A time-related parametric risk factor analysis for postoperative atrial fibrillation after heart surgery

Spencer J. Melby, MD, James F. George, PhD, Desiree J. Picone, MD, Jerald Payden Wallace, MD, James E. Davies, MD, David J. George, and James K. Kirklin, MD

Objectives: Multiple mechanisms may be involved in postoperative atrial fibrillation. Therefore, our objective was to determine the risk factors for postoperative atrial fibrillation as a function of time after coronary artery bypass grafting or valve surgeries to determine which risk factors might predominate at different times.

Methods: Parametric hazard functions were determined for 1583 patients and then in subgroups (coronary artery bypass grafting alone, mitral valve procedure, and aortic valve replacement +/- coronary artery bypass grafting). Multivariable risk factor analyses were performed, and the risk for postoperative atrial fibrillation was estimated.

Results: The risk for postoperative atrial fibrillation for all patients was highest immediately postoperatively and at 48 hours. The initial peak risk declined to approximately zero within 18 hours postoperatively. A second peak occurred at 48 hours, followed by a slow decline over the following 4 to 7 days. The time intervals encompassing these peaks were termed phase I and phase II. Predominant risk factors in phase I were older age (relative risk [RR], 1.6; $P = .006$), longer crossclamp time (RR, 1.3; $P = .001$), and mitral valve procedure (RR, 2.5; $P = .0001$). In phase II, these were older age (RR, 3.0; $P < .0001$), greater weight (RR, 1.6; $P < .0001$), and Caucasian race (RR, 2.5; $P = .006$). For patients receiving a mitral valve procedure, the risk for postoperative atrial fibrillation in phase II was higher and remained elevated for as long as 9 days postoperatively in comparison with isolated coronary artery bypass grafting, for which the risk returned to near baseline by postoperative day 6.

Conclusions: Phase I and phase II periods are associated with distinct risk factors; therefore, it is likely that the mechanisms of postoperative atrial fibrillation change over time. (J Thorac Cardiovasc Surg 2015;149:886-92)

See related commentary on page 893.

Atrial fibrillation (AF) is a common problem after cardiac surgery. Despite the many existing treatment strategies, including prophylactic medications, up to 50% of adult patients who undergo cardiac surgery experience this postoperative complication, and the incidence is increasing as the average age of the population increases.¹ During AF, the atria lose normal sinus rhythm and convert to a disorganized conduction pattern. This increases the risks of clot formation and potential embolism, hemodynamic

compromise from reduced ventricular filling, ventricular dysrhythmias, and symptoms associated with these conditions.¹ Although AF is sometimes well tolerated, the risk for postoperative stroke is approximately 3 times higher in patients with AF.² The average hospital stay is prolonged 1 to 2 days, and patients have an increased risk of early death.^{3,4} The 30-day and 6-month mortality risk is increased 2-fold in patients who experience postoperative atrial fibrillation (POAF).^{3,5} The extra time in the hospital and necessary interventions result in increased costs of approximately \$10,000 per patient.⁴

Some well-known risk factors for POAF after cardiac surgery include advanced age, increased atrial size, low blood serum electrolytes, and combined cardiac procedures, for example, valve repair plus coronary artery bypass grafting (CABG). Advanced age is the most consistent predisposing factor, with a 75% increase in the risk of developing POAF per decade.⁶ Recent studies have implicated increased body mass index, prolonged ventilation,⁷ and perioperative inflammation as additional risk factors.^{2,6,8,9} Although there has been extensive research into the cause of POAF, mechanisms are still poorly understood. Good treatment and preventative options remain elusive.^{2,6} A common time course for patients without a history of AF is onset at postoperative

From the Division of Cardiothoracic Surgery, Department of Surgery, The University of Alabama at Birmingham, Birmingham, Ala.

Funded by an institutional grant from the University of Alabama at Birmingham.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Feb 20, 2014; revisions received Nov 4, 2014; accepted for publication Nov 8, 2014; available ahead of print Dec 19, 2014.

