



Relationship between Blood Transfusion and Increased Risk of Atrial Fibrillation after Coronary Artery Bypass Graft Surgery

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Abstract

Background: New-onset atrial fibrillation (AF) after cardiac surgery contributes to increased morbidity, hospital length of stay, and resource utilization. Although many aspects of AF after cardiac surgery have already been elucidated, the mechanism by which cardiac surgery predisposes patients to AF has hitherto remained unknown. Recent evidence supports the notion that blood transfusion enhances the inflammatory response, thereby increasing the incidence of post-operative AF.

Methods: This retrospective study was conducted on 2095 patients who underwent coronary artery bypass grafting (CABG) alone or accompanied by valve surgery between January 2005 and July 2007. Variables associated with the development of new-onset AF were identified using logistic regression.

Results: Intensive care unit blood transfusion increased the risk of AF (odds ratio per unit transfused, 1.16; 95% confidence limits, 1.14, 1.24; $P < 0.001$). Blood transfusion was performed in 487 patients and was associated with a significant increase in new-onset of AF (45.9% vs. 37.9%; $P < 0.01$).

Conclusion: Homologous blood transfusion can increase the incidence of new-onset AF after CABG. This factor should be considered in identifying patients who might benefit from prophylaxis in order to prevent this common post-operative complication and the adverse consequences thereof.

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Keywords: Blood transfusion • Atrial fibrillation • Risk • Coronary artery bypass

Introduction

New-onset atrial fibrillation (AF) occurs in 10% to 43% of patients in hospital in the wake of cardiac surgical procedures¹⁻⁶ and is believed to contribute to increased morbidity,¹⁻⁴ hospital length of stay,¹⁻³ and resource utilization.^{2,3} Although the demographic, clinical, and

electrophysiological substrates as well as the peri-operative risk factors of new-onset AF have been identified, the mechanism whereby cardiac surgery predisposes patients to AF has eluded the scientific community.¹⁻⁵ Usually, the incidence of AF is greater in patients with previous AF, chronic obstructive pulmonary disease, right coronary artery stenosis, valve surgery, and increased P-wave duration as

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well as in patients not receiving beta-blockers after surgery and in those with a low left ventricular ejection fraction.^{3,4} Furthermore, the technical considerations that may predispose patients to AF include venting through superior pulmonary vein, more systemic hypothermia, division of the anterior aortic fat pad, and post-operative right atrium pacing.

Appropriate management of AF requires the identification and treatment of potential risk factors.¹⁻³ AF can result from ischemia, atrial distention, increased sympathetic tone, electrolyte imbalance particularly hypokalemia and hypomagnesemia precipitated by diuresis, acid-base disturbance, sympathomimetic medications, pneumonia atelectasis, and pulmonary edema.²⁻⁸

Recent evidence supports an inflammatory mechanism in the development of AF.⁷⁻⁹ Given that red blood cell (RBC) transfusion modulates the inflammatory response to cardiac surgery by changing the plasma concentrations of inflammatory mediators and augmenting the inflammatory response,¹⁰ we sought to test the hypothesis that RBC transfusion could increase the risk of post-operative AF in patients undergoing cardiac surgery with cardiopulmonary bypass. The clinical classifications of AF are summarized in Table 1.

Table 1. Clinical classifications of atrial fibrillation (AF)

Paroxysmal	AF lasting 7 or fewer days and terminating spontaneously
Persistent	AF lasting more than 7 days that does not terminate spontaneously but requires cardioversion. If the first episode of AF does not terminate spontaneously, it is also designated persistent
Permanent	AF in which sinus rhythm cannot be sustained after cardioversion and the patient and physician have decided against further efforts to restore sinus rhythm

Methods

This study was performed on 1623 patients who underwent CABG alone in Imam Khomeini Medical Center, Tehran University of Medical Sciences, between January 2005 and July 2007. The pre-operative data of the patients are shown in Table 2. Patients and procedural variables associated with the development of new-onset AF were identified by logistic regression. All the patients had continuous, round-the-clock heart rhythm monitoring during their intensive care unit (ICU) stay. After the patients were transferred to the post-operative ward, any irregular rhythm was detected

through a routine vital sign checking conducted every 6 hours; long lead II was recorded immediately if any irregularity was felt in the pulse. The patients were divided into two groups: those with new post-operative AF (whether or not receiving blood products) and the ones without new-onset AF (whether or not receiving blood products) during observation. The total amount of the homologous transfused blood and the number of its products in the operating room and ICU were accurately detected in the files.

Table 2. Pre-operative data of patients (n=1623)

Age (y)*	62±15
Gender	
Male	802(49.4%)
Female	821(50.6%)
NYHA 1/2/3/4 (%)	15/48/37/0
Diseased coronary artery*	3±0.5

*Data are presented as mean±SD

NYHA, New York heart association classification

For the analysis of the descriptive statistics and the categorical variables, the chi-square or Fisher's exact test was used as appropriate. The level of statistical significance was set at a P-value<0.05. All the statistical analyses were performed with SPSS software.

