Diastolic dysfunction, cardiopulmonary bypass, and atrial fibrillation after coronary artery bypass graft surgery

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Background. Atrial fibrillation (AF) is a common complication after coronary artery bypass graft (CABG) surgery, and is associated with increased morbidity, mortality, and utilization of healthcare resources. Diastolic dysfunction (DD) causes a range of changes in left atrial structure and function that may predispose patients to increased risk of AF. We hypothesized that patients with either new or worsened grade of DD after cardiopulmonary bypass (CPB) would have higher prevalence of AF after CABG surgery. The current study sought to determine an association between the dynamic changes in diastolic function during the perioperative period and postoperative AF in patients undergoing CABG surgery.

Methods. A total of 109 patients undergoing elective CABG surgery were assessed for the presence of DD before and after CPB. All patients were monitored for the development of AF after surgery for the entire hospital stay.

Results. DD was present in 89 (81%) and 91 (83%) patients before and after CPB. Thirty-four (31%) patients had either new or worsened grade of DD after CPB. Postoperative AF was present in 30 (27.5%) patients, including 15 (44%) patients with either new or worsened DD, and 15 (20%) patients with either unchanged or improved DD (P = 0.009). Independent predictors of postoperative AF included age ≥ 65 yr [odds ratio (OR) 4.207, 95% confidence interval (CI) 1.527, 11.588], and new or worsened DD (OR 4.145, 95% CI 1.519, 11.356).

Conclusions. New or worsened DD after CABG surgery is associated with an increased incidence of postoperative AF.


Keywords: atrial fibrillation; coronary artery bypass; echocardiography, transoesophageal; heart failure, diastolic

Accepted for publication: 19 March 2014

New-onset atrial fibrillation (AF) is a common complication after cardiac surgery. The reported incidence of postoperative AF after coronary artery bypass graft (CABG) surgery varies between 27% and 41%.1–3 It is associated with increased morbidity and mortality,1,4 prolonged intensive care unit, and hospital length of stay, and also greater utilization of healthcare resources.5 The recognized predictors of postoperative AF include advanced age, male gender, previous history of AF, congestive heart failure, obesity, anaemia, poor renal function, left ventricular hypertrophy, and left atrial enlargement.1,4,5

Echocardiographic predictors of postoperative AF include patent foramen ovale,6 increased left atrial area and volume,8 high left atrial appendage area, and low pulmonary vein systolic/diastolic velocity ratio.10 Newer echocardiographic measures that have been found to be associated with postoperative AF include total atrial conduction time,8 and left atrial peak systolic strain, strain rate, and early diastolic strain rate.9

Diastolic dysfunction (DD) is frequently present in patients undergoing cardiac surgery.11 12 It has been reported to be an independent risk factor for the future development of congestive heart failure and cardiac death.13 14 Recently, evidence has emerged that the presence of preoperative DD is associated with the development of new AF after cardiac surgery.5,15 DD causes a range of pathophysiological alterations in left atrial structure and function, which may predispose patients to atrial arrhythmias.16
The current study sought an association between the dynamic changes in diastolic function during the perioperative period and postoperative AF in patients undergoing CABG surgery. We hypothesized that patients with either new or worsened grade of DD after cardiopulmonary bypass (CPB) would have higher prevalence of AF after CABG surgery.

Methods

Ethics approval

The study was approved by the Institutional Research Ethics Board (REB #03-0873-A), and was registered with http://www.clinicaltrials.gov (unique identifier: NCT00188903). Written informed consent was obtained from all patients.

Patient population

A total of 123 patients undergoing elective CABG surgery with CPB were included in the study. Patients were excluded if they had a history of AF, emergency or redo-CABG, a surgical procedure in addition to CABG, greater than mild mitral regurgitation (MR), or if transoesophageal echocardiography was contraindicated.

Anaesthetic and surgical management

All routine cardiac medications were continued up to the morning of the surgery. Patients were pre-mediated with 2–4 mg of lorazepam 1–2 h before surgery. Anaesthetic technique was standardized to include midazolam 0.05 mg kg\(^{-1}\), fentanyl 8–10 \(\mu\)g kg\(^{-1}\), propofol 0.5–2 mg kg\(^{-1}\), and pancuronium 0.1 mg kg\(^{-1}\) for the induction of anaesthesia. Maintenance of anaesthesia was accomplished with 0.5–1.5% isoflurane and fentanyl 3–6 \(\mu\)g kg\(^{-1}\).

