Preoperative serum levels of interleukin-6 and interleukin-8 as predictors of the development of postoperative atrial fibrillation among patients undergoing coronary artery bypass grafting surgery

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Objectives
The aim of the study was to evaluate the ability of preoperative estimation of serum interleukins (IL-6 and IL-8) for predicting the possibility of development of postoperative atrial fibrillation (POAF) among patients who have undergone coronary artery bypass grafting (CABG) surgery.
Patients and methods
The study included 90 patients who underwent CABG, with a mean age of 63.8 ± 4.7 years. All patients underwent on-pump surgery with a mean aortic cross-clamping time of 65.9 ± 14.6 min and a mean cardiopulmonary bypass (CPB) time of 99.1 ± 19.7 min. Preoperative blood samples were collected for enzyme-linked immunosorbent assay estimation of serum IL-6 and IL-8 levels.
Results
After CABG surgery, 24 patients developed POAF (26.7%); five were female and 19 were male with a mean age of 64.1 ± 5.2 years. Four patients had a history of previous atrial fibrillation (AF), whereas 20 patients had no history of preoperative AF. Mean aortic clamping and CPB times were significantly longer in POAF patients compared with AF-free patients. Mean preoperative serum IL-6 and IL-8 levels were significantly higher in patients compared with controls, with significantly higher levels in POAF patients compared with AF-free patients. There was a positive significant correlation between the occurrence of POAF and history of preoperative AF, preoperative serum levels of IL-6 and IL-8, and aortic clamping and CPB times. Regression analysis defined elevated serum levels of IL-6 and IL-8, prolonged aortic clamping and CPB times, and history of preoperative AF as predictors of the occurrence of POAF among patients undergoing CABG in decreasing order of significance.
Conclusion
Inflammatory factors play a prominent role in the pathogenesis of POAF; high preoperative serum levels of IL-6 and IL-8 could aid in identification of patients liable to develop POAF, especially when associated with prolonged clamping time or preoperative history of AF.

Keywords:
coronary artery bypass grafting surgery, postoperative atrial fibrillation, preoperative interleukin-6 and interleukin-8 levels

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Introduction

Atrial fibrillation (AF) is still considered the most common form of arrhythmia occurring after cardiac surgery with varying incidence depending on the type of surgery and patients' preoperative data. It generally occurs between 24 and 96 h postoperatively, with a peak incidence on the second postoperative day. AF occurs in ~28–33% of patients undergoing coronary artery bypass grafting (CABG) and in 30–63% of those operated upon for coexisting ischemic heart and valve disease. AF is often temporary and disappears after the recovery of mechanical and metabolic functions [1–3].

With continuous ECG monitoring, the incidence of AF after CABG reported in previous studies and varying from 10 to 50% has not decreased despite improvements in anesthetic and surgical techniques. Furthermore, AF potentially leads to complications, including stroke, extended duration of hospitalization, and higher incidence of readmissions, increasing the cost of hospitalization and the incidence of postoperative morbidity and mortality after cardiac surgery [4,5].

The identification of risk factors for developing postoperative atrial fibrillation (POAF) has produced inconsistent results, with the exception of increasing age, and the prediction quality has seldom been assessed. A clinically useful prediction model for

POAF in CABG patients is still lacking. If patients at high risk of developing POAF could be identified, prophylactic efforts would be more focused. With targeted treatment such as antiarrhythmic medication or atrial pacing, possible side effects could be avoided in patients not likely to benefit from this treatment [6–8].

The pathogenesis of POAF is complex and multifactorial and includes preoperative, intraoperative, and postoperative factors. These involve excessive catecholamine production, postoperative autonomic imbalance, mobilization of interstitial fluid resulting in changes in intravascular volume status, and neurohumoral changes. The leading causes of POAF include ischemic myocardial injury due to hypotension and inadequate cardioprotection, postincision surgical trauma, and handling of the heart, local inflammation, temporarily reduced left ventricular function after surgery, and increased left atrial pressure due to anesthesia [9].

Electrophysiological studies have shown that most paroxysms of AF are initiated by rapid focal arrhythmias originating in the region of the pulmonary veins. Inflammatory changes have been reported in the atria in some patients with focal tachycardias. In addition, atrial biopsy specimens in some patients with idiopathic paroxysmal AF refractory to antiarrhythmic therapy showed marked inflammatory infiltrates, myocyte necrosis, and fibrosis. These findings may point to underlying inflammatory mechanisms involving the atria and/or the region of the pulmonary veins that might trigger focal tachyarrhythmias and induce proarrhythmic structural and electrical changes that could increase the propensity to AF in these patients [10,11].

