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Title	Decreased gene expression of fatty acid binding protein 3 in the atrium of patients with new onset of atrial fibrillation in cardiac perioperative phase
Author(s)	Shingu, Yasushige; Yokota, Takashi; Takada, Shingo et al.
Citation	Journal of cardiology, 71(1), 65-70 https://doi.org/10.1016/j.jjcc.2017.07.003
Issue Date	2018-01
Doc URL	https://hdl.handle.net/2115/72285
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Rights(URL)	https://creativecommons.org/licenses/by-nc-nd/4.0/
Type	journal article
File Information	JCardiol71_65.pdf

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Original article

Decreased Gene Expression of Fatty Acid Binding Protein 3 in the Atrium of Patients with the New Onset of Atrial Fibrillation in Cardiac Perioperative Phase

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Key words: postoperative atrial fibrillation, fatty acid binding protein, cardiac surgery

Text word count: 2946 words

Abstract

Background: Post-operative atrial fibrillation (POAF) frequently occurs after cardiac surgery. However, the mechanisms of POAF have not been fully elucidated. We aimed to examine whether pre-operative atrial gene expression related to cardiac metabolism is changed in patients with POAF.

Methods: Right atrial tissue was obtained during surgery from 38 patients who underwent cardiac surgery from 2013 to 2015. Atrial expression levels were determined by RT-PCR for the following genes: glucose transporter type 4, peroxisome proliferator-activated receptor-α, fatty acid translocase, carnitine palmitoyltransferase 1B, and fatty acid binding protein 3 (*FABP3*). To investigate fatty acid β-oxidation and tricarboxylic acid cycle capacities in the mitochondria, β-hydroxyacyl CoA dehydrogenase and citrate synthase activity levels were spectrophotometrically determined.

Results: POAF within 7 days after surgery was observed in 18 (47%) patients. POAF patients were significantly older, had a larger left atrial diameter, and had reduced expression of *FABP3*, a fatty acids transport gene in the cytosol, compared to those in the non-POAF group. Reduced *FABP3* expression predicted POAF independent of age and atrial size. In contrast, fatty acid β-oxidation enzymatic activity was comparable between the groups.

Conclusions: *FABP3* gene expression in the atrium was reduced in patients with POAF. These findings suggest a potential link between altered fatty acid transport in the atrium and increased AF onset after cardiac surgery.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Post-operative AF (POAF) frequently occurs after cardiac surgery and can induce thromboembolic events and heart failure, prolong the hospital stay, and increase the total medical cost, leading to a poor prognosis.[1] The incidence of POAF is as high as 20-30%, even with the use of beta-blockers, which are the only recommended prophylactic medication for POAF.[2, 3] Furthermore, the mechanisms of POAF have not been fully elucidated.

Recent studies suggest that a reduced utilization of fatty acids in the heart contributes to the progression of left ventricular (LV) hypertrophy, LV remodeling, and chronic heart failure.[4, 5] In addition, various types of arrhythmia, including atrial tachycardia, are observed at a higher rate in children with inherited fatty acid oxidation deficiencies.[6] Therefore, POAF might be attributable to impaired fatty acid metabolism in the atrium.

Fatty acid binding protein-3 (FABP3; also known as heart FABP [H-FABP]), a small cytoplasmic protein, has been isolated from a wide range of tissues, including heart and skeletal muscles. FABP3 is involved in the uptake of fatty acids and their subsequent transport towards the mitochondrial β-oxidation system.[7]

The aim of the present study was to determine whether gene expression related to cardiac fatty acid metabolism, including fatty acid transport, is changed in the atrium of patients with POAF.

Materials and Methods

Subjects

A prospective short-term, observational study was conducted at a single center. A total of 52 consecutive patients who underwent cardiovascular surgery between 2013 and 2015 were potentially eligible for the study. The exclusion criteria included emergent surgery, a lack of myocardial specimen availability due to severe scar formation, and a clinical history of chronic or paroxysmal AF. After applying the exclusion criteria, 38 patients remained. The university ethics committee approved the research protocol (No, 012-0141) and written informed consent was obtained from each patient. The study was registered in the UMIN Clinical Trials Registry: UMIN000012405.

