Relationship Between Early Post-Pericardiotomy Syndrome and Atrial Fibrillation After Cardiac Surgery

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ABSTRACT

Introduction: Post-operative atrial fibrillation (POAF) and post-pericardiotomy syndrome (PPS) are common complications of cardiac surgery. Both PPS and POAF are associated with increased morbidity, mortality, costs and length of stay after cardiac surgery. Inflammation is involved in the pathogenesis of both PPS and POAF; however, the relationship between PPS and POAF remains unclear. The aim of this study was to examine the relationship between early PPS and POAF in patients who underwent cardiac surgery.

Patients and Methods: Records of patients who underwent on-pump coronary artery bypass graft (CABG) surgery were retrospectively reviewed. A total of 60 consecutive patients who were diagnosed with POAF were included in the study, while 142 consecutive patients who were not diagnosed with POAF were included as controls.

Results: An early PPS development was significantly higher in patients with POAF than in patients without POAF (61.7% vs 45.8%, p= 0.04). Logistic regression analysis demonstrated that patients with POAF had 1.9-times increased risk for developing early PPS (OR, 1.9; 95% CI, 1.03-3.5; p= 0.04).

Conclusion: This study showed that POAF was associated with an increased incidence of early PPS in patients who underwent isolated CABG surgery. Therefore, patients with POAF should be closely monitored for the occurrence of early PPS.

Key Words: Post-pericardiotomy syndrome; post-operative atrial fibrillation; coronary artery bypass graft surgery

Kalp Cerrahisi Yapılan Hastalarda Erken Dönemde Gelişen Postperikardiyotomi Sendromu ve Atriyal Fibrilasyon Arasındaki İlişki

ÖZET

Giriş: Postoperatif atriyal fibrilasyon (POAF) ve postperikardiyotomi sendromu (PPS) kalp cerrahisinin sık görülen komplikasyonları arasında yer alır. POAF ve PPS uzamış yatış süreleri, yüksek morbidite ve mortalite oranları ve yüksek sağlık bakım maliyetleri ile ilişkili bulunmuştur. Her iki komplikasyonun da patogenezinde inflamasyon suçlanmakla birlikte, PPS ve POAF arasındaki ilişki açıklığa kavuşmamıştır. Bu çalışmanın amacı koroner baypas yapılan hastalarda, erken dönemde gelişen PPS ve POAF arasındaki ilişkiyi incelemektir.

Hastalar ve Yöntem: Kliniğimizde kardiyopulmoner baypas altında koroner baypas operasyonu yapılmış olan hastaların kayıtları retrospektif olarak incelendi. Takibinde POAF gelişmiş olan ardışık 60 hasta çalışmaya dahil edildi. Takiplerinde POAF gelişmeyen koroner baypas cerrahisi yapılmış ardışık 142 hasta kontrol grubuna dahil edildi.

Bulgular: POAF gelişen hastalarda, POAF gelişmeyen hastalarla karşılaştırıldığında erken PPS gelişme sıklığı anlamlı olarak daha yüksek bulunmuştur (%61.7 vs %45.8, p= 0.04). Lojistik regresyon analizinde, POAF gelişen hastalarda erken PPS gelişme riskinin daha fazla olduğu saptandı (Odds oranı 1.9, %95 güven aralığı 1.03-3.5, p= 0.04).

Sonuç: Çalışmamızda, izole koroner baypas ameliyatı yapılmış ve POAF gelişen hastalarda, erken PPS gelişim riskinin POAF gelişmeyen hastalarla karşılaştırıldığında daha fazla olduğu saptandı. POAF gelişen hastalar, erken PPS gelişimi açısından yakından takip edilmelidir.

Anahtar Kelimeler: Postperikardiyotomi sendromu; postoperatif atriyal fibrilasyon; koroner baypas

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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia that is encountered after cardiac surgery. Post-operative AF (POAF) is associated with increased morbidity, mortality, costs and length of stay after cardiac surgery. The reported incidence of new-onset POAF after coronary artery bypass graft (CABG) surgery range from 20% to 40%. However, the underlying mechanism remains unclear[1-5].

