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Measures of left atrial function predict incident atrial fibrillation in STEMI patients treated with primary percutaneous coronary intervention

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ABSTRACT

Rationale: Atrial fibrillation (AF) is the most common arrhythmia following acute myocardial infarction (AMI). Maximal left atrial (LA) volume is the only echocardiographic atrial parameter employed clinically to assess risk of AF development.

Objective: This study sought to determine the prognostic value of left atrial functional measures such as left atrial emptying fraction (LAEF) and left atrial expansion index (LAi) in predicting incident AF in the post-STEMI setting.

Methods and results: STEMI patients treated with primary percutaneous coronary intervention (pPCI) at Gentofte Hospital, Denmark were prospectively enrolled from September 2006 to December 2008 and had an echocardiogram performed a median 2 days (interquartile-range: 1-3 days) following pPCI. LA maximal volume, LA minimal volume, LAEF and LAi were measured from echocardiograms of 373 patients using the area-length method. End point was incident AF. Median follow-up time was 5.6 years (interquartile-range: 5.0-6.1 years), 24 patients (6%) developed incident AF, and follow-up was 100%. In multivariable Cox regression, LAEF and LAi but not maximal LA volume remained independent predictors of AF. Results were similar in competing risk analysis treating all–cause mortality as a competing risk. LAEF and LAi, but not maximal LA volume, added incremental prognostic information in predicting incident AF when added to the CHARGE-AF risk score and the CHA2DS2-VASc score.

Conclusion: LAEF and LAi independently predicted incident AF following STEMI and added incremental prognostic information in addition to established predictors of AF. Maximal LA volume was not an independent predictor of incident AF after multivariable adjustment.

1. Introduction

Complications following acute myocardial infarctions (MI) include both atrial and ventricular arrhythmias. Of these, ventricular arrhythmias pose the greatest risk of adverse outcome. Atrial fibrillation (AF), however, is far more common than ventricular arrhythmias following MI [1]. AF is associated with several adverse outcomes such as recurrent MI, progressive heart failure, stroke and malignant ventricular arrhythmias [2,3] Furthermore, asymptomatic episodes of paroxysmal AF are suspected to be a significant contributor to the underlying pathology of cryptogenic strokes [4]. The increased morbidity associated with AF can be reduced if proper treatment is initiated early, mainly through reduction of ischemic stroke (IS) risk from anti-coagulant and anti-platelet therapy [5]. Also, effective management of AF through cardioversion and medication is possible [6]. Lastly, ablation procedures display increased success rate if performed before significant atrial fibrosis develops as a result of AF, stressing the need for early intervention [7]. This calls for effective prediction and assessment of new-onset AF risk in ST-elevated myocardial infarction (STEMI) patients to improve overall prognosis and to reduce the risk of stroke and progressive heart failure following STEMI.

Echocardiographic assessment of AF risk is based on parameters of left ventricular (LV) diastolic function such as maximal left atrial (LA) volume or E/e′. E/e′, LA diameter, maximal LA volume and its index (LAVI) have all displayed proficiency in prediction of AF [8,9]. Despite this, only minimal LA volume and left atrial emptying fraction (LAEF), neither E/e′ nor maximal LA volume, were independently associated with paroxysmal AF in patients with ischemic strokes or transient ischemic attacks [10]. Furthermore, in a prospective cohort of 2200 patients with dyspnea, left atrial expansion index (LAi) but not LAVI accurately predicted persistent AF [11]. This suggest that less commonly employed echocardiographic parameters such as LAEF and LAi may offer incremental prognostic information compared to maximal LA volume in prediction of new-onset AF. Only measurement of maximal LA volume is included in current guidelines [12]. This study seeks to

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determine whether adding measures of LA function such as LAEF and LAi provides incremental prognostic information compared to maximal LA volume in predicting new-onset AF in STEMI patients treated with pPCI.

