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Original Article

Protective Effect of Eicosapentaenoic Acid on Insulin Resistance in Hyperlipidemic Patients and on the Postoperative Course of Cardiac Surgery Patients: The Possible Involvement of Adiponectin

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Accumulated studies have shown that ω-3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) have protective roles against inflammatory responses such as hyperlipidemia, diabetes mellitus (DM) and cardiovascular diseases. Here we examined the effects of administering EPA to hyperlipidemic patients and other patients undergoing cardiac surgery to determine whether this treatment would increase plasma EPA levels and to clarify the association between EPA treatment and adiponectin production in hyperlipidemic patients. We also assessed the effect of preoperative EPA administration on postoperative adverse events such as postoperative atrial fibrillation (POAF) and postoperative infection in the cardiac surgery patients. The EPA administration significantly increased the serum EPA concentrations in both patient populations ($p < 0.001$). In the hyperlipidemic patients, the EPA administration significantly increased plasma adiponectin levels ($p < 0.05$), accompanied by a decrease in insulin resistance designated by the HOMA-IR (homeostasis model assessment of insulin resistance) score ($p < 0.05$) and Hs-CRP (high sensitivity C-reactive protein) value ($p < 0.05$). In the cardiac surgery patients, no significant effect of EPA on cardiac adverse events such as POAF was observed. However, our results clearly demonstrated that both the neutrophil-to-lymphocyte ratio and the 2nd-line antibiotic requirement in the EPA group were significantly decreased compared to the untreated control group ($p < 0.05$). We suggest that EPA administration may exert anti-inflammatory effects in patients with hyperlipidemia and in those undergoing cardiac surgery, possibly through an increase in plasma adiponectin levels.

Key words: eicosapentaenoic acid, adiponectin, hyperlipidemic patients, cardiac surgery, atrial fibrillation

The intake of ω–3 polyunsaturated fatty acids (PUFAs), which are abundant in marine fish

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meat and oil, has been shown to have many beneficial effects. Accumulated studies have shown that PUFAs such as eicosapentaenoic acid (EPA) have protective properties against cardiovascular disease (CVD) [1–3]. A high intake of PUFAs was suggested as one possible reason for the relatively low prevalence of CVD in Japan [4]. EPA treatment prevented and reversed insulin resistance in high-fat diet-induced obese mice via adipose tissue inflammation, and an increase in the EPA/arachidonic acid (AA) ratio was reported to be associated with improved arterial stiffness in obese patients with dyslipidemia [5]. The mechanisms underlying these beneficial effects are based on interference with the AA cascade that produces pro-inflammatory eicosanoids, the formation of novel bioactive lipid mediators, and changes in the pattern of adipocytokine secretions [6].

The dysregulation of pro- and anti-inflammatory adipocytokine production is associated with the metabolic syndrome, suggesting that inflammatory changes in obese adipose tissue may critically contribute to the development of many aspects of the metabolic syndrome, which can progress to diabetes and atherosclerosis. Among many adipocytokines, adiponectin is unique in that it is the only established adipocytokine with antiatherogenic and anti-inflammatory properties [7, 8]. Adiponectin also increases tissue fat oxidation, leading to reduced levels of fatty acids and tissue triglyceride content, thus enhancing insulin sensitivity in the liver and skeletal muscle [9, 10]. Because plasma adiponectin concentrations are decreased in obese subjects [11], extensive research has been conducted to investigate the upregulation of adiponectin and its cognate receptors for the treatment of obesity-related metabolic sequelae [7].

Cardiac surgery (including cardiopulmonary bypass [CPB]) initiates a systemic inflammatory response syndrome (SIRS) that may lead to considerable postoperative mortality as well as complications. This syndrome arises mainly due to contact between the blood and the artificial surfaces of the bypass circuit [12–14]. Attempts to prevent this inflammatory response following cardiac surgery by pharmacological means are warranted, because a reduction in the inflammatory response may contribute to the protection of organ function and hence to improved recovery from surgical revascularization procedures. Adipose tissue secretes both pro-inflammatory cytokines such as interleukin-6 (IL-6) and anti-inflammatory mediators such as adiponectin. Inflammation has been implicated in the pathogenesis of postoperative cardiac adverse events such as postoperative atrial fibrillation (POAF). We previously reported that a daily preoperative administration of pentoxifylline (PTX) contributed to the attenuation of CPB-induced SIRS through the reduction of serum IL-6 levels [15].

In the present study, we sought to determine whether the administration of EPA could increase plasma EPA levels and also to clarify the association between EPA administration and adiponectin production in patients with hyperlipidemia. We also attempted to assess the effect of preoperative EPA administration on postoperative adverse events such as POAF and postoperative infection in patients who underwent cardiac surgery. Because in previous studies the group of patients with postoperative infections had significantly lower adiponectin levels throughout the perioperative period than the uninfected group [16–19], the present study provides important insight into the therapeutic implications of EPA treatment in patients with hyperlipidemia and/or cardiac surgery.

