Neopterin as a predictive biomarker of postoperative atrial fibrillation following coronary artery bypass grafting

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ABSTRACT

Background: The pathophysiology of postoperative atrial fibrillation (POAF) is multifactorial. Inflammation and increased oxidative stress play a significant role in POAF development. Neopterin, a biomarker of cellular immune response that enhances oxidative stress and increases the cytotoxic potential of activated macrophages and dendritic cells, was recently found as an independent predictive biomarker of non-operative atrial fibrillation. However, as far as we know, neopterin has never been investigated in POAF.

Aims: The study aimed to assess neopterin concentration as a prognostic biomarker of POAF following coronary artery bypass grafting (CABG).

Methods: One hundred one patients (80.2% males, 85% off-pump, 15% on-pump) were included. Blood samples were taken from patients for analysis of serum neopterin and high-sensitive C-reactive protein (hs-CRP) at three time points: (1) before operation (NP0); (2) on the first day after operation (NP1); and (3) between the fifth and eighth day after the procedure (NP5–8). All factors (preoperative, echocardiographic, and surgical), significant in univariate analysis, were included in a multivariable logistic regression analysis.

Results: POAF occurred in 30 patients (30%). In the analyzed multivariable logistic regression models, the independent predictors of POAF occurrence were: higher NP0 concentration (odds ratio [OR], 1.16; 95% confidence interval [CI], 1.02–1.38 for continuous and OR, 3.75; 95% CI, 1.39–10.1 for NP0 cut-off >8.7 nmol/l), higher body mass index (OR, 1.15; 95% CI 1.02–1.29), history of pulmonary disease (OR, 6.72; 95% CI 1.57–28), increased diastolic thickness of the interventricular septum (OR, 1.45; 95% CI, 1.14–1.83), and duration of operation (OR, 1.01; 95% CI, 1.03–1.36).

Conclusions: We found that elevated neopterin concentration before CABG may be a predictive biomarker of POAF.

Key words: coronary artery bypass grafting, inflammatory biomarker, neopterin, postoperative atrial fibrillation

WHAT'S NEW?

The study investigated the prognostic value of neopterin in postoperative atrial fibrillation occurrence following elective coronary artery bypass. Neopterin, a biomarker of inflammation, has been recently found as an independent predictive factor of non-operative atrial fibrillation. In the current study, for the first time, we have documented that elevated neopterin concentration can also be an useful prognostic biomarker in postoperative arrhythmia. Multivariable logistic regression analysis identified neopterin concentration before operation, adjusted for body mass index, age, total cholesterol concentration and left atrium diastolic diameter, echocardiographic factors, as well as operative factors, as independent predictors of postoperative atrial fibrillation.

INTRODUCTION

Most episodes of postoperative atrial fibrillation (POAF) occur within the first six days after cardiac operations, with a peak of incidence on the second and third postoperative days [1]. The occurrence of POAF is associated with not only postoperative complications, increased duration and costs of hospitalization [2], but also with higher late mortality and more frequent episodes of atrial fibrillation during long-term follow-up [3]. The pathophysiology of POAF is highly complex, and its development is a net result of numerous factors. Many of them enhance and promote an inflammatory process that is considered crucial in POAF development [4]. It was observed that POAF incidences reached a peak on the second and third postoperative days, simultaneously with the highest concentrations of C-reactive protein (CRP) [5], interleukin 2 [6], and interleukin 6 [7]. Interestingly, cardiopulmonary bypass (CPB) has also been documented as a factor associated with systemic inflammation through complement activation. However, CPB application was not a predictive factor of POAF in several studies [8, 9], while it was an independent POAF predictor in other studies (e.g., in the elderly with high surgical risk) [10, 11]. Furthermore, oxidative stress is known to be one of the mechanisms of POAF development [12–14].

Neopterin is a biological marker for cellular inflammation, generated by activated (stimulated *via* interferon γ) macrophages and dendritic cells. The principal mode of action for neopterin is to enhance cytotoxic activity of macrophages and dendritic cells [15] through intensifying oxidative stress and the the formation of reactive oxygen species. Neopterin generation at the cost of tetrahydrobiopterin synthesis, which is a cofactor of nitric oxide synthase (NOS), leads to tetrahydrobiopterin depletion and, in turn, to NOS uncoupling and creation of reactive oxygen (O_2) [16]. Increased concentration of neopterin has been observed in diseases that are characterized by inflammation and upregulated inflammatory response. Higher neopterin concentration was associated with ischemic heart disease [17], chronic heart failure with reduced [18] and preserved ejection fraction [19], pulmonary arterial hypertension, and inoperable chronic thromboembolic pulmonary hypertension [20]. Moreover, dedicated studies showed that higher neopterin concentration was a predictive biomarker of death and adverse events. Increased postoperative neopterin concentration was predictive of postoperative complications following cardiac surgery such as circulatory, respiratory, liver, and renal failure, as well as blood coagulation disorders [21, 22]. Similarly, a higher concentration of neopterin was associated with cognitive disorders in elderly patients after coronary artery bypass grafting (CABG) or CABG with valve replacement [23]. To our knowledge, the prognostic value of neopterin for POAF development after CABG has never been investigated.

