Prognostic Implications of Nonobstructive Coronary Artery Disease in Patients Undergoing Coronary Computed Tomographic Angiography for Acute Chest Pain

Roy Beigel, MD[a,b], Sella Brosh, MD[a], Orly Goitein, MD[b,c], Einat Guttman, BSc[b], Ilia Novikov, PhD[d], Amit Segev, MD[a,b], Yariv Gerber, PhD[b], Dan Oieru, MD[a], Eli Konen, MD[b,c], Hanoch Hod, MD[a,b], and Shlomi Matetzky, MD[a,b,*]

Coronary computed tomographic angiography can detect nonobstructive atherosclerotic lesions that would not otherwise have been detected with functional cardiac imaging. Currently, limited data exist regarding the clinical significance of these lesions in patients with acute chest pain. The aim of our study was to examine the prognostic significance of these nonobstructive findings in a patient population presenting with acute chest pain. We evaluated 959 consecutive patients who underwent coronary computed tomographic angiography for investigation of acute chest pain. The patients were classified as having normal (n = 545), nonobstructive coronary artery disease (CAD; defined as any narrowing <50% diameter stenosis; n = 312), or obstructive CAD (narrowing of ≥50% diameter stenosis; n = 65). Follow-up data for a minimum of 12 months (mean 27 ± 11) was obtained for any major adverse coronary events consisting of death, nonfatal acute coronary syndrome, and coronary revascularization. Compared to patients with normal coronary arteries, those with nonobstructive CAD were older and had a greater prevalence of CAD risk factors. The incidence of major adverse coronary events was equally low among both these groups (0.6% vs 1.3%, for the normal and nonobstructive groups, respectively, p = 0.2). In conclusion, patients with either nonobstructive CAD or normal findings, as evaluated by coronary computed tomographic angiography, for acute chest pain during an intermediate-term follow-up period had equally benign clinical outcomes.   © 2013 Elsevier Inc. All rights reserved. (Am J Cardiol 2013;111:941–945)

Coronary computed tomographic angiography (CCTA) has emerged as an excellent noninvasive diagnostic modality to assess coronary artery disease (CAD) in low- to moderate-risk patients.[1–4] Because of its high negative predictive value, CCTA is particularly useful in excluding significant coronary artery stenosis in patients with acute chest pain who have an atypical presentation.[5–7] Patients found to have obstructive CAD using CCTA, defined as coronary plaques causing a ≥50% reduction in the luminal diameter, are known to have a worse prognosis than those with normal or nonobstructive (<50% luminal stenosis) CAD.[8–13] However, when evaluating patients presenting with acute chest pain, CCTA can identify nonobstructive, atherosclerotic plaques, that might or might not be related to patient symptoms, and probably would not have been detected using functional cardiac imaging. Currently, few data exist regarding the long-term prognostic significance of nonobstructive CAD found using CCTA, especially in patients presenting with acute chest pain. The aim of our study was to examine the prognostic significance of nonobstructive CAD detected using CCTA in a large cohort of consecutive, nonselective, real-world patients presenting with acute chest pain and undergoing evaluation by a dedicated chest pain unit (CPU) team using a strict protocol.

Methods

The study cohort included 959 consecutive patients who presented with acute chest pain and were admitted to the CPU. All patients were referred for CCTA within 24 hours of admission after acute coronary syndrome (ACS) had been ruled out. The patients underwent CCTA, after a ≥12-hour observation period to rule out ACS, when a repeat electrocardiogram was done, with findings unchanged from baseline, and the findings from a repeat cardiac biomarker evaluation were negative. The inclusion criteria for undergoing evaluation by CCTA included no previous history of CAD; age ≤70 years; weight ≤120 kg; sinus rhythm; no known contraindication to iodine contrast administration; and serum creatinine <1.4 mg/dl.

All findings from CCTA were interpreted by staff cardiologists and roentgenologists. Coronary computed tomographic angiographic studies were classified as showing normal coronary arteries (no evidence of coronary atherosclerosis); nonobstructive CAD (any evidence of

coronary atherosclerosis with <50% luminal narrowing); obstructive CAD (evidence of coronary atherosclerosis with ≥50% luminal narrowing); or inconclusive test results because of technical difficulties.

