Title
Use of Advanced CT Technology to Evaluate Left Atrial Indices in Patients with a High Heart Rate or with Heart Rate Variability: The Converge Registry.

Journal
Journal of Nuclear Medicine Technology, 49(1)

ISSN
0091-4916

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Publication Date
2021-03-01

DOI
10.2967/jnmt.120.253781

Peer reviewed

<u>Title:</u> Evaluation of Left Atrium Indices among High Heart Rate and Atrial Fibrillation patients with Advancement in Computed Tomography (CT) Technology: The CONVERGE Registry

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Abstract:

Background: Early detection of left atrium (LA) dysfunction proposed to provide insight into the pathophysiology and clinical management of several cardiovascular diseases. We intended to assess the ability of current generation coronary computed tomographic angiography (CCTA) to measure LA volume (LAV) in individuals in a prospective Registry, comparing patients with high heart rate (HiHR) of $\geq$ 70bpm to those with atrial fibrillation (AFib).

Methods: Using the prospective CONVERGE Registry of patients undergoing 256 detector CCTA (Revolution, GE Healthcare, Milwaukee WI), we identified 121 high HR patients (74 men; mean age 62.7$\pm$12.5yrs) and 102 patients with AFib (72 men; mean age 60.5$\pm$11.0yrs). Quantitative data analyses of LAV was performed using automated methods on a workstation and software (AW4.6; GE Medical Systems, Waukesha, WI, USA) and mid-diastolic phases were chosen for measurements from CCTA. A student's t test, Wilcoxon rank-sum or chi-square tests assessed baseline parameters. Univariate and multivariate linear regression analysis was used to assess LAV and LAV index (LAVI) while adjusting potentially confounding variables.

Results: Mean LAV in AFIB subjects was significantly higher (148.6 ± 57.2mL), compared to HiHR subjects (102.1 ± 36.5mL), p<0.0001. Similarly, mean LAVI in AFIB subjects was significantly higher (72.4 ± 28.1 ml/m^2) than HiHR subjects' LAVI, (51.5 ± 19.0 ml/m^2) p<0.0001. After adjusting age, BMI, gender, diabetes, hypertension, hyperlipidemia, and smoking and those with AFib had on average higher LAV measures by 41.2±6.7 mL and LAVI by 23.1±3.4 ml/m^2, p<0.0001.

Conclusion: Recent advancements in CT technology including improvement in spatial and temporal resolution with wide volume coverage have allowed CCTA as a non-invasive alternative to echocardiography in providing the detailed LA complex morphology and function in addition to coronary anatomy without additional radiation, scanning or contrast requirements.

Introduction

Left atrial (LA) enlargement, as determined by echocardiography, has been emerged as a strong predictor of common cardiovascular disease outcomes such as atrial fibrillation (AFib), stroke, congestive heart failure and cardiovascular (CV) death.[1] LA dilation promotes stasis of blood, which in turn increases the risk of thrombus formation and the potential for embolization. Several studies have shown the clinical usefulness of doppler-derived left ventricular (LV) diastolic function to predict CV mortality and morbidity.[2,3] However, due to these significant LV measurements, attention was drawn towards diastolic dysfunction markers, such as left atrial volume (LAV). Tsang et al demonstrated the strong association of LAV with LV diastolic dysfunction.[1] The stroke prevention in AFib study and cardiovascular health study reported the significant association between stroke and LA dimensions.[4,5] Early detection of LA dysfunction is proposed to provide insight into the pathophysiology and clinical management of several diseases in which LA dysfunction may be present.

Recent advancements in cardiovascular imaging modalities and their clinical application have contributed significantly to assess the LA complex morphology and function and its interrelationship with LV, aorta, and pulmonary artery. Previous studies have shown that three-dimensional echocardiography (3D-echo) has better accuracy and reproducibility when compared to two-dimensional echocardiography (2D-echo), however 3D-echo is not widely used in clinical practice.[6] Echocardiographic parameters of LA dimension include LA anteroposterior diameter, LA area and volume. These parameters are more globally descriptive, and they remain normal in the early phases of disease. Furthermore, LAV measured by echocardiograms are highly dependent on image quality and have been shown to underestimate the LAV when compared to LAV measured by contrast-enhanced cardiac computed tomography (CT) or cardiac magnetic resonance (CMR) imaging.[7]

The aim of present study was to investigate the ability of current generation Revolution coronary computed tomography angiography (CCTA) to measure LAV in high heart rate (HiHR) and atrial fibrillation (AFib) population, who were prospectively enrolled in the CONVERGE Registry of patients undergoing 256 detector CCTA (Revolution, GE Healthcare, Milwaukee WI).

