



Predictors of post-operative atrial fibrillation in patients undergoing cardiac surgery: the potential role of epicardial adipose tissue

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Background: Post-operative atrial fibrillation (POAF) is a common complication following cardiac surgeries, however current risk factors lack predictive accuracy. Our aim was to investigate whether computed tomography (CT) measurement of epicardial adipose tissue (EAT) improves risk prediction over clinical predictors of POAF.

Methods: Fifty-six patients who underwent aortic valve replacement (AVR) and/or coronary artery bypass graft (CABG) during 2013 to 2015 were identified retrospectively. Peri-operative clinical characteristics were collected, and epicardial fat dimensions were measured using CT.

Results: POAF occurred in 27 patients (48.2%). The incidence of POAF was greater in patients undergoing CABG with or without AVR compared to AVR alone (64% *vs.* 32%, $P=0.018$). Univariate logistic regression model showed CHA2DS2-VASc score [odds ratio (OR): 1.629; 95% CI: 1.086–2.443; $P=0.018$] and EuroSCORE II (OR: 1.528; 95% CI: 1.006–2.320; $P=0.047$) to be significantly associated with POAF. Between-group analysis showed left atrial (LA) diameter was significantly associated with POAF compared to no-POAF (4.18 ± 0.74 *vs.* 3.74 ± 0.36 cm; $P=0.047$). The sum of right coronary artery fat pocket and inferior interventricular (IV) groove was higher in POAF patients (7.75 ± 1.70 *vs.* 6.87 ± 2.27 ; $P=0.05$). A novel scoring system comprising EuroSCORE II, CHA2DS2-Vasc and LA diameter was created which was significantly associated with POAF risk compared to CHA2DS2-Vasc alone (receiver operator curve AUC 0.804; 95% CI: 1.162–15.180; $P=0.029$). However, adding EAT to the POAF scoring system did not improve the risk prediction model for POAF (AUC 0.79; 95% CI: 1.083–12.998; $P=0.037$).

Conclusions: A novel POAF prediction scoring system including LA diameter, EuroSCORE II and CHA2DS2-Vasc was strongly associated with POAF and may be a useful clinical tool when planning cardiac surgery. Addition of EAT did not improve risk prediction beyond clinical predictors. Further large-scale studies are required to assess the validity and usefulness of the scoring system.

Keywords: Atrial fibrillation (AF); cardiac surgical procedures; coronary artery bypass; computed tomography (CT)

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Introduction

Post-operative atrial fibrillation (POAF) is reported in 15% to 40% of patients in the early post-operative period after coronary artery bypass graft (CABG), and in 40% to 50% of patients after isolated valve surgery or combined CABG/valve surgery (1-3). Up to 20% of patients may not revert to sinus rhythm within 24 hours of POAF onset in patients without previous history of atrial fibrillation (AF) (4). Moreover, POAF is associated with increased duration of hospitalisation, healthcare costs, and incidence of stroke or need for a permanent pacemaker with associated mortality (1,5).

Many cardiovascular risk factors have been associated with AF, however they lack predictive accuracy to identify patients who will develop POAF (6,7). There has been recent interest in the potential of epicardial adipose tissue (EAT) as a marker of both coronary artery disease (CAD) and risk of future AF. Increasing evidence seems to indicate pericardial fat as a metabolically active tissue modulating the adjacent myocardial tissue in paracrine and vasocrine manners with production of pro-atherogenic and pro-inflammatory adipokines (8-10). Several studies including the Framingham Heart Study (11), the Multi-Ethnic Study of Atherosclerosis (12) and others have demonstrated a relationship of increased pericardial fat volume with CAD, atherosclerosis, progression of coronary plaque burden and AF (13-15).

In the context of cardiac surgery, inflammation due to cardiopulmonary bypass, ischemia and oxidative stress have been implicated in the development of POAF (16-18). A recent study showed that pericardial fat volume measured on computed tomography (CT) is strongly associated with AF after CABG, independent of traditional risk factors (19). With the advent of non-invasive imaging techniques, it would be useful to predict POAF in patients undergoing cardiac surgery utilizing pre-operative characteristics on routine investigations. Such prediction would allow for pre-emptive anti-arrhythmic therapy that could potentially decrease AF occurrence post-operatively. Therefore, our aim was to investigate clinical predictors of POAF, including whether EAT improves risk prediction.

Methods

The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by Institutional Ethics Committee. Fifty-six consecutive patients who

underwent first-time aortic valve replacement (AVR) or on-pump CABG with or without AVR during 2013 to 2015 were included in this study. Patients who had undergone thoracic CT scan in the previous six months were included in the study from the Mount Hospital Cardiothoracic Database. Consent was gained after the patients' procedures for inclusion of their data in this study. Patients with permanent AF, prior permanent pacemaker or AF ablation were excluded to avoid bias in POAF incidence. Study variables included age, sex, body mass index (BMI), smoking status, medications, comorbidities and pre- and post-operative laboratory tests. POAF was defined as any documented episode of AF post-operatively, both treated and untreated, during hospital stay. Echocardiogram and coronary angiogram performed within six months prior to the patients' surgery was included in the data collection.

