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Predictors of Atrial Fibrillation Developing in Hospital Stage After Coronary Artery Bypass Surgery

Aim	To identify independent predictors associated with in-hospital atrial fibrillation (AF) following coronary artery bypass grafting (CABG).
Material and methods	The study included 80 patients (88.75% men) who had elective CABG surgery at the Sklifosovsky Research Institute of Emergency Medicine. Based on the development of AF during the hospital stage of treatment (up to 10 days after CABG surgery), patients were divided into two groups. The group with AF consisted of 19 patients, and the group without AF consisted of 61 patients. All patients underwent electrocardiography (ECG), transthoracic echocardiography (EchoCG) with calculation of the left ventricular (LV) geometry type, and assessment of operational indexes. During surgery, biopsy of a part of the right atrial (RA) appendage was taken from 61 patients to verify the severity of myocardial fibrosis on a four-score scale where 0 is no interstitial fibrosis, 1 is slight fibrosis, 2 is moderate fibrosis, and 3 is severe fibrosis.
Results	All included patients had a low risk of developing postoperative complications according to the EuroSCORE II scale. According to EchoCG data, patients with AF had significantly higher ratios of left ventricular myocardial mass to body surface area (LVMM/BSA) (p=0.0006) and of left atrial volume to body surface area (LA volume/BSA), p=0.008). The distribution of patients by type of LV geometry was as follows: in the group with AF, 52.63% (n=10) of patients were diagnosed with concentric LV hypertrophy (LVH) whereas in the group without AF, the majority of patients (83.60%, n=51) had normal LV geometry and concentric LV remodeling (LVR) (p<0.0001). According to the results of histological study, patients of the AF group more frequently had moderate and severe interstitial fibrosis in the AF appendage (p=0.003). After multivariate regression and ROC analysis, the predictive value remained for concentric LVH (p=0.002), LVMM/BSA ratio ≥97 g/m^2 (p=0.006), LA volume/BSA ratio ≥34.4 ml/m^2 (p=0.04), and for RA appendage interstitial fibrosis score ≥2 (p=0.004). Based on the identified predictors, a regression model was developed to predict the development of AF at the hospital stage after CABG (p<0.0001). The sensitivity and specificity of the model were 86.67% and 78.26%, respectively.
Conclusion	In patients at low perioperative risk, the LVMM/BSA ratio ≥97 g/m^2, the LA volume ratio/BSA ≥34.4 ml/m^2, a RA appendage interstitial fibrosis score ≥2, and the presence of LVH were independent predictors of the development of AF at the hospital stage after CABG operation.

