

Mingalimova A.R.^{1,2}, Drapkina O.M.¹,
Sagirov M.A.², Mazanov M.Kh.², Argir I.A.², Kharitonovna N.I.²

¹ National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia

² N.V. Sklifosovsky Research Institute of Emergency Medicine, Moscow, Russia

THE ROLE OF ATHEROSCLEROTIC CORONARY ARTERIES LESIONS IN THE DEVELOPMENT OF NEW-ONSET ATRIAL FIBRILLATION AFTER CORONARY ARTERY BYPASS SURGERY

<i>Aim</i>	To study the relationship between the type of circulation, severity and localization of atherosclerotic damage of coronary arteries, results of laboratory and instrumental tests, and historical data in patients with multivascular coronary lesions and atrial fibrillation (AF) that developed after coronary bypass surgery.
<i>Material and methods</i>	This was a novel, retrospective study of data of patients after elective coronary bypass surgery at the Cardiac Surgery Department #1 of the N. V. Sklifosovsky Research Institute of Emergency Care from December, 2018 through December, 2020. The study included 100 patients. The main group consisted of 20 patients whose early postoperative period (first 7 days after surgery) was complicated with postoperative atrial fibrillation (POAF) (mean age, 65.15±9.7 years). The comparison group included 80 patients without the POAF complication during the early postoperative period (mean age, 62.0±9.16 years). Prior to the coronary bypass surgery, all patients underwent clinical, laboratory, and instrumental examination. Based on data of selective coronary angiography, localization, severity of coronary atherosclerotic damage (according to angiographic classification), number of affected arteries, and the type of circulation were taken into account.
<i>Results</i>	Intergroup differences in the incidence and localization of myocardial infarctions in history, severity of arterial hypertension in history, class of chronic heart failure (according to the New York Heart Association, NYHA, classification), and heart rate were absent. 100% of patients had left atrial (LA) dilatation not correlated with the development of AF in the early postoperative period. According to data of coronary angiography, there was no statistically significant association between the type of circulation and the development of POAF. The right type of myocardial blood supply prevailed in patients of both groups. There was no correlation between the severity and localization of coronary atherosclerotic lesions and the development of AF in the early postoperative period.
<i>Conclusion</i>	The development of AF following coronary bypass surgery was not associated with features of coronary atherosclerotic lesions, which may indicate active development of inter- and intra-systemic anastomoses in patients with long-term history of chronic coronary atherosclerosis.
<i>Keywords</i>	Postoperative atrial fibrillation; ischemic heart disease; coronary bypass; atherosclerosis
<i>For citations</i>	Mingalimova A.R., Drapkina O.M., Sagirov M.A., Mazanov M.Kh., Argir I.A., Kharitonovna N.I. The role of atherosclerotic coronary arteries lesions in the development of new-onset atrial fibrillation after coronary artery bypass surgery. <i>Kardiologiia</i> . 2021;61(12):41–48. [Russian: Мингалимова А.Р., Драпкина О.М., Сагиров М.А., Мазанов М.Х., Аргир И.А., Харитоновна Н.И. Роль поражения коронарного русла в развитии фибрилляции предсердий, впервые развившейся после операции коронарного шунтирования. <i>Кардиология</i> . 2021;61(12):41–48]
<i>Corresponding author</i>	Mingalimova A.R. E-mail: alfia.ravisonva@mail.ru