Patients with obstructive CAD by CCTA were referred for invasive coronary angiography and treated accordingly. Patients with normal findings or nonobstructive CAD were discharged with adequate recommendations for lifestyle modifications (i.e., smoking cessation, dietary changes, and physical activity). In patients with nonobstructive CAD, lipid-lowering therapy (statin) was initiated, regardless of the low-density lipoprotein levels with a target low-density lipoprotein cholesterol goal of <70 mg/dl, plus aspirin. Follow-up data for ≥1 year, with a mean follow-up period of 27 ± 11 months, was obtained for the entire study population. The follow-up data were obtained by 2 study investigators, who were unaware of the coronary computed tomographic angiographic findings, from either an outpatient clinic visit or a telephone interview using a prespecified questionnaire. The prespecified clinical end points during follow-up were recurrent episodes of chest pain, additional diagnostic tests (both noninvasive and invasive) performed because of chest pain, repeated hospitalizations for chest pain suspected as ACS, ACS (consisting of chest pain in the presence of either electrocardiographic changes suggestive of myocardial ischemia or infarction and/or troponin elevation), coronary revascularization (either percutaneous or bypass grafting), and death. The primary study end points were prespecified major adverse coronary events (MACE), coronary revascularization (urgent and nonurgent), ACS, and death. The number of events was counted as 1 per patient (counted as the first event) even if that patient experienced several events. The secondary end points included cardiovascular MACE consisting of ACS and/or cardiovascular death. For patients without available follow-up data, we reviewed the medical records and used the national population registry of the Ministry of Interior to evaluate whether the outcome of death had occurred. The results of the first 444 patients included in the present analysis have been previously reported.[14]

All coronary computed tomographic angiographic scans were performed using a 64-slice scanner (Brilliance 64, Philips Medical Systems, Cleveland, Ohio), with retrospective electrocardiographic gating. Heart rate control was achieved by oral β-blocker administration (propranolol 20 to 50 mg) 1 hour before scanning. Intravenous β-blocker administration (metoprolol 5 to 15 mg) was added if heart rate increased to >70 beats/min. The first scan was acquired with prospective gating for calcium score evaluation, with the scan volume starting at the lung apices and ending at the level of the diaphragm. Per protocol, patients with a high calcium score (Agatson score ≥800) were excluded from additional analysis; however, none of the patients who were referred for CCTA in our cohort had a high calcium score (>800). The contrast-enhanced scan was acquired with retrospective gating. A mean bolus of 80 ml (range 70 to 110) of nonionic contrast medium (Iomeron [iomeprol]) was injected into an antecubital vein at a flow rate of 4 to 6 ml/s. The scanning parameters included voltage, 120 kV (increased to 140 kV in patients weighing >100 kg); effective tube current, 800 to 1,235 mA; slice collimation, 64 × 0.625 mm;
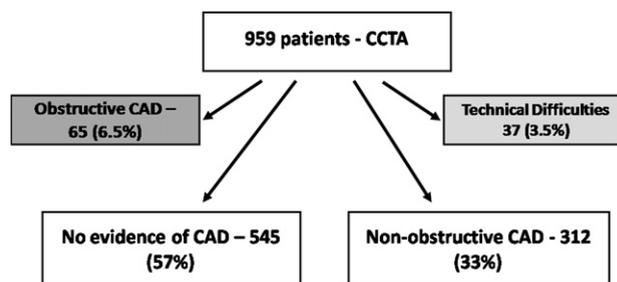

Figure 1. Patient distribution of study cohort.

gantry rotation time, 400 ms; pitch, 0.2 (reduced to 0.17 in patients weighing >100 kg). Dose modulation (full radiation dose only during 40% to 80% of the RR interval) was applied whenever possible to decrease radiation exposure. Diastolic phases (70% to 80% of the RR interval) were used for data reconstruction as the default. Systolic phases (35% to 45% of the RR interval) were used if heart rate increased to >70 beats/min. Each vessel was reconstructed using curved multiplanar reformats (extended workspace, Philips Medical Systems). All studies were analyzed and interpreted by experienced radiologists and cardiologists specializing in cardiovascular imaging. As previously stated, the patients were divided into 4 groups: (1) normal coronary arteries, (2) nonobstructive CAD, (3) obstructive CAD, and (4) inconclusive test owing to technical difficulties. The institutional ethics committee approved the present study.

Statistical analysis was performed using SPSS, version 12 (SPSS, Chicago, Illinois). Continuous variables are presented as mean ± SD or median and interquartile range and categorical variables as percentages. Continuous variables were compared using the Student *t* test if data followed a normal distribution and using the Wilcoxon rank sum test, if the data were skewed. Categorical variables were compared using the chi-square test or Fisher's exact test when indicated. All tests were 2-sided, and p values <0.05 were considered statistically significant.