Keywords	Postoperative atrial fibrillation; coronary bypass grafting; myocardial fibrosis; concentric left ventricular hypertrophy
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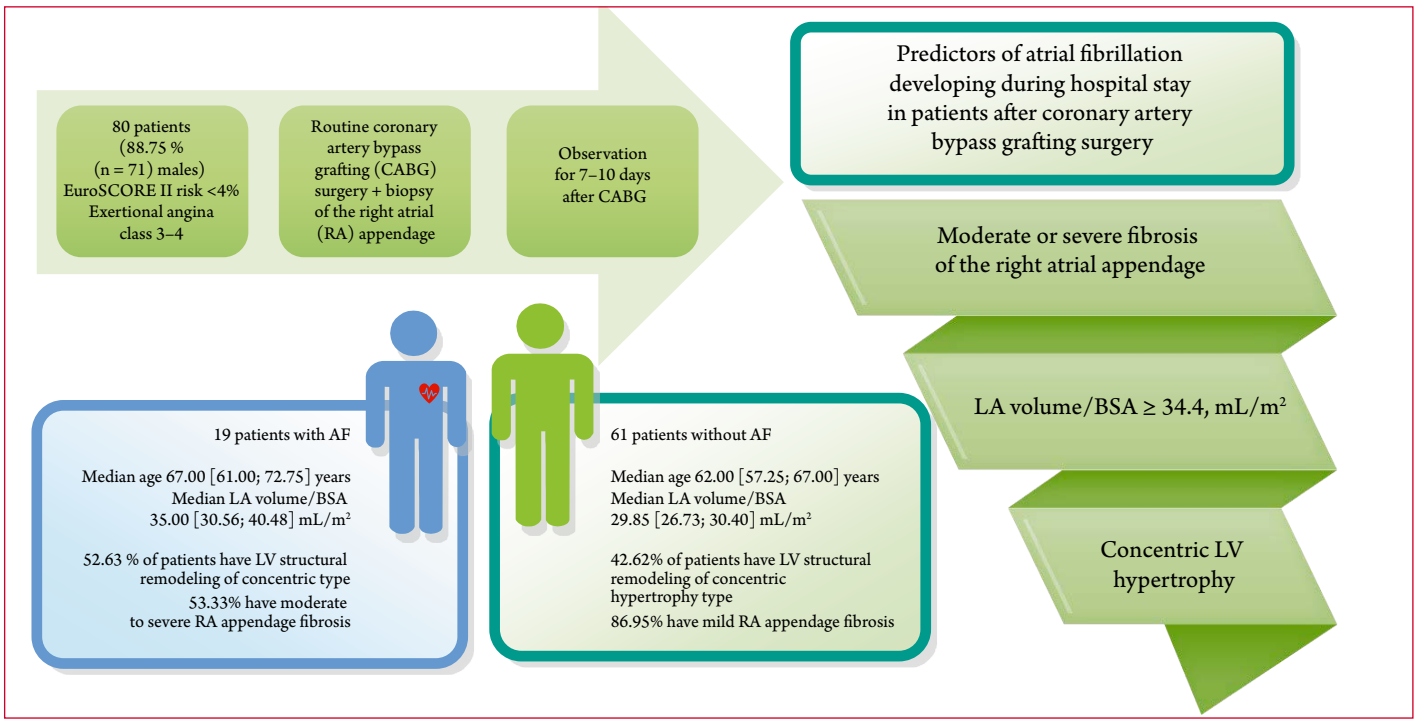
Atrial fibrillation (AF) develops in 27–40% of cases within the first week after coronary artery bypass grafting (CABG) surgery and is associated with an increased risk of thromboembolism, progression of heart failure, and cardioembolic stroke, thus increasing early and late postoperative mortality [1, 2].

Type 2 diabetes mellitus, thyroid disorders, and chronic heart failure with reduced ejection fraction (HFrEF) are well-known risk factors for postoperative AF [3–5]. In clinical practice, however, there is a group of patients without the above-described comorbidities who develop AF in the postoperative period.

The predictive ability of various available preoperative clinical examination and laboratory tests for postoperative AF is still controversial. The high prevalence of this pathology and insufficient sensitivity of diagnostic

Central Illustration. Predictors of Atrial Fibrillation Developing in Hospital Stage After Coronary Artery Bypass Surgery



CABG, coronary artery bypass grafting; RA, right atrium; LV, left ventricle; AF, atrial fibrillation; LA volume/BSA, the ratio of left atrial volume to body surface area, EuroSCORE II, The European System for Cardiac Operative Risk Evaluation II

techniques necessitated the search for new patient examination strategies as a part of AF risk stratification in the early postoperative period after CABG.

Objective

Identify independent predictors associated with AF developing in post-CABG patients during hospital stay.

Material and Methods

Prospective observational study included 80 patients with documented chronic coronary syndrome and multivessel coronary disease, who underwent routine CABG surgery in the Cardiac Surgery Department No. 1 of the Sklifosovsky Research Institute for Emergency Medicine from December 2020 to May 2022.

Inclusion criteria: clinical picture of exertional angina class 3–4, age above 18 years, routine CABG.

Exclusion criteria: thyroid diseases, type 2 diabetes mellitus, history of any form of AF (the absence of AF was registered by ECG before the surgery, according to the medical history, available medical records, and the results of outpatient 24 hour Holter ECG monitoring), clinical examination or laboratory findings evidencing acute coronary syndrome and chronic HFrEF according to echocardiogram.

The study was conducted in compliance with the Good Clinical Practice and the principles of the Declaration of Helsinki. The study protocol was approved by the ethics committee of the National Medical Research Center of Internal and Preventive Medicine (Minutes No. 02–04/20 dated 19/03/2020). Upon admission to the hospital, each patient signed an informed consent for treatment and taking part in the study.