Introduction

One of the most frequent cardiovascular complications occurring during the early post-operative period following cardiac surgeries is atrial fibrillation (AF), which typically develops for the first time following coronary bypass surgery (18–40% of cases) [1]. Patients with post-operative AF (POAF) are at higher risk of cardiovascular mortality, stroke, other arrhythmias complicating post-operative re-

habilitation than those without this condition [2]. Therefore, cardiologists responsible for managing patient health over the long-term post-operative period, whether practicing in a cardiac surgery department of a hospital or an outpatient department, should focus on the early detection of risk factors in order to prevent this type of arrhythmia. The main characteristics of the examined patients are severe multivessel coronary artery disease, a history of

myocardial infarctions (often repeated), along with postinfarction cardiosclerosis in the several artery systems. During more than half a century of the history of coronary artery bypass grafting (the first autovenous coronary stenosis bypass surgery was performed by R. Favaloro in 1967), many markers associated with the development of POAF have been identified in different patient groups [1]. Therefore, the objective of our work was to study the relation of POAF with coronary artery disease patterns, along with the results of clinical and laboratory examinations, as well as the medical history of patients with multivessel coronary artery disease.

Material and methods

The original retrospective study included patients who had undergone elective coronary artery bypass grafting in the Cardiac Surgery Department #1 in Sklifosovsky Research Institute for Emergency Medicine from December 2018 to December 2020. Multivessel coronary disease was an indication of elective myocardial revascularization in patients along with a clinical picture of angina pectoris of functional class (FC) III–IV. All patients underwent clinical and laboratory examinations. The smoking status of patients was identified during the clinical examination. Pre-operative echocardiography was carried out using an expert-class ultrasound device Vivid E9 (USA). Heart chamber dimensions, including ventricular mass and function, were estimated in all patients prior to carrying out surgery. Echocardiographic criteria of the left atrial (LA) dimension was the calculated mean LA volume index (normal LA volume index is 22 ± 6 mL/m²; increased LA dimensions were considered as LA dilation regardless of the patient's sex). Using the Judkins (1967) selective coronary angiography technique, the location and severity of coronary atherosclerosis (from hemodynamically significant stenosis and complete occlusion of the vessel lumen to irregular inner) were taken into consideration, along with the number of vessels involved, as well as the type of blood supply. Obesity was assessed in accordance with the WHO criteria by body mass index (BMI).

All patients underwent conventional coronary artery bypass grafting: mammocoronary bypass grafting of the left anterior descending artery (LAD); coronary artery bypass grafting (CABG) of the left circumflex artery (LCX) and right coronary artery (RCA) systems, as well as, in some cases, the diagonal artery (DA). The surgery was performed

using cardiopulmonary bypass (CPB) in 99% of cases; one surgery was carried out off-pump. During aortic cross-clamping, the myocardium was protected via normothermic blood cardioplegia. The cross-clamp was removed after performing distal bypass anastomoses with coronary arteries. On the lateral part of the ascending aorta, proximal anastomoses with the aorta were formed during parallel CPB and restored cardiac activity. Then, after turning off CPB, the post-operative wound was sutured. The time of cross-clamping, duration of CPB, intraoperative blood loss volume and intravenous infusion volume were recorded in all patients.

Depending on the development of early post-operative AF (within up to 7 days after coronary artery bypass grafting), patients were divided into two groups comprising the main group of patients with POAF (n=20) and the comparison group of patients without POAF in the early post-operative period (n=80). The first attack of AF was considered as an episode of arrhythmia lasting at least 30 seconds, recorded by ECG or a bedside monitor in the cardio-surgical ICU.

The inclusion criteria formed a clinical pattern of exertional angina FC III–IV, the presence of indications and absence of contraindications for coronary artery bypass grafting, as well as an age of less than 80 years at the time of surgery.

Exclusion criteria were: thyroid diseases; diabetes mellitus type 2; a history of AF; valvular heart disease requiring surgery; a clinical pattern of acute coronary syndrome.

The study protocol was designed following the Declaration of Helsinki and approved by the facility's ethics committee. All patients signed informed consent at admission to the hospital for the use of clinical data for scientific research. All patient data were labeled and depersonalized for analysis.

The statistical analysis was performed using GraphPad Prism 8.4.3. The Kolmogorov–Smirnov and Shapiro–Wilk tests were applied to estimate the normality of distribution. The statistical significance of the differences between the groups of patients with and without AF was determined using the Student's t-test (for normally distributed data) or the Mann–Whitney U-test (for non-normally distributed data).

