Cardiovascular computed tomography for diagnosis and risk stratification of coronary artery disease

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Chapter 13

Incremental prognostic value of left ventricular function analysis over non-invasive coronary angiography with multi-detector computed tomography

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Abstract

The purpose of this study was to determine the prognostic value of CTA derived left ventricular (LV) function analysis and to assess its incremental prognostic value over the detection of significant stenosis using CTA. In 728 patients (400 males, mean age 55 ± 12 years) with known or suspected CAD the presence of significant stenosis (≥ 50% stenosis) and LV function were assessed using CTA. LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and LV ejection fraction (LVEF) were calculated. LV function was assessed as a continuous variable and using cutoff values (LVEDV > 215 ml, LVESV > 90 ml, LVEF < 49%). The following events were combined in a composite end-point: all-cause mortality, non-fatal myocardial infarction, and unstable angina pectoris requiring hospitalization. On CTA, a significant stenosis was observed in 221 patients (30%). During follow-up [median 765 days, 25th–75th percentile: 493–978) an event occurred in 45 patients (6.2%). After multivariate correction for clinical risk factors and CTA, LVEF < 49% and LVESV > 90 ml were independent predictors of events with an incremental prognostic value over clinical risk factors and CTA. In conclusion, the present results suggest that LV function analysis provides independent and incremental prognostic information beyond anatomic assessment of CAD using CTA.

Introduction

Multidetector computed tomography coronary angiography (CTA) has emerged as an important non-invasive imaging modality by providing direct anatomic assessment of coronary artery disease (CAD).[1-3] Recently, several studies have shown that, in addition to its value for the diagnosis of CAD, stenosis detection with CTA may also be useful for risk stratification.[4-7] Furthermore, besides the assessment of coronary anatomy, left ventricular (LV) function may be evaluated using information derived from the same CTA data set.[8-10] LV function is an established prognostic marker, as has been demonstrated using several imaging modalities including left ventriculography, echocardiography, magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT).[11-14] However, no data are currently available concerning the prognostic significance of CTA derived LV function assessment. The purpose of the present study was therefore to determine the prognostic value of CTA derived LV function analysis and to assess its incremental prognostic value over the detection of significant coronary artery stenosis using CTA.

Methods

The study group consisted of consecutive patients with suspected or known CAD who were clinically referred for CTA because of chest pain, a positive or inconclusive exercise electrocardiogram (ECG) test, or an elevated risk profile for cardiovascular disease. The study population is part of a large ongoing registry exploring the prognostic value of CTA.[15] For the current analysis, only patients with a CTA examination of diagnostic image quality and with additional LV function data were included. Exclusion criteria for CTA examination were: 1) (supra)ventricular arrhythmias, 2) renal failure (glomerular filtration rate < 30 ml/min), 3) known allergy to iodine contrast material, 4) severe claustrophobia or 5) pregnancy.

CTA Data Acquisition

CTA studies were performed using a 64-row (n=647) or 320-row (n=81) multidetector scanner (Aquilion 64, and Aquilion ONE, respectively, Toshiba Medical Systems, Otawara, Japan). One hour prior to the examination, a single dose of oral beta-blocker medication was administered to patients with a heart rate ≥ 65 bpm, unless contraindicated. Based on a pre-defined beta-blocking medication administration protocol, patients with a heart rate between 65 and 75 bpm received 50 mg metoprolol while patients with a heart rate ≥ 75 bpm received 100 mg metoprolol. The total amount of non-ionic contrast media (Iomeron 400; Bracco, Milan, Italy) injected into the antecubital vein was 60-100 ml (depending on body weight and scanner type) at a flow rate of 5.0 ml/s or 6.0 ml/s, followed by a saline flush of 25-50 ml. In order to synchronize the arrival of the contrast media, bolus arrival was

detected using a real-time bolus tracking technique.[16] All images were acquired during a single inspiratory breath-hold of maximally 12 seconds. For 64-row CTA, a helical-scanning technique was used as previously described.[17, 18] In brief, during the scan, the ECG was registered simultaneously for retrospective gating of the data. A collimation of 64 x 0.5 mm was used. Additional scan parameters were: 400 ms or 500 ms gantry rotation time depending on cardiac frequency, 120 kV tube voltage and 300-350 mA (depending on body-mass index (BMI) and thoracic geometry). During 320-row CTA, the ECG was registered simultaneously for prospective triggering of the data. In order to perform LV function analysis, ECG-triggered tube modulation was used, as previously described.[19]