The current prospective comparative study was designed to evaluate the predictability of preoperative estimation of serum interleukins (IL-6 and IL-8) in the development of POAF among patients undergoing CABG surgery.

Patients and methods

The current study was conducted at the Departments of Cardiosurgery and Anesthesia, Naser Insurance Institute, from January 2011 to February 2013. After approval of the study protocol by the Local Ethical Committee and obtaining fully informed written consent from patients, consecutive patients assigned for isolated elective coronary revascularization surgery with cardiopulmonary bypass (CPB) were enrolled in the study. Exclusion criteria included the presence of preoperative heart failure, cardiogenic shock, surgery other than CABG, or combined surgery (CABG + valve surgery). Immunocompromised patients, patients maintained on immunosuppressant drugs, or patients who had a history of previous thromboembolic diseases were also excluded from the study.

The study also included 10 apparently healthy sex-matched and age-matched individuals chosen from those attending the hospital blood bank for blood donation and who had passed the preliminary blood bank investigations; these 10 individuals were considered as control for the serum cytokine levels.

Preoperative data included age, sex, smoking, associated medical conditions, and preoperative history of previous AF. Intraoperative data included aortic cross-clamp time and CPB time. Arrhythmia incidence was monitored during the first 3 postoperative days using 72-h Holter ECG recording, and the frequency of occurrence of POAF was determined.

Preoperative blood samples (5 ml) were collected under complete aseptic conditions at the time of induction of anesthesia, transferred to clean dry tubes, and allowed to clot; serum was then separated in clean dry Eppendorf tubes to be stored at -80°C until assayed for the estimation of serum IL-6 [12] and IL-8 levels [13] using an ELISA kit.

Patients who developed AF after CABG surgery were classed under one group, the 'POAF group', and those who did not develop AF were classed under another group, the AF-free group.

Statistical analysis

Data obtained were presented as mean ± SD, ranges, numbers, and ratios. Results were analyzed using the Wilcoxon rank-sum test for unrelated data (*Z*-test) and the χ^2-test. Possible relationships were investigated using Pearson's linear regression. Regression analysis using the stepwise method was used for evaluation of the independent predictors for the possibility of occurrence of POAF. Statistical analysis was conducted using the SPSS (version 15, 2006) for Windows statistical package. *P*-values less than 0.05 were considered statistically significant.

Results

The study included 90 patients who underwent CABG; 70 (77.8%) were male and 20 (22.2%) were female, with a mean age of 65.6 ± 7.1 years (range 49–82 years). All patients had additional preoperative morbidities in varied combinations; 65 patients were dyslipidemic with high serum total cholesterol level and low serum high-density lipoprotein level as indicated by routine preoperative investigations, 42 (46.7%) patients were

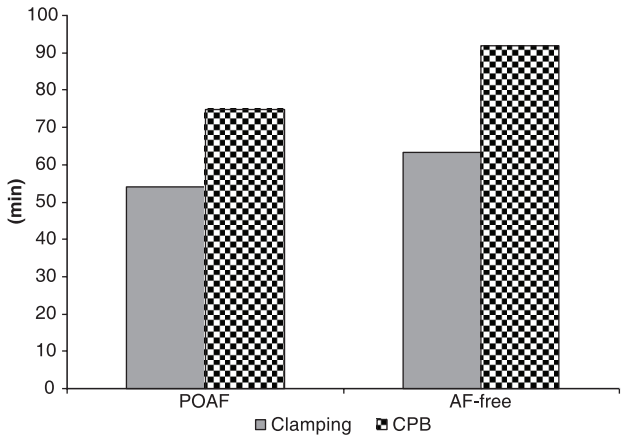
hypertensive, 37 (41.1%) patients were diabetics, and four (4.4%) patients had a history of preoperative AF. Of the studied patients, four patients (4.4%) had single-vessel disease, 23 patients (25.6%) had two-vessel disease, and 63 patients (70%) had three-vessel disease with a mean number of 2.7 ± 0.6 occluded vessels (range 1–3 vessels; Table 1). All patients underwent conventional on-pump CABG surgery with a mean aortic cross-clamping time of 65.9 ± 14.6 (range 45–95 min) and mean CPB time of 99.1 ± 19.7 (range 70–165 min).

