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Abnormal Left Ventricular Filling and Postoperative Atrial Fibrillation After Cardiac Surgery

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Abstract

Objective: Diastolic dysfunction has been associated with the development of atrial fibrillation (AF) in the community and recently in the postoperative setting. We hypothesized that abnormal left ventricular filling predicts AF after cardiac surgery, a common marker of poor outcomes.

Methods: Cohort study of 233 consecutive patients, who underwent coronary artery bypass grafting (CABG) and/or valve surgery. Early and late mitral inflow velocity (E, A) and deceleration time (DT) and early mitral annular velocity (e') were obtained from echo within 6 months prior to cardiac surgery. Associations with postoperative AF were studied with multivariable logistic regression.

Results: Postoperative AF occurred in 65 (28%) of patients, who were on average older, more likely to have had prior episodes of AF, had larger inferior vena cava diameter and shorter DT (189 ± 62ms vs. 214 ± 63ms, p=0.007). Multivariable adjusted analyses demonstrated only DT (odds ratio [OR] 0.65 (95% confidence interval [CI] 0.40-0.97), older age (OR 2.62 (95% CI 1.68 - 4.10) and prior episodes of atrial fibrillation (OR 7.20, CI 1.41-36.8) to be independent predictors of postoperative AF. Patients with a DT ≤ 200ms (n=117) had a significantly longer length of hospital stay compared with those who had DT > 200ms (n=116) (median 7 days (interquartile range [IQR] 5-10) vs. 6 days (IQR 5-7, p=0.0002).

Conclusion: In patients who undergo cardiac surgery, a shorter DT of early mitral inflow identified greater risk for postoperative AF and a longer hospital stay. These results provide useful information for preoperative risk assessment and mechanistic understanding of postoperative AF.

Introduction

Atrial fibrillation (AF) after cardiac surgery is a common marker of increased complication rate, mortality and costs.[1, 2] Diastolic dysfunction (DD) is strongly associated with AF in the community[3-6] and recently diastolic dysfunction on echo has been associated with postoperative AF after cardiac surgery[7] and lung resection.[8] We hypothesized that greater E/e' and shorter DT, both validated measures of left ventricular filling pressure and wall stiffness, are associated with occurrence

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of postoperative AF after cardiac surgery.

Methods

Patients

Three hundred and twelve consecutive patients underwent coronary artery bypass grafting (CABG), valve surgery or both between January 2008 and September 2010 at MetroHealth Medical Center, a large urban academic safety net hospital in Cleveland, Ohio. We excluded patients who underwent MAZE procedure (n=3), vascular surgery or traumatic cardiac repair (n=2), patients

Table 1 Patient Characteristics

Variable	No POAF (n=168)		POAF (n=65)		P-value
Demographic	Mean/N	±SD/(%)	Mean/N	±SD/(%)	
Age, years	56	±11	65	±11	<.0001
BMI, kg/m^2	31	±5.9	30	±6.1	0.1
Male	102	(61)	41	(69)	0.7
Race Caucasian	109	(66)	45	(64)	0.3
Black	46	(27)	14	(22)	0.4
Hispanic	13	(7.7)	6	(9.2)	0.7
Clinical Data					
Prior atrial arrhythmia	2	(1.2)	12	(18)	<.0001
COPD	23	(14)	9	(14)	0.9
Diabetes Mellitus	71	(42)	26	(40)	0.9
Hypertension	147	(88)	52	(80)	0.2
Left Ventricular End Diastolic Pressure, mmHg	16	±5.2	16	±5.6	0.7
Echocardiographic data					
Left ventricular Ejection fraction by Echo, %	54	±13	52	±14	0.2
Left atrial volume, ml	36	±29	37	±27	0.7
Left atrial diameter, cm	3.8	±0.7	3.9	±0.7	0.1
E-wave, cm/s	83	±34	90	±29	0.1
A-wave, cm/s	77	±25	74	±24	0.4
E/A ratio	1.16	±0.55	1.34	±0.67	0.05
E'-wave, cm/s	6.3	±3.1	6.7	±3	0.3
E/E'	14	±7.9	14.8	±6	0.6
Deceleration Time, ms	214	±63	189	±62	0.007
Inferior Vena Cava size, cm	1.7	±0.2	1.9	±0.2	0.01
Lab data					
Creatinine, mg/dl	1.1	±0.9	1.1	±0.9	1
Hematocrit, g/dl	39	±4.9	39	±6.2	0.5
Medication use					
ACE inhibitor	109	(65)	35	(54)	0.2
Angiotensin receptor blocker	19	(11)	5	(8)	0.4
Beta blocker	147	(88)	53	(82)	0.3
Calcium channel blockers	31	(18)	18	(17)	0.9
Statin	141	(84)	48	(74)	0.1
Surgical					
CABG	141	(84)	52	(80)	0.6
Aortic valve replacement	24	(14)	13	(20)	0.4
Mitral valve replacement	6	(3.6)	7	(11)	0.07
Mitral valve repair	2	(1.2)	2	(3.1)	0.7

