ORIGINAL ARTICLE

Role of Preexisting Proarrhythmic Atrial Remodeling in Post-Coronary Artery Bypass Grafting Atrial Fibrillation

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ABSTRACT

Introduction: Due to its deleterious effects, early identification of patients at risk of postoperative AF (POAF) is of critical importance. Preexisting proarrhythmic atrial remodeling could contribute to this increased risk. Therefore, we aimed to evaluate the presence of preexisting proarrhythmic atrial remodeling and its impact on POAF occurrence in patients undergoing coronary artery bypass grafting (CABG).

Methods: Data regarding atrial structural (atrial size and histology), electrical (P-wave and atrial action potential parameters, mRNA expression of several AF-related genes), and autonomic (heart rate variability parameters) proarrhythmic remodeling were compared between patients with (AF; n=11) and without (no-AF; n=19) POAF. Impact of POAF on postoperative outcomes was also evaluated.

Results: No significant difference was observed in atrial electrical parameters between the two groups (all p>0.05). However, compared with no-AF, AF patients had more important subepicardial adipose infiltration (p=0.02) and higher markers of parasympathetic and sympathetic modulation (both p=0.03). Patients with POAF had longer hospital stay and more often presented postoperative renal dysfunction (both p=0.04).

Conclusion: These findings suggest that preexisting atrial structural (i.e., increased atrial subepicardial adiposity) and autonomic (i.e., sympatho-vagal coactivation) alterations could favor the occurrence of POAF. At its turn, POAF was associated with altered postoperative outcomes in CABG patients.

Keywords: adipose tissue, atrial remodeling, coronary artery bypass grafting, postoperative atrial fibrillation, sympatho-vagal coactivation.

REZUMAT

Introducere: Date fiind efectele sale negative, identificarea precoce a pacienților aflați la risc de a dezvolta fibrilație atrială postoperatorie (FAPO) are o importanță critică. Remodelarea atrială proaritmică preexistentă ar putea contribui la acest risc. Ne-am propus să evaluăm prezența remodelării atriale preexistente și impactul acesteia asupra apariției FAPO la pacienți supuși unui bypass aorto-coronarian (BPAC).

Metode: Date privind remodelarea proaritmică atrială structurală (dimensiunea și histologia atrială), electrică (parametrii undei P și ai potențialului de acțiune atrial, expresia ARNm a unor gene asociate FA) și autonomă (parametrii variabilității ritmului cardiac) au fost comparate între pacienți cu (FA; n=11) și fără (no-FA; n=19) FAPO. Impactul FAPO asupra evoluției postoperatorii a fost de asemenea evaluat.

Rezultate: Nu s-au observat diferențe semnificative în parametrii electrici între cele două grupuri (toate p>0,05). Față de no-FA, pacienții FA au prezentat însă infiltrare adipoasă subepicardică mai importantă (p=0,02) și markeri mai ridicați de modulare simpatică și parasimpatică (ambele p=0,03). Pacienții cu FAPO au prezentat mai des disfuncție renală și spitalizare mai lungă (ambele p=0,04).

Concluzie: Aceste rezultate sugerează că modificări atriale structurale (creșterea adipozității subepicardice) și autonome (coactivare simpato-vagală) preexistente ar putea favoriza FAPO. La rândul ei, FAPO a fost asociată cu evoluție mai nefavorabilă la pacienții cu BPAC.

Cuvinte cheie: bypass aorto-coronarian, coactivare simpato-vagală, fibrilație atrială postoperatorie, remodelare atrială, țesut adipos.

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained postoperative arrhythmia, occurring in up to 40% of patients who undergo coronary artery bypass grafting (CABG)[1]. In these patients, postoperative AF (POAF) has been shown to alter the hemodynamic status and augment the risk of heart failure, and to increase both short- and long-term mortality rates[2]. Although a causal relationship could not be established in all cases, POAF occurrence has been associated with multiple postoperative complications, including acute myocardial infarction, renal dysfunction, prolonged mechanical ventilation, as well as with prolonged hospitalization[3]. The most undesirable complication of AF remains stroke, which occurs in more than one third of patients who develop post-CABG AF[4]. Given the debilitating nature of AF, early interventions to prevent AF occurrence could provide invaluable clinical benefit. However, since not all patients will develop POAF, exposing all CABG patients to the inherent risks of prophylactic antiarrhythmic medication would obviously outweigh the potential benefits of such an approach[5]. Meanwhile, early identification of patients who are most prone to develop POAF could provide a much safer and more efficient approach.

To date, studies have identified several risk factors that favor POAF. Attempts have also been made to develop scoring systems that could predict POAF risk[6]. Most of these scoring systems include patient's clinical characteristics identified as important contributors to POAF occurrence such as age, heart failure, chronic obstructive pulmonary disease or heart valve surgery. However, in patients without significant comorbidities, these scores remain highly inadequate[7]. Moreover, although numerous patients may share similar risk factors, not all of them will develop POAF. Previous studies have shown that the risk of AF increases exponentially with increasing severity and duration of certain risk factors (e.g., hypertension), suggesting that the risk of POAF is more likely to be related to the degree of atrial proarrhythmic remodeling induced by these risk factors rather than to their presence per se[6,8]. Although numerous clinical and experimental studies have shown that preexisting atrial remodeling precedes and favors the occurrence of AF[8-11], data regarding the presence and the severity of atrial remodeling in patients undergoing CABG and the potential impact of such preexisting remodeling on the occurrence of post-CABG AF are limited.

Accordingly, we aimed to evaluate the presence and the severity of atrial electrical, structural, and autonomic remodeling in patients undergoing elective CABG procedures and to assess its relationship with the occurrence of post-CABG AF. The impact of post-CABG AF on in-hospital outcomes was also evaluated.