Patients and Methods

Clinical research I. We randomly separated 60 hyperlipidemic patients (total cholesterol > 220 mg/dL) into an experimental group of 31 patients and a control group of 29 patients. The patients (31 males, 29 females) were aged 54 to 84 yrs (median 71 yrs), and they had all been treated at cardiovascular outpatient clinic in Fukuyama Medical Center in the 3-yr period from January 2010 to February 2013. These patients had a history that included hypertension, coronary heart disease, arrhythmia, chronic heart failure, diabetes mellitus and hyperlipidemia. None of the patients had a history that included cancer, significant systemic disease, history of inflammatory disease, and serum creatinine greater than 2.0 mg/dL. Their hyperlipidemic status was diagnosed according to fasting serum total cholesterol_> 220 mg/dL. The experimental group received EPA 900 mg daily for 3 to 6 months (EPA group), and the control group did not receive EPA. The study protocol was approved by the Fukuyama Medical Center Trust Ethics Committee. Written informed consent was obtained from all patients.

Clinical data were obtained upon admission. The patients' demographic data, medical history and medication for hyperlipidemia, hypertension, diabetes mellitus (DM), prior coronary heart disease (CHD) and current smoking status were recorded. Hypertension was defined as systolic blood pressure of 140 mmHg or more and/or diastolic blood pressure of 90 mmHg or more, and the use of antihypertensive therapy. DM was defined as recurrent or persistent hyperglycemia, and was diagnosed when the patient demonstrated any one of the following: fasting plasma glucose level > 126 mg/dL, plasma glucose levels > 200 mg/dL 2 h after a 75-g oral glucose load, as in a glucose tolerance test, and symptoms of hyperglycemia and casual plasma glucose > 200 mg/L. Each patient's height and body weight were measured, and the body mass index (BMI) was calculated. Obesity was defined as a BMI > 25. The criteria used for a diagnosis of CHD were an old myocardial infarction and angina pectoris based on the patient's clinical history, electrocardiogram and myocardial scintigraphy or coronary angiography findings. The patient's clinical characteristics and drug administration status are summarized in Table 1.

Blood samples were collected in the morning after an overnight fast and examined. The concentrations of triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) were measured enzymatically on an autoanalyzer (Hitachi 7600-110; Hitachi High-Technologies, Tokyo) using reagent kits from Daiichi Pure Chemicals (Tokyo). Fasting blood glucose (FBG) was measured on ABL 700 analyzer (Radiometer Medical A/S, Copenhagen, Denmark). The serum concentrations of insulin were measured by a chemiluminescence immunological assay. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated with the following formula: [fasting insulin (μU/mL)] × [fasting glucose (mg/dL)]/405. We determined the serum levels of HbA1c by conducting ionic exchange high-pressure liquid chromatography with commercial products.

We measured the serum levels of visfatin C using Visfatin C-terminal (Human) EIA kit (Phoenix

Table 1 Clinical characteristics of the EPA and Control group patients with hyperlipidemia

	EPA group (n = 31)	Control group (n = 29)	*p*
Age (years)	71.0 ± 8.4	70.5 ± 7.9	ns
Sex (male %)	18 (58.1)	13 (44.8)	ns
BMI (kg/m^2)	25.0 ± 4.5	25.7 ± 3.9	ns
CHD (%)	17 (54.8)	11 (37.9)	ns
Hypertension (%)	28 (90.3)	27 (93.1)	ns
DM (%)	12 (38.7)	12 (41.4)	ns
Current smoker (%)	1 (3.2)	0 (0)	ns
Drug treatment			
Lipid-lowering therapy			
Statins (%)	22 (71.0)	20 (69.0)	ns
Fibrates (%)	7 (22.6)	7 (24.1)	ns
Antihypertensive therapy			
CCB (%)	18 (58.1)	19 (65.5)	ns
ACEI/ARB (%)	23 (74.2)	22 (75.9)	ns
Diuretics (%)	9 (29.0)	7 (24.1)	ns
β blocker (%)	14 (45.2)	14 (48.3)	ns
Oral hypoglycemic agent			
SU (%)	3 (9.7)	3 (10.3)	ns
α-GI (%)	4 (12.9)	6 (20.7)	ns
Metformin (%)	5 (16.1)	0 (0)	ns
Pioglitazone (%)	6 (19.3)	4 (13.8)	ns

BMI, body mass index; CHD, coronary heart disease; DM, diabetes mellitus; CCB, calcium channel blocker; ACE-I, angiotensin converting-enzyme inhibitors; ARB, angiotensin II type I receptor blockers; SU, sulfonyl urea; α-GI, α-glucosidase inhibitor; ns, not significant.