who were on anti-arrhythmic medications before surgery (n=2), who had greater than mild mitral stenosis (n=12) or no available echocardiogram within 180 days of surgery or with incomplete assessment of Doppler and/or tissue Doppler (n=60). Thus 233 patients were available for our analyses. Differences between included and excluded patients are shown in online supplemental materials (E-Table 1).

Patient Data

Demographic, cardiac and non-cardiac co-morbidity data and procedural data were obtained from electronic medical records. Echocardiographic data were obtained from the last echocardiogram before surgery within 6 months. Early mitral inflow velocity (E) and its deceleration time (DT), late mitral inflow velocity (A) and their ratio (E/A) as well as early septal and lateral mitral annular velocity (e') were measured from apical windows with pulsed wave Doppler and tissue Doppler, respectively and derived from averaging up to 3 measurements where available. The average between septal and lateral e' (averaged) measurements were used for analyses.[9] Subsequently the ratio of E/e' was calculated.[9] Left ventricular ejection fraction (LVEF) and left atrial volume were obtained by area length method.[10] Left ventricular hypertrophy was diagnosed if left ventricular mass index was greater than 110 g/m2 in women or 120 g/m2 in men.[10]

Left ventricular end-diastolic pressure (LVEDP) was obtained from last left heart catheterization before cardiac surgery (missing in 36 patients; missing data was slightly higher in patients with AF vs. no AF [23% vs. 13%]).

Our Institutional Review Board approved this study without the requirement for individual written patient consent.

Definition of Postoperative AF

According to the Society of Thoracic Surgeons national cardiac database, postoperative AF was defined as any episode of AF requiring treatment with rate controlling or anti-arrhythmic medications or electrical cardioversion after surgery and before hospital discharge.[11] All patients were continuously telemetry-monitored until discharge from the hospital.

Statistical Methods

Continuous variables are summarized using mean ± standard deviation and are compared using a two-tailed student's t-test or Whitney-Mann-U-test if skewed. Categorical variables are summarized by frequencies and percentages and are compared using χ^2 statistics. Odds ratios [OR] with 95% confidence intervals [CI] are reported for multivariable-adjusted variables and compare the 25th with 75th percentile of values for continuous variables (i.e. age). Because there was a skewed distribution, length of intensive care unit and hospital stay are reported as median and interquartile range (IQR) and compared with Wilcoxon rank sum test.

To adjust for confounding patient variables, we adjusted E/e' and DT with known risk factors for postoperative AF in our logistic regression model (age, body mass index, gender, race, history of hypertension, atrial fibrillation, diabetes, hyperlipidemia, renal disease, chronic obstructive pulmonary disease, preoperative beta blocker, ACE inhibitor, Angiotensin receptor blocker (ARB), statin use, LVEF, left atrial size, presence of left ventricular hypertrophy on echo, surgery type, LVEDP). Nonlinear relationships between continuous patient variables and postoperative AF were evaluated by introducing restricted cubic splines into the model, however we did not find evidence of nonlinearity of measured variables. We also created a parsimonious prediction model with nested variable selection at an adjusted alpha level of 0.05. We evaluated this prediction model with C-statistic, Hosmer-Lemeshow goodness-of-fit test and bootstrap-derived model calibration (predicted vs. observed probabilities) and created a nomogram to estimate multivariable-adjusted risk for AF given these model predictors. To identify predictors of DT as a continuous variable and group membership of DT<200ms we created a parsimonious linear and logistic regression model, respectively.