MATERIALS AND METHODS

Study population and design

Consecutive patients with coronary artery disease hospitalized for an elective CABG procedure at the Emergency Institute for Cardiovascular Diseases and Transplantation Targu Mures between March 2016 and June 2017 were prospectively evaluated. Patients were included in the study if they were admitted to hospital for a first-time elective CABG procedure, if they were hemodynamically stable at the moment of inclusion, and if they were ≥18 years of age. Exclusion criteria were: concomitant valve replacement or other intervention planned to be performed within the same procedure, systemic inflammatory diseases, and treatment with steroids or other anti-inflammatory drugs. Patients with a history of AF were also excluded. Median sternotomy and standard extracorporeal circulation (ECC) were used in all patients. All patients included in the study signed written informed consent. The research protocol complied with the Helsinki Declaration and was approved by the local Ethics Committees.

Patients were divided into two groups (i.e., AF and no-AF), according to the presence or absence of post-CABG AF. For patients to be allocated to their according groups, all patients underwent continuous 12-lead Holter ECG monitoring from day-1 post-CABG up to the day of discharge using CardioMem 3000® systems (GETEMED/GE Healthcare). Post-CABG AF was defined as the occurrence of AF episode(s) lasting ≥30 s during post-CABG hospitalization. Clinical characteristics (i.e., age, gender, body mass index [BMI], creatinine clearance), comorbidities (i.e., obesity, arterial hypertension, diabetes mellitus, history of stroke), and ongoing drug therapy were recorded for each patient. The CHA_2DS_2VASc and SYNergy between PCI with TAXUS™ and Cardiac Surgery (SYNTAX I) scores were also calculated. The duration of ECC, of aortic clamping, and the total duration of the CABG procedure were also recorded for each patient.

To assess the presence and severity of preexisting atrial remodeling and its relationship with post-CABG AF, all patients underwent (Figure 1) surface ECG recording and echocardiographic assessment on admission. Continuous 24-h 12-lead ECG Holter moni-

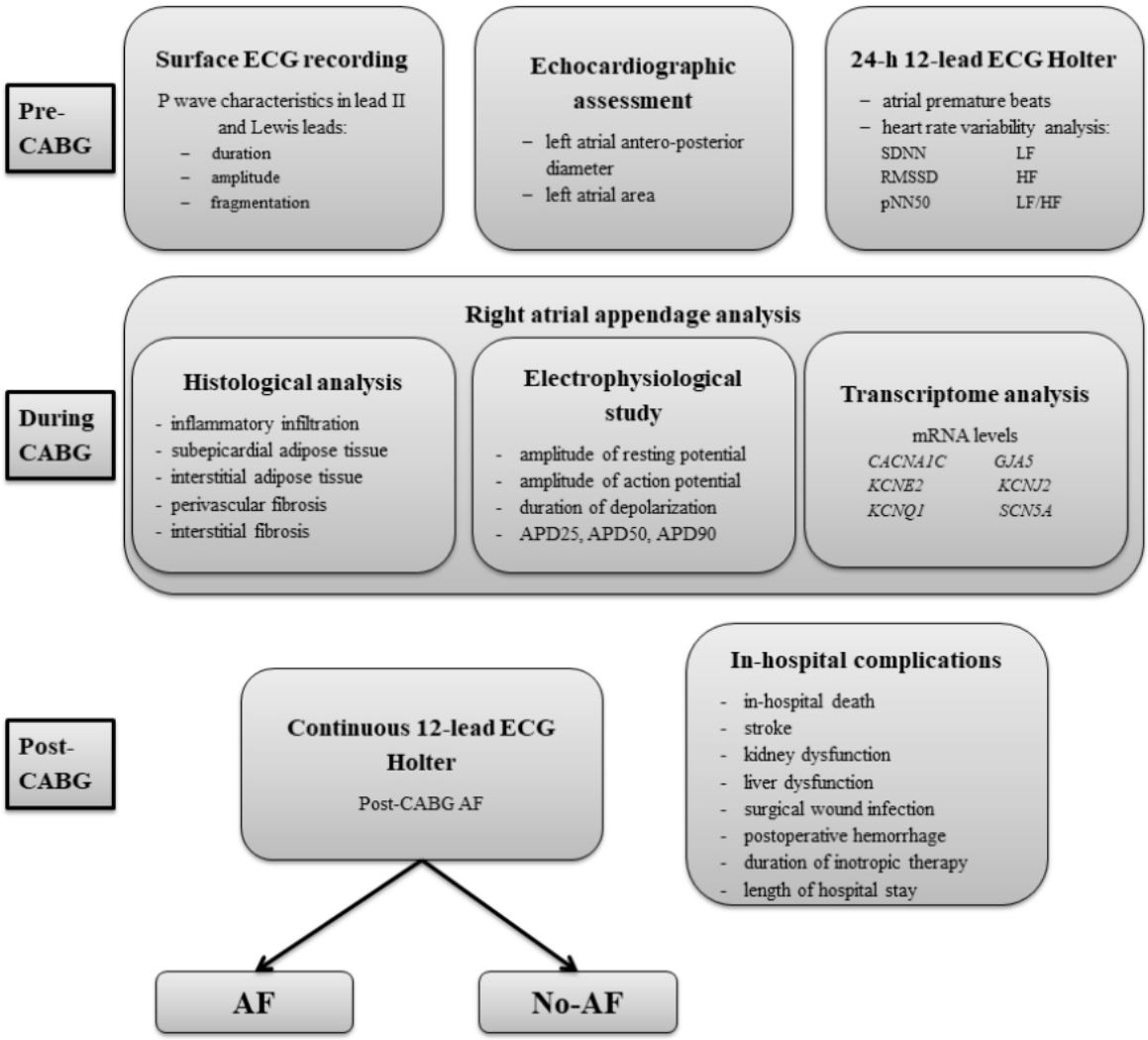

Figure 1. Flow chart of the study design
AF – atrial fibrillation; APD25 – action potential duration to 25% of complete repolarization; APD50 – action potential duration to 50% of complete repolarization; APD90 – action potential duration to 90% of complete repolarization; CABG – coronary artery bypass grafting; CACNA1C – calcium voltage-gated channel subunit alpha 1c; GAPDH – glyceraldehyde 3-phosphate dehydrogenase; GJA5 – gap junction protein alpha 5; HF – high-frequency components; HR – heart rate; KCNE2 – potassium voltage-gated channel subfamily E member 2; KCNJ2 – potassium inwardly rectifying channel subfamily J member 2; KCNQ1 – potassium voltage-gated channel subfamily Q member 1; LF – low-frequency components; LF/HF – ratio between low-frequency and high-frequency components; mRNA – messenger ribonucleic acid; pNN50 – proportion of successive RR intervals that differed by >50 ms; RMSSD – root mean square of successive differences between normal heartbeats; SCN5A – sodium voltage-gated channel alpha subunit 5; SDNN – standard deviation of normal RR intervals

