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Title: Evaluation of left atrium indices among high heart rate and heart rate variability patients with advancement in computed tomography technology: The CONVERGE registry.

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Key words: Left atrial volume, heart rate variability, high heart rate, arrhythmia, motion artifacts.

Abstract:

Introduction: We intended to assess the ability of current generation 256-slice coronary computed tomographic angiography (CCTA) to measure LA volume (LAV) comparing patients with high heart rate (HiHR) of $\geq$ 70bpm and heart rate variability such as atrial fibrillation (AFib).

Methods: Using the prospective CONVERGE Registry of patients undergoing 256 detector CCTA (Revolution, GE Healthcare, Milwaukee WI), we enrolled 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) after obtaining the informed consent. Quantitative data analyses of LAV was performed using automated methods on a workstation and software (AW4.6; GE Medical Systems, Waukesha, WI, USA) and end-systolic 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: Misalignments and motion artifacts of CCTA images affects the CT diagnostic performance especially in patients with elevated heart rates or profound arrhythmia. However, the new generation Revolution CCTA provides the detailed LA complex morphology and function in HiHR and AFib patients in addition to coronary anatomy without additional radiation, scanning or contrast requirements.

Introduction

Computed tomography (CT) technology has significantly improved since its introduction into clinical practice in 1972 (*1*). Coronary computed tomography angiography (CCTA) is a rapidly evolving, non-invasive imaging technique to evaluate the presence, extent, and severity of coronary artery disease (CAD) (*2*). In cardiac CT imaging modalities such as coronary artery calcium and CCTA the patients high, irregular, or high and irregular heart rate variation plays an important role on the imaging quality. Pre-scan β-blockers are commonly administered to achieve a resting heart rate < 65bpm, thereby reducing the number of motion artifacts. However, previous studies have demonstrated a significant negative correlation between mean heart rate and image quality ($r = 0.80$, $P < .001$) (*3*). During the scanning, a significant variations in heart rate (e.g., from 41 to 100 bpm are equivalent to an R-R interval ranging from 1463 to 600 msec) results in improper recording of electrocardiogram-gated data and severe discontinuities in the reconstructed cardiac images especially in individuals with atrial fibrillation (AFib) or other arrhythmia (*4*). The temporal window suited for imaging (e.g., mid- to end-diastole) is shortened due to increased motion speed of coronary vessels in high heart rate (HiHR) patients, whereas the temporal variability of diastolic phase is increased between contiguous cardiac cycles in individuals with AFib. This inaccurate location of temporal windows creates motion artifacts and prevent adequate visualization and assessment of coronary vessels. However, progressive improvement in temporal resolution and electrocardiogram-gated capability of new generation CT scan minimize the motion related imaging artifacts and may reduce the need for prescan β-blockers (*5,6*). The electrocardiogram-gating with tube current modulation capability automatically acquire images at diastolic phases for lower heart rates and both systolic and diastolic phases for higher heart rates.

Recent advancements in cardiovascular imaging modalities and their clinical application have contributed significantly to assess the left atrium (LA) complex morphology and function and its interrelationship with left ventricle, aorta, and pulmonary artery along the coronary arteries. 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 (*5*). Echocardiographic parameters of LA dimension include LA antero-posterior diameter, LA area and volume. These parameters are more globally descriptive, and they remain normal in the early phases of disease. Furthermore, left atrial volume (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 CT or cardiac magnetic resonance imaging (*6*).

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

Methods

Study Population:

Using the prospective CONVERGE Registry of patients undergoing 256 detector CCTA (Revolution, GE Healthcare, Milwaukee WI), we identified 121 HiHR patients with sinus rhythm (74 men; mean age 62.7±12.5yrs) and 102 patients with AFib (72 men; mean age 60.5±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 ≥ 70bpm and a clinical indication of CCTA, were enrolled after obtaining the written informed consent form that has been approved by Institutional Review Board of The Lundquist Institute. 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 scans were performed with a 256-slice CT scanner (Revolution CT; General Electric Healthcare Technologies). Both contrast and non-contrast scans were performed for evaluation of the extent of coronary artery calcium (CAC) and coronary plaque volume as previously published (*7–10*). Prescan oral metoprolol were used to achieve a resting HR< 65 bpm and we enrolled those individuals whose HR ≥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 as previously published. Autogating capability of Revolution CT scan automatically acquire diastolic phases for lower heart rates and both systolic and diastolic phases for higher heart rates. Each scan was done in a single-beat acquisition within one cardiac cycle, regardless of heart rate. 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 coronary artery calcium, 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) (*11*).