During the study period, 24 patients developed POAF (POAF group) with a frequency of 26.7%. Five women and 19 men developed POAF with a mean age of 67 ± 8.3 years (range 49–82 years). Four patients had a history of previous AF, whereas 20 patients were preoperatively free. Patients with POAF were nonsignificantly older than AF-free patients. However, mean aortic clamping and CPB times were significantly longer in POAF patients compared with AF-free patients (Table 2; Fig. 1).

Mean preoperative serum IL-6 and IL-8 were significantly ($P < 0.05$) higher in patients compared with controls, with significantly ($P < 0.05$) higher preoperative serum levels of IL-6 (Fig. 2) and IL-8 (Fig. 3) in patients who developed POAF compared with AF-free patients (Table 3).

There was a positive significant correlation between the occurrence of POAF and history of preoperative AF, preoperative serum levels of IL-6 and IL-8, and aortic clamping and CPB times (Table 4). Regression analysis for verification of these parameters as predictors of the possibility of occurrence of POAF defined elevated serum levels of IL-6 as a significant predictor in five models, elevated serum levels of IL-8 in four models, prolonged aortic clamping time in three models, prolonged CPB time in two models, and history of preoperative AF in one model (Table 5).

Figure 1



Mean aortic clamping and CPB times of studied patients categorized according to the occurrence of POAF. AF, atrial fibrillation; CPB, cardiopulmonary bypass; POAF, postoperative atrial fibrillation.

Discussion

The incidence of POAF in this study was 26.7% among CABG patients. The frequency was in

Table 1 Patients' enrollment data

Data	Findings
Age (years)	
Strata	
<60	
N (%)	17 (21.1)
Mean ± SD	56.5 ± 2.9 (49–59)
60–69	
N (%)	62 (66.7)
Mean ± SD	65.2 ± 2.9 (60–69)
70–79	
N (%)	4 (4.4)
Mean ± SD	74.1 ± 3.1 (70–78)
>80	
N (%)	7 (7.8)
Mean ± SD	80.9 ± 0.9 (70–82)
Total	65.6 ± 7.1 (49–82)
Sex [*N* (%)]	
Male	70 (77.8)
Female	20 (22.2)
Additional comorbidities [*N* (%)]	
Dyslipidemia	65 (72.2)
Hypertension	42 (46.7)
Diabetes mellitus	37 (41.1)
Atrial fibrillation	4 (4.4)
Number of occluded vessels [*N* (%)]	
One	4 (4.4)
Two	23 (25.6)
Three	63 (70)
Mean ± SD	2.7 ± 0.6

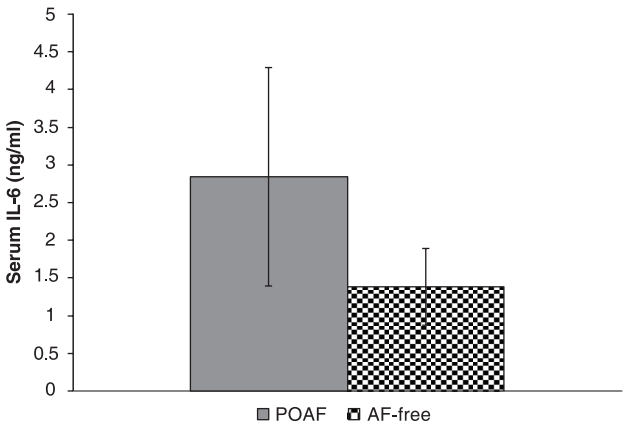
Data are presented as mean ± SD and numbers; ranges and percentages are in parentheses.

Table 2 Patients' characteristics and operative data categorized according to the frequency of postoperative atrial fibrillation

	POAF	AF-free
Number of patients [*N* (%)]	24 (26.7)	66 (73.3)
Age (years)	67 ± 8.3 (49–82)	65.1 ± 6.7 (53–82)
Sex (M : F)	19 : 5	51 : 15
Number of occluded vessels	2 ± 0.8 (1–3)	1.7 ± 0.8 (1–3)
Aortic cross-clamping time (min)	72.9 ± 15.5 (50–95)*	63.4 ± 13.4 (45–85)
CPB time (min)	114.9 ± 23.2 (89–165)*	93.4 ± 14.7 (70–120)