In the current study, the predominant purpose was to evaluate neopterin concentration as a prognostic biomarker of POAF following CABG. In addition, the study was designed to determine if the preoperative or postoperative concentration was a better prognostic factor of POAF.

METHODS

Patients

One hundred one patients (80.2% males) with advanced coronary artery disease were found to be eligible for elective CABG by our Heart Team and recruited in a single-center prospective observational study. Detailed patient characteristics are shown in Tables 1 and 2.

Exclusion criteria included emergency operation, other operation than isolated CABG, history of atrial fibrillation or flutter, pacemaker implantation, clinical symptoms of infection (body temperature >38°, current antibiotic or systemic steroid therapy, acute or chronic renal failure on dialysis, current hyperthyroidism). Medical interview, physical examination, 12-lead electrocardiogram, and transthoracic echocardiography were performed on every patient. All subjects signed informed consent and the Ethics Committee of the University of Medical Sciences in Poznan, Poland, approved the study (no. 546/13).

Surgery

The method of CABG was a choice of the surgeon. Only operations done by surgeons with at least 5-year experience were taken into consideration.

On-pump operations were performed *via* median sternotomy, in moderate systemic hypothermia (27°–29°). CPB was conducted through an arterial cannula in the ascending aorta and a venous cannula in the right atrium. Cold cardioplegic (4°) arrest with the use of St. Thomas Hospital No. 2 solution, in an initial dose of 10 ml/kg, then

Table 1. Detailed baseline patient characteristics and comparison of preoperative factors in patients with postoperative atrial fibrillation (the POAF group) and without POAF (the non-POAF group)

	All patients (n = 101)	POAF group (n = 30)	Non-POAF group (n = 71)	*P*-value
Age, years, mean (SD)	62.6 (7.3)	65 (6)	62 (8)	0.03
Sex				0.59
Female, n (%)	19 (18)	7 (23)	13 (18)	
Male, n (%)	81 (82)	13 (77)	58 (82)	
Weight, kg, mean (SD)	83.3 (13)	86 (10)	82 (14)	0.15
Height, cm, mean (SD)	169.9 (9)	169 (8)	170 (9)	0.68
BMI, kg/m^2, median (IQR)	28.8 (26.8–30.9)	29.6 (27.8–32.8)	28.1 (25.8–30.7)	0.03
Heart failure with LVrEF, n (%)	17 (17)	7 (23)	10 (14)	0.26
Diabetes mellitus, n (%)	38 (38)	15 (50)	23 (32)	0.12
History of stroke or TIA, n (%)	10 (10)	5 (17)	5 (7)	0.15
History of AMI, n (%)	68 (68)	22 (73)	46 (65)	0.49
History of PCI, n (%)	33 (33)	11 (37)	22 (31)	0.64
Hypertension, n (%)	88 (87)	29 (97)	59 (83)	0.10
Pulmonary disease, n (%)	11 (11)	7 (23)	4 (6)	0.01
Hypothyroidism, n (%)	10 (10)	3 (10)	7 (10)	1.0
LM stenosis, n (%)	35 (35)	13 (43)	19 (27)	0.11
Two vessel-disease, n (%)	19 (19)	5 (16.7)	14 (19.7)	0.94
Three vessel-disease, n (%)	82 (81)	25 (83.3)	57 (80.3)	0.94
SYNTAX II score, mean (SD)	30.8 (4.5)	31.2 (4.5)	30.3 (5.9)	0.68
LAD stenosis, % of stenosis, median (IQR)	80 (60–95)	80 (60–90)	80 (70–95)	0.73
Cx stenosis, % of stenosis, median (IQR)	78 (20–90)	80 (70–90)	75 (20–90)	0.28
RCA stenosis, % of stenosis, median (IQR)	87 (60–100)	90 (80–100)	85 (60–100)	0.25
Peripheral artery stenosis, n (%)	22 (22)	8 (27)	14 (20)	0.29
Carotid artery stenosis, n (%)	8 (8)	3 (10)	5 (7)	0.69
Lower limb artery stenosis, n (%)	14 (14)	5 (17)	9 (13)	0.75
Atheromatic plaque in the aorta, n (%)	14 (14)	4 (13)	10 (14)	1.0
Cigarette smoking				
Active, n (%)	35 (35)	11 (37)	24 (34)	0.65
Within last 10 years, n (%)	6 (6)	1 (3)	5 (7)	0.67
>10 years ago, n (%)	35 (35)	10 (33)	25 (35)	1.0
Drugs				
ACEI, n (%)	73 (73)	23 (76)	50 (70)	0.63
ARB, n (%)	12 (12)	3 (10)	9 (13)	1.0
ASA, n (%)	97 (96)	27 (90)	70 (100)	0.08
β-blocker n (%)	83 (82)	24 (80)	59 (83)	0.78
Ca-blocker, n (%)	23 (23)	6 (20)	17 (24)	0.80
Spironol/eplerenone, n (%)	14 (14)	7 (23)	7 (10)	0.11
Statin, n (%)	100 (99)	30 (100)	70 (100)	1.0
Diuretics, n (%)	28 (28)	12 (40)	16 (23)	0.09