Address for reprints: Spencer J. Melby, PhD, Division of Cardiothoracic Surgery, Department of Surgery, Washington University in St. Louis and Barnes Jewish Hospital, 660 S Euclid Ave, Box 8234, St. Louis, MO 63110 (E-mail: melbys@wustl.edu).

0022-5223/\$36.00

Copyright © 2015 Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2014.11.032>

Abbreviations and Acronyms

AF	= atrial fibrillation
CABG	= coronary artery bypass grafting
ICU	= intensive care unit
POAF	= postoperative atrial fibrillation
RR	= relative risk

day 2 with resolution within a few weeks from surgery.⁶ However, a model characterizing the time-related risk for AF and the risk factors associated with the incidence at different times has not been described. Such a model would provide insights into possible predictive risk factors for POAF, which could then drive specific investigations into treatment options at specific postoperative time intervals. The aim of this study was to determine the risk of POAF as a function of time in patients undergoing CABG or mitral valve replacement/repair. The resulting parametric time-related hazard models were then used to determine specific risk factors for POAF at different postoperative time points.

MATERIALS AND METHODS

Between January 1, 2009, and December 31, 2011, 1852 patients underwent CABG, a mitral valve procedure, an aortic valve procedure, or a combined valve procedure with or without CABG at a single academic institution. Those with a known history of AF ($n = 228$) were excluded. Furthermore, 15 patients' charts were not available, and they were excluded. In 26 patients who experienced POAF, the day and time of the initial onset were unable to be determined and they were excluded from the analysis, leaving 1583 patients for the analysis. Of the 1583 patients, 423 experienced POAF, as identified by cardiac monitoring. Anonymized data were obtained from electronic medical records after approval by the University of Alabama at Birmingham Internal Review Board according to established guidelines. Patients were monitored continuously by telemetry with 24-hour real-time evaluation of rhythm and rate. Monitoring continued until discharge on all patients, including those who had no arrhythmias. New-onset AF was defined as 1 or more periods of AF lasting at least 30 seconds while in the hospital after cardiac surgery in a patient with no history of AF. Monitoring began after the surgery and continued until discharge from the hospital. Patients with POAF were treated with antiarrhythmic medication or direct current cardioversion when indicated at the discretion of the surgeon. No ablation procedures were performed in these patients.

Data Analysis

Nonparametric estimates of freedom from POAF were obtained using the Kaplan–Meier method. P values for stratified nonparametric comparisons were determined using the log-rank test. To determine the time-related risks for POAF as a function of time, we used parametric 3-phase risk models in the hazard domain as described by Blackstone and colleagues.¹⁰ The more commonly used semiparametric Cox proportional hazard model assumes a constant proportional risk across time, therefore only allowing estimates of the change in risk with respect to different intervals in time. Analyses of risk in the parametric hazard domain allow estimation of the instantaneous risk at each moment in time starting with time zero, which, for this study, was the time of entry into the intensive care unit (ICU) after surgery. As implemented in this study, this allows identification of up to 3 separate but overlapping phases of hazard. The

effect of risk factors is estimated by proportional hazards regression within each phase of hazard. To estimate the risk, we calculated the following:

$$\lambda(t) = u_1 g_1(t, x) + u_2 g_2(t, x) + u_3 g_3(t, x).$$

Where each u is a log-linear function of the hazard phase; g_1 , g_2 and g_3 are shaping functions; t is the time to event; and x represents the risk factors. The unique advantage of this method is the ability to closely model the actual changing hazard (risk) over time and the ability to generate nomograms based on solutions to the multivariable equations after entering patient variables most consistent with the group under study.^{11–14} All statistics were performed using SAS software (SAS Institute, Inc, Cary, NC) in conjunction with custom software used for hazard analysis (for additional details, see <http://www.clevelandclinic.org/heartcenter/hazard>).

Separate time-related hazard analyses were also performed on 3 subgroups: patients who underwent CABG alone, mitral valve procedures, or aortic valve replacement/repair $\pm$ CABG.