Pharmaceuticals, Burlingame, CA, USA). Predictors of adiponectin and leptin were measured using commercially available kits. The serum levels of high sensitivity C-reactive protein (Hs-CRP) were determined using an Auto CRP MX type (Nissui Seiyaku, Tokyo, Japan).

Statistical analysis. We used a repeated-measures analysis of variance (ANOVA) (control and EPA-treated groups x before and after the treatment) to access the comparative effect of EPA treatment on the measured variables. All data are expressed as the mean ± standard deviation (SD) or standard error (SE). The post-EPA treatment values were calculated as the values relative to the pre-EPA treatment values. A two-tailed, paired *t*-test was applied for the evaluation of changes from baseline conditions to those at 3–6 months. Comparisons of the means between the two groups at base line or post-treatment were performed using Student's *t*-test. The changes from baseline conditions to those at 3–6 months are abbreviated as△. We performed a stepwise multivariate regression analysis using a model in which the dependent variable was adiponectin, with the following explanatory variables: leptin, visfatin, FBG, insulin, HOMA-IR, HbA1c, LDL-C, HDL-C, TG, eGFR, Hs-CRP and the treatment with EPA. All statistical analyses were performed using the Stat View program version 5.0 for Windows (SAS Institute, Cary, NC).

Clinical research II. Patients requiring cardiac surgery were enrolled in this study. The exclusion criteria included recent history of atrial fibrillation or arrhythmia, and treatment with anti-arrhythmic agents (*e.g.*, β-blocker), nonsteroidal anti-inflammatory drugs (NSAIDs) or steroids. Pacemaker users were also excluded. We randomly divided the 22 patients into an experimental group of 10 patients and a control group of 12 patients. The patients (13 males, 9 females) were aged 54 to 86 yrs (median 70.5 yrs), and treated at Iwakuni clinical center from February 2013 to March 2014. The diagnoses were 8 angina pectoris (36%), 7 aortic valve stenosis (32%), 5 mitral valve regurgitation (23%), others (9%). None of the patients had a history undergoing cardiac surgery. The experimental (EPA) group received an oral EPA administration of 1,800 mg/day, and the Control group did not. In the EPA group, the EPA administration was started on preoperative day 31 and was continued for 1 months. All patients gave their written consent before being enrolled in the study, which was approved by the Iwakuni Medical Center Trust Ethics Committee. Written informed consent was obtained from all patients.

An anthropometric examination of the patients was performed. All patients were measured and weighed. Their clinical characteristics, diagnoses, risk factors and operative procedures are summarized in Table 2. The serum fatty acid composition including components such as EPA and AA was determined by the gas-chromatography method (SRL, Tokyo). The determination of other various other serum parameters was accomplished as described in above for Clinical Research I. The patient's urine levels of cathecholamines were measured by radioassay using the TOSOH CA test by high-performance liquid chromatography downstream promoter element (HPLC-DPE) technique (SMS, Tokyo), and their urine levels of cortisol were determined using the Chemilumi ACS-E Cortisol CLIA kit by Chemilumi ADVIA Centaur (Siemens Healthcare Diagnostics, Malvern, PA). Patients profiles and the pre-, peri-and postoperative clinical data for both groups are listed in Table 3.

Statistical analysis. The statistical analysis of the Clinical Research II results was performed using PASW Statistics 18.0 (SPSS, Chicago, IL, USA). Fisher's exact tests were performed to assess the univariate analysis of the categorical data, and Student's *t*-test was used to assess the quantitative data. *P*-values < 0.05 were considered significant.

Results

Comparison of clinical profiles and pretreatment data of various parameters in the EPA and the Control groups of hyperlipidemic patients. There were no significant differences in the patients' profiles (*i.e.*, sex, age, BMI, surgical stress, surgical procedures, CHD, hypertension, DM, drug administration status) between the EPA group and the Control group (Table 1). As shown in Table 3, no significant differences were also observed in the pretreatment data of various parameters between the two groups except for the TG value: EPA group 177.3 ± 78.1 mg/dL, Control group 120.2 ± 42.2 ($p < 0.05$).