Length of hospital stay was compared between patients with DT < 200ms and patients with DT ≥ 200ms and patients with vs. without postoperative AF with Wilcoxon rank sum test with continuity correction.

We repeated analyses in subgroups: (1) Patients with echo data obtained within 7 days of surgery (n=123), (2) patients who underwent isolated CABG (n=179), (3) patients who underwent isolated valve surgery (n=40).

Study data were collected and managed using REDCap electronic data capture tools.[12] R version 2.12.1 (©2010 The R Foundation for Statistical Computing, www.r-project.org) was used for statistical analyses.

Results

Postoperative AF occurred in 65 (28%) of 233 included patients. As shown in Table 1, patients, who developed postoperative AF were older (65 ± 11 years vs. 56 ± 11, p<.0001), more likely to have had prior AF (18% vs. 1.2%, p<.0001), had a shorter DT (189 ± 62ms vs. 214 ± 63ms, 0.007) and a greater E/A ratio (1.16 ± 0.55 vs. 1.34 ± 0.67, p=0.046) and a larger inferior vena cava size (1.9 ± 0.2cm vs 1.7 ± 0.2cm, p=0.01). After multivariable adjustment, DT (odds ratio (OR) for 25th vs.75th percentile 0.63, 95% confidence interval (CI) 0.4-0.97), age (OR 2.62, CI 1.68-4.1), and prior episodes of AF (OR 7.2, CI 1.41-36.8) were independent predictors of postoperative AF. Other indices of left ventricular filling (E, e', E/e') were not associated with postoperative AF. The parsimonious prediction model with these 3 variables had a C-statistic of 0.77, indicating good model discrimination, passed the goodness-of-fit test (p=0.39) and had acceptable bootstrap-derived calibration with a mean absolute prediction error of 0.02 compared to a mean absolute prediction error of 0.016 of the prediction model with all variables included.

Figure 1: Multivariable adjusted probability of developing postoperative AF with varying early mitral inflow deceleration time (DT) amongst decades of patient age. In older patients the risk for AF is relatively higher with short DT compared to younger patients. A 50-year-old patient is at relatively low risk for postoperative AF irrespective of DT

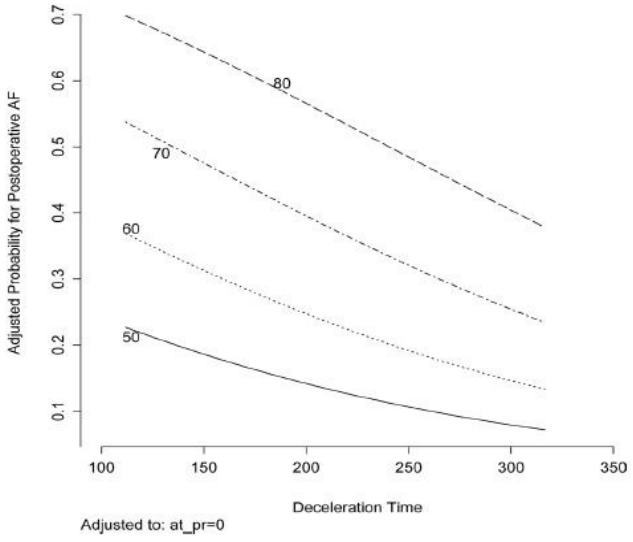


Figure 1 demonstrates that the effect of DT on the risk of postoperative AF varies with patient age: The slope appears slightly steeper in older patients indicating that older patients with short DT are at relatively higher risk for AF compared to younger patients with a short DT. Patient characteristics that were associated with shorter DT in multivariable linear regression were lower LVEF (correlation coefficient r=0.31, p<0.001, OR 0.38, CI 0.23-0.62), no preoperative use of ARBs (OR 1.91, CI 1.18-3.08)and larger inferior vena cava size (OR 0.31, CI 0.11-0.92).