EAT measurements

CT scans performed within six months prior to the surgery included a range of different scan protocols performed for varying clinical indications, hence, the study included both contrast and non-contrast scans, and scans with and without cardiac ECG gating. A consultant radiologist, blinded to the POAF status of the subjects, measured the EAT parameters in this study. EAT measurements can substantially differ between contrast-enhanced and non-contrast CT, but can be reconciled by threshold modification (20). Therefore, an upper threshold on fat volume of -15 Hounsfield unit (HU) for contrast CT was used and -45 HU threshold for non-contrast CT images (20). The EAT thickness measurements were made using protocol described by Yorgun *et al.* (21). Multiplanar reconstructions of the axial raw data were created in the horizontal long axis (four-chamber) view, and ventricular short axis and at the basal, mid ventricular and apical levels on a workstation (Advantage Windows GE Healthcare) with a slice thickness of 3 mm. EAT was defined as the adipose tissue between the myocardium and the epicardium. EAT thickness measurements were performed from seven short-axis view segments (*Figure 1*) including right ventricular (RV) anterior free wall superior, RV anterior free wall inferior, RV superior wall, RV diaphragmatic wall, superior interventricular (IV) groove, left ventricular (LV) lateral wall. The mean of measurements taken at those levels (basal, mid, apical) was used for analyses.

The left atrium (LA) short-axis view (*Figure 1B*) was reconstructed as a plane perpendicular to the long axis of

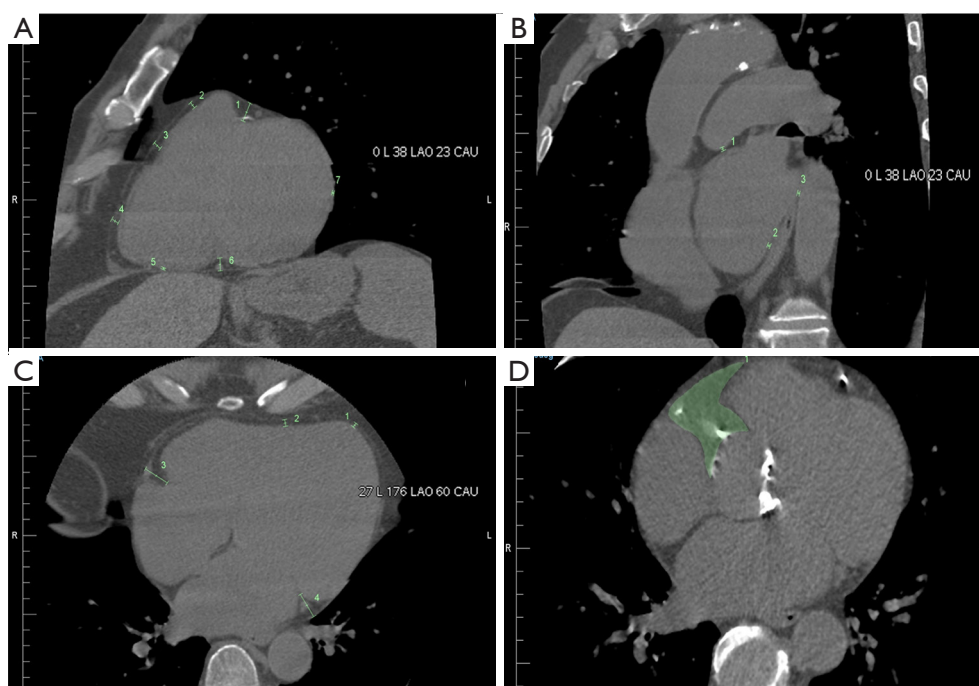


Figure 1 Representative images of epicardial adipose tissue (EAT) and peri-coronary fat measurements. (A) Parasternal short-axis views including superior interventricular (IV) groove [1], right ventricular (RV) superior wall [2], RV anterior free wall superior [3], RV anterior free wall inferior [4], RV diaphragmatic wall [5], inferior IV groove [6] and left ventricular (LV) lateral wall [7]; (B) short-axis view at the level of the mid left atrium (LA), peri-atrial fat measurements from LA-pulmonary artery [1], LA-esophagus [2] and LA-descending aorta [3]; (C) horizontal long-axis (four-chamber) view showing LV apex [1], RV apex [2], right atrioventricular (AV) groove [3] and left AV groove [4]; (D) area of diastolic right coronary artery fat pocket (RCA-FP).

standard two- and four-chamber views of LA at the level of the mid LA. In this short-axis view, the periatrial EAT thickness was measured (in mm) as the shortest distance between the mid LA wall and the esophagus (LA-Eso), main pulmonary artery (LA-PA), and descending thoracic aorta (LA-Desc Ao).