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. Volumes were calculated using Simpson's method (*12*). Images were reconstructed with a1.25mm slice thickness. The end-systolic 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 (*13*).

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 high heart rate (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, body mass index, body surface area, self-reported chest pain, diabetes mellitus, and hypertension 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)

Discussion:

This study, to the best of our knowledge, is the first to assess the ability of 256-slice Revolution CT scanner for LAV measurements among patients with high and irregular heart rates. We found significant higher LAV measurements among individuals with AFib compared to HiHR patients ($p<0.0001$).

Heart rate variability plays a vital role in the diagnostic accuracy of CCTA and the inter-examination HRV results in inaccurate temporal window of R-R intervals resulting in the impairment of electrocardiogram-gated reconstruction image technique. Leschka et al.(*14*) have shown that the heart rate variability positively correlated with the image quality and the diagnostic accuracy of CCTA was reduced with increasing heart rate variability ($r= 0.61$, $p< 0.01$). Brodoefel and his colleagues reported a negative correlation of heart rate variability with image quality of all coronary segments or individual coronary arteries, whereas heart rate variability did not effect the diagnostic specificity of dual-source CCTA (*15*). Ropers et al.(*16*) demonstrated that the diagnostic accuracy of CCTA was not influenced by heart rate. Furthermore, Zhang et al.(*17*) concluded that average heart rate had no effect on the diagnostic accuracy of cardiac CT, whole heart rate variability was found to have a significant effect on the senstitvity and specificity of CCTA. Misalignments and motion artifacts of CTA images affects the CT diagnostic performance especially in patients with elevated heart rates or profound arrhythmia. In the past few years, advances in software (e.g., automatic recognition and editing of heart rhythm irregularities) and scanner technology (e.g., faster rotation time or increased temporal resolution) capabilities has allowed for the effective and efficient imaging provides the accurate measurements of cardiac volumes and function compared to prior generations of CCTA. All these previous studies assessed the diagnostic accuracy and image quality of cardiac CT for coronary arteries. In the present study we evaluated the ability of cardiac CT for LAV measurements in heart rate variability individuals.

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 (*18*). The determining of LA function simultaneously with left ventricle 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 cardiac magnetic resonance (*19*). 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 (*20*). Iterative reconstruction ability of new generation CT scanners reduce image noise without compromising the diagnostic quality, which permits a significant reduction in effective radiation dose. Andreini et al.(*21*) 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 similar parameters of Revolution CT scanner to evaluate LAV measurements in our study population. Additionally, previous study have demonstrated that the new generation 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 + 0.75 mSv vs 1.9 mSv (interquartile range, 1.7- 2.7 mSv); p=0.01} (*20*).

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 cardiovascular disease (*22*). Leschka et al.(*23*) have demonstrated that dual-source CCTA provides the best image quality at diastole (70% of RR interval) at various heart rates (35-117bpm). Walker et al.(*24*) 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.(*25*) 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 + 36.5 mL and AFib 148.6 + 57.2 mL) and LAVI (HiHR 51 + 19.0 mL/m2 and AFib 72.4 + 28.1 mL/m2) in our study population were slightly larger and this might be due to HiHR and AFib population with documented CAD.

LA enlargement has been emerged as a strong predictor of common cardiovascular disease outcomes such as AFib, stroke, congestive heart failure and cardiovascular death (*26*). 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 diastolic function to predict cardiovascular mortality and morbidity (*27*, *28*). However, due to these significant left ventricle measurements, attention was drawn towards diastolic dysfunction markers, such as LAV. Tsang et al demonstrated the strong association of LAV with left ventricular diastolic dysfunction (*26*). The stroke prevention in AFib study and cardiovascular health study reported the significant association between stroke and LA dimensions (*29*, *30*). 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.

Limitations: The current study had several limitations. First, the LAV measured from CCTA is not compared with simultaneous echocardiography or magnetic resonance imaging or previous CT generations. Secondly, left ventricle function, aortic function and pulmonary artery hemodynamics were not determined along with the LAV in the present study. Thirdly, we did not assess any follow-up measurements of LAV in our study population. Fourth, we did not show the relationship among LAV and conventional risk factors. Additional research is necessary to determine the importance of volumetric LAV to predict the mortality and morbidity in high risk individuals such as AFib, stroke, congestive heart failure and cardiovascular death.

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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;