 10%, the required number
125 of cases was set to 15. An exact Clopper-Pearson 95% CI was obtained for the primary endpoint,
126 that is, the incidence of POAF within 3 days after surgery. Changes in blood FABP4 levels were
127 evaluated using paired t-tests; the average change was indicated with 95% CI. Correlation between
128 the preoperative FABP4 levels and predicted POAF rates were examined using Pearson's
129 coefficient (r). The data were analyzed using GraphPad Prism (version 9.4.1, GraphPad Software,
130 San Diego, CA, USA) and EZR (Jichi Medical University Saitama Medical Center, Saitama, Japan)
131 for R. EZR is a modified version of R commander which is designed to add statistical functions
132 frequently used in biostatistics.

133

134

135 **Results**

136 ***Preoperative data***

137 Fifteen patients were enrolled in the study. Two patients were excluded; one for refusal to consume
138 L-Cartin® FF due to its sourness and another due to postoperative delirium. Finally, 13 subjects
139 who completed the protocol were included in this study.

140 **Table 1** shows the patients' preoperative characteristics. The median age of the patients
141 was 70 years (64, 76). Three-quarters of the patients had advanced cancer (stage II–IV) and more
142 than half of the patients had hypertension. Twenty-three percent of the patients received β -blockers
143 preoperatively. The BNP value was missing in one patient; thus, the predicted POAF rate was
144 calculated in 12 patients. The median predicted POAF rate was 24% (17%, 34%).

145 **Table 2** shows the preoperative hemodynamic parameters. All patients had normal sinus
146 rhythm and the heart rate was 71 (61, 76) bpm before surgery. The patients had normal left
147 ventricular size, ejection fraction, and no significant valve dysfunction. The left atrial volume index
148 was 31 (25, 40) mL/m², and 5 (38%) of the patients had an abnormally large left atrium (> 34
149 mL/m²) [17].

150

151 ***Operative and postoperative data***

152 **Table 3** shows the operative and postoperative data. Robotic surgery was performed in three cases,
153 and video-assisted thoracoscopic surgery was performed in the remaining cases. The retrosternal
154 route was used for esophageal reconstruction in most patients. One patient died of systemic
155 metastasis 57 days after the surgery. One patient developed pericarditis that subsided after fluid
156 drainage. The cancer pathologies encountered in the study were squamous cell carcinoma in 10
157 patients (77%), adenocarcinoma in 2 (15%), and melanoma in 1 (8%). There were no side effects of
158 L-carnitine (e.g., loose stool, diarrhea, flush, or hypoglycemia).

159

160 ***Incidence of POAF***

161 POAF was observed in only one patient; the incidence of POAF was 7.7% (95% CI 0.2%–36%).
162 The patient was a man in his 80s with cStage I cancer who did not receive β -blockers and
163 neoadjuvant therapy, and underwent video-assisted thoracoscopic surgery with retrosternal
164 esophageal reconstruction. The predicted preoperative POAF rate was 31%. Although POAF
165 persisted from POD1 to POD2 for 10 h, he did not present with hypotension or tachycardia. The AF
166 spontaneously returned to normal sinus rhythm without treatment. None of the patients presented
167 with atrial flutter.

168

169 ***Blood FABP4 levels***

170 **Fig. 2a** shows the changes in the blood FABP4 levels. The mean serum FABP4 levels changed
171 from 10.3 to 7.0 ng/mL ($P = .054$). The average change was -3.3 ng/mL (95% CI -6.6 to -0.1
172 ng/mL). **Fig. 2b** shows the predicted POAF rate as a function of preoperative FABP4 levels. A
173 positive correlation was observed between the preoperative FABP4 level and predicted POAF rate
174 ($r = 0.564$, 95% CI, -0.02 to 0.860).