toring (CardioMem 3000®; GETEMED/GE Healthcare) was also performed in all patients prior to CABG to evaluate the presence and severity of preexisting autonomic remodeling, as well as the presence and burden of pre-CABG atrial arrhythmic events. During the CABG procedure, the right atrial appendage, normally removed during fixation of the ECC cavo-atrial cannula and routinely considered 'surgical waste', was collected and divided into three samples. One sample was used for electrophysiological studies, one for histological analyses, and one for transcriptome analyses, as described below. To evaluate the occurrence of post-CABG AF, all patients underwent continuous post-CABG 12-lead ECG Holter monitoring, as described above. Clinically relevant postoperative in-hospital outcomes were also recorded, as described below.

Assessment of preexisting atrial electrical remodeling

To assess the presence and severity of preexisting atrial electrical remodeling, P wave characteristics (i.e., duration, amplitude, fragmentation) were evalu-

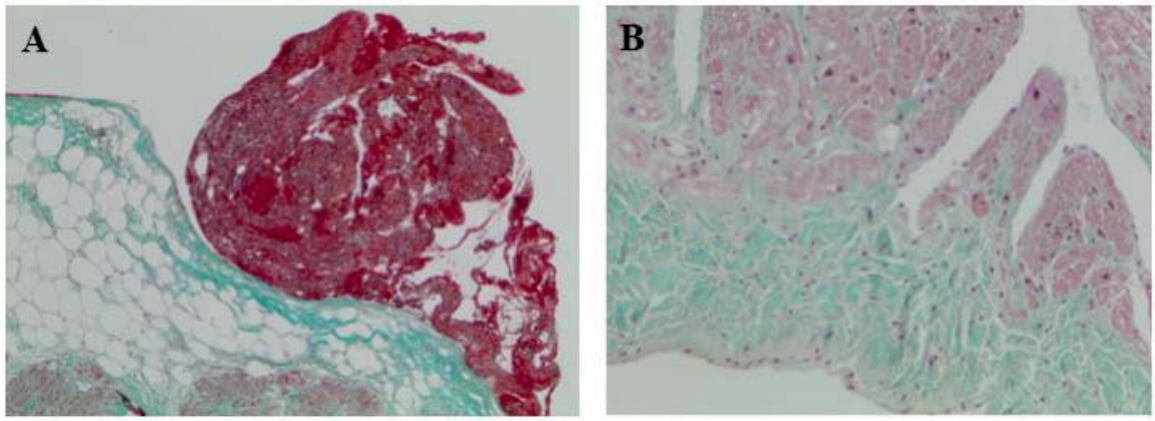

Figure 2. Typical histological findings in (A) patients who developed and (B) patients who did not develop post-coronary artery bypass grafting atrial fibrillation. Masson's trichrome staining. Compared to patients without atrial fibrillation (B), increased subepicardial adipose tissue can be noticed in patients with postoperative atrial fibrillation (A).

ated in lead II and Lewis leads using the surface ECG recordings obtained on admission. The burden of pre-CABG atrial arrhythmic events (i.e., atrial premature beats) was also evaluated using the continuous 24-h 12-lead ECG recordings obtained prior to CABG.

Electrophysiological study of a right atrial appendage sample was also performed. Upon collection, the sample was immediately placed into Krebs-Henseleit solution (118 mM NaCl, 4.7 mM KCl, 25 mM $NaHCO_3$, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4,

Table 1. Clinical and surgical characteristics and ongoing drug treatment in patients who developed versus patients who did not develop post-coronary artery bypass grafting atrial fibrillation

	AF (n = 11)	No-AF (n = 19)	p value
Baseline clinical characteristics			
Age (years)	66 (60-72)	58 (55-64)	0.04
Male gender (n, %)	9 (78.94)	15 (81.81)	>0.99
Body mass index (kg/m^2)	26.08 (23.94-30.84)	27.34 (24.38-31.05)	0.58
Left ventricular ejection fraction (%)	50 (45-60)	50 (45-55)	0.74
SYNTAX I score (points)	32.0 (23.5-35.0)	22.0 (17.0-28.0)	0.08
Creatinine clearance (ml/min/1.73 m^2)	89.98 (63.76-120.60)	92.42 (72.89-111.90)	0.80
Medical history			
Obesity (n, %)	3 (27.27)	5 (25.31)	>0.99
Hypertension (n, %)	11 (100.00)	18 (94.73)	>0.99
Diabetes mellitus (n, %)	6 (54.54)	5 (26.31)	0.23
Stroke (n, %)	3 (27.27)	3 (15.7%)	0.64
CHA_2DS_2VASc score (points)	3 (3-5)	2 (2-4)	0.04
Ongoing drug treatment			
Angiotensin converting enzyme inhibitor (n, %)	10 (90.90)	14 (73.68)	>0.99
Antialdosteronic (n, %)	0 (0.00)	2 (10.52)	>0.99
Statin (n, %)	9 (81.81)	18 (94.73)	>0.99
Beta-blocker (n, %)	9 (81.81)	18 (94.73)	0.26
Surgical parameters			
Total duration of the intervention (min)	247 (225-318)	222 (200-276)	0.26
ECC duration (min)	113 (95-138)	89 (64-129)	0.23
Aortic clamping time (min)	71 (49-79)	45 (37-74)	0.20

Quantitative data are expressed as median (interquartile range). Categorical data are expressed as number (percentage). p-values refer to comparisons between patients with (AF) and without (no-AF) post-coronary artery bypass grafting atrial fibrillation based on the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables.
AF – atrial fibrillation; ECC – extracorporeal circulation

and 11 mM glucose) and transferred into the Steiert organ bath. After a 30-min equilibration period, the right atrial appendage sample was electrically stimulated and atrial action potentials were recorded. The amplitudes of the resting and of the action potential and the duration of depolarization and that of the action potential to 25% (APD25), 50% (APD50), and 90% (APD90) of complete repolarization were measured.

