Received: 27 July 2020 | Revised: 29 September 2020 | Accepted: 5 November 2020

DOI: 10.1111/eci.13456

ORIGINAL PAPER

WILEY

The impact of volume substitution on post-operative atrial fibrillation

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Abstract

Background: Post-operative atrial fibrillation (POAF) represents a common complication after cardiac valve or coronary artery bypass surgery. While strain of atrial tissue is known to induce atrial fibrillating impulses, less attention has been paid to potentially strain-promoting values during the peri- and post-operative period. This study aimed to determine the association of peri- and post-operative volume substitution with markers of cardiac strain and subsequently the impact on POAF development and promotion.

Results: A total of 123 (45.4%) individuals were found to develop POAF. Fluid balance within the first 24 hours after surgery was significantly higher in patients developing POAF as compared to non-POAF individuals (+1129.6 mL [POAF] vs +544.9 mL [non-POAF], $P = .044$). Post-operative fluid balance showed a direct and significant correlation with post-operative N-terminal pro-brain natriuretic peptide (NT-ProBNP) values ($r = .287$; $P = .002$). Of note, the amount of substituted volume significantly proved to be a strong and independent predictor for POAF with an adjusted odds ratio per one litre of 1.44 (95% CI: 1.09-1.31; $P = .009$). In addition, we observed that low pre-operative haemoglobin levels at admission were associated with a higher need of intraoperative transfusions and volume-demand.

Conclusion: Substitution of larger transfusion volumes presents a strong and independent predictor for the development of POAF. Via the observed distinct association with NT-proBNP values, it can reasonably be assumed that post-operative atrial fibrillating impulses are triggered via increased global cardiac strain. Optimized pre-operative management of pre-existing anaemia should be considered prior surgical intervention in terms of a personalized patient care.

KEYWORDS

atrial fibrillation, cardiac strain, cardiac surgery, volume substitution

1 | INTRODUCTION

As the most prominent cardiac arrythmia atrial fibrillation (AF) mirrors a common cause of thromboembolic events and therefore increases morbidity and mortality for affected patients. Post-operative atrial fibrillation (POAF) represents a specific complication frequently occurring after cardiothoracic surgery such as coronary artery bypass graft (CABG) or cardiac valve interventions.[1] Despite POAF shows self-limiting characteristics in many cases, affected individuals hold an increased risk for mortality and morbidity, a higher rate of hospital readmission rates and longer need for intensive care unit (ICU) care and hospitalization after surgery.[2-5] Furthermore, quality of life was found to be negatively affected,[6] and POAF is believed to act as a precursor for atrial fibrillation (AF) from a long-term perspective.[7,8] Apparently, POAF is not only limited to impact on the days after surgery but can also occur in mid-term period after surgery (<3 months).[9,10]

1.1 | A link between POAF and cardiac strain

Perrier and co-workers investigated risk factors for the development of POAF, including a leading role of pre-operative therapeutic approaches.[11] Atrial fibrosis and hypertrophy, significantly higher left atrial volume index, severe atrial fibrosis as well as reduced left atrial appendage flow velocity have been described in POAF patients after CABG surgery,[12-14] all of which suggest an impact of cardiac strain on POAF development. However, data on the association of NT-proBNP and ANP levels with POAF remain heterogenous.[15-17]

Perioperative blood component substitution is suggested to be associated with morbidity and mortality in a general surgery patient population—interestingly, an association with stroke risk was described.[18-20] Transfusions present an inflammatory stimulus and additional strain of the cardiovascular system, both of which might serve as POAF triggers.[21,22] Of note, data on the impact of volume substitution including transfusion of blood components such as red blood cell (RBC), fresh frozen plasma (FFP) or haemostatic factors on the development of POAF remain scarce and inconclusive.[23]

Therefore, we aimed to determine the association of peri- and post-operative volume substitution with markers of cardiac strain and subsequently the impact on POAF development and promotion.

