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Original Article

Efficacy of multi-detector coronary computed tomography angiography in comparison with exercise electrocardiogram in the triage of patients of low risk acute chest pain

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ABSTRACT

Objectives: To compare the safety and diagnostic efficacy of coronary computed tomography angiography (CTA) with exercise electrocardiography (XECG) in triaging patients of low risk acute chest pain.

Background: Noninvasive assessment of coronary stenosis by CTA may improve early and accurate triage of patients presenting with acute chest pain to the emergency department (ED).

Methods: Low risk patients of possible acute coronary syndrome (ACS) were included in the study. The patients in CTA arm with significant stenosis (≥50%) underwent catheterization, while those with no or intermediate stenosis (<50%) were discharged from ED and followed up periodically for six months for major adverse cardiovascular events (MACE). The same protocol was applied for XECG arm. Outcomes included: safety and diagnostic efficacy.

Results: A total of 81 (41 CTA and 40 XECG) patients were enrolled. In this study CTA was observed to be 100% sensitive and 95.7% specific in diagnosing MACE in low risk patients of chest pain presenting to the ED, with a PPV of 94.7% and an NPV of 100%.The overall diagnostic efficacy was 97.6%. XECG was observed to be 72.7% sensitive and 96.6% specific in diagnosing MACE with a PPV of 88.9% and NPV of 90.3% in low risk chest pain patients presenting to the ED. The overall diagnostic accuracy was 90%.

Conclusion: CTA is an excellent diagnostic tool in ED patients with low risk of ACS, with minimum time delay as compared to XECG, and also is safe for triaging such patients.

1. Introduction

There are >8 million visits to emergency departments (EDs) for chest pain or other symptoms consistent with myocardial ischemia annually in the United States, which makes this the second most frequent cause of ED encounters in adults[1]; however, only a minority of these patients have a life-threatening condition. Failure to detect acute coronary syndrome (ACS) and inadvertent discharge of such patients from the ED may exceed 2%, with a risk adjusted mortality ratio that is nearly 2-fold that of patients hospitalized for ACS, and it is

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also associated with substantial liability.[2] Thus, rapid, optimal therapy for patients with ACS must be balanced against recognition of patients with noncritical syndromes for whom hospitalization and extensive evaluation are unnecessary, expensive, potentially hazardous, and an ineffective use of limited resources. To achieve this goal, most strategies have used stress testing, with or without cardiac imaging, on the basis of the premise that a negative result markedly reduces the likelihood of ACS .The absence of obstructive CAD indicated by computed tomography coronary angiography (CTCA) has recently been used to confirm very low risk of ACS. We examined performance characteristics of CTA and compared it with exercise electrocardiogram for diagnosing or excluding an ACS in patients presenting to the ED with possible ischemic chest pain and examined the relation to clinical outcome during a 6 month follow-up period.

2. Methods

2.1. *Study population*

The study was a prospectively planned analysis of CTA and XECG data, collected during a 1-year period from April 2010 to March 2011 at King George Medical University, Lucknow, India, in which consecutive patients presenting to the ED with possible ischemic chest pain were considered for study inclusion. The standard ED protocol in the medical center triages patients with symptoms suggestive of ACS on the basis of American College of Cardiology/American Heart Association 2002 guidelines. The study included patients with low and intermediate risk of ACS. Intermediate risk patients had clinical symptoms of definite ischemic origin but without high-risk features. Low risk patients had symptoms of uncertain origin but compatible with possible ACS. This included patients with recent chest discomfort at rest not entirely typical of ischemia and free of pain when initially evaluated and without new ECG changes or elevated biomarkers.

We necessarily excluded from the study patients with contraindication to intravenous contrast agents (contrast allergy) or elevated serum creatinine (>1.3 mg/dL for men, >0.9 mg/dL for women), Patients with atrial fibrillation, frequent ventricular ectopy (>10 extra systoles per minute), patients who have documented CAD by prior invasive coronary angiography or coronary CT angiography and/or patients with coronary artery stents, prior angioplasty, or prior coronary artery bypass grafts (CABG); and patients who have had prior cardiac imaging (within the past year) with normal result including invasive coronary angiography, coronary CT angiography, or nuclear stress testing were also excluded.