On the horizontal long axis (four-chamber) view (*Figure 1C*), EAT was measured from four segments including LV apex, RV apex and peri-coronary areas [left atrioventricular (AV) groove and right AV groove]. Total EAT thickness was calculated as the sum of EAT thickness measurements from eleven segments including the apical four chamber views and the short-axis views

The EAT volumetric measurements were made using protocol described by Saremi *et al.* (22). The right coronary artery fat pocket area (RCA-FP) (*Figure 1D*) was defined as the area of EAT at the level of RCA origin located between the right atrium, ascending aorta, and RV outflow tract measured in the axial plane. The anterior border of the RCA-FP was limited by the pericardial line extending

between its closest points with the anterior margins of the RA and right ventricle outflow tract.

Statistical analysis

Continuous variables are presented as mean values \pm standard deviation (SD) for normally distributed data, or median and interquartile ranges for non-parametric data. Univariate analyses were performed on continuous variables using Mann-Whitney U test. Categorical variables are presented as percentages and differences between nominal variables were analyzed using the chi-square test. Logistic regression analysis was performed for the level of significance of risk factors and between-group relationships. A multivariate logistic regression model was performed to estimate the odds ratio (OR) of POAF while controlling for potential confounding variables and/or known risk factors of AF, but not including those variables in the CHA₂DS₂-Vasc or EuroSCORE II, to avoid interdependence (BMI, valvular heart disease, diabetes mellitus, LV-EF, pre-operative

Table 1 Post-operative atrial fibrillation prediction scoring system

Prediction score for each risk factor	1 point if at least
CHA ₂ DS ₂ -Vasc	2
EuroSCORE II	4.8
LA diameter (cm)	4.8
Sum of RCA-FP and IIG	11.4

Each risk factor predicted atrial fibrillation above the threshold presented in this table. The total score was determined by the sum of the CHA₂DS₂-Vasc and one point for every risk factor that was above the threshold. IIG, inferior interventricular groove; LA, left atrium; RCA-FP, right coronary artery fat pocket area.

creatinine, pre-operative hemoglobin, statin and aspirin use). P values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS® statistical software (version 23; SPSS Inc., Chicago, IL, USA).

POAF prediction scoring system

Using the most significantly associated variables found in this study (CHA₂DS₂-Vasc score, LA diameter, EuroSCORE II, and EAT) we developed a POAF prediction scoring system (*Table 1*) using cut-off values of twice the standard deviation for each variable. For the CHA₂DS₂-Vasc score, the cut-off score was allocated as ≥ 2 as this normally represents high-risk patients in whom anticoagulation is recommended (23). Each patient's POAF prediction score comprised of the sum of their CHA₂DS₂-Vasc score plus one point for every variable that exceeded the cut-off score.

Results

In the study cohort of 56 patients (79% male), POAF occurred in 48% of patients. Three patients had pre-operative paroxysmal or persistent AF (5%). POAF occurred most commonly on day three post-operation. Twenty-eight patients underwent first-time AVR procedures and 28 patients received CABG with or without AVR. The incidence of POAF was greater in patients undergoing CABG with or without AVR compared to AVR alone (64% *vs.* 32%, $P=0.018$).

The clinical characteristics of the study population are shown in *Table 2*. Of note, the median age was higher in the POAF population (81 years, range: 70.0–84.0 years) than the no-POAF population (76 years, range: 57.5–81.0 years)

($P=0.043$). Univariate logistic regression model showed CHA₂DS₂-VAsc score [odds ratio (OR): 1.629; 95% CI: 1.086–2.443; $P=0.018$] and EuroSCORE II (OR: 1.528; 95% CI: 1.006–2.320; $P=0.047$) to be significantly associated with POAF. Pre-operative investigations including echocardiography and angiography results are outlined in *Table 3*. Between-group analysis showed left atrial (LA) diameter was significantly associated with POAF compared to no-POAF (4.18 \pm 0.74 *vs.* 3.74 \pm 0.36 cm; $P=0.047$). Patients with POAF had numerically, but not significantly, higher E:E' ratios (18.00 \pm 9.44 *vs.* 12.81 \pm 4.44; $P=0.08$).

Intraoperative characteristics (*Table 3*) including longer bypass time (median 96 mins, range: 76.0–110.0 mins *vs.* median 75 mins, range: 65.0–89.5 mins; $P=0.007$) and cross-clamp time (median 68 mins, range: 60.0–87.0 mins *vs.* median 58 mins, range: 46.5–67.0 mins; $P=0.013$) were also associated with POAF. Furthermore, POAF was significantly associated with increased hospital stay (10.3 \pm 4.3 *vs.* 8.2 \pm 4.2 days; $P=0.005$) and ICU stay (3.8 \pm 1.9 *vs.* 2.4 \pm 1.1 days; $P<0.005$).