RESULTS

Patient Characteristics

Univariate comparisons for the entire patient cohort of known risk factors for POAF showed significant differences in patients who experienced POAF. Such patients tended to be older (66.1 ± 11.5 years vs 58.7 ± 13.5 years, $P < .0001$) and to have longer crossclamp times (62.7 ± 40.6 minutes vs 50.7 ± 36.6 minutes, $P < .0001$) (Table 1). Other continuous variables, including body mass index, weight, and preoperative serum creatinine were not significantly different, whereas categorical variables related to crossclamp time or length of surgery were significant (Table 1). Patients with episodes of POAF more frequently underwent cardiopulmonary bypass ($P = .007$), received blood products ($P < .0001$), or were treated for valvular disease ($P \leq .05$) (Table 2). A history of smoking in the year before surgery was slightly higher among those who did not develop POAF (32% vs 26%, $P = .02$). A list of all surgeries performed is shown in Table 3.

Postoperative Atrial Fibrillation Occurrence With Respect to Time Postsurgery

The univariate comparisons showed risk factors for POAF for the entire patient cohort averaged across time. Kaplan–Meier (product-limit) analysis of freedom from AF suggests a nonconstant risk for POAF as a function of time, because the actuarial freedom from POAF data exhibits nonlinear distinct changes in the curve: a steep decrease in the first day followed by a relative plateau and then another decrease over days 2 to 4. This demonstrates an increased risk during those 2 time periods (Figure 1, A, and Figure 2, A). Inspection of the Kaplan–Meier curve shows that the majority of patients who experienced POAF did so within the first 5 days postoperatively. To better understand the kinetics of risk associated with POAF, we performed a time-related parametric hazard analysis to determine the probability of POAF at a given instant in time postsurgery while in the hospital. Figure 1, A, depicts the hazard for POAF with time zero as entry into the ICU

TABLE 1. Patient characteristics: Continuous variables

TABLE 1. Patient Characteristics: Continuous Variables							
Variable	Atrial fibrillation						P value
	No			Yes			
	N	Mean	SD	N	Mean	SD	
Age	1160	58.7	13.5	423	66.1	11.5	<.0001
BMI	1157	29.2	6.3	422	29.3	5.8	.7
Weight	1157	85.7	20.4	423	87.2	19.7	.2
Crossclamp time	1153	50.7	36.6	423	62.7	40.6	<.0001
Preoperative Serum creatinine	1153	1.33	1.50	420	1.27	0.92	.4

BMI, Body mass index; SD, standard deviation.

from the operating room. Two periods of maximum risk for POAF are identified: (1) immediately after leaving the operating room and (2) approximately 2 days after surgery. The initial peak hazard, although very high, declines to approximately zero within the first 24 hours. The hazard

then rapidly increases to another peak at approximately 48 hours, declining steadily over the following 10 days. These 2 phases of hazard for POAF, hereafter designated phase I and phase II, are kinetically distinct (Figure 1, B), therefore suggesting that they may be associated with distinct risk factor profiles. Phase I accounted for 115 POAF events, and phase II accounted for 307 POAF events.

To address this question, we performed a multivariate analysis in the hazard domain in which risk factors for phase I and phase II are considered independently and concomitantly, and found distinct risk factor profiles associated with each phase (Table 4). Longer crossclamp time ($P = .001$) and mitral valve procedures ($P = .0001$) are predominant in phase I, whereas higher weight ($P < .0001$) and Caucasian race ($P = .006$) are only predominant in phase II. Older age at the time of surgery is more dominant during phase II (relative risk [RR], 3.0)

