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Left atrial volume and index by multi-detector computed tomography: Comprehensive analysis from predictors of enlargement to predictive value for acute coronary syndrome (ROMICAT study)

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ABSTRACT

Objectives: We aimed to identify the predictors of left atrial (LA) enlargement by multi-detector computed tomography (CT) and determine its association and predictive value for acute coronary syndrome (ACS).
Background: LA enlargement is associated with myocardial ischemia and coronary artery disease (CAD) and is a strong predictor for cardiovascular events. These studies were performed primarily with echocardiography. With the rise of cardiac CT, LA volume can be readily measured.
Methods: In 377 emergency department patients with chest pain, we performed 64-slice CT for coronary artery assessment. We derived LA volumes (LAV_{max}, LAV_{min}) and indices ($LAVI_{max}$, $LAVI_{min}$) using a threshold-based volumetric method.
Results: Subjects, with cardiac risk factors or CAD by CT, had larger LA (ΔLAV_{max} 9.1 ml, $p=0.004$; ΔLAV_{min} 8.1 ml, $p=0.001$; $\Delta LAVI_{max}$ 3.3 ml/m^2, $p=0.03$; $\Delta LAVI_{min}$ 3.4 ml/m^2, $p=0.006$) than controls. Predictors of LA enlargement were related to risk factors for diastolic dysfunction. ACS risk was greater in patients with top quartile LAV_{max} (odds ratio [OR] 3.4, $p=0.02$) and LAV_{min} (OR 4.7, $p=0.01$) than lowest quartile, but not when indexed. Similarly, the predictive values of LA volumes were incrementally better when added to CT finding of indeterminate stenosis (LAV_{max}: *C* statistic 0.62 to 0.70, $p=0.046$; LAV_{min}: *C* statistic 0.65 to 0.73, $p=0.008$), but not when indexed.
Conclusions: Risk factors related to diastolic dysfunction are independent predictors of LA enlargement. LA enlargement by volumes are associated with a 3–5 fold increase risk for ACS and have incremental value for predicting ACS when added to the CT finding of indeterminate stenosis.

1. Introduction

Left atrial (LA) size has been associated with coronary artery disease (CAD) and shown to provide incremental prognostic value for the detection of myocardial ischemia for stress testing [1–4]. It is a powerful independent predictor of cardiovascular events and mortality in both asymptomatic patients and in those with CAD [5–8]. However, these LA assessments were performed using echocardiography, which measured diameters or required geometric shape assumptions for volumetric calculations.

With the increase use of cardiac multi-detector computed tomography (CT) for the noninvasive evaluation of suspected CAD, three-dimensional (3D) visualization of the left atrium is readily available for analysis without additional testing. While the excellent negative predictive value of cardiac CT angiography has been well established for the evaluation of acute chest pain, the positive predictive value has been less ideal [9–11]. Additional data such as LA enlargement may be incrementally beneficial in the evaluation of these patients.

Thus, in this study, we aimed to quantify LA volumes and indices as measured by CT in a large cohort and identify the predictors of LA enlargement. In addition, we sought to determine the association and incremental predictive value of LA enlargement to the cardiovascular event of acute coronary syndrome (ACS) in patients presenting to the emergency department (ED) with a chief complaint of chest pain.

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2. Materials and methods

2.1. Study population

"The Rule Out Myocardial Infarction Using Computer Assisted Tomography" (ROMICAT) trial was a prospective observational cohort study of consecutive adult patients at low-to-intermediate likelihood of acute coronary syndrome who presented to the emergency department of Massachusetts General Hospital with acute chest pain whose initial electrocardiogram (ECG) and biomarkers were inconclusive and were awaiting hospital admission over a cumulative period of 18 months ending May 2007. The details of the study design have been previously reported [12] and notable for the exclusion of patients with atrial fibrillation. All eligible patients who consented underwent ECG gated contrast enhanced 64-slice CT. Patients received standard of care to rule out ACS during index hospitalization, including serial ECGs, biomarkers, cardiac testing (stress test or cardiac catheterization). Our institutional review board approved the study protocol and all patients provided written informed consent.