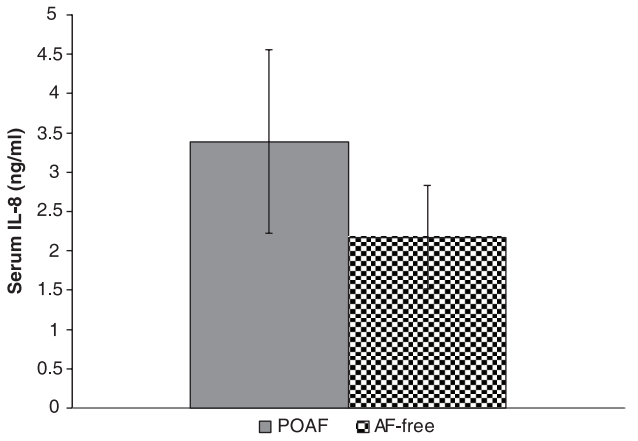
Data are presented as mean ± SD and numbers; ranges and percentages are in parentheses; AF, atrial fibrillation; CPB, cardiopulmonary bypass; POAF, postoperative atrial fibrillation.

Figure 2



Mean (±SD) preoperative serum level of IL-6 in studied patients categorized according to the development of POAF. AF, atrial fibrillation; IL-6, interleukin-6; POAF, postoperative atrial fibrillation.

Figure 3



Mean (±SD) preoperative serum level of IL-8 in studied patients categorized according to the development of POAF. AF, atrial fibrillation; IL-8, interleukin-8; POAF, postoperative atrial fibrillation.

Table 3 Mean pre-operative serum IL-6 and IL-8 levels estimated in studied patients categorized according to occurrence of POAF compared to control levels

	IL-6 (ng/ml)	IL-8 (ng/ml)
Control (*n*=10)	0.446 ± 0.142 (0.216–0.68)	0.324 ± 0.142 (0.216–0.68)
AF-free (*n*=66)	1.386 ± 0.51 (0.66–2.76)*	2.17 ± 0.66 (1.45–4.32)*
POAF (*n*=24)	2.84 ± 1.45 (0.76–6.73)*†	3.39 ± 1.17 (1.78–6.13)*†

Data are presented as mean ± SD and numbers; ranges and percentages are in parentheses; *significance versus controls; †significance versus AF-free; AF, atrial fibrillation; IL, interleukin; POAF, postoperative AF.

Table 4 Correlation coefficient between frequency of atrial fibrillation and preoperative and operative data

	r	*P*
Age	0.157	>0.05
Male sex	0.120	>0.05
Preoperative AF	0.434	<0.001
Preoperative IL-6 level	0.552	<0.001
Preoperative IL-8 level	0.604	<0.001
Aortic clamping time	0.299	0.004
CBP time	0.486	<0.001

AF, atrial fibrillation; CPB, cardiopulmonary bypass; IL, interleukin; *r*, correlation coefficient; $P < 0.05$, significant difference.

Table 5 Regression analysis for evaluated parameters as predictors of postcoronary artery bypass grafting atrial fibrillation

	β	*T*	Significance (*P*)
Model 1			
History of preoperative AF	0.220	3.154	0.002
High preoperative serum IL-6	0.340	4.538	<0.001
High preoperative serum IL-8	0.306	4.384	<0.001
Prolonged CPB time	0.221	3.211	0.002
Prolonged aortic clamping time	0.241	3.362	0.001
Model 2			
High preoperative serum IL-6	0.392	4.900	<0.001
High preoperative serum IL-8	0.329	4.670	<0.001
Prolonged CPB time	0.221	3.066	0.003
Prolonged aortic clamping time	0.264	3.285	0.001
Model 3			
Prolonged aortic clamping time	0.269	3.194	0.002
High preoperative serum IL-6	0.399	4.765	<0.001
High preoperative serum IL-8	0.355	4.834	<0.001
Model 4			
High preoperative serum IL-6	0.532	6.973	<0.001
High preoperative serum IL-8	0.388	5.084	<0.001
Model 5			
High preoperative serum IL-6	0.604	7.104	<0.001

β, standardized coefficient; AF, atrial fibrillation; CPB, cardiopulmonary bypass; IL, interleukin; $P < 0.05$, significant difference.

agreement with that previously reported by Mariscalco and Engström [14], who reported that the overall incidence of AF was 25.6%, ranging from 22.7% for CABG to 44% for a combination of CABG and aortic valve replacement. However, recent studies reported discrepant frequencies concerning POAF; Ben Ahmed *et al.* [15] reported an incidence of 9.8%, whereas Helgadottir *et al.* [16] reported an incidence of 44%. This difference could be attributed to the constitutional, preoperative, and operative parameters of studied patients and the sample size in these studies.