The entire heart was imaged in a single heart beat, attaining maximal tube current during 75% of R-R interval (in patients with stable heart rate < 60 beats per minute (bpm)), during 65-85% of R-R interval (in patients with a heart rate 60-65 bpm) or during 30-80% of R-R interval (in patients with a heart rate >65 bpm). Outside the pre-defined interval, tube current was 25% of the maximal tube current. In patients with a heart rate > 65 bpm images were acquired during multiple heart beats (typically two). A collimation of 320 x 0.5 mm was used. Additional scan parameters were: 350 ms gantry rotation time, 120-135 kV tube voltage and 400-580 mA (depending on BMI and thoracic geometry). For the 64-row CTA scanner, the estimated average radiation dose for CTA was 17.6 ± 5.6 mSv. For the 320-row CTA scanner, the estimated average radiation dose for single heart beat CTA's using ECG-triggered tube modulation was 10.7 ± 3.6 mSv. In patients in whom CTA image acquisition was performed during multiple heart beats average estimated radiation dose was 16.7 ± 6.3 mSv.

Coronary arteries were evaluated using the reconstruction dataset with the least motion artifacts, typically acquired during an end-diastolic phase. To assess LV function and LV volumes, 10 series of 2.0-mm slices were reconstructed from the same dataset at every 10% throughout the cardiac cycle, starting at early systole (0% of cardiac cycle) to end-diastole (90% of cardiac cycle).

Data Analysis

CTA and LV function reconstructions were transferred to a remote workstation with dedicated analysis software (for 64-row CTA reconstructions: Vitrea 2, Vital Images, Minnetonka, MN, USA; for 320-row CTA reconstructions: Vitrea FX 1.0, Vital Images, Minnetonka, MN, USA). The presence of coronary stenosis was assessed by scrolling through axial images, combined with visual assessment of curved multiplanar reconstructions in ≥ 2 orthogonal planes. CTA examinations were evaluated on a patient basis for the presence of a significant stenosis (≥ 50% luminal narrowing) by two experienced observers. Discrepancies in interpretation were resolved by consensus.

For the purpose of LV function analysis, appropriate phases for LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV) were acquired, by selecting the smallest and largest cross-sectional LV cavity areas respectively. Upper limit of the LV was determined at the basal level of the mitral valve and the start of the LV outflow tract, as previously described.[20] Endocardial borders were outlined using a semi-automated method from the base to the apex on the short-axis cine images by an independent observer. Papillary muscles were excluded from the ventricular cavity. The LVEDV and LVESV volumes were calculated and the LVEF was derived by subtracting the LVESV from the LVEDV and dividing the result by the LVEDV.9 Observers for LV function analysis were blinded to CTA data.

End-points

Patient follow-up data were gathered by a single observer, blinded to the baseline CTA results, using clinical visits and/or standardized telephone interviews. A composite end-point was constructed using the following events: all-cause mortality, non-fatal myocardial infarction, and unstable angina pectoris requiring hospitalization. Non-fatal infarction was defined based on criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the ECG.[21] Unstable angina was defined according to the European Society of Cardiology guidelines as acute chest pain with or without the presence of ECG abnormalities, and negative cardiac enzyme levels.[22]

Statistical Analysis

Statistical analysis was performed using SPSS software (version 16.0, SPSS Inc., Chicago, Illinois). Quantitative data were expressed as mean ± standard deviation (SD). Categorical variables were described as numbers and percentages. Cox regression analysis was used to determine the prognostic value of the presence of significant stenosis and LV function parameters on CTA. First, univariate analysis of baseline characteristics, the presence of significant stenosis and LV function parameters was performed using a composite end-point of all-cause mortality, non-fatal infarction, and unstable angina. For each variable, a hazard ratio (HR) with a 95%-confidence interval (CI) was calculated. Increased LVEDV and LVESV were defined as LVEDV > 215 ml, LVESV > 90 ml and reduced LVEF was defined as LVEF < 49%, as described previously.23 These values were determined using the 95% confidence interval boundaries for 3-dimensional LV dimensions and function as determined by CTA.[23] After univariate analysis, several multivariate models were created to correct LV function parameters for clinical risk factors and the presence of significant stenosis on CTA. In case variables showed strong interrelation (Pearson's correlation coefficient >0.8), variables were excluded from the same multivariate model. Finally, the incremental value of LV function variables over clinical risk factors (age, gender, smoking and known CAD) and the presence of significant stenosis on CTA was assessed by calculating the global chi-square values. A p-value < 0.05 was considered statistically significant.