TABLE 2. Patient characteristics: Categorical variables

		Atrial fibrillation				P value†
Variable	Values	No		Yes		
		N*	n (%)	N*	n (%)	
Gender	Male	1158	761 (66)	422	275 (65)	.8
	Female		397 (34)		147 (35)	
Use of CPB	Yes	1160	990 (85)	423	383 (91)	.007
	No		170 (15)		40 (9)	
History of smoking (within 1 y of surgery)	Yes	1151	369 (32)	423	110 (26)	.02
	No		782 (68)		313 (74)	
History of MI	Yes	1151	371 (32)	420	126 (30)	.4
	No		780 (68)		294 (70)	
History of CVA	Yes	1152	114 (10)	419	37 (9)	.5
	No		1038 (90)		382 (91)	
History of diabetes	Yes	1153	384 (33)	421	160 (38)	.08
	No		769 (67)		261 (62)	
History of cerebrovascular disease	Yes	1152	180 (16)	419	66 (16)	.95
	No		972 (84)		353 (84)	
Preoperative dialysis	Yes	1151	55 (4.8)	420	19 (4.5)	.8
	No		401 (95)		401 (95)	
History of peripheral vascular disease	Yes	1152	134 (12)	419	46 (11)	.7
	No		1018 (88)		373 (89)	
History of CABG	Yes	1152	102 (8.8)	419	49 (12)	.09
	No		1050 (91)		370 (88)	
History of valve replacement	Yes	1155	78 (6.8)	419	24 (5.7)	.5
	No		1077 (93)		395 (94)	
Intraoperative blood products given	Yes	1158	565 (49)	422	253 (60)	<.0001
	No		593 (51)		169 (40)	
Aortic valve replacement	Yes	1160	285 (25)	423	139 (33)	.001
	No		875 (75)		284 (67)	
Mitral valve replacement	Yes	1160	101 (8.7)	423	58 (14)	.003
	No		1059 (91)		365 (86)	
Mitral valve repair	Yes	1160	116 (10)	423	57 (13)	.05
	No		1044 (90)		366 (87)	
History of hypertension	Yes	1153	855 (74)	420	330 (79)	.07
	No		298 (26)		90 (21)	

CABG, Coronary artery bypass grafting; CPB, cardiopulmonary bypass; CVA, cardiovascular accident; MI, myocardial infarction. *The number of patients in whom the data for a given variable were available. †Comparison by chi-square of AF group with expected ratio.

TABLE 3. Procedures performed in patients

Variable	N	POAF (%)
Isolated CABG	826	186 (23)
Isolated AVR	226	63 (28)
CABG + AVR	119	46 (39)
Isolated MV replacement	73	23 (32)
CABG + MV replacement	28	12 (43)
AVR + MV replacement	17	7 (41)
Isolated MV repair	93	26 (28)
CABG + MV repair	46	19 (41)
Other valve procedures	116	28 (24)
CABG + other valve procedures	38	12 (32)

AVR, Aortic valve replacement; CABG, coronary artery bypass grafting; MV, mitral valve; POAF, postoperative atrial fibrillation.

than phase I (RR, 1.6). These different risk profiles indicate that POAF during phases I and II may have a different array of contributing mechanisms. Multivariable analysis did not find a difference in the risk of POAF based on the use of any preoperative medications (beta-blockers, angiotensin-converting enzyme inhibitors, statins) or undergoing a combined valve procedure.

Unadjusted comparison between those who did not experience POAF and those who experienced POAF in the first 24 hours versus those who had POAF after the first 24 hours (phase I vs phase II) showed that renal failure was more prevalent in the groups with POAF (10% and 11% in the POAF groups vs 4.7% in the non-POAF group $P < .0001$), and those who had POAF had a higher chance of being discharged on antiarrhythmic medications (93% [320/345] of patients who experienced POAF after 24 hours vs 81% [52/64] of patients who had POAF in the first 24 hours, $P = .003$) compared with those who had no POAF (12% [131/1127], $P < .0001$) (Figure 3). There was also an increased discharge rate of patients taking warfarin (35% [144/409] of those with POAF vs 26% [291/1126] without POAF, $P = .0003$). No statistical difference between those who experienced POAF and those who did not was seen regarding transient

ischemic attack or cardiovascular accident (1.0% vs 0.7% $P = .6$); however, the length of stay was significantly longer in those who had POAF: a median of 7.1 days (5.3-9.2, Q1 to Q3) versus 5.2 days (4.2-7.0 Q1 to Q3) ($P < .0001$).