2 | METHODS

2.1 | Study population

In this prospective cohort study, patients scheduled for elective coronary artery bypass graft (CABG) and/or cardiac valve surgery at the Department for Cardiac Surgery, Vienna General Hospital, Medical University of Vienna, were enrolled between May 2013 and October 2016. Only patients scheduled for either elective CABG, valve replacement, valvular reconstruction or a combination of CABG and valvular surgery were eligible for inclusion. Inclusion criteria consisted of admission for elective surgery and sinus rhythm at hospital admission. Exclusion criteria were nonelective surgery, an age <18 years, refusal to give informed consent for study inclusion and an AF episode within two months before hospital admission. However, all enrolled participants were AF naïve individuals, free of any previous history of AF.

Ethical approval for this study (Ethical Committee No. 1110/2013) was provided by the Ethical Committee of the Medical University of Vienna, Austria (Chairperson Ernst Singer), on 12 March 2013. The study protocol complies with the Declaration of Helsinki, and data reporting was performed according to the STROBE and MOOSE guidelines.

2.2 | Data acquisition and patient follow-up

Patient data including patient characteristics and medical history were assessed at the time of study inclusion and inserted into a predefined record abstraction form. Values of routine laboratory parameters were assessed at the time of hospital admission, immediately after surgery and prior to hospital discharge. Levels of NT-proBNP were assessed daily during the hospital stay to elucidate the baseline level and the maximum increase after surgery in accordance to the local laboratory standards of the Medical University of Vienna (Roche Diagnostics, Switzerland).

Patients were continuously followed during the entire hospitalization including peri- and post-operative care at both the intensive care unit (ICU) and normal ward. Peri- and post-operative patient data were obtained via predefined case record forms. The peri- and post-operative fluid management was screened in 24-hour intervals after the index surgical event. Patients were screened for the transfusion of red blood cells (RBC), platelets, fresh frozen plasma (FFP), prothrombin complex concentrates (PCC), fibrinogen, anti-thrombin III (AT-III) and desmopressin. The respective individual fluid balance at the ICU 24 hours after the surgical procedure was calculated and validated by study personnel.

To ascertain the onset of an episode of AF after surgery, all participants received a permanent 6-lead surface ECG monitoring until discharge. Electronic ECG tracings of all individuals were continuously screened. AF episodes were documented and validated via a 12-lead surface ECG. POAF was defined in accordance to the guidelines of the European Society of Cardiology as a new onset of atrial fibrillating

impulses (usually self-terminating) after major cardiac surgery in patients that were in sinus rhythm before surgical intervention.

2.3 | Statistical analysis

Continuous data are presented as median and the respective interquartile range (IQR) and compared among subgroups using Mann-Whitney *U* test. Categorical data are presented as counts and percentages and compared using chi-square test were appropriate.

Binary logistic regression was applied to elucidate the impact of the variables on the development of POAF. Continuous variables were log-transformed prior to regression analysis when applicable to ensure conformity of normal distribution. Data were reported as adjusted odds ratio (OR) for multivariate regression analysis and as their respective 95% confidence interval (CI). Presented odds ratios for continuous values refer to an increase per one litre of substituted volume. The multivariate model was adjusted for potential confounders as follows: gender, age, BMI, CKD (eGFR < 60 mL/min), CAD and valve disease, extracorporeal circulation time and aortic clamp time. The correlation of continuous variables was analysed using Spearman's correlation testing.

Statistical significance was defined by two-tailed *P*-values of <.05. Data analysis was performed using SPSS 22.0 (IBM, USA).

3 | RESULTS

3.1 | Baseline characteristics

A total of 271 patients were included for final analysis (72% male, 99% Caucasian). A detailed report of baseline characteristics is illustrated in Table 1: In short, patients' age was found to be significantly higher in the POAF subgroup (72.8 [66.8-76.7] years vs 65.9 [57.7-73.5] years, $P < .001$). While patients' cardiovascular history turned out to be balanced in patients w/o POAF with regard to conventional risk factors such as hypertension, diabetes, previous acute myocardial infarction (AMI), or chronic obstructive pulmonary disease (COPD), individuals presenting with combined coronary artery disease (CAD) and cardiac valve disease were at higher risk for POAF development ($P = .012$). Moderate chronic kidney disease (eGFR < 60 mL/min) was found also to be associated with POAF ($P = .002$) (Table 2).