Methods

Patients:

Using the prospective CONVERGE Registry of patients undergoing 256 detector CCTA (Revolution, GE Healthcare, Milwaukee WI), we identified 121 high HR patients (74 men; mean age 62.7$\pm$12.5yrs) and 102 patients with AFib (72 men; mean age 60.5$\pm$11.0yrs). In total 223 (146 men; mean age, 61.7±11.9 yrs) eligible participants, age between 25 to 80 years with weight < 300 lbs and HR $\geq$ 70bpm and a clinical indication of CCTA, were enrolled after obtaining the written informed consent form that has been approved by Institutional Review Board (IRB) of the Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center. Our current study was conducted according to the principles expressed in the Declaration of Helsinki.

We excluded patients with known history of valvular diseases (n=1), cancer (n=1), chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2 within 30 days of the CT) (n=3), insufficient CCTA image quality (n=4) or a history of intravenous contrast allergy (n=2).

Evaluation of Cardiovascular Risk Factors:

Prior to CCTA, demographics of all the participants along with the blood pressure, height, weight and a focused history of cardiovascular risk factors were obtained from each patient. Clinical history was ascertained through patients interview and clinical questionnaire. Previous history of hypertension, diabetes mellitus and hyperlipidemia were defined with medications targeted at managing them. Current cigarette smokers or those who quit smoking within 3 months of testing were established to have a positive smoking history. A clinically significant family history of coronary artery disease was defined as that occurring in a prior relative less than 65 years of age in women and less than 55 years of age in men.

CCTA scan and Image acquisition:

All CT scans were performed with a with a 256-slice CT scanner (Revolution CT; General Electric Healthcare Technologies), and SOMATOM Definition Flash instrument (Siemens Medical Solutions, Erlangen, Germany). Prescan oral metoprolol were used to achieve a resting HR< 65 bpm and we enrolled those individuals whose HR $\geq$70 bpm even after beta-blockade therapy. Sublingual nitroglycerin 0.4mg was administered immediately before contrast injection. A contrast medium (Omnipaque 350; General Electric Healthcare Technologies) was injected at a rate of 5.0 mL/s using a triple-phase contrast protocol: 60-cc contrast, followed by 20cc of contrast and 30 cc of saline, followed by a 50-ml saline flush. We used electrocardiogram-gated contrast-enhanced CCTA was performed, with scan initiation 20 mm above the level of the left main artery to 20 mm below the inferior myocardial apex. The scan parameters were rotation speed 0.28 s/rotation (with no table motion), 256 slice CT × 0.625 mm collimation, tube voltage 120 kVp, and effective mA 122 to 740 mA based up on BMI of the patient which was automatically determined by the system. Autogating capability of Revolution CT scan automatically acquire diastolic phases for lower HRs and both systolic and diastolic phases for higher HRs. Each scan was done in a single-beat acquisition within one cardiac cycle, regardless of HR. After scan completion, multiphasic reconstruction of the CCTA scans was performed, with reconstructed images from 70% to 80% by 5% increments and 5% to 95% by 10% increments.

Before CCTA, a prospective nonenhanced coronary calcium scan was performed. For quantitative assessment of CAC, the Agatston score was calculated using a 3-mm CT slice thickness and a detection threshold of ≥130 HU involving ≥1 mm2 area/lesion (3 pixels).[8]

LAV Analysis:

Quantitative data analyses were performed using automated methods on a workstation and software (AW4.6; GE Medical Systems, Waukesha, WI, USA) that used a Hounsfield unit-based endocardial border detection technique. Images were reconstructed with a1.25mm slice thickness. The mid-diastolic phases were chosen for measurements of LAV. The LA appendage and pulmonary veins were not included in the LAV measurement. After adjustment for the body surface area, the LA volume index (LAVI) was estimated using the DuBois formula.[9]

Statistical Analysis:

Continuous variables are expressed as means ±SDs, while categorical variables are stated as counts and percentages. A student’s t test, Wilcoxon rank-sum or chi-square tests assessed differences in all baseline parameters between AFib and HiHR subjects. Univariate and multivariate linear regression analysis was used to examine the relationship between LAV and LAVI while adjusting for potentially confounding variables. A P value of <0.05 was considered as significant. SAS software (version 9.4) carried out all statistical analyses.

