

# Diastolic function and new-onset atrial fibrillation following cardiac surgery

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## ABSTRACT

**Background:** Numerous studies have reported predictors of new-onset postoperative atrial fibrillation (POAF) following cardiac surgery, which is associated with increased length of stay, cost of care, morbidity, and mortality. The purpose of this study was to examine the association between preoperative diastolic function and occurrence of new-onset POAF in patients undergoing a variety of cardiac surgeries at a single institution. **Methods:** Using data from a prospective study from November 2007 to January 2010, a retrospective review was conducted. The diastolic function of each patient was determined from preoperative transthoracic echocardiograms. Occurrence of new-onset POAF was prospectively noted for each patient in the original study. Demographic and operative characteristics of the study population were analyzed to determine predictors of POAF. **Results:** Of 223 patients, 91 (40.8%) experienced new-onset POAF. Univariate predictors of POAF included increasing age, male gender, operations involving mitral valve repair/replacement, nonsmoking, hypertension, increased intraoperative pulmonary artery pressure, grade I diastolic dysfunction, abnormal diastolic function of any grade, decreased medial  $e'$ , elevated medial  $E/e'$ , and increased left atrial volume. Multivariate predictors of POAF included increasing age, increased left atrial volume, and elevated initial intraoperative pulmonary artery pressure. Even after exclusion of patients with hypertrophic obstructive cardiomyopathy or those undergoing mitral valve operations, diastolic dysfunction was not a multivariate predictor of POAF. **Conclusions:** In the patient population studied here, preoperative diastolic dysfunction was not predictive of POAF. In addition to increasing age, initial intraoperative pulmonary artery systolic pressure and left atrial volume were both significant multivariate predictors of POAF.

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## INTRODUCTION

Postoperative atrial fibrillation (POAF) affects 18–64% of patients following cardiac surgery.<sup>[1-12]</sup> While controversy exists as to whether POAF increases morbidity and mortality or is merely associated with it,<sup>[8]</sup> at a minimum it leads to an increased length of hospital stay and cost of care.<sup>[1,7,11,13,14]</sup>

Multiple studies have reported perioperative predictors of POAF.<sup>[2,6-8,12,14]</sup> Predictive models for POAF are of interest as they may allow

for selective use of preventative strategies in at-risk patients so that the benefits of therapy outweigh associated risks. A recent study found abnormal preoperative diastolic function to be associated with POAF in patients undergoing coronary artery bypass grafting and/or valvular repair/replacement.<sup>[12]</sup> To our knowledge, this is the only study to report diastolic dysfunction as a risk factor for POAF.

Given that only one previous study has shown diastolic dysfunction to be associated with POAF, the purpose of the current study was to

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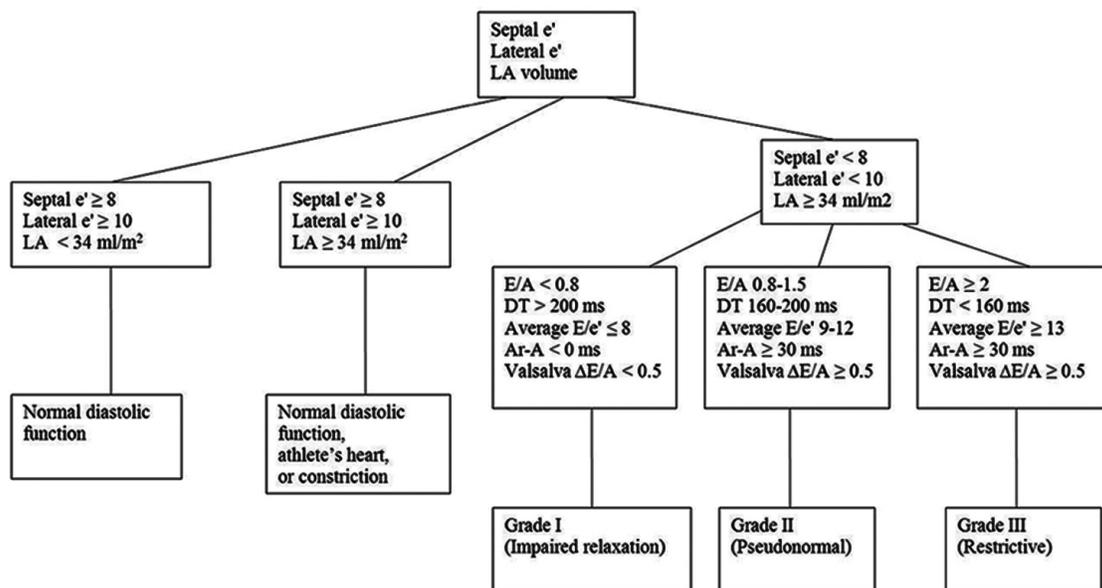
examine the association between preoperative diastolic function and occurrence of new-onset POAF in patients undergoing a variety of cardiac surgeries at a single institution.