Time-Related Risk for Postoperative Atrial Fibrillation Depending on Procedure

Because subgroups of patients undergoing cardiac surgery have a wide range of risk factors for POAF, the patients were divided by procedure type to better evaluate differences that might occur between groups. It was determined that although the shapes of the hazard curves were similar, the hazard risks were different with respect to overall risk and duration of risk between each of the subgroups.

Mitral valve procedures contribute strongly to the overall risk of POAF, as shown in both univariate and multivariate analyses. Therefore, we considered patients receiving isolated CABG or mitral valve procedures ± CABG to determine whether these procedures differentially contribute to the risk for POAF with respect to time. Figure 2, A, shows a Kaplan–Meier plot stratified by whether the patient received isolated CABG or mitral valve surgery. The Kaplan–Meier plot overlays the predicted freedom from POAF as determined by the parametric hazard models, which produce results that are not statistically different. As expected, we observed significantly lower freedom from POAF among patients in whom mitral valve repair or replacement was performed. A plot of the hazard for POAF with respect to time indicates that, as shown earlier, the hazard for POAF during phase I is increased (Figure 2, B). In phase II, a higher, more persistent risk for POAF exists among patients with mitral valve procedures compared with patients who had isolated CABG, extending at least to 8 days.

The persistence of the hazard for POAF in the mitral valve group relative to that seen in the isolated CABG group

FIGURE 1. Kaplan–Meier plot and parametric risk model for POAF. A, Combined plot showing a Kaplan–Meier plot of actuarial freedom from POAF in the entire cohort of 1583 patients in the study (closed blue circles). Overlaid onto the Kaplan–Meier plot is a nomogram of a solution for a multivariable equation (solid blue line – dotted lines represent 70% confidence limits) incorporating the time-related hazard for POAF (red line – dotted lines represent the 70% confidence limits). B, Time-related hazard for POAF with phase I (red line) and phase II (blue line) shown separately. Note that the sum of these functions results in the plot (red line) shown in A. OR, Operating room; POAF, postoperative atrial fibrillation.

PM

FIGURE 2. A, Predicted freedom from POAF for a white man aged 60 years with a body mass index of 28 kg/m² and a crossclamp time of 60 minutes (solid lines) undergoing isolated CABG (blue) or mitral valve repair or replacement (red). Closed circles denote the actuarial data (Kaplan–Meier) with the standard error of the mean indicated by the error bar. Dotted lines flanking the predictive plots are the 70% confidence limits. B, Time-related hazard plots for POAF comparing isolated CABG and mitral valve procedure. C, Depiction of the ratio of the hazard for POAF in patients receiving mitral valve repair or replacement over those receiving an isolated CABG procedure with respect to time after leaving the operating room. The dotted lines represent the 70% confidence limits. Note that a ratio greater than 1 means an increased risk for AF in patients receiving a mitral valve procedure relative to those receiving isolated CABG. D, Comparison of the parametric hazard curves for patients receiving aortic valve replacement or repair, isolated CABG, or mitral valve repair or replacement. The dotted lines represent the 70% confidence limits. CABG, Coronary artery bypass grafting; OR, operating room.

is illustrated in Figure 2, C. This shows that the ratio of the POAF hazard (mitral procedure/CABG) is elevated on postoperative day 1 and between days 3 and 9, clearly indicating a period of enhanced risk for POAF among patients receiving a mitral valve procedure versus CABG. Analysis of these 2 curves demonstrated that between postoperative days 2 and 10, 18.8 POAF events would be predicted in 100 patients undergoing CABG, whereas 34.4 new POAF events are predicted in 100 patients who underwent a mitral valve procedure.

A hazard analysis of aortic valve procedures generated similar results, intermediate between mitral procedures and

isolated CABG, which were not significantly different than isolated CABG or mitral valve procedures (Figure 2, D).