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; Cx, circumflex artery; IQR, interquartile range; LAD, left descending coronary artery; LM, left main; PCI, percutaneous coronary intervention; POAF, postoperative atrial fibrillation; RCA, right coronary artery; LVrEF, left ventricular reduced ejection fraction; SD, standard deviation; TIA, transient ischemic attack

repeated every 30 minutes; infused antegrade to the aortic root was applied as a protective measure. Distal anastomoses were done during cardiac arrest, whereas proximal anastomoses were performed on the beating heart, with a partially clamped aorta.

Off-pump operations were also performed *via* median sternotomy but in normothermia. Distal anastomoses were done on the beating heart, using negative pressure-based stabilizers and intravascular shunts, while proximal anastomoses were done with a partially clamped aorta.

Blood sampling

Peripheral venous blood samples were taken from every patient at three time points: (1) before operation (NP0); (2) on the first day after operation, and (3) between the fifth and eighth day after operation for analysis of serum neopterin and hs-CRP. The blood samples for preoperative neopterin testing were obtained the day before operation. Then they were centrifuged at 10000 g (10 min) and preserved at –80°C for future analysis. Enzyme immunoassay Neopterin (ELISA, DRG International, Inc., Springfield, NJ, US) was used to assess serum neopterin concentration.

Heart rhythm analysis

Heart rhythm was monitored with continuous telemetry during the time from surgery to discharge from the hospital. Episodes of atrial fibrillation lasting at least 30 seconds were classified as POAF. When POAF occurred, short episodes that lasted less than one hour and that were well tolerated were managed without any antiarrhythmic

Table 2. Detailed baseline patient characteristics and comparison of preoperative, surgical, and postoperative factors in patients with postoperative atrial fibrillation (the POAF group) and without POAF (the non-POAF group)

	All patients (n = 101)	POAF group (n = 30)	Non-POAF group (n = 71)	*P*-value
Echocardiography				
EF, %, median (IQR)	55 (50–60)	55 (50–60)	57 (50–60)	0.42
LV, mm, median (IQR)	48 (43–52)	51 (43–55)	47 (43–51)	0.07
LA, mm, mean (SD)	38 (5)	39 (5)	37 (5)	0.06
RV, mm, mean (SD)	29 (4)	30 (4)	29 (4)	0.54
Ao asc., mm, mean (SD)	33 (6)	34 (7.5)	32 (6)	0.18
PWd, mm, mean (SD)	12 (3)	12.5 (2.3)	12 (2.5)	0.35
IVSd, mm, median (IQR)	13 (11–14)	13.5 (13–15)	12 (11–13)	<0.001
ECG				
Beats per minute, median (IQR)	62 (58–73)	63 (57–73)	62 (58–72)	0.95
Pathological Q or QS, n (%)	55 (54)	18 (60)	37 (52)	0.51
Laboratory parameters				
ESR, mm/h, median (IQR)	11 (5–18)	10 (5–13)	12 (5–18)	0.29
Hb, mmol/l, mean (SD)	8.9 (0.7)	9.0 (0.7)	8.9 (0.8)	0.54
WBC, 10^3/µl, mean (SD)	7.8 (1.9)	8.1 (2.2)	7.6 (1.7)	0.30
RDW, %, median (IQR)	13.8 (13.4–14.2)	14 (0.8)	13.7 (1.0)	0.29
T-chol, mmol/l, median (IQR)	3.8 (3.2–4.5)	3.4 (3.0–4.17)	4.0 (3.4–4.7)	0.02
LDL-cholesterol, mmol/l, median (IQR)	2.0 (1.6–2.6)	1.8 (1.5–2.4)	2.0 (1.6–2.7)	0.10
HDL-cholesterol, mmol/l, median (IQR)	1.13 (0.9–1.3)	1.1 (0.9–1.2)	1.2 (0.9–1.4)	0.25
TAG, mmol/l, median (IQR)	1.2 (0.9–1.7)	1.3 (0.9–1.6)	1.2 (0.9–1.8)	0.85
eGFR, ml/kg/1.73 m^2, mean (SD)	90.8 (24.5)	86 (23)	93 (25)	0.24
Off-pump, n (%)		26(86)	60 (85)	1.0
On-pump, n (%)		4 (14)	11 (15)	
Number of grafts, median (IQR)		3 (2–3)	2 (2–3)	0.24
Duration of operation, min, mean (SD)		191 (42)	165 (80)	0.08
IABP, n (%)		0 (0)	2 (3)	1.0
Red blood concentrate transfusions, median (IQR)		2 (0–2)	1 (0–2)	0.24

