Epicardial Adipose Tissue and Postoperative Atrial Fibrillation

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Research Article

Abstract

Background. Atrial fibrillation (AF) often occurs after cardiac surgery and is associated to increased risk of stroke and mortality. Several evidence support the important role of inflammation in the pathogenesis of postoperative atrial fibrillation (POAF). It is known that an increased volume and a pro-inflammatory phenotype of epicardial adipose tissue (EAT) are both associated with AF onset in non surgical context. In the present study, we aim to evaluate whether also POAF occurrence may be triggered by an exalted production of inflammatory mediators from EAT.

Methods. The study population was composed of 105 patients, with no history of paroxysmal or permanent AF, undergoing elective cardiac surgery. After clinical evaluation, all patients performed an echocardiographic study including the measurement of EAT thickness. Serum samples and EAT biopsies were collected before surgery. Levels of 10 inflammatory cytokines were measured in serum and EAT conditioned media. After surgery, cardiac rhythm was monitored for 7 days.

Results. Forty-four patients (41.3%) developed POAF. As regard to cardiovascular therapy, only statin use was significantly lower in POAF patients (65.1% vs. 84.7%; p-0.032). Levels of Monocyte Chemoattractant Protein-1 (MCP-1), in both serum and EAT, were significantly higher in POAF patients (130.1 pg/ml vs. 68.7 pg/ml; $p = < 0.001$; 322.4 pg/ml vs. 153.4 pg/ml; $p = 0.028$ respectively). EAT levels of IL-6 were significantly increased in POAF patients compared to those in sinus rhythm (126.3 pg/ml vs. 23 pg/ml; $p = < 0.005$).

Conclusion

Higher EAT levels of IL6 and MCP1 are significantly associated with the occurrence of POAF. Statin therapy seems to play a role in preventing POAF. These results might pave the way for a targeted use of these drugs in the perioperative period.

Introduction

Atrial fibrillation (AF) represents the most common arrhythmia occurring after cardiac surgery. The incidence of postoperative AF (POAF) ranges between 20% and 50% according to the type of surgical procedure, with higher rates after valve replacement or repair respect to isolated coronary artery bypass grafting (CABG) surgery (1–4). Combined procedures (CABG and valvular surgery) present the highest incidence of this complication, reaching up to 80% (5).

POAF occurrence determines a significant increase in stroke risk, morbidity and mortality with consequent increase of hospitalization time and healthcare costs (6).

Although the pathogenesis of POAF remains uncertain, accumulating evidence suggest an important role of inflammatory mechanisms and mediators. In particular, the interleukin- 6 (IL-6), recognized as a primary cytokine in the inflammatory cascade, has been identified as one of the main molecules involved

in the development of POAF (4,7–9). Interestingly, the epicardial adipose tissue (EAT), the visceral fat depot of the heart, produces numerous pro-inflammatory cytokines which can affect the myocardium through paracrine or vasocrine mechanisms (10, 11). Moreover, increased EAT thickness is associated with higher levels of secreted inflammatory mediators and with the onset of atrial fibrillation (10,12).

The aim of this study was to evaluate the correlation between EAT secretory profile and POAF occurrence in patients undergoing cardiac surgery.

Results

Patient characteristics

Table 1 illustrates demographic, clinical, and echocardiographic characteristics of the study population. In the overall population, the mean age was 67.8 ± 9.7 (range 45–84) years and 27.6% of patients were females. Eighty percent of patients had hypertension, 46.2% were diabetics, 60.2% had dyslipidemia and 38.8% were smokers. Mean body mass index (BMI) was 27.8 ± 4.3. Mean left ventricular ejection fraction (LVEF) was 59.3 ± 10.6%. Mean EAT thickness was 10.7 ± 3.6 mm. As regard to drug therapies, 87.1% of patients assumed beta-blockers, 72.3% ACE-inhibitors/sartans, 40.6% calcium-channel blockers, 87.1% antiplatelet and 76.5% statins.