To evaluate a potential preexisting atrial electrical remodeling at a molecular level, the right atrial appendage sample collected for transcriptome analysis was rapidly immersed into RNA stabilizing solution (RNAlater; Thermo Fisher Scientific, Waltham, MA) and the mRNA levels of several genes previously associated with AF occurrence (i.e. *CACNA1C, GJA5, KCNE2, KCNJ2, KCNQ1,* and *SCN5A*) were analyzed. Total iPrep PureLink RNA Kits and iPrep Purification Tool (Thermo Fisher Scientific) were used to isolate RNA and the SuperScript VILO cDNA synthesis kit (Thermo Fisher Scientific) was used to perform reverse transcription. The mRNA expression levels of the six target genes were analyzed using TaqMan Gene Expression Assays (Thermo Fisher Scientific). All experiments were performed on a 7500 Fast Dx Real-Time PCR System (Applied Biosystems, Waltham, MA). The mRNA levels of the target genes were normalized with *GAPDH* housekeeping gene levels and compared between patients with and without POAF.

Assessment of preexisting atrial structural remodeling

To assess atrial structural remodeling, left atrial (LA) antero-posterior diameter and LA area were evaluated by transthoracic echocardiography and compared between the two groups. Histological analysis of a right atrial appendage sample was also performed. The sample was rapidly immersed into 10% formalin and processed for paraffin histology. Deparaffinized tissue sections were then stained with Masson's trichrome and Hematoxylin-Eosin and the presence and the degree of inflammatory infiltration, subepicardial and interstitial adipose tissue, and perivascular and interstitial fibrosis were evaluated semiquantitatively using a 0-3 scale, where 0 indicated the absence, 1 indicated the presence of mild, 2 indicated the presence

Table 2. Multi-approach assessment of preexisting atrial electrical remodeling in patients who developed versus patients who did not develop post-coronary artery bypass grafting atrial fibrillation

	AF (n = 11)	No-AF (n = 19)	p value
Surface ECG parameters			
P-wave duration (ms)			
Lead II	80 (80-120)	100 (80-100)	0.32
Lewis lead	80 (60-80)	80 (80-100)	0.22
P-wave amplitude (mV)			
Lead II	0.10 (0.05-0.10)	0.10 (0.10-0.15)	0.15
Lewis lead	0.05 (0.05-0.10)	0.05 (0.05-0.10)	0.89
P-wave fragmentation (n, %)			
Lead II	3 (27.27)	8 (42.10)	0.61
Lewis lead	6 (54.54)	9 (47.36)	0.68
12-lead Holter ECG parameters			
Atrial premature beats / 24-h	858 (0-109)	7 (4-21)	0.26
mRNA levels (normalized with *GAPDH*)			
CACNA1C	28.24 (26.32-29.27)	28.01 (25.82-29.29)	0.52
GJA5	26.18 (25.25-28.84)	25.84 (24.41-28.14)	0.43
KCNE2	31.86 (31.16-32.50)	31.72 (30.67-32.71)	0.79
KCNJ2	30.58 (29.75-32.28)	30.47 (28.9-32.35)	0.76
KCNQ1	28.92 (27.92-30.38)	29.07 (27.02-29.71)	0.76
SCN5A	27.81 (27.08-30.32)	27.92 (25.55-29.14)	0.39

Quantitative data are expressed as median (interquartile range). Categorical data are expressed as number (percentage). p-values refer to comparisons between patients with (AF) and without (no-AF) post-coronary artery bypass grafting atrial fibrillation based on the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables.
AF – atrial fibrillation; CACNA1C – calcium voltage-gated channel subunit alpha 1c; GAPDH – glyceraldehyde 3-phosphate dehydrogenase; GJA5 – gap junction protein alpha 5; KCNE2 – potassium voltage-gated channel subfamily E member 2; KCNJ2 – potassium inwardly rectifying channel subfamily J member 2; KCNQ1 – potassium voltage-gated channel subfamily Q member 1; mRNA – messenger ribonucleic acid; SCN5A – sodium voltage-gated channel alpha subunit 5

of moderate, and 3 indicated the presence of severe changes in the analyzed parameters. The results were compared between patients with and without post-CABG AF.

Assessment of preexisting cardiac autonomic remodeling

To evaluate cardiac autonomic remodeling, heart rate variability (HRV) analysis was performed using the continuous 24-h 12-lead ECG recordings obtained prior to CABG. The standard deviation of normal RR intervals (SDNN), the root mean square of successive differences between normal heartbeats (RMSSD), and the proportion of successive RR intervals that differed by >50 ms (pNN50) were analyzed as time domain parameters. The low-frequency (LF) and the high-frequency (HF) components of the HRV spectrum and the ratio between the two (i.e., LF/HF) were analyzed as frequency domain parameters. All parameters were compared between the AF and no-AF groups.

Post-coronary artery bypass grafting in-hospital complications

All patients were prospectively monitored for clinically-relevant postoperative events up to the time of discharge. The occurrence of in-hospital death, stroke, and kidney and/or liver dysfunction were recorded as major post-CABG complications. Liver dysfunction was defined as a ≥3-fold increase in liver enzymes and kidney dysfunction as an increase in plasma creatinine with ≥0.5 mg/dL compared to baseline values. Surgical wound infection and postoperative hemorrhage were noted as minor complications. The duration of inotropic therapy and the length of hospitalization were also recorded.