2.2. *Exercise electrocardiogram*

A group of patients who were eligible (those with normal baseline ECG and serum markers of myocardial necrosis, and no clinical suspicion of pulmonary embolism, aortic dissection, or pericarditis) underwent an ED physician directed symptom-limited treadmill exercise test (Bruce protocol) during initial diagnostic triage. Requirements before exercise ECG testing that should be considered in the emergency department setting are 2 sets of cardiac enzymes at 4 h intervals should be normal, ECG at the time of presentation, and pre exercise 12-lead ECG shows no significant change, absence of rest ECG abnormalities that would preclude accurate assessment of the exercise ECG, From admission to the time results are available from the second set of cardiac enzymes: patient asymptomatic, lessening chest pain symptoms, or persistent atypical symptoms and absence of ischemic chest pain at the time of exercise testing.

The exercise ECG testing facility conform to the American Heart Association (AHA) guidelines for clinical exercise ECG testing laboratories.

Exercise tests without ischemic responses in patients who fail to achieve 6 METs or who fail to achieve 85% of age-predicted maximum heart rate should be considered inconclusive. Patients with a conclusively positive or negative treadmill test were hospitalized or discharged respectively. We examined the correlation between XECG findings and definitive diagnosis of ACS on the basis of standard diagnostic tests. A diagnosis of ACS was made in patients who had ≥1 of the following: elevated cardiac biomarkers within 7 days of XECG, or coronary stenoses ≥50% at invasive coronary angiography (ICA) not explained by previously known disease. For patients discharged from the ED, follow up by telephone was performed the next day, 1 week after ED discharge, and after 6 months. We inquired about major adverse cardiovascular events (MACE), defined as death, myocardial infarction, or unplanned revascularization, and about repeat ED visits or hospitalization for unstable angina. Overall MACE rate was the combination of in-hospital and follow up events.

3. CTA

Another group of eligible patients were included in CTA arm.

CTA scans (Brilliance 64, Philips Brilliance 64, Philips Medical Systems, Cleveland, Ohio) were performed with retrospective ECG gating. An oral (metoprolol 50–100 mg) and/or intravenous (metoprolol 2.5–10 mg) B-blocker (or oral calcium antagonist [verapamil 80 mg] in asthmatic patients) was used to lower heart rate. Oral B-blocker was administered when heart rate was >70 bpm 1 h before scanning .If heart rate was still >70 bpm on arrival to the CT suite and no medical contraindication existed, intravenous metoprolol was added.

The coronary calcium score (Agatston score) was measured in a non-contrast-enhanced scan when applicable. A contrast-enhanced scan was then performed with a bolus of 40–150 mL contrast medium (Ultravist 370 mg I/mL; Schering AG, Berlin, Germany) injected into an antecubital vein at a flow rate of 5–6 mL/s, followed by a 50 mL saline chaser bolus.

Scanning was performed at 120 kV, effective tube current 600–1000 mA (higher mA in obese patients), slice collimation 64 x 0.625 mm acquisition, 0.4 s gantry rotation time, and pitch 0.2. Overall scan time (as well as breath hold) was usually <15 s. Total time for the CTA examination was typically 10–15 min. All patients gave written informed consent according to a protocol approved by the institutional review board.

Patients in whom the ED CTA showed obstructive ≥50% luminal stenosis was the CTA-positive group. CTA-positive

patients (provisional ACS) underwent further diagnostic testing and observation in the hospital. The patients with normal or non obstructive CTA scans (CTA-negative patients) underwent additional ED observation to complete serial ECG and measurement of biomarkers at least 6–9 h apart, and, if they were pain free and all biomarker and ECG tests were negative, they were discharged from the hospital. All patients were followed up over a 6 month period.

