Left atrial functional measurements utility in predicting long-term risk of atrial fibrillation after isolated CABG

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Abstract

Abstract Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia following coronary artery bypass grafting (CABG). We hypothesized that measures of left atrial (LA) function would be useful in predicting AF in patients undergoing CABG. **Methods and Results** In the study, 611 patients were included after CABG. All patients had echocardiograms performed preoperatively and LA functional measurements were assessed. These measurements were LA maximum volume index (LAVmax), LA minimum volume index (LAVmin) and LA emptying fraction (LAEF). The endpoint was AF occurring >14 days after surgery. During the follow-up period of a median of 3.7 years, 52 (9%) developed AF. The mean age was 67 years, 84% were male and the average left ventricle ejection fraction was 50 %. No differences were observed between the patients developing AF and those who did not develop AF. No functional LA measurements were significant predictors of AF in the whole CABG population. However, in patients with normal-sized LA (n=532, events: 49), both LAEF and LAVmin were univariable predictors of AF. When the functional measurements were adjusted for the CHADS $_2$ score, both LAVmin (HR=1.07 (1.01-1.13), p=0.014) and LAEF (HR: 1.02 (1.00-1.03, p= 0.023)), remained significant predictors. **Conclusion** No echocardiographic measurements were significant predictors of AF after CABG. In patients with a normal LA size, LAVmin as well as LAEF were significant predictors of AF. **Keywords:** atrial fibrillation; cardiac surgery; left atrium; echocardiography

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Background :

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Methods and Results

In the study, 611 patients were included after CABG. All patients had echocardiograms performed preoperatively and LA functional measurements were assessed. These measurements were LA maximum volume index (LAVmax), LA minimum volume index (LAVmin) and LA emptying fraction (LAEF). The endpoint was AF occurring >14 days after surgery.

During the follow-up period of a median of 3.7 years, 52 (9%) developed AF. The mean age was 67 years, 84% were male and the average left ventricle ejection fraction was 50 %. No differences were observed between the patients developing AF and those who did not develop AF. No functional LA measurements were significant predictors of AF in the whole CABG population. However, in patients with normal-sized LA (n=532, events: 49), both LAEF and LAVmin were univariable predictors of AF. When the functional measurements were adjusted for the $CHADS_2$ score, both LAVmin (HR=1.07 (1.01-1.13), p=0.014) and LAEF (HR: 1.02 (1.00-1.03, p= 0.023)), remained significant predictors.

ConclusionNo echocardiographic measurements were significant predictors of AF after CABG. In patients with a normal LA size, LAVmin as well as LAEF were significant predictors of AF.

Keywords: atrial fibrillation; cardiac surgery; left atrium; echocardiography

Introduction

Coronary artery bypass grafting (CABG) is the most performed major cardiovascular surgery procedure in the US, constituting half of all major cardiovascular procedures (1). The most common postoperative arrhythmia following CABG is atrial fibrillation (AF) (2) (3). AF is also the most common cardiac arrhythmia overall with increased risk of stroke (4). Hence, being able to identify patients at risk of AF is key to prescribing anticoagulants and preventing ischemic strokes. With correct screening, the risk of post-operative complications can be reduced as the treatment and monitoring of the patient can be individually tailored. Currently, congestive heart failure, hypertension, age >75 years, diabetes, and previous stroke/transient ischemic attack ($CHADS_2$) are used to determine the appropriate anticoagulant treatment for patients to prevent strokes. This scoring system is associated to the development of post-operative AF (POAF) and is also used to predict AF (5). However, an improved model for predicting AF in patients with a CABG may decrease mortality due to a decrease in the number of patients experiencing stroke. Patients are routinely examined before CABG with an echocardiogram to identify valvular disease and to evaluate the systolic function. Currently, the most widely used echocardiographic measurement in the clinic for predicting AF is the maximal volume of the left atrium (LAVmax) (6). Several studies have found that functional measurements of the left atrium (LA), such as the LA emptying fraction (LAEF) and the LA minimum volume index (LAVmin), are useful in predicting AF (7,8). Since it seems that the LA functional measures can play a role in predicting AF, we hypothesized that: 1. The LA functional measurements would be better predictors than LAVmax for AF following CABG. Furthermore, we hypothesized that: 2. LA functional measurements would be significant predictors of AF even in patients with a normal LA size.