Abbreviations, Ao (asc.), dimension of the ascending aorta; ECG, electrocardiogram; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; HDL-cholesterol, high-density lipoprotein cholesterol; IABP, intra-aortic balloon pump; IVSd, diastolic interventricular septum dimension; LA, left atrium; LDL-cholesterol, low-density lipoprotein cholesterol; LV, left ventricle; PWd, posterior wall of the left ventricular diastolic dimension; RDW, red blood cell distribution width; RV, right ventricular dimension; TAG, triglycerides; T-chol, total cholesterol; WBC, white blood cells count; other — see Table 1

treatment. Longer episodes of POAF or POAF leading to hemodynamic worsening were treated with intravenous amiodarone; in cases of pharmacotherapy failure, electrical cardioversion was performed.

Postoperative period

All patients routinely received I generation cephalosporin intravenous for up to 48 hours as the infection prophylaxis. The following postoperative complications were recorded: postoperative wound infection, body temperature ≥38°C, *Clostridium difficile* infection, urinary tract infection, pleural abscess or pneumonia, several red blood cell concentrate transfusions, prolonged antibiotic therapy, cognitive impairment, pericardial effusion or tamponade, renal failure with the need of hemofiltration, pleural effusion, pneumothorax, acute heart failure, increased alanine transaminase (ALAT) or aspartate transaminase (ASPAT) >8 times the upper limit of normal (ULN), acute limb ischemia. Additionally, the duration of hospitalization was compared in the POAF and non-POAF groups.

Statistical analysis

The normality distribution of all variables was checked with the Shapiro-Wilk test. Data are presented as mean (standard deviation [SD]) or median values (interquartile range [IQR]) as appropriate. Group comparison was conducted using a t-test or Mann–Whitney U test for continuous data depending on distribution, and an exact Fisher test for categorical variables. A receiver operating characteristics (ROC) curve was plotted to establish a cut-off point of variables in the POAF group vs. the non-POAF group. The area under the curve (AUC) of the ROC curve of more than 0.60 was regarded as good discrimination. The univariable logistic regression was used to discriminate significant prognostic factors of POAF. The multivariable logistic regression analysis model included the variables with the *P*-value logistic regression (p[LR]) <0.2 and information value (IV) >0.3 in the univariable model. IV was derived by statistical quantitative analysis of data based on information theory. We used a combined model of IV and p(LR) to predict POAF occurrence. The multivariable models were divided into three models: preoperative, surgical, and echocardiographic. These results were shown as odds ratio (OR) with 95% confidence intervals (CI). Neopterin concentration was analyzed both as continuous and dichotomous variables (the cut-off value derived from ROC curve analysis). *P*-values <0.05 were considered statistically significant. Statistical analysis was performed using Statistica 12 and PQStat 1.6.6.