We examined the correlation between ED CTA findings and definitive diagnosis of ACS on the basis of standard diagnostic tests. A diagnosis of ACS was made in patients who had ≥1 of the following: elevated cardiac biomarkers within 7 days of CTA, or coronary stenosis ≥50% at ICA (as in TIMI 3B & FRISC 2 studies) not explained by previously known disease. For patients discharged from the ED, follow up by telephone was performed the next day, 1 week after ED discharge, and after 6 months. We inquired about major adverse cardiovascular events (MACE), defined as death, myocardial infarction, or unplanned revascularization, and about repeat ED visits or hospitalization for unstable angina. Overall MACE rate was the combination of in-hospital and follow up events.

3.1. *Clinical covariates*

We prospectively collected data on demographics, risk factor profile, and clinical course in all patients. Presence of risk factors (i.e., hypertension, hypercholesterolemia, and diabetes mellitus) was established from actual measurements obtained during the hospitalization or related medication use.

3.2. *Statistical analysis*

Statistical analysis was performed with the use of SPSS 15 software package. We calculated sensitivity, specificity, and positive and negative predictive values of CTA and XECG findings for diagnosis of ACS and for prediction of MACE to 6 months of follow up. A probability value of <0.05 was considered significant for statistical testing. Demographics, traditional risk factors, clinical events, and prevalence of plaque and stenosis as detected by coronary CTA are presented as mean ± SD or median and interquartile range for continuous variables and as percentages for categorical variables.

We determined the utility of coronary CTA/XECG to guide triage decisions in the ED using 2 different analytic strategies. To determine the accuracy of coronary CTA/XECG, we calculated conventional measures of diagnostic accuracy (sensitivity, negative predictive value [NPV], specificity, and positive predictive value [PPV]) and test-positive and -negative likelihood ratios with 95% confidence intervals (CIs) based on a binomial distribution for the absence of plaque and the absence of significant stenosis for the detection of ACS. The chi-square test was used to compare proportions and measures of diagnostic accuracy between groups.

4. Results

4.1. *Patient characteristics*

A total of 81 (41 CTA and 40 XECG) patients were enrolled in the study.

Both the arms (CTA & XECG) in this study were matched for demographic and other baseline characteristics and therefore were comparable ($p > 0.05$) [Table 1& Graph 1].

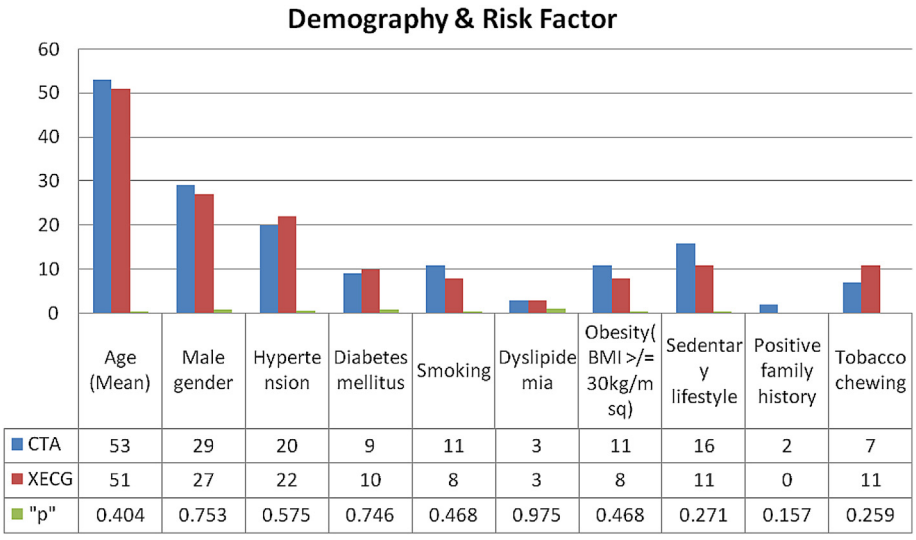
4.2. *CTA results*

Diagnostic accuracy: In the CTA group 19/41 (46.3%) tested positive; 1/41 (2%) tested negative came back with chest pain (MACE on follow up). These 20/41 underwent ICA.17 Out of 20

Table 1 – Comparison of demographic and baseline characters in two study groups.