Statistical analysis

Categorical data are expressed as absolute numbers and percentages. Due to the relatively small number of patients included in the study, all continuous variables are presented as median and interquartile range and the Mann-Whitney test was applied for between-group comparisons regardless of distribution. Fisher's exact test was used for comparison of categorical data. Spearman's rank correlation method was used to assess correlations between the electrophysiological parameters and the occurrence of post-CABG AF. Multiple logistic regression analysis was used to assess the ability of POAF to independently predict post-CABG length of hospital stay and occurrence of post-CABG renal dysfunction. The models were adjusted for age. A p-value < 0.05 was considered statistically significant. All parameters were measured in a blinded manner and all data were analyzed using MedCalc version 12.4.3.0 (MedCalc Software, Ostend, Belgium).

RESULTS

In total, 30 patients were included in the present study. Post-CABG AF occurred in 11 (36.6%) of the study patients. Based on the occurrence of post-CABG AF, patients were divided into two groups: patients who developed post-CABG AF (AF; n = 11) and patients who did not develop post-CABG AF (no-AF; n = 19).

Compared with their non-arrhythmic counterparts (Table 1), AF patients were older (p = 0.04) and had higher CHA_2DS_2VASc scores (p = 0.04). There were no other significantly different clinical characteristics between the two groups (all p >0.05). Ongoing drug treatment was also similar between AF and no-AF patients (Table 1).

Table 3. Parameters of atrial structural remodeling in patients who developed versus patients who did not develop post-coronary artery bypass grafting atrial fibrillation

	AF (n = 11)	No-AF (n = 19)	p value
Echocardiographic parameters			
LA antero-posterior diameter (mm)	37 (35-40)	38 (34-40)	0.63
LA area (cm^2)	19.25 (16.88-20.52)	18.90 (17.30-19.00)	0.38
Histological parameters (semiquantitative analysis)			
Inflammatory infiltrate (score)	1.00 (0.00-2.00)	1.00 (1.00-1.37)	0.70
Subepicardial adipose tissue (score)	2.00 (1.00-3.00)	1.00 (1.00-1.50)	0.02
Interstitial adipose tissue (score)	0.00 (0.00-1.12)	0.50 (0.00-1.00)	0.89
Perivascular fibrosis (score)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.71
Interstitial fibrosis (score)	1.00 (0.00-1.00)	1.00 (0.25-1.00)	0.89

Data are expressed as median (interquartile range). p-values refer to comparisons between patients with (AF) and without (no-AF) post-coronary artery bypass grafting atrial fibrillation based on the Mann-Whitney U test.
AF – atrial fibrillation; LA – left atrium

Table 4. Heart rate variability parameters in patients who developed versus patients who did not develop post-coronary artery bypass grafting atrial fibrillation

	AF (n = 11)	No-AF (n = 19)	p value
Mean HR (bpm)	71.50 (66.00-82.25)	64.00 (61.50-69.50)	0.03
Time domain parameters			
SDNN (ms)	118.00 (95.25-172.80)	101.00 (86.00-140.00)	0.60
RMSSD (ms)	89.00 (45.75-172.00)	53.00 (41.50-67.50)	0.03
pNN50 (%)	9.87 (2.75-20.00)	6.00 (3.00-10.50)	0.39
Frequency domain parameters			
LF (ms^2)	11.70 (2.49-19.35)	18.85 (10.90-26.93)	0.13
HF (ms^2)	51.80 (40.90-64.20)	62.30 (48.03-71.98)	0.21
LF/HF	0.22 (0.10-0.56)	0.30 (0.21-0.44)	0.31

Data are expressed as median (interquartile range). p-values refer to comparisons between patients with (AF) and without (no-AF) post-coronary artery bypass grafting atrial fibrillation based on the Mann-Whitney U test.
AF – atrial fibrillation; HF – high-frequency components; HR – heart rate; LF – low-frequency components; LF/HF – ratio between low-frequency and high-frequency components; pNN50 – proportion of successive RR intervals that differed by >50 ms; RMSSD – root mean square of successive differences between normal heartbeats; SDNN – standard deviation of normal RR intervals

Multi-approach assessment of preexisting atrial electrical remodeling

Multi-approach assessment of ECG, electrophysiological, and molecular data failed to reveal any markers of preexisting atrial electrical remodeling in patients who developed post-CABG AF. P-wave duration, amplitude, and fragmentation were not significantly different between the two groups neither in lead II nor in the Lewis leads (all p >0.05; Table 2). Pre-CABG atrial arrhythmic burden and mRNA expression levels of the six studied genes encoding for atrial ion channels were also similar between the two groups (all p >0.05; Table 2).

Viable myocytes were only found in six of the 30 atrial appendage samples used for the electrophysiological study; two were collected from AF and four from no-AF patients. Hence, direct comparison of these parameters between the two groups could not be performed. However, when correlations were ascertained, none of the evaluated action potential parameters was significantly correlated with the occuerence of POAF (all p >0.05).

Preexisting atrial structural remodeling

None of the analyzed echocardiographic parameters (Table 3) was significantly different in patients with AF compared with those who did not develop post-CABG AF (all p >0.05). However, patients who developed POAF had more important subepicardial adipose tissue compared to those who did not (p = 0.02; Table 3). Although POAF patients were older than their non-arrhythmic counterparts, there was no significant correlation between age and the amount of subepicardial adipose tissue (p = 0.92). None of the other analyzed histological parameters was significantly different between the two groups (all p >0.05; Table 3). Figure 2 depicts typical histological findings in patients with and without post-CABG AF.

Preexisting cardiac autonomic dysfunction

None of the frequency domain parameters of the HRV spectrum (Table 4) was significantly different between the two groups (all p >0.05). However, RMSSD, a marker of parasympathetic modulation, and mean heart rate were both significantly higher in the group of patients who developed POAF than in their non-arrhythmic peers (both p = 0.03; Table 4).

Post-coronary artery bypass grafting in-hospital complications

A single patient included in the study died during follow-up, who did not present POAF until the time of death. Despite the development of POAF, the duration of inotropic treatment was similar in the AF versus the non-AF groups (0 [0-3] vs. 1 [0-2] days, p = 0.81). Occurrence of postoperative liver dysfunction (18.18% vs. 15.78%, p = 1.00), minor complications (54.54% vs. 31.57%, p = 0.45), and stroke (9.09% vs. 0.00%, p = 0.36) was also similar regardless of the presence or absence of post-CABG AF. However, occurrence of post-CABG renal dysfunction (45.45% vs. 15.78%, p = 0.04) and length of hospital stay (17.00 [12.00-20.00] vs. 12.50 [10.75-14.75] days, p = 0.04) were significantly more important in patients who developed POAF than in those who did not. After adjusting for age, POAF remained an independent predictor of length of hospital stay (p = 0.04), but not of renal dysfunction (p = 0.07).