Post-pericardiotomy syndrome (PPS) also represents a common post-operative complication in cardiac surgery and remains an important cause of morbidity after cardiac surgery. PPS occurs in 10%-40% of patients after cardiac surgery[6-9]. In the first post-operative week, pericardial effusions are considered to occur from surgical bleeding. Pericardial effusions occurring for > 7 days after the surgery are usually associated with PPS and can result in cardiac tamponade, which may be life-threatening[7]. Although PPS pathogenesis remains unclear, PPS is considered to be an autoimmune phenomenon that results from an inflammatory response[10-14].

Several risk factors are associated with the development of POAF, including race (Caucasians), gender (male), aged > 60 years, history of AF, obesity, metabolic syndrome, hypertension (HT), thyroid disease, ischemic cardiomyopathy, chronic obstructive pulmonary disease (COPD), heart failure, withdrawal of beta-blockers or angiotensin-converting enzyme inhibitors, mitral valve disease, left atrial enlargement, cardiopulmonary bypass (CPB), pre-operative digoxin use and a high EuroSCORE rating[15].

Previous studies suggested a relationship between systemic inflammation and POAF[16]. PPS is also considered to result from an inflammatory response. Thus, we hypothesised that early PPS is related to new-onset AF after CABG surgery. To the best of our knowledge, this is the first study to examine the relationship between AF and PPS.

PATIENTS and METHODS

Study Population

This study was approved by the local ethics committee and complies with the requirements of the Declaration of Helsinki. We retrospectively reviewed the medical records of patients who underwent first-time CABG surgery with CPB between January 2011 and June 2015. The study group included 60 consecutive patients who developed AF after first-time CABG surgery with CPB. The control group comprised 142 consecutive patients who did not develop AF after first-time CABG surgery with CPB.

The exclusion criteria were as follows: (1) haematological disorders, (2) rheumatic heart disease, (3) thyroid disorders, (4) redo-CABG, (5) off-pump CABG, (6) no post-operative echocardiography available, (7) presence of active or chronic inflammatory or autoimmune diseases, (8) left atrial enlargement (> 4.5 cm), (9) history of arrhythmia, (10) moderate or severe mitral regurgitation, (11) patients who died within 2 weeks of surgery and (12) post-operative effusion in the first week after surgery.

The diagnosis of PPS was established when patients met two of the five following criteria: unexplained post-operative fever persisting beyond the first post-operative week (without alternative causes), pleuritic chest pain, pericardial or pleural friction rub, new pleural effusion and new pericardial effusion after surgery[7]. Although not considered as an independent diagnostic criterion, elevated systemic inflammation marker levels (such as C-reactive protein and erythrocyte sedimentation rate) were used to diagnose PPS. POAF was defined as the presence of AF on the echocardiogram (ECG), lasting for > 30 s.

Diabetes mellitus was defined as having a fasting plasma glucose level of ≥ 126 mg/dL or a treatment with an insulin or a hypoglycaemic agent. HT was defined as the systolic blood pressure of > 140 mmHg, diastolic blood pressure of > 90 mmHg or the use of an antihypertensive medication. Hyperlipidaemia was defined as the total serum cholesterol (TC) level of ≥ 200 mg/dL and/or low-density lipoprotein cholesterol level of ≥ 130 mg/dL and/or triglyceride level of ≥ 200 mg/dL and/or a history of current use of lipid-lowering regimen.

Low cardiac output syndrome (LCOS) was diagnosed if the patient required an intra-aortic balloon pump in the operating room or intensive care unit (ICU) because of a haemodynamic compromise. LCOS was also diagnosed if the patient required an inotropic medication to maintain the systolic blood pressure of > 90 mmHg for at least 30 min in ICU, after optimising the preload and afterload and correcting all the electrolyte and blood gas abnormalities[17]. Severe right coronary artery stenosis was defined as a lesion of ≥ 70%.

Surgical Technique

All procedures were performed with median sternotomy using general anaesthesia. Standard non-pulsatile CPB with a roller pump and membrane oxygenator was used. CPB was established between the ascending aorta and right atrium using a dual-stage venous cannula. Intermittent antegrade/retrograde blood cardioplegia and systemic hypothermia (28°C) were used. The left internal mammary artery was used for surgical revascularization of the left anterior descending artery in all cases. Concentrated erythrocyte suspensions were added to a pump prime volume if a haematocrit level of > 20% during CPB was to be maintained. The mean arterial pressure during CPB was stabilised between 50 and 70 mmHg.