Methods

PopulationIn total, 782 patients undergoing isolated CABG at Gentofte Hospital from January 2006-May 2011 were screened in this retrospective cohort. Patients were not included if they had rescue CABG performed, did not have an echocardiogram available nor if they had significant valvular disease defined as at least moderate mitral regurgitation or aortic valve stenosis. Of the remaining 700 patients, those with known AF were excluded (n=54), so were patients already on anticoagulation for other reasons (n=2), and 13 patients with postoperative AF (defined as AF occurring within 14 days) (9). Patients in whom LA measures could not be performed were also excluded (n=20). In total, 611 patients were left for inclusion in the present analysis. Baseline data on medicine, comorbidities, laboratory and angiographic findings were recorded by reviewing the hospital charts.

EndpointThe endpoint was the development of any form of AF, which was obtained through diagnostic codes (ICD10: I48.9) from the Danish National Patient Registry.

Biochemical analysis The patients had blood samples drawn when admitted to the hospital. These samples were analyzed for hemoglobin, creatine kinase MB, C-reactive protein and creatinine.

EchocardiographyEchocardiography was performed at a median of 15 (IQR: 8;32) days prior to surgery. Examinations were performed using a Vivid Dimension (GE Healthcare; Horten, Norway) with a 3.5-MHz transducer. Analysis of the echocardiographic images was done offline as post-processing analysis (EchoPAC BT 11.1.0. GE Vingmed Ultrasound AS) by a single, experienced analyst blinded to follow-up information.*Conventional echocardiography*LV dimensions (interventricular septal thickness, left posterior wall diameter and internal LV diameter) were measured in the parasternal long-axis view at end-diastole and used to calculate the LV mass index (LVMI) by Deveraux's formula (10). LAVmin and LAVmax were measured by the biplane area-length method and corrected for body surface area (BSA). LAEF was calculated by$LAEF = \frac{LAVmax-LAVmin}{\text{LAVmax}} \bullet 100\%$. Left ventricular ejection fraction (LVEF) was measured using the biplane Simpson's model.

Transmitral inflow patterns (E-wave, A-wave, E/A, E-wave deceleration time) were measured by pulsed-wave Doppler imaging with the sample placed at the mitral valve leaflets. Pulsed-wave Doppler imaging was used to measure the myocardial relaxation velocity (e') in the septal and lateral walls.

StatisticsStatistical analysis was performed using STATA 14 (StataCorp LP, College Station, TX). Stratification was done by the outcome of AF. Categorical variables are displayed as total numbers and percentages and were compared using χ^2-test. Continuous variables with a Gaussian distribution are displayed as a mean ±SD and were compared using Student t test. Continuous variables showing non-Gaussian distribution are displayed as median with interquartile ranges (IQR) and were compared using Wilcoxon rank sum test.

Univariable Cox proportional hazards regression analyses were used for the three measurements of the LA: LAVmin, LAVmax, and LAEF. Multivariable Cox regression analyses were also applied to adjust for confounders and to obtain fitted hazard ratios. This was performed in two models: (1) Adjusting for potential confounders identified within the cohort: gender, age, heart rate and hemoglobin, (2) adjusting for $CHADS_2$ score. The association between LA measurements and outcome were tested for interaction with gender and hypertension. Stratified analysis was performed for patients based on a normal LA (LAVmax<34 mL/m^2). Univariable as well multivariable Cox regressions were applied in the same way as for the entire population. Cox proportional-hazard models were constructed for this subgroup based on incidence rate of AF stratified by low and high LAEF and low and high LAVmin. Harrell's C-statistics were calculated from univariable Cox regression to estimate the predictive value of the LA measurements.

A p-value of <0.05 was cut off point for significance in the analyses.

ResultsDuring a median follow up time of 3.7 years (IQR: 2.6;4.9), 52 patients (9 %) developed AF. Baseline characteristics of the patients are displayed in table 1. The mean age was 67 years, LVEF was 50 %, 84 % were male, 68 % were hypertensive and 26 % were diabetic.