In contrast, El-Chami *et al.* [17] retrospectively determined an incidence of POAF of 18.83% among patients who underwent cardiac revascularization surgery over a period of 15 years.

The current study evaluated the predictive significance of preoperative estimation of IL-6 and IL-8 to exclude the effect of operative stress and surgical manipulations on these parameters. In hand with preoperative estimations, Kinoshita *et al.* [18] found that high preoperative C-reactive protein (CRP) level

is independently associated with the occurrence of AF after isolated off-pump coronary bypass surgery.

Patients who developed POAF had significantly higher preoperative serum IL-6 and IL-8 levels in comparison with controls. Moreover, there was a positive correlation between serum levels of these markers and occurrence of POAF. The data suggested an inflammatory basis for the possibility of development of POAF in patients undergoing CABG.

In line with the data, Guo *et al.* [19] and De Gennaro *et al.* [20] documented that there is plausible evidence linking inflammation to the initiation and perpetuation of AF and AF-related thrombosis. The proposed mechanisms linking inflammation and the prothrombotic AF state include endothelial activation/damage, production of tissue factor from monocytes, increased platelet activation, and increased expression of fibrinogen.

Sabol *et al.* [21] reported significantly higher levels of inflammatory markers in patients with POAF compared with patients with sinus rhythm but no significant differences in the levels of markers of oxidative stress; the data excluded oxidative stress as the underlying cause for the development of POAF and supported the assumption of an inflammatory basis for POAF. Nagashima *et al.* [22] reported increased epicardial adipose tissue volume and elevation of inflammatory biomarkers in AF patients, with significantly higher levels in persistent rather than paroxysmal AF patients. Cheng *et al.* [23] reported significantly higher levels of serum amyloid protein A, high-sensitivity CRP, tumor necrosis factor-a, IL-1, and IL-6 in AF patients compared with controls. The role of proinflammatory cytokines in pathogenesis of POAF was supported by Wu *et al.* [24]. They found that the concentration of serum IL-8 was significantly higher at 2 h and on the first and second postoperative days; there was also higher serum IL-10 levels on the first postoperative day in patients with postoperative AF. To substantiate the fact, Sezai *et al.* [25] found that landiolol and bisoprolol prevented postoperative AF and attributed their results to the anti-ischemic, anti-inflammatory, and antioxidant effects of these β-blockers.

We found that patients who developed POAF had significantly longer aortic clamping time and CPB time. In support of these findings, Koletsis *et al.* [26] found that the intraoperative factors that appeared to have a significant correlation with the occurrence of postoperative AF were CPB time longer than 120 min and myocardial ischemia index less than 0.27 ml m^2/kg min.

Regression analysis defined high preoperative serum IL-6 and IL-8 levels, aortic clamping and CPB times, and history of preoperative AF as predictors of the occurrence of POAF among patients undergoing CABG, in decreasing order of significance. In support of the high predictability of estimation of serum levels of inflammatory markers, especially IL-6, for the possibility of development of AF after CABG, Ucar *et al.* [27] reported that elevated serum levels of IL-6 and high-sensitivity CRP are associated with the development of POAF and predict prolonged ICU stay and intubation time. Kaireviciute *et al.* [28] found that high intracardiac levels of IL-6 in samples obtained from the right atrial appendage, left atrium, and left atrial appendage were associated with AF and suggested that an intracardiac inflammatory environment that manifests perioperatively may predispose to the development of postoperative AF. Hadi *et al.* [29] reported that IL-6 levels, CRP, and other cytokines may have a prognostic value in AF, whereas cytokine-lowering therapies, statins, angiotensin-converting enzyme inhibitors, and other anti-inflammatory agents may have a role in the treatment of AF.

The results of this study and review of literature suggest that inflammation plays a prominent role in the pathogenesis of post-CABG AF. High preoperative serum levels of IL-6 and IL-8 could aid in the identification of patients liable to develop POAF, especially when associated with prolonged clamping time or preoperative history of AF. We recommend large-scale studies for identification of cutoff points for these cytokines for identification of patients liable to develop POAF.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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