Results:

Baseline demographics and clinical characteristics are summarized in Table 1. The mean age of participants was 61.7 ±11.9 years and 65% of the 223 cohort were male. A total of 223 subjects with LAV measures were analyzed. 122 AFib (mean age 60.5 ±11.0 yrs.; 61%

men) and 121 HiHR (mean age 62.7 ± 12.5 yrs; 71% men) subjects were identified. Age, gender, smoking use, and hyperlipidemia were not significantly different between the AFib and HiHR groups, but ethnicity, BMI, BSA, self-reported chest pain, DM and HTN were.

Mean LAV in AFib subjects was significantly higher (148.6 ± 57.2 ml), compared to HiHR subjects (102.1 ± 36.5 ml), p<0.0001. Similarly, mean LAVI in AFib subjects was significantly higher (72.4 ± 28.1 ml/m^2) than HiHR subjects' LAVI, (51.5 ± 19.0 ml/m^2) p<0.0001. After adjusting for age, BMI gender, diabetic status, hypertension, hyperlipidemia, history of myocardial infarction and smoking habits, those with subjects with AFib had on average higher LAV by 41.2±6.7 ml and higher LAVI by 23.1±3.4 ml/m^2, p<0.0001. (Table 2)

Table 1: Baseline Characteristics

	Total (n= 223)	**HiHR (n=121)**	**AFib (n=102)**	**P-value**
Age (years)	61.7 ±11.9	62.7 ± 12.5	60.5 ±11.0	0.16
Men, n (%)	146 (65)	74 (61)	72 (71)	0.14
Ethnicity				<.0001
Hispanic, n (%)	82 (37)	20 (17)	62 (61)	
White, n (%)	82 (37)	68 (56)	14 (14)	
African American, n (%)	20 (9)	4 (3)	16 (16)	

Asian, n (%)	25 (11)	16 (13)	9 (9)	
Other, n (%)	14 (6)	13 (11)	1 (1)	
Chest Pain, n (%)	42 (19)	29 (24)	13 (13)	0.03
Hypertension, n (%)	157 (70)	72 (60)	85 (83)	0.0001
Dyslipidemia, n (%)	140 (63)	81 (67)	59 (58)	0.16
Diabetes mellitus, n (%)	67 (30)	24 (20)	43 (42)	0.0003
History of MI, n (%)	31 (14)	10 (8)	21 (21)	0.008
Current smoking, n (%)	19 (9)	7 (6)	12 (12)	0.11
Body mass index (kg/m^2)	30.6 ± 6.7	28.7 ± 5.9	32.8 ±6.9	<.0001
Body surface area ($m^{2)}$	2.0 ±0.3	2.0 ±0.3	2.1 ± 0.3	0.03
Heart Rate(bpm)	71.4 ±9.8	71.4 ±9.8	66.5 ± 10.1	0.01
Systolic blood pressure (mmHg)	131.3+19.2	136.1 ±18.6	125.5±18.4	<.0001
Diastolic blood pressure (mmHg)	78.8 ±10.9	78.2 ±11.1	79.5 ±10.8	0.3893
CAC score	631.65 ± 1,294.9	724.6 ± 1,416.8	524.1 ±1,135.4	0.227
LAV (ml)	123.4 ±52.4	102.1 ±36.5	148.6 ± 57.2	<.0001
LAVI (ml/m^2)	61.1 ±25.7	51.5 ±19.0	72.4 ± 28.1	<.0001

All comparisons between the HiHR and AFib groups were performed using Student's t-test, Wilcoxon rank-sum or chi-square tests.
Abbreviations: MI, myocardial infarction; CAC, coronary artery calcium; LAV, left atrial volume; LAVI, left atrium volume index;

Table 2: Relationship between left atrial measurements and high heart rate or atrial fibrillation subjects.