The patients who developed AF showed a trend towards being older (70 years vs 67 years) but were otherwise similar with respects to clinical characteristics compared to the group free of AF.

LAEF was the only echocardiographic measure that differed significantly between the outcome groups at baseline.

Predictive value of the atrial functional measurements Uni- and multivariable Cox regressions are displayed in Table 2. LAEF was the only significant predictor in the univariable and multivariable model 1. No other LA measures were significantly associated with AF. No effect modification was found for hypertension nor gender with respects to the association between AF and any of the three LA measures ($p>0.05$ for all). In patients with a normal-sized LA (n=531 with 49 events), both LAVmin and LAEF were significant predictors of AF in the univariable model, table 2), whereas LAVmax was not. In the multivariable model, both LAEF and LAVmin remained significant predictors of AF when adjusted for potential confounders (gender, age, heart rate, and hemoglobin) (LAEF: HR=1.02 (1.01-1.04), p=0.007, per % decrease and LAVmin: HR=1.08 (1.02-1.14), p=0.005, per mL/m^2 increase). When adjusting for the $CHADS_2$ score, both LAEF and LAVmin remained independent predictors of outcome (LAEF: HR: 1.02 (1.00-1.03, p= 0.023 and LAVmin: HR=1.07 (1.01-1.13), p=0.014, per mL/m^2 increase). LAVmin had the highest C-statistic and even higher than the $CHADS_2$ score (0.60 vs 0.58), although this difference was not statistically significant.

In patients with normal size LA, high LAEF (>47%) were not statistically less likely to develop AF during follow up time (figure 1). However, we found a significant association between high LAVmin (>11 mL/$m^{2)}$and risk of AF in this subgroup, such that high LAVmin posed an increased risk of AF: HR= 1.95 (1.08-3.51), p for log rank =0.02 (figure 2).

DiscussionThe main finding from the present study is that no echocardiographic measurement independently predict AF after CABG. However, LAVmin and LAEF are independent predictors of outcome in patients with a normal-sized LA – and both were better than the conventionally used LAVmax. These echocardiographic measurements may be useful in predicting AF in patients with normal sized LA who are at higher risk of AF. This may be because LAVmax is a measure of LA structure rather than LA function. In contrast to both LAEF and LAVmin are more related to LA function, since LAEF is an indirect measurement of the atrial ability eject blood into the LV and a larger LAVmin is equivalent to a stiffer LA without the ability to contract in the diastole leaving a large residual volume, which is hypothesized to be a direct contributing factor to developing AF (11) (12).

LAVmax has been shown to be a significant predictor of AF, however, we found in the present CABG cohort that LAVmax was not associated with subsequent AF (13). Since it is already known that LA dilation can lead to AF, it is important to have a tool that can identify patients at risk, who do not have this trademark (12). A large percentage of patients who develop AF in the present study had a normal-sized LA as determined by the LAVmax (n=14 equivalent to 27 % of AF events) which emphasizes the need to identify measures of more subtle LA impairment which are also associated with an increased risk of AF. Other echocardiographic measurements of both structure and function have previously proven significant in predicting AF in CABG patients, such as LA diameter, epicardial fat and LA expansion index – solidifying the fact that a pre-operative echocardiography is an important measure to risk stratify patients for post-OP AF (14, 15, 16).

LAEF was a significant predictor of outcome in uni- and multivariable models in this subgroup of patients with normal-sized LA. LAEF has previously been proven to be a significant predictor of AF in patients with ischemic stroke and patients undergoing radiofrequency catheter ablation (17, 18). Unfortunately, the aforementioned studies did not present data on LAVmin.

LAVmin has been shown to result in the highest predictive performance, as determined from the C-statistic, of the functional measurements when added to the CHADS$_2$ score (19). The CHADS$_2$ score is constructed from categorical variables, which makes it easier for clinicians to use, but this also simplifies the risk factors for developing AF. The added value beyond clinical parameters may imply that we will be able to identify patients at risk of AF at an even earlier point and better prevent its associated complications.

