Increased IL-12p70 levels in intraoperative pericardial fluid is predictive of postoperative atrial fibrillation onset after coronary artery bypass surgery

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Research Article

Keywords: Intraoperative pericardial fluid, Postoperative atrial fibrillation, Magnetic Luminex assay, IL12p70

Posted Date: May 26th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2953316/v1

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Abstract

Background

Postoperative atrial fibrillation (POAF) is the most frequent complication after heart surgery, prolonging hospital stays, as well as increasing morbidity and death. Previous studies have investigated the determinants of post-heart surgery AF; however, the risk factors contributing to POAF occurrence after coronary artery bypass graft surgery (CABG) remains largely unknown.

Objective

The purpose of this study was to determine if biomarker levels, such as cytokines, within intraoperative pericardial fluid could be used as predictive markers for POAF onset among CABG individuals.

Methods

180 patients with no atrial arrhythmia history, who have undergone CABG, were identified, and the human magnetic Luminex assay was used to measure the levels of 36 pericardial fluid cytokines. POAF development was continuously monitored, using both postoperative electrocardiograms and telemetry strips, until the time of discharge.

Results

POAF was found in 30/124 patients (24.19%). These patients, compared to those with normal sinus rhythms (SR), had significantly higher levels of the interleukin (IL)-12p70 cytokine within their intraoperative pericardial fluids (p < 0.001). Subsequently, IL-12p70 was found to be an independent risk factor for POAF (OR = 1.201; 95% CI, 1.001–1.510; P = 0.014), and ROC analysis determined that the cut-off threshold for predicting POAF onset was 116.435 pg/ml, based on the maximum Youden index (area under the curve: 0.816).

Conclusion

In this study, we demonstrated that increased IL-12p70 levels within intraoperative pericardial fluid was an independent risk factor for POAF, particularly at levels above the cut-off of 116.435pg/ml. This finding thus could serve as a possible marker for detecting future POAF.

1. Introduction
Post-operative atrial brillation (POAF) is a prevalent complication after various surgical procedures, occurring in 20–50% of individuals after cardiac, 10–30% after non-cardiac thoracic, and 5–10% after vascular or major colorectal surgeries [1–4]; it typically occurs between postoperative days 2–4 [5, 6]. With respect to coronary artery bypass graft surgery (CABG), POAF incidence has been found to be between 25–40% [7], and its occurrence is not related to the surgery itself, which may or may not involve cardiopulmonary bypass (CPB) [8]. Its occurrence also significantly increases stroke risk, morbidity, and mortality, with consequent elevations in hospital stay duration and overall costs [9], as well as being associated with four- to fivefold higher risk for recurrent AF in the next 5 years [10, 11]. Furthermore, POAF has been linked to increased morbidities and mortalities, both short- and long-term, for other diseases, such as congestive heart failure, renal insufficiency, and serious infection, which themselves stem from long hospital stays or myocardial infarction [12, 13].

Age, AF history, gender, reduced left ventricular ejection fraction, left atrial hypertrophy, previous valvular cardiac surgery, hypertension, diabetes, and being overweight have all been recognized as risk factors for POAF [13–15]. However, it is still unknown whether there are factors that could predict POAF among specific individuals, or the underlying mechanisms behind its occurrence. One possible etiology, though, may be the presence of structural substrates pre-operation, which increases atrial electrical re-entry risk, leading to higher incidences for post-operative cardiac physiological perturbations. This has been noted in previous studies, which have highlighted that pre-operational (pre-AF) and POAF share a common pathogenesis pathway. However, this pathway is affected by the influence of predisposing complications, such as inflammation, sympathetic stimulation, and cardiac ischemia, all of which are present among CABG individuals with POAF, and increase their vulnerability for AF induction and maintenance [6]. As a result, further analysis to elucidate POAF pathophysiology, in the context of pre-AF, is necessary, which could then be utilized for developing targeted preventative and treatment strategies.