2. Methods

2.1. Population

The data and study population has been previously described [13]. STEMI patients undergoing pPCI were prospectively enrolled from September 2006 to December 2008 at Gentofte University Hospital, Denmark. All patients had an echocardiographic examination performed a median of 2 days after pPCI. STEMI diagnosis criteria were: 1) chest pain for longer than 30 min but <12 h and either >2 mm of ST elevation in 2 contiguous precordial leads, >1 mm of ST elevation in 2 contiguous limb leads or a newly developed left bundle branch block. Inclusion into the study also required a blood Troponin I level (TnI) of >0.5 μg/L. Initially, 391 patients were included. Eighteen patients were subsequently excluded due to either poor image quality or known history of AF, leaving 373 patients for analysis. Baseline data was ascertained after inclusion into the study. Hypercholesteromia was defined as the use of cholesterol-lowering medication prior to STEMI. Hypertension was defined as the use of anti-hypertensive medication prior to STEMI, a systolic blood pressure ≥140 mm Hg during or a diastolic blood pressure ≥90 mm Hg during hospitalization. Diabetes was defined as either fasting plasma glucose levels over 7 mmol/L, non-fasting glucose over 11.1 mmol/L or the use of anti-diabetic medication. Heart rate was derived from an average of the 3 apical echocardiographic views: apical 4 chamber, apical 2 chamber and the apical longitudinal long-axis view.

2.2. Ethics

The study was approved by a regional scientific ethics committee, the Danish Data Protection Agency and complies with the ethical policies set forth by the second Declaration of Helsinki.

2.3. Reperfusion and management

All patients underwent pPCI treatment as directed in contemporary guidelines [14]. Before coronary intervention, patients were administered 300 mg acetylsalicylic acid, 600 mg clopidogrel and 10,000 international units of unfractioned heparin. The administration of glycoprotein inhibitors was left to the discretion of the operator. After pPCI, patients were treated with anti-platelet, anti-thrombotic and beta-antagonistic medication, as directed in contemporary guidelines [14].

2.4. End point and outcomes

The endpoint chosen was incident AF. Endpoints were followed up through use of International Classification of Disease codes (ICD-10) from the Danish Board of Health's National Patient Registry.

2.5. Echocardiographic examination and analysis

All echocardiographic examinations were performed by experienced clinicians using GE Vivid 7 machines with a 3.5-MHz probe. These were stored on a digital image vault before undergoing off-line analysis by one investigator experienced in echocardiographic post-processing analysis (EchoPac, GE Healthcare, Horten, Norway). This investigator was blinded to both clinical data and outcomes.

2.6. Conventional echocardiography

Interventricular septum diameter (IVSd), left ventricular internal diameter (LVIDd) and left ventricular posterior wall thickness (LVPWd) were measured in the parasternal long axis view at end diastole. LV filling pressures were estimated through mitral valve inflow patterns using Doppler pulsed wave at the mitral valve leaflet tips in the apical 4 chamber view. Early diastolic mitral annular velocity (e′) was obtained using pulsed-wave tissue Doppler imaging in the mitral annulus. Left ventricular ejection fraction (LVEF) was obtained through the modified Simpson's biplane method. End systolic and end diastolic left atrial volumes were measured by the area-length method with subsequent calculation of both LAEF ((end systolic LA volume − end diastolic LA volume) / end systolic LA volume) and LAi ((end systolic LA volume − end diastolic LA volume) / end diastolic LA volume).

2.7. Speckle tracking echocardiography

Longitudinal ventricular strain was obtained through speckle tracking in the apical 4 chamber, apical 2 chamber and the apical longitudinal long-axis view. The speckle tracking region of interest was defined through the use of a semi-automated process. This process was based on definition of the ventricular endocardial-blood interface by the operator through point and click with subsequent detection of the epicardial border and division of the ventricular myocardial wall into 6 segments by the program. In case of one of these segments displaying unsatisfactory tracking as determined by the investigator, manual correction of the segment was attempted. If manual correction still resulted in unsatisfactory tracking, the segment was excluded by the operator. Therefore, in each view the ventricular wall was tracked in 6 segments, resulting in a total of 18 segments for GLS calculation.