All patients underwent standard laboratory tests and clinical examinations before surgery, including ECG (WelchAllyn CP 200, USA), and echocardiography in the left lateral decubitus position using a Vivid E9 ultrasound system (USA) equipped with a 3.5 MHz sector probe to estimate the sizes of the heart chambers, weight, and ventricular function.

Left ventricular (LV) geometry was defined based on calculations of the ratio of LV mass (LVM) to the body surface area (BSA) and LV relative wall thickness (LVRWT). LVRWT was calculated by the following formula: 2 x LV posterior wall thickness (mm)/LV end-diastolic dimension (mm). The following types of LV geometry were distinguished: normal LV geometry: normal LVM/BSA ratio (≤95 g/m² for females and ≤ 115 g/m² for males) and RWT ≤ 0.42; concentric LV remodeling: normal LVM/BSA ratio and RWT >0.42; concentric LV hypertrophy: increased normal LVM//BSA ratio (> 95 g/m² for females and >115 g/m² for males) and RWT >0.42; eccentric LV hypertrophy: increased LVM//BSA ratio and RWT ≤ 0.42 [6].

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The standard procedure was followed in each case for the CABG surgery. The following indicators were evaluated after the surgery: the duration of aortic cross-clamping (min), the duration of cardiopulmonary bypass (CPB; min), the total duration of the surgery (min), intraoperative blood volume loss (mL), and the number of distal anastomoses.

AF was diagnosed after CABG if AF paroxysm lasting at least 30 seconds was registered in 3 time intervals:

- By a bedside cardiac monitor in cardiac surgery ICU (within days 1–2 after surgery);
- In the ECG record when AF symptoms appear (within up to 10 days after the surgery);
- In the 24 hour Holter ECG on days 710 (before discharge) after the CABG surgery (for the diagnosis of asymptomatic AF).

During the CABG surgery, a biopsy of the right atrial (RA) appendage was performed for light microscopy histology during the connection of a CPB machine in each patient. The severity of atrial fibrosis was assessed in 10 fields of view at ×200 magnification in a light microscope (Zeiss Axio Scope.A1, Germany) by a 4 point scale: 0 – no interstitial fibrosis; 1 – mild interstitial fibrosis; 2 – moderate interstitial fibrosis; 3 – severe interstitial fibrosis [7].

Statistical analysis was performed in Excel 2016 (Microsoft, USA) and MedCalc (MedCalc Software, Belgium). Normally distributed quantitative data were expressed as the mean values and standard deviations (M ± SD), non-normally distributed data were presented as the medians and interquartile ranges (Me [Q25%; Q75%]). The frequency of detection (%) was determined for qualitative data. The statistical significance of the differences between the study groups was determined using the Mann-Whitney U-test for continuous variables, the Pearson's χ^2 test for qualitative variables, and Fisher's exact test for small samples.

Binary logistic regression analysis was used to study the possible relationship between certain factors and the presence of signs. ROC analysis was conducted to assess the quality of the prognostic model and determine the cut-off points. The zero difference hypothesis was rejected if the probability of being mistakenly rejected did not exceed 5% ($p < 0.05$).

Results

Main patient characteristics are presented per study groups in Table 1. All included patients had a low risk of postoperative complications (EuroSCORE II < 4%). The main group included 19 patients who developed AF in the early postoperative period in a mean of 2.0 [2.0; 3.6] days. The control group included 61 patients who had no AF in the early postoperative period.

Patients with AF were statistically significantly older (p=0.03), had a lower body mass index (p=0.04), and higher blood creatinine (p=0.04). History of chronic obstructive pulmonary disease was more common in the AF group (p = 0.03).

The evaluation of preoperative drug therapy showed no differences between patients, two patients with AD took amiodarone and propafenone at the outpatient stage due to frequent supraventricular extrasystole (200.50 [33.00; 1336.00] supraventricular premature beats in the main group versus 33.50 [7.50; 178.80] premature beats in the control group, p=0.004).