POAF-susceptible individuals have been found to possess plasma protein and metabolite levels distinct from those who do not develop POAF. More specifically, POAF onset has been associated with elevated B-type natriuretic peptide (BNP), cholesteryl ester transfer protein (CETP) and glutathione peroxidase 3 (GPX3), as well as decreased phospholipid transfer protein (PLTP) and apolipoprotein-C3 (APOC3) [16, 17]. However, these studies only examined pre-operative plasma, which serves as a reflection of the overall body state, rather than the heart specifically. Therefore, determining metabolite level differences between POAF and non-POAF patients, specifically related to alterations in cardiac functioning, is of great importance. As the heart and surrounding tissues have been noted to produce multiple physiologically active substances, identifying and measuring the levels of pericardial factors associated with increased POAF risk, prior to CABG, could serve as an approach for developing diagnosis and treatment approaches, as well as aiding in understanding its pathogenesis. This approach has been supported by recent clinical studies, which found that a number of biological indicators were elevated specifically in pericardial fluid, compared to plasma. For instance, Manghelli et al. [18] showed that pericardial fluid mitochondrial DNA was closely related with POAF progression, while Liu et al. [19] revealed the presence of a causal relation between pericardial interleukin (IL)-6 and POAF in a non-paced POAF mouse model. This causal link was through IL-6 being an essential cytokine for promoting profibrotic pathways among
cardiac myocytes, via the pSTAT3 mechanism, during the early postoperative phase, which in turn increases vulnerability to POAF. All of these findings, therefore, indicate that inflammatory mechanisms and mediators present in pericardial fluid may play significant roles in POAF onset [20], suggesting that pericardial fluid biomarker analysis could serve as a viable approach for predicting cardiac disease occurrence, such as POAF.

In this study, we aimed to investigate whether mediators in pericardial fluids could serve as biomarkers for increased POAF susceptibility in CABG patients. We found that out of the 36 pericardial fluid cytokines analyzed under Magnetic Luminex assays, only increases in IL-12p70 levels, above the cut-off value of 116.435pg/ml, was significantly associated with increased POAF risk. Therefore, IL-12p70 could serve as a potential biomarker for predicting POAF occurrence.

2. Methods

2.1 Study design and participants

A retrospective analysis of prospectively-collected pericardial fluid from patients with no history of atrial arrhythmia, undergoing elective CABG, was conducted at Beijing An-Zhen Hospital. Pericardial fluid was collected intraoperatively from February 2022- October 2022, and frozen. Patient exclusion criteria were as follows: CABG combined with other surgical procedures, such as valve replacement/repair, preoperative arrhythmia/pre-AF, lack of informed written consent, and post-surgery fatalities. After applying exclusion criteria, fluid was collected from 124 patients, of which after CABG, 30 (24.19%) developed POAF, and 94 (75.81%) retained proper sinus rhythm (SR). Out of those 124 patients, in accordance with the Lonjon et al. recommendations [21], 56 were chosen for the study by matching the most pertinent clinical parameters, including age, gender, and potential clinical features, such as body mass index (BMI), diabetes, high blood pressure, EuroSCORE, triglycerides, total cholesterol, and other routine biochemical parameters. To obtain balanced exposure cohorts, pre-operation, between POAF and SR patients, propensity score matching was conducted, in which based on a propensity score with a standard caliper width of 0.2, POAF and SR patients were matched in a 1:1 ratio. Consequently, 20 participants were assigned to each cohort (Table 1). Routine biochemical parameters were then assessed using the Hitachi-7600 (Tokyo, Japan) chemical analyzer in the Biochemical Laboratory department, with quality control being conducted using blinded quality control samples. The research protocol was approved by the Medical Ethics Committee of Beijing An-Zhen Hospital and conformed to the principles outlined in the Declaration of Helsinki. All patients provided written informed consent.
Table 1
Preoperative characteristics of patients with POAF and SR