The numerical variables corresponding to the normal distribution are presented as the mean and standard deviation ($M \pm SD$); the variables not corresponding to the normal distribution are presented as the median and interquartile range (Me (Q25; Q75)). Discrete variables were compared using

Table 1. Clinical characteristics and medical history of patients subjected to coronary artery bypass grafting depending on the development of POAF

Parameters		Patients without AF (n=80)	Patients with AF (n=20)	p
Age, years		62.00±9.16	65.15±9.70	0.17
Male, n (%)		70 (87.5)	15 (75.00)	0.16
Body mass index, kg/m ²		28.11±4.05	29.08±4.37	0.34
Normal weight and overweight, n (%)		54 (67.50)	10 (50.00)	0.14
Obesity grade 1 and higher, n (%)		25 (31.25)	9 (45.00)	0.24
Underweight, n (%)		1 (1.25)	1 (5.00)	0.62
Heart rate, bpm		69±15.75	65±10.75	0.13
Glomerular filtration rate, mL/min/1.73m ²		77.39±17.22	68.15±16.13	0.03
Smoking, n (%)		29 (36.25)	9 (45.00)	0.47
History of myocardial infarction, n (%)	LAD	19 (23.75)	3 (15.00)	0.39
	LCX	8 (10.00)	1 (5.00)	0.48
	RCA	13 (16.25)	4 (20.00)	0.68
	PDA (RCA) or PDA (LCX) depending on the type of circulation	1 (1.25)	0 (0.00)	0.61
History of percutaneous coronary intervention, n (%)	BDA	34 (42.50)	5 (25.00)	0.15
	Stenting	33 (41.25)	5 (25.00)	0.18
Arterial hypertension grade, n (%)	1	3 (3.75)	1 (5.00)	0.79
	2	11 (13.75)	2 (10.00)	0.65
	3	63 (78.75)	17 (85.00)	0.53
CHF NYHA FC, %	I-II	72 (90.00)	18 (90.00)	> 0.99
	III-IV	5 (6.25)	1 (5.00)	0.83
COPD, n (%)		1 (1.25)	0 (0.00)	0.61
Treatment, n (%)	Beta-blockers	57 (71.25)	12 (60.00)	0.33
	Statins	55 (68.75)	14 (70.00)	0.91
	Sartans	24 (30.00)	5 (25.00)	0.65
	ACE inhibitors	31 (38.75)	7 (35.00)	0.75
	Antiarrhythmic therapy	3 (3.75)	0 (0.00)	0.37

M±SD – mean value and standard deviation; LAD – left anterior descending artery; LCX – left circumflex artery; RCA – right coronary artery; PDA (RCA) – posterior descending artery arising from the right coronary artery; PDA (LAD) – posterior descending artery arising from the left anterior descending artery; BDA – balloon dilation angioplasty; CHF – chronic heart failure; COPD – chronic obstructive pulmonary disease; ACE – angiotensin-converting enzyme.

Pearson's χ^2 and Fisher's two-tailed test. The zero-difference hypothesis was rejected if the probability of being mistakenly rejected did not exceed 5% ($p < 0.05$).

Results

The results of the data analysis given in Table 1 show that the mean age of patients was 65.15±9.70 years in the group of patients with POAF; in patients without POAF, the mean age was 62.0±9.16 years

($p=0.17$). The majority of patients in both groups were male: 75% ($n=15$) in the POAF group and 87.5% ($n=70$) in the non-POAF group. There were no sex-related intergroup differences ($p > 0.99$). The anthropometric characteristics did not differ between the groups; the body mass index did not exceed 29.08±4 kg/m² in either group ($p=0.34$). Only one patient in each group (5% of patients with AF, 1.25% of patients without AF) was underweight (BMI < 18.5 kg/m²).