DISCUSSION

AF is the most common arrhythmia in the United States, affecting 2 to 3 million people per year.^{15–17} It is not surprising that it is also the most common arrhythmia that occurs after cardiac surgery.^{2,6,18,19} The manipulation/trauma to the heart, including the atria, the large fluid shifts that occur with cardiac surgery, and the presence of underlying atrial disease, which is common in patients undergoing heart surgery, predispose patients for this complication. Indeed, more than 20% of patients who undergo routine CABG and up to 50% of patients who undergo CABG combined with mitral valve surgery have this complication. The cumulative burden on the health care system is large because the average length of hospital stay is prolonged by 1 to 2 days and the cost per patient is increased by \$10,000, resulting in a cumulative financial impact in the United States of 4 billion dollars per annum.^{3,4} Our study found similar increases in the common complications of prolonged length of stay, increased renal failure, and need for additional medications.

Although POAF is a common complication after surgery, the proportional risk and risk factors for POAF as a function

TABLE 4. Multivariable analysis of postoperative atrial fibrillation

Variable	Relative risk (95% CL)*	P value
Phase 1		
Age at time of surgery (70 vs 50 y)	1.7 (1.2–2.3)	.0007
Crossclamp time (70 vs 35 min)	1.2 (1.1–1.4)	.002
Mitral valve procedure	2.3 (1.5–3.6)	<.0001
Phase 2		
Age at time of surgery (70 vs 50 y)	3.2 (2.4–4.4)	<.0001
Weight at time of surgery (100 vs 70 kg)	1.7 (1.4–2.2)	<.0001
Caucasian patient	2.1 (1.2–3.6)	.008

CL, Confidence limit. *Comparisons of RR for continuous variables are made for the 25th and 75th percentile values of the variable. CLs are the confidence limits of the estimates of the coefficients for each variable.

FIGURE 3. Depiction of the proportion of patients requiring antiarrhythmic medications or who experienced renal failure or cerebral vascular accidents. Proportions are a function of the total number of patients within each category. All comparisons were made using chi-square analysis. CVA, Cerebrovascular accident; POAF, postoperative atrial fibrillation.

of time postsurgery have not been described. By using a parametric time-related hazard analysis, we determined that a 2-phase hazard model best fits the actuarial risk for POAF in the study group. This analysis demonstrated that the risk for POAF is increased over baseline during 2 distinct time intervals that we have termed phase I and phase II. In phase I, the hazard for POAF is highest starting at hour zero (defined as the time of transfer into the ICU after surgery), but it rapidly declines to a nadir after 18 hours. A second peak in the hazard for POAF occurs between postoperative hours 24 and 48, and then decreases steadily until discharge from the hospital (Figure 1). Because there are 2 distinct phases, it is possible that there are distinct risk factor profiles associated with each phase. We found both shared and distinct risk factors for phase I and phase II. Older age at the time of surgery was a common risk factor, although it was stronger in phase II than in phase I. Of note, longer crossclamp time, mitral valve procedure, higher weight at the time of surgery, and Caucasian race were not shared between phases I and II. It is reasonable to speculate that the peak risk in phase I (crossclamp time and mitral valve procedure) is due to stress induced by ischemia and physical manipulation of the heart. The increased risk of POAF in time phase I for those who had a longer crossclamp time supports this notion. Unique factors for peak risk in phase II (weight at the time of surgery and Caucasian race) are more difficult to place in the context of known mechanisms. The association with race in nonsurgical patients with AF and in those with POAF has been reported.²⁰⁻²³ These findings, which are present in the phase II but not in phase I, implicate a possible different underlying cause for each phase.

The risk factors described for phases I and II are found for the combined patient cohort. Dissecting the patient group further by stratifying the hazard analysis by patients treated with CABG versus those treated with a mitral valve procedure revealed more detail regarding levels of risk over time for POAF associated with mitral valve procedures. We showed that the hazard for POAF persists longer at higher levels for patients who underwent mitral valve

procedures than for those who underwent CABG. These findings are not surprising because mitral valve disease is clearly associated with atrial disease, including underlying scar and fibrosis, enlargement, and atrial arrhythmias.

The generation of inflammatory responses and adaptations to oxidative stress take time to develop after an initial insult and are therefore good candidates for mechanisms involved in phase II of POAF. Mitral valve procedures done on atria with underlying disease coupled with direct trauma to the atrial tissue also may contribute to increased local inflammatory responses.^{7,24} Neutrophils and macrophages express Toll-like receptors that can sense intracellular material in the environment, causing inflammatory cells to activate and recruit other inflammatory cells. The timing of this inflammatory induction coincides with the second peak in the phase II hazard of POAF. Further investigation in these areas will likely help elucidate some of the factors that are contributive to the causes of POAF in phase II.