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unmatched</th>
<th>Propensity score matched</th>
<th>P-value</th>
<th>Unmatched</th>
<th>Propensity score matched</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POAF (N = 30)</td>
<td>SR (N = 94)</td>
<td></td>
<td>POAF (N = 20)</td>
<td>SR (N = 20)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.06 ± 8.40</td>
<td>63.45 ± 4.68</td>
<td>0.648</td>
<td>63.84 ± 7.84</td>
<td>63.30 ± 7.16</td>
<td>0.607</td>
</tr>
<tr>
<td>Male sex</td>
<td>24 (80.00)</td>
<td>75 (79.70)</td>
<td>0.360</td>
<td>15 (75.00)</td>
<td>15 (75.00)</td>
<td>1.000</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.25 ± 3.01</td>
<td>25.63 ± 2.59</td>
<td>0.257</td>
<td>25.66 ± 3.34</td>
<td>25.62 ± 2.71</td>
<td>0.930</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (80.00)</td>
<td>58 (61.70)</td>
<td>0.020</td>
<td>14 (70.00)</td>
<td>16 (80.00)</td>
<td>0.265</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (53.33)</td>
<td>41 (43.62)</td>
<td>0.239</td>
<td>13 (65.00)</td>
<td>15 (75.00)</td>
<td>0.593</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.64 (1.09, 1.81)</td>
<td>1.60 (1.18, 1.83)</td>
<td>0.826</td>
<td>1.58 (1.04, 1.92)</td>
<td>1.60 (1.09, 1.94)</td>
<td>0.866</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>3.99 ± 0.87</td>
<td>4.19 ± 0.88</td>
<td>0.237</td>
<td>4.00 ± 0.98</td>
<td>4.20 ± 0.93</td>
<td>0.144</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>0.97 ± 0.19</td>
<td>1.05 ± 0.25</td>
<td>0.118</td>
<td>1.00 ± 0.22</td>
<td>1.00 ± 0.20</td>
<td>0.758</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.13 ± 0.70</td>
<td>2.27 ± 0.73</td>
<td>0.319</td>
<td>2.17 ± 0.78</td>
<td>2.32 ± 0.71</td>
<td>0.165</td>
</tr>
<tr>
<td>LP(a) (nmol/L)</td>
<td>33.10 (6.33, 100.10)</td>
<td>29.60 (4.33, 102.20)</td>
<td>0.949</td>
<td>37.80 (10.65, 98.03)</td>
<td>44.40 (16.60, 117.50)</td>
<td>0.332</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59.43 ± 7.17</td>
<td>60.98 ± 6.74</td>
<td>0.255</td>
<td>62.60 ± 4.65</td>
<td>62.20 ± 6.07</td>
<td>0.776</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>37.27 ± 3.92</td>
<td>35.35 ± 4.24</td>
<td>0.001</td>
<td>37.22 ± 4.34</td>
<td>35.55 ± 3.85</td>
<td>0.274</td>
</tr>
<tr>
<td>Logistic EuroSCORE II b</td>
<td>5.87 ± 2.09</td>
<td>5.26 ± 1.38</td>
<td>0.082</td>
<td>5.81 ± 2.08</td>
<td>5.52 ± 1.65</td>
<td>0.262</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>4.09 ± 0.90</td>
<td>4.25 ± 0.85</td>
<td>0.348</td>
<td>4.18 ± 0.72</td>
<td>4.20 ± 0.71</td>
<td>0.807</td>
</tr>
<tr>
<td>Number of coronary grafts</td>
<td>3.57 ± 0.77</td>
<td>3.30 ± 0.70</td>
<td>0.067</td>
<td>3.42 ± 0.80</td>
<td>3.47 ± 0.63</td>
<td>0.626</td>
</tr>
</tbody>
</table>

POAF, postoperative atrial fibrillation; SR, sinus rhythm; BMI, body mass index; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LP (a), Lipoprotein-a; LVEF, left ventricular ejection fraction. LAD, left atrial diameter. Data displayed as mean ± standard deviation, median values (+ interquartile range), n (%). Differences between groups were analyzed by the Fisher test, Student t test, χ² test, or Wilcoxon rank-sum test.