All patients underwent median sternotomy. Harvesting of saphenous veins and internal thoracic arteries as conduits was performed according to the standard institutional practice. Heparin was given to maintain activated clotting time >400 s. Management of CPB included systemic temperature drift to 33–34°C, \(\alpha\)-stat pH management, mean perfusion pressure between 60 and 80 mm Hg, and pump flow rates of 2.0–2.4 litre min\(^{-1}\) m\(^{-2}\). Myocardial protection was achieved with intermittent antegrade and retrograde cold blood cardioplegia if required. Before separation from CPB, patients were rewarmed to 36–37°C. After separation from CPB, heparin was neutralized with protamine.

Management of separation from CPB and choice of inotropic support were at the discretion of the anaesthesia care team. After completion of surgery, all patients were transferred to cardiovascular intensive care unit (CVICU) for postoperative ventilation and monitoring.

Assessment of diastolic function

Diastolic function was assessed intraoperatively at two time intervals: first, after induction of anaesthesia (before CPB) and, secondly, after the chest closure (after CPB). Measurements were made during periods of haemodynamic stability with no manipulations of loading conditions. Echocardiographic data were acquired using an Agilent Technologies Sonos 5500 (Andover, MA, USA) ultrasound system equipped with multiplane transoesophageal probes. Peak early (\(E\)) and late (\(A\)) mitral pulsed-wave Doppler flow profiles of ventricular filling velocities were measured. Deceleration time (DT) was calculated using the extrapolation of the upper \(E\) wave deceleration slope, as the time from the peak \(E\)-wave velocity to zero baseline. Pulmonary vein \(A\)-wave reversal velocities and duration were recorded. Tissue Doppler was used to measure mitral lateral annular early (\(e'\)) and late (\(a'\)) velocities. All measurements were acquired during apnoea using a sweep speed of 100 mm s\(^{-1}\) and stored for further analysis. Both \(E/A\) and \(E/a'\) ratios were calculated. Pulmonary venous \(A\)-wave duration was compared with mitral inflow \(A\)-wave duration (\(Ar–A\)).

DD was diagnosed and graded according to the American Society for Echocardiography (ASE) recommendations for the assessment of left ventricular diastolic function.\(^{1,2}\) DD was defined as lateral mitral \(e'<10\) cm s\(^{-1}\). Those patients who had DD were then graded according to the severity of DD, that is, impaired relaxation, pseudonormalization, and restrictive patterns, utilizing DT, \(E/A\), \(E/a'\), and \(Ar–A\) measurements.

- Impaired relaxation: DT>200 ms, \(E/A<0.8, E/a'\leq 8,\) and \(Ar–A<0.\)
- Pseudonormalization: DT=160–200 ms, \(E/A=0.8–1.5, E/a'=9–12, Ar–A=0–30\) ms.
- Restrictive pattern: DT<160, \(E/A>2.0, E/a'\geq 13,\) and \(Ar–A>30.\)

Echocardiographic data were reviewed by two ASE certified echocardiographers who were blinded to the outcome of interest. Diastolic function and the severity grading of DD were assessed before and after CPB in all patients. All patients were classed into two groups: Group A (patients with either unchanged, improved grade, or resolved DD) and Group B (patients with either new or worsened grade of DD).

Assessment of AF

All patients were assessed for the development of postoperative AF from the day of surgery to hospital discharge. Patients were monitored with continuous telemetry both in the CVICU and on the surgical floor for 2–5 days. Patients were considered to have AF if telemetry displayed an irregular rhythm, with either the absence of \(P\) waves or the presence of atrial fibrillatory waves, that did not resolve spontaneously. After telemetry was discontinued, patients were considered to have AF if they required either pharmacological intervention or cardioversion to restore normal sinus rhythm. All diagnoses were confirmed by a cardiologist-interpreted 12-lead electrocardiogram report.

Sample size justification and statistical analysis

Previously, we reported that the prevalence of AF after CABG surgery was 36%.\(^3\) Assuming that the rate of AF in patients with either new or worsened grade of DD would increase to 48%, and given the prevalence of AF in patients with normal diastolic function of 22%, with \(\alpha=0.05,\) and \(1–\beta=0.8,\) a group of 104 patients would be required. Allowing for 20% attrition, a total sample size would increase to 123 patients.
Univariate analysis

Descriptive analysis was performed for the variables of interest. Associations between the outcome and independent variables, including patient characteristics and clinical factors, were assessed with the \( \chi^2 \) and Fisher’s exact tests for categorical variables, and with the Mann–Whitney \( U \)-test for continuous variables. Unadjusted odds ratios (ORs) and 95% Wald confidence intervals (CIs) were also computed.