	Univariate, unadjusted			Multivariate, adjusted*		
	β	SE	P-value	β	SE	P- value
LAV	-46.42	6.33	<.0001	-41.18	6.76	<.0001
LAVI	-20.86	3.17	<.0001	-23.10	3.39	<.0001

*Adjusted for age, BMI gender, diabetic status, hypertension, hyperlipidemia, history of myocardial infarction and smoking habits.
Abbreviations: β, standardized regression coefficient; SE, standard error; LAV, left atrial volume; LAVI, left atrium volume index;

Discussion:

CT technology has significantly improved since its introduction into clinical practice in 1972.[10] CCTA is a rapidly evolving, non-invasive imaging technique to evaluate the presence, extent, and severity of coronary artery disease (CAD).[11] CCTA provides full volumetric data of all the 4 cardiac chambers, which makes LAV measurement possible without the need for any geometric assumption of the LA parameters.[12] The determining of LA function simultaneously with LV function, aortic function and pulmonary artery hemodynamics will provide a better understanding of the role of the LA on cardiovascular homeostasis in normal subjects and in patients with cardiovascular diseases. CCTA measures the LAV accurately when compared to CMR.[13] Due to high contrast to noise ratio, CCTA provides high image quality with spatial temporal resolution, excellent endocardial border definition and software based motion correction.[14] Iterative reconstruction (IR) ability of new generation CT scanners reduce image noise without compromising the diagnostic quality, which permits a significant reduction in effective radiation dose. Additionally, our group have demonstrated that the new generation GE Revolution CT have a significant improvements to obtain excellent quality of images with lower radiation compared to Aquilion ONE Vision, Toshiba CT scanner {1.50 $\pm$ 0.75 mSv vs 1.9 mSv (interquartile range, 1.7- 2.7 mSv); p=0.01}.[14]

CCTA is considered as a reliable tool to detect or rule out coronary stenosis in individuals with regular and low heart rates (< 65bpm). Prescan β-blockers are commonly administered to achieve a resting heart rate < 65bpm, thereby reducing the number of motion artifacts. However, progressive improvement in temporal resolution of cardiac CT minimize the motion related imaging artifacts and may reduce the need for prescan β-blockers.[15,16] Ropers et al.[15] demonstrated that the diagnostic accuracy of CCTA was not influenced by heart rate. Andreini et al.[17] reported 98.5 % of diagnostic accuracy of Revolution CT, which was equipped with 0.23mm spatial resolution, 0.28 sec gantry rotation time, and an intracycle motion correction algorithm, to detect CAD in AFib patients with mean heart rate of 83 bpm. We used the same parameters of Revolution CT scanner to evaluate LAV measurements in our study population.

Previous studies have shown that LA volumetric measurements are more accurate than linear dimension measurements to evaluate the asymmetric LA remodeling and considered as a strong predictor of CVD.[18] Kircher et al.[19] and Vandenberg et al.[20] have shown that echocardiographically measured LAV was proved to have good correlation or underestimation compared to LAV measurements of cine CT, biplane contrast ventriculography, and MRI. Walker et al.[21] reported the cardiac CT mid-diastolic phase normal LAVI values at slow and regular heart rates as 20.8 to 49.8 mL/m^2 (LAV as 37.7-98.7 mL) and Osawa et al.[22] reported 35.2 ± 10.9 mL/m^2 LAVI values in young adults with suspected CAD. These studies excluded the AFib population and more over the mean heart rate of their study population was approximately < 70bpm. The mid-diastolic phase mean values of LAV (HiHR 102.1 $\pm$ 36.5 mL and AFib 148.6 $\pm$ 57.2 mL) and LAVI (HiHR 51 $\pm$ 19.0 mL/m^2 and AFib 72.4 $\pm$ 28.1 mL/m^2) in our study population were slightly larger and this might be due to HiHR and AFib population.

Our current study demonstrated the ability of 256-slice Revolution CT scanner to measure the LAV in HiHR and AFib individuals. Misalignments and motion artifacts of CTA images affects the CT diagnostic performance especially in patients with elevated heart rates or profound arrhythmia. However, the recent progress in software and hardware capabilities has allowed for the effective and efficient imaging provides the accurate measurements of cardiac volumes and function with minimal radiation dose compared to prior generations of CCTA.

Limitations: The current study has several limitations. First, the study was a prospective multiple center observational study, but without simultaneous echocardiography or magnetic resonance imaging to compare the baseline LAV measurements. Secondly, LV function, aortic function and pulmonary artery hemodynamics were not determined along with the LAV in the present study. Additional research is necessary to determine the importance of volumetric LAV to predict the mortality and morbidity in high risk individuals such as atrial fibrillation (AFib), stroke, congestive heart failure and cardiovascular (CV) death.

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