## METHODS

This study was approved by the local institutional review board. A retrospective review was conducted from data obtained from a randomized, double-blind, placebo-controlled trial aimed at determining whether or not a single bolus of lidocaine or amiodarone intraoperatively was effective at preventing ventricular fibrillation after aortic cross-clamp removal in patients undergoing cardiac surgery.<sup>[15]</sup> All patients had provided written informed consent for the original trial acknowledging that further review of their records may occur. Enrollment occurred from November 1, 2007 to January 1, 2010. A blinded study coordinator followed all patients during their hospitalization for the occurrence of new-onset POAF based on electrocardiographic evidence or notations in hospital notes. These data were maintained in a prospective fashion. Patients were included in the current study if they had completed the original trial, were 18 years of age or greater, had undergone resting transthoracic echocardiogram at our institution within 1-year of operation, and had no history of preoperative atrial fibrillation or atrial flutter.

Preoperative, intraoperative, and postoperative data collected during the original study were utilized.<sup>[15]</sup> Blinded authors (DWB, WJM) retrieved additional echocardiographic data related to diastolic function from the electronic preoperative resting transthoracic echocardiogram report. Two blinded authors (KHR, WJM) certified in advanced perioperative transesophageal echocardiography graded each available patient's diastolic function according to guidelines provided by the American Society of Echocardiography [Figure 1].<sup>[16]</sup> Discrepancies in grading were resolved by a third blinded author (JNP) certified in advanced perioperative transesophageal echocardiography. Preoperative transesophageal echocardiograms are not routinely performed at our institution for all patients and were, therefore, not included in the determination of diastolic function. In addition, due to rapidly changing hemodynamics intraoperatively, parameters of diastolic function are not typically interrogated intraoperatively with transesophageal echocardiography and were not included in this study.

Descriptive statistics for categorical variables are reported as frequency and percentage while continuous variables are reported as mean (standard deviation) or median (range) as appropriate. Categorical variables were compared between patients with and without POAF using Chi-squared test or Fisher's exact test,



**Figure 1:** Approach to determination of diastolic function. <sup>1</sup>Deceleration time, left atrial <sup>1</sup>Reproduced with permission from Nagueh et al.<sup>[16]</sup>

and continuous variables were compared using two sample *t*-test or Wilcoxon rank sum test where appropriate. Logistic regression models were used to

find the univariate and multivariate predictors of POAF. The multivariable model considered as univariately significant variables ( $P < 0.05$ ) with model selection

**Table 1: Demographic and operative characteristics of the study population according to new-onset postoperative atrial fibrillation occurrence**