Multivariate analysis

Multivariate logistic regression was used to examine the relationship between change in diastolic function and postoperative AF while controlling for potential confounders. The Hosmer–Lemeshow modelling strategy was used to build the multivariate model. First, separate univariate analyses were conducted on each independent variable and the dependent variable, postoperative AF. Variables were selected for inclusion in the multivariate model based on Wald \( P \)-values of <0.3. Variables were added to the unadjusted model one at a time in the ranking order of the Wald test significance, allowing for variables with lower \( P \)-values being added earlier. If the change in OR was <10% at each step, the variable was excluded from the model. Lastly, variables with univariate \( P \)-values of >0.3, but that were clinically important, were returned to the final model.

Covariate effect

The Wald test was used to assess the significance of each covariate in the final multivariate model. A \( P \)-value of <0.05 was considered significant. The coefficient estimates, ORs, and 95% CIs were recorded.

Goodness of fit

The fit of the optimal model was assessed with various tests, including the likelihood ratio (LR), score and Wald tests. These tests compared the selected model (intercept and covariates) with the intercept-only model. Low \( P \)-values suggest that the selected model fits with the data significantly better than the intercept-only model. The Hosmer–Lemeshow test was also used to assess the goodness of fit, where actual event frequencies were compared with expected event frequencies based on the selected model. In addition, the discriminative power of the model was assessed by using the concordance index, \( c \), which is equal to the area under the receiver operating characteristic curve.

Results

A total of 123 patients were recruited in the study. Twelve patients were excluded from analysis because of conflicting echocardiographic data determining the presence or grade of DD. A further two patients were excluded because of the additional procedures performed during the planned surgery; one patient required a mitral valve repair, and the other had a replacement of ascending aorta with circulatory arrest.

DD was present in 89 (81%) and 91 (83%) patients before and after CPB. The frequency and severity of DD at baseline and after CPB are reflected in Figure 1A and B, respectively. After CPB, 75 patients were identified to have unchanged, improved grade, or resolved DD (Group A), and 34 patients had either new or worsened grade of DD (Group B). Both groups were similar with respect to patient characteristic data and surgical characteristics (Table 1).

Out of 20 patients who presented with normal diastolic function at baseline, 12 were identified with DD after CPB; nine patients had impaired relaxation, one pseudonormalization, and two restrictive patterns. DD was no longer present after CPB in two patients with pseudonormalization, and eight patients with impaired relaxation.

Postoperative AF was identified in a total of 30 (28%) patients after CABG surgery. AF was present in 12 (17%) and 18 (45%) patients in the <65 and ≥65 yr of age, respectively, \( P=0.0039 \). Patients with either new or worsened DD had significantly higher rates of AF when compared with the group with either resolved, improved, or unchanged DD (Fig. 2). Postoperative morbidity and mortality was similar between the two groups (Table 2).

The patterns of DD changed significantly in patients with AF from baseline to post-CPB. Normal diastolic function was present in four (13%) patients at baseline and one (3%) patient after CPB. Similarly, impaired relaxation pattern decreased from 14 (47%) to 6 (20%) patients conversely, there was an increase in the proportion of patients with pseudonormal pattern of DD from 11 (37%) to 20 (67%) patients after CPB. And finally, there was an increase in the proportion of patients with restrictive pattern of DD from 1 (3%) at baseline to 3 (10%) post-CPB.

There was no significant difference in the incidence of MR in the two groups. Before CPB, mild MR was present in 26 of 75 (35%) patients in Group A and 13 of 34 (38%) patients in Group B (\( P=0.72 \)); similarly, mild MR after CPB was present in 18 of 75 (24%) patients in Group A and eight of 34 (24%) patients in Group B (\( P=0.96 \)).

The multivariate logistic regression model showed that independent predictors of AF after CABG surgery included age ≥65 yr and new/worsened DD. Patients more than 65 yr of age had 4.2 times the odds of developing AF after CABG surgery compared with younger patients. Patients with either new or worsened DD after CPB had 4.1 times the odds of developing postoperative AF compared with patients with either resolved, improved, or unchanged DD (Table 3). The model fit was good with the LR, score, and Wald test \( P \)-values of 0.0047, 0.0059, and 0.0200, respectively. The Hosmer–Lemeshow test confirmed that the model fit was good \( P=0.7946 \), with \( c \)-statistic of 0.757 indicating adequate model discrimination.