DISCUSSIONS

Postoperative AF complicates more than 40% of cardiac surgery procedures, being the most common perioperative arrhythmia[1]. Although POAF has a generally favorable long-term prognosis, it can contribute to considerable increase in in-hospital morbidity and mortality, as well as in the length of hospital stay[2]. The mechanisms that contribute to the occurrence of POAF are not fully known. However, they are thought to include perioperative phenomena such as inflammation, sympathetic activation, and cardiac ischemia[12]. All these phenomena appear to combine to trigger AF, whereas preexisting factors are often present and increase atrial vulnerability to AF induction and maintenance[10,12]. Countless previous studies have associated the presence and severity of atrial remodeling with AF[10-12]. However, data on the presence and severity of atrial remodeling in patients undergoing CABG and on its impact on post-CABG AF occurrence are extremely limited. A better understanding of preexisting atrial remodeling in patients who develop post-CABG AF could allow us to improve CABG outcomes and to identify new therapeutic strategies.

The main findings of the present study are that: (1) patients who developed AF after cardiac surgery were older and had higher CHA_2DS_2VASc scores than their non-arrhythmic counterparts; (2) the amount of subepicardial adipose tissue was higher in patients who developed post-CABG AF than in those who did not; (3) patients who developed POAF appeared to present preoperative sympatho-vagal coactivation; and (4) had longer hospital stay than their non-arrhythmic peers.

Similar to our results, previous studies have also associated POAF occurrence with advanced age[14]. The frequency of this arrhythmia is increasing with age, possibly due to increased occurrence and magnitude of atrial changes in the elderly[15]. Recent studies have also shown a correlation between CHA_2DS_2VASc preoperative score, which combines cardiovascular and non-cardiovascular characteristics to determine risk of stroke in AF patients, and POAF, suggesting that this instrument could be a potential predictor of POAF[14]. In the absence of other relevant differences, the age difference observed in our study between the two groups most likely contributed to the higher CHA_2DS_2VASc score observed in patients who developed post-CABG AF than in those who did not.

Preoperative atrial changes defined as 'structural remodeling' have been linked to changes in intra-atrial conduction and to increased propensity to POAF occurrence[13]. Kitzman and Edwards reported that fibrosis and LA dilation, which are also typical morphological changes in elderly patients[16], contributed to higher vulnerability to develop POAF[17]. In our study, LA size and atrial fibrosis were not significantly different between patients who developed post-CABG AF and those who did not, and this was most likely due to the overall low degree of atrial structural (both echocardiographic and histological) remodeling presented by both AF and no-AF patients. Indeed, the patients evaluated in this study were relatively young and did not present important LA enlargement, whereas data in the literature suggest that in chronic settings AF rarely occurs when LA size is < 44 mm[18]. In addition, both patients who developed AF and those who did not were extensively treated with renin-angiotensin-aldosterone system blockers and statins, which could have contributed to the limitation of atrial structural remodeling[19]. However, patients who developed POAF had more important subepicardial adipose tissue compared to those who did not, and this structural feature could have contributed to the occurrence of AF through the multiple local effects of proinflammatory cytokines released by the subepicardial adipose tissue[20]. Inflammation induced by cytokines released by the local adipose tissue has been shown to act on the ganglionated plexuses located within the pericardial fat, affecting both the sympathetic and the parasympathetic branches of the autonomic nervous system[20]. Once induced, vagal activation could then favor heterogeneous atrial effective refractory periods shortening and atrial conduction slowing, promoting re-entry and AF[20]. Meanwhile, increased sympathetic tone induced by the abundant pericardial fat could increase predisposition to AF by altering calcium dynamics and augmenting atrial automaticity[20].

Indeed, studies have suggested that CABG could favor POAF occurrence by altering the autonomic modulation of the atria and increasing atrial cells' sensitivity to catecholamines[21]. Systemic sympathetic tone has been shown to increase in response to surgical trauma-induced inflammation, suggesting that beta-blockers could thus be of potential benefit in this setting[22]. However, data on preexisting autonomic tone changes in patients who develop POAF are much more limited. In the present study, mean baseline heart rate, an indirect marker of sympathetic activity, was significantly higher in patients who developed POAF than in those who did not. In parallel,

HRV analysis revealed significantly higher values of RMSSD, an accepted index of parasympathetic modulation, in patients who developed POAF compared to those who did not. Thus, a preexisting simultaneous activation of both the sympathetic and parasympathetic nervous systems appears to be present in patients who develop POAF, whereas sympatho-vagal coactivation has been shown to promote AF occurrence in various settings[23]. Similarly to our results, previous studies have also shown indirect signs of increased parasympathetic and/or sympathetic tone in patients who develop POAF compared with patients who remain in sinus rhythm[24,25]. In addition, perioperative beta-blockers usage has been shown to reduce, whereas drugs that increase sympathetic tone have been shown to increase POAF incidence[22].

Finally, previous studies have identified re-entry circuits near areas with high pericardial fat burden, suggesting that pericardial fat may alter the electrophysiological properties of the heart[20]. In the present study, there were no significant differences between the two groups in P wave characteristics. In line with these findings, previous studies have shown that although atrial conduction time prolongation may not be present during sinus rhythm, such prolongation occurs with rapid pacing prior to and could contribute to AF initiation[26]. Contrarily, in a previous study, preoperative P-wave duration was reported as a parameter predictive of POAF[27]. However, a 140 ms cut-off value was used to define prolonged P wave in that study[27], whereas in the present study P wave duration was normal (i.e., ≈80 ms) in both AF and no-AF patients. Recent studies have also linked pericardial adiposity with atrial action potential alterations such as increased amplitude of atrial resting membrane potential, reduced depolarizing threshold, and presence of ectopic foci[20]. In the present study, the duration of atrial depolarization and that of the overall atrial action potential, as well as the number of premature atrial contractions were not significantly different in patients who developed POAF compared to those who did not. Chronic statin treatment and/or renin-angiotensin-aldosterone blockers, which were used in most of the study patients, could have affected these results by reducing pericardial fat-related inflammation and oxidative stress and their consequent impact on atrial electrophysiology in these patients[28].