Data Collection

Demographic, clinical and laboratory parameters were collected from the medical records of patients. All chest X-Rays and ECGs were reassessed. The temperatures of patients were obtained from their charts.

Transthoracic echocardiography and chest X-Ray were performed before discharge and on post-operative day 15 ± 1 for all patients as a part of a standard protocol for post-operative management. The existence of a pericardial effusion was determined using echocardiography. In our hospital, pericardial effusion is evaluated in all available echo windows and is measured during the diastolic cardiac phase. The existence of a pleural effusion was determined using chest X-Ray.

In all patients, aspirin was discontinued 1 week prior to the surgery and was resumed within 6-12 h after the surgery. Patients were not post-operatively administered NSAIDs.

Statistical Analysis

Statistical analysis was conducted using the SPSS version 17 (SPSS Inc Chicago, IL, USA) for Windows. All variables were investigated using visual (histograms and probability plots) and analytic methods (Kolmogorov-Smirnov test) to determine whether they are normally distributed. Continuous variables were reported as means and standard deviations for normally distributed variables and as medians and interquartile range for non-normally distributed variables. Categorical variables were presented using numbers and percentages.

A comparison between the two groups was performed using the chi-square test for qualitative variables, independent t-test for normally distributed continuous variables and Mann-Whitney U test for non-normally distributed continuous variables. Logistic regression analysis was performed to evaluate the relationship between PPS and POAF. P values of < 0.05 were considered statistically significant.

RESULTS

Study Population

Pre-operative characteristics of patients with POAF (n= 60; 54 males; mean age, 62.4 ± 9.3) and those without POAF (n= 142; 105 males; mean age, 57.4 ± 9.9) are presented in Table 1. Patients with POAF were significantly older (p= 0.001) and the percentage of males was found to be greater than patients without POAF (p= 0.01). A significantly higher incidence of COPD (p< 0.001), smoking (p= 0.02), metabolic syndrome (p= 0.005) and lower pre-operative ejection fraction (p= 0.03) were observed in patients with POAF than in those without POAF. In addition, a significantly lower incidence of beta-blocker usage (p= 0.04) and statin usage (p= 0.01) was observed in the pre-operative period in patients with POAF than in those without POAF. There were no statistically significant differences in other demographic characteristics between the two groups (Table 1).

Intra- and post-operative data of the patients are presented in Table 2. The occurrence of early PPS was significantly higher in patients with POAF than in those without POAF (61.7% vs 45.8%, p= 0.04). Emergency operation incidence (p= 0.01), number of transfusions (p< 0.001), post-operative bleeding (p< 0.001), incidence of re-exploration (p= 0.01), incidence of LCOS (p= 0.001), ventilation time (p< 0.001) and post-operative infection rates (p< 0.001) were significantly higher in patients with POAF than in those without POAF. A significantly longer ICU stay was observed for patients with POAF than for those without POAF (p= 0.001). Post-operative statin usage (p= 0.01) and post-operative beta-blocker usage

Table 1. Differences in clinical and biochemical characteristics of patients with respect to the presence or absence of post-operative atrial fibrillation

	POAF group (n= 60)	Control group (n= 142)	p
Age, years, mean ± SD	62.4 ± 9.3	57.4 ± 9.9	0.001
Gender, male, n (%)	54 (90)	105 (73.9)	0.01
HL, n (%)	33 (55)	58 (40.8)	0.06
HT, n (%)	35 (58.3)	97 (68.3)	0.17
DM, n (%)	14 (23.3)	44 (31)	0.27
COPD, n (%)	25 (41.7)	26 (18.3)	< 0.001
Smoking, n (%)	47 (78.3)	88 (62)	0.02
Obesity, n (%)	21 (35)	45 (31.7)	0.64
BMI, kg/m², median (IQR)	28.5 (26.6-31.2)	26.5 (27.8-30.7)	0.6
Metabolic syndrome, n (%)	32 (53.3)	46 (32.4)	0.005
EF, %, mean ± SD	50.5 ± 8.6	53 ± 7.1	0.03
Pre-operative statin usage, n (%)	56 (93.3)	141 (99.3)	0.01
Pre-operative B bloker, n (%)	57 (95)	141 (99.3)	0.045
Pre-operative ACE inhibitor usage, n (%)	53 (88.3)	132 (93)	0.28
Pre-operative CaCB usage, n (%)	8 (13.3)	16 (11.3)	0.68