S.No.	Characteristic	CTA ($n = 41$)		XECG ($n = 40$)		χ^2/t	"p"
		No.	%	No.	%		
1.	Age (mean ± SD) (range)	52.90 ± 8.91		51.20 ±0.35 (30–71)		0.839	0.404
2.	Male gender	29	70.7%	27	67.5%	0.099	0.753
3.	Hypertension	20	48.8%	22	55%	0.314	0.575
4.	Diabetes mellitus	9	22.0%	10	25%	0.105	0.746
5.	Smoking	11	26.8%	8	20%	0.526	0.468
6.	Dyslipidemia	3	7.3%	3	7.5%	0.001	0.975
7.	Obesity (BMI ≥30 kg/m sq)	11	26.8%	8	20.0%	0.526	0.468
8.	Sedentary lifestyle	16	39.0%	11	27.5%	1.210	0.271
9.	Positive family history	2	4.9%	0	0%	2.001	0.157
10.	Tobacco chewing	7	17.1%	11	27.5%	1.274	0.259
11.	Heart rate (mean ± SD) (range)	81.73 ± 8.69 (70–110)		83.23 ± 11.32 (100–190)		−0.667	0.507
12.	SBP (mean ± SD) (range)	130.98 ± 19.21 (100–170)		133.25 ± 18.05 (100–190)		−0.549	0.585
13	DBP (mean ± SD) (range)	80.00 ± 9.75 (70–110)		81.75 ± 9.03 (70–100)		−0.838	0.405
14.	S. creatinine (mean ± SD) (range)	0.89 ± 0.20 (0.6–1.4)		0.79 ± 0.13 (6–1.0)		2.763	0.007
15.	RBS (mean ± SD) (range)	107.83 ± 35.31 (60–190)		106.20 ± 43.59 (65–255)		0.185	0.854
16.	Total cholesterol (mean ± SD) (range)	151.93 ± 27.88 (108–228)		148.73 ± 26.26 (104–250)		0.532	0.596
17.	HDL (mean ± SD) (range)	44.46 ± 5.82 (30–54)		44.90 ± 6.65 (28–53)		−0.315	0.754
18.	LDL (mean ± SD) (range)	93.95 ± 23.76 (46–137)		98.73 ± 26.16 (49–197)		−0.860	0.392
19.	TG (mean ± SD) (range)	142.66 ± 39.82 (71–230)		131.38 ± 31.37 (70–219)		1.414	0.161

Both the groups were matched and were comparable ($p > 0.05$).



Graph 1 – Comparison of baseline characters.

(85%) were true positive, 1 out of 20 (5%) cases were true negative, 2 out of 20 (10%) were false positive [Table 2, Graph 2].

In our study CTA was observed to be 100% sensitive and 95.7% specific in diagnosing ACS in low to intermediate risk patients of chest pain presenting to the ED, with a PPV of 94.7% and an NPV of 100%. Combining angiographic and clinical results for CTA group overall diagnostic efficacy was 97.6% [Graph 3].

An example of how CTA images look like (as in one of the patient in the study) in multiplanar reformat displayed as thick slice maximum intensity projection & three dimensional volume rendered format is shown in Figs. 1 and 2 respectively.

5. Vessel/segmental assessment

Among the three vessels, maximum sensitivity was observed for RCA (100%) whereas maximum specificity was observed for LCx (91.7%). The sensitivity was minimum for LCx (66.7%) while specificity was minimum for LAD (62.5%). Overall maximum diagnostic efficacy was observed for RCA (94.4%) and minimum for LAD (74.4%).

For the 10 vessel segments analyzed the, CTA was most sensitive for proximal segments (100%) while minimum for distal segments where it has high specificity. Diagnostic efficacy of CT ranged from 61.1% (LAD Prox) to 100% (RCA distal). The highest sensitivity was obtained for LAD Prox and RCA Prox (100%) the minimum sensitivity was obtained for LAD Distal and LCX Distal (0%). Maximum specificity was obtained for LAD Mid, LAD distal, LCX distal and LCX Om (100%) whereas minimum specificity was obtained for LAD Prox (46.2%). The positive predictive value was maximum for LAD Mid and LCX Om (100%) whereas the minimum PPV was for LCX Prox (33%). The negative predictive value was maximum for LAD Prox, RCA Prox and RCA distal (100%) whereas it was minimum for LAD Mid (68%).