The comparison of the echocardiographic parameters before the CABG surgery showed a higher LA volume/BSA ratio (p = 0.008), larger LVPW thickness (p=0.006) and interventricular septal thickness (p=0.02) in the AF group were diagnosed. Tricuspid insufficiency grade 1 was also more common in the AF group (p=0.006) (Table 2).

LVM and the LVM/BSA ratio were significantly higher in the AF group (p = 0.01 and p = 0.0006, respectively). There were the following groups according to the LV geometry: 52.63% of patients with AF had concentric LV hypertrophy and the majority of patients without AF (83.60%) had normal LV geometry and concentric LV remodeling (p < 0.0001).

The outcomes of the postoperative stage are presented in Table 3.

Histological examination was performed in 15 patients with AF and 46 control patients. Interestingly, mild fibrosis was diagnosed in 86.95% of cases in the control group and moderate and severe interstitial RA appendage fibrosis was more common in the AF group (Table 4).

The next stage was the search for predictors of AF developing during hospital stay after CABG. A univariate analysis of the indicators associated with AF (p<0.05) that tend to be statistically significant (p<0.1) at all stages of surgical treatment is presented in Table 5, then the statistically significant indicators were included in a multivariate analysis adjusted for sex, age, and surgical indicators.

Further, a ROC analysis was conducted to calculate the threshold values for the factors associated with the development of arrhythmia (Table 6).

The threshold LVM/BSA ratio was ≥ 97 g/m^2 (OR 8.78; 95% CI: 1.86–41.30, p=0.006). However, this parameter was not included in the final regression model, given that the LVM//BSA ratio is used to calculate LV geometry type, because more independent factors were chosen.

Table 1. Main patient characteristics

Parameters		Patients with AF (n = 19)	Patients without AF (n = 61)	p
Age, years		67.00 [61.00; 72.75]	62.00 [57.25; 67.00]	0.03
Male, n (%)		18 (94.74)	54 (88.52)	0.84
Body mass index, kg/m²		26.70 [25.35; 28.60]	29.10 [26.25; 31.80]	0.04
Arterial hypertension grade, n (%)	0–1	0 (0)	9 (15.00)	0.34
	2	5 (26.31)	13 (21.31)	
	3	15 (73.68)	38 (63.93)	
Chronic obstructive pulmonary disease, n (%)		4 (21.05)	3 (4.91)	0.03
Treatment, n (%)	Beta-blockers	12 (63.15)	45 (73.77)	0.19
	Propafenone	1 (5.26)	0 (0.00)	0.08
	Amiodarone	1 (5.26)	0 (0.00)	0.08
	Statins	12 (63.15)	43 (70.49)	0.33
EuroSCORE II, %		1.30 [0.81; 2.51]	0.87 [0.72; 1.77]	0.03
Blood biochemistry				
Triglycerides, mmol/L		1.42 [0.98; 2.20]	1.46 [0.99; 1.94]	0.77
TSH, mIU/L		1.22 [0.7275; 1.75]	1.31 [0.72; 2.40]	0.30
FT4, pmol/L		11.94 [10.84; 14.09]	12.30 [11.69; 13.38]	0.68
Glucose, mmol/L		5.35 [4.81; 6.35]	5.40 [4.83; 5.79]	0.76
HbA1c, %		5.90 [5.70; 6.00]	5.80 [5.50; 6.00]	0.08
TC, mmol/L		3.96 [3.12; 5.07]	4.12 [3.47; 4.77]	0.52
LDL cholesterol, mmol/L		2.37 [1.87; 3.22]	2.44 [1.88; 3.03]	0.87
HDL cholesterol, mmol/L		0.99 [0.86; 1.20]	1.07 [0.95; 1.27]	0.30
Creatinine, μmol/L		97.85 [90.24; 106.50]	90.90 [84.25; 103.40]	0.04
GFR, mL/min/1.73m²		68.10 ± 15.53	76.00 ± 18.07	0.11

The data are expressed as the medians and interquartile ranges (Me [Q25%; Q75%]), the means ± standard deviation (M ± SD), and the absolute and relative numbers of patients (n (%)). EuroSCORE II, The European System for Cardiac Operative Risk Evaluation II; TSH, thyroid stimulating hormone; HbA1c, glycated hemoglobin; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; GFR, glomerular filtration rate.