2.2 Collecting and storing pericardial fluid

CABG surgery was conducted under general anesthesia, followed by endotracheal intubation with a single lumen, and median sternotomy. The procedure was conducted on beating hearts, without CPB, and it, along with perioperative care, were identical for each patient. To maximize surgical timeframes and
eliminate confounding variables, all pericardial fluid specimens were collected via suction through a sterilized, disposable syringe immediately during intraoperative opening of the pericardium, but prior to receiving heparin injections. A minimum of 1 mL pericardial fluid was collected from each patient, and care was taken to ensure that no blood was mixed in during the collection process. After collecting the fluid, samples were placed in sterile containers, and immediately stored at -80°C until testing.

2.3 Luminex assays

Magnetic Luminex® Assays are antibody microarrays, based on magnetic beads, that are able to be simultaneously quantified in a single sample [22]. The presence of POAF-associated biomarkers within pericardial fluid was detected using the Luminex (R&D Systems, Inc., Minneapolis, MN, USA) panel. Prior to conducting these assays, all pericardial fluid samples were diluted to appropriate concentrations, in order to ensure that the cytokine concentration questions were within the dynamic detectability range. Furthermore, all standards and samples were performed in duplicate, according to the manufacturer's guidelines. A total of 36 cytokines were thus analyzed: tumor necrosis factor (TNF)-α, glycoprotein (gp) 130, platelet-derived growth factor (PDGF)-BB, chemokine (C-C motif) ligand 1 (CCL1), IL-8, fibroblast activation protein (FAP)-α, IL-10, fatty acid binding protein 4 (FABP4), angiopoietin-1 and 2, chemokine (C-X-C motif) ligand 13 (CXCL13), interferon (IFN)-γ, IL-1ra, CCL18, IL-12p70, CCL3, CCL4, insulin-like growth factor binding protein 1 (IGFBP-1), CXCL16, IL-17, adiponectin, CCL26, granulocyte-macrophage colony-stimulating factor (GM-CSF), fibroblast growth factor 2 (FGF2), cardiac troponin, leptin, CXCL5, osteopontin, BNP, thrombopoietin, IL-1β, oncostatin M, CXCL11, IL-6, cluster of differentiation 40 (CD40) ligand and CCL17.

2.4 Evaluation and treatment of POAF after CABG

AF has been observed to be able to occur during (perioperative) or after (POAF) heart surgery procedures. POAF was defined as newly-onset occurrences of AF during the time period immediately post-operation and has been considered a medically significant issue. However, POAF could vary from asymptomatic and self-terminating bouts to AF lasting for at least 30 seconds [23], which was the main outcome observed among our patients.

Heart rhythms were constantly observed for all hospitalized patients in this study using either bedside arrhythmia monitors or telemetry. Suspected AF were verified using an extra 12-lead electrocardiogram, and individuals diagnosed with POAF were provided with 2 management options: rhythm or rate control. Rhythm control was recommended for patients who were hemodynamically unsteady, highly symptomatic, possessing anticoagulant contraindication, or were already subject to electrical cardioversion, amiodarone, or both, while rate control was preferred for all other patients, as those would spontaneously return to normal SR within 6 weeks post-discharge. Additionally, all patients with AF >1–2 days were prescribed anticoagulants unless contraindicated7.

2.5 Determining the predictive variables for increased POAF risk and statistical analyses
All statistical analyses were conducted using SPSS (25.0.0.0) and R (4.1.3) software. To identify the variables most strongly associated with increased POAF risk, both uni- and multivariate logistic regression analyses were conducted. Receiver operating characteristic (ROC) curve analysis was then carried out to determine the most optimal cut-off point for those variables. Net clinical benefits for the identified variables was determined using decision curve analysis (DCA).

In order to account for any confounding variations for variables between POAF and SR cohorts, a 1:1 optimum matching technique was employed. Continuous variables with normal distribution were shown as mean ± standard deviation (SD); otherwise, they were displayed as median (interquartile range). Continuous variables with normal distribution were analyzed using the Students’t test, while those with non-normal distribution were analyzed using the Wilcoxon rank-sum test. Categorical variables were compared using the $\chi^2$-square test with Yates adjustment.