175 The operative parameters reflecting surgical invasiveness and postoperative laboratory data
176 including FABP4 of each patient were shown in **Table 4**. In only one case (No. 13) who needed
177 transfusion, FABP4 did not decrease after surgery and the value stayed relatively high (16.7 ng/ml).
178 While the postoperative value of FABP4 of the POAF case (No. 8) was 6.5 ng/ml, white blood cell
179 count and hemoglobin were relatively high, suggesting inflammation and dehydration in this case.

180

181 **Discussion**

182 We demonstrated that the incidence of POAF after esophageal cancer was 7.7% with perioperative
183 L-carnitine administration. Furthermore, it was suggested that L-carnitine could reduce FABP4

184 levels.

185

186 ***Safety of perioperative administration of L-carnitine***

187 L-Cartin® did not produce any side effects during the study. Although one patient refused to
188 consume L-Cartin® because of its sourness, the overall tolerability of the medication was
189 acceptable. As L-Cartin® is a solution, it is easy to administer it through surgically inserted enteral
190 tubes. L-carnitine is absorbed only in the small intestine without significant first-pass degradation
191 [18]. Thus, administration via enteral tubes after surgery is comparable to oral intake in terms of
192 pharmacokinetics. Perioperative oral intake of L-Cartin® in patients undergoing heart surgery is
193 reportedly safe and well-tolerated [12]. Additionally, it has more advantages over administration of
194 β -blockers and amiodarone, which may cause several adverse events, including bradycardia and
195 hypotension.

196

197 ***Incidence of POAF under L-carnitine administration***

198 While no study has used L-carnitine in esophageal surgery, one randomized study reported that
199 perioperative administration of L-carnitine (3 g/day) reduced the incidence of POAF from 19.4% to
200 7.5% in 134 patients undergoing CABG [11]. The POAF reduction rate was calculated to be 61%.
201 In our current study, the incidence of POAF was 7.7%, with a median predicted POAF rate of 24%.
202 Furthermore, in a meta-analysis of L-carnitine for the secondary prevention of cardiovascular
203 disease, the reduction rate of ventricular arrhythmia was estimated to be 65% [10]. Consequently,
204 L-carnitine may have the potential to reduce arrhythmias, which needs to be confirmed in future
205 randomized studies with larger sample sizes.

206

207 ***Blood FABP4 levels and L-carnitine***

208 A positive correlation was determined between the preoperative FABP4 levels and predicted POAF
209 rate in the current study. In a recent large cohort study, plasma concentrations of 363 unique
210 proteins were compared between patients with non-congested and severely congested heart failure
211 [7]; FABP4 was one of the most strongly upregulated proteins and proposed as a new biomarker for
212 heart failure. Preoperative FABP4 levels were also positively correlated with BNP levels in our
213 study (data not shown). In another prospective study that analyzed several adipokines in the plasma
214 of patients undergoing AF ablation, FABP4 level was the best indicator of left atrial adipose tissue
215 volume and a predictor of AF recurrence after catheter ablation [8]. Collectively, blood FABP4
216 levels could be a new marker for the prediction of AF and heart failure.

217 Reduction of FABP4 levels by L-carnitine was suggested in this study; the average change
218 in serum FABP4 levels was -3.3 ng/mL (95% CI -6.6 to -0.1 ng/mL) after 5-days of L-carnitine
219 administration. Two of the three patients whose FABP4 levels dropped by > 5 ng/mL had high
220 preoperative BNP levels (144 and 153 pg/mL); however, they had no heart failure symptoms.
221 Further studies examining the relationship between changes in FABP4 levels and heart failure are
222 required. While there have been no reports of changes in serum FABP4 levels after L-carnitine
223 administration, treatment with L-carnitine suppressed the increase in FABP4 gene expression in a
224 burn-induced cellular injury model of hepatocytes [19]. Although the mechanism remains unclear,
225 L-carnitine may have a reductive effect on FABP4 levels.