Results

The present study recruited 1623 patients, comprising 802 (49.4%) men and 821 (50.6%) women with a mean age of 62±15 years. Table 2 depicts the pre-operative characteristics of the patients.

AF was detected in 223 (45.9%) of 487 patients who received blood products and in 571 (37.9%) of 1508 patients who did not. The mean cross-clamp time was 58.9±5 and 65.6±5 minutes in those who developed and the ones who did not develop new-onset AF, respectively. Further results are summarized in Table 3.

Table 3. Homologous transfused blood products and risk of AF*

Variable	AF	NO AF	P value
Total transfused blood units	2±2.8	1.1±2	<0.01
Transfused blood units in OR	1±1.8	0.7±1.4	<0.01
Transfused blood units in ICU	1.2± 2.2	0.5±1.3	<0.01
Transfused platelet in OR (%)	10.2	5.9	<0.01
Transfused platelet in ICU (%)	10.4	5.2	<0.01
Transfused fresh frozen plasma in ICU (%)	11.4	6.8	<0.01

*Data are presented as mean±SD

AF, Atrial fibrillation; NO AF, No Atrial fibrillation; OR, Operating room; ICU, Intensive care unit



Discussion

In the present study, aside from older age, prior history of AF, beta-blocker withdrawal, longer aortic clamp time, and ICU inotropic usage, ICU blood transfusion increased the risk of AF (odds ratio unit transfused, 1.16; 95% confidence limits, 1.14, 1.24; $P < 0.001$). Our findings offer important prognostic information for the development of post-operative AF beyond the traditionally described risk factors. Whether the increased occurrence of AF in patients receiving transfusion is related to inflammatory changes or whether it is through another mechanism is unknown; nevertheless, it appears that transfusion is strongly and consistently associated with an increased risk of AF.⁹

According to a study performed in Cleveland clinic by Koch and collaborators between February 2002 and January 2005, 5841 patients underwent isolated CABG with or without valve replacement. Patients and procedural variables associated with the development of new-onset AF were identified by logistic regression. ICU blood transfusion increased the risk of AF (odds ratio per unit transfused, 1.18; 95% confidence limits, 1.14, 1.23; $P < 0.0001$). For the 1360 propensity-matched pairs, ICU and RBC transfusion was associated with a significant increase in AF (620 (46%) vs. 522 (38%); $P < 0.001$). They concluded that blood transfusion following cardiac surgery could increase the incidence of new-onset AF.¹¹

Also, a prospective study in the field was performed on 140 consecutive patients in the Netherlands by Fransen E. and collaborators to investigate whether intra-operative blood transfusion could affect the release of pro-inflammatory mediators in patients undergoing cardiac surgery. They measured the plasma levels of bactericidal/permeability-increasing (BPI) protein as a marker of neutrophil activation, interleukin-6 (IL-6), lipopolysaccharide-binding protein (LBP), and C-reactive protein (CRP). In addition, these mediators, except for CRP, were also measured in packed red cell (PC) units administered to these patients. Thirty-six patients received PC units intra-operatively. BPI levels in the patients who received transfusion were significantly higher at 0.5 and 4 hours after aortic unclamping than those in the patients without transfusion ($P < 0.05$). In addition, the levels increased in tandem with the number of PC units administered. IL-6 levels at 0.5, 4, and 18 hours after aortic unclamping were also significantly higher in the patients who received transfusion ($P < 0.01$). BPI was found in all the units of PC tested at concentrations up to 15 times the pre-operative plasma levels in the patients. However, PC IL-6 could be detected in none of the samples. The plasma levels of LBP and CRP were similar in both patient groups. LBP was found in very low concentrations in all PC units. The patients who received intra-operative transfusions had a worse post-operative performance. The authors

concluded that intra-operative PC transfusions contributed to the inflammatory response after cardiac surgery both by enhancing the response and by directly changing the plasma concentrations of inflammatory mediators.¹² Furthermore, chiming in with our findings, they reported that intra-operative PC transfusion was associated with a worse post-operative performance.

A peri-operative identification of factors related to the development of AF is valuable because AF is a frequent complication associated with post-operative morbidity and cost.^{13,14} To successfully risk-stratify patients for interventional pharmacological trials aimed at reducing AF, there needs to be a clearer understanding of the factors that predispose patients to the development of AF in the post-operative period. Transfusion of RBC is a modifiable process of care that increases the risk of this common post-operative complication.^{11,15} Strategies to reduce the complication following cardiac surgery will impact morbid outcomes and hospital resource utilization. ICU blood transfusion is allied with an increased occurrence of post-operative AF after cardiac surgery. This factor should be taken into account in identifying patients who might benefit from prophylaxis to prevent this common post-operative complication.

Conclusion

The results of this study showed that homologous blood transfusion could increase the incidence of new-onset AF after CABG. This factor should be considered in identifying patients who might benefit from prophylaxis in order to prevent this common post-operative complication and the adverse consequences thereof, although further more extensive studies are necessary to confirm it.

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