Effect of EPA administration on various parameters in the hyperlipidemic patients. The preoperative EPA administration significantly

increased the patients' serum concentration of EPA by approximately twofold ($p < 0.001$) relative to the baseline values, resulting in a significant increase in the EPA/AA ratio ($p < 0.001$). The EPA treatment also significantly increased the serum levels of adiponectin ($p < 0.05$). The insulin resistance, determined by the HOMA-IR, was significantly improved in the EPA group ($p < 0.05$), but not in the Control group. In addition, the level of Hs-CRP in the EPA group was significantly decreased ($p < 0.05$). No significant changes in the serum levels of leptin, visfatin, LDL-C, HDL-C, and TG were observed in either

Table 2 Pre-operative demographic characteristics of the 22 EPA group and Control group patients undergoing cardiac surgery

	EPA group (n = 10)	Control group (n = 12)	*p*
Age (years)	71.6 ± 4.8	69.6 ± 8.6	ns
Height (cm)	156.6 ± 9.5	158.2 ± 5.3	ns
Weight (kg)	54.7 ± 14.6	56.1 ± 8.7	ns
Sex (Male/Female)	4/6	9/3	ns
Diagnosis			
Angina pectoris	5/10	3/12	ns
Aortic valve stenosis	2/10	5/12	ns
Aortic valve regurgitation	1/10	0/12	ns
Mitral valve regurgitation	1/10	4/12	ns
Ventricular septal defect	1/10	0/12	ns
NYHA			
Class Ⅰ	4/10	7/12	ns
Class Ⅱ	6/10	5/12	ns
Class Ⅲ	0/10	0/12	ns
Class Ⅳ	0/10	0/12	ns
EF	60.0 ± 10.4	68.3 ± 7.9	ns
Normal LVF (.50%)	7/10	12/12	ns
Risk factors			
Hyperlipidemia	4/10	8/12	ns
Hypertension	9/10	10/12	ns
Smoking	5/10	7/12	ns
Obesity	1/10	2/12	ns
Peripheral arterial disease	1/10	0/12	ns
Serum levels			
Creatinine (mg/dL)	0.97 ± 0.37	0.95 ± 0.28	ns
CK-MB (>25 IU/mL)	0/10	0/12	ns
CRP (>1.0 mg/dL)	1/10	0/12	ns
Insulin (μU/mL)	15.4 ± 14.6	14.2 ± 19.3	ns
HOMA-IR	4.2 ± 3.6	3.6 ± 4.4	ns
FBG (mg/dl)	120.4 ± 34.4	111.3 ± 19.2	ns
Operation			
Operation Time (min)	191.3 ± 40.3	226.7 ± 53.1	ns
Blood Loss (mL)	516.3 ± 298.5	287.0 ± 222.9	ns
Surgical Procedure	OPCAB : 5 AVR : 3 MVP : 1 VSD closure : 1	OPCAB : 3 AVR : 5 MVP : 2 MVR : 2	

OPCAB, off pump CABG; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; MVP, mitral valve plasty; MVR, mitral valve replacement; VSD, ventricular septal defect.

Table 3 Pretreatment data of various parameters of the EPA and Control group patients with hyperlipidemia

	EPA group (n = 31)	Control group (n = 29)	*p*
EPA (μg/mL)	83.0 ± 52.6	73.2 ± 37.2	ns
AA (μg/mL)	185.1 ± 63.0	164.7 ± 49.8	ns
EPA/AA	0.4 ± 0.3	0.5 ± 0.2	ns
Adiponectin (μg/mL)	10.4 ± 7.1	14.5 ± 3.5	ns
Leptin (ng/mL)	10.8 ± 9.7	11.1 ± 7.0	ns
Visfatin (ng/mL)	6.4 ± 1.3	6.50 ± 1.17	ns
FBG (mg/dL)	112.4 ± 21.7	106.9 ± 15.6	ns
Insulin (μU/mL)	9.3 ± 5.3	8.2 ± 5.6	ns
HOMA-IR	2.9 ± 1.8	2.3 ± 1.8	ns
HbA_{1C} (%)	5.8 ± 0.9	5.6 ± 0.5	ns
LDL-C (mg/dL)	122.5 ± 32.0	117.0 ± 25.4	ns
HDL-C (mg/dL)	52.6 ± 12.7	57.9 ± 11.4	ns
LDL-C/HDL-C	2.5 ± 1.1	2.1 ± 0.6	ns
Triglyceride (mg/dL)	177.3 ± 78.1	120.2 ± 42.2	$P < 0.05$
eGFR (ml/min/1.73 m^2)	63.2 ± 16.2	62.4 ± 19.0	ns
Hs-CRP (mg/dL)	0.3 ± 0.4	0.2 ± 0.3	ns

(mean ± SD)

FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assesment of insulin resistance; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; AA, arachidonic acid; Hs-CRP, high sensitivity C-reactive protein.