In subgroup analyses of patients whose echo data were obtained within 7 days before surgery, patients undergoing isolated CABG, and isolated valve surgery the relationship between DT and postoperative AF remained significant (E-Table 2).

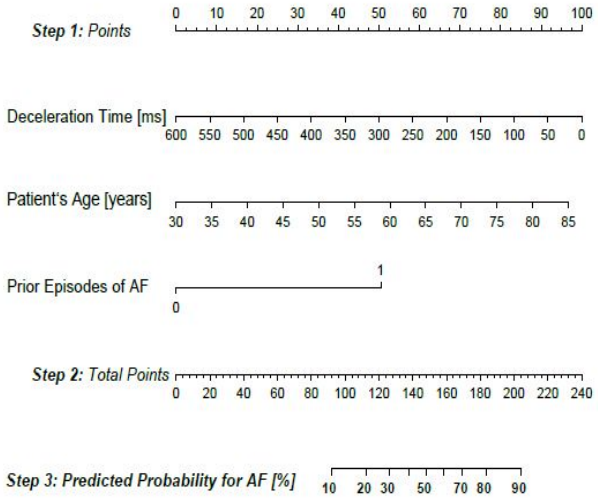
Patients with a DT<200ms had both a longer intensive care unit stay (3 days (IQR 2-4 days) vs. 2 days (IQR 1-3 days), p=0.0023), and hospital stay (7 days (IQR 5-10 days) vs. 6 days (IQR 5-7), p=0.00026). We also observed longer ICU stay (2 days [IQR 2-3] vs. 2 days [IQR 1-2], p=0.0007) and hospital stay (7 days [IQR 5-9] vs. 5 days [IQR 4-7, p=0.0021]), in patients with E/e' > 10.

Finally, Figure 2 shows a nomogram, which can be used in clinical practice to predict occurrence of postoperative AF given patients' age, prior episodes of AF and DT. For example, a 70-year-old patient (70 points) with no prior episodes of AF (0 points) and a DT of 350 ms (40 points, total of 110 points) has predicted risk to develop AF after surgery of approximately 17%, while the same patient with a DT of 150 ms (75 points, total of 145 points) of almost 50%.

Discussion

Our study of patients undergoing cardiac surgery at a single safety-net county hospital demonstrates

Figure 2: Nomogram for risk prediction of postoperative AF Extrapolate patient's age, presence/absence of prior episodes of AF and echo-derived mitral inflow velocity deceleration time (DT) to the first line and add points for total point score (fifth line) which can then be extrapolated to an estimate of the probability (%) of for AF after surgery from the last line



early mitral inflow deceleration time, a measure of left ventricular filling pressure and wall stiffness, to be a strong predictor of postoperative atrial fibrillation, and abnormal DT and E/e' to predict prolonged ICU and hospital stay. These findings provide useful information for risk prediction in daily practice, mechanistic insights and potential new therapeutic targets to improve surgical outcomes.

The association between diastolic dysfunction and AF in the community, especially in the elderly and those with congestive heart failure[4-6] has been well established. Recently, left ventricular diastolic dysfunction has been shown to be a predictor of postoperative AF after cardiac surgery.[7] Although these findings support our study results, grading of diastolic dysfunction has been shown to be difficult in clinical practice with an interobserver correlation of about 50%.13 E/e', an established surrogate of LVEDP, has been shown to be predictive for AF after lung transplant.[8] This finding suggests that elevated LVEDP may be mechanistically related to the development of postoperative AF in lung transplant. With progression from mild to severe diastolic dysfunction, LVEDP increases.[8] Combining these observations, elevated LVEDP secondary to diastolic dysfunction may be correlated with the development of postoperative AF. However, there is little evidence for such hypothesis currently. Aronson and colleagues showed recently, that a restrictive left ventricular filling pattern (defined as E/A [i.e. early/late mitral inflow velocity] >1.5 and DT <130ms) is associated with new onset AF after myocardial infarction.[14] DT as a continuous variable showed a non-linear relationship, with a marked increase in risk for AF below a 200ms cut-off in their study, confirming our results in a different patient population. Contrary to our hypothesis, we found no significant association between E/e' and postoperative AF. Interestingly, we also did not find an association between invasively measured LVEDP and postoperative AF, confirming that preoperatively elevated left ventricular pressure, whether measured invasively or non-invasively, alone may not be related to postoperative AF. De Waal and colleagues15 reported in a small series of 20 patients undergoing on-pump CABG that DT shortens after surgery as ventricular stiffness increases, while E/e' and calculated pulmonary capillary wedge pressure did not change. Although left ventricular stiffness also increased in 12 patients undergoing off-pump CABG, their DT did not change significantly. Given these results, we hypothesize that a stiffer left ventricle (with a shorter DT) is more sensitive to volume and pressure changes in the perioperative period, causing fluctuations of left atrial pressure and wall stretch, which increases ectopic atrial activation from pulmonary veins and induces AF.[16] It is unclear whether De Waal and colleagues' findings also correlate with the fact that off-pump CABG is associated with decreased occurrence of postoperative AF.[17] In our study, all but 2 surgeries were done with cardiopulmonary bypass support.