In this substudy, we excluded patients with a history of severe mitral or aortic valvular disease. A total of 377 patients, whom there was full visualization of the left atrium on the multi-phase reformatted (MPR) dataset of the CT, were included in our analysis. In the analysis of patients with cardiac risk factors versus controls, we excluded subjects with a prior history of hypertension (HTN), diabetes mellitus, hyperlipidemia, prior history of CAD, history of LV dysfunction, any coronary artery plaque as determined by CT, or ACS during index hospitalization for our control group.

2.2. CT data acquisition

CT imaging was performed using a standard 64-slice CT coronary angiography (Sensation 64, Siemens Medical Solutions, Forchheim, Germany) protocol that was acquired at end inspiration with a test bolus protocol and included the administration of sublingual nitroglycerin (0.6 mg) and intravenous beta-blocker (metoprolol 5–20 mg) for those with the baseline heart rate >60 beats per minute and no other contraindications. A test bolus protocol was used to determine the optimal timing of contrast injection (20 ml contrast agent followed by 40 ml saline, flow rate of 5 ml/s). Contrast agent (80–100 ml, Iodhexodol 320 g/cm^3, Visipaque, General Electrics Healthcare, Princeton, NJ, USA) with 40 ml saline was injected intravenously at a rate of 5 ml/s.

CT images were acquired in spiral mode, gantry rotation time of 330 ms, 64 × 0.6 mm slice collimation, tube voltage of 120 kV, maximum effective tube current of 850 mAs, with ECG-correlated tube current modulation used when appropriate. The maximum effective tube current was on during the time interval from 470 ms to 140 ms before the next expected R wave and the tube current was reduced by 80% during the remaining portion of the cardiac cycle. Reconstructions were performed using retrospectively ECG-gated half-scan algorithm for a temporal resolution of 165 ms. At this temporal resolution, transaxial images were reconstructed for 10 phases, each at 10% of the RR-interval, for the MPR dataset with 1.5 mm slice thickness and 1.5 mm increments for volumetric and functional analyses.

2.3. CT measurements

Two experienced readers, blinded to the clinical outcome, performed the CT measurements offline using dedicated cardiac workstations. Quantitative LA volumes, which included the left atrial appendage but excluded the pulmonary veins, were obtained at end-systole and end-diastole. We used a highly reproducible threshold-based method for quantifying LA volume three-dimensionally without geometric shape assumptions, as previously validated [13]. Briefly, LA volumes were derived by pure volumetric summation of manually traced regions of interests on sequential axial 1.5 mm thick slices with a threshold window width set at 100–1000 Hounsfield units using a dedicated semi-automated volumetric software program (Volume Viewer, Leonardo, Siemens Medical Solutions, Forchheim, Germany). The maximum LA volume (LAV_{max}) was measured from the end-systolic phase just before the mitral valve opening with the largest LA cavity and smallest LV cavity, as determined qualitatively from multiplanar LV short-axis, two-chamber, and four-chamber views. Conversely, the minimum LA volume (LAV_{min}) was measured from the end-diastolic phase at the mitral valve closure with the smallest LA cavity and largest LV cavity. LAV_{max} and LAV_{min} were indexed to body surface area (BSA) as $LAVI_{max}$ and $LAVI_{min}$, respectively. Quantitative LV measurement of LV ejection fraction (LV EF) was derived from automated software (Vital Images, Minnetonka, Minnesota). The presence of coronary atherosclerotic plaque and indeterminate stenosis were visually classified by two experienced CT readers, as described previously [12,14].