Post-operative AF

POAF has been reported to occur within 2–4 days after cardiac surgery, with a peak incidence of ~70% by the end of the fourth post-operative day and in >80% the arrhythmia terminates by the end of the fifth post-operative day.[8, 9] Various definitions of POAF duration (from 30 seconds to 30 minutes) have been reported.[10-12] In the present study, POAF was defined as AF lasting at least 5 minutes within 7 days after the surgery. The electrocardiogram was monitored for 24 hours a day using a telemetry system (FUKUDA DENSHI, Tokyo, Japan). The therapeutic strategy for POAF involved anticoagulation, normalization of serum potassium, and infusion of class I antiarrhythmic agents. Cardioversion was performed when hemodynamic compromise was evident. Amiodarone was used for refractory POAF.

Pre-operative echocardiography

A Vivid Seven system (GE/Vingmed, Milwaukee, WI, USA) with an M3S (2.5-3.5 MHz) transducer, Aplio system (Toshiba Medical Systems, Tokyo, Japan) with a 2.5 MHz transducer, or a Philips system (Philips Ultrasound, Bothell, WA, USA) with a 2.5 MHz transducer was used for pre-operative echocardiography. Left ventricular end-diastolic/end-systolic dimensions and the left atrial diameter were measured from the parasternal long axis view. Left ventricular ejection fraction was measured using the modified Simpson method. The mitral regurgitation grade was determined using the regurgitation jet area-to-left atrium ratio (1: mild, <20%; 2: moderate, 20%-40%; 3: severe, >40%). The tricuspid regurgitation grade was determined using the regurgitation jet area (1: mild, <5 cm^2; 2: moderate, 5-10 cm^2; 3: severe, >10 cm^2). Aortic valve stenosis was defined using the valve area (1: mild, >1.5 cm^2; 2: moderate, 1.0-1.5 cm^2; 3: severe, <1.0 cm^2). Aortic valve regurgitation was determined using a combination of jet width/outflow tract, pressure half time, and diastolic reverse flow at the abdominal aorta (1: mild; 2: moderate; 3: severe).[13] The E and A waves of the transmitral flow (E/A) were measured using pulse Doppler. Deceleration time was measured as the time interval from the maximum E wave point to baseline levels.

Atrial electromechanical delay was determined using tissue Doppler as the time interval from the onset of the P-wave on the electrocardiogram to the beginning of the A' wave at the lateral and medial mitral annulus.[14] Intra-left atrial electromechanical delay was then calculated as the difference between the lateral and medial electromechanical delay.[15]

Blood glucose, insulin, and free fatty acid levels

Within two days before surgery, blood was collected in the early morning after 10 hours of fasting in all patients. Blood glucose, insulin, and free fatty acid levels were measured using enzymatic and colorimetric methods. Just after the blood collection, an oral glucose tolerance test (OGTT, 75 g) was performed in the non-diabetic patients (n=32/38; one non-diabetic patient could not tolerate glucose intake). The glucose tolerance types were defined according to the guidelines of the Japan Diabetes Society (2012) using the blood glucose level at 120 minutes after OGTT ingestion as follows: normal, blood glucose <139 mg/dl; impaired, blood glucose 140-199 mg/dl; diabetic, blood glucose >200 mg/dl. Homeostasis Model Assessment (HOMA) R and β (parameters of insulin resistance and secretion, respectively) were calculated as follows: HOMA-R = (fasting insulin, μU/ml) x (fasting glucose, mg/dl) / 405; HOMA-β = 360 x (fasting insulin, μU/ml) / [(fasting glucose, mg/dl) – 63].

Myocardium biopsy, surgical procedures, and myocardial protection

Before the establishment of cardiopulmonary bypass, right atrial myocardial tissue (10 x 10 mm) was excised from the insertion point of a two-staged drainage cannula. The tissue was frozen and stored at -80°C until analysis. Aortic valve replacement was performed in 27/38 patients (71%), aortic root replacement in 5/38 (13%), total arch replacement in 6/38 (16%), and concomitant coronary artery bypass grafting in 5/38 (13%). All procedures were conducted under cardiac arrest using both antegrade (15 ml/kg) and retrograde (7.5 ml/kg) cardioplegia (15°C) with a 1:1 mixture of blood and Myotector® (Mochida. Pharmaceutical Co., Ltd., Tokyo, Japan). Cardioplegia was introduced every 30 minutes thereafter. The amount of antegrade solution was reduced

to 7.5 ml/kg starting at the second infusion. A terminal warm antegrade cardioplegia was conducted just before de-clamping of the aorta.