Table 2. Echocardiographic characteristics before CABG in patients with and without AF

Parameters		Patients with AF (n = 19)	Patients without AF (n = 61)	p
LVEF, %		60.00 [48.00; 62.00]	58.00 [51.00; 61.00]	0.53
LVPW thickness, mm		11.00 [10.25; 12.00]	10.00 [10.00; 11.00]	0.006
IVS thickness, mm		12.00 [11.00; 17.50]	11.50 [10.63; 12.00]	0.02
LA dimension, mm		38.50 [36.00; 42.00]	38.00 [36.00; 40.00]	0.27
LA volume, mL		65.00 [60.00; 75.00]	60.00 [54.00; 69.50]	0.07
LA volume/BSA, mL/m²		35.00 [30.56; 40.48]	29.85 [26.73; 34.40]	0.008
Degree of tricuspid regurgitation, n (%)	0	1 (5.26)	18 (29.50)	0.006
	1–2	18 (94.74)	43 (70.50)	
LV mass, g		220.00 [189.50; 307.75]	194.00 [160.25; 222.25]	0.01
LVM/BSA, g/m²		121.00 [102.50; 157.50]	97.00 [78.75; 112.75]	0.0006
LV geometry, n (%)	Normal LV geometry	1 (5.26)	25 (40.98)	< 0.0001
	Concentric LV remodeling	3 (15.79)	26 (42.62)	
	Concentric LV hypertrophy	10 (52.63)	4 (6.56)	
	Eccentric LV hypertrophy	5 (26.32)	6 (9.84)	

The data are expressed as the medians and interquartile ranges (Me [Q25%; Q75%]), and the absolute and relative numbers of patients (n (%)). LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior wall; IVS, interventricular septum; LA, left atrium; BSA, body surface area; LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass.

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The obtained values were included in the prognostic model. Area under the ROC curve was 0.915 (95% CI: 0.813–0.970) (Figure 1).

The presented regression model is statistically significant (df=3; χ^2=30.04; p<0.0001). Based on the value of the R2 coefficient of determination, the model explains 57% of the observed variance in the AF patients during hospital stay after CABG and is described by the following equation:

$$P = 1/(1 + e\text{-}z) \times 100\%,$$

where $z = -3.752 + 3.287A_{\text{concentric LV hypertrophy}} + 1.799ALA_{\text{volume/BSA} \geq 34.4\ \text{mL/m}^2} + 1.799A_{\text{moderate or severe RA appendage}}$, P is the probability of developing AF during hospital stay after the surgery, A is presented as binary variables (0 is the absence of a sign, 1 is the presence of a sign).

The cut-off value of the P logistic function at the highest value of the Youden index was 0.124. The risk of developing AF during hospital stay after the CABG surgery is predicted if the value of the P logistic function is higher than or equal to this value. The sensitivity and specificity of the model were 86.67% and 78.26%, respectively. The predictive value of the positive and negative results was 79.09% and 84.73%, respectively.

Discussion

Our findings on the frequency and timing of the development of AF after CABG are comparable with the results of earlier studies, which is our sample is representative despite its relatively small size.

According to the echocardiographic findings, patients with AF had higher estimated LV mass, and structural remodeling of the LV myocardium such as concentric LV hypertrophy was an independent predictor that increased 26.78-fold the odds of developing AF during hospital stay after surgery (95% CI: 3.42–209.37; p=0.002).

There are no papers on the relationship between LV remodeling and AF associated with cardiac surgery. However, Dzhanashiya al. (2008) noted that supraventricular arrhythmias were statistically significantly more common in patients with hypertrophic types of LV remodeling (pII = 0.015 and pIII = 0.0003) compared to non-hypertrophic types [8].

In the analysis of arrhythmias in elderly and senile patients depending on the types of LV remodeling, Gadzhieva et al. (2013) revealed a predominance of a combination of supraventricular and ventricular extrasystoles with a significant predominance among patients with concentric LV hypertrophy (p<0.001), AF was also prevalent in the group with concentric LV hypertrophy [9].