Table 1
Demographic and clinical characteristics of the study population

	Overall (n = 105)	NO POAF (n = 61; 58.7%)	POAF (n = 44; 41.3%)	p-value
Gender (female) n (%)	29 (27.6)	15 (24.6)	14 (31.8)	0,508
Age n (%)	67.8+-9.7 (45 to 84)	65+-9.9 (45 to 84)	71.6+-8 (46 to 83)	**< 0.001**
Hypertension n (%)	84 (80.8)	47 (77)	37 (86)	0,317
Diabetes n (%)	48 (46.2)	29 (47.5)	19 (44.2)	0,842
Dyslipidemia n (%)	62 (60.2)	38 (62.3)	24 (57.1)	0,683
Smokers n (%)	40 (38.8)	25 (41)	15 (35.7)	0,492
BMI (kg/m2)	27.8+-4.3 (19.7 to 41.2)	28.1+-4.4 (21.4 to 41.2)	27.4+-4.2 (19.7 to 37.7)	0,474
LVEF (%)	59.3+-10.6 (33 to 81)	59.1+-10.9 (33 to 81)	59.6+-10.2 (35 to 79)	0,8
EAT (mm)	10.7+-3.6 (0 to 20)	9.6+-3.6 (0 to 15)	11.3+-3.5 (5 to 20)	0,099
Beta blockers n (%)	88 (87.1)	53 (89.8)	35 (83.3)	0,377
Calcium-channel blockers n (%)	41 (40.6)	26 (44.1)	15 (35.7)	0,42
ACE-inhibitors/sartans n (%)	73 (72.3)	43 (72.9)	30 (71.4)	1
Statins n (%)	78 (76.5)	50 (84.7)	28 (65.1)	**0,032**
Antiplatelet n (%)	88 (87.1)	54 (91.5)	34 (81)	0,14
Left Atrial Volume (> 34 ml/m2) n (%)	35 (33.3)	17 (31.5)	18 (47.4)	0,184
E/A	0.9 [0.8; 1.2] (0.5 to 4.1)	0.9 [0.7; 1.2] (0.5 to 4.1)	0.9 [0.8; 1.3] (0.5 to 3.3)	0,771
E/E'	12 [7.7; 17.4] (4.8 to 32)	10 [6.6; 14] (4.8 to 23)	13.6 [10.4; 20.5] (7.3 to 32)	0,013
LVESD (mm)	29 [28; 31] (2.6 to 38)	28.5 [28; 30.5] (28 to 35)	29 [26.5; 32.5] (2.6 to 38)	0,962

For numerical variables, values are expressed as median [1st quartile; 3rd quartile] (min to max).

BMI, bodymass index; LVEF, left ventricular ejection fraction; EAT, epicardial adipose tissue; LVESD, left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter.

	Overall (n = 105)	NO POAF (n = 61; 58.7%)	POAF (n = 44; 41.3%)	p-value
LVEDD (mm)	48 [45; 51] (37 to 61)	48 [44.5; 53] (37 to 58)	48 [45; 51] (40 to 61)	0,918
Interventricular septum (mm)	10 [8; 12] (6 to 15)	10 [8; 12] (6 to 15)	10 [9; 12] (6 to 13)	0,851
Posterior Wall (mm)	9 [7.2; 11] (6 to 14)	9.5 [7; 10.8] (7 to 14)	9 [8; 11] (6 to 11)	0,982
Left ventricular mass (gr)	154.9 [124.1; 190.2] (87.1 to 349)	153 [118.5; 186.1] (87.1 to 349)	156.9 [124.9; 210.4] (90 to 234)	0,85
Left ventricular mass index gr/m2	69.7 [12.1; 92.9] (0.7 to 163.9)	69.9 [45.7; 92] (0.7 to 163.9)	64.6 [1.3; 98] (0.8 to 131.1)	0,597
RWT	0.39 [0.32; 0.45] (0.22 to 0.58)	0.38 [0.31; 0.48] (0.24 to 0.58)	0.4 [0.33; 0.44] (0.22 to 0.55)	0,704
For numerical variables, values are expressed as median [1st quartile; 3rd quartile] (min to max).				
BMI, bodymass index; LVEF, left ventricular ejection fraction; EAT, epicardial adipose tissue; LVESD, left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter.				

POAF occurred in 41.3% (n = 44 pts) of the study population. Interestingly, patients with POAF were older (71.6 ± 8 vs. 65 ± 9.9; p = < 0.001) and had a worse diastolic function (E/e' 13.6 vs. 10; p = 0.01) compared to non POAF. No differences were found in cardiovascular risk factors and other clinical characteristics between POAF and non POAF patients. Of note, as regard to cardiovascular therapy, only statin use was significantly lower in patients who developed POAF (65.1% vs. 84.7%; p = 0.032).