	No POAF (n=132)	POAF (n=91)	OR	95% CI	P
Age (years)	57.3±14.8	67.4±11.2	1.06	1.03-1.08	<0.001
Height (cm)	172.1±10.2	173.5±10.2	1.01	0.99-1.04	0.303
Weight (kg)	87.4±17.2	92.3±20.4	1.01	1-1.03	0.055
Gender: Female	46	20	0.53	0.29-0.97	0.040
Left ventricular ejection fraction (%)	64.9±9.9	63.3±11.8	0.99	0.96-1.01	0.283
Procedures <sup>a</sup>					
CABG performed	42	33	1.22	0.69-2.14	0.490
Aortic valve repair/replacement performed	38	36	1.62	0.92-2.85	0.094
Mitral valve repair/replacement performed	14	19	2.22	1.05-4.71	0.037
Tricuspid valve repair/replacement performed	1	5	7.62	0.87-66.31	0.066
Septal myectomy performed	59	31	0.64	0.37-1.11	0.113
Other procedure (s) performed	3	3	1.47	0.29-7.43	0.644
Medical history					
Diabetes mellitus	10	14	2.22	0.94-5.24	0.069
Coronary artery disease	48	33	1.00	0.57-1.74	0.988
Current smoker	15	3	0.27	0.07-0.95	0.041
COPD	4	3	1.09	0.24-5.00	0.910
Hypertension	47	48	1.05	1.17-3.48	0.011
Preoperative medications					
Beta blocker	83	56	0.94	0.54-1.64	0.839
ACE inhibitor/ARB	29	28	1.58	0.86-2.90	0.140
Statin	51	41	1.30	0.76-2.24	0.339
Digoxin	1	2	2.94	0.26-33.00	0.381
Amiodarone	1	1	1.46	0.09-23.60	0.792
Initial mean intraoperative pulmonary artery pressure (mmHg)	30.5±8.4	34.3±10.4	1.05	1.01-1.08	0.005
Duration of aortic cross-clamp (min)	45.1±26.9	52.7±34.3	1.01	1.00-1.02	0.067
Duration of cardiopulmonary bypass (min)	63.7±39.2	73.1±43.3	1.01	1.00-1.01	0.105

OR: Odds ratio, CI: Confidence interval, ACE: Angiotensin converting enzyme, ARB: Angiotensin receptor blocker, COPD: Chronic obstructive pulmonary disease, CABG: Coronary artery bypass grafting, POAF: Postoperative atrial fibrillation. <sup>a</sup>Procedure performed may be in conjunction with other procedures listed as such totals exceed 132 for no POAF and 91 for POAF

**Table 2: Echocardiographic characteristics of the study population according to new-onset postoperative atrial fibrillation occurrence**

Variable	No POAF (n=132) (%)	POAF (n=91) (%)	OR	95% CI	P
Left ventricular mass (g)	272±101	294±115	1.00	1.00-1.00	0.147
Left ventricular mass index (g/m <sup>2</sup> )	135±45	142±52	1.00	1.00-1.01	0.269
Left atrial volume (cc)	85±28	97±41	1.01	1.00-1.02	0.018
E wave velocity (m/s)	0.871±0.29	0.886±0.37	1.15	0.50-2.61	0.746
A wave velocity (m/s)	0.808±0.29	0.867±0.28	2.08	0.79-5.41	0.136
E/A ratio	1.18±0.53	1.11±0.624	0.78	0.47-1.28	0.325
Deceleration time (ms)	230±57	235±61	1.02 <sup>a</sup>	0.97-1.06	0.532
e' medial (m/s)	0.065±0.06	0.054±0.02	0.23 <sup>b</sup>	0.06-0.88	0.032
e' lateral (m/s)	0.073±0.03	0.069±0.03	0.51 <sup>b</sup>	0.16-1.59	0.244
E/e' medial	15.8±7.3	18.0±9.1	1.03	1.00-1.07	0.049
E/e' lateral	13.0±6.3	13.6±6.6	1.01	0.97-1.06	0.528
Diastolic grade I (impaired relaxation) <sup>c</sup>	46 (34.8)	42 (46.2)	2.57	1.15-5.76	0.021
Diastolic grade II (pseudonormal) <sup>c</sup>	46 (34.8)	32 (35.2)	1.96	0.86-4.46	0.109
Diastolic grade III (restrictive) <sup>c</sup>	9 (6.8)	6 (6.6)	1.88	0.54-6.50	0.319
Any abnormal diastolic grade <sup>c</sup>	101 (76.5)	80 (87.9)	2.23	1.06-4.72	0.035