Analysis of gene expression related to cardiac energy metabolism in the atrium

Quantitative real-time reverse transcription polymerase chain reaction (RT-PCR) was used to analyze gene expression related to cardiac energy metabolism in the atrium for the following genes: glucose transporter type 4 (*GLUT4*), peroxisome proliferator-activated receptor-α (*PPAR-α*), cluster of differentiation 36 / fatty acid translocase (*CD36*), carnitine palmitoyltransferase 1B (*CPT1B*), and fatty acid binding protein 3 (*FABP3*). Myocardial mRNA was isolated from frozen tissue samples using the High Pure RNA Tissue Kit (Roche, Penzberg, Germany), and was then reverse transcribed into cDNA using the Transcriptor First Strand cDNA Synthesis Kit (Roche, Penzberg, Germany). Subsequently, RT-PCR was performed using the FastStart Essential DNA Probes Master (Roche, Penzberg, Germany) and Real-time Ready Assay (Roche Assay ID: 146462, *GLUT4*; 146286, *PPAR-α*; 144833, *CD36*; 126501, *CPT1B*; 118811, *FABP3*; 102054, *GAPDH*). Polymerase chain reaction amplification was then performed with a reaction volume of 20 μL using LightCycler Nano (Roche, Penzberg, Germany), under the conditions specified by the manufacturer. After the initial denaturation and activation of the enzyme for 10 min at 95°C, 45 cycles of denaturation at 95°C for 10 s, and annealing and extension at 60°C for 30 s were performed. The results were normalized to *GAPDH* transcription levels.

Enzymatic activities related to mitochondrial fatty acid β-oxidation and tricarboxylic acid cycle in the atrium

β-hydroxyacyl CoA dehydrogenase (β-HAD; a key enzyme in fatty acid β-oxidation) and citrate synthase (CS; a key enzyme in the tricarboxylic acid [TCA] cycle) activity levels were spectrophotometrically determined in the tissue homogenate from the myocardium samples as previously described.[16]

Statistical analysis

Data are reported as means ± SD. Group differences were evaluated using Student's t-tests for continuous variables and chi-square tests for categorical variables. A multivariate logistic-regression analysis was conducted using the parameters reaching statistical significance in the univariate analyses. All reported P values are two-sided; those under 0.05 were considered to be statistically significant. Data were analysed using SPSS version 17.0 software (SPSS Inc. Chicago, IL, USA).

Results

Patient characteristics

Table 1 shows the pre-operative characteristics for the POAF and non-POAF groups. POAF was observed in 18/38 (47%) patients within 7 days after surgery. POAF recurrence was also observed in 7/18 (39%) patients after 7days of post-operative period during the hospital stay, but all the 18 POAF patients discharged home with sinus rhythm. The patients in the POAF group were significantly older compared to those in the non-POAF group. The use of beta blockers and statins was not different between the groups. Diabetes mellitus (under medication therapy) tended to be more frequent in the

POAF group compared to that in the non-POAF group, without statistical significance (P=0.17).

Table 2 shows the surgical procedural characteristics in the POAF and non-POAF groups. Concomitant CABG was more frequent in the POAF group. POAF and non-POAF groups also did not differ in cardiopulmonary bypass or aortic cross clamp times.

Echocardiographic parameters

Table 3 shows the pre-operative echocardiographic parameters in the POAF and non-POAF groups. Only the diameter of the left atrium was significantly larger in the POAF group compared to that in the non-POAF group. The electromechanical delay parameters were comparable between the groups.

Blood glucose, insulin, and free fatty acid levels

Table 4 shows the pre-operative blood glucose, insulin, and free fatty acid levels in the POAF and non-POAF groups. The fasting glucose level tended to be higher in the POAF group compared to that in the non-POAF group, without statistical significance (P=0.10). Serum free fatty acid levels were comparable between the groups. In addition, the insulin resistance parameters were not different between the groups.

Gene expression analysis of the atrial myocardium

Fig. 1 shows the results of the gene expression analysis of genes related to cardiac metabolism for the right atrial myocardium. *FABP3* expression was significantly reduced in the POAF group compared to that in the non-POAF group. The expression

levels of the other genes were comparable between the groups. Regarding the recurrence of POAF after 7 days of post-operative period until hospital discharge, the pre-operative gene expression of *FABP3* was not different between the POAF-recurrence group and the non-POAF-recurrence group (P=0.72).