EAT and serum inflammatory profile

IL-1β, IL-1ra, IL-6, IL-8, IL-13, FGF, IFN-γ, MCP-1, RANTES/CCL5 and TNF-α were detected in serum samples and EAT conditioned media obtained from all patients. No significant differences were found in serum levels of the pro-inflammatory mediators, except for MCP-1 which was significantly higher in patients who developed POAF than in those who remained in sinus rhythm (130.1 pg/ml vs. 68.7 pg/ml; p = ≤ 0.001; Table 2). Interestingly, also EAT levels of MCP-1 were significantly higher in patients with POAF (322.4 pg/ml vs. 153.4 pg/ml, p = 0.028; Fig. 1; Table 3) even after adjusting the analysis for age, statin use and atrial volume, using general linear model (p = 0.008). Moreover, EAT levels but not serum levels of IL-6 were significantly increased in patients who developed POAF compared to those in sinus rhythm (126.3 pg/ml vs. 23 pg/ml; p = 0.005; Fig. 1; Table 3). The difference remained statistically significant in adjusted analysis (p = 0.043).

Table 2
Serum inflammatory profile

	Overall (n = 105)	Non POAF (n = 61; 58.7%)	POAF (n = 44; 41.3%)	p-value
	median [1st quartile; 3rd quartile] (min to max)			
IL-1b pg/ml	7.6 [6; 8.6] (2.7 to 28.4)	7.6 [6.9; 8.6] (2.7 to 11.4)	7.3 [4.8; 9] (2.8 to 28.4)	0,413
IL-1ra pg/ml	444.9 [251; 803.1] (112.3 to 2173)	441.1 [220.2; 660.9] (112.3 to 1981.6)	461.2 [321.5; 998.4] (118.6 to 2173)	0,13
IL-6 pg/ml	33.5 [28.7; 42.7] (7.6 to 238.3)	33 [28.7; 41.2] (15.7 to 93.6)	36.2 [25.9; 51.2] (7.6 to 238.3)	0,456
IL-8 pg/ml	43.3 [35; 61.4] (21.3 to 369.7)	39.7 [34.2; 55.8] (21.3 to 103.7)	45.6 [34.9; 78.8] (26.7 to 369.7)	0,13
IL-13 pg/ml	13 [9.4; 17.1] (2.9 to 48)	12.5 [9.4; 16.6] (4.4 to 23.9)	13.2 [9.4; 18.8] (2.9 to 48)	0,469
FGF basic pg/ml	105.7 [75; 148.2] (25.2 to 285.2)	123 [77.4; 148.2] (59.1 to 174)	81.7 [71.3; 150.6] (25.2 to 285.2)	0,264
IFN-g pg/ml	194.9 [164.7; 241.2] (76.5 to 1046.1)	194.9 [171.2; 229.8] (76.5 to 477.4)	186 [155.7; 318.4] (80.9 to 1046.1)	0,969
MCP-1 (MCAF) pg/ml	85 [58.1; 136.5] (49.1 to 433.3)	68.7 [55.7; 120.7] (49.1 to 184.8)	130.1 [72.5; 172.3] (53.3 to 433.3)	**0,001**
RANTES pg/ml	10014.6 [5219.9; 23118.6] (376.3 to 109073.5)	9473.7 [3838.4; 23503.8] (376.3 to 52846.2)	10898.4 [6373.3; 23779] (498.2 to 109073.5)	0,439
TNF-α pg/ml	97.3 [75.7; 116.1] (21.3 to 397.6)	97.3 [81.1; 108] (21.3 to 182.8)	93.3 [55.3; 129.8] (22.6 to 397.6)	0,973
IL, Interleukin; FGF, Fibroblast Growth Factor; IFN-γ, Interferon-γ; MCP-1, Monocyte Chemoattractant Protein-1; RANTES/CCL5, Regulated on Activation Normal T-cell Expressed and Secreted; TNF-α, Tumor Necrosis Factor-α				