Table 4 The effect of EPA on various parameters in the hyperlipidemic patients relative to the baseline values

	EPA group (n = 31)	(after/before)	Control group (n = 29)	(after/before)
EPA (μg/mL)	2.0 ± 0.1**	(164.1 ± 65.7/83.0 ± 52.6)	1.0 ± 0.1	(69.8 ± 34.9/73.2 ± 37.2)
AA (μg/mL)	0.9 ± 0.1	(173.4 ± 56.7/185.1 ± 63.0)	1.1 ± 0.1	(174.2 ± 46.3/164.7 ± 49.8)
EPA/AA	2.3 ± 0.2**	(1.00 ± 0.57/0.44 ± 0.26)	1.0 ± 0.1	(0.49 ± 0.27/0.47 ± 0.24)
Adiponectin (μg/mL)	1.3 ± 0.1*	(12.48 ± 8.49/10.41 ± 7.08)	1.0 ± 0.1	(14.75 ± 4.97/14.49 ± 3.45)
Leptin (ng/mL)	1.1 ± 0.2	(12.26 ± 14.58/10.78 ± 9.67)	1.0 ± 0.0	(10.79 ± 6.46/11.14 ± 7.04)
Visfatin (ng/mL)	0.9 ± 0.0	(6.00 ± 1.45/6.42 ± 1.33)	1.0 ± 0.1	(6.52 ± 1.69/6.50 ± 1.17)
FBG (mg/dL)	1.0 ± 0.0	(110.1 ± 18.4/112.4 ± 21.7)	1.1 ± 0.0	(112.5 ± 15.4/106.9 ± 15.6)
Insulin (μU/mL)	0.8 ± 0.1*	(7.53 ± 3.73/9.32 ± 5.30)	1.1 ± 0.1	(8.84 ± 4.93/8.16 ± 5.57)
HOMA-IR	0.7 ± 0.1*	(2.13 ± 1.24/2.87 ± 1.79)	1.1 ± 0.2	(2.62 ± 1.72/2.29 ± 1.81)
HbA_{1C} (%)	1.0 ± 0.1	(5.62 ± 0.63/5.78 ± 0.88)	1.0 ± 0.0	(5.52 ± 0.41/5.60 ± 0.53)
LDL-C (mg/dL)	0.9 ± 0.1	(111.6 ± 34.6/122.5 ± 32.0)	1.0 ± 0.0	(113.7 ± 21.4/117.0 ± 25.4)
HDL-C (mg/dL)	1.0 ± 0.1	(53.9 ± 13.3/52.6 ± 12.7)	1.0 ± 0.0	(60.0 ± 10.8/57.9 ± 11.4)
LDL-C/HDL-C	0.9 ± 0.1	(2.18 ± 0.81/2.50 ± 1.10)	0.9 ± 0.1	(1.96 ± 0.53/2.10 ± 0.59)
Triglyceride (mg/dL)	0.9 ± 0.1	(148.2 ± 49.2/177.3 ± 78.1)	1.0 ± 0.1	(124.7 ± 48.3/120.2 ± 42.2)
eGFR (ml/min/1.73 m^2)	1.0 ± 0.1	(62.2 ± 20.0/63.2 ± 16.2)	1.0 ± 0.1	(61.1 ± 17.3/62.4 ± 19.0)
Hs-CRP (mg/dL)	0.6 ± 0.1*	(0.17 ± 0.17/0.29 ± 0.42)	4.9 ± 0.7	(0.83 ± 0.56/0.17 ± 0.28)

(mean ± SE)

FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assesment of insulin resistance; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; AA, arachidonic acid; Hs-CRP, high sensitivity C-reactive protein; *$p < 0.05$, **$p < 0.001$

groups (Table 4).

Effect of EPA on adiponectin, HOMA-IR and CRP in the hyperlipidemic patients. To determine the risk factors independently influencing the changes of plasma adiponectin and HOMA-IR, we performed stepwise multivariate regression analyses, the results of which are shown in Supplemental Tables S3 and S4. This analysis revealed EPA treatment as a factor that increased the plasma adiponectin concentrations and decreased the HOMA-IR (Table 5).

The clinical profiles of the EPA and Control group patients undergoing with cardiac surgery. There were no significant differences in age, weight, sex, surgical stress or surgical procedures between the Control and EPA groups. In addition, no significant differences were found between the groups in their preoperative hemodynamic data or in the number of risk factors for cardiovascular surgery (Table 2).

Effect of EPA administration on the postoperative course. The preoperative EPA treatment significantly increased the patients' plasma EPA levels ($p < 0.001$) and significantly decreased their AA levels ($p < 0.02$), resulting in significantly decreased EPA/AA ratios ($p < 0.001$) compared to the Control group. However, the insulin resistance as designated by the plasma levels of insulin/FBS and HOMA-IR was not significantly improved in the EPA group. No significant differences in various other postoperative parameters including the length of intensive care unit (ICU) and hospital stay were observed between the two groups. In addition, there were no significant differences in postoperative adverse events between the groups (Table 6).

