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# Patterns of cytokine release and association with new onset of post-cardiac surgery atrial fibrillation

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**Introduction:** Postoperative Atrial Fibrillation (POAF) is a common complication of cardiac surgery, associated with increased mortality, stroke risk, cardiac failure and prolonged hospital stay. Our study aimed to assess the patterns of release of systemic cytokines in patients with and without POAF.

**Methods:** A post-hoc analysis of the Remote Ischemic Preconditioning (RIPC) trial, including 121 patients (93 males and 28 females, mean age of 68 years old) who underwent isolated coronary artery bypass grafting (CABG) and aortic valve replacement (AVR). Mixed-effect models were used to analyze patterns of release of cytokines in POAF and non-AF patients. A logistic regression model was used to assess the effect of peak cytokine concentration (6 h after the aortic cross-clamp release) alongside other clinical predictors on the development of POAF.

**Results:** We found no significant difference in the patterns of release of IL-6 ( $p = 0.52$ ), IL-10 ( $p = 0.39$ ), IL-8 ( $p = 0.20$ ) and TNF- $\alpha$  ( $p = 0.55$ ) between POAF and non-AF patients. Also, we found no significant predictive value in peak concentrations of IL-6 ( $p = 0.2$ ), IL-8 ( $p = >0.9$ ), IL-10 ( $p = >0.9$ ) and Tumour Necrosis Factor Alpha (TNF- $\alpha$ ) ( $p = 0.6$ ), however age and aortic cross-clamp time were significant predictors of POAF development across all models.

**Conclusions:** Our study suggests no significant association exists between cytokine release patterns and the development of POAF. Age and Aortic Cross-clamp time were found to be significant predictors of POAF.

## KEYWORDS

cardiac surgery, cytokines, post-operative atrial fibrillation, aortic valve replacement, coronary artery bypass grafting

## Introduction

Postoperative atrial fibrillation (POAF) is a common complication of cardiac surgery, with the incidence rate being up to 60%, depending on the type of surgery (1). It is associated with an increased risk of early and long-term mortality, early and long-term stroke, renal impairment, cardiac failure and haemodynamic instability (2, 3). It is known that surgery with the use of cardiopulmonary bypass (CPB) elicits a systemic inflammatory response syndrome (SIRS) and the release of systemic cytokines that have been suggested to be associated with the development of POAF (4–7). Furthermore, it is thought that inflammation can alter the electrophysiology and structure of the heart leading to increased vulnerability to atrial fibrillation (8) (AF).

The aim of this study was to evaluate the hypothesis that systemic cytokines, particularly IL-6, IL-8, IL-10 and TNF- $\alpha$ , would have significantly different patterns of release in patients with and without POAF undergoing coronary artery bypass grafting (CABG) or aortic valve replacement (AVR) surgery. To test this hypothesis, we undertook a post-hoc analysis of the remote ischemic preconditioning (RIPC) trial database.

## Materials and methods

The RIPC trial was approved by the London-Harrow Research Ethics Committee (reference number REC number 12/LO/1361) and was registered to the International Standard Randomized Controlled Trial Number (ISRCTN) registry with the ID 33084113 (doi: 10.1186/ISRCTN33084113). The RIPC trial aimed to assess the effect of remote ischaemic preconditioning in 124 patients undergoing isolated CABG and AVR on cardiac injury, metabolic stress, and inflammatory response (9) between February 2013 and April 2015. The RIPC intervention comprised four 5-min cycles of upper limb ischaemia, induced by a blood pressure cuff inflated to 200 mmHg, followed by a 5 min period of reperfusion by deflating the cuff. The expression of relevant cytokines was assessed using the MILLIPLEX<sup>®</sup> MAP Human High Sensitivity T Cell Magnetic Bead Panel as per the RIPC trial. Cytokines were measured at baseline (before the operation) and 6, 12, 24, 48 and 72 h after the aortic cross-clamp release. For the cytokine analysis, we have used GraphPad Prism version 8.4.3 GraphPad Software, La Jolla California USA, www.graphpad.com. Because some cytokine measurements were missing per time-point, we performed the analysis by fitting a mixed-effects model to assess changes in nucleotide metabolism between AF and non-AF patients. We tested for data outlier cytokine measurements using a ROUT method (10) and removed from the analysis: 1 outlier in the IL-6 data, 21 in the IL-10 data, 1 outlier in the IL-8 data and 9 outliers in the TNF- $\alpha$  data. For the analysis of baseline characteristics, we used R version 1.4.1717, gtsummary. Categorical variables were summarised as counts and percentages and compared by the chi-square test, Continuous variables were summarised as mean and standard deviation (SD) or median and interquartile range, as appropriate per their distribution tested with Shapiro-Wilks test, and compared using t-test or rank-sum test. Three patients in the original trial had preoperative AF and were excluded from the analyses. We used logistic regression models to assess the effect of each cytokine at 6 h post-reperfusion (the returning of blood to the heart) along with age and cross-clamp time. We have chosen to include in the model the 6-hour post-reperfusion time point because this is when the cytokine concentrations peaked. We have performed subgroup analysis for patients undergoing AVR or CABG to assess whether cytokine have a procedure-specific effect.