3. Results

3.1 Baseline clinical features of the study population

A total of 180 patients underwent first-time CABG during the study period, of 124 were included into this study, after applying exclusion criteria, for monitoring their postoperative heart rhythms. There, 94 (75.81%) remained with SR, and 30 (24.19%) developed POAF (Fig. 1), which occurred between days 1–5 post-surgery (average 2.25 days). All 30 POAF patients were able to regain normal SR after being administered intravenous antiarrhythmic agents. From those patients with SR or POAF, 2 cohorts were established, each containing 20 patients, henceforth referred to as the SR or POAF cohorts. Prior to adjusting for preoperative characteristic to ensure 1:1 matching between the 2 cohorts, POAF patients more frequently had a history of hypertension and possessed larger left atrial diameters, compared to SR patients (Table 1).

3.2 Pericardial fluid IL-12p70 was an independent risk factor for POAF

The Magnetic Luminex test was used to assess the association of 36 pericardial fluid cytokines with POAF occurrence, where it was observed that IL-12p70 levels were significantly higher among POAF patients, compared to those in the SR cohort ($p < 0.001$; Fig. 2). Uni- and multivariate logistic regression analyses were then conducted on those 36 pericardial fluid cytokines, to determine their association with POAF onset risk. Statistically significant ($P < 0.05$) factors identified from univariate logistic regression analysis were then incorporated into the multivariable logistic regression model, which corrected for factors such as age, gender, BMI, hypertension, presence of diabetes, left atrial diameter, left ventricular ejection fraction, EuroSCORE II, and number of grafts. After these corrections were applied, IL-12p70 was the only cytokine to be independently associated with POAF, in which increased pericardial fluid IL-12p70 corresponded with elevated risk ($OR = 1.201; 95\% \text{ CI}, 1.001–1.510; P = 0.014$; Table 2).
Table 2
POAF univariate and multiple logistic regression models.

<table>
<thead>
<tr>
<th></th>
<th>Univariate model</th>
<th></th>
<th>Multiple model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95%CI</td>
<td>P-value</td>
</tr>
<tr>
<td>IL12p70</td>
<td>1.019</td>
<td>1.001–1.330</td>
<td>0.025</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.940</td>
<td>0.883–1.052</td>
<td>0.450</td>
</tr>
<tr>
<td>Gender</td>
<td>1.00</td>
<td>0.255–3.926</td>
<td>1.000</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.049</td>
<td>0.873–1.269</td>
<td>0.538</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.575</td>
<td>0.618–5.690</td>
<td>0.267</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.741</td>
<td>0.263–2.147</td>
<td>0.593</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>1.102</td>
<td>0.934–1.275</td>
<td>0.957</td>
</tr>
<tr>
<td>LAD</td>
<td>0.879</td>
<td>1.130–5.251</td>
<td>0.525</td>
</tr>
<tr>
<td>EuroSCORE II</td>
<td>0.880</td>
<td>0.830–0.952</td>
<td>0.035</td>
</tr>
<tr>
<td>Number of grafts</td>
<td>3.124</td>
<td>1.002–4.783</td>
<td>0.323</td>
</tr>
</tbody>
</table>

3.3 The optimal cut-off value for IL-12p70 levels was 116.435 under ROC analysis, and demonstrated clinical utility under DCA

To determine the cut-off point for IL-12p70 levels being indicative of increased POAF risk, ROC curve analysis was conducted using the “pROC” package in R software. There, the maximal Youden index (Youden index = sensitivity + specificity-1) was selected to obtain the optimal threshold value, and the maximal ROC-optimized cutoff value was found to be 116.435 pg/ml with a corresponding sensitivity of 96.20% and specificity of 56.50%. The area under the curve (AUC) was 0.816 (Fig. 3). This value was then confirmed using both uni- and multivariate logistic regression analyses, in which for new_IL-12p70, which was the categorial variable representing the cut-off value 116.435 pg/ml, p = 0.00336 for univariate, and 0.00975 for multivariate models. Both of these results indicated that the cutoff point of 116.435 pg/ml for IL-12p70 was statistically significant; thus, patients with IL-12p70 > 116.435 pg/ml were more likely to develop POAF than those below the cut-off point. As a result, these patients should be of the utmost priority for developing both prevention and treatment strategies for POAF.