The results of pre-operative laboratory markers showed that creatinine (0.98 mg/dL [POAF] vs 0.93 mg/dL [non-POAF]; $P = .031$) and NT-proBNP (809.2 pg/mL [POAF] vs 332.3 pg/mL [non-POAF]; $P < .001$) values proved to be higher in the POAF subgroup, while haemoglobin was found to be significantly lower (13.0 mg/dL [POAF] vs 13.6 mg/dL [non-POAF]; $P = .014$) in patients developing POAF. Concerning post-operative laboratory markers, peak NT-proBNP was elevated in POAF patients (2572.0 pg/mL [POAF] vs 1364.0 pg/mL [non-POAF]; $P < .001$) (Table 3).

3.2 | Perioperative parameters

The fraction of patients receiving RBC transfusions after surgical intervention was significantly higher in the POAF subgroup (57.7% [POAF] vs 31.8% [non-POAF]; $P < .001$). Similar results were obtained concerning fresh frozen plasma (FFP) transfusions (7.3% [POAF] vs 0.7% [non-POAF]; $P = .004$). Also, patients substituted with prothrombin complex concentrates (PCC) had a significantly increased rate of POAF (14.1% [POAF] vs 6.1% [non-POAF]; $P = .019$).

When more than five RBC transfusions were given, the POAF rate was at 83.3%, in comparison to 34.0% in the group of patients who did not receive any RBC transfusion. Patients who received RBC transfusions had significantly lower haemoglobin levels at hospital admission ($P < .001$, median: 12.4 mg/dL vs 14.0 mg/dL). There was a significant association between RBC transfusions and post-operative NT-proBNP levels (2928.0 pg/mL [RBC] vs 1469.0 pg/mL [non-RBC]; $P = .001$).

While there was a clinically relevant difference in post-operative NT-proBNP levels of patients receiving and not receiving FFP transfusions (7220.0 pg/mL [FFP] vs 1762.0 pg/mL [non-FFP]; $P = .075$), this finding did not reach significance due to the small number of individuals being treated with FFPs. NT-proBNP values were higher in patients receiving FFP transfusions, but unfortunately the subgroup appeared underpowered (FFP: n = 10 vs non-FFP: n = 261). There was a significant association between PCC substitution and post-operative NT-proBNP levels (4848.5 pg/mL [PCC] vs 1757.0 pg/mL [non-PCC]; $P = .043$). Almost all patients having received PCC also received other transfusions at the same time.

There was a significant difference concerning the reception of any transfusion (RBC, platelet, FFP) (60.2% [POAF] vs 38.5% [non-POAF]; $P < .001$). Total average transfusion volume was significantly elevated in the POAF subgroup (605.6 mL [POAF] vs 227.1 mL [non-POAF]; $P < .001$). Moreover, fluid balance within the first full 24 hours after surgery was significantly higher in patients developing POAF (1129.6 mL [POAF] vs 544.9 mL [non-POAF]; $P = .044$).

Patients having received any transfusions showed significantly higher post-operative NT-proBNP values (2860.0 pg/mL [transfusion] vs 1486.5 pg/mL [no transfusion]; $P = .002$). Of note, the total amount of transfusions showed a strong correlation with post-operative NT-proBNP levels