POAF: Postoperative atrial fibrillation, CI: Confidence interval, OR: Odds ratio. <sup>a</sup>OR determined per 10 ms, <sup>b</sup>OR determined per 0.1 m/s, <sup>c</sup>OR as compared to normal diastolic function

using the stepwise method (backward and forward methods resulted in the same model). All statistical tests were two-sided with the alpha level set at 0.05 for statistical significance.

## RESULTS

Of 342 patients completing the original trial,<sup>[15]</sup> 223 patients met enrollment criteria for the current study. Demographic and surgical characteristics stratified according to POAF occurrence for patients meeting inclusion criteria are shown in Table 1. Preoperative transthoracic echocardiographic findings, stratified according to the occurrence of POAF, are listed in Table 2.

Ninety-one of the 223 patients (40.8%) experienced POAF. Univariate patient and surgical predictors of POAF included increasing age, male gender, operations involving mitral valve repair/replacement, nonsmoking, hypertension, and increased initial intraoperative pulmonary artery pressure [Table 1]. Mean time from preoperative transthoracic echocardiogram to surgery was  $36 \pm 47$  days (median 22 days). Preoperative echocardiographic predictors of POAF on univariate analysis were grade I diastolic dysfunction, abnormal diastolic function of any grade, decreased medial  $e'$ , elevated medial  $E/e'$ , and increased left atrial volume [Table 2].

On multivariate analysis, age, increased left atrial volume, and elevated initial intraoperative pulmonary artery pressure were associated with POAF. No individual echocardiographic measurements of diastolic function parameters aside from left atrial volume were associated with POAF on multivariate analysis [Table 3].

Due to controversies in diastolic function determination in patients with hypertrophic obstructive cardiomyopathy (HOCM),<sup>[16]</sup> the data were reanalyzed after exclusion of 92 HOCM patients. In the remaining 131 patients, multivariate predictors of POAF included age (odds ratio [OR]: 1.06, 95% confidence interval [CI]: 1.03–1.11,  $P < 0.001$ ) and elevated initial intraoperative

mean pulmonary artery pressure (OR: 1.04, 95% CI: 1.00–1.08,  $P = 0.038$ ).

Given that left atrial enlargement and pulmonary hypertension may result from mitral valve dysfunction, the data were reanalyzed after exclusion of 33 patients who underwent mitral valve operation. Of the remaining 190 patients, multivariate predictors of POAF included age (OR: 1.06, 95% CI: 1.03–1.09,  $P < 0.001$ ), male gender (OR: 2.14, 95% CI: 1.00–4.58,  $P = 0.0495$ ), and elevated initial intraoperative pulmonary artery pressure (OR: 1.05, 95% CI: 1.01–1.09,  $P = 0.0195$ ).

Randomization of patients in the original trial had no effect on the incidence of POAF. Of patients experiencing POAF, 29/91 (32%) had received an intraoperative intravenous bolus of amiodarone, compared to 46/132 (35%) who did not experience POAF ( $P = 0.648$ ).

Eighty of 91 patients (88%) who developed POAF were treated with amiodarone in the postoperative period, compared with 11/132 (8%) without POAF. Patients who developed POAF had longer stays in the intensive care unit ( $1.2 \pm 1.0$  days vs.  $1.5 \pm 1.9$  days,  $P = 0.001$ ) and in the hospital ( $5.2 \pm 1.8$  vs.  $7.2 \pm 4.9$ ,  $P < 0.001$ ) than did patients who were free of POAF.

## DISCUSSION

In the current study, neither individual echocardiographic parameters of diastolic function or grade of diastolic function were predictors of POAF on multivariate analysis. However, pulmonary artery systolic pressure and left atrial volume were both significant predictors of POAF. Thus, clinical sequelae of diastolic dysfunction may be of value in predicting patients that will develop POAF after cardiac surgery.