The clinical utility of IL-12p70 > 116.435 pg/ml was then investigated with decision curve analysis (DCA), using 3 models: 1) IL-12p70, 2) Other clinical characteristics, and 3) IL-12p70 + clinical characteristics. There, it was found that model 3 had the greatest clinical utility, followed by model 1 and 2, indicating that utilizing the cut-off of IL-12p70 > 116.435 pg/ml yielded greater benefits for predicting POAF, compared to other clinical characteristics. However, the combination of IL-12p70 and clinical characteristics was even more beneficial than for IL-12p70 alone (Fig. 4).
4. Discussion

In this study, we found from human Magnetic Luminex assays of 36 pericardial fluid cytokines that the presence of the IL-12p70 cytokine was associated with POAF onset after CABG. More specifically, POAF patients had significantly higher IL-12p70 levels, compared to those with normal SR. Furthermore, we also delineated a cut-off point for this association to be applicable, namely at IL-12p70 levels > 116.435 pg/ml, from ROC curve analysis, and demonstrated it was of clinical utility under DCA. This discovery could thus serve as a possible future diagnostic approach for identifying CABG patients most at risk for developing POAF after surgery, in which those with pericardial fluid IL-12p70 > 116.435 pg/ml would be tagged for monitoring and, if necessary, subsequent treatment for the disease.

To the best of our knowledge, this study was the first to highlight the connection between IL-12p70 levels and POAF, though multiple previous studies have illustrated the presence of correlations between various inflammatory factors and POAF risk\(^1\). These studies, though, primarily focused on patient plasma, in which preoperative plasma samples were collected from individuals undergoing CABG; these samples were then examined using proteomics, metabolomics, and bioinformatics to measure the levels of various proteins and metabolites, and their association with POAF. However, the applicability of the findings from these studies for identifying POAF risk has been limited, due to them yielding mixed results, in which the association between one metabolite with POAF risk found in one study may not be applicable in another separate study [24]. This inconsistency between studies regarding plasma biomarkers may be due to the presence of local inflammation affecting the atria, which limits their clinical utility for accurately predicting POAF risk.

Owing to these limitations of plasma proteins and metabolites for serving as biomarkers for POAF risk, alternative sources, such as pericardial fluid proteins and metabolites, have become the subject of great interest. For instance, Nakamura et al. [25], in a prospective study, obtained pericardial fluid from a consecutive series of 42 individuals receiving CABG, and evaluated atrial and natriuretic peptide concentrations to determine whether correlations were present between them and POAF onset after CABG. They found that AF occurred in 9/42 (21%) patients receiving CABG, and that pericardial fluid BNP levels was independently associated with POAF occurrence. These results were in line with the findings from our study, in which pericardial fluid BNP was higher in the POAF cohort versus that of SR. However, this increase in our study was not statistically significant, possibly owing to the smaller sample size comprising the cohorts. It should be noted, though, that this lack of statistical significance is also supported by Manghelli et al. [18], who analyzed 36 pericardial fluid intraoperative cytokines and chemokines, including BNP, and found no significant relationship between their levels and POAF occurrence. This observation was also supported by our findings, in which intraoperative pericardial fluid BNP levels were not related to POAF onset.