Table 2. Prevalence and localization of coronary lesions per group

Parameters		Patients without AF (n=80)	Patients with AF (n=20)	p
Type of circulation, n (%)	Balanced	9 (11.25)	3 (15.00)	> 0.99
	Right	65 (81.25)	15 (75.00)	0.53
	Left	6 (7.50)	2 (10.00)	0.71
Left main coronary artery, n (%)*		30 (37.50)	8 (40.00)	0.83
Left anterior descending artery, n (%)*	Proximal part	64 (80.00)	13 (65.00)	0.15
	Middle part	61 (76.25)	14 (70.00)	0.56
	Distal part	32 (40.00)	8 (40.00)	> 0.99
Intermediate artery, n (%)*		6 (7.50)	1 (5.00)	> 0.99
Diagonal artery, n (%)*		42 (61.25)	10 (50.00)	0.84
Left circumflex artery, n (%)*	Proximal part	48 (60.00)	12 (60.00)	> 0.99
	Middle part	44 (55.00)	9 (45.00)	0.42
	Distal part	29 (36.25)	5 (25.00)	> 0.99
Obtuse marginal artery, n (%)*		45 (56.25)	12 (60.00)	0.76
Right coronary artery, n (%)*	Proximal part	46 (57.50)	14 (70.00)	0.30
	Middle part	45 (56.25)	13 (65.00)	0.47
	Distal part	44 (55.00)	10 (50.00)	0.68
Posterior descending artery of the right coronary artery or posterior descending artery of the left circumflex artery, n (%)*		14 (17.50)	7 (35.00)	0.08
Posterolateral branch of the right coronary artery, n (%)*		11 (13.75)	3 (15.00)	> 0.99

* – any coronary artery lesions from lumen irregularity to occlusion.

Table 3. Echocardiographic characteristics of patients with CAD depending on the presence of post-operative AF

Parameters	Patients without AF (n=80)	Patients with AF (n=20)	p
Aortic root diameter, cm	3.40 (3.20; 3.60)	3.35 (3.125; 3.50)	0.27
Left atrial dimension, cm	3.7 (3.6; 4.0)	3.7 (3.525; 4.075)	0.90
Left atrial volume, mL	58 (46.25; 68.00)	60 (49.00; 65.00)	0.76
Left atrial volume index, mL/m ²	29.58±7.01	29.69±6.69	0.94
Right ventricular dimension, cm	2.6 (2.5; 2.6)	2.6 (2.6; 2.6)	0.80
End-diastolic dimension, cm	4.7 (4.5; 5.1)	4.8 (4.525; 4.975)	0.99
End-systolic dimension, cm	3.35 (3.2; 3.8)	3.2 (3.1; 3.575)	0.12
End-diastolic volume, mL	108 (98.25; 125)	106.5 (94.25; 109.8)	0.16
End-systolic volume, mL	46 (40; 57.75)	40 (35.25)±(43.50)	0.01
Left ventricular ejection fraction, %	57.5 (48; 61)	62.50 (57; 64)	0.009
Interventricular septal thickness, cm	1.1 (1.1; 1.3)	1.1 (1.0; 1.3)	0.97
Left ventricular posterior wall thickness, mm	1.1 (1.0; 1.2)	1.05 (1.0; 1.1)	0.36
Left ventricular mass, units	218.5 (195.0; 255.8)	211 (191.0; 235.8)	0.19
Mean pulmonary artery pressure, mm Hg	21.0 (19.0; 25.0)	21.0 (19; 24.75)	0.76
Diastolic dysfunction type I, n (%)	46 (57.50)	15 (75.00)	0.15
Mitral regurgitation grade II or higher, n (%)	5 (6.25)	0 (0.00)	0.25

The numerical variables corresponding to the normal distribution are presented as the mean and standard deviation (M±SD), as well as the variables not corresponding to the normal distribution, are presented as the median and interquartile range (Me (Q25; Q75)).