EAT measurements

EAT measurements on CT (*Table 4*) that demonstrated a trend to significance but with $P>0.05$ were inferior IV groove (1.67 \pm 0.45 *vs.* 1.47 \pm 0.37 cm; $P=0.06$) and RCA-FP (6.08 \pm 1.59 *vs.* 5.41 \pm 2.16 cm²; $P=0.08$). The sum of these two parameters was significantly associated with POAF (7.75 \pm 1.70 *vs.* 6.87 \pm 2.27; $P=0.05$).

POAF prediction scoring system

A novel POAF risk prediction scoring system was created, outlined in *Table 1*. Multivariate logistic analysis (*Table 5*) revealed the scoring system using CHA₂DS₂-VAsc score only was not statistically significant in predicting POAF (OR, 5.916; 95% CI: 0.876–39.949; $P=0.068$). However, the CHA₂DS₂-VAsc score and LA diameter was strongly associated with POAF (OR, 3.792; 95% CI: 1.142–12.586; $P=0.029$). Adding EuroSCORE II improved the scoring system and was most powerfully associated with POAF, with each increase in score raising the risk of POAF by 4.2x (OR, 4.201; 95% CI: 1.162–15.180; $P=0.029$). Adding EAT to the components of the scoring system was still associated with POAF (OR, 3.752; 95% CI: 1.083–12.998; $P=0.037$) but did not improve upon the simpler scoring system using clinical and echocardiographic variables.

Receiver operator curve analysis (*Figure 2*) showed

Table 2 Clinical pre-operative data of patients undergoing CABG and/or AVR, with or without post-operative atrial fibrillation

Variable	All patients (n=56)	AVR (n=28)	CABG or CABG + AVR (n=28)	POAF positive (n=27)	POAF negative (n=29)	P value
Age, years	78 (65.5–82.0)	76 (58.0–82.0)	79 (70.3–82.8)	81 (70.0–84.0)	76 (57.5–81.0)	0.043
Male	44 (79%)	20 (71%)	24 (86%)	21 (78%)	23 (79%)	0.889
BMI, kg/m ²	28.7 (24.4–31.7)	30.5 (25.4–33.2)	28.5 (23.0–30.4)	28.7 (22.6–32.1)	28.6 (25.0–31.6)	0.825
Current smoker	4 (7%)	2 (7%)	2 (7%)	1 (4%)	3 (10%)	0.323
Hypertension	44 (79%)	20 (71%)	24 (86%)	23 (85%)	21 (72%)	0.244
Dyslipidaemia	46 (82%)	20 (71%)	26 (93%)	22 (81%)	24 (83%)	0.901
Diabetes	13 (23%)	6 (21%)	7 (25%)	6 (22%)	7 (24%)	0.867
Heart failure	4 (7%)	1 (4%)	3 (11%)	3 (11%)	1 (3%)	0.257
FMHx of premature CAD	9 (16%)	3 (11%)	6 (21%)	3 (11%)	6 (21%)	0.325
Paroxysmal AF	3 (5%)	2 (7%)	1 (4%)	2 (7%)	1 (3%)	0.605
Prior stroke	1 (2%)	0	1 (4%)	1 (4%)	0	0.224
Prior TIA	4 (7%)	3 (11%)	1 (4%)	3 (11%)	1 (3%)	0.257
Chronic renal failure	5 (9%)	0	5 (18%)	4 (15%)	1 (3%)	0.126
PVD	5 (9%)	2 (7%)	3 (11%)	2 (7%)	3 (10%)	0.699
Hypothyroidism	6 (11%)	2 (7%)	4 (14%)	3 (11%)	3 (10%)	0.926
COPD	1 (2%)	1 (4%)	0	0	1 (3%)	0.248
Scoring systems						
EuroSCORE II, %	1.63 (0.87–2.61)	1.33 (0.80–2.42)	2.11 (1.16–3.47)	2.23 (1.16–3.70)	1.26 (0.67–2.13)	0.006
CHA ₂ DS ₂ -Vasc	4 [2.0–4.8]	3 [2–4]	4 [3–5]	4 [4–5]	3.0±1.6	0.019
Regular medications						
Beta-blockers	19 (34%)	5 (18%)	14 (50%)	10 (37%)	9 (31%)	0.635
Calcium channel blocker	18 (32%)	6 (21%)	12 (43%)	11 (41%)	7 (24%)	0.184
ACEI	20 (36%)	7 (25%)	13 (46%)	9 (33%)	11 (38%)	0.72
ARB	22 (39%)	12 (43%)	10 (36%)	14 (52%)	8 (28%)	0.063
Statins	45 (80%)	19 (68%)	26 (93%)	23 (85%)	22 (76%)	0.38
Aspirin	33 (59%)	13 (46%)	20 (71%)	17 (63%)	16 (55%)	0.554
Amiodarone	1 (2%)	1 (4%)	0	1 (4%)	0	0.224

ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin 2 receptor blockers; AVR, aortic valve replacement; BMI, basal metabolic index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; FMHx, family history; POAF, post-operative atrial fibrillation; PVD, peripheral vascular disease; TIA, transient ischemic attack.

similar results with a score combining CHA₂DS₂-VASC score, LA diameter and EuroSCORE II having the highest association with POAF (AUC 0.804; P=0.006) (*Figure 2B*), but EAT did not improve the predictability (AUC 0.792; P=0.008) (*Figure 2D*). However, the combined graph showing the ROC curves (*Figure 2E*) revealed the models

to have similar predictability and therefore warrants further investigations to determine the usefulness of EAT.