As patients increase in age, they are more prone to have AF in general, and this principle remains true with POAF. In older patients, the atria are predisposed to arrhythmia due to fibrosis and scarring. In addition, prolonged heart disease tends to enlarge the atria and cause fibrosis, known risk factors for AF.^{2,25,26} Furthermore, inflammation also appears to be related to age, but the extent to which immunity is affected by age and the mechanisms of any effects remain unknown. This study confirmed that age is a risk factor for POAF, but also showed that it is a risk factor for AF over time with a quantitatively different effect during the phase I (immediately postoperatively within 24 hours [RR, 1.6]) and phase II (RR, 3.0, which occurs between 24 and 72 hours) (Table 4).

Study Limitations

This retrospective review is limited by potential bias inherent in any such study. There were limitations of data that were available for review of these patients. Such potentially significant factors included the postoperative

use of beta-blockers or angiotensin-converting enzyme inhibitors and statins, and echocardiographic findings of atrial size and function. A limitation of the statistical analysis allowed for identification of only the first occurrence of POAF; therefore, any patient with this complication within phase I would not have been included in the multivariable analysis during phase II (ie, patients were counted as having POAF only on the first postoperative occurrence; subsequent bouts of POAF were, by necessity, ignored). This could confound some risk factors in time phase II. Different risk factors were found for each time phase of POAF in a multivariable analysis that supports the investigation of whether differing mechanisms for each time period exist; however, it is beyond the scope of this study to determine such mechanisms.

CONCLUSIONS

In patients undergoing cardiac surgery for coronary disease or valve pathology, the hazard for POAF was bimodal, suggesting that the 2 phases are the result of distinct mechanisms that overlap in time. Patients who undergo mitral valve procedures had a prolonged risk of POAF during phase II on postoperative days 4 to 8. Further investigation into the potential different mechanisms of POAF with respect to time (phase I vs II) is clearly warranted. Subsequent interventions could then be tailored for each phase.

The authors thank Robert N. Brown for thoughtful statistical insights and comments.