Table 4. Operational indicators of patients with CAD depending on the presence of post-operative AF

Parameters	Patients without AF (n=80)	Patients with AF (n=20)	p
Time of CPB, min	93.80±35.07	96.25±36.84	0.78
Time of CPB, min	54.24±22.50	52.30±19.31	0.72
Blood loss, mL	500 (400; 500)	500 (400; 600)	0.98
Volume of i/v infusion, mL	2400 (2028; 2800)	2475 (2025; 3471)	0.33
Off-pump surgery, n (%)	2 (2.5)	0 (0.0)	0.47
Duration of surgery, min	251.0 (231; 300)	273.5 (225.3; 325.8)	0.42
Number of bypasses	3 (3; 4)	4 (3; 4)	0.56

The numerical variables corresponding to the normal distribution are presented as the mean and standard deviation (M±SD); variables not corresponding to the normal distribution are presented as the median and interquartile range (Me (Q25; Q75)); CPB, cardiopulmonary bypass.

Table 5. Comparison of laboratory indicators of patients subjected to coronary artery bypass grafting depending on the development of POAF

Parameters	Patients without AF (n=80)	Patients with AF (n=20)	p
Total cholesterol, mmol/L	4.77±1.06	4.47±1.10	0.26
HDL-C, mmol/L	2.73±0.82	2.69±0.82	0.03
LDL-C, mmol/L	2.66 (2.15; 3.23)	2.60 (2.07; 3.40)	0.98
Atherogenicity index	2.38 (1.45; 3.73)	1.51 (1.30; 2.96)	0.06
Triglycerides, mmol/L	1.75 (1.30; 2.44)	2.37 (1.73; 3.65)	0.01
Creatinine, µmol/L	92.23 (84.10; 99.93)	95.20 (83.35; 120.60)	0.06
Potassium, mmol/L	4.52±0.46	4.57±0.45	0.69
Hemoglobin, g/L	143.43±15.39	143.95±12.44	0.88
WBCs, 10 ⁹ /L	6.84 (5.73; 7.54)	6.435 (5.95; 8.10)	0.63
Platelets, 10 ⁹ /L	209.5 (167.3; 242.0)	205.5 (185.8; 262.8)	0.61
Fasting glycemia, mmol/L	5.235 (4.860; 5.608)	5.085 (4.793; 6.025)	0.46

The numerical variables corresponding to the normal distribution are presented as the mean and standard deviation (M±SD); variables not corresponding to the normal distribution are presented as the median and interquartile range (Me (Q25; Q75)). HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol.

There were no differences between the groups in the incidence of myocardial infarction of any localization (LAD, LCX, RCA, PDA) or in the rate of percutaneous coronary intervention (PCI) (balloon angioplasty and coronary artery stenting). There were no intergroup differences in the presence of arterial hypertension (AH). The majority of

patients in both groups had a history of high blood pressure (BP) grade 3 and chronic heart failure (CHF) NYHA FC I–II (Table 1). Smoking, pre-operative medication (beta-blockers, statins, sartans, angiotensin-converting enzyme (ACE) inhibitors, antiarrhythmic drugs (sotalhexal, amiodarone) did not significantly affect the development of AF in

the post-operative period. Glomerular filtration rate (GFR) was significantly lower in patients with POAF ($p=0.03$).

As shown in Table 2, there is no statistically significant correlation between blood supply type and the development of POAF. In both groups, myocardial blood supply was dominated by RCA. A comparison of the groups shows that the severity and localization of coronary atherosclerosis were not associated with the development of AF in the early post-operative period.

A comparison of echocardiographic parameters (Table 3) shows that, other than the absolute values of end-systolic volume (ESV), wall thickness and myocardial mass, the dimensions of the heart chambers did not correlate with the development of AF in the early post-operative period. However, LVESV was statistically significantly lower ($p<0.01$) in patients with POAF, while LVEF was significantly higher ($p<0.009$). According to our findings, the groups did not differ in the prevalence of hemodynamically significant mitral regurgitation (grade 2 or more), LA dilation, and diastolic dysfunction type 1.