Discussion

Incidence of atrial arrhythmias after cardiac surgery has

Table 3 Investigative peri-operative data of patients undergoing CABG and/or AVR with and without post-operative atrial fibrillation

Variable	All patients (n=56)	AVR (n=28)	CABG or CABG + AVR (n=28)	POAF positive (n=27)	POAF negative (n=29)	P value
Echocardiography						
LVEF, %	59.5±12.5	63.7±10.8	54.8±12.8	60.1±13.3	64.0±11.7	0.628
LA diameter, cm	4.00±0.64	3.87±0.42	4.11±0.79	4.18±0.74	3.74±0.36	0.047
LVEDD, cm	4.50±0.70	4.55±0.78	4.45±0.63	4.38±0.68	4.40±0.73	0.187
IVS, cm	1.33±0.23	1.33±0.18	1.33±0.29	1.35±0.26	1.30±0.21	0.725
LVPW, cm	1.24±0.20	1.28±0.21	1.20±0.20	1.27±0.18	1.30±0.22	0.203
E:E' ratio	15.41±7.70	12.42±3.02	18.84±9.95	18.00±9.44	12.81±4.44	0.08
Angiography						
Gensini score	3.25±3.56	0.74±0.84	5.04±3.68	3.76±3.99	2.44±2.67	0.346
Sullivan score	15.65±14.75	4.97±6.88	23.27±14.18	17.48±15.37	12.77±13.79	0.276
Vessel score	0.86±1.07	0.07±0.26	1.43±1.08	0.95±1.05	0.71±1.14	0.386
Pre-operative laboratory results						
Hemoglobin, g/L	135.5±16.2	133.2±17.5	137.9±14.8	133.8±15.3	137.1±17.2	0.426
Creatinine, μmol/L	96.3±27.8	91.0±22.3	101.6±32.0	100.6±30.3	92.3±25.2	0.265
Sodium, mmol/L	139.1 ±2.9	139.1±2.7	139.2±3.1	138.8±2.7	139.5±3.0	0.438
Diabetic BSL	7 (13%)	3 (11%)	4 (14%)	3 (11%)	4 (14%)	0.761
Intra-operative variables						
Bypass time, m	84 (71.0–99.0)	75 (68.5–84.0)	98.5 (84.3–114.8)	96 (76.0–110.0)	75 (65.0–89.5)	0.007
Cross-clamp time, m	63 (54.5–79.5)	61.5 (54.5–66.3)	77 (52.8–100.5)	68 (60.0–87.0)	58 (46.5–67.0)	0.013

AVR, aortic valve replacement; BSL, blood sugar level; CABG, coronary artery bypass grafting; IVS, interventricular septal thickness (end-diastolic); LVEF, left ventricular ejection fraction; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVPW, left ventricular posterior wall thickness; POAF, post-operative atrial fibrillation.

been reported to range from 10% to 65% (24,25). In our study, POAF was present in 48% of patients after cardiac surgery, including AVR alone or CABG with or without AVR. This study also confirmed that POAF most often occurs within the first few days after cardiac surgery, with the peak incidence on post-operative days two and three (26,27).

Increasing age has been correlated with POAF in previous studies. Age-related structural or electrophysiological changes appear to lower the threshold for postoperative atrial tachyarrhythmias in the elderly (1,7,26). Our study showed that higher age was associated with POAF. However, this could be confounded by higher average age of patients receiving CABG procedures (76±9 *vs.* 72±15 years), and POAF was more prevalent in patients undergoing CABG with or without AVR compared to AVR alone (64% *vs.* 32%, *P*=0.018).

Several mechanisms are involved in the pathogenesis of POAF. Dispersion in atrial refractoriness causes multiple local re-entry wavelets, which can be induced by surgical trauma, manipulation and myocardial ischemia. Furthermore, increased sympathetic activation, exaggerated inflammatory response and oxidative stress may contribute to the development of POAF (16,28). Related to this, cardiopulmonary bypass and cross-clamp times, type of cardioplegia, and CABG surgical techniques are regarded as critical in determining ischemic injury (29). Hence, this study explored POAF in patients undergoing AVR alone and patients undergoing on-pump CABG with or without AVR to compare the incidence of POAF and EAT characteristics in these two different populations. Patients undergoing AVR alone had shorter bypass time [75 (68.5–84.0) *vs.* 98.5 (84.3–114.8) mins] and cross-clamp time [61.5