226

227 ***Limitations***

228 The present study has several limitations. First, the observation duration for POAF identification
229 was only three days after surgery. Although POAF usually occurs within this period [4], we may
230 have underestimated the rate of POAF during hospitalization. Second, the predicted POAF rate was
231 estimated using an application developed in the U.S. In the analysis of 45 patients with esophageal

cancer operated from 2019 to 2020 in our hospital, the median POAF score was 19.1 (IQR: 13.1, 27.1). POAF was observed in 25% (2/8) of the patients with the score > 30% and in 0% (0/37) of the patients with that < 30%. Further study would be necessary to validate the application in a large cohort of Japanese patients. Third, we did not measure the blood concentration of free carnitine. We previously established that free carnitine serum levels doubled after a 9-day perioperative oral intake of L-Cartin® in patients undergoing heart surgery (same age group as the current study) [12]. Although we believe that carnitine concentrations were also elevated in the current study, further studies to confirm the L-carnitine pharmacokinetics in the setting of enteric surgery are required. Fourth, several factors other than L-carnitine may affect blood FABP4 levels; anesthesia, surgery, and nutritional state of the patients might have changed blood FABP4 levels. We do not know whether the decrease in FABP4 is due to the L-carnitine administration or the surgery. Future studies that assess FABP4 levels in the control group to determine the independent effects of L-carnitine on FABP4 levels are required. Lastly, we do not know the effects of β -blockers in the current study. A stratification with perioperative β -blockers administration might be necessary in future randomized trials.

247

248 **Conclusions**

249 The incidence of POAF after perioperative administration of L-carnitine for esophageal cancer was
250 7.7%. A correlation between blood FABP4 levels and POAF risk was identified, and L-carnitine
251 reduced the FABP4 levels. This preliminary study will contribute to the planning of sample size in
252 future randomized trials.

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258

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262

263 **Conflict of Interest statement**

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267

268

269 **References**

- 270 1. Horikoshi Y, Goyagi T, Kudo R, Kodama S, Horiguchi T, Nishikawa T. The suppressive
271 effects of landiolol administration on the occurrence of postoperative atrial fibrillation and
272 tachycardia, and plasma IL-6 elevation in patients undergoing esophageal surgery: A
273 randomized controlled clinical trial. *J Clin Anesth.* 2017;38:111-6.
- 274 2. Chin JH, Moon YJ, Jo JY, Han YA, Kim HR, Lee EH, et al. Association between
275 Postoperatively Developed Atrial Fibrillation and Long-Term Mortality after
276 Esophagectomy in Esophageal Cancer Patients: An Observational Study. *PLoS One.*
277 2016;11:e0154931.
- 278 3. Tisdale JE, Wroblewski HA, Wall DS, Rieger KM, Hammoud ZT, Young JV, et al. A
279 randomized, controlled study of amiodarone for prevention of atrial fibrillation after
280 transthoracic esophagectomy. *J Thorac Cardiovasc Surg.* 2010;140:45-51.
- 281 4. Ojima T, Iwahashi M, Nakamori M, Nakamura M, Katsuda M, Iida T, et al. Atrial
282 fibrillation after esophageal cancer surgery: an analysis of 207 consecutive patients. *Surg*
283 *Today.* 2014;44:839-47.
- 284 5. Guaita-Esteruelas S, Guma J, Masana L, Borrás J. The peritumoural adipose tissue
285 microenvironment and cancer. The roles of fatty acid binding protein 4 and fatty acid
286 binding protein 5. *Mol Cell Endocrinol.* 2018;462:107-18.
- 287 6. Velliou M, Sanidas E, Papadopoulos D, Iliopoulos D, Mantzourani M, Toutouzas K, et al.
288 Adipokines and atrial fibrillation: The important role of apelin. *Hellenic J Cardiol.*
289 2021;62:89-91.
- 290 7. Pandhi P, Ter Maaten JM, Anker SD, Ng LL, Metra M, Samani NJ, et al. Pathophysiologic
291 Processes and Novel Biomarkers Associated With Congestion in Heart Failure. *JACC Heart*
292 *Fail.* 2022;10:623-32.