Of note, in the RIPC trial, the remote ischaemic preconditioning intervention was no effect compared to the sham on the outcomes of interest, including cytokine patterns. Therefore, we have included in the post-hoc analysis both arms of the study (9) (sham and intervention) and performed the

analysis. However, we must acknowledge that this post-hoc trial analysis should be viewed as hypothesis-generating only (11, 12). The AF outcome was recorded during hospitalization and was not followed-up on discharge. None of the patients (CABG or AVR) had a posterior pericardiotomy performed.

## Results

### Baseline characteristics of POAF and No-AF cohorts

Data was analyzed for 121 patients (77% male, 23% female, mean age 68 years old). Sixty-four patients (53%) underwent CABG, while 57 (47%) underwent AVR. Of these, 32% experienced POAF ( $N=39$ , 26 males, mean age of 74). Patient characteristics and risk factors were broadly balanced between groups, with few statistically significant differences between the POAF and No-AF cohorts (Table 1). The POAF cohort patients were significantly older (74 vs. 65) ( $p < 0.001$ ), more likely to be in NYHA Class III (21% vs. 17%) ( $p = 0.003$ ), had a longer time on CPB (95 min vs. 82 min) ( $p = 0.003$ ), and aorta cross clamped time (63 min vs. 48 min) ( $p < 0.001$ ).

### Effect of postoperative AF on mortality, stroke and length of hospital stay

The outcomes for the POAF cohort and no-AF cohort are presented in Table 2. There was no statistically significant difference in the occurrence of cerebrovascular accident (CVA) or transient ischemic attack (TIA) between POAF and non-AF patients (7.7% vs. 9.8%, ( $p > 0.9$ )). However, there was a statistically significant increase in hospital stay for POAF patients compared to no-AF patients (8 days vs. 6 days, ( $p = 0.002$ )).

### Analysis of cytokine profiles

After fitting a mixed-effects model, we found no significant difference in the patterns of release of IL-6 ( $p = 0.52$ ), IL-10 ( $p = 0.39$ ), IL-8 ( $p = 0.20$ ) and TNF- $\alpha$  ( $p = 0.55$ ) between POAF and non-AF patients (Figure 1).

### Effect of cytokine concentration in prediction for post-op AF

Using a logistic regression model, we tested whether the peak concentration of each of the cytokines analyzed is a predictor for POAF alongside age and cross-clamp times (Table 3). We found no significant predictive value in peak concentrations of IL-6 ( $p = 0.2$ ), IL-8 ( $p > 0.9$ ), IL-10 ( $p > 0.9$ ) and Tumour Necrosis Factor Alpha (TNF- $\alpha$ ) ( $p = 0.6$ ), however age and aortic cross-clamp time were significant predictors of POAF across all 4 models. We have also performed subgroup analyses of patients undergoing aortic

TABLE 1 Baseline characteristics of AF and non-AF patients.