Effect of EPA administration on postoperative white blood cells counts and antibiotics requirement. The neutrophil counts at postoperative days (PODs) 1 and 3 in the EPA group were significantly lower than those in the Control group ($p < 0.05$), respectively. In contrast, no significant differences were observed in the lymphocyte counts between the groups throughout the observation period. In addition, the neutrophil to lymphocyte ratios (NLR) at PODs 1 and 3 in the EPA group were significantly decreased compared to those in the Control group ($p < 0.05$), respectively (Table 7). The EPA pretreatment significantly decreased the requirement for a 2nd-line antibiotic ($p < 0.05$) (Table 7).

Discussion

The present study's results revealed that the EPA administration significantly increased the serum levels of EPA and the EPA/AA ratio in patients with hyperlipidemia and in those undergoing cardiac surgery. The results also showed a significant concomitant increase in the serum levels of adiponectin in the hyperlipidemic patients. Our findings suggested that a significant increase in the plasma EPA level could increase adiponectin production in humans, which is consistent with previous reports that EPA increased adiponectin production in adipocytes and in mice [20–25].

The mechanism by which PUFAs modulate adiponectin secretion is not fully understood. Several studies indicated that EPA increases the adiponectin concentration in 3T3-L1 adipocytes and prostaglandins (PGs) of the 3-series formed from EPA increase the secretion of adiponectin, in part through a PPAR-γ-dependent mechanism [20–25].

Previous studies demonstrated that adiponectin has insulin-sensitizing properties as well as anti-inflammatory and anti-atherogenic properties [26, 27]. In the present study, EPA administration significantly decreased the serum insulin level and HOMA-IR index of hyperlipidemic patients, indicating that the EPA administrations improved insulin resistance, as was previously clarified in several animal models of obesity and diabetes [28]. Our stepwise multivariate regression analyses (using the variables shown in Table 1) clearly demonstrated that only the treatment with EPA was an independent determinant of plasma adiponectin concentrations and HOMA-IR in the hyperlipidemic patients (Table 5). Therefore, the improvement of insulin resistance in EPA-treated patients with hyperlipidemia is possibly through EPA-induced adiponectin secretion.

We also found that EPA treatment significantly lowered the plasma level of Hs-CRP in hyperlipidemic patients (Table 4). This anti-inflammatory property of the EPA treatment was confirmed by the results of the stepwise multivariate regression analyses, which showed that the EPA treatment was associated negatively with ΔCRP (Table 5). This result also indicates that the observed anti-inflammatory effect in the EPA-treated hyperlipidemic patients also occurred via a plasma adiponectin increase. These results are consis-

Table 5 Stepwise multivariate regression analyses for changes in plasma adiponectin and HOMA-IR after EPA treatment in hyperlipidemic patients

(1) Plasma adiponectin

	Partial regression coefficient	Standardized partial regression coefficient	*P* value	95% confidence interval	
Constant	−0.93		0.37	−3.01	1.15
EPA treatment	3.14	0.33	0.04	0.09	6.19
ΔCRP	−2.61	0.39	0.02	0.45	4.77

(2) HOMA-IR

	Partial regression coefficient	Standardized partial regression coefficient	*P* value	95% confidence interval	
Constant	−0.25		0.34	−0.79	0.28
EPA treatment	−1.07	0.41	0.01	0.32	1.83
ΔCRP	0.72	0.39	0.01	0.19	1.23

ΔCRP: changes from baseline C-reactive protein (CRP) to those at 3 months.

Table 6 The effect of EPA on various parameters including postoperative adverse events

	EPA group (n = 10)	Control group (n = 12)	*p*
One Day before Operation			
EPA (μg/mL)	250.1 ± 83.1	122.0 ± 49.8	$p < 0.001$
AA (μg/mL)	93.0 ± 13.1	103.1 ± 13.8	$p < 0.05$
EPA/AA	2.7 ± 0.5	1.2 ± 0.4	$p < 0.001$
Insulin (μU/mL)	10.9 ± 12.3	5.0 ± 4.0	ns
HOMA-IR	3.5 ± 4.8	1.1 ± 0.9	ns
FBG (mg/dl)	107.5 ± 38.2	93.0 ± 11.4	ns
Post Operative Day 1			
Catecholamine requirement	4/10	4/12	ns
CRP(mg/dL)	3.1 ± 1.9	3.2 ± 1.9	ns
SOFA score	3.3 ± 2.0	4.3 ± 1.6	ns
Adrenalin (μg/L)	328.1 ± 300.4	169.2 ± 107.3	ns
Noradrenalin (μg/L)	175.1 ± 207.1	120.8 ± 65.0	ns
Dopamine (μg/L)	486.2 ± 784.9	1092.1 ± 1887.5	ns
Cortisol (μg/L)	3827.8 ± 3998.3	2050.7 ± 999.7	ns
Length of ICU stay (days)	2.3 ± 0.6	2.0 ± 0	ns
Length of Hospital stay (days)	29.3 ± 5.4	30.1 ± 7.4	ns
Adverse events			
Antiarrhythmic agent (other than β-blockers)	0/10	0/12	ns
Delayed tamponade	0/10	2/12	ns
gastrointestinal bleeding	0/10	0/12	ns
TIA	0/10	0/12	ns
AF	3/10	4/12	ns

(mean ± SD)

SOFA, sequential organ failure assessment; TIA, transient ischemic attacks; AF, atrial fibrillation.