Table 3
EAT inflammatory profile

	Overall (n = 105)	Non POAF (n = 61; 58.7%)	POAF (n = 44; 41.3%)	p-value
	median [1st quartile; 3rd quartile] (min to max)			
IL-1b pg/ml	3.2 [2.1; 20] (1.2 to 227.7)	2.8 [2; 9.4] (1.2 to 82.4)	4.1 [2.3; 50.5] (1.2 to 227.7)	0,07
IL-1ra pg/ml	473.3 [57; 1445.8] (1.2 to 21640.2)	308.7 [51.2; 2195.9] (1.2 to 21640.2)	811.2 [68.5; 1434.3] (29.7 to 14413.5)	0,316
IL-6 pg/ml	38.7 [9.9; 255.9] (2.6 to 129652.6)	23 [9.3; 174.5] (2.6 to 968.5)	126.3 [14; 20624.3] (7.5 to 129652.6)	**0,005**
IL-8 pg/ml	44.9 [11.3; 274.3] (4.2 to 335428.2)	35.1 [10.4; 246.9] (4.4 to 2618.9)	81.6 [14.6; 9216.2] (4.2 to 335428.2)	0,087
IL-13 pg/ml	3 [2.5; 3.9] (2.1 to 136.9)	2.9 [2.4; 3.5] (2.1 to 44.7)	3.5 [2.4; 10.3] (2.1 to 136.9)	0,076
FGF basic pg/ml	501.2 [287.4; 942] (40.8 to 3416.2)	505 [321.4; 1041.5] (40.8 to 3416.2)	473.6 [273.2; 656] (143.1 to 3324.3)	0,485
IFN-g pg/ml	95.6 [40.9; 144.6] (20.8 to 432.2)	90.2 [36.7; 122.2] (20.8 to 235.5)	110.6 [44.7; 235.2] (22.4 to 432.2)	0,057
MCP-1(MCAF) pg/ml	199.2 [53; 531.6] (17.3 to 23675.8)	153.4 [39.2; 379.6] (17.3 to 6993.6)	322.4 [87.2; 9341.2] (17.5 to 23675.8)	**0,028**
RANTES pg/ml	166.3 [87.3; 313.4] (24.7 to 1065.3)	139.8 [82.6; 275.4] (24.7 to 1034.6)	177.8 [115.5; 389.5] (39.4 to 1065.3)	0,333
TNF- α pg/ml	28 [20.8; 40.8] (14.9 to 227.6)	26 [20.3; 34.2] (15.5 to 77.5)	35 [20.8; 91.9] (14.9 to 227.6)	0,057

IL, Interleukin; FGF, Fibroblast Growth Factor; IFN-γ, Interferon-γ; MCP-1, Monocyte Chemoattractant Protein-1; RANTES/CCL5, Regulated on Activation Normal T-cell Expressed and Secreted; TNF-α, Tumor Necrosis Factor-α

Discussion

POAF represents one of the most frequent complication after cardiac surgery and accounts for a significant increase of stroke risk, disability and mortality. Although many intraoperative and clinical factors seem to be involved in the development of POAF, its pathogenesis remains still unclear. Recent evidence suggest that inflammation can alter atrial conduction, facilitating multiple re-entry wavelets, thus predisposing to the development of POAF (15,16).

EAT, the visceral fat depot of the heart, located between the myocardium and the visceral layer of pericardium, is mainly represented in the atrio-ventricular and inter-ventricular grooves, and along the lateral wall of the right ventricle (11). In pathologic condition, EAT produces and secretes numerous

inflammatory mediators (12,17). The absence of fascial boundaries allows a tight connection with surrounding tissues and coronary arterial vessels. Numerous evidence suggest a strong association between increased EAT thickness and atrial fibrillation (11).

In this study we evaluated, for the first time, the potential association between the levels of EAT-secreted pro-inflammatory cytokines and the development of POAF in patients undergoing elective cardiac surgery, without history of paroxysmal or persistent atrial fibrillation.

Consistent with previous studies, we have found that patients who developed POAF were older than those who remained in sinus rhythm throughout the postoperative period (15,18). It is known that aging is characterized by a chronic low-grade inflammation and is associated with degenerative and inflammatory modifications in atrial anatomy, such as dilation and fibrosis, which are responsible for the alterations of the atrial electrophysiological properties (19–21). The EAT thickness increases with age and the release of proinflammatory adipocytokines from cardiac visceral fat into the systemic circulation may contribute to the inflammatory state, which in turn promotes the accumulation and inflammation of EAT (21–23). Furthermore, it is well known that extracorporeal circulation is also characterized by a systemic inflammatory response (4,24). In the present study, EAT thickness tended to be higher in POAF compared to non POAF patients, although the difference between groups did not reach the statistical significance. To note, EAT thickness mean value in POAF population was higher than that reported as cut-off value (10 mm) in a recent study from our group that has validated the echocardiographic assessment of EAT thickness at the level of the Rindfleisch fold (13).