To our knowledge, only one previous study has evaluated the association between diastolic function and POAF. Melduni *et al.* reported on 351 patients also from our institution undergoing isolated coronary artery bypass grafting and/or valve repair/replacement.<sup>[12]</sup> No patients from that study were included in the current study. The rates of POAF were similar between the previous study and ours (38.5% and 40.8% respectively). Grade 0 (normal), I, II, and III diastolic dysfunction were encountered preoperatively in 18.8%, 39.5%, 35.0%, and 6.7%, respectively, of all patients in the current study, compared to 22.5%, 29.6%, 41.1%, and 6.8% in the study of Melduni *et al.*

**Table 3: Multivariate analysis of predictors of new-onset postoperative atrial fibrillation**

Variable	OR	95% CI	P
Age (years)	1.06	1.04-1.09	<0.001
Pulmonary artery systolic pressure (mmHg)	1.04	1.00-1.08	<0.001
Left atrial volume (cc)	1.01	1.00-1.02	<0.001

CI: Confidence interval, OR: Odds ratio

Left ventricular diastolic function grade was found by Melduni *et al.* to be an independent predictor for POAF. Conduction heterogeneity secondary to fibrosis of the cardiac chambers associated with aging is hypothesized to increase susceptibility to POAF in the setting of surgical insult.<sup>[12,17-19]</sup> Contrary to Melduni *et al.*, diastolic dysfunction was not associated with POAF in the current study, despite the fact that preoperative diastolic dysfunction of any grade was more common in the current study and both studies had comparable frequencies of pseudonormal (grade II) and restrictive (grade III) filling patterns. The characterization of diastolic dysfunction may be difficult in patients with HOCM due to significant variations in mitral inflow patterns due to individual differences in compliance and relaxation.<sup>[16]</sup> Even after excluding patients with HOCM, on multivariate analysis diastolic dysfunction was not associated with POAF in our study.

Our report shares similarities with the study by Melduni *et al.* in that no single echocardiographic parameter of diastolic function was predictive of POAF on multivariate analysis. However, the studies differ in that we were unable to show an association between the grade of diastolic function and POAF. We used a single set of national guidelines<sup>[16]</sup> for the grading of diastolic function [Figure 1], whereas Melduni *et al.* used this set of guidelines as well as other previously published reports of significant parameters echocardiographic parameters. These slightly dissimilar protocols for grading diastolic function may explain the differences in our findings. However, it is important to highlight the fact the grading of diastolic function is an inexact science, and a given patient's echocardiographic findings may not conform to published algorithms for diastolic grading. Inter-institutional variability and reviewer subjectivity in the grading of diastolic function may make it difficult to include diastolic grade into global predictive models of POAF.

Our results also agree with those of Melduni *et al.* with respect to increasing left atrial volume as a predictor of POAF. The significance of this finding is difficult to assess. Left atrial enlargement accompanies chronic mitral stenosis and regurgitation, and patients in our study presenting for mitral valve surgery were more likely to experience POAF ( $P = 0.037$ ). When patients undergoing mitral valve surgery were excluded, increased left atrial volume was no longer associated with POAF on multivariate analysis. Left atrial enlargement is also found in patients with advanced degrees of diastolic

dysfunction,<sup>[16]</sup> though in the current study, there was no difference in the presence of advanced diastolic dysfunction between the two groups. Unlike the reports of Melduni, we also included initial intraoperative pulmonary artery systolic pressure in our model, which was predictive of POAF. Our findings of increasing age, left atrial size, and elevated pulmonary artery pressures being associated with POAF are similar to other studies.<sup>[1,10,14,20]</sup> Thus, it may be that more objective clinical sequelae of diastolic dysfunction such as pulmonary hypertension and left atrial dilation are more predictive of POAF than grading of diastolic dysfunction.