p: p values for between-group comparisons, POAF: Post-operative atrial fibrillation, BMI: Body mass index, HL: Hyperlipidaemia, HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, EF: Ejection fraction, ACE: Angiotensin-converting enzyme, CaCB: Calcium channel blocker.

Table 2. Differences in intra- and post-operative clinical characteristics of patients with respect to the presence or absence of post-operative atrial fibrillation

	POAF group (n= 60)	Control group (n= 142)	p
Emergency operation, n (%)	6 (10)	3 (2.1)	0.01
Number of anastomoses, mean ± SD	3.4 ± 0.99	3.61 ± 1.03	0.36
CPB time, min, mean ± SD	95.4 ± 24.7	96.7 ± 24.5	0.73
Cross clamp time, min, mean ± SD	62.7 ± 19.4	63.9 ±18.8	0.67
Number of transfusions, mean ± SD	3.4 ± 1.9	2.2 ± 1.5	< 0.001
Bleeding, 24 h, median (IQR)	725 (500-1237.5)	550 (400-750)	< 0.001
Re-exploration n (%)	5 (8.3)	2 (1.4)	0.01
LCOS, n (%)	10 (16.7)	5 (3.5)	0.001
IABP, n (%)	3 (5)	2 (1.4)	0.13
Ventilation time, h, mean ± SD	11.4 ± 6	8 ± 3.6	< 0.001
Post-operative renal failure, n (%)	0	0	
Post-operative infection, n (%)	12 (20)	1 (0.7)	< 0.001
PPS, n (%)	37 (61.7)	65 (45.8)	0.04
ICU stay, days, mean ± SD	1.65 ± 1.2	1.2 ± 0.6	0.001
Hospital stay, days, mean ± SD	6.1 ± 1.4	5.8 ± 0.9	0.1
Post-operative statin usage, n (%)	55 (91.7)	140 (98.6)	0.01
Post-operative beta-bloker usage, n (%)	53 (88.3)	136 (95.8)	0.049
Post-operative ACEI usage, n (%)	57 (95)	139 (97.9)	0.26
Post-operative CaCB usage, n (%)	1 (1.7)	8 (5.6)	0.2

p: p values for between-group comparisons, POAF: Post-operative atrial fibrillation, CPB: Cardiopulmonary bypass, LCOS: Low cardiac output syndrome, IABP: Intra-aortic balloon pump, PPS: Post-pericardiotomy syndrome, ICU: Intensive care unit, ACEI: angiotensin-converting enzyme inhibitor, CaCB: Calcium channel blocker.

(p= 0.049) were significantly lower in patients with POAF than in those without POAF. There were no differences in the other characteristics of the patients.

Multivariate Analysis

Patients with POAF were found to have 1.9-times increased risk for developing early PPS (OR, 1.9; 95% CI, 1.03-3.5; p= 0.04).

DISCUSSION

In this study, patients with POAF were found to have 1.9-times increased risk for developing early PPS after CABG surgery. To the best of our knowledge, this is the first study to examine the relationship between early PPS and AF in patients who underwent CABG surgery.

Although PPS pathogenesis remains unclear, PPS is considered to be an immune-mediated inflammatory process that is triggered by a cardiac antigen exposure[10-12,18]. Previous studies showed the presence of an anti-heart antibody (AHA) at high titres in patients with PPS[10,18]. Myocardial muscle injury during surgery leads to a release of autoantigens. The release of these autoantigens can trigger host immune responses with the subsequent production of AHAs and immune complexes. Previous studies found a significant correlation between the development of PPS and increased immune complexes. They also demonstrated a significant correlation between post-operative AHA and increased immune complexes, suggesting a pathogenic role[18]. Furthermore, cardiac surgery with CPB initiates a systemic inflammatory response, and this may enhance the development of PPS[19].