Characteristic	Overall, N = 121 <sup>1</sup>	No AF, N = 82 <sup>1</sup>	AF, N = 39 <sup>1</sup>	p-value <sup>2</sup>
Procedure				<b>&lt;0.001</b>
CABG	64 (53%)	54 (66%)	10 (26%)	
AVR	57 (47%)	28 (34%)	29 (74%)	
Age(years)	68 (61, 75)	65 (58, 71)	74 (68, 76)	<b>&lt;0.001</b>
Sex				0.067
Male	93 (77%)	67 (82%)	26 (67%)	
Females	28 (23%)	15 (18%)	13 (33%)	
Body mass index (kg/m <sup>2</sup> )	27.5 (25.1, 32.5)	27.4 (24.9, 32.3)	27.5 (25.4, 32.7)	>0.9
CCS class				0.10
0	31 (26%)	15 (18%)	16 (41%)	
1	27 (22%)	19 (23%)	8 (21%)	
2	52 (43%)	39 (48%)	13 (33%)	
3	10 (8.3%)	8 (9.8%)	2 (5.1%)	
4	1 (0.8%)	1 (1.2%)	0 (0%)	
NYHA class				<b>0.003</b>
1	28 (23%)	26 (32%)	2 (5.1%)	
2	70 (58%)	41 (50%)	29 (74%)	
3	22 (18%)	14 (17%)	8 (21%)	
4	1 (0.8%)	1 (1.2%)	0 (0%)	
LV function				0.4
Good (EF > 50%)	100 (83%)	66 (80%)	34 (87%)	
Poor (<50% and >30%)	21 (17%)	16 (20%)	5 (13%)	
Creatinine (mg/dl)	81 (72, 98)	81 (73, 99)	83 (70, 94)	0.7
Previous CVA/TIA	11 (9.1%)	8 (9.8%)	3 (7.7%)	>0.9
Smoking status				0.8
Smoking	13 (11%)	10 (12%)	3 (7.7%)	
Ex-smoking	56 (46%)	37 (45%)	19 (49%)	
Peripheral vascular disease	4 (3.3%)	2 (2.4%)	2 (5.1%)	0.6
Pulmonary disease	25 (21%)	15 (18%)	10 (26%)	0.4
Neurological dysfunction	1 (0.8%)	1 (1.2%)	0 (0%)	>0.9
Previous MI	18 (15%)	15 (18%)	3 (7.7%)	0.13
Hypertension	97 (80%)	66 (80%)	31 (79%)	0.9
Hypercholesterolaemia	91 (75%)	66 (80%)	25 (64%)	0.051
Diabetes				>0.9
NIDDM	26 (21%)	17 (21%)	9 (23%)	
IDDM	5 (4.1%)	4 (4.9%)	1 (2.6%)	
Pre-op beta-blocker	67 (55%)	47 (57%)	20 (51%)	0.5
Pre-op statin	88 (73%)	63 (77%)	25 (64%)	0.14
Cardiopulmonary bypass time (min)	84 (74, 101)	82 (71, 94)	95 (80, 113)	<b>0.003</b>
Aortic cross-clamp time (min)	51 (39, 65)	48 (37, 56)	63 (50, 81)	<b>&lt;0.001</b>

AVR, aortic valve replacement; CCS, Canadian cardiovascular society; CABG, coronary artery bypass grafting; IDDM, insulin-dependent diabetes mellitus; LV, left ventricular; NYHA, New York heart association; NIDDM, non-insulin-dependent diabetes mellitus; TIA, transient ischaemic attack; CVA, cerebrovascular accident.

<sup>1</sup>n (%); Median (IQR).

<sup>2</sup>Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

TABLE 2 Outcomes of AF and non-AF cohorts.

Characteristic	Overall, N = 121 <sup>1</sup>	No AF, N = 82 <sup>1</sup>	AF, N = 39 <sup>1</sup>	p-value <sup>2</sup>
Mortality	0 (0%)	0 (0%)	0 (0%)	
CVA or TIA	11 (9.1%)	8 (9.8%)	3 (7.7%)	>0.9
Hospital stays (days)	7 (6, 8)	6 (5, 8)	8 (6, 10)	0.002

CVA, cerebrovascular accident; TIA, transient ischemic attack.

<sup>1</sup>n (%); Median (IQR).

<sup>2</sup>Fisher's exact test; Wilcoxon rank sum test.

valve replacement or coronary artery bypass grafting and found no significant effect of peak cytokines on development of atrial fibrillation (Table 1 and Supplementary Table 2).

## Discussion

Cardiac surgery with the use of CPB stimulates the release of proinflammatory and anti-inflammatory cytokines as part of the systemic inflammatory response to surgery (SIRS) (13–15). SIRS after cardiac surgery is multifactorial: contact activation of plasma proteins as blood encounters artificial surfaces of the bypass circuit (16), ischaemic reperfusion injury to the brain (17), heart (18), lungs (19) and other organs as a by-product of aortic cross-clamping and endotoxemia (13). It has been shown that pro-inflammatory cytokines play a crucial role in fuelling the inflammatory process, with TNF- $\alpha$  concentrations peaking early after cardiac surgery and IL-6 and IL-8 concentrations peaking later (20, 21).