TABLE 1 Baseline characteristics

	Total study population (n = 271)	POAF (n = 123)	Non-POAF (n = 148)	*P*-value
Clinical characteristics				
Age, years (IQR)	69 (60-75)	72 (66-76)	65 (57-73)	**<.001**
Male gender, n (%)	195 (72.0)	79 (64.2)	116 (78.4)	**.010**
BMI, kg/m^2 (IQR)	27.1 (24.5-30.4)	27.6 (24.5-31.2)	27.1 (24.5-29.9)	.249
SBP at admission, mm Hg (IQR)	130 (118-140)	130 (116-142)	130 (119-140)	.974
DBP at admission, mm Hg (IQR)	71 (63-80)	70 (62-80)	71 (65-82)	.119
Heart rate at admission, bpm	70 (63-80)	70 (63-80)	70 (63-80)	.566
Cardiac diseases and comorbidities				
Smoking history, n (%)	152 (56.1)	63 (51.2)	89 (60.1)	.084
Coronary vessel disease, n (%)	161 (59.4)	77 (62.6)	84 (56.8)	.353
Valve disease, n (%)	194 (71.6)	95 (77.2)	99 (66.9)	.067
CAD and valve disease, n (%)	87 (32.1)	49 (39.8)	38 (25.7)	**.012**
Previous MI, n (%)	69 (25.5)	34 (27.6)	35 (23.6)	.492
Previous stroke or TIA, n (%)	25 (9.2)	8 (6.5)	17 (11.5)	.158
Hypertension, n (%)	222 (81.9)	104 (84.6)	118 (79.7)	.339
Type II Diabetes Mellitus, n (%)	85 (31.4)	43 (35.0)	42 (28.4)	.260
COPD	37 (13.7)	20 (16.3)	17 (11.5)	.254
Chronic kidney disease, n (%)	40 (14.8)	27 (22.0)	13 (8.8)	**.002**
Pre-operative laboratory values (at admission)				
Creatinine, mg/dL (IQR)	0.94 (0.79-1.18)	0.98 (0.79-1.30)	0.93 (0.79-1.08)	**.031**
Cholesterol, mg/dL (IQR)	164 (133-195)	165 (136-191)	163 (126-198)	.752
Triglycerides, mg/dL (IQR)	116 (79-156)	115 (78-152)	117 (82-162)	.628
HbA_{1c}, % (IQR)	5.6 (5.2-6.4)	5.7 (5.3-6.4)	5.6 (5.2-6.1)	.465
Haemoglobin, mg/dL (IQR)	13.4 (12.1-14.4)	13.0 (11.6-14.3)	13.6 (12.4-14.7)	**.014**
Leukocytes, 10^9/L (IQR)	7.15 (6.02-8.45)	7.09 (5.64-8.44)	7.17 (6.25-8.68)	.157
CRP, mg/dL (IQR)	0.22 (0.09-0.51)	0.26 (0.12-0.49)	0.17 (0.07-0.52)	.053
NT-proBNP, pg/mL (IQR)	466 (197-1622)	809 (363-2154)	332 (150-840)	**<.001**
Troponin T, ng/mL(IQR)	0.02 (0.01-0.05)	0.04 (0.02-0.09)	0.02 (0.01-0.04)	.244
Post-operative laboratory parameters (ICU)				
Leukocytes, 10^9/L (IQR)	14.0 (10.6-18.5)	13.9 (10.5-17.9)	14.1 (10.7-19.2)	.370
Maximum CRP, mg/dL (IQR)	19.6 (14.3-23.3)	19.5 (14.4-23.1)	19.7 (14.2-23.8)	.865
NT-proBNP, pg/mL (IQR)	1940 (940-3736)	2572 (1504-5903)	1364 (703-2374)	**<.001**
Chronic cardiac medication				
Beta-blockers, n (%)	154 (56.8)	78 (63.4)	76 (51.4)	**.046**
ACE-inhibitors, n (%)	104 (38.4)	50 (40.7)	54 (36.5)	.483
ARB, n (%)	76 (28.0)	37 (30.1)	39 (26.4)	.496
Diuretics, n (%)	75 (27.7)	42 (34.1)	33 (22.3)	**.030**
Statins, n (%)	171 (63.1)	77 (62.6)	94 (63.5)	.877
Digitoxin, n (%)	1 (0.4)	0 (0.0)	1 (0.7)	.361

Note: Categorical data are presented as counts and percentages, continuous data as medians and interquartile ranges (IQR). Mann-Whitney *U* test and chi-square test were used to assess differences between subgroups.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; bpm, beats per minute; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HbA_{1c}, haemoglobin A_{1c}; MI, myocardial infarction; mmHg, millimetres mercury; NT-proBNP, N-terminal pro-brain natriuretic peptide; TIA, transistoric ischaemic attack.

Bold values are indicates significant *p*-values.