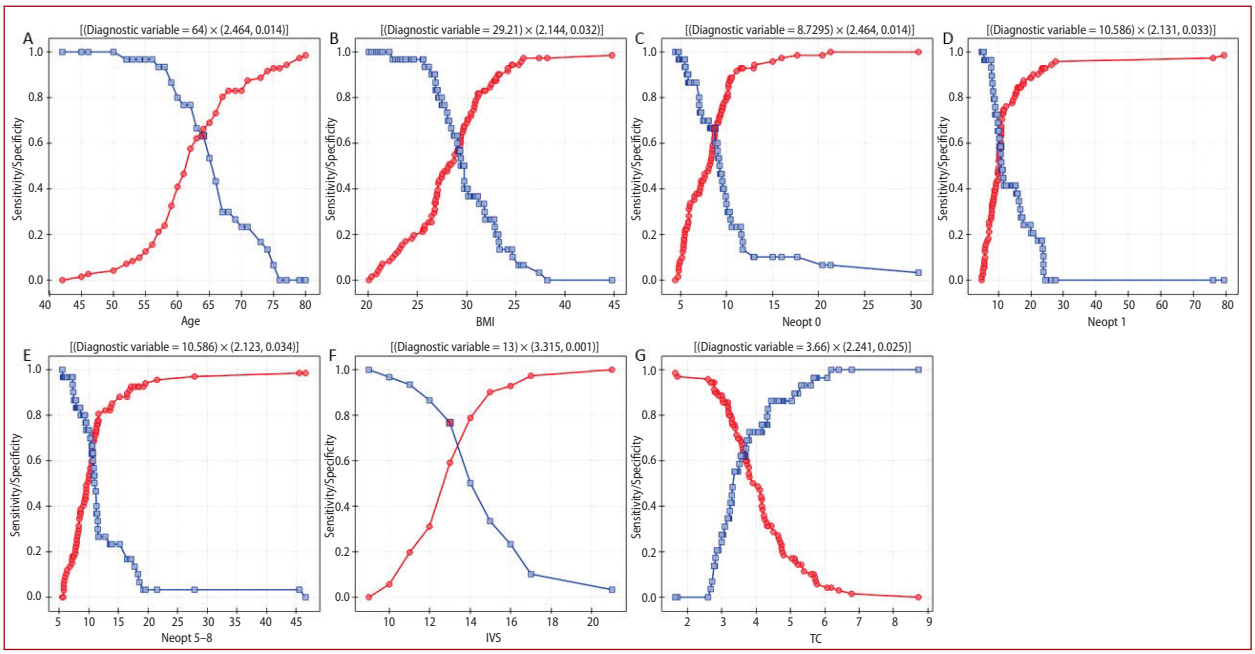

Figure 1. Cut-off values derived from receiver operating characteristic analyses. **A.** 64 years (area under the curve [AUC], 0.66; 95% confidence interval [CI], 0.54–0.77) for age; **B.** 29.2 kg/m^2 (AUC, 0.64; 95% CI, 0.52–0.75; $P = 0.03$) for body mass index; **C.** 8.7 nmol/l (AUC, 0.66; 95% CI, 0.54–0.77) for neopterin concentration before operation (Neopt0); **D.** 10.6 nmol/l (AUC, 0.64; 95% CI, 0.52–0.75) for neopterin concentration 1 day after operation (Neopt1); **E.** 10.6 (AUC, 0.64; 95% CI, 0.52–0.75) for neopterin concentration between 5 and 8 days after operation (Neopt5–8); **F.** 13 mm (AUC, 0.71; 95% CI, 0.6–0.82) for interventricular septum (IVS), and **G.** 3.7 mM/l (AUC, 0.64; 95% CI, 0.52–0.77) for total cholesterol concentration (TC)

RESULTS

The mean age in the study group was 62.6 (7.3) years. POAF occurred in 30 patients (30%). Most patients experienced the onset of POAF on the second (n = 13, 43%) and third (n = 9, 30%) postoperative days, while in two patients (7%) POAF occurred on the fourth day, and on the first, sixth, seventh, ninth, tenth, and thirteenth day each in one patient (20%). In 10 patients (33.3%) recurrence of POAF was observed. The median duration time of POAF was 7 (2.5–18) hours. In four patients (13.3%), POAF lasted longer than 48 hours. In two of them (6%) oral anticoagulants (antagonists of vitamin K) were introduced. Twenty-seven (90%) patients with POAF received intravenous amiodarone; in three patients (10%), POAF resolved spontaneously without any additional treatment, and in one patient (3%), electrical cardioversion was successfully performed. No sustained ventricular arrhythmias were observed during the postoperative period. Fifteen (15%) patients underwent surgery with CPB. All patients were in sinus rhythm at the time of hospital discharge.

In the intergroup comparison (the POAF group vs. the non-POAF group), statistically significant factors associated with POAF included higher neopterin concentration before operation (NP0, Figure 1; Supplementary material, *Figure S1*), on the first day after operation (NP1, Figure 1; Supplementary material, *Figure S1*) and between the fifth and eighth day after operation (NP5–8, Supplementary material, *Figure S1*); older age, higher body mass index, lower total cholesterol concentration (T-chol), higher diastolic interventricular septum thickness (IVSd), pulmonary disease, left atrial (LA) diastolic dimension (Tables 1–3). Neither hs-CRP concentration before operation nor hs-CRP concentration after operation showed any difference in the POAF group vs. the non-POAF group (Table 3). There was no significant difference in neopterin concentration concerning the operation method: on-pump vs. off-pump (Table 3). Moreover, neither the number of coronary arteries involved nor SYNTAX Score II differed markedly between the POAF and non-POAF subset of surgically treated individuals (Table 2).