Table 7 The effect of EPA on WBC counts and antibiotics requirement

	EPA group (n = 10)	Control group (n = 12)	p
WBC counts			
neutrophils (/μL)			
POD 1	9,712 ± 194	12,045 ± 164	$p < 0.05$
POD 3	9,183 ± 287	12,728 ± 418	$p < 0.05$
POD 7	5,245 ± 149	7,205 ± 246	ns
lymphcyte (/μL)			
POD 1	790 ± 58	781 ± 97	ns
POD 3	1,333 ± 213	1,214 ± 315	ns
POD 7	1,766 ± 149	1,977 ± 228	ns
Neutrophil to lymphocyte ratio (NLR)			
POD 1	13.3 ± 4.7	17.1 ± 6.2	$p < 0.05$
POD 3	8.2 ± 4.0	13.7 ± 5.9	$p < 0.05$
POD 7	3.3 ± 1.4	4.4 ± 2.6	ns
Anitbiotics requirement			
prophylatic			
sulbactam sodium/amikacin sulfate	10/10	12/12	ns
2nd line	1/10	4/12	$p < 0.05$
sulbactam sodium	0	1	ns
sulbactam sodium/amikacin sulfate	0	1	ns
meropenem hydrate	1	0	ns
vancomycin hydrochloride	0	2	ns
Type of infection			
pneumonia	0	4	−
urinary tract infection	1	0	−

(mean ± SD)

POD, post operative day.

tent with previous reports that the eicosanoids derived from EPA have less inflammatory activities compared to those of AAs [29–31], and the beneficial effects of PUFAs may be attributable to the modulation of adipocytokine secretion [32, 33].

Adiponectin is also known to exert a regulatory role in atherogenesis. A recent study demonstrated that the adiponectin concentrations in the serum and peri-coronary fat of patients without coronary artery disease (CAD) were significantly higher than those of patients with CAD [34]. In addition, the imbalance of adipocytokine signals in the epicardial adipose tissue was strongly linked to human coronary atherosclerosis [35]. There is also a report that the level of adiponectin mRNA in the epicardial adipose tissue in patients with CAD was also significantly lower than in patients without CAD [36]. Another group suggested that a low adiponectin level may contribute to a higher incidence of postcardiac surgery atrial fibrillation in obese patients [37]. We found previously that serum adiponectin levels were negatively associated with obesity and CAD [38]. Obesity is an independent risk factor for CVD and promotes CVD risk. Bariatric surgery has gained favor because it ameliorates CVD, and the underlying mechanism was proposed to be through the modulation of adipokine secretion [39].

Together the above-cited reports provide extensive evidence in humans and in mouse and *in vitro* models of the cardioprotective effects of adiponectin, and it would seem that adiponectin is a promising marker for the monitoring of cardiovascular risk factors. Atrial fibrillation is the most common postoperative arrhythmia, with significant consequences on patient health. POAF complicates up to 8% of all noncardiac surgeries, 3%～30% of noncardiac thoracic surgeries, and 16%～46% of cardiac surgeries. POAF has been associated with increased morbidity, and mortality, and longer, more costly hospital stays [40]. It was reported that cardiac surgery significantly increased both the insulin and blood glucose levels of the patients, resulting in the postoperative development of insulin resistance [41]. The results of our clinical

research I study clarified that the EPA administration enhanced adiponectin production and improved insulin resistance in patients with hyperlipidemia. Based on that result, we designed the Clinical Research II study to evaluate the impact of preoperative EPA administration on patients with cardiac surgery.

However, no significant differences were observed between the EPA and Control groups regarding the parameters of catecholamine requirement, CRP, Sequential Organ Failure Assessment (SOFA) score, stress hormone, length of ICU stay, length of hospital stay, insulin resistance and cardiac adverse events such as POAF, although the EPA pretreatment significantly increased the plasma EPA levels and AA levels (Table 6). The postoperative effect of EPA on cardiac surgery patients have been controversial. There is evidences that the treatment of infants undergoing CPB with a lipid emulsion containing EPA improved fatty acid status and resulted in a lower inflammatory response after cardiac surgery [42]. In addition, a recent study demonstrated that perioperative EPA infusions significantly increased EPA concentrations in platelet and atrial tissue membranes within 12 h of the first EPA administration and decreased biological and clinical signs of inflammation, suggesting that peri- operative EPA might be beneficial in elective cardiac surgery with CPB [43]. In contrast, it was reported that treatment with EPA had no effect on the incidence of POAF in patients undergoing open heart surgery [44], and that neither higher habitual circulating PUFAs levels nor achieved levels or changes following short-term fish oil supplementation were associated with the risk of POAF [45].