Table 4 Epicardial adipose tissue measurements of patients undergoing AVR or CABG with and without post-operative atrial fibrillation

EAT segments (cm)	All patients (n=56)	AVR (n=28)	CABG or CABG + AVR (n=28)	POAF positive (n=27)	POAF negative (n=29)	P value
Apical four chamber view						
Pericoronary fat tissue (right AV groove)	1.61±0.35	1.59±0.35	1.64±0.34	1.67±0.29	1.56±0.39	0.25
Pericoronary fat tissue (left AV groove)	1.30±0.29	1.29±0.33	1.32±0.25	1.33±0.25	1.29±0.33	0.53
LV apex	0.27±0.11	0.29±0.12	0.25±0.09	0.27±0.12	0.28±0.10	0.68
RV apex	0.59±0.24	0.63±0.26	0.55±0.21	0.58±0.22	0.59±0.26	1.00
Short axis view						
RV anterior free wall, superior	1.30±0.47	1.33±0.47	1.26±0.48	1.28±0.47	1.32±0.48	0.79
RV anterior free wall, inferior	1.51±0.61	1.56±0.71	1.46±0.51	1.49±0.48	1.53±0.73	0.9
RV superior wall	1.24±0.43	1.30±0.50	1.18±0.34	1.22±0.32	1.26±0.51	0.73
RV diaphragmatic wall	0.61±0.20	0.60±0.23	0.61±0.17	0.58±0.20	0.63±0.20	0.32
Superior interventricular groove	2.68±0.76	2.51±0.80	2.84±0.69	2.75±0.83	2.61±0.69	0.69
Inferior interventricular groove	1.56±0.42	1.50±0.33	1.63±0.49	1.67±0.45	1.47±0.37	0.06
LV lateral wall	0.80±0.24	0.84±0.26	0.76±0.22	0.82±0.26	0.78±0.23	0.5
Epicardial fat thickness, total	13.47±1.68	13.44±2.78	13.5±2.62	13.64±2.47	13.31±2.89	0.63
Short-axis view at the level of the mid LA						
LA to pulmonary artery	0.23±0.15	0.24±0.13	0.22±0.16	0.21±0.07	0.26±0.19	0.86
LA to esophagus	0.19±0.08	0.20±0.09	0.17±0.06	0.17±0.07	0.21±0.08	0.06
LA to aorta	0.32±0.21	0.23±0.10	0.40±0.25	0.34±0.23	0.30±0.19	0.46
EAT area at level of RCA origin						
RCA-FP area (diastole, cm ²)	5.73±1.92	5.83±2.14	5.63±1.70	6.08±1.59	5.41±2.16	0.08
Sum of RCA-FP and IIG	7.29±2.05	7.32±2.22	7.26±1.90	7.75±1.70	6.87±2.27	0.05

AV, atrioventricular; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; EAT, epicardial adipose tissue; IIG, inferior interventricular groove; LV, left ventricular; LA, left atrium; POAF, post-operative atrial fibrillation; RCA, right coronary artery; RCA-FP, right coronary artery fat pocket; RV, right ventricular.

Table 5 Multivariate logistic regression analyses for predicting post-operative atrial fibrillation using the prediction scoring system

Variable	Odds ratio	95% CI	P value
A: CHA ₂ DS ₂ -Vasc	5.916	0.876–39.949	0.068
B: CHA ₂ DS ₂ -Vasc + LA diameter	3.792	1.142–12.586	0.029
C: CHA ₂ DS ₂ -Vasc + LA diameter + EuroSCORE II	4.201	1.162–15.180	0.029
D: CHA ₂ DS ₂ -Vasc + LA diameter + EAT	3.375	1.062–10.725	0.039
E: CHA ₂ DS ₂ -Vasc + LA diameter + EuroSCORE II + EAT	3.752	1.083–12.998	0.037

EAT, epicardial adipose tissue; LA, left atrium.