The cut-off value derived from ROC curve analysis was 8.7 nmol/l (AUC, 0.66; 95% CI, 0.54–0.77; $P = 0.01$) for NP0, 10.6 nmol/l (AUC, 0.64; 95% CI, 0.52–0.75; $P = 0.03$) for NP1, and 10.6 nmol/l (AUC, 0.64; 95% CI, 0.52–0.75; $P = 0.03$) for NP5-8; 64 years (AUC, 0.66; 95% CI, 0.54–0.77; $P = 0.01$) for age; 29.2 kg/m^2 (AUC, 0.64; 95% CI, 0.52–0.75; $P = 0.03$) for body mass index (BMI); 3.7 nmol/l (AUC, 0.64; 95% CI, 0.52–0.77; $P = 0.03$) for T-chol concentration; and 13 mm (AUC, 0.71; 95% CI, 0.6–0.82; $P < 0.001$) for IVSd (Figure 1).

In univariate logistic regression analysis significant predictive factors of POAF were: NP0, NP0 cut-off >8.7 nmol/l, BMI, age, T-chol, history of pulmonary disease, IVSd, left ventricular diastolic dimension (LVd), ascending aorta diameter (Ao asc), LA and duration of operation (Table 1; Supplementary material, *Figure S1*).

Stepwise multivariable logistic regression analysis, adjusted for BMI, age, T-chol, and pulmonary disease identified NP0 (OR, 1.19; 95% CI, 1.02–1.38 for continuous and

Table 3. Comparison of neopterin and high sensitivity C-reactive protein (hs-CRP) concentrations before operation (NP0, hs-CRP0), on the first day (NP1, hs-CRP1), and between the fifth and eighth day after operation (NP5–8, hs-CRP5–8) in patients with postoperative atrial fibrillation (POAF) vs. without POAF and with cardiopulmonary bypass (CPB, on-pump) vs. without CPB (off-pump)

	POAF group (n = 30)	Non-POAF group (n=71)	*P*-value	On-pump group (n = 15)	Off-pump group (n = 86)	*P*-value
NP0, nmol/l, median (IQR)	9.2 (7.0–10.4)	8.0 (5.8–9.5)	0.01	6.5 (5.3–9.6)	8.5 (6.0–10.0)	0.18
NP1, nmol/l, median (IQR)	10.9 (9–17.5)	10.0 (7.1–11.7)	0.03	10.3 (7.2–15.0)	10.2 (8.2–15.2)	0.84
NP5-8, nmol/l, median (IQR)	11.0 (9.5–12.8)	9.6 (7.9–11.3)	0.03	9.3 (7.1–14.0)	10.5 (8.3–11.5)	0.22
hs-CRP, nmol/l, median (IQR)	1.4 (0.06–5.0)	1.4 (0.2–3.1)	0.69	1.1 (0.06–5.0)	1.5 (0.1–3.3)	0.32
hs-CRP1, nmol/l, median (IQR)	19.5 (15.6–33.2)	19.0 (15.1–26.0)	0.70	21.2 (17.1–41.1)	19.1 (15.1–26.0)	0.48
hs-CRP5-8 , nmol/l, median (IQR)	17.1 (8.5–21.0)	15.5 (12.0–19.6)	0.79	14.6 (9.5–23.0)	15.8 (11.8–19.6)	0.92

Abbreviations: IQR, interquartile range; other — see Table 1

Table 4. Multivariable logistic regression models for postoperative atrial fibrillation (POAF) following coronary artery bypass grafting (CABG)

	NP0 continuous	NP0 dichotomous (>8.7 nmol/l)
	OR (95% CI)	OR (95% CI)
Preoperative factors		
NP0	1.19 (1.02–1.38)	3.75 (1.39–10.1)
BMI, kg/m^2	1.15 (1.02–1.29)	1.14 (1.02–1.29)
Pulmonary disease	6.72 (1.57–28.74)	6.52 (1.51–28.19)
Age, years	1.05 (0.97–1.13)	1.06 (0.98–1.15)
T-chol	0.73 (0.43–1.23)	0.74 (0.43–1.26)
Surgical factors		
NP0	1.18 (1.0–1.02)	3.5 (1.41–8.66)
Duration of operation	1.01 (1.03–1.36)	1.00 (0.99–1.02)
Echocardiographic factors		
NP0	1.13 (0.97–1.31)	3.26 (1.26–8.4)
IVSd	1.45 (1.14–1.83)	1.42 (1.11–1.81)
LVd	1.06 (0.97–1.16)	1.06 (0.97–1.16)
Ao (asc)	1.00 (0.93–1.09)	0.99 (0.91–1.07)
LA	1.04 (0.94–1.16)	1.06 (0.95–1.17)