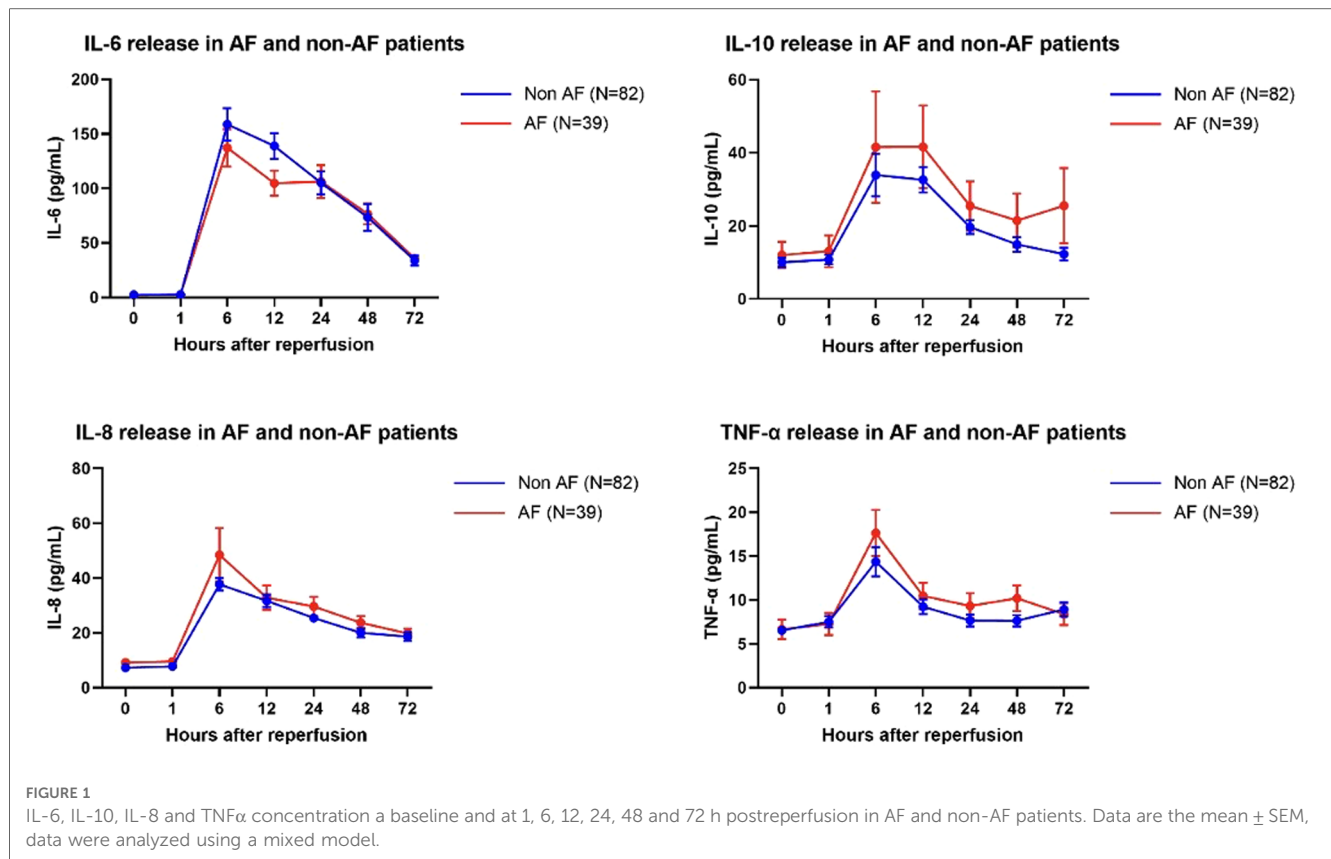


TABLE 3 The effect of IL-6, IL-10, IL-8 and TNF $\alpha$  in logistic regression models for prediction of POAF.

Predictors	IL-6 model			IL-10 model			IL-8 model			TNF $\alpha$ -model		
	Odds Ratios	CI	p	Odds Ratios	CI	p	Odds Ratios	CI	p	Odds Ratios	CI	p
Age (years)	1.09	1.04–1.15	<b>0.001</b>	1.09	1.04–1.15	<b>0.001</b>	1.09	1.04–1.15	<b>0.001</b>	1.09	1.04–1.14	<b>0.001</b>
Aortic cross clamp time (min)	1.04	1.01–1.06	<b>0.003</b>	1.04	1.02–1.06	<b>0.001</b>	1.04	1.02–1.06	<b>0.001</b>	1.04	1.02–1.06	<b>0.001</b>
IL-6 (pg/ml)	1.00	0.99–1.00	0.156									
IL-10 (pg/ml)				1.00	0.99–1.01	0.911						
IL-8 (pg/ml)							1.00	0.99–1.01	0.911			
TNF $\alpha$ (pg/ml)										1.01	0.98–1.03	0.616
Observations	118			119			119			119		
R <sup>2</sup> Tjur	0.256			0.244			0.244			0.245		

Bold values indices are statistically significant of p-value.