Significantly higher levels of MCP-1, both in serum and in EAT secretomes, were found in patients who developed POAF. The expression of the gene coding for MCP-1 can be induced by a variety of mediators, including numerous interleukins, platelet derived growth factor, and vascular endothelial growth factor (25). MCP-1 is mainly produced by monocytes and macrophages and exerts potent chemotactic and activating effects on CCR2-positive leukocytes. Several studies have reported that serum MCP-1 levels are independently associated with atrial fibrillation (7,25).

IL-6 levels were significantly higher in EAT secretomes of patients who developed POAF. Numerous evidence have demonstrated elevated serum levels of IL-6 in patients who develop POAF (25–27). IL-6 is a pleiotropic cytokine with a variety of biological activities. It is produced not only by immune cells and immune accessory cells including monocytes and macrophages, but also by endothelial cells, vascular smooth-muscle cells, adipocytes and ischemic cardiomyocytes. It stimulates the synthesis of several acute-phase reaction proteins (7). Of note, in our study, EAT production of this pro-inflammatory cytokine was higher in POAF patients and resulted significantly associated with atrial arrhythmia. Although left atrial volume is known to be an important factor in conditioning AF occurrence, no differences in this parameter were found between POAF and non POAF patients. Furthermore, differences in EAT levels of MCP-1 and IL-6 between POAF and non POAF patients remained significant even after adjusting the analysis for age, statin use prior to surgery and left atrial volume. We also excluded the other possible causes of POAF, such as electrolyte imbalance or acid-base disturbances.

Interestingly, statin intake was lower in patients who developed POAF compared with those who remained in sinus rhythm. We hypothesize that this result could be ascribed to the known anti-inflammatory and pleiotropic effect of statins. A randomized, controlled trial (ARMYDA-3) demonstrated that treatment with 40 mg of atorvastatin daily for 7 days significantly reduces the incidence of new-onset POAF and shortens the length of hospital stay in patients undergoing cardiac surgery with CPB (28). Moreover, a recent meta-analysis from Yuan et al, including 20 randomized controlled trials of patients who underwent cardiac surgery, concluded that preoperative statin therapy might be promising for the prevention of POAF, especially for patients undergoing isolated CABG surgery (29). In this regard, our group has previously demonstrated, both in vivo and in vitro, that statin administration reduces EAT secretion of IL-6 and IL-8 levels in patients with aortic stenosis (30).

Conclusion

The present study has evaluated for the first time the association of the pro-inflammatory secretory profile of EAT with the onset of POAF in patients undergoing cardiac surgery. It is plausible that the inflammatory substrate is mainly promoted by the EAT secretion of IL-6 and MCP-1. Statin therapy seems to play a protective role, mediated by the reduction of EAT levels of IL-6, thus paving the way for a targeted use of these drugs in the peri-operative period. Further studies will be needed to confirm these findings and investigate the role of cardiac visceral fat in the pathogenesis of POAF.

Methods

Study population: the study population included 105 patients, without history of paroxysmal or permanent atrial fibrillation, undergoing elective surgery for CABG or valve replacement for severe aortic stenosis at the cardiac surgery unit of University of Naples "Federico II". The presence of chronic inflammatory diseases and/or cancer represented exclusion criteria, given their association with systemic and/or visceral fat inflammation. Demographic and clinical data including drug therapies were collected from all patients. The study protocol was compliant to the ethical guidelines of the 1975 Declaration of Helsinki. All the study procedures received approval by our institution's human research committee (Protocol n.301/19). All patients provided written informed consent before their inclusion into the study.

Transthoracic Echocardiography: before cardiac surgery, all patients underwent complete echocardiographic study, performed with a VIVID E9 (GE Healthcare) machine. In addition to the standard parameters, the maximum EAT thickness was evaluated, from the parasternal long-axis view, at end systole, between the right ventricle and the ascending aorta (13). Measurements of EAT thickness were performed offline by two independent blinded echocardiographers. The average value from three cardiac cycles was used for the statistical analysis.