Table 5 shows the results of the multivariate analysis of pre-operative parameters for the prediction of POAF. Reduced *FABP3* expression was a predictor of POAF, independent of age and left atrial diameter.

Enzymatic activities related to mitochondrial fatty acid β-oxidation and TCA cycle in the atrium

The analysis of enzymatic activity was performed in only 19/38 patients due to a shortage in myocardial tissue. However, the pre-operative characteristics of these 19 patients were comparable to those of the whole cohort (i.e., only age and *FABP3* expression significantly differed between the POAF (n=10) and non-POAF (n=9) patients in this subsample). β-HAD activity was comparable between the groups (108 ± 44 vs. 92 ± 32 nM/min/mg protein, respectively, P=0.38). CS activity was also comparable between the groups (82 ± 47 vs. 76 ± 23 nM/min/mg protein, respectively, P=0.77).

Discussion

In the present study, atrial myocardial *FABP3* expression was shown to be significantly reduced in patients with POAF, independent of age and left atrial diameter. This finding may contribute to the identification of the mechanism underlying POAF and may aid in the development of new prophylactic strategies for POAF in the future.

Possible mechanisms of POAF – previous reports

Structural and electrical remodeling are two elements proposed in the possible mechanisms of POAF. Structural remodeling includes the pre-operative atrial damage associated with heart disease (atrial dilatation and fibrosis), which leads to changes in the mechanical function[17] and conduction properties of the heart, and therefore contributes to the formation of new re-entry foci.[18] Electrical remodeling involves electrophysiological changes such as a shortening of the refractory period and calcium overload.[19] In cardiac surgery, ischemic myocardial damage due to inadequate cardio-protection, traumatic pericarditis and myocarditis, and an increase in adrenergic tone, may contribute to electrical remodeling. Structural and electrical remodeling is inevitable in cardiac surgery and is difficult to address in terms of prophylaxis for POAF.

Several biological factors including inflammation and autonomic nervous abnormalities can be potential substrates for POAF.[19] Bruins, et al. have reported that elevation of complement-C-reactive protein complex (C4d-CRP) in the blood after the cardiac surgery was associated with onset of post-operative arrhythmia.[20] In the present study, maximum levels of serum CRP, an inflammation marker, within 7 days after the surgery were comparable between the POAF and the non-POAF groups (11 ± 4

vs. 9 ± 4 mg/dl, P=0.25). Previous randomized trials have shown that there was no preventive effect of POAF by administration of anti-inflammatory agents (non-steroidal anti-inflammatory drugs and corticosteroids) and these agents increased risk of infection.[21, 22] However, we could not eliminate the potential role of local inflammation in the atrium in the onset of POAF. In addition, Dimmer, et al. have analyzed heart rate variability after CABG using the standard deviation of all RR intervals recorded by Holter ECG. They concluded that autonomic imbalance characterized by a moderate increase in the sympathetic activity preceded POAF.[23] The underlying mechanism of sympathetic activation and POAF may be calcium overload that induces triggered activity (after-depolarization) in the heart.[24]

We propose that "metabolic remodeling" should be considered as a third element in POAF. Thus far, few reports exist regarding cardiac energy metabolism in POAF.[10] In a large prospective cohort study of 4,175 cases aged over 65 years, higher plasma free fatty acid was determined to be a risk factor for AF, independent of age, sex, race, hypertension, and diabetes mellitus.[25] The authors suggested a potential mechanism involving the production of lysophospholipids via a breakdown of membrane lipids and acylcarnitine from circulating free fatty acid. Furthermore, free fatty acid may inhibit the Na^+/ K^+/ATPase pump with a subsequent increase in intracellular sodium and calcium, inducing arrhythmias. In another prospective cohort study of 15,792 participants, diabetes and HbA1c levels were reported to be associated with an increased risk of AF.[26] The authors suggested that an increased risk of LV hypertrophy due to insulin resistance results in a predisposion to AF. Although POAF was not the end-point in these two studies, these studies demonstrate that cardiac metabolic remodeling is an important player in AF.