Table 2 – CT ($n = 41$) & XECG ($n = 40$).

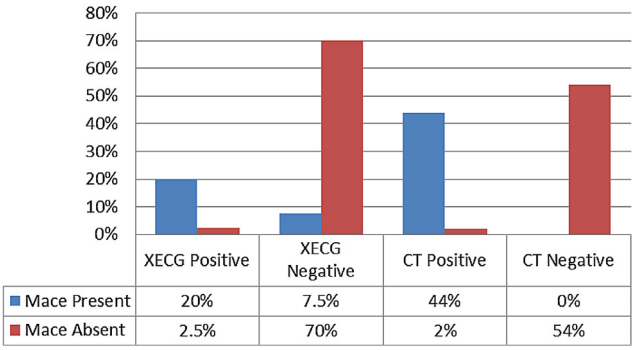
	XECG positive	XECG negative	CT positive	CT negative
MACE present	8 (20%)	3 (7.5%)	18 (44%)	0 (0%)
MACE absent	1 (2.5%)	28 (70%)	1 (2%)	22 (54%)

5.1. *XECG results*

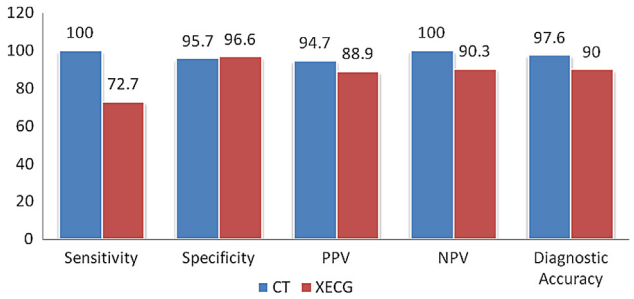
5.1.1. *Diagnostic accuracy*

In SOC, 14 out of 40 (35%) underwent ICA, 10 cases as part of the primary diagnostic strategy and 4 cases during the 6 month follow-up period owing to recurrent chest pain (MACE) 0.8/14 were true positive (57%), 2/14 were false positive (14%), 1/14 was true negative (7%), and 3/14 were false negative (21%) [Table 2, Graph 2].

XECG was observed to be 72.7% sensitive and 96.6% specific in diagnosing MACE (in-hospital + follow up)with a PPV of 88.9% and NPV of 90.3% in low to intermediate risk chest pain patients presenting to the ED. Combining angiographic and clinical results for SOC group, the overall diagnostic accuracy was 90% [Graph 3].



Graph 2 – Comparison of CT & XECG in diagnosing MACE.



Graph 3 – Diagnostic efficacy of XECG & CTA ($p < 001$).

5.2. *Duke score*

There were 5/40 (12.5%) patients with Duke score ≤10 and remaining 35 (87.5%) had Duke score in the range of −10 to +5. Minimum score observed was −37 whereas maximum score observed was +5. It was observed that the proportion of patients with lower Duke score had more MACE as compared to those with higher Duke score ($p = 0.005$) [Table 3].

6. Discussion

Acute chest pain prompts patients to undergo ED evaluation to exclude acute coronary syndromes. Alarmingly, up to 8% of patients with acute coronary syndromes are misdiagnosed and inappropriately discharged home.[3,4] Of these patients with initially normal electrocardiograms and cardiac enzymes (low risk), only a minority actually suffers from myocardial ischemia.[5] However, because of the consequences of failure to diagnose acute coronary syndromes, it is standard practice to evaluate all such patients with serial electrocardiograms and cardiac enzymes over 8–12 h, followed by stress study. This approach is time consuming and resource intensive. CTA has emerged as an important tool in making a rapid diagnosis in patients with CAD. We attempted to study its efficacy in patients with chest pain at low risk for CAD & comparing it with standard of care i.e. exercise electrocardiogram.

A total of 81 patients of chest pain with low to intermediate risk for ACS were studied. The demographic and other baseline characteristics of the groups assigned to CTA (41 patients) and SOC with exercise ECG (40 patients) were comparable ($p > 0.05$).