References

- Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. *J Am Coll Cardiol*. 2008;51:793-801.
- Maesen B, Nijs J, Maessen J, Alessie M, Schotten U. Post-operative atrial fibrillation: a maze of mechanisms. *Europace*. 2012;14:159-74.
- Attaran S, Shaw M, Bond L, Pullan MD, Fabri BM. Atrial fibrillation postcardiac surgery: a common but a morbid complication. *Interact Cardiovasc Thorac Surg*. 2011;12:772-7.
- Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M, et al. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. *Circulation*. 1996;94:390-7.
- Bramer S, van Straten AH, Soliman Hamad MA, Berreklouw E, Martens EJ, Maessen JG. The impact of preoperative atrial fibrillation on early and late mortality after coronary artery bypass grafting. *Eur J Cardiothorac Surg*. 2010;38:373-9.
- Rostagno C. Atrial fibrillation in patients undergoing surgical revascularization: an update on pharmacologic prophylaxis. *Cardiovasc Hematol Agents Med Chem*. 2012;10:325-38.
- Bramer S, van Straten AH, Soliman Hamad MA, Berreklouw E, van den Broek KC, Maessen JG. Body mass index predicts new-onset atrial fibrillation after cardiac surgery. *Eur J Cardiothorac Surg*. 2011;40:1185-90.
- Sabol F, Jakubova M, Mitro P, Bomba A, Chmelařova A, Petrasova D, et al. [Is there a relationship between inflammatory markers, oxidative stress and post-operative atrial fibrillation?] *Vnitř Lek*. 2012;58:730-4.
- Rodrigo R, Korantzopoulos P, Cereceda M, Asenjo R, Zamorano J, Villalabeitia E, et al. A randomized controlled trial to prevent post-operative atrial fibrillation by antioxidant reinforcement. *J Am Coll Cardiol*. 2013;62:1457-65.
- Blackstone EH, Naftel DC, Turner ME. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. *J Am Stat Assoc*. 1986;81:615-24.
- Bourge RC, Kirklin JK, Naftel DC, McGiffin DC. Predicting outcome after cardiac transplantations: lessons from the Cardiac Transplant Research Database. *Curr Opin Cardiol*. 1997;12:136-45.
- Chin C, Naftel DC, Singh TP, Blume ED, Luikart H, Bernstein D, et al. Risk factors for recurrent rejection in pediatric heart transplantation: a multicenter experience. *J Heart Lung Transplant*. 2004;23:178-85.
- George JF, Taylor DO, Blume ED, Kirklin JK, Naftel DC, Brown RN, et al. Minimizing infection and rejection death: clues acquired from 19 years of multi-institutional cardiac transplantation data. *J Heart Lung Transplant*. 2011;30:151-7.
- Chinnone R, Webber SA, Dipchand AI, Brown RN, George JF, Pediatric Heart Transplant S. A 16-year multi-institutional study of the role of age and EBV status on PTLTD incidence among pediatric heart transplant recipients. *Am J Transplant*. 2012;12:3061-8.
- Melby SJ, Zierer A, Bailey MS, Cox JL, Lawton JS, Munfakh N, et al. A new era in the surgical treatment of atrial fibrillation: the impact of ablation technology and lesion set on procedural efficacy. *Ann Surg*. 2006;244:583-92.
- Go AS. The epidemiology of atrial fibrillation in elderly persons: the tip of the iceberg. *Am J Geriatr Cardiol*. 2005;14:56-61.
- Wakili R, Voigt N, Kaab S, Dobrev D, Nattel S. Recent advances in the molecular pathophysiology of atrial fibrillation. *J Clin Invest*. 2011;121:2955-68.
- Orenes-Pinero E, Montoro-Garcia S, Banerjee A, Valdes M, Lip GY, Marin F. Pre and post-operative treatments for prevention of atrial fibrillation after cardiac surgery. *Mini Rev Med Chem*. 2012;12:1419-31.
- Bar-Cohen Y, Silka MJ. Management of postoperative arrhythmias in pediatric patients. *Curr Treat Options Cardiovasc Med*. 2012;14:443-54.
- Borzecki AM, Bridgers DK, Liebschutz JM, Kader B, Kazis LE, Berlowitz DR. Racial differences in the prevalence of atrial fibrillation among males. *J Natl Med Assoc*. 2008;100:237-45.
- Marcus GM, Olgin JE, Whooley M, Vittinghoff E, Stone KL, Mehra R, et al. Racial differences in atrial fibrillation prevalence and left atrial size. *Am J Med*. 2010;123:375.e1-7.
- Shen J, Lall S, Zheng V, Buckley P, Damiano RJ Jr, Schuessler RB. The persistent problem of new-onset postoperative atrial fibrillation: a single-institution experience over two decades. *J Thorac Cardiovasc Surg*. 2011;141:559-70.
- Almassi GH, Peci SA, Collins JF, Shroyer AL, Zenati MA, Grover FL. Predictors and impact of postoperative atrial fibrillation on patients' outcomes: a report from the Randomized On Versus Off Bypass trial. *J Thorac Cardiovasc Surg*. 2012;143:93-102.
- Bramer S, van Straten AH, Soliman Hamad MA, van den Broek KC, Maessen JG, Berreklouw E. New-onset postoperative atrial fibrillation predicts late mortality after mitral valve surgery. *Ann Thorac Surg*. 2011;92:2091-6.
- Tsai CT, Lai LP, Kuo KT, Hwang JJ, Hsieh CS, Hsu KL, et al. Angiotensin II activates signal transducer and activators of transcription 3 via Rac1 in atrial myocytes and fibroblasts: implication for the therapeutic effect of statin in atrial structural remodeling. *Circulation*. 2008;117:344-55.
- Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. *J Am Coll Cardiol*. 2008;51:802-9.