Results

From the registry, additional LV function measurements (derived from CTA) were available in 813 patients. In 29 patients (3.6%) the CTA examination was of non-diagnostic image quality and these patients were excluded from the study. Furthermore, a total of 56 patients (6.9%) were lost to follow up. As a result, the patient group consisted of 728 individuals. The main clinical characteristics of the population are listed in Table 1. In summary, 55% was male and the mean age was 55 ± 12 years.

Table 1. Patient characteristics

Gender (male / female)	328 / 400
Age (years)	55 ± 12
Reason for Referral	
Typical chest pain	83 (12%)
Atypical chest pain	189 (26%)
Non-anginal chest pain	132 (18%)
Elevated risk profile	213 (29%)
Positive or inconclusive exercise ECG	111 (15%)
Clinical Risk Factors	
Diabetes	222 (31%)
Hypercholesterolemia	261 (36%)
Hypertension	317 (44%)
Family history of coronary artery disease	309 (42%)
Smoking	137 (19%)
Obesity (BMI ≥ 30 kg/m^2)	143 (20%)
Known CAD	96 (13%)

Baseline CTA and LV function

In the study population of 728 patients, a significant stenosis (luminal narrowing ≥ 50%) was identified on CTA in 221 patients (30%). When evaluating LV volumes, an average LVEDV of 138 ± 38 ml was observed. For LVESV an average value of 52 ± 29 ml was observed. As a result, average LVEF was 64 ± 10%. Increased LVEDV (> 215 ml) and LVESV (> 90 ml) were present in 31 patients (4.3%) and 50 patients (6.9%), respectively. A reduced LVEF (< 49%) was present in 43 patients (7.3%).

Follow-up

The median follow-up period was 765 days (25th–75th percentile: 493–978); an event occurred in 45 patients (6.2%). All-cause death was reported in 23 patients (3.2%), non-fatal myocardial infarction occurred in 7 patients (1.0%), and 15 patients (2.0%) were admitted to the hospital due to unstable angina.

Survival Analysis

Univariate analysis of clinical risk factors, significant stenosis on CTA and LV function analysis parameters is depicted in Table 2. Of the clinical risk factors, age, smoking and known CAD were significant predictors of events. Also, the presence of a significant stenosis on CTA was identified as a significant predictor of events. Regarding LV function, all three parameters (LVEDV, LVESV and LVEF) were significant univariate predictors when assessed as continuous variables and categorical variables, using predefined cutoff values.

Table 2. Univariate predictors of events

	HR (95%-CI)	p-value
Baseline clinical Characteristic		
Age	1.04 (1.01-1.07)	0.005
Male gender	1.36 (0.75-2.49)	0.315
Diabetes	1.03 (0.55-1.93)	0.939
Hypercholesterolemia*	0.73 (0.38-1.39)	0.333
Hypertension†	0.89 (0.53-1.73)	0.958
Family history of coronary artery disease‡	0.61 (0.32-1.15)	0.125
Smoking	2.31 (1.25-4.25)	0.007
Obesity (BMI ≥ 30 kg/m^2)	0.55 (0.22-1.39)	0.205
Known CAD	2.74 (1.46-5.13)	0.002
CTA		
Significant stenosis	3.52 (1.59-7.83)	0.002
LV function (continuous)		
LVEDV (per 10 ml increase)	1.07 (1.00-1.14)	0.048
LVESV (per 10 ml increase)	1.10 (1.03-1.18)	0.006
LVEF (per % increase)	0.97 (0.94-0.99)	0.006
LV function (categorical)		
LVEDV > 215 ml	2.89 (1.22-6.86)	0.016
LVESV > 90 ml	3.95 (1.99-7.84)	<0.001
LVEF < 49%	3.82 (1.93-7.57)	<0.001

Multivariate models were created correcting for clinical risk factors (age, gender, smoking and known CAD) and significant stenosis on CTA. The prognostic value of LV volumes and LVEF are shown in Table 3. A total of six models were created. In the first three models LVEDV, LVESV and LVEF were assessed as continuous variables. In the last three models the predictive value of LV function was determined using the pre-defined cutoff values to indicate reduced LV function. Although none of the continuous LV function variables remained independent predictors of events, using the pre-defined cutoff values as markers for reduced LV function, increased LVESV and reduced LVEF provided additional prognostic information over clinical risk factors (age, gender, smoking, known CAD) and significant stenosis on CTA. Figure 1 illustrates the incremental prognostic value, depicted by chi-square value, of LVESV > 90 ml over age, gender, smoking, known CAD and significant stenosis on CTA (p <

0.05). Similarly, Figure 2 shows that LVEF < 49% has incremental value ($p < 0.05$), and thus enhanced risk stratification beyond the detection of significant stenosis using CTA.