- 293 8. Lopez-Canoa JN, Baluja A, Couselo-Seijas M, Naveira AB, Gonzalez-Melchor L, Rozados
294 A, et al. Plasma FABP4 levels are associated with left atrial fat volume in persistent atrial
295 fibrillation and predict recurrence after catheter ablation. *Int J Cardiol.* 2019;292:131-5.
- 296 9. Sepandar F, Daneshpazhooh M, Djalali M, Mohammadi H, Yaghubi E, Fakhri Z, et al. The
297 effect of l-carnitine supplementation on serum levels of omentin-1, visfatin and SFRP5 and
298 glycemic indices in patients with pemphigus vulgaris: A randomized, double-blind, placebo-
299 controlled clinical trial. *Phytother Res.* 2020;34:859-66.
- 300 10. DiNicolantonio JJ, Lavie CJ, Fares H, Menezes AR, O'Keefe JH. L-carnitine in the
301 secondary prevention of cardiovascular disease: systematic review and meta-analysis. *Mayo*
302 *Clin Proc.* 2013;88:544-51.
- 303 11. Dastan F, Talasaz AH, Mojtahedzadeh M, Karimi A, Salehiomran A, Bina P, et al.
304 Randomized Trial of Carnitine for the Prevention of Perioperative Atrial Fibrillation. *Semin*
305 *Thorac Cardiovasc Surg.* 2018;30:7-13.
- 306 12. Shingu Y, Katoh N, Ooka T, Katoh H, Wakasa S. L-Carnitine supplementation for the
307 prevention of postoperative atrial fibrillation in aortic valve surgery. *Gen Thorac Cardiovasc*
308 *Surg.* 2021;69:1460-6.
- 309 13. Japan Esophageal S. Japanese Classification of Esophageal Cancer, 11th Edition: part I.
310 *Esophagus.* 2017;14:1-36.
- 311 14. Japan Esophageal S. Japanese Classification of Esophageal Cancer, 11th Edition: part II and
312 III. *Esophagus.* 2017;14:37-65.
- 313 15. Wineinger NE, Barrett PM, Zhang Y, Irfanullah I, Muse ED, Steinhubl SR, et al.
314 Identification of paroxysmal atrial fibrillation subtypes in over 13,000 individuals. *Heart*
315 *Rhythm.* 2019;16:26-30.

316 16. Amar D, Zhang H, Tan KS, Piening D, Rusch VW, Jones DR. A brain natriuretic peptide-
317 based prediction model for atrial fibrillation after thoracic surgery: Development and
318 internal validation. *J Thorac Cardiovasc Surg.* 2019;157:2493-9 e1.

319 17. Alonso Gomez AM, Sierra LT, Mora NM, Toledo E, Alonso A, Uriarte MG, et al. Left
320 atrial strain improves echocardiographic classification of diastolic function in patients with
321 metabolic syndrome and overweight-obesity. *Int J Cardiol.* 2022;348:169-74.

322 18. Matsuda K, Yuasa H, Watanabe J. Fractional absorption of L-carnitine after oral
323 administration in rats: evaluation of absorption site and dose dependency. *Biol Pharm Bull.*
324 1998;21:752-5.

325 19. Li P, Xia Z, Kong W, Wang Q, Zhao Z, Arnold A, et al. Exogenous L-carnitine ameliorates
326 burn-induced cellular and mitochondrial injury of hepatocytes by restoring CPT1 activity.
327 *Nutr Metab (Lond).* 2021;18:65.