Results

The study included 959 consecutive patients who presented to the emergency department with acute chest pain, were admitted to the CPU, and were further evaluated by CCTA. As per protocol, CCTA was performed only after ruling out ACS, which was determined from the repeat cardiac biomarker evaluation findings, an absence of recurrent ischemic changes on the ST-T analyzer during an observation period of ≥12 hours, and/or repeat electrocardiography. Figure 1 illustrates the patient distribution: of the 959 consecutive patients who underwent CCTA after ruling out ACS. Of these patients, 37 (3.5%) had a noninterpretable scan because of technical difficulties, 65 patients (6.5%) had obstructive CAD and, per protocol, were referred for invasive coronary angiography, 545 patients (57%) had normal coronary arteries, and 312 patients (33%) had nonobstructive CAD. Thus, 857 patients with a technically adequate study and either normal findings or nonobstructive CAD were the focus of the present evaluation. The patient baseline characteristics are listed in

Table 1
Baseline characteristics

Variable	CCTA		p Value
	Normal (n = 545)	Nonobstructive CAD (n = 312)	
Age	48 ± 9.1	52 ± 8.6	<0.01
Men	328 (60%)	226 (72%)	0.05
Smoker	171 (32%)	124 (40%)	<0.001
Diabetes mellitus	42 (8%)	28 (9%)	0.5
Hypertension*	123 (23%)	109 (35%)	<0.001
Hyperlipidemia†	199 (37%)	160 (51%)	<0.001
Family history of coronary artery disease	203 (37%)	110 (35%)	0.1
Total cholesterol (mg/dl)	182 ± 33	182 ± 33	0.8
Low-density lipoprotein (mg/dl)	113 ± 25	115 ± 26	0.2
High-density lipoprotein (mg/dl)	45 ± 12	41 ± 11	<0.001
Triglycerides (mg/dl)	125 ± 62	144 ± 80	<0.001
Creatinine (mg/dl)	0.96 ± 0.16	0.99 ± 0.15	0.4
C-reactive protein (mg/L)	5 ± 8.3	5.7 ± 18	0.8

Data are presented as mean ± SD or n (%).

* Defined as either a known medical history of hypertension and/or currently treated for hypertension.

† Defined as either a known medical history of hyperlipidemia and/or currently treated with low-density lipoprotein-lowering therapy.

Table 2
Patient outcomes during follow-up period

Variable	CCTA		p Value
	Normal	Nonobstructive CAD	
Follow-up duration (mo)	28 ± 11	25 ± 11	0.1
Recurrent chest pain	134 (26%)	81 (28%)	0.6
Additional diagnostic tests	57 (11%)	60 (21%)	<0.001
Invasive coronary angiography	4 (0.8%)	7 (2.4%)	0.05
Readmission for suspected acute coronary syndrome	23 (4%)	22 (7%)	0.2
Coronary revascularization	2 (0.4%)	3 (0.9%)	0.2
Acute coronary syndrome	2 (0.4%)	2 (0.6%)	0.6
Death	1 (0.1%)	1 (0.3%)	0.86
Cardiovascular death	0	0	
Major adverse coronary events (revascularization, acute coronary syndrome, death)	3 (0.6%)	4 (1.3%)	0.2

Data are presented as mean ± SD or n (%).

Table 1. Patients with nonobstructive CAD were older (age 52 ± 9 vs 48 ± 9 years, p <0.01), more likely be men (72% vs 60%, p = 0.05), with a higher risk profile for coronary disease, including an unfavorable lipid profile, compared to those who with normal coronary arteries. The C-reactive protein levels did not differ between the 2 groups.

Complete follow-up data were available at a mean duration of 28 ± 11 and 25 ± 11 months for the normal and nonobstructive groups, respectively (p = 0.1). For 54 patients (6%), for whom complete follow-up data were not obtainable, we screened the National Population Registry of the Ministry of Interior for the outcome of mortality for all who were alive. The clinical outcomes of the 2 study groups

are listed in Table 2. In both groups, the number of patients who had recurrent chest pain was similar, as was the number of those readmitted because of chest pain. Nevertheless, those with nonobstructive CAD underwent significantly more additional testing during the follow-up period, both noninvasive (21% vs 11%, p <0.001) and coronary angiography (2.4% vs 0.8%, p = 0.05). However, ultimately, no difference was seen in the number of patients who underwent coronary revascularization by either percutaneous coronary angiography or coronary artery bypass grafting (0.4% vs 0.9%, p = 0.2). The MACE rate was comparably low at 0.6% and 1.3% for the normal and nonobstructive groups, respectively (p = 0.2). One noncardiovascular death occurred in each group, of malignancy in both cases. The rate of cardiovascular MACE was also low and comparable, consisting of only 2 patients in each group (0.4% vs 0.6% for the normal and nonobstructive groups, respectively, p = 0.6), of whom only 1 patient in each group experienced a myocardial infarction.