Tissues and serum collection: serum samples and EAT biopsies were collected from all patients undergoing cardiac surgery before the cardiopulmonary bypass (CPB). EAT biopsy samples (average 0.1 to 0.5 g) were taken between the free wall of the right ventricle and the anterior surface of the ascending

aorta. EAT secretomes were obtained as follows: tissues were weighted, cut into small pieces, and transferred into a 12-well plate. According to tissue weight, serum-free Dulbecco modified Eagle medium (DMEM) (1 mL medium/0.1 g tissue) was added to the well and incubated at 37°C in a CO2 incubator. After 24 h, medium was collected and centrifuged at 14,000g to remove debris and analyzed for cytokines content, as described below.

Serum and EAT conditioned media were screened for the concentration of IL-1β, IL-1ra, IL-6, IL-8, IL-13, basic Fibroblast Growth Factor (FGF), Interferon (IFN)-γ, Monocyte Chemoattractant Protein (MCP)-1, Regulated on Activation Normal T-cell Expressed and Secreted (RANTES/CCL5), and Tumor Necrosis Factor (TNF)-α, using the Bio-Plex multiplex Human Cytokine and Growth factor kits (Bio-Rad) according to the manufacturer's protocol.

Materials: Media were from Lonza (Lonza Group Ltd., Basel, Switzerland).

ECG monitoring: after surgery, heart rate and rhythm were monitored for 7 days, by continuous telemetry (ApexPro 7-lead system; General Electric Medical Systems), at the cardiac intensive care unit. Atrial fibrillation has been termed as irregularly atrial rhythm without clear P waves that was confirmed by a 12-lead ECG. In this study, POAF was defined as any episode of atrial fibrillation lasting more than 5 minutes, with or without symptoms requiring intervention to maintain hemodynamic stability, arisen in the seven days following the cardiac surgery. POAF episodes recorded in condition of hemodynamic and volemic balance were considered for analysis. We excluded POAF episodes potentially related to a sudden fluid loss (diuretic administration, postoperative bleeding, etc..), low blood oxygenation or intravenous high inotropic dose administration.

Anesthesia and surgical technique: Surgical technique and perioperative management were the same for all patients according to the specific surgical procedure. Perioperative anesthesiologic management was the same in all cases: according to the institutional protocol, surgical anesthesia was obtained with continuous intravenous infusion of Propofol + Remifentanil + Cisatracurium, while fluid balance was managed paying attention to the hemodynamic conditions, in order to obtain a mean arterial pressure of at least 70 mmHg. Perioperative drugs management was carried out according to the 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery (14). Before CPB, heparin was intravenously administered at a dose of 300 units/Kg in all cases; protamine need was assessed using the HMS Plus Hemostasis Management system (Medtronic, Minneapolis, MN, USA). Transesophageal echocardiography was routinely performed before the surgical incision in order to assess myocardial and cardiac valves function during and after the surgical procedure. All patients underwent surgery through a standard full sternotomy approach and hypothermic CPB. In order to optimize the surgical times and to avoid confounding factors, all tissue collections were performed before the heparin administration and the placement of extracorporeal circulation cannulas. Surgical excision of EAT was performed from the fat pad of right ventricle infundibulum near the atrioventricular groove, using only a surgical scalpel blade no.11 (without using diathermic) in order to prevent any additional inflammatory damages. After collection, all biopsies were placed in a sterile pipe and quickly transferred to the laboratory to preserve

EAT secreting activity. Extracorporeal circulation was performed through aortic and atrio-caval cannulation. All patients requiring high doses of inotropic drugs during their intensive care unit stay were excluded from the study due to the known pro-arrhythmogenic effect (Epinephrine or Norepinephrine > 0,1µg/Kg/min or Dobutamine > 5 µg/Kg/min). At the end of surgery, all patients were moved into the cardiac surgery intensive care unit and weaned from the mechanical ventilation after at least 2 hours of general postoperative monitoring. Fluid intake was regulated to achieve a central venous pressure of at least 10 mmHg according to the cardiac anatomy and myocardial function. All patients received $MgSO_4$ continuous intravenous infusion in a dose of 17,5 gr in the first 24 hours after the surgery as anti-arrhythmia prophylaxis. Packed red cells were transfused only in presence of serum Hemoglobin lower than 8 g/dl while Fresh frozen plasma was used as plasma expander only in case of postoperative bleeding.