When we investigated predictors of shorter DT, only lower LVEF, larger inferior vena cava size and absence of preoperative ARB use was statistically significantly related (Table 2). These associations were of modest magnitude and only explained 15% of the variance of DT, which make conclusive statements about mechanisms impossible.

Beta blockers have been shown to increase DT in patients with heart failure.[18] This could in part explain the efficacy of beta blockers in the prevention of postoperative AF.[19] We have shown that preoperative therapy with angiotensin receptor blockers is not associated with postoperative AF.20 Although it has been previously described that lowering blood pressure improves left ventricular diastolic relaxation, these effects are not specific to ARBs.[18] There are preliminary data that suggest that statins, which have shown to reduce post-

Table 2 Comparison of Multivariable-adjusted Predictors of Postoperative AF in Pre-specified Subgroups

	Echo obtained within 7 days (n=123)		Isolated CABG (n=179)		Isolated valve surgery (n=40)	
Predictors	**Estimate**	**P-value**	**Estimate**	**P-value**	**Estimate**	**P-value**
DT	-0.013	0.0057	-0.01	0.028	-0.016	0.088
E	0.023	0.47	0.016	0.31	0.19	0.16
E/A	0.72	0.39	0.56	0.29	0.91	0.18
e'	0.19	0.56	-0.14	0.35	-0.32	0.71
E/e'	-0.15	0.41	-0.12	0.11	-0.65	0.21
Age	0.11	0.0001	0.09	<.0001	0.13	0.037
Prior episodes of AF	-1.29	0.47	1.61	0.081	8.86	0.83

operative AF in small randomized experiments,[21, 22] also improve myocardial stiffness and fibrosis.[23] Our results show that patients with higher filling pressures have prolonged ICU and hospital stay. Whether reduction of filling pressures before and immediately after surgery with diuretics or afterload reduction can improve outcomes remains to be studied.

Limitations

Inherent limitations of observational studies, such as confounding and selection bias have to be considered, however our approach of including consecutive patients undergoing cardiac surgery at an academic county hospital represents a more "real world" experience when compared to studies from tertiary referral centers.[7] Indices of left ventricular filling may change over time and may not have been representative of those at time of cardiac surgery. However, we analyzed the subgroup of patients whose echo data were obtained within 7 days of surgery and confirmed the results found in the overall cohort. We did not measure diastolic dysfunction as a categorical variable on purpose, because of its high interobserver variability of up to 50%.[13] Also, in older patients, mild diastolic dysfunction (abnormal relaxation type) may represent the norm rather than pathology and can therefore not be used for risk assessment in this high risk age group. Our approach of assessing left ventricular filling with E/e' and DT as continuous variables seems therefore more appropriate and clinically relevant.

Conclusions

Shorter deceleration time of early mitral inflow is associated with an increased risk of postoperative AF and may therefore not only be useful for preoperative risk assessment and guidance of prophylactic medication use, but also provides new insights of underlying mechanisms and potential new therapeutic targets. Whether perioperative hemodynamic optimization of left ventricular filling decreases occurrence of postoperative AF remains to be studied.

Disclosures

No disclosures relevant to this article were made by the authors.

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