Our present data do not support the beneficial effects of EPA on cardiac adverse events. This may be attributable to the selection of patients. None of the cardiac surgery patients enrolled in this study were hyperlipidemic, and the obese patients in the EPA and the Control groups were only 10.0% (1/10) and 16.7% (2/12), respectively. In addition, all of the cardiac surgery patients were diagnosed as Class I or II by the NYHA classification (Table 2). To better test the data of pre-operative EPA treatment on cardiac adverse events, future studies should include high-risk patients with hyperlipidemia, obesity, DM and NYHA III or IV.

However, we found that the pre-EPA treatment significantly decreased the neutrophil to lymphocyte ratio (NLR) values (Table 6). Recent research clearly demonstrated that the NLR was associated with severe, extensive and complex CAD and could be used to predict the presence of moderate to severe involvement prior to CAD with a quite satisfactory sensitivity and specificity [46]. It was also reported that the NLR was a useful marker to predict subsequent, mortality in patients admitted for myocardial infarction with ST-segment elevation [47, 48]. Several studies found that cardiovascular mortality was significantly higher in an elevated-NLR group compared to a low-NLR group [49–51]. The NLR has thus attracted attention as an easily obtained marker of inflammation [52, 53].

Mechanistically, neutrophils are known to induce plaque disruption by releasing proteolytic enzymes and superoxide radicals. They contribute to the plugging of microvessels and cause myocardial ischemia [54, 55]. In light of this, we suspect that pre-operative EPA treatment could be a novel therapy for the effective prevention of postoperative adverse events, even though in the present study we did not observe a positive effect of EPA on patients undergoing cardiac surgery. There have been reports that the NLR is a prognostic aid for conditions other than cardiac events, such as for the prognosis in cancer-burden patients [56–59], suggesting that the NLR indicates the status of cell-mediated immunity.

In the present study of patients undergoing cardiac surgery, the pre-operative EPA treatment significantly increased the plasma EPA levels, resulting in an increase in plasma adiponectin levels and significantly decreasing the NLR. The plasma levels of adiponectin and the NLR were thus negatively associated. Previous studies showed that patients with a postoperative infection had significantly lower adiponectin levels throughout the perioperative period than the uninfected group [16, 17], indicating that preoperative adiponectin levels may be useful for anticipating the development of a postoperative infection.

In addition, recent research demonstrated that plasma adiponectin was decreased in septic patients and negatively correlated with the SOFA score, and that the plasma adiponectin levels of survivors with sepsis was gradually increased and the levels in non-survicors was decreased [18, 19]. Our present find-

ings showed that the requirement of 2nd-line antibiotics in the EPA group was significantly decreased compared to that of the Control group (Table 6), indicating that the preoperative EPA administration might decrease the incidence of bacterial infections following cardiac surgery, possibly through the increase in the plasma adiponectin level.

Adipose tissue is well known to secret both pro-inflammatory cytokines such as IL-6 and anti-inflammatory mediators such as adiponectin. It was suggested that increased epicardial adipose tissue may play a pivotal role in the development of coronary disease through the impairment of adiponectin secretion [60]. Inflammatory responses triggered by obesity, hyperlipidemia and surgical stress have been implicated in the pathogenesis of arrhythmia, and increased epicardial adiponectin may thus contribute to the maintenance of sinus rhythm [61, 62]. The protective effects of adiponectin on coronary artery diseases were described as being attributable to adiponectin's anti-inflammatory, anti-atherogenic and insulin-sensitizing properties by inhibiting macrophage-mediated inflammation [63-66].

In conclusion, our present results demonstrated that EPA administration could increase plasma EPA levels, resulting in increased plasma adiponectin levels in patients with hyperlipidemia and in patients who are undergoing a cardiac surgery. This adiponectin increase might be associated, at least in part, with a decrease in the NLR, resulting in a decreased risk of postoperative infection through enhanced cell-mediated immunity in patients undergoing cardiac surgery. Although we did not observe positive effects of EPA treatment on adverse events such as POAF in the patients undergoing cardiac surgery, the protective effects of EPA on cardiovascular events cannot be denied in obese and > NYHA 3 patients through an improved adiponectin imbalance. Our results thus provide important insights into the therapeutic implications of EPA administration in patients with hyperlipidemia and those who will undergo cardiac surgery. Further research is warranted to clarify the protective effects of EPA against cardiac adverse events in large-scale studies and in elective patients.

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