TABLE 2 Fluid management

	Total study population (n = 271)	POAF (n = 123)	Non-POAF (n = 148)	*P*-value
Any transfusion received, n (%)	131 (48.3)	74 (60.2)	57 (38.5)	**<.001**
Total transfusion volume, mL (IQR)	378.0 (291.3-464.7)	605.6 (453.3-757.8)	227.1 (163.6-290.5)	**<.001**
ICU 24 h fluid balance, mL (IQR)	780.0 (220.5-1992.5)	1129.6 (406.0-2336.8)	544.9 (176.9-1497.0)	**.044**
Red blood cell transfusion, n (%)	118 (43.5)	71 (57.7)	47 (31.8)	**<.001**
Platelet transfusion, n (%)	37 (13.7)	21 (17.1)	16 (10.8)	.135
Fresh frozen plasma transfusion, n (%)	10 (3.7)	9 (7.3)	1 (0.7)	.004
Fibrinogen, n (%)	77 (28.4)	41 (33.3)	36 (24.3)	.102
Antithrombin III, n (%)	18 (6.6)	10 (8.1)	8 (5.4)	.370
Prothrombin complex concentrate, n (%)	27 (10.0)	18 (14.6)	9 (6.1)	**.019**
Desmopressin, n (%)	17 (6.3)	9 (7.3)	8 (5.4)	.518

Note: Categorical data are presented as counts and percentages, continuous data as medians and interquartile ranges (IQR). Mann-Whitney *U* test and chi-square test were used to assess differences between subgroups. *Any transfusion received* and *total transfusion volume* summarizes red blood cell, platelet and fresh frozen plasma transfusions.

Abbreviation: ICU, intensive care unit.

Bold values are indicates significant *p*-values.

TABLE 3 Regression analyses for POAF occurrence

	Crude OR (95% CI)	*P*-value	*Adjusted OR (95% CI)	*P*-value
Total transfusion volume	1.46 (1.18-1.81)	**0.001**	1.44 (1.09-1.31)	**0.009**

Note: Logistic regression model for the association of total transfusion volume (mL) and the development of POAF.

*The multivariate model was adjusted for gender, age, body mass index, chronic kidney disease, coronary artery disease, valve disease, extracorporal circulation time and aortic clamp time. All continuous data were log-transformed prior to analysis. Odds ratios (OR) and the respective confidence intervals (CI) refer to a risk increase per one litre of transfusion volume.

Bold values are indicates significant *p*-values.

($r = .311$; $P < .001$), and there was a correlation between fluid balance during ICU stay and post-operative NT-proBNP ($r = .287$, $P = .002$).

3.3 | Regression analyses

Within a logistic regression model, we observed that the total volume of fluid substitution received during surgery showed a strong and direct association with the development of POAF with an OR per 1-L of 1.46 (95% CI: 1.18-1.81; $P = .001$), as well a direct association with increasing post-operative NT-proBNP levels ($P < .001$, OR per 1-L: 1.21, 95% CI: 1.07-1.38).

After comprehensive adjustment for potential confounding values (gender, age, BMI, CKD) and surgery-related characteristics (CAD and valve disease, extracorporal circulation time and aortic clamp time) within the multivariable model, the total volume of fluid substitution remained a strong and independent predictor for POAF ($P = .009$, OR per 1-L: 1.44, 95% CI: 1.09-1.31).

4 | DISCUSSION

To the best of our knowledge, the present investigation mirrors the first in literature highlighting the prognostic value of fluid management for the prevention of POAF after cardiac surgery. The presented baseline data are mainly in line with similar reports in literature, therefore suggesting to represent an overall representative patient cohort. Of note, the observed POAF incidence was high with 45.4% when compared to international data. This may partly be explained by the high median age of the study population (69.8 [60.5-75.4] years) and the tertiary care setting of the present investigation. Considering comorbidities, patients with active kidney disease and those at risk mirrored by serum creatinine were more likely to develop POAF. This finding is also in line with international reports: as Chua et al[24] reported impaired kidney function to be associated with cardiac diastolic dysfunction and left ventricular hypertrophy, which lead to left atrium enlargement causing increased POAF incidence. Moreover, we observed that patients presenting with both

coronary artery and valve disease were more likely to experience POAF. This might be due to the higher complexity of the surgical procedure itself and therefore an increased likelihood of receiving larger transfusion volumes both peri- and post-operatively. Furthermore, univariate analysis of intraoperative parameters showed that both aortic clamp time and extracorporal circulation time (being indicators of the complexity of surgery) proved to be significant POAF predictors.