Clinical perspectiveAF is associated with increased mortality due to increased risk of cardioembolic stroke (20,21). When also considering the increasing prevalence of AF, it is important to accurately predict the risk of AF in the individual patient (22). Because LAVmin and LAEF significantly predict AF in patients with normal LAVmax, they may supplement LAVmax. Since echocardiography is already used routinely for patients undergoing CABG, further assessing LA function could be a time-efficient approach to provide an accurate risk assessment of AF can consequently prevent stroke.

LimitationsWe do not have insight as to the monitoring process of the patients as the endpoint was drawn from patient registers. Also, patients initially excluded due to postoperative AF events could have developed clinical AF later, and we did not account for this in the present study. As this was a retrospective study, we cannot exclude the possibility of residual confounding.

We did not measure the LA volume at the p-wave, and can therefore not exclude that more detailed information on passive versus active LAEF could provide valuable information on the risk of AF.

It should also be kept in mind that the CHADS$_2$ score was originally developed to predict stroke in AF patients and is therefore not optimized for AF prediction, but has nonetheless been proposed as a clinical prediction tool for AF (23).

ConclusionNo echocardiographic LA measurement was an independent predictor of AF for the entire population. However, for the subgroup with normal LA volume, LAVmin and LAEF were significant predictors of AF. These findings should be investigated further in prospectively designed studies.

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Disclosures

None

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Figure legends

Figure 1

Title: Risk of AF according to LAEF in patients with normal size LA

Caption: X-axis displays follow up time, Y-axis displays the probability of staying AF free. The plot is stratified by high LAEF and low LAEF, with the cutoff being 47 %. The solid blue line represents the likelihood of staying AF free for the high LAEF subgroup and the light blue area is the 95 % confidence interval. The solid red line represents the likelihood of staying AF free for the low LAEF subgroup and the light red area is the 95 % confidence interval. The subgroup with high LAEF had a higher probability of staying AF free with a HR of 1.47, however it was not statistically significant (p value for log-rank=0.18). Data is plotted for patients with LAVI < 34 mL/m^2 .

LAEF: Left atrium emptying fraction : AF: Atrial fibrillation. HR: Hazard Ratio

Figure 2

Title: Risk of AF according to LAVmin in patients with normal size LA

Caption: X-axis displays follow up time, Y-axis displays the probability of staying AF free. The plot is stratified by high LAVmin and low LAVmin, with the cutoff being 11 mL/m^2. The solid blue line represents the likelihood of staying AF free for the low LAVmin subgroup and the light blue area is the 95 % confidence interval. The solid red line represents the likelihood of staying AF free for the high LAVmin subgroup and the light red area is the 95 % confidence interval. The graph displays a statistically significant lower probability of staying AF free for the subgroup with high LAVmin (p value for log rank= 0.02). Data is plotted for patients with LAVI < 34 mL/m^2 .

LAVmin: Left atrium minimal volume , AF: Atrial fibrillation, HR: Hazard Ratio

Table 1: Baseline characteristics

Characteristic	All (n=611)	No AF (n=559)	AF (n=52)	P-value
Age, years	67±9	67±9	70±7	0.054
Male sex, n (%)	514 (84 %)	473 (85 %)	41 (79 %)	0.28
Hypertension, n (%)	413 (68 %)	372 (67 %)	41 (79 %)	0.07
Diabetes, n (%)	156 (26 %)	145 (26 %)	11 (21 %)	0.45
Heart rate, beats per minute	70±13	70±13	69±15	0.51
Body mass index, kg/m^2	27±4	27±4	27±5	0.78
Smoking status, n (%) Current Former Never	184 (3) 294 (48) 133 (22)	167 (30) 264 (47) 128 (23)	17 (33) 30 (58) 5 (10)	0.08
Previous myocardial infarction, n (%)	138 (23 %)	127 (23 %)	11 (21 %)	0.80
Previous stroke, n (%)	63 (10 %)	56 (10 %)	7 (14 %)	0.43