Interpretation of decreased atrial FABP3 expression in POAF patients

Fatty acids are the major substrates for energy production (70%) in the working adult heart under normal physiological conditions. The fatty acid metabolic pathway consists of several events, including fatty acid uptake into the cytosol, transport of fatty acids from the cytosol into the mitochondria, fatty acid uptake into the mitochondria, and fatty acid β-oxidation in the mitochondria. As a lipid chaperone, the cytosolic FABP3 protein is involved in fatty acid transport towards the mitochondrial β-oxidation system and is therefore essential for fatty acid oxidation in the cells.[7] Since *CD 36* and *CPT-1β* expression (involved in the uptake of fatty acids into the cytosol and mitochondria, respectively) and β-HAD activity (an enzyme involved in fatty acid β-oxidation) in the atrium were comparable between the groups, the reduced *FABP3* expression in the POAF group may directly result in abnormal fatty acid metabolism in the atrium via the limited utilization of fatty acids in the mitochondria.

FABP3 has also a crucial role in lipotoxicity, eliminating toxic free fatty acids and their intermediates (ceramides, diacylglycerols, and long-chain acyl-CoAs) in the cytosol by transporting them to the sites of metabolic conversion.[27] Inhibition of this vital transport pathway in the heart has been reported to be associated with cardiomyopathy after cyclophosphamide and doxorubicin therapy.[28, 29] Although we did not measure the cytosolic content of fatty acid intermediates in the atrium, the decreased *FABP3* expression in the atrium of patients with POAF may be related to an accumulation of fatty acid intermediates. The preexisting lipotoxicity may exacerbate mitochondrial damage, reported to be one of the mechanisms of POAF.[30, 31]

Possible cause of decreased atrial FABP3 expression before cardiac surgery

Mitochondrial reactive oxygen species (ROS) release has been previously shown to be increased with an accumulation of intramyocellular lipids in the atrium of patients with type 2 diabetes.[32] Oxidative stress can lead to downregulation of *FABP3* expression in the atrium. However, in the present study, parameters related to insulin resistance or type 2 diabetes were comparable between groups (except for fasting blood glucose levels, which tended to be higher in POAF patients). During the process of atrial structural remodeling consequent to various AF risk factors (such as mitral regurgitation, congestive heart failure, and hypertension), inflammation and subsequent fibrosis occur in the atrium, which leads to AF susceptibility[33] and may also decrease atrial *FABP3* gene expression. Although in the present study, we did not assess fibrosis in the atrial myocardium, there was no correlation between the gene expression of *FABP3* and the right atrial diameter (P=0.64). Further studies are needed to clarify the mechanism underlying the altered atrial gene expression of *FABP3* in patients with POAF.

Limitations

Several limitations of the present study should be addressed. First, the number of the subjects was small. Second, the present study cannot prove a causal relationship between decreased atrial *FABP3* gene expression before cardiac surgery and the increased onset of AF within 7 days after the surgery. We did not evaluate the accumulation of fatty acid intermediates in the atrium due to the limited samples. Thus, further mechanistic studies are necessary.

Conclusions

The present study demonstrated that pre-operative *FABP3* gene expression in the atrium is reduced in patients with POAF, independent of age and left atrial diameter. These findings suggest a potential link between altered fatty acid transport in the atrium and increased AF onset after cardiac surgery.

Acknowledgments

This study was supported by KAKENHI Grant-in-Aid for Young Scientists (B) (Grant Number JP24791453). We would like to thank Editage (www.editage.jp) for English language editing.

Disclosures

The authors have no conflicts of interest to declare.

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Figure legends

Figure 1. Gene expression analysis in the right atrial myocardium: (A) *PPAR-α*, (B) *CD36*, (C) *FABP3*, (D) *CPT1B*, and (E) *GLUT4*. *CD36*, cluster of differentiation 36 / fatty acid translocase; *CPT1B*, carnitine palmitoyltransferase 1B; *FABP3*, fatty acid binding protein 3; *GLUT4*, glucose transporter type 4; *PPAR-α*, peroxisome proliferator-activated receptor-α.