It has been suggested that a significant, systemic increase in cytokine concentrations in the blood may contribute to an increased risk of POAF. In particular, increased levels of IL-6 and TNF- $\alpha$  post-operatively have been reported to be associated with POAF (22–25). Furthermore, Maesen et al. (26) suggested that corticosteroids reduce the incidence of POAF due to their inhibition of cytokine release. It is unclear to what extent the systemic cytokine response correlates to inflammation at an atrial tissue since we could not perform a histological analysis in these atrial samples. However, it has been shown that atrial fibrillation is indeed associated with local, atrial tissue inflammation that promotes oxidative stress and electrical instability.

The main finding of our study was that in patients undergoing isolated CABG or AVR, there were no significant differences in

the patterns of release of cytokines IL-6, IL-10, IL-8 and TNF- $\alpha$  between those that developed postoperative atrial fibrillation and those who did not. Furthermore, we found no effect of cytokines on development of POAF in patients undergoing atrial fibrillation.

Our results mirror the report from Wu et al. (7) who in a study of 113 CABG patients found that IL-6, IL-8 and IL-10 all had similar patterns of release in patients with POAF and also non-AF patients. Our findings are also similar to Ishida et al. (27), who provided evidence that TNF- $\alpha$  and IL-8 are released in similar patterns for patients who developed POAF and those who did not. In contrast to the work by Ishida et al, we found no difference in IL-6 release patterns between patients who developed POAF and non-AF patients. Furthermore, IL-6 was not a significant predictor for the development of POAF (4–7).

Our study also concluded that older age was an independent risk factor for the development of POAF, similar to the report of Mathew et al. (28), which showed a 10-year increase in age increases AF odds by 75%. Additionally, Todorov et al. (29) determined that there was an odds ratio of 1.448 per decade increase in age in the development of AF. Turkkolu et al. (30) found older age to be a statistically significant predictor of POAF following cardiac surgery.

A longer aortic cross-clamp time was found to be a statistically significant factor in the development of POAF (Table 3). Our data supports a Hashemzadeh et al. (31) study which also concluded that a longer aortic cross-clamp time is associated with POAF development ( $p = 0.040$ ). Further data collected by Qureshi et al. (32) also agreed with our conclusion of an increased aortic cross-clamp time and proposed aortic cross-clamping time should be kept under 60 min.

As well as a longer aortic cross-clamp time, we found that a longer time spent on CPB was a statistically significant factor in the development of POAF ( $p = 0.003$ ). Again, this aligns with Hashemzadeh et al. (31) whose study found statistical significance in increased CPB time correlating to POAF development.

Finally, our study found the POAF cohort spent significantly longer in hospital (2 days more); similar to the report of Park et al. (33), which concluded POAF patients had an average postoperative stay 2.4 days longer than non-AF patients. Several other studies have concluded that POAF patients have a significantly longer hospital stay with a variation by region, in Asia the excess hospital stay is 4.99 days (34, 35) compared to the USA, where the excess stay is 3.2 days (36).

## Strengths and limitations

The current study analyses the association between cytokines and POAF after cardiac surgery in one of the largest series to date. However, the results of the current study should be viewed as hypothesis-generating since the study is a post-hoc analysis of the trial, and it was not specifically powered to assess the effect of cytokines on the development of POAF, and it was powered to assess the effect of RIPC on cytokines as part of the original trial. Furthermore, we have attempted to construct a prediction model in a relatively small sample size; therefore, we have to acknowledge the possible risk of overfitting in our prediction analysis. More extensive studies are needed to assess the external validity of our results.

## Conclusions

Our study suggests no significant association exists between cytokine release patterns and the development of POAF in patients undergoing coronary artery bypass surgery or aortic valve surgery. Age and Aortic Cross-clamp time were found to be significant predictors of POAF.

## Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

## Author contributions

RK, MG, AD, SS, MM, TD, GA and DF: Have made (a) Substantial contributions to research design, or the acquisition, analysis, or interpretation of data; (b) drafting the paper or revising it critically; and (c) approval of the submitted and final versions.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fsurg.2023.1205396/full#supplementary-material>

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