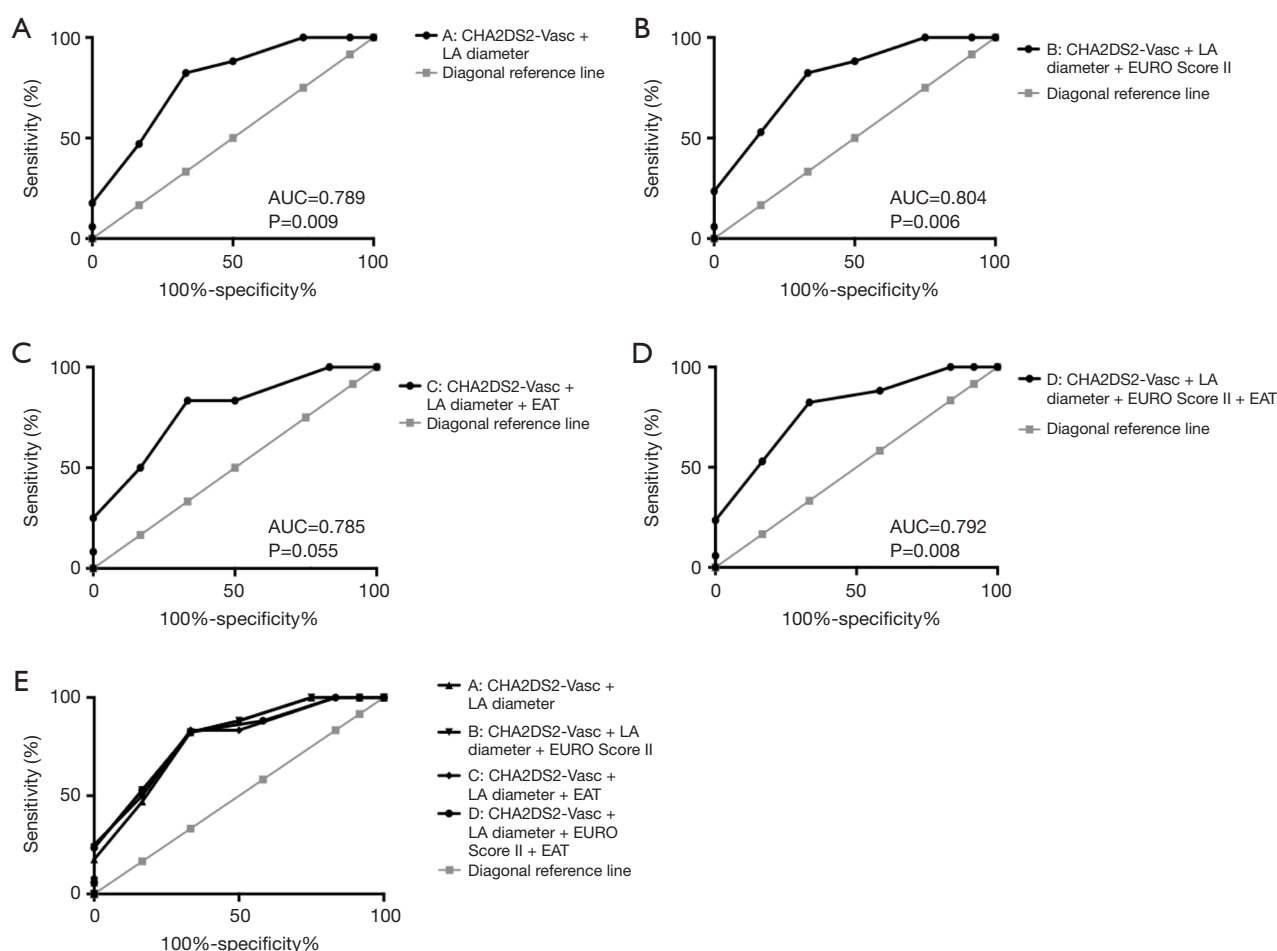


Figure 2 Area under the curve analyses of the post-operative atrial fibrillation prediction scoring system. (A) CHA₂DS₂-Vasc and left atrial (LA) diameter; (B) CHA₂DS₂-Vasc, LA diameter and EuroSCORE II; (C) CHA₂DS₂-Vasc, LA diameter and epicardial adipose tissue (EAT); (D) CHA₂DS₂ -Vasc, LA diameter, EuroSCORE II and EAT; (E) area under the curve plot showing models A, B, C, and D.

(54.5–66.3) *vs.* 77 (52.8–100.5) mins] compared to patients undergoing CABG with or without AVR. CABG is a longer and more invasive procedure, which could contribute to the increased incidence of POAF compared to AVR alone (64% *vs.* 32%, $P=0.018$). Furthermore, this study demonstrated that bypass time ($P=0.007$) and cross-clamp time ($P=0.013$) are associated with POAF. A study has shown that while circulating levels of IL-18 protein was similar in patients undergoing CABG and valve replacement, their gene expression of IL-18 was higher in the EAT tissue of CABG patients compared to valve replacement patients (30). This adds to the notion that EAT has pro-inflammatory and pro-atherogenic properties (8-10) and could potentially contribute to increased POAF.

A number of pre-operative patient characteristics have

been associated with POAF. The widely used CHA₂DS₂-VAsc score that is used to stratify stroke risk in AF patients has also been shown to predict POAF (31,32). One study has found mean CHA₂DS₂-VAsc scores in POAF and no-POAF groups to be 3.6 ± 1.7 and 2.8 ± 1.7 respectively (33). Our study also confirmed this finding with higher mean CHA₂DS₂-VAsc scores in POAF patients (4.0 ± 1.3 *vs.* 3.0 ± 1.6).