According to Table 4, neither the time of aortic cross-clamping, intraoperative blood loss volume, intravenous infusion volume, nor the time of CPB, were statistically significantly correlated with the development of POAF.

There were no differences in the laboratory findings between groups other than the levels of triglycerides ($p=0.01$) and HDL cholesterol ($p=0.03$).

Discussion

Coronary artery disease (CAD) is the main cause of death in the working-age population of most countries. Despite the vigorous development of drug therapies, CAD increases the risk of AF by 4–5 times [3, 4]. Coronary atherosclerosis is a long and progressive process that leads to impaired circulation along with ischemic damage in the myocardium responsible for bioelectrical activity in the heart. Although extensive research has been carried out, the role of coronary flow impairment in the development of AF is still not fully understood.

The development of AF following coronary artery bypass grafting depends on many factors, which can be roughly divided into three groups: pre-operative, intraoperative and post-operative factors. LA myocardial fibrosis is a pre-operative factor known to be associated with the development of AF [5–8]. Chronic hypoxia caused by LA branch atherosclerosis may be a mechanism for the formation

of new multiple diffuse arrhythmogenic sites in the LA. Long-term ischemia results in morphological changes: endogenous inflammation followed by myocardial fibrosis and LA remodeling [4].

According to our findings, 100% of the patients examined had LA dilatation, which was not significantly associated with the development of AF in the early post-operative period. Patients in the study group had multivessel coronary artery disease and a concomitant pathology that complicated the course of the background disease. CAD is mainly associated with AH, DM type 2, chronic kidney disease, metabolic syndrome, which are independent predictors of AF [9, 10]. However, our study identified intergroup differences in the presence and severity of concomitant pathologies due to the strict selection criteria for myocardial revascularization surgery, including achieving target levels of HbA1c and target BP levels in the cardiac surgery department, as well as weight loss.

The main intraoperative risk factors for developing POAF include the duration of CPB, the time of aortic cross-clamping and the volume of blood loss. CPB is considered the main reason for developing a systemic inflammatory response in the post-operative period following cardiac surgery [11]. Moreover, cardioplegia – i.e., drug-induced cardiac arrest – prevents post-ischemic cardiac dysfunction. The absence of a statistically significant correlation of the above risk factors with the development of AF in the post-operative period may be due to the use of a cardioplegia solution and the normothermic setting.

Our study did not examine the effects of post-operative risk factors of the development of AF, such as the time of artificial ventilation, as well as the duration and doses of inotropic drugs. In conclusion, the long-term history of CAD, postinfarction cardiosclerosis in the study group affects the atrial myocardium, making it more vulnerable to intraoperative ischemia, inflammation and electrolyte disorders [12–14]. Well-developed collateral circulation in the occluded coronary artery systems can be a powerful reserve for compensatory blood flow in the myocardium and cardiac conduction system in chronic ischemia.

The incidence of AF following coronary artery bypass grafting is consistent with the published data (post-operative AF developed in 20% of patients). However, the main question remains open: what factors have the most influence on the risk of developing POAF? In order to address this highly relevant issue, it is necessary to carry out more multidisciplinary studies.

Conclusion

According to our study, the development of atrial fibrillation following coronary artery bypass grafting was not associated with coronary atherosclerosis; this may indicate the vigorous development of intrasystemic and intersystemic anastomoses in patients with a long-term history of chronic coronary syndrome.

For this reason, the sole use of coronary angiography to identify a direct relationship between the involvement of individual coronary arteries and the development of post-operative atrial fibrillation can be problematic. Since the effect on the development of post-operative atrial fibrillation of collateral

circulation in the arterial systems, which are responsible for blood supply to the sinoatrial node and left atrium, is currently unclear, further research is required.

Limitations

Our study was limited by retrospective design and a relatively small sample, which did not allow the causative correlation between AF and CAD to be evaluated.

No conflict of interest is reported.

The article was received on 25/01/2021

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