Characteristic	All (n=611)	No AF (n=559)	AF (n=52)	P-value
Periphery artery disease, n (%)	69 (11 %)	65 (12 %)	4 (8 %)	0.39
Chronic obstructive lung disease, n (%)	40 (7 %)	36 (6 %)	4 (8 %)	0.73
CCS class, n (%) 1 2 3 4	52 (9) 476 (78) 78 (13) 5 (1)	42 (8) 438 (78) 74 (13) 5 (1)	10 (19) 38 (73) 4 (8) 0	*0.024*
Unstable during surgery, n (%)	28 (5 %)	27 (5 %)	1 (2 %)	0.34
Number of diseased vessels, n (%) 1 2 3 or more	5 (1) 125 (21) 481 (79)	4 (1) 110 (20) 445 (80)	1 (2) 15 (29) 36 (69)	0.18
CHADS2 score, n (%) 0 1 2 3 4 5	92 (15) 228 (37) 205 (34) 43 (7) 35 (4) 8 (2)	85 (15) 216 (39) 181 (32) 39 (7) 31 (6) 7 (1)	7 (14) 12 (23) 24 (46) 4 (8) 4 (8) 1 (2)	0.26
Biochemical	Biochemical	Biochemical	Biochemical	Biochemical
Hemoglobin, mmol/L	8,4±0.8	8,4±0.8	8,5±0.9	0.38
Creatinine, µmol/L	95 (82;108)	95 (82;108)	92 (83;102)	0.42
Creatine Kinase MB, µg/L	27 (20;37)	27 (20;38)	28 (22;35)	0.87
C-Reactive Protein, mg/L	4 (2;9)	4 (2;9)	3 (2;11)	0.69
Echocardiography	Echocardiography	Echocardiography	Echocardiography	Echocardiography
LVEF, %	50±11	51±11	50±12	0.62
LVMI, g/m^2	89 (74;110)	88 (74;110)	95 (83;108)	0.14
LVIDd, cm	4,96±0.68	4.96±0.68	4.97±0.69	0.90
LAVmax, mL/m^2	24±9	24±9	24±7	0.84
LAEF, %	44±16	45±15	40±20	*0.036*
LAVmin, mL/m^2	14±7	14±7	14±6	0.44
e', cm/s	7.3±2.2	7.4±2.2	7.0±1.8	0.26
E/e'	10.0 (8,2;12,5)	10.0 (8.1;12,5)	9.5 (8.2;12.0)	0.98
E/A	0.89 (0.73;1.15)	0.89 (0.73;1.14)	0.90 (0.73;1.24)	0.61
DT, ms	224±67	224±68	228±60	0.62

Continuous variables showing Gaussian distribution are presented as means ± standard deviation. Variables not showing Gaussian distribution are presented by median with interquartile range. CCS: Canadian cardiovascular society rating for angina, CABG: Coronary artery bypass grafting, eGFR: estimated glomerular filtration rate, LVEF: Left ventricle ejection fraction, LVMI: Left ventricle mass index, LVIDd: Left ventricle inner diameter in diastole, LAVmin: Left atrium volume index, LAVmin: Left atrium end-diastolic volume index, LAEF: Left atrium ejection fraction, e': Early diastolic relaxation velocity, E/e': Ratio of early transmitral filling to early diastolic relaxation velocity, E/A: Ratio of early to late transmitral filling, DT: Deceleration of early transmitral filling.

Table 2: Cox regression for atrial measurements

Entire population (n=611 with 52 events)

Parameters	Univariable model	Univariable model

	HR (95% CI)	p-value
LAEF, per 1% decrease	1.02 (1.00-1.04)	*0.022*
LAVmin, per 1 mL/m^2 increase	1.01 (0.98-1.05)	0.40
LAVmax, per 1 mL/m^2 increase	1.00 (0.97-1.03)	0.84
LAVmax<34 mL/m^2 (n=531 with 49 events)	LAVmax<34 mL/m^2 (n=531 with 49 events)	LAVmax<34 mL/m^2 (n=531
LAEF, per 1% decrease	1.02 (1.01-1.04)	*0.007*
LAVmin, per 1 mL/m^2 increase	1.07 (1.02-1.13)	*0.005*
LAVmax, per 1 mL/m^2 increase	1.03 (0.99-1.08)	0.18

HR: Hazard ratio, CI: Confidence interval, LAEF: Left atrium emptying fraction, LAVmin: Left atrium end-diastolic volume index, LAVmax: Left atrium volume index.