Discussion

Over the past two decades, DD has generated a significant amount of academic and clinical attention. Our data demonstrate that the presence of new or worsened DD after CPB is associated with an increased risk of AF after CABG surgery. To our knowledge, this is the first study that has addressed the dynamic changes in diastolic function that occur during
the perioperative period, in relation to the risk of postoperative AF after CABG surgery. The rate of AF was increased more than two-fold in patients with either new or worsened grade of DD, when compared with patients with either unchanged, resolved, or improved grade of DD.

We also confirmed the well-established relationship between age and postoperative AF, with age $>65$ yr being associated with an almost three-fold increase in the incidence of postoperative AF. Increasing age is a consistent and reliable predictor of postoperative AF. Furthermore, age is associated with abnormal diastolic function because of altered ventricular relaxation and compliance, and DD has been proposed to be the common mechanism linking the observed increased incidence of postoperative AF with advancing age.

A relationship between DD and postoperative AF has previously been demonstrated. Melduni and colleagues showed an exponential increase in the incidence of postoperative AF as the severity of DD increased, based on preoperative outpatient assessment of diastolic function using transthoracic echocardiography. The authors reported the prevalence of AF in 35%, 58%, and 71% of patients with impaired relaxation, pseudonormalization, and restrictive patterns of DD, respectively, when compared with only 5% of patients with normal diastolic function. Our data add to this finding, by further demonstrating that it may not be solely the presence of preoperative DD that is important, but the relative change in diastolic function that occurs after myocardial revascularization with CABG.

The new development or worsening of DD after CPB is likely a consequence of the ischaemia–reperfusion injury. This phenomenon is known to be associated with a variety of adverse events, including arrhythmia, myocardial stunning, low cardiac output, and perioperative myocardial infarction. Furthermore, myocardial interstitial oedema may reduce left ventricular compliance, leading to a temporary deterioration in diastolic function after cardiac surgery. It is important to note that

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**Fig 1** Patients with and without DD after (A) induction of anaesthesia and (B) CPB.
Diastolic dysfunction and atrial fibrillation

patients who developed AF after surgery were more likely to have an advanced severity of DD, that is, either pseudonormal or restrictive patterns of DD. The improvement in the grade of DD and the resolution of DD after CPB were likely related to the resolution of preoperative ischaemia, reflecting optimization of atrial and global myocardial blood flow. This phenomenon may be protective against the development of postoperative AF.

DD and AF share many common risk factors, such as age, hypertension, diabetes, and obesity. In non-surgical patient populations with DD, the incidence of AF may be as high as 27%. AF increases the risk of death and thromboembolic complications in patients with DD. The mechanistic links between DD and AF are thought to be three-fold:

1. Atrial dilation and stretch are considered to be proarrhythmic because of both the ‘multiple wavelet hypothesis’ (whereby increased left atrial size allows multiple wavelets of re-entry) and atrial fibrosis (which impairs uniform conduction).
2. Furthermore, left ventricular DD causes an increase in left atrial pressure, which in turn increases the stretch of the pulmonary veins, which is known to be associated with the development of AF.
3. The current study should be viewed in the light of several limitations. First, we examined AF that occurred during the period of hospital stay. AF that may have occurred after hospital discharge was not included in the analysis, and therefore, our incidence of AF may have been underestimated. However, the peak occurrence of postoperative AF is usually between postoperative days 2 and 5, which is well within the period of primary admission, and, the overall rate of AF at 28% in the current study is in accordance with the literature reports. Secondly, we did not assess the patients for response to treatment of AF and conversion to sinus rhythm. However, the conversion rate in patients after CABG surgery is fairly high, occurring either spontaneously or after treatment, in most patients before discharge from hospital. Thirdly, we did not reassess diastolic function before discharge. As a result, our findings