Abbreviations: LVd, diastolic dimension of the left ventricle; NP0: concentration of neopterin before operation; OR, odds ratio; other — see Tables 1 and 2

OR, 3.75; 95% CI, 1.39–10.1 for cut-off >8.7 nmol/l) as an independent predictor of POAF (Table 4). After adjustment for echocardiographic factors, NP0 >8.7 nmol/l was also an independent predictive factor (OR, 3.26; 95% CI, 1.26–8.4; Table 4), as well as after adjustment for surgical factors (OR, 1.18; 95% CI, 1.0–1.02 for NP0 continuous and OR, 3.5; 95% CI, 1.41–8.66 for NP0 >8.7 nmol/l, Table 4). Other independent predictors of POAF were BMI, pulmonary disease, IVSd, and duration of operation (Table 4).

In-hospital mortality was 0%. Postoperative complications occurred in 38 (38%) patients. The length of hospitalization was significantly longer in the POAF group (10 [7–13] days) vs. the non-POAF group (8 [7–9] days; *P* <0.01). The most common complication was postoperative wound infections (14% of patients). In the POAF group compared to the non-POAF group, all postoperative complications combined (*P* <0.001; OR, 9.5; 95% CI, 3.5–25.2), wound infections (*P* <0.001; OR, 8.4; 95% CI, 2.4–29.6), all infections combined (*P* <0.001; OR, 7.2; 95% CI, 2.38–21.9), and cognitive impairment (*P* = 0.02; OR, 6.9; 95% CI, 1.3–37.9) occurred significantly more frequently. All observed postoperative complications in the POAF and non-POAF groups are presented in Table 5.

DISCUSSION

In our series of patients, postoperative atrial fibrillation occurred in 30 subjects (30%), which is consistent with the incidence of POAF after elective CABG reported in other studies with continuous rhythm monitoring [2]. The use of CPB did not significantly affect the incidence of POAF, which may indicate that inflammation associated with surgical trauma itself, change of pressures in the atria, volume overloading, activation of the sympathetic nervous system, patient comorbidities, as well as atrial remodeling have a greater influence on POAF development than a surgical technique. This supports findings from the study by Kim et al. [13], in which no difference in nicotinamide adenine dinucleotide phosphate (NADPH) activity before and after CPB use was observed. In addition, in the current study, neopterin concentration also did not significantly differ

Table 5. Postoperative complications in the postoperative atrial fibrillation (POAF) group vs. the non-POAF group

	POAF group (n = 30)	non-POAF group (n = 71)	*P*-value
All postoperative complications combined, number of patients (%)	22 (73)	16 (23)	<0.001
Length of hospitalization, days, median (IQR)	10 (7–13)	8 (7–9)	0.01
Packed red blood cell concentrate, n	2 (0–2)	1 (0–2)	0.45
Temperature ≥38°C, n (%)	2 (7)	2 (3)	0.58
All infections combined, n (%)	12 (40)	6 (8)	<0.001
postoperative wound infection, n (%)	10 (33)	4 (6)	<0.001
other infections (*Clostridium difficile*, urinary tract infection, pleural abscess, or pneumonia), n (%)	2 (7)	2 (3)	0.58
Prolonged antibiotic therapy, n (%)	7 (23)	6 (8)	0.05
Cognitive impairment, n (%)	5 (17)	2 (3)	0.02
Pericardial effusion or tamponade, n (%)	3 (10)	2 (3)	0.15
Hemofiltration, n (%)	1 (3)	1 (1)	0.51
Pleural effusions, n (%)	4 (13)	4 (6)	0.23
Acute heart failure, n (%)	3 (10)	1 (1)	0.08
Other complications: increased ALAT or ASPAT >8 × ULN			
Acute limb ischemia, pneumothorax, n (%)	2 (7)	2 (3)	0.58

Abbreviations: ALAT, alanine transaminase; ASPAT, aspartate transaminase; ULN, upper limit of normal; other — see Table 1