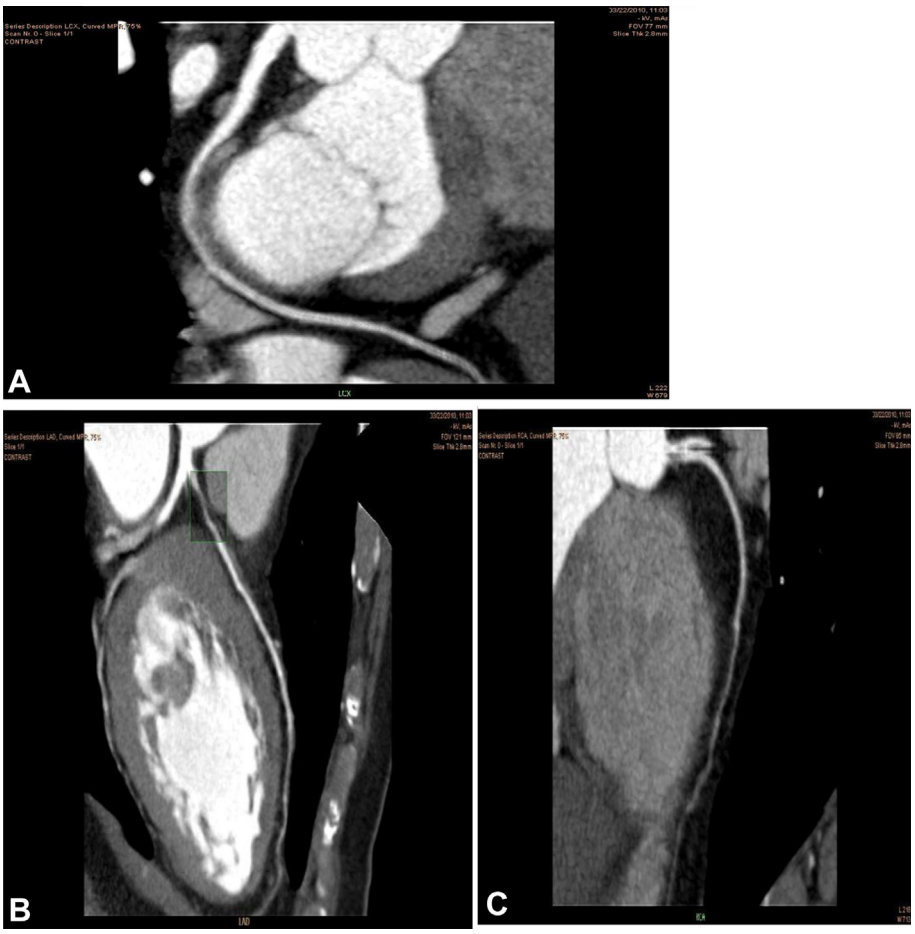


Fig. 1 – Multiplanar reformat displayed as thick slice maximum intensity projection. Distal segment of LCx shows narrowing of <50% stenosis for a segment of approx 8 mm. Obtuse marginal branches are normal A. *Proximal LAD shows more than 50 % stenosis for a segment of approx 5 mm* B. RCA curved, is small in caliber with normal ostea. No calcification or plaque seen. Distal RCA and its branches are normal. Non dominant C.