2.4. Risk factor and outcome assessment

Cardiovascular risk factors and medical history were assessed at the time of subject's enrollment based on self-report or obtained from the medical records during the index hospitalization. Body mass index (BMI) was defined as weight (kilograms) divided by the height squared (meters). BSA was calculated using the Dubois formula [15]. Hypertension was defined as systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg or current antihypertensive treatment. Diabetes mellitus was defined as a fasting plasma glucose ≥126 mg/dL or treatment with a hypoglycemic agent. Hyperlipidemia was defined as total cholesterol of ≥200 mg/dl or treatment with a lipid lowering medication. Documented history of CAD included previous myocardial infarction or coronary revascularization. Family history of CAD was defined as having a first-degree female (<65 years) or male (<55 years) relative with a documented history of myocardial infarction (MI) or sudden cardiac death. History of LV dysfunction was obtained from review of prior echocardiography or nuclear imaging reports. Subjects were classified as smokers if they had smoked at least one cigarette per day in the year prior to the study.

An adjudication panel of 2 physicians, who were blinded to CT, reviewed the medical records and determined the diagnosis of ACS during index hospitalization. ACS was defined as either an acute myocardial infarction or unstable angina, according to the AHA/ACC/ESC guidelines [16]. Disagreement was solved by consensus, which included an additional cardiologist.

2.5. Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation (SD) and interquartile ranges [IQR] for continuous variables and as frequency and percentages for nominal variables. The differences in means between groups were determined using Student's *t* tests. To evaluate the associations between risk factors and LA volumes and indices, relationships with univariate parameters and LA measurements were assessed using Pearson's correlation for continuous variables and Student's *t* tests for categorical variables. BMI was not included for the index measurements due to its collinearity with BSA. For the multivariable linear regression models, we included all univariate variables that may be associated with LA measurements ($p < 0.15$). We also included gender in the $LAVI_{min}$ multivariable model for face validity, although its relation was not significant in univariate analysis. For analysis of LA measurements and ACS, Student's *t* tests were used to compare the difference in mean values. We then dichotomized the LA volumes and indices into the top quartile versus the lowest quartile. We used logistic regression to examine the association of LA measurements for ACS and evaluated the incremental predictive value of the LA measurements for the detection of ACS by comparing the *C* statistic of nested models using the likelihood ratio test. Baseline model included the CT finding of indeterminate stenosis and subsequent models included this CT finding with the addition of the individual LA measurements. The interobserver variability for LA measurements was determined for 25 randomly selected studies and assessed using intraclass correlation coefficient (ICC). The LA measurements by two independent readers had excellent reproducibility with ICC for LAV_{max} of 0.998 and for LAV_{min} of 0.986. A 2-tailed *p*-value of <0.05 was considered to indicate statistical significance. All analyses were performed using SAS (Version 9.1.3, SAS Institute Inc., Cary, North Carolina) and SPSS (Version 16.0, Chicago, Illinois).

3. Results

3.1. Baseline characteristics in the ROMICAT cohort

In our cohort of 377 ED patients presenting with chest pain and without atrial fibrillation and significant left-sided valvular heart disease, mean heart rate during CT scan 65 ± 12 beats per minutes with the following CT scanning variables: beta-blockers given in 236 (63%) of patients, sublingual nitroglycerin given in 299 (80%), with ECG tube modulation performed in 167 (46%) of patients. The average age was 53 ± 12 years (range 21 to 89 years), 240 (64%) were men, and LV function was preserved (mean LV EF 67 ± 9%). There were 176 (47%) of patients without any coronary artery plaque by CT. For the cardiovascular event

Table 1
Demographics of the study group.

Characteristics	Total $n = 377$
Age, yrs	53.4 ± 12.0
Men	240 (64%)
BSA, m^2	2.00 ± 0.27
BMI, kg/m^2	29.2 ± 6.0
Hypertension	161 (42%)
Diabetes mellitus	44 (12%)
Hyperlipidemia	153 (41%)
History of documented CAD	43 (11%)
FH of premature CAD	94 (25%)
History of LV dysfunction	14 (4%)
Smoker	192 (51%)
No CAD[a]	176 (47%)
ACS during index hospitalization	38 (10%)
LV EF, %[a]	67.5 ± 9.4

BSA denotes body surface area; BMI, body mass index; CAD, coronary artery disease; FH, family history; LV, left ventricular; ACS, acute coronary syndrome; and EF, ejection fraction.

[a] CT measurement.