2.8. Statistical analysis

All statistical analysis was carried out using STATA 13 for Mac OS. Gaussian-distributed, continuous variables were compared between groups using two-tailed Student's *t*-test and displayed as means ± SD. Variables not displaying Gaussian distribution were compared through the Mann Whitney *U* test and displayed as median with inter-quartile ranges (IQR). Categorical values were compared through the chi-squared test. To analyze trends, linear regression of means across tertiles of LAEF was performed. In Fig. 1, the Kaplan-Meier method was used to estimate the cumulative incidence of AF during the follow-up period. In Table 2, survival analysis was conducted through both univariable and multivariable Cox regressions. The number of events limited the extent of our multivariable adjustment ($n = 24$). Model 1 is adjusted for age, sex, diabetes and hypertension. Model 2 is adjusted for age, sex, diabetes, hypertension, GLS, E/e′ and peak TnI levels. Competing risk analysis treating all-cause mortality as a competing risk was carried out in order to asses potential influence of all-cause mortality on the association of the examined parameters with the development of incident AF. Interaction analysis was used to assess any interaction of LAEF and LAi with either age, sex, presence of hypertension or systolic function assessed as GLS with regards to prediction of incident AF, however none were significant. Net reclassification analysis [15] was used to assess the incremental prognostic value of adding LA volumes and LA functional measures to easily obtainable prediction models for AF such as the CHARGE-AF score [16] and the CHA2DS2-VASc score [17,18]. In order to assess the association between LAEF and other echocardiographic parameters, restricted cubic spline regression was carried out. Statistical significance was defined as a two-sided $p < 0.05$.

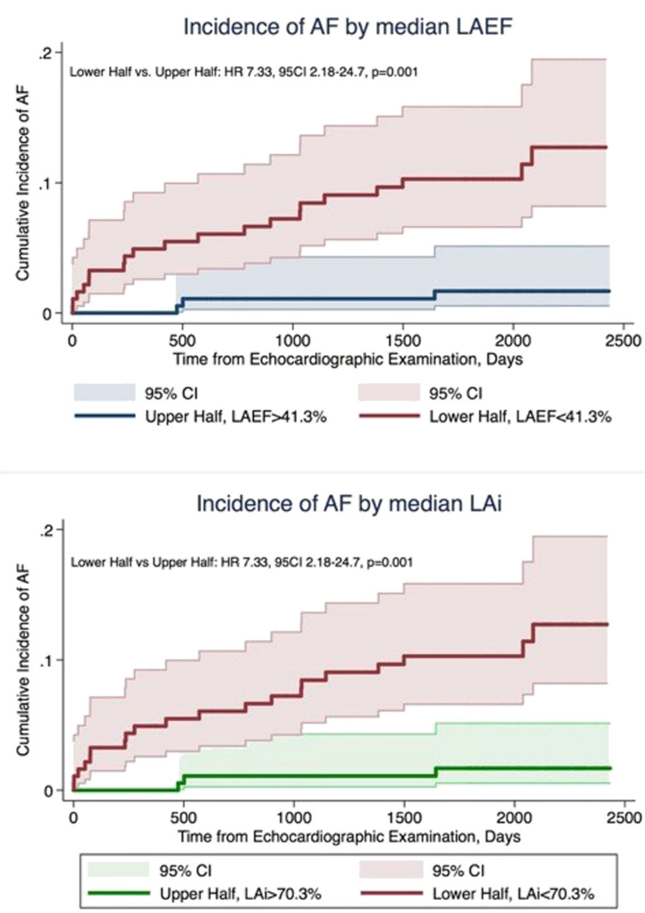

Fig. 1. Kaplan-Meier failure curves for median of LAEF and median of LAi. The curves depict the cumulative incidence of atrial fibrillation (AF) in the population stratified by median of left atrial emptying fraction (LAEF) and by median of left atrial expansion index (LAi).