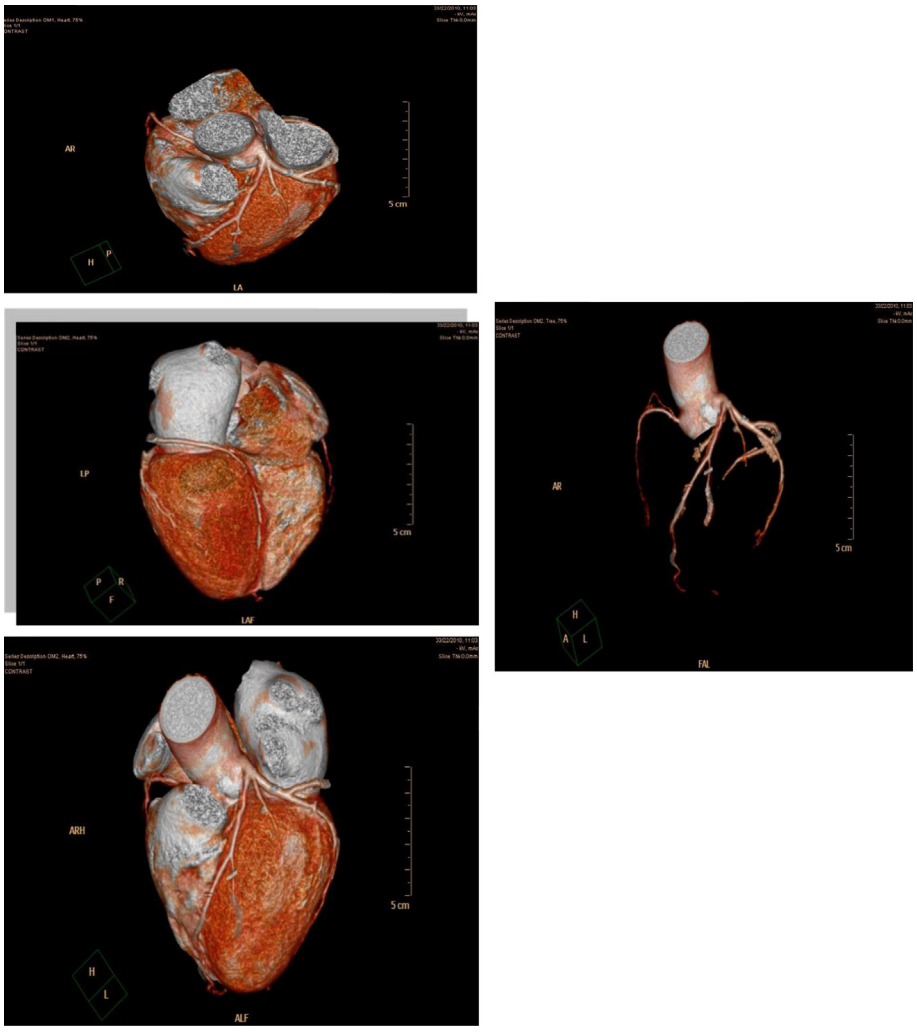


Fig. 2 – Three dimensional volume rendered format useful for anatomic overview.

Diagnostic performance of CTA *(Patient based analysis)* in *various studies is summarized in* Table 4.

There has been 1 prospective randomized trial that compared early XECG to early coronary angiography in 123 low risk patients presenting with chest pain to determine whether a negative invasive approach reduced repeat ED visits[6]. Coronary angiography detected CAD more frequently than XECG (19% versus 7%, respectively). Although more patients in the former group proceeded to revascularization, there was no difference in cardiac events at 1-year follow up; however, angiography lowered recidivism to the ED for chest pain compared with the noninvasive strategy (10% versus 30% of patients, respectively).

Because of the low risk of these patients, the small but definite risk of complications from invasive evaluation, and the utility of noninvasive tests, coronary angiography cannot be considered a first step in the assessment of this group, but there may be a role for CTA in selected patients.

Table 3 – Association of Duke score with MACE.

Variable	Duke score ≤10		Duke score between −10 and −5		χ^2	p
	No. ($n = 5$)	%	No. ($n = 35$)	%		
MACE absent	1	20	28	80	7.900	0.005
MACE present	4	80	7	20		

6.1. *CTA: vessel based analysis*

CTA was most sensitive in picking disease in RCA and least in LCx. It was most specific for LCx and least for LAD. Thus overall best diagnostic efficacy of CTA was observed for RCA and least for LAD.

In a study by Meijboom WB et al[14] sensitivity was maximum for LAD whereas it was most specific to find disease in left main.

For the 10 vessel segments analyzed, CTA was most sensitive for proximal segments (100%) while being minimum for distal segments where it had high specificity.

Table 4 – Studies of CTA in ED in low risk chest pain patients in nutshell.