Figure 1

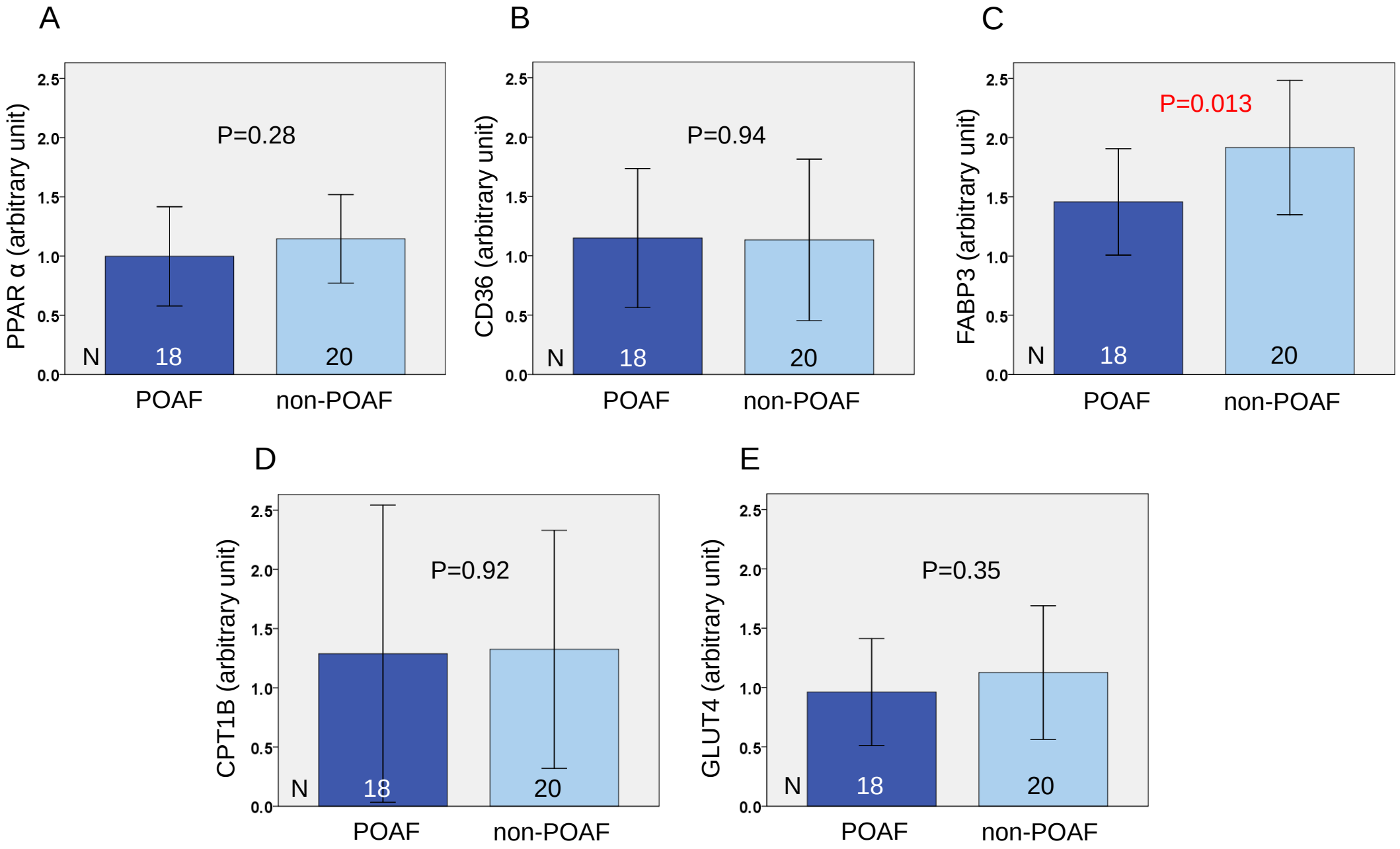
A
PPAR α (arbitrary unit)
P=0.28
N
18
20
POAF
non-POAF
B
CD36 (arbitrary unit)
P=0.94
N
18
20
POAF
non-POAF
C
FABP3 (arbitrary unit)
P=0.013
N
18
20
POAF
non-POAF
D
CPT1B (arbitrary unit)
P=0.92
N
18
20
POAF
non-POAF
E
GLUT4 (arbitrary unit)
P=0.35
N
18
20
POAF
non-POAF