Table 3. Surgical indicators of patients depending on the presence of early postoperative AF

Parameters	Patients with AF (n = 19)	Patients without AF (n = 61)	p
Duration of cross-clamping, min	54.00 [36.00; 73.00]	51.00 [35.50; 65.00]	0.69
Duration of cardiopulmonary bypass, min	97.50 [45.00; 119.80]	97.50 [72.00; 123.80]	0.99
Off-pump surgery, n (%)	2 (10.53)	7 (11.47)	0.84
Duration of surgery, min	289.00 [225.50; 321.00]	251.00 [222.00; 301.00]	0.43
Number of bypasses, n	3.0 [3.0; 4.0]	3.0 [3.0; 4.0]	0.37

The data are expressed as the medians and interquartile ranges (Me [Q25 %; Q75 %]), and the absolute and relative numbers of patients (n (%)).

Figure 1. Characteristic curve of the dependence of the logistic function P on AF developing during hospital stay after CABG

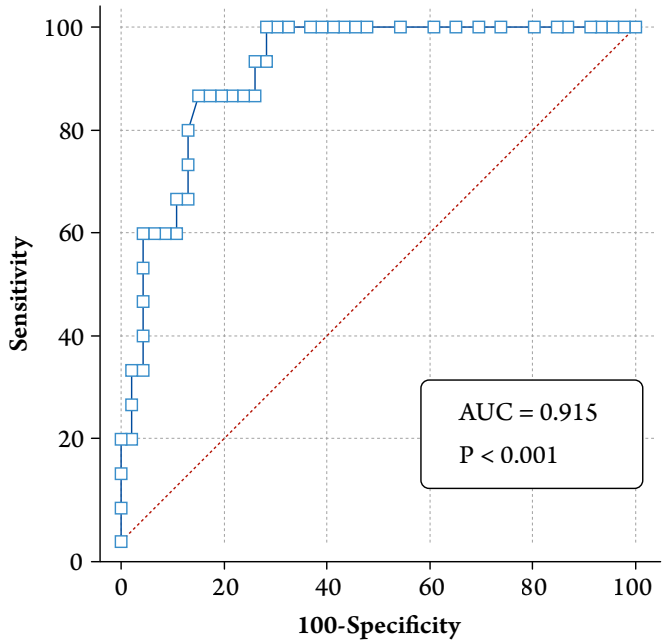

Table 4. Comparative characteristics of the severity of interstitial fibrosis in the study groups

Parameters		Patients with AF (n = 15)	Patients without AF (n = 46)	p
Degree of interstitial fibrosis	Mild, n (%)	7 (46.67)	40 (86.95)	0.003
	Moderate, n (%)	7 (46.67)	6 (13.05)	
	Severe, n (%)	1 (6.66)	0.00	

The datva are presented as the absolute and relative numbers of patients (n (%)).

Table 5. Data of univariate and multivariate regression analysis of the association of preoperative parameters with AF developing during hospital stay after CABG

Parameter	Univariate analysis		Multivariate analysis*	
	OR (95 % CI)	p	OR (95 % CI)	p
Age, years	1.07 (1.00–1.15)	0.03	–	–
BMI, kg/m²	0.86 (0.74–1.00)	0.06	–	–
COPD, n	5.15 (1.04–25.56)	0.04	–	–
RCA stenosis >70 %	2.16 (1.05–4.41)	0.03	–	–
LVPW thickness, mm	1.68 (1.09–2.59)	0.02	–	–
IVS thickness, mm	1.43 (1.08–1.97)	0.01	–	–
LV mass, g	1.01 (1.005–1.02)	0.003	–	–
LVM/BSA, g/m²	1.03 (1.01–1.02)	0.001	1.04 (1.00–1.07)	0.03
Concentric LV hypertrophy	15.83 (4.08–61.44)	0.0001	21.58 (3.39–171.23)	0.003
Eccentric LV hypertrophy	5.16 (1.36–19.57)	0.01	–	–
LA volume, mL	1.04 (0.99–1.08)	0.07	–	–
LA volume/BSA, mL/m²	1.11 (1.02–1.20)	0.01	2.13 (1.03–4.29)	0.04
Tricuspid regurgitation grade 1	0.39 (0.13–1.21)	0.10	–	–
EuroSCORE II risk, %	1.90 (1.07–3.37)	0.03	–	–
Interstitial fibrosis degree	7.21 (1.99–26.12)	0.002	21.63 (2.43–155.70)	0.007
HbA1c, %	6.38 (0.93–43.82)	0.06	–	–
Blood creatinine, mmol/L	0.99 (0.98–1.01)	0.90	–	–