First author	Year	*n*	Sensitivity	Specificity	PPV	NPV	DA
Udo Hoffmann[7]	2006	103	77%	87%	35%	100%	
Hollander[8]	2007	54	100%	85%	46%	100%	
Michael J Gallagher[10]	2007	85	86%	92%	50%	99%	
Rubinshtein Ronen[9]	2007	58	92%	76%	52%	97%	
Gabija Pundziute[11]	2007	100				100%	
Goldstein[12]	2007	197				100%	95%
Miller[13]	2008	291	85%	90%	91%	83%	
W Bob Meijboom[14]	2008	360	99%	64%	86%	97%	
Sung A Chang[15]	2008	268				100%	
Cury RC[16]	2008	445	95%	86%	61%	99%	
Hollander[17]	2009	568				100%	
Hoffman[18]	2009	368		87%		98%	

The low risk study population in the CTA arm had a low calcium score (<400 U) as well which may have contributed to its high diagnostic accuracy.

In our study myocardial bridging was found in 4 out of 41 (10%) patients .This appears to be an important cause of non atherosclerotic chest pain in the ED and should be kept as a differential diagnosis.

Exercise Testing in ED has been validated by multiple studies that included approximately 3000 patients who underwent XECG after >12 h of negative observation (Table 5). No adverse effects of early XECG were reported. The low positive predictive value for an ACS and its variability among studies is likely related to the differences in the study cohorts. Although the positive predictive value is low, the number of unnecessary admissions is reduced.

Gianrossi et al[19] investigated the variability of the reported diagnostic accuracy of the exercise ECG for CAD by applying meta-analysis and found mean sensitivity of 68%, lower mean specificity of 74%; there also was a lower predictive accuracy of 69%. This means that ex-ECG is an inadequate diagnostic modality for ruling out CAD ≥50% for patients with acute chest pain and low risk/pre test probability of disease.

6.2. *Study limitations*

An important drawback of the present study was the relatively short follow up interval for enough hard cardiac events, such as MI and cardiac death, to happen and the limited number of patients. Because low risk patients inherently have low event rates and the number of patients in our study was small, there were few patients who underwent invasive angiography or had MACE events, making it difficult to evaluate the true incidence of false positive and false negative CTA findings.

7. Clinical implications

CTA scanning has the potential to change clinical practice with respect to ED triage in patients with chest pain of uncertain origin. Although the benefits of clinical and noninvasive testing with the use of stress testing and myocardial scintigraphy are well established, the direct anatomic information provided by CTA scanning may have a major impact on ED decision making, especially in patients in whom other tests are equivocal.

Table 5 – Studies of XECG in ED* includes studies in which results of exercise ECG tests could be distinguished from those of other forms of stress testing.

Reference	No. of patients	Positive tests, %[a]	Negative predictive value, %[b]	Positive predictive value, %[b]	Adverse exercise test events
Tsakonls et al[78]	28	18	100		0
Kerns et al[79]	32	0	100		0
Gibler et al[80]	782	1	99	44	0
Gomez et al[c, 69]	100	7	100	0	0
Zalenski et al[81]	224	8	98	16	0
Polanczyk et al[82]	276	24	98	15	0
Kirk et al[83]	212	13	100	57	0
Diercks et al[84]	747	3	99	37	0
Sarullo et al[86]	190	30	99	77	0
Amsterdam et al[77]	1000	13	89	33	0
Ramakrishna et al[85]	125	27	100	8	0

[a] Positive exercise ECG.
[b] Based on clinical follow-up or further cardiac evaluation.
[c] Randomized controlled trial.
Adapted from Amsterdam et al.[20]

The very high negative predictive value is especially valuable in ruling out coronary artery disease in patients who have a low to intermediate pre test likelihood of CAD. CTA has a lower positive predictive value with vessel or segment-based analysis than with patient based analysis, but the negative predictive values are similar. These data suggest that coronary CTA cannot supplant coronary angiography in determining which vessels have critical coronary stenosis and need revascularization. Coronary CTA, however, seems to be extremely reliable in ruling out critical coronary artery disease and excluding patients who do not require further evaluation by invasive angiography. In fact, this strong negative predictive accuracy is cited as the reason for preferentially performing coronary CTA in patients who have chest pain and a low to intermediate pre test likelihood of coronary stenosis.

Conflicts of interest

All authors have none to declare.

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