Numerous factors, such as inflammation, atrial remodeling, preexisting atrial fibrosis, myocardial ischemia, and autonomic nervous system activation, along with atrial substrates, have been suggested to participate in POAF development, all of which increase patient vulnerability to its induction and
maintenance [6, 26]. Accumulating evidence have suggested that inflammation is crucial to POAF etiology, in which in earlier studies, it has been found to possibly alter atrial conduction, in turn triggering POAF pathogenesis [27]. Increased IL-6 levels have been detected in the pericardial drainage of POAF patients in a prospective study, suggesting that a surgery-induced intracardiac inflammatory microenvironment may result in transient POAF. This finding, however, has been contradicted by our study, in which after analyzing intraoperative pericardial fluid levels for various inflammatory factors, only IL-12p70 had a significant increase under POAF, compared to normal SR conditions. IL-12p70, a heterodimer comprised of p40 and p35 subunits, is secreted by macrophages and dendritic cells, and is essential for NK cell stimulation, differentiation, growth, as well as IFN-γ synthesis from these cells and Th1. Furthermore, IL-12p70 increases perforin, granzymes, and adhesion molecule expression, which enhances CD8+ T and NK cytotoxicity. Additionally, the antigen presentation capabilities of macrophages and dendritic cells are enhanced by IL-12p70. Collectively, these findings suggested that inflammation modulated by IL-12p70 is linked to the development of coronary artery disease [28, 29]. However, the specific details regarding the role of IL-12p70 in the inflammatory process are still largely undefined, though our findings suggest that inflammatory cytokines was already present within the pericardial fluid of coronary heart disease patients prior to CABG, and this pre-existing inflammation may contribute to POAF onset. Nevertheless, further studies are needed to fully elucidate the exact role of IL-12p70 in POAF.

There are some limitations in our study, one of which was the difficulty of collecting pericardial fluid, resulting in small sample sizes that were not able to meet the requirements of event per variable. Therefore, the outcomes determined from this study may not be sufficiently strong. However, the sample size was still large enough to be able to detect significant differences in pericardial fluid cytokine levels between POAF and normal SR individuals. Furthermore, preoperative data of patients were also matched 1:1 between POAF and normal SR cohorts to adjust for confounding factors. Nevertheless, future studies with larger sample sizes are required to validate our findings and address the underlying basis behind the IL-12p70 increase in POAF.

In conclusion, POAF patients, compared to those with normal SR, had increased intraoperative pericardial fluid IL-12p70 levels after CABG. This association between increased IL-12p70 and POAF was also related to increased susceptibility for developing the disease, as it has been found that AF could occur as a result of increases in inflammation, fibrosis, and atrial remodeling-related cytokines, along with the presence of a pre-existing susceptible atrial substrate. In fact, the relation between higher IL-12p70 and POAF was particularly evident at IL-12p70 > 116.435, which could serve as a cut-off point for predicting POAF onset in prospective CABG patients. Therefore, IL-12p70 could serve as a useful biomarker for increased POAF susceptibility, particularly as pericardial fluid could be collected during the open-heart surgery process for CABG.

**Abbreviations**

BMI Body mass index
CABG  Coronary artery bypass graft surgery
CPB  Cardiopulmonary bypass
DCA  Decision curve analysis
HDL-C  High-density lipoprotein cholesterol
IL-12p70  Interleukin-12p70
LAD  Left atrial diameter
LDL-C  Low-density lipoprotein cholesterol
LVEF  Left ventricular ejection fraction
Lp (a)  Lipoprotein-a
POAF  Postoperative atrial fibrillation
ROC  Receiver operating characteristic
SR  Sinus rhythms
TC  Total cholesterol
TG  Triglyceride

Declarations

Acknowledgements
Not applicable.

Authors’ contributions

Yuhua Liu and Enzehua Xie : Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Cuntao Yu, Kun Hua and Xiubin Yang : Conception and design; manuscript writing; final approval of manuscript.

Yunxiao Yang, Zhongyi Han  Analyzed and interpreted the data.

Funding

This work was supported by Beijing Natural Science Foundation (7222049).
Data Availability

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The research protocol was approved by the Medical Ethics Committee of Beijing An-Zhen Hospital and conformed to the principles outlined in the Declaration of Helsinki. All patients provided written informed consent.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

References


Figures
Figure 1

Flow chart of the study. CABG, coronary artery bypass grafting; POAF, postoperative atrial fibrillation. SR, sinus rhythm.
Figure 2

Intraoperative pericardial fluid IL-12p70 levels in group 1 (POAF) and group 2 (SR) groups. POAF, postoperative atrial fibrillation. SR, sinus rhythm.
Based on the ROC curve, the cutoff point of IL-12p70 was calculated. The calculated cutoff point used the maximum Youden index (Youden index = sensitivity + specificity - 1).
DCA was performed to evaluate the clinical net benefit.

Figure 4