* Adjusted for sex, age, surgical indicators. BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVPW, left ventricular posterior wall; IVS, interventricular septum; LA, left atrium; BSA, body surface area; LVM, left ventricular mass; EuroSCORE II, The European System for Cardiac Operative Risk Evaluation II; HbA1c, glycated hemoglobin.

Table 6. Predictors of developing AF during hospital stay after CABG

Predictor	OR	95% CI	Regression coefficient	p
Constant	–	–	-3.752	–
LA volume/BSA ≥34.4, mL/m²	6.04	1.12–32.65	1.799	0.04
Moderate or severe fibrosis of the RA appendage	17.05	2.48–116.78	1.799	0.004
Concentric LV hypertrophy	26.78	3.42–209.37	3.287	0.002

LVEDV, left ventricular end-diastolic volume; LA, left atrium; BSA, body surface area; LV, left ventricle.

LA usually dilates following an increase in pressure in the hypertrophied LV in diastolic myocardial dysfunction. Our multivariate analysis showed that the LA volume / BSA ratio >34.4 mL / m² was an independent predictor of developing AF after CABG, which is consistent with the findings by Ferreira et al. (2018) and Rubanenko et al. (2022), according to which an increase in the LV diameter was also an independent factor increasing the odds of developing postoperative AF [10, 11].

Being the gold standard for the diagnosis of myocardial fibrosis, histological examination demonstrated an aggravation of signs of structural remodeling in patients with AF. In particular, the volume of interstitial RA appendage fibrosis (biopsy taken during the installation of CPB) increased to moderate and severe in the group of patients with AF (p=0.004) was noted in the PP ears taken at the stage of IC connection according to the results of the analysis.

Our findings are comparable with the results obtained by Bokeria et al. (2005) who showed that interstitial fibrosis and severe changes in the cell myofibrillar apparatus, even myolysis, were observed in the RA appendage in 100% of cases in the AF patient group after CABG [12]. Nakai et al. (2007) showed the degree of interstitial fibrosis of RA appendage tended to correlate with the incidence of postoperative AF (p = 0.08) [13].

Contradictory data was presented by Cosgrave et al. (2006) who did not find in 94 patients any association between 10 features of interest in the RA appendage, including myolysis, fibrosis, and lipofuscin pigmentation with the development of postoperative AF [14].

Despite the fact that the mechanisms of AF development and maintenance usually come from LA and pulmonary veins, practical and ethical considerations prompted us to study RA samples – this is

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a limitation characteristic of many earlier studies [12–14]. Nevertheless, it should be noted that the RA appendage tissue reflects most of the pathological changes observed in both chronic AF and dilated cardiomyopathy [15].

We have proposed a prognostic model based on the above-described predictors that can be used in clinical practice to identify patients who are at high risk of AF during hospital stay following CABG. This model will also contribute to the development of algorithms aimed at improving outcomes after myocardial revascularization.

Limitations

The study has a small sample and a single-center design. Moreover, histological assessment of the degree of the RA appendage fibrosis requires extra time, which may limit the reproducibility of the method.

Conclusion

Thus, as well as standard laboratory and clinical examinations, the LA volume/BSA ratio, the LVM/BSA ratio should be calculated before the coronary artery bypass grafting surgery and the type of LV remodeling should be determined at admission to the hospital. Intraoperative biopsy of a RA appendage for the histological examination can be performed to clarify the risk of AF during hospital stay after coronary artery bypass grafting in patients without concomitant pathology and at a low surgical risk according to the EuroSCORE II score.

No conflict of interest is reported.

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