In non-surgical AF, changes in ion channels have been shown to favor AF occurrence and maintenance[29]. In the present study, mRNA expression levels of the six studied genes encoding for atrial ion channels were not significantly different between patients who developed and those who did not develop POAF. Together with the lack of difference in action potential parameters, these results suggest that the function of these ion channels was not altered prior to CABG in patients who developed POAF. In line with our findings, previous studies have also shown that the function of ion channels was not altered in preoperative atrial biopsies of patients who developed POAF[30,31].

Despite a significantly higher CHA_2DS_2VASc score in patients with POAF, both the risk for stroke and that for minor complications were similar in the two groups in the present study, regardless of the presence or absence of the arrhythmia. Although the occurrence of post-CABG kidney dysfunction was significantly more common in POAF patients than in their non-arrhythmic counterparts, the association between POAF and post-CABG kidney dysfunction was lost in the multiple regression analysis, suggesting that other factors may play a more important role in the occurrence of this postoperative complication. However, in line with previous studies[32], the length of hospital stay was significantly longer in patients who developed post-CABG AF compared with those who did not, suggesting that reducing the incidence of POAF could have a significant impact on cost-effective patient care[33].

Potential limitations

Our study has a number of limitations. This is a single-center study and, as a result, the number of patients included in the study was rather small. More accurate data could be obtained by increasing the number of patients included in future studies. Also, the study population was relatively homogeneous and, although our results are in line with those of previous studies, extrapolation of these results to the entire population of patients undergoing CABG should be done with caution. The electrophysiological study was particularly affected by the small sample size, since viable atrial myocytes were only found in six of the 30 atrial tissue samples, precluding adequate electrophysiological data comparisons. However, compared to other similar studies, in which the success rate of the electrophysiological study has usually been around 10%, the success rate in the present study was considerably higher (i.e., 20%). Remodeling of the right atrial appendage, evaluated in the present study, may not fully reflect histological and/or functional changes in the left atrium. However, recent evidence has shown the existence of proarrhythmic changes in the right atri-

al appendage in various clinical conditions associated with AF[34]. In addition, although the incidence of POAF was relatively high in the present cohort, the population evaluated in our study was relatively healthy (i.e., relatively low SYNTAX and CHA_2DS_2VASc scores) and young (i.e., mean age 65.27 ± 5.85 years). As a result, preexisting (structural, electrical, and autonomic) remodeling was quite limited, as reflected by the data obtained in both AF and no-AF patients. This low remodeling burden is likely to have contributed to the lack of significant differences observed in most of the studied parameters between the two groups. Studying larger populations, with higher cardiovascular risk and more important cardiovascular disease burden could bring important additional information in this regard. Thus, above all, the present study should be viewed as a basis for future larger-scale studies.

CONCLUSIONS

This prospective study shows that in relatively young patients with relatively low cardiovascular disease burden that undergo CABG, POAF is associated with higher degree of atrial subepicardial adiposity and with cardiac sympatho-vagal coactivation. These preoperative changes could contribute to the increased propensity of these patients to POAF and could thus represent a starting point for implementing and/or developing new therapeutic strategies to reduce POAF risk. Further work must now focus on validating these results in larger patient cohorts in order to improve post-CABG AF risk prediction and develop the next generation of preventative strategies.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

Acknowledgments: The authors would like to thank their fellow surgeons from the Department of Cardiovascular Surgery within the Emergency Institute for Cardiovascular Diseases and Transplantation Targu Mures for their invaluable help in atrial sample collection. This work was supported by a grant of the Romanian Ministry of Education and Research, CNCS-UEFISCDI, project number PN-III-P1-1.1-PD-2019-0181, within PNCDI III.