Table 3. Multivariate models for the prediction of events

	HR (95%-CI)	p-value
LV function (continuous)		
LVEDV (per 10 ml increase)	1.05 (0.99-1.13)	0.123
LVESV (per 10 ml increase)	1.06 (0.98-1.15)	0.119
LVEF (per % increase)	0.98 (0.96-1.01)	0.177
LV function (categorical)		
LVEDV > 215 ml	1.98 (0.79-4.95)	0.143
LVESV > 90 ml	3.11 (1.45-6.67)	0.004
LVEF < 49%	2.61 (1.22-5.60)	0.014

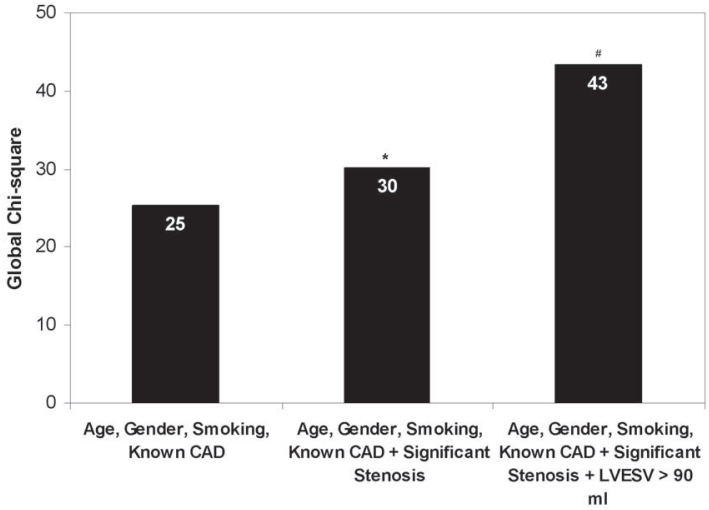

Figure 1. Bar graph illustrating the incremental prognostic value (depicted by chi-square values on the y-axis) of LVESV > 90 ml over age, gender, smoking, known CAD and significant stenosis. The presence of significant stenosis on CTA has a significant incremental prognostic value over age, gender, smoking and known CAD (*). A further incremental prognostic value over clinical risk factors and significant stenosis on CTA is observed with the addition of LVESV > 90 ml (#).

Discussion

The main finding of the current study is that CTA derived LV function may provide important prognostic information beyond the detection of significant stenosis on CTA.

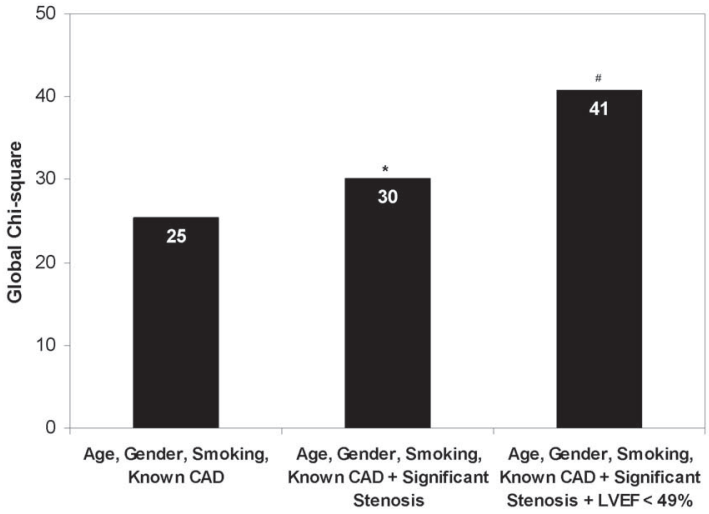

Figure 2. Bar graph illustrating the incremental prognostic value (depicted by chi-square values on the y-axis) of LVEF < 49% over age, gender, smoking, known CAD and significant stenosis on CTA. The presence of significant stenosis on CTA has a significant incremental prognostic value over age, gender, smoking and known CAD (*). A further incremental prognostic value over clinical risk factors and significant stenosis on CTA is observed with the addition of LVEF < 49% (#).