In the multivariable model 1, we adjusted for age, gender, heart rate, and hemoglobin concentration. In multivariable model 2, we only adjusted for the $CHADS_2$ score.

Figures

Figure 1

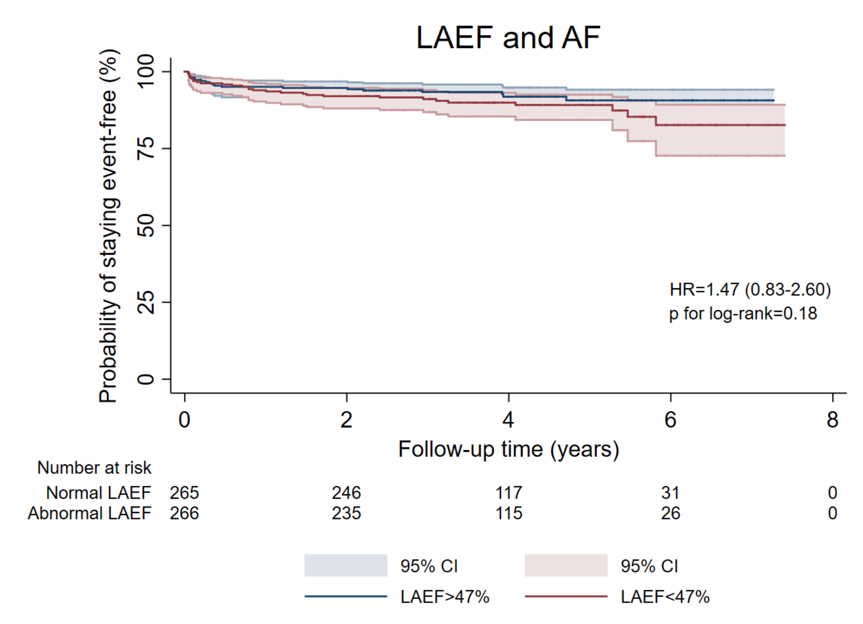
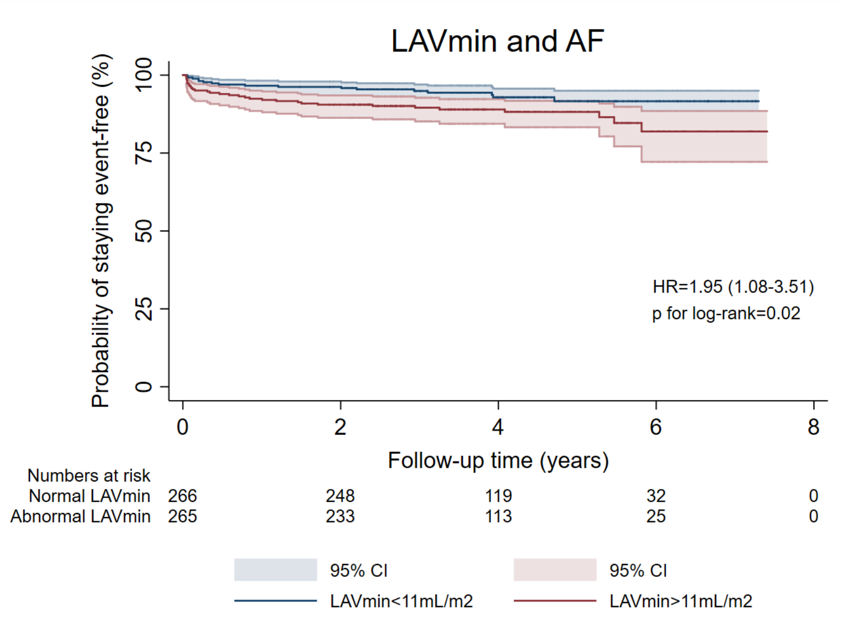


Figure 2


LAVmin and AF
Probability of staying event-free (%)
0
25
50
75
100
0
2
4
6
8
Follow-up time (years)
HR=1.95 (1.08-3.51)
p for log-rank=0.02
Numbers at risk
Normal LAVmin 266 248 119 32 0
Abnormal LAVmin 265 233 113 25 0
95% CI
95% CI
LAVmin<11mL/m2
LAVmin>11mL/m2