in the on-pump group compared to the off-pump group. However, in the previous study, CPB use was shown to be associated with higher postoperative neopterin concentration when compared to the off-pump group [30]. In the literature, four studies were designed to evaluate neopterin concentration in relation to non-operative atrial fibrillation (AF) [31–34]. In these reports, a higher concentration of neopterin was found in patients with AF compared to those without arrhythmia. However, to the best of our knowledge, the association of neopterin concentration with POAF occurrence after CABG has never been investigated. In the current study, we have documented a higher concentration of neopterin (NP0, NP1, and NP5–8) in patients with the new onset of AF compared to patients without POAF development following elective CABG. Furthermore, a stepwise multivariable analysis adjusted for age, BMI, T-chol, history of pulmonary disease, echocardiographic parameters, and surgical factors, showed NP0 as a significant factor in the prediction of POAF. These results indicate that inflammation plays an important role in POAF development. Similarly, in a recent large cohort study, a higher neopterin concentration after adjustment for age, sex, BMI, creatinine, current smoking, diabetes mellitus, systemic hypertension, as well as hs-CRP level was an independent predictor of non–operative AF. The limitation of the mentioned study is that none of the echocardiographic nor electrocardiographic variables were included in the analysis [31]. In our study, apart from elevated preoperative neopterin concentration, significant independent factors of POAF included a thicker interventricular septum (IVS), higher BMI, and a history of pulmonary disease. In addition, the efficacy of electrical cardioversion of non-operative atrial fibrillation was higher in non-obese patients compared to the obese group [35]. While higher BMI and pulmonary disease are well-established predictive factors of POAF, a thicker IVS as a predictor of POAF has not been widely described in the literature [36, 37]. Thus, even though in the current study the diagnosis of systemic hypertension was not identified as a predictive factor of POAF, we speculate that a higher diastolic IVS dimension might be a marker of uncontrolled systemic hypertension and may be a better prognostic factor of the arrhythmia. Among surgical factors, in the univariate analysis, the duration of operation had the highest predictive value of POAF. Preoperative, as well as postoperative white blood cell (WBC) count, was found higher in patients with POAF in one study, but WBC count as a predictive factor of POAF was not confirmed in other studies [8]. Moreover, it has been found previously that CRP was a predictive factor of non-operative AF [9], while results of studies evaluating the impact of CRP concentration on POAF have been so far inconclusive [1, 10–12]. In the previous study, a synthesis-based review article, CRP and some other markers (e.g., BNP or interleukin 6) had controversial clinical utility in predicting POAF [13]. Thus, it should be stressed that of the laboratory parameters examined in the current study (such as hs-CRP, WBC, RDW, erythrocyte sedimentation rate, and creatinine concentration), only neopterin concentration (NP0, NP1, and NP5–8) was significantly higher in the POAF group compared to the non-POAF group, while T-chol concentration was lower in POAF group. According to the univariate analysis, NP0 concentration (continuous and cut-off >8.7) was the highest predictive value of POAF compared to NP1 and NP5–8 concentrations. The explanation why the preoperative concentration of neopterin was a better predictor of POAF than postoperative neopterin concentration, may be that other significant chronic factors existed before operation, such as age, left atrial or ventricular remodeling and patient comorbidities have a stronger influence on POAF occurrence than acute factors directly related to operation, such as CPB use or operation duration. All these chronic factors are potentially reflected by higher NP0 concentration. However, it is well known that blockade of the upregulated sympathetic nervous system during operation is of relevance too; therefore, in the current

study, most patients (82%) received beta-blockers before and after operation. According to our results, the POAF occurrence was associated with longer hospitalization, as well as postoperative complications. Interestingly, among them, the infective complications (P <0.001) and cognitive impairment (P = 0.02) were significantly more frequent in the POAF group compared to the non-POAF group, thus, we hypothesize these complications may be reflected by higher concentration of an inflammatory marker like neopterin. Contrary to the neopterin concentration, the concentration of CRP showed only a trend toward higher values in the POAF group but did not reach statistical significance, which indicates that neopterin may be a more accurate prognostic biomarker.

In summary, in terms of the multifactorial etiology of POAF and worse outcomes for patients who develop this type of arrhythmia, there is a great need to introduce a simple test to identify patients at the highest risk of POAF and implement additional preventive strategies such as administration of amiodarone. Thus, our findings have a clinical impact on the selection and further management of patients at the highest risk of POAF occurrence who should be treated with particular caution during the postoperative period. Therefore, we believe that a higher serum neopterin concentration before operation (cut-off value, 8.7 nmol/l) may help in the identification of patients at risk of POAF development.

Limitations

This study has several limitations that may have an impact on the findings. Firstly, the number of on-pump patients (15%) was relatively small, and any attempt to find detailed differences between coronary artery bypass grafting on the beating heart and in CPB would have been afflicted with likely bias. Therefore, it must be stressed that comparison between these groups was not the main purpose of our analysis. Secondly, evaluation of left atrial remodeling was presented exclusively as an anterior-posterior dimension of the left atrium measured on transthoracic echocardiography. We are aware of the fact that the left atrial volume is regarded to be a more specific parameter.

CONCLUSIONS

We found that neopterin concentration before operation adjusted for age, BMI, T-chol, pulmonary disease, echocardiographic parameters, and surgical factors may be POAF predictive. Regarding the highly complex pathophysiology of POAF, elevated preoperative serum neopterin concentration is one of the potential predictive factors of POAF.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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