Discussion

The present study is 1 of few to examine the long-term prognostic significance of nonobstructive CAD by CCTA in a homogenous patient population presenting with acute chest pain in a real-life setting. During a mean follow-up of about 2.5 years, the patients with nonobstructive CAD had a favorable course, comparable to those with normal CAD. No cardiovascular deaths occurred in either group, nor were there any significant differences in the incidence of ACS, which occurred only infrequently in both groups during the follow-up period of >2 years.

With the advancement of imaging techniques and improvement in picture resolution, CCTA has emerged as an excellent noninvasive modality for the assessment of CAD in various populations.[3,4] The accuracy of CCTA to detect significant coronary artery stenosis has been high in many published studies,[14–17] with a sensitivity rate of 76% to 99%, specificity of 87% to 99%, positive predictive value of 56% to 89%, and, probably most importantly, a negative predictive value of 95% to 100%.[2] However, most published studies that have examined the prognostic value of CCTA were performed in elective patients, comparing patients with or without obstructive CAD. Only a few of these studies compared the outcomes of patients with nonobstructive CAD to the outcomes of those with normal findings,[8–13] and even fewer in the setting of acute chest pain.[14,18–20] A recent meta-analysis that included 9,592 patients undergoing CCTA for various reasons demonstrated an event rate (consisting of a composite of death, myocardial infarction, and revascularization) of 0.17%, 1.41%, and 8.84% annually for those with normal, nonobstructive, and obstructive CAD, respectively.[21] In the present meta-analysis, the difference between those with normal coronaries and those with nonobstructive CAD achieved statistical significance.

Patients who present with acute chest pain suspected to be of coronary origin pose a specific subgroup that necessitates the initial exclusion of ACS. Although investigation of acute chest pain represents a major indication for performing CCTA,[22] only a limited number of studies have evaluated the

prognostic significance of ≥1 year of nonobstructive CAD by CCTA in this patient population.[14,18−20] Hollander et al[18] examined 481 patients with acute chest pain with <50% luminal stenosis found by CCTA. During a 1-year follow-up period, 1 death (assumed to be of noncoronary origin) and 13 rehospitalizations (for suspected ACS) but no events of myocardial infarction and/or revascularization occurred. A substudy of the Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT) trial, which evaluated patients with acute chest pain using CCTA in an emergency department setting, showed that in patients without CAD detected by CCTA, the 2-year MACE rate included revascularization and ACS, with death standing at 0%.[19] In those patients with nonobstructive CAD, the MACE rate was 4.6%.[19] However, most of the events in the non-obstructive disease group were driven by revascularization. The present study finding of an absence of a significant association between nonobstructive CAD by CCTA and the risk of ACS and/or mortality throughout long-term follow-up is in accordance with these trials showing a benign outcome for patients without obstructive findings by CCTA, with most events driven by revascularization and not by myocardial infarction and/or death.[6,18,19] The absence of an increase in the need for coronary revascularization in our study compared to the ROMICAT 2 study might be accounted for by the routine recommendations for lifestyle modifications and the initiation of statin therapy in those with non-obstructive findings. These recommendations could delay plaque progression or even help regress the plaque burden,[23,24] thereby decreasing the need for revascularization within 18 to 24 months.[25,26]

The recently published study by Andreini et al[20] was the first to show that CCTA was able to provide long-term prognostic information. Patients without evidence of CAD had an excellent prognosis at 52 months compared to those with obstructive CAD. Patients with nonobstructive CAD showed a cumulative event-free survival significantly lower than that of those without CAD. However, once again, these differences were mostly driven by differences in revascularization, with no significant differences in the occurrence of death and/or ACS. It should be noted that the latter study included a rather heterogeneous group of patients, with only 43% presenting with chest pain (acute or chronic) and 30% with previous positive stress test findings. Accordingly, as much as 38% of patients were found to have obstructive lesions at CCTA compared to a much lower incidence in previous studies of patients with acute chest pain.[6,19] Our predefined strict protocol for evaluating patients with acute chest pain using CCTA excluded patients with any evidence of ischemia or myocardial injury during the qualifying event, in accordance with the current appropriate criteria.[22]

The limitations of our study were that this was a single-center observational study from real-life CPU experience. Per protocol, statin therapy was recommended with a target low-density lipoprotein level of <70 mg/dl for all patients discharged from the CPU with the diagnosis of non-obstructive CAD. However, we have no follow-up data on patient compliance regarding this recommendation.

In conclusion, patients with either nonobstructive CAD or normal findings evaluated by CCTA for acute chest pain

during an intermediate-term follow-up had equal, benign clinical outcomes. Our findings should be seen as hypothesis generating and need to be validated further in a much larger multicenter, blinded, randomized cohort, that also possibly evaluates the use of statins for the prevention of CAD progression in a subpopulation of patients with non-obstructive CAD found by CCTA.

Disclosures

The authors have no conflicts of interest to disclose.

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