Postoperative atrial fibrillation increases costs associated with cardiac surgery by several thousand dollars and hospital length of stay by 1–6 days as observed in the current study.<sup>[1,7,13,14,20,21]</sup> Preventative treatment is of interest to mitigate an increase in morbidity, cost, and hospital length of stay associated with POAF. Multiple different prophylactic strategies have been studied in an attempt to decrease the occurrence of POAF. In a systematic review of randomized controlled trials of adults undergoing cardiac surgery, the following prophylactic interventions were found to significantly reduce the rate of POAF: Amiodarone,  $\beta$ -blockers, magnesium, sotalol, atrial pacing, and posterior pericardiectomy.<sup>[22]</sup> This review found that hospital cost was decreased by \$1,250 and length of hospital stay decreased by two-thirds of a day in patients receiving effective prophylactic interventions.

Although not significantly different in effectiveness from  $\beta$ -blockade, amiodarone may be preferred over  $\beta$ -blockers in patients with contraindications to  $\beta$ -blockers or those with a concern over myocardial depression following postoperative  $\beta$ -blocker administration.<sup>[23]</sup> Prophylactic amiodarone administration exposes patients to risk of side effects such as pulmonary toxicity, QT prolongation, symptomatic bradycardia, atrioventricular block, thyroid toxicity, and hepatotoxicity.<sup>[24,25]</sup> In addition, although one meta-analysis demonstrated effectiveness of perioperative intravenous amiodarone (1 g/day for 2 days after operation) at preventing POAF after isolated coronary artery bypass grafting, in cardiac surgeries involving valve repair/replacement only preoperative orally administered amiodarone was effective at preventing POAF.<sup>[5,25]</sup> This example of POAF prophylaxis, along with its concomitant risk of medication-induced complications, emphasizes the value of models to predict patients at high risk for POAF. It is important that prophylactic strategies be applied to patients who may

benefit the most while avoiding exposing patients at low risk of POAF to the potential side effects of unnecessary antiarrhythmic therapy. Patients in the current study were enrolled in a protocol designed to assess the impact of intraoperative amiodarone or lidocaine on ventricular fibrillation. Patients who received intravenous bolus administration of amiodarone up to 450 mg versus placebo in the original randomized trial<sup>[15]</sup> showed no benefit in freedom from POAF ( $P = 0.41$ ).

Occurrence of new-onset POAF in 40.8% of patients following cardiac surgery is consistent with previous reports including those from own institution.<sup>[1-12]</sup> The fact that 88% of patients experiencing POAF were treated with amiodarone suggest that these were clinically-significant episodes of POAF.

Limitations of this study include all those inherent to a retrospective review. However, the data were maintained in a prospective database as part of a randomized trial. Being a tertiary referral center involves the additional limitation that patients may seek care at outside institutions for events in the interim between preoperative testing (e.g. transthoracic echocardiogram) and surgery. Since transthoracic echocardiograms are not routinely repeated in the days immediately prior to surgery, it is possible that patients may have experienced events in this interim that may have changed their baseline diastolic function at the time of surgery. Although this study included patients with HOCM, a condition that renders diastolic function determination difficult, even after exclusion of these patients, diastolic dysfunction was not associated with POAF. This study is also limited in that various interventions known to prevent POAF such as postoperative beta blockade, atrial pacing, etc., were not examined. In addition, although amiodarone may be used to treat postoperative arrhythmias other than atrial fibrillation (e.g. ventricular arrhythmias or other supraventricular arrhythmias), this study was not designed to study the differences in incidences of these arrhythmias among patients receiving prophylactic intraoperative amiodarone compared to placebo.

## CONCLUSIONS

In this relatively large patient series, diastolic dysfunction was not associated with POAF following a variety of cardiac surgeries. Diastolic dysfunction may not be a predictor of POAF as only one previous study has shown this association. Therefore, caution should

be exercised before including diastolic dysfunction in predictive models of POAF. Our study is consistent with other reports showing that increasing age, left atrial size, and elevated pulmonary artery pressures are predictors of POAF.

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