Abnormally increased LV filling pressures gradually increase LA volumes (34). As a non-invasive marker of filling pressures, the E:E' ratio is often used (35). Patients with POAF had numerically, but not significantly, higher E:E' ratios (18.00 ± 9.44 *vs.* 12.81 ± 4.44 ; $P=0.08$). Patients with diastolic LV relaxation abnormalities are particularly prone to LA enlargement, and our study showed higher numerical values in the standard marker for diastolic

dysfunction using echocardiography. The borderline P value is most likely due to our small sample size. A larger LA is associated with development of AF, and cardiovascular events (36,37). Our study showed that increased LA diameter has the potential to predict POAF in the setting of cardiac surgery. Echocardiography is routinely performed pre-operatively, and parameters such as LA diameter could be used in with other markers to predict POAF and screen for high-risk patients.

There is increasing interest in the role of EAT in predicting cardiovascular disease. The largest study stems from the Framingham Heart Study. 2,317 participants' pericardial fat volume was characterized with CT, which predicted AF risk independent of other measures of adiposity (11). It is to be noted that as the Framingham Heart Study investigated multiple variables with multiple outcomes, there is a possibility of a type 1 statistical error. A recent study showed pericardial fat volume to be associated with POAF after CABG procedures (19). However, to the authors' knowledge, no studies have used EAT to predict POAF after AVR surgery. EAT measurements in the clinical setting have been limited due to its time-consuming process, however automated approaches are currently being investigated in the literature (38,39). Saremi *et al.* have shown that diastolic RCA-FP surface area is a quick, reproducible estimate of total EAT (22). We have shown that a combination of an EAT thickness parameter (IIG) and an EAT area measurement (RCA-FP) is associated with POAF incidence after AVR alone or CABG with or without AVR. Using pre-operative contrast and non-contrast CT scans, these EAT parameters could potentially be measured routinely in the clinical setting to predict POAF risk. However from our data, such an approach does not appear to add further POAF predictive value compared to other POAF risk factors in the prediction scoring system, and its potential future role in pre-operative evaluation requires large-scale studies.

POAF is a complication that can have implications for our current ageing populations. Hospital length of stay after CABG can be extended by two to four days with additional healthcare costs due to POAF (27). Our study demonstrated that hospital and ICU stay was extended by two days. The burden of POAF could be prophylactically reduced by predicting high-risk patients using pre-operative characteristics identified in our POAF prediction scoring system. Assessed in a meta-analysis of ten trials, amiodarone is one such prophylaxis. Amiodarone was associated with a significant reduction in the rate of POAF or atrial flutter (40). However, all anti-arrhythmic drugs, including

amiodarone, have significant potential side effects limiting their use routinely in all patients undergoing cardiac surgery. Targeting amiodarone therapy for those most likely to develop POAF is attractive, with potential savings in morbidity and duration of hospital stay.

In our study, multivariate logistic regression analysis and ROC analysis have shown that the POAF prediction scoring system using LA diameter, EuroSCORE II and CHA₂DS₂-VASc was strongly associated with POAF prior AVR alone or CABG with or without AVR (AUC 0.804; OR, 4.201; 95% CI: 1.162–15.180; P=0.029). Univariate analysis revealed the sum of IIG and RCA-FP to be associated with POAF (7.75±1.70 *vs.* 6.87±2.27; P=0.05), however the addition of EAT to the POAF prediction scoring system did not improve the risk prediction model for POAF (AUC 0.79; OR, 3.752; 95% CI: 1.083–12.998; P=0.037). The POAF prediction scoring system we have described in this study could help clinicians recognize high-risk patients for POAF preventative treatment before cardiac surgery.

There are several limitations to the study. Firstly, a major limitation of this study was the small sample size and therefore the results would be statistically underpowered. Further large-scale studies are required to validate the usefulness and accuracy of the POAF prediction score. Much of the data relied on the use of a database from a single centre, however our primary database was validated using demographic variables from two sources, independent of each other. Secondly, this was a retrospective study and as such there may be a lack of standardization in the data collected especially in regard to the CT data and pre-operative investigative data. Neither EuroSCORE II nor CHA₂DS₂-VASc is used conventionally to predict AF incidence. However, the increased mortality and morbidity risk that EuroSCORE II predicts may be related to longer stays in hospital due to complications including POAF. These variables are likely to be interrelated; therefore a combined scoring system such as the one outlined in this paper, could be useful. Furthermore, post-discharge POAF episodes were not included; therefore POAF incidence could be underestimated. However, as demonstrated in our study, POAF most likely occurs on post-operative days two and three. Patients with pacemakers and permanent AF were excluded, therefore the usefulness of EAT measurements for predicting POAF in these patients is still to be determined.

Conclusions

This study identifies a novel model to assess POAF risk

using clinical pre-operative characteristics of patients undergoing AVR alone or CABG with or without AVR. The combination of EuroSCORE II, CHA₂DS₂-VASc and LA diameter was strongly associated with POAF. EAT did not add further strength in predicting POAF in our scoring system. Given the small sample size, any potential role for EAT in predicting POAF would need validation in large-scale studies.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jxym.2018.07.04>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Human Research Ethics Committee of The University of Notre Dame Australia and written informed consent was obtained from all patients.

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