The underlying mechanisms involved in the development of POAF are multifactorial, including ischaemia-reperfusion (IR) injury, surgical manipulations, autonomic imbalance in the post-operative period, excessive production of catecholamines, fluid shifts and oxidative stress[20-22]. Previous studies have also suggested a role of inflammation in the pathogenesis of AF. Inflammation was shown to lead to inhomogeneous atrial conduction and prolong atrial conductivity and contribute to electrical remodelling[21]. In addition, inflammation was shown to induce cellular degeneration, apoptosis and subsequent atrial fibrosis and dilation and lead to structural remodelling[23,24]. Major surgical trauma leads to systemic inflammatory responses[25,26]. CPB during cardiac surgery has been shown to exacerbate inflammatory responses that are induced by surgical stress and promote the release of different cytokines, particularly TNF-α, IL-1 and IL-6[27].

The elevated perioperative plasma levels of systemic markers of inflammation (such as complements, C-reactive protein or white blood cells) and pro-inflammatory cytokines

(such as IL-6 and TNF-alpha) have been reported in patients with POAF, with a peak incidence on post-operative day 2[28]. In the same manner, POAF has a peak incidence on post-operative day 2, which matches the pattern displayed by the serum levels of inflammatory biomarkers[29,30]. Treatment with several anti-inflammatory agents has been reported to reduce the prevalence of POAF, supporting the hypothesis that inflammation has a role in the pathogenesis of POAF[31]. In addition to systemic inflammation, local inflammation was reported to play a role in the pathogenesis of POAF[31]. This observation was confirmed by histological findings. Leukocyte infiltration has been observed in the atrial tissue of patients with AF[32]. During cardiac surgery, the formation of reactive oxygen species (ROS) is increased from surgical trauma, IR injury and CPB. Both local and systemic inflammations further increase the formation of ROS[33]. ROS are essential for normal cellular homeostasis. However, an excessive production of ROS leads to oxidative stress[33]. An increase in the myocardial oxidative stress can cause an electrical myocardial remodelling and a subsequent decrease in the effective refractory period to action potential, leading to ventricular arrhythmias and AF[33]. Increased plasma levels of myeloperoxidase (MPO) (an oxidizing agent secreted from infiltrating leukocytes), myocardial oxidation markers (such as peroxynitrite and superoxide), NAD(P)H oxidase and an increased MPO deposition in the atrial tissue was observed in patients with AF[34].

Similar to patients with POAF, those with PPS had high post-operative levels of pro-inflammatory (IL-6 and IL-8) and lower levels of anti-inflammatory (IL-1 and IL-10) cytokines[13]. Furthermore, another study showed an increase in pro-inflammatory cytokine (IL-8 and IL-1β) levels in the early post-operative period[14].

Thus, an increased occurrence of early PPS in patients with POAF may be explained by an aggravated systemic inflammatory response and the increased levels of circulating inflammatory mediators along with an ongoing systemic inflammatory response induced by cardiac surgery.

This study has several limitations. First, the major limitation of this study is related to the definition of PPS because there is no general agreement on how to diagnose the syndrome. There are no pathognomonic features of this condition. Second, this was a retrospective, single-centre study. Although the patients with a pericardial effusion in the first post-operative week were excluded, some patients may have developed a haemorrhagic pericardial effusion after the first post-operative week because patients who developed AF received anti-aggregants and anticoagulant therapy, which is another limitation of the study. Finally, the markers of systemic inflammation (such as C-reactive protein and erythrocyte sedimentation rate) were not compared between the groups because they were not routinely examined.

CONCLUSIONS

This study showed that POAF was associated with an increased incidence of early PPS in patients who underwent isolated CABG surgery. Therefore, patients with POAF should be closely monitored for the occurrence of early PPS.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: US
Analysis/Interpretation: US, AE, ED
Data Acquisition: US, FA, KK
Writing: US, AE, ED
Critical Revision: ED
Final Approval: All of authors

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