330 **Figure legends**

331 **Fig. 1** Study protocol. ECG, electrocardiogram; FABP4, fatty acid-binding protein 4; IC, informed
332 consent; POAF, postoperative atrial fibrillation

333

334 **Fig. 2** Blood FABP4 levels. (a) Changes in blood FABP4 level (n = 13). (b) Predicted POAF rate as
335 a function of the preoperative FABP4 levels (n = 12). The red marker indicates the patients with
336 POAF. FABP4, fatty acid-binding protein 4; POAF, postoperative atrial fibrillation

Table 1. Preoperative patients' characteristics

Variables	n = 13
Male, n (%)	10 (77)
Age, yrs, median (IQR)	70 (64, 76)
BMI, kg/m ² , median (IQR)	22 (19, 24)
Neoadjuvant therapy	
None, n (%)	3 (23)
Chemotherapy, n (%)	7 (54)
Chemoradiotherapy, n (%)	3 (23)
cStage	
0, n (%)	1 (8)
1, n (%)	2 (15)
2, n (%)	3 (23)
3, n (%)	7 (54)
4, n (%)	0 (0)
Diabetes mellitus, n (%)	2 (15)
Hypertension, n (%)	7 (54)
Dyslipidemia, n (%)	3 (23)
Medications	
β -blockers, n (%)	3 (23)
Statins, n (%)	6 (46)
Plasma BNP, pg/mL, (n = 12), median (IQR)	13 (8, 41)
Predicted POAF rate, (%) (n = 12), median (IQR)	24 (17, 34)

BMI, body mass index; BNP, brain natriuretic peptide; IQR, interquartile range

POAF, postoperative atrial fibrillation

Table 2. Preoperative hemodynamic parameters

Variables	n = 13
Systolic BP, mm Hg, median (IQR)	118 (110, 129)
Diastolic BP, mm Hg, median (IQR)	71 (61, 76)
Electrocardiogram	
Heart rate, bpm, median (IQR)	75 (61, 83)
PQ, ms, median (IQR)	161 (131, 178)
QRS, ms, median (IQR)	101 (94, 107)
Transthoracic echocardiography (n = 12)	
LVDd, mm, median (IQR)	47 (43, 49)
LVEF, %, median (IQR)	61 (57, 67)
Left atrial volume index, mL/m ² , median (IQR)	31 (25, 40)

BP, blood pressure; IQR, interquartile range; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction

Table 3. Operative and postoperative data

Variables	n = 13
Robotic surgery, n (%)	3 (23)
Retro-sternal / posterior mediastinal route, n (%)	12 (92) / 1 (8)
Three-field lymph node dissection, n (%)	10 (77)
Operative time, min, median (IQR)	550 (498, 628)
Bleeding, mL, median (IQR)	55 (25, 220)
Transfusion, n (%)	1 (8)
Postoperative hospital stay, days, median (IQR)	23 (21, 40)
Postoperative complications	
Side effects of L-carnitine, n (%)	0 (0)
Aspiration pneumonia, n (%)	1 (8)
Recurrent laryngeal nerve palsy, n (%)	1 (8)
Pericarditis, n (%)	1 (8)
Death (systemic metastasis), n (%)	1 (8)

IQR, interquartile range

Table 4. Operative parameters reflecting surgical invasiveness and postoperative laboratory data of each patient

Case No.	Operation time (min)	Bleeding (ml)	Transfusion (Yes/No)	Laboratory data at the postoperative day 3							
				FABP4 (ng/ml)	WBC (/μL)	CRP (mg/dL)	Hb (g/dL)	TP (g/dL)	BUN (mg/dL)	Cr (mg/dL)	K ⁺ (mEq/L)
1	530	30	No	3.6	7200	4.0	10.2	4.9	9	0.69	4.0
2	457	55	No	2.5	10100	7.2	12.8	5.8	8	0.61	4.4
3	640	130	No	8.1	18100	20.0	10.5	4.5	28	0.8	4.7
4	422	300	No	21.8	8300	10.0	7.2	5.1	29	0.75	4.6
5	582	50	No	6.3	5000	13.3	10.0	5.6	8	0.45	3.5
6	528	0	No	2.3	6800	6.7	11.6	4.9	11	0.77	4.3
7	616	40	No	0.8	12600	10.3	8.9	6.3	8	0.71	3.8
8*	604*	0*	No*	6.5*	12700*	12.0*	13.0*	5.1*	24*	1.06*	4.6*
9	543	70	No	2.6	7000	2.9	10.3	5.0	11	0.81	3.9
10	550	140	No	3.1	9200	11.9	10.5	5.6	14	0.79	3.9
11	852	440	No	5.7	7200	22.5	10.6	6.0	19	0.55	3.9
12	467	20	No	10.8	11600	14.1	7.8	4.9	19	0.54	4.2
13	773	1400	Yes	16.7	7500	8.0	8.6	5.6	72	1.57	4.0

BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; FABP4, fatty acid binding protein 4; Hb, hemoglobin; K, potassium ions; TP, total protein; WBC, white blood cell. *The asterisks indicate the patient with postoperative atrial fibrillation (case No. 8).

Fig. 1

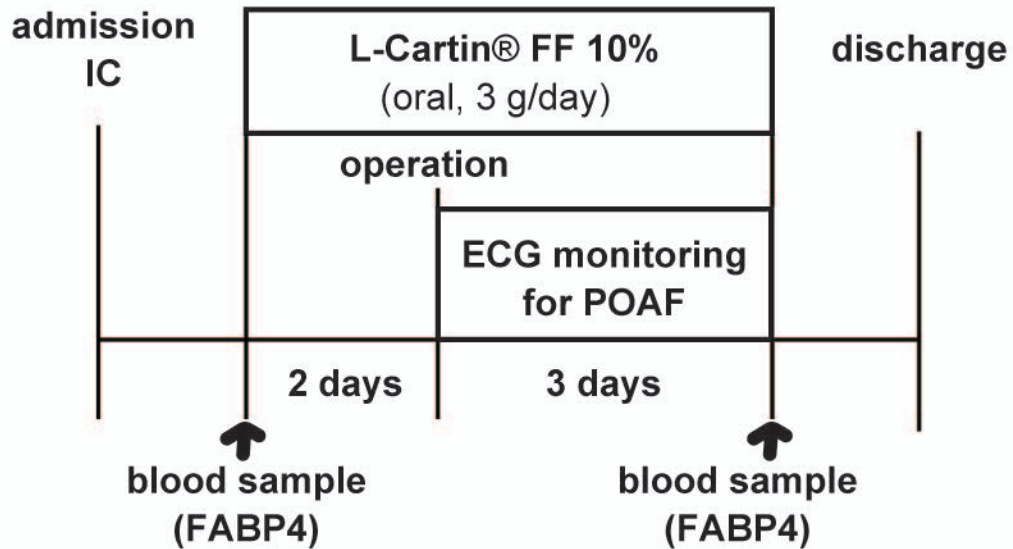
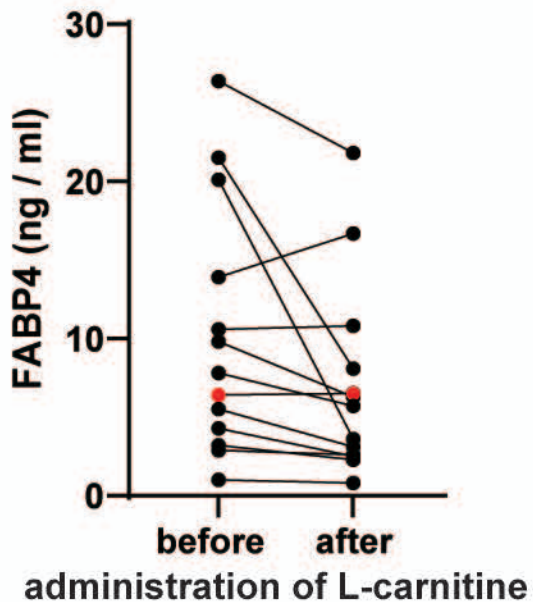


Fig. 2

a



b