LV volumes and LVEF are used extensively as clinical markers of cardiac function. In patients with known CAD, LV function analysis provides important information for risk assessment and further management.[11, 24] Post myocardial infarction patients with a normal LVEF have a relatively good prognosis, whereas the risk of future events has been shown to increase with deteriorating LVEF.[25] LV function analysis may also be useful in patients with suspected CAD. Using 2-dimensional echocardiography in 2,948 patients without prevalent CAD, Devereux and colleagues showed that LVEF < 40% was a strong predictor of cardiovascular death (RR 6.9, CI 3.0-15.9, p<0.001) and all-cause mortality (RR 4.8, CI 2.8-8.1, p<0.001), independent of clinical risk factors.[12] In a study by Sharir and colleagues, evaluating 1680 patients referred for gated SPECT, LVEF < 45% and ESV > 70 ml were identified as optimal thresholds to accurately stratify patients into high risk and low risk groups.[14] Importantly, patients with a normal LVEF or LVESV had a substantially lower annual mortality rate (regardless of the degree of perfusion abnormalities on SPECT) than patients with reduced LVEF or increased LVESV. In the current study, the prognostic value of LV function measurements on CTA was evaluated. LV volumes and LVEF provided prognostic information independent of baseline clinical variables. These findings illustrate that measurements of LV function (and volumes) from CTA acquisitions can be beneficial in defining patient risk and if available, should be incorporated into the clinical report.

Importantly, patients undergoing CTA are primarily referred for assessment of CAD. As this anatomic information has been established to provide prognostic information, ([4-6] an important objective of the current study was to determine the additional value of LV function analysis beyond the detection of significant CAD. Limited information is available regarding the additional prognostic value of LV function over the non-invasive angiographic assessment of CAD using CTA. In a recent study by Min and colleagues, evaluating 5330 consecutive patients without known CAD with a mean follow up of 2.3 ± 0.6 years, the addition of LV function measured by CTA significantly increased risk correlation for death. Annualized mortality rates in patients with significant CAD and LVEF ≤ 50% was significantly higher (3.79%) than in patients with significant CAD and LVEF > 50% (1.76%).[26] Furthermore, Chow and co-workers recently determined the incremental prognostic value of LV function measured with CTA in 2,076 consecutive patients with a mean follow up of 16 ± 8 months. It was shown that LVEF had incremental prognostic value over CAD severity (HR 1.47, 95% CI 1.17-1.86).[27] These data indicate that LV function is an important predictor of survival with incremental value to CTA. In line with these results, the present study suggests that, although the assessment of significant CAD on CTA is a powerful predictor, LV function parameters provide independent incremental value in predicting adverse events. Thus, the addition of LV function analysis to CTA may further improve risk stratification of patients with known of suspected CAD referred for stenosis detection.

Limitations

Several limitations of the present study merit consideration. First, 6.9% of patients were lost to follow-up. Second, regional wall motion abnormalities were not assessed in the present study. Third, the present study is limited by a relatively small patient number. Fourth, CTA is inherently associated with radiation exposure.[28] As a result, prospective ECG triggering was recently introduced for the purpose of radiation reduction.[29, 30] This technique allows image acquisition during a small portion of the cardiac cycle which significantly reduces the radiation exposure. However, as a result data are no longer acquired throughout the entire cardiac cycle, thereby eliminating the possibility of simultaneous LV function analysis from the same dataset. Although LV function may still be assessed, it has become at the expense of increased radiation exposure, also when using ECG-triggered tube current modulation. Therefore, the necessity of LV function analysis using CTA should be carefully weighed against the increase in radiation burden. Importantly, LV function analysis may also be performed using radiation free modalities, such as echocardiography or magnetic resonance imaging. Accordingly, although in the present study LV function was derived from CTA, LV function analysis may enhance risk stratification beyond the presence of significant stenosis on CTA regardless of the modality used to derive this information. Additional studies are warranted to gain better understanding of the integration of angiographic and LV function data to refine risk stratification.

Conclusion

The present results suggest that LV function analysis provides independent and incremental prognostic information beyond anatomic assessment of CAD using CTA.

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