Table 1. Pre-operative characteristics

	Total (n=38)	POAF (n=18)	non-POAF (n=20)	P value
Age	69±15	75±6	64±19	0.018
Male	19 (50%)	8	11	0.52
BMI	22±3	23±2	22±4	0.11
Heart rate	68±11	66±10	69±12	0.41
SBP, mmHg	119±18	124±15	114±20	0.10
DBP, mmHg	59±12	57±11	61±13	0.30
Diabetes mellitus	5 (13%)	4	1	0.17
eGFR, ml/min/1.73m^2	69±18	65±13	73±21	0.20
Medications				
beta blockers	11 (29%)	6	5	0.72
statins	16 (42%)	9	7	0.35
Total cholesterol, mg/dl	182±34	183±26	183±40	0.95
Triglyceride, mg/dl	109±43	101±44	117±43	0.26
HbA1c, %	5.6±0.7	5.7±0.7	5.4±0.4	0.26

Mean±SD. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; POAF, post-operative atrial fibrillation; SBP, systolic blood pressure.

Table 2. Surgical procedural characteristics in POAF and non-POAF groups

	Total (n=38)	POAF (n=18)	non-POAF (n=20)	P value
Aortic valve replacement	27	14	13	0.49
Aortic root replacement	6	1	5	0.18
Aortic arch replacement	6	3	3	1.00
Coronary artery bypass grafting	4	4	0	0.041
Cardiopulmonary bypass time, min	204±100	200±91	208±109	0.81
Aortic cross clamp time, min	133±62	133±58	133±67	0.99

Mean±SD. POAF, post-operative atrial fibrillation.

Table 3. Pre-operative echocardiographic parameters

	Total (n=38)	POAF (n=18)	non-POAF (n=20)	P value
LVDd, mm	52±11	54±10	51±12	0.54
LVDs, mm	35±12	36±11	35±13	0.85
LVEF, %	61±11	64±8	58±13	0.15
LAD, mm	40±8	44±7	36±8	0.001
Aortic valve stenosis	1.3±1.5	1.5±1.5	1.1±1.5	0.42
Aortic valve regurgitation	1.6±1.1	1.6±1.1	1.6±1.1	0.87
Mitral valve regurgitation	1.0±0.4	0.9±0.5	1.0±0.3	0.40
Tricuspid valve regurgitation	0.7±0.6	0.8±0.4	0.7±0.7	0.67
E wave, cm/s	78±22	78±23	80±21	0.81
A wave, cm/s	89±30	93±30	85±30	0.46
E/A	1.01±0.58	0.98±0.65	1.04±0.51	0.75
DcT, ms	252±77	269±76	236±76	0.20
Electromechanical delay				
time to A' (lateral), ms	84±23	83±22	85±26	0.74
time to A' (medial), ms	60±14	59±10	62±17	0.56
intra-left atrial delay, ms	24±16	24±16	24±16	0.99

Mean±SD. DcT, deceleration time; LAD, left atrial diameter; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; POAF, post-operative atrial fibrillation.

Table 4. Pre-operative blood glucose, insulin, and free fatty acid levels

	Total (n=38)	POAF (n=18)	non-POAF (n=20)	P value
Fasting glucose, mg/dl	102±16	107±20	98±10	0.10
Glucose at 120 min after OGTT ingestion, mg/dl	157±43 (n=32)	152±41 (n=13)	160±45 (n=19)	0.63
glucose tolerance type				0.85
normal	13 (41%)	6	7	
Impaired	13 (41%)	5	8	
diabetes mellitus	6 (19%)	2	4	
Insulin, μU/ml	5.7±3.2	6.1±3.6	5.4±2.9	0.50
HOMA-R	1.49±1.00	1.70±1.22	1.32±0.76	0.27
HOMA-β	54±28	51±24	57±30	0.57
Free fatty acid, μEq/L	407±224	384±246	425±209	0.60

Mean±SD. HOMA, homeostasis model assessment; OGTT, oral glucose tolerance test (75 g); POAF, post-operative atrial fibrillation.

Table 5. Multivariate analysis for POAF

	Coefficient	SE	Wald	P value	Odds ratio	95% CI
Intercept	-9.363	5.780	2.624			
Age	0.086	0.068	1.585	0.21	1.090	0.953-1.246
LAD	0.163	0.091	3.210	0.07	1.177	0.985-1.406
FABP3	-2.142	1.076	3.966	0.046	0.117	0.014-0.967

95% CI, 95% confidence interval for the estimated odds ratio; *FABP3*, fatty acid binding protein 3; LAD, left atrial diameter; POAF, post-operative atrial fibrillation; SE, estimated precision of the coefficients.