Table 1 Patient characteristic variables and surgical characteristics. Data expressed as mean (sd), number of patients (%), or median (range)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group B (n = 34)</th>
<th>Group A (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60 (41–80)</td>
<td>61 (39–80)</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>31 (91)</td>
<td>65 (87)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.9 (4.4)</td>
<td>29.2 (4.4)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;40%</td>
<td>3 (9)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Coexisting illness [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (29)</td>
<td>25 (33)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (65)</td>
<td>53 (71)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2 (6)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>12 (35)</td>
<td>27 (36)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4 (12)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Preoperative medication [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>22 (65)</td>
<td>49 (65)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>13 (38)</td>
<td>37 (49)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>8 (23)</td>
<td>15 (20)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>31 (91)</td>
<td>64 (85)</td>
</tr>
<tr>
<td>Statins</td>
<td>29 (85)</td>
<td>64 (85)</td>
</tr>
<tr>
<td>Intraoperative variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBP time (min)</td>
<td>84 (27)</td>
<td>87 (25)</td>
</tr>
<tr>
<td>Number of distal anastomoses (n)</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
</tr>
</tbody>
</table>

Fig 2 Rates of postoperative AF.

Table 2 Postoperative complications and length of stay. Data expressed as number of patients (%), and median (range)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group B (n = 34)</th>
<th>Group A (n = 75)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of inotropes [n (%)]</td>
<td>8 (23)</td>
<td>21 (28)</td>
<td>0.625</td>
</tr>
<tr>
<td>Myocardial infarction [n (%)]</td>
<td>1 (3)</td>
<td>3 (4)</td>
<td>0.785</td>
</tr>
<tr>
<td>Renal impairment [n (%)]</td>
<td>7 (20)</td>
<td>12 (16)</td>
<td>0.559</td>
</tr>
<tr>
<td>Stroke [n (%)]</td>
<td>1 (2.9)</td>
<td>2 (2.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Death [n (%)]</td>
<td>0 (0)</td>
<td>1 (1.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>7 [4–15]</td>
<td>6 [4–41]</td>
<td>0.680</td>
</tr>
</tbody>
</table>

Table 3 Multivariate analysis: adjusted OR with outcome of postoperative AF. LRT P = 0.0047; score P = 0.0059; Wald P = 0.0200; Hosmer–Lemeshow P = 0.7946; c = 0.757

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient estimate</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD (new or worsened vs resolved, improved or unchanged)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (≥65 vs &lt;65 yr)</td>
<td>1.4368</td>
<td>4.207</td>
<td>1.527, 11.588</td>
<td>0.0054</td>
</tr>
<tr>
<td>CBP bypass time</td>
<td>0.00620</td>
<td>1.006</td>
<td>0.988, 1.025</td>
<td>0.5050</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>−0.2667</td>
<td>0.766</td>
<td>0.281, 2.090</td>
<td>0.6025</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>−0.4206</td>
<td>0.657</td>
<td>0.238, 1.814</td>
<td>0.4173</td>
</tr>
<tr>
<td>Left ventricular grade</td>
<td>0.1490</td>
<td>1.161</td>
<td>0.568, 2.372</td>
<td>0.6828</td>
</tr>
</tbody>
</table>
are restricted to the immediate perioperative period. Fourthly, 12 patients were excluded from the analysis because of incomplete or conflicting data that prevented accurate diagnosis and grading of DD. However, it is well known that a small number of patients with DD have inconsistent echocardiographic findings that may be impossible to resolve. Lastly, our study was limited to patients undergoing elective CABG surgery, and consequently, our findings could not be extrapolated to other patient populations.

**Implications for clinical practice**

Prophylaxis for postoperative AF is largely empirical, and varies greatly with institutional and individual practice. Identification of patients at higher than average risk of postoperative AF may allow prophylactic therapies to be directed more selectively. Furthermore, with the future advent of new, specific lusitropic agents, targeted therapy for perioperative DD may reduce the incidence of AF, and accordingly, the risk of postoperative morbidity, mortality, and cost to the healthcare system.

**Conclusion**

New or worsened DD after CABG surgery is associated with an increased incidence of postoperative AF. Perioperative identification of these patients may allow targeted prophylactic antiarrhythmic therapy or stricter postoperative monitoring for arrhythmias. With the development of novel specific lusitropic agents, it may be possible to use them as a new modality for the prevention of postoperative AF in this patient population.

**Authors’ contributions**

C.M.A.: analysis and interpretation of data, drafting, and revising manuscript; M.Y.: analysis and interpretation of data, drafting, revising manuscript, and final approval of the manuscript; M.M. and R.K.: data collection, review, and final approval of the manuscript; J.C. and V.R.: data review and final approval of the manuscript; G.D.: study conception and design, data review and analysis, critical revision of the manuscript, and final approval of the manuscript.

**Declaration of interest**

None declared.

**Funding**

This work was funded through departmental support.

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Handling editor: A. R. Absalom