References

1. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, Barash PG, Hsu PH, Mangano DT. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 2004;291:1720-29.
2. Villareal RP, Hariharan R, Liu BC, Kar B, Lee VV, Elayda M, Lopez JA, Rasekh A, Wilson JM, Massumi A. Complications of bypass surgery postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol 2004;43:742-8.
3. Steinberg BA, Zhao Y, He X, Hernandez AF, Fullerton DA, Kevin L Thomas KL, Mills R, Klaskala W, Peterson ED, Piccini JP. Management of postoperative atrial fibrillation and subsequent outcomes in contemporary patients undergoing cardiac surgery: insights from the Society Of Thoracic Surgeons CAPS-Care Atrial Fibrillation Registry. Clin Cardiol 2014;37:7-13.
4. Lahtinen J, Biancari F, Salmela E, Mosorin M, Satta J, Rainio P, Rimpiläinen J, Lepojärvi M, Juvonen T. Postoperative atrial fibrillation is a major cause of stroke after on-pump coronary artery bypass. Ann Thorac Surg 2004;77:1241-4.
5. Geng M, Lin A, Nguyen TP. Revisiting antiarrhythmic drug therapy for atrial fibrillation: reviewing lessons learned and redefining therapeutic paradigms. Front Pharmacol 2020;11:1-23.
6. Burgos LM, Seoane L, Parodi JB, Espinoza J, Brito VG, Benzadón M, Navia D. Postoperative atrial fibrillation is associated with higher scores on predictive indices. J Thorac Cardiovasc Surg 2019;157:2279-86.
7. Cameron MJ, Tran DTT, Abboud J, Newton EK, Rashidian H, Dupuis JY. Prospective external validation of three preoperative risk scores for prediction of new onset atrial fibrillation after cardiac surgery. Anesth Analg 2018;126:33-8.
8. Balan AI, Scridon A. Atrial fibrillation – an orchestra of classic and modern risk factors. Acta Medica Marisiensis 2019;65:80-6.
9. Serban RC, Balan AI, Perian M, Pintilie I, Somkereki C, Huţanu A, Scridon A. Atrial electrical remodeling induced by chronic ischemia and inflammation in patients with stable coronary artery disease. Chin J Physiol 2019;62:11-6.
10. Cuculici A, Guta A, Mandes L, Covaliov A, Patru AE, Ceck C, Apetrei E. P-wave dispersion and echocardiographic atrial indices as predictors of paroxysmal atrial fibrillation. Rom J Cardiol 2019;29:229-36.
11. Petre I, Iancovici S, Onciul S, Tautu OF, Nastasa A, Dorobantu M. Left atrial function – novel ecocardiographic markers for detecting atrial fibrillation in hypertensives. Rom J Cardiol 2018;28:311-18.
12. Shingu Y, Kubota S, Wakasa S, Ooka T, Tachibana T, Matsui Y. Postoperative atrial fibrillation: mechanism, prevention, and future perspective. Surg Today 2012;42:819-24.
13. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. Circ Arrhythm Electrophysiol 2008;1:62-73.
14. Perrier S, Meyer N, Minh TH, Announe T, Bentz J, Billaud P, Mommerot A, Mazzucotelli JP, Kindo M. Predictors of atrial fibrillation after coronary artery bypass grafting: a bayesian analysis. Ann Thorac Surg 2017;103:92-7.
15. Dun W, Boyden PA. Aged atria: electrical remodeling conducive to atrial fibrillation. J Interv Card Electrophysiol 2019;25:9-18.
16. Karamichalakis N, Letsas KL, Vlachos K, Georgopoulos S, Bakalakos A, Efremidis M, Sideris A. Managing atrial fibrillation in the very elderly patient: challenges and solutions. Vasc Health Risk Manag 2015;11:555-62.
17. Kitzman DW, Edwards WD. Age-related changes in the anatomy of the normal human heart. Journal Gerontol 2019;45:33-9.
18. Henry WL, Morganroth J, Pearlman AS, Clark CE, Redwood DR, Itscoitz, Epstein SE. Relation between echocardiographically determined left atrial size and atrial fibrillation. Circulation 1976;53:273-9.
19. Fang L, Murphy AJ, Dart AM. A clinical perspective of anti-fibrotic therapies for cardiovascular disease. Front Pharmacol 2017;8:1-8.

20. Scridon A, Dobreanu D, Chevalier P, Şerban RC. Inflammation, a link between obesity and atrial fibrillation. Inflamm Res 2015;64:383-93.
21. Liu L, Nattel S. Differing sympathetic and vagal effects on atrial fibrillation in dogs: role of refractoriness heterogeneity. Am J Physiol 1997;273:H805-16.
22. Iliuta L, Christodorescu R, Filpescu D, Moldovan H, Radulescu B, Vasile R. Prevention of perioperative atrial fibrillation with beta-blockers in coronary surgery: betaxolol versus metoprolol. Interact Cardiovasc Thorac Surg 2009;9:89-93.
23. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: Pathophysiology and therapy. Circ Res 2014;114:1500-15.
24. Jideus L, Ericson M, Stridsberg M, Nilsson L, Blomström P. Diminished circadian variation in heart rate variability before surgery in patients developing postoperative atrial fibrillation. Scand Cardiovasc J 2001;35:238-44.
25. Kališnik JM, Hrovat E, Hrastovec A, Avbelj V, Žibert J, Geršak B. Severe cardiac autonomic derangement and altered ventricular repolarization pave the way to postoperative atrial fibrillation. Innovations: Innov Technol Tech Cardiothorac Vasc Surg 2015;10:398-405.
26. Zaman JAB, Harling L, Ashrafian H, Darzi A, Gooderham N, Athanasiou T, Peters NS. Post-operative atrial fibrillation is associated with a pre-existing structural and electrical substrate in human right atrial myocardium. Int J Cardiol 2016;220:580-8.
27. Steinberg JS, Zelenkofske S, Wong SC, Gelernt M, Sciacca R, Menchavez E. Value of the P-wave signal-averaged ECG for predicting atrial fibrillation after cardiac surgery. Circulation 1993;88:2618-22.
28. Fang WT, Li HJ, Zhang H, Jiang S. The role of statin therapy in the prevention of atrial fibrillation: a meta-analysis of randomized controlled trials. Br J Clin Pharmacol 2012;74:744-56.
29. Bosch RF, Zeng X, Grammer JB, Popovic K, Mewis C, Kühlkamp V. Ionic mechanisms of electrical remodeling in human atrial fibrillation. Cardiovasc Res 1999;44:121-31.
30. Workman AJ, Pau D, Redpath CJ, Marshall GE, Julie A Russell JA, Kane KA, John Norrie J, Rankin AC. Post-operative atrial fibrillation is influenced by beta-blocker therapy but not by pre-operative atrial cellular electrophysiology. J Cardiovasc Electrophysiol 2006;17:1230-38.
31. Swartz MF, Fink GW, Lutz CJ, Taffet SM, Berenfeld O, Vikstrom KL, Kasprowicz K, Bhatta L, Puskas F, Kalifa J, Jalife J. Left versus right atrial difference in dominant frequency, K+ channel transcripts, and fibrosis in patients developing atrial fibrillation after cardiac surgery. Heart Rhythm 2009;6:1415-22.
32. Ghurram A, Krishna N, Bhaskaran R, Kumaraswamy N, Jayant A, Kerala P, Varma PK. Patients who develop post-operative atrial fibrillation have reduced survival after off-pump coronary artery bypass grafting. Indian J Thorac Cardiovasc Surg 2020;36:6-13.
33. Kosuma P, Wachirasrisirikul S, Jedsadayanmata A. Attributable costs of postoperative atrial fibrillation among patients undergoing cardiac surgery. Cardiol Res Pract 2018;2018:3759238.
34. Jansen HJ, Bohne LJ, Gillis AM, Rose RA. Atrial remodeling and atrial fibrillation in acquired forms of cardiovascular disease. Heart Rhythm O2 2020;1:147-59.