As a highly validated risk marker for major cardiac adverse events, NT-proBNP was found to be associated with the development of POAF also in our study population. Since elevated NT-proBNP values reflect myocardial strain through increased intracardial pressures, they can serve as a valid surrogate parameter for this morbidity. Moreover, cardiac volume strain on atrial tissue leads to longer conduction pathways which by itself is a promoting force for atrial fibrillation.[25-27] Of utmost importance, we were able to demonstrate a highly significant correlation between the total amount of peri- and post-operative transfusion volume and increased post-operative NT-proBNP levels. This observation suggests that transfusions are adding further cardiac strain during the post-operative course, which subsequently leads to atrial arrythmia and therefore POAF.

4.1 | High total transfusion burden as a POAF promotor

Reception of RBC transfusions, FFP and PCC were found to be associated with POAF, as well as with elevated post-operative NT-proBNP levels. Considering the application of any substitution, our findings highlighted a strong and independent predictive potential of the development of POAF. Overall, the provided detailed analyses of individual transfusion products and total fluid balance showed that it was mainly a question of the entire amount of substituted volume influencing POAF occurrence: Patients who were extensively transfused had a higher odds of developing POAF when compared with individuals receiving low transfusion efforts. Therefore, it seems intuitive that a substitution-triggered increased volume strain is responsible for the observed elevated POAF incidence.

Our data highlight the fact of high FFP and RBC transfusion rates promoting the incidence of atrial fibrillation. However, it needs to be considered that the advantage of FFP administration in controlling haemostatic balance outweighs the risk of POAF; of note, the increased risk should be taken into clinical consideration for further patient care.

Of utmost importance, patients presenting with lower haemoglobin (Hb) levels at admission were more likely to receive aggressive fluid management including a higher rate of RBC transfusions and also to develop POAF. This leads to the question whether a more focused pre-operative management of Hb values can reduce the amount of RBC transfusions during surgery, and therefore lower the subsequent POAF burden. Considering this fact, a controversy regarding the transfusion necessity of stable patients with 'low' Hb values is raised.[21] Even more, Gerber et al[28] described patients undergoing cardiac surgery are tolerating lower haemoglobin/haematocrit values better than traditionally expected and proposed RBC transfusions to be reserved for clear and strict indications. Currently, an initiative was introduced by the European Union to reduce the unnecessary application of transfusions through better blood product management.[29] In line with those recommendations, pre-operative management of pre-existing anaemia should be considered prior surgical intervention in terms of a personalized patient care and the reduction of POAF burden.

4.2 | Limitations

This study was conducted on a single centre basis; therefore, a clinical practice bias specific to the general hospital of Vienna is possible—this especially concerns the selection of patients from this tertiary care centre perspective.

5 | CONCLUSION

Both the application and amount of perioperative transfusions during cardiac surgery render patients prone to POAF. Substitution of larger transfusion volumes presents a strong and independent predictor for POAF. Via the observed distinct association with NT-proBNP values, it can reasonably be assumed that post-operative atrial fibrillating impulses are triggered via volume-induced cardiac strain. Low pre-operative haemoglobin levels at admission were associated with higher rates of intraoperative RBC transfusions. It is therefore advisable to restrict the amount of transfusions being administered in order to lessen cardiac strain and subsequently POAF incidences. Optimized pre-operative management of pre-existing anaemia should be considered prior surgical intervention in terms of a personalized patient care.

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

SS, AP, MS, LK, NK, FH, TF, GL, BS, AN and PS contributed in data acquisition and study design. SS, AP and PS crafted the manuscript and executed data analyses. GL, BS and AN supervised the study process, contributed in study design amended the manuscript. All authors critically revised and approved the final version of the manuscript.

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How to cite this article: Schnaubelt S, Pilz A, Koller L, et al. The impact of volume substitution on post-operative atrial fibrillation. *Eur J Clin Invest*. 2021;51:e13456. https://doi.org/10.1111/eci.13456