Statistical analysis: all statistical analyses were conducted using the statistical platform R (vers. 4.0). Standard descriptive statistics were used to describe the sample: absolute frequencies and percentages for categorical factors and either mean ± standard deviation (std. dev.) or median with range in case of numerical variables. Accordingly, between-groups comparisons were based on the chi-square test (or Fisher exact test where appropriate), the t test for independent samples, or the Mann-Whitney U test. To account for imbalances between the two groups, the inflammatory mediators' levels were log-transformed and the difference between groups were assessed using a linear model where age, statin use and atrial volume were entered as covariates.

All tests were two-sided with a p value < 0.05 denoting statistical significance. Due to exploratory nature of all the analyses, no adjustments were made for multiple comparison.

Declarations

Ethics approval and consent to participate: Ethical Committee of Federico II, Protocol n.301/19

Consent for publication: Not Applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: PL has enrolled patients, has collected clinical/anamnestic data, has performed echocardiograms and elaborated the manuscript. CM and CP have performed echocardiograms. CG and PE have performed epicardial adipose tissue biopsies during cardiac surgery. CS and FP have analysed serum samples and epicardial fat biopsies for the concentration of proinflammatory interleukins. GG, CT, CR and AI have enrolled patients and have collected clinical/anamnestic data. BD has performed the

statistical analysis. FN, LD and PV have designed the project and have revised the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1.
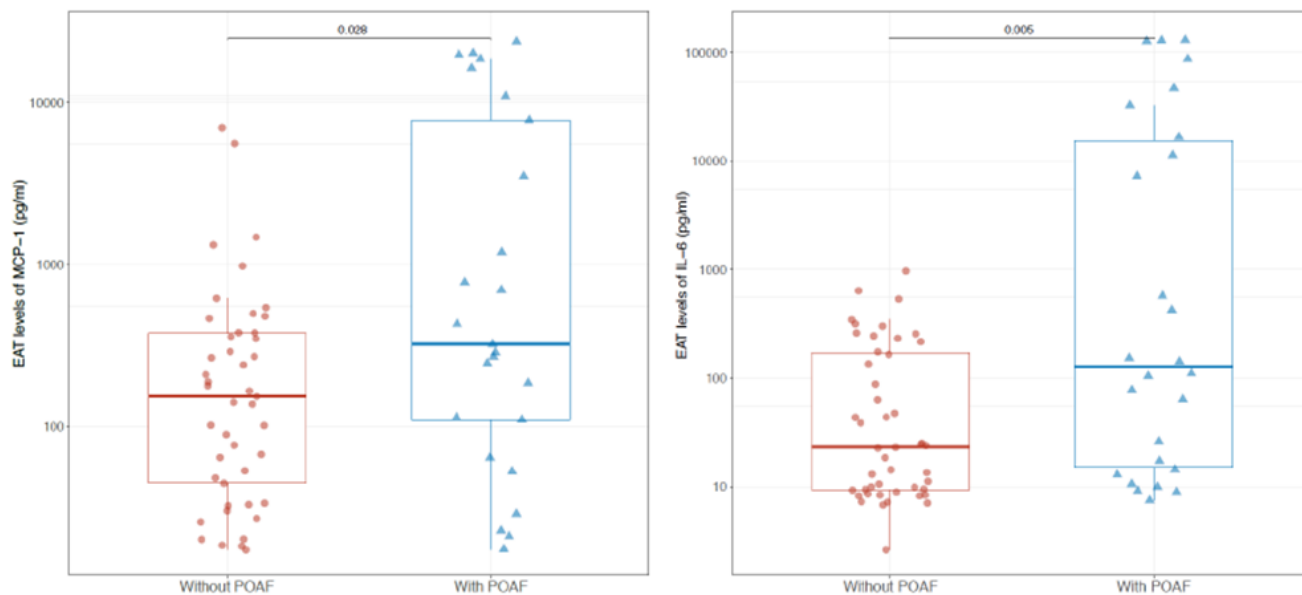
Figure 1

EAT levels of MCP-1 and IL-6 in POAF and non POAF patients.