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Prognostic Interplay of Coronary Artery Calcification and Underlying Vascular Dysfunction in Patients With Suspected Coronary Artery Disease

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Objectives This study sought to evaluate the interrelation of atherosclerotic burden, as assessed by coronary artery calcium (CAC) score and coronary vascular function, as assessed by quantitative estimates of coronary flow reserve (CFR), with respect to prediction of clinical outcomes.

Background The contribution of coronary vascular dysfunction, atherosclerotic burden, and the 2 combined to cardiac events is unknown.

Method A total of 901 consecutive patients underwent ^{82}Rubidium myocardial perfusion imaging (MPI) positron emission tomography (PET) and CAC scan. All patients had normal MPI. The primary endpoint was a composite of major adverse cardiac events (MACE) including cardiac death, nonfatal myocardial infarction, late revascularization, and admission for heart failure.

Results At baseline, CFR decreased (2.15 ± 0.72, 2.02 ± 0.65, and 1.88 ± 0.64, $p < 0.0001$) with increasing levels of CAC (0, 1 to 399, and ≥400). Over a median of 1.53 years (interquartile range: 0.77 to 2.44), there were 57 MACE. Annual risk-adjusted MACE rates were higher for patients with CFR <2.0 compared with ≥2.0 (1.9 vs. 5.5%/year, $p = 0.0007$) but were only borderline associated with CAC (3.1%, 3.4%, and 6.2%/year for CAC of 0, 1 to 399, and ≥400, respectively; $p = 0.09$). Annualized adjusted MACE was increased in the presence of impaired CFR even among patients with CAC = 0 (1.4% vs. 5.2%, $p = 0.03$). Cox proportional hazards analysis revealed that CFR improved model fit, risk discrimination, and risk reclassification over clinical risk, whereas CAC only modestly improved model fit without improving risk discrimination or reclassification.

Conclusions In symptomatic patients with normal MPI, global CFR but not CAC provides significant incremental risk stratification over clinical risk score for prediction of major adverse cardiac events. (J Am Coll Cardiol 2013;61: 2098–106) © 2013 by the American College of Cardiology Foundation

Coronary artery calcium (CAC) is absent in normal coronary arteries, whereas its presence and magnitude reflects the overall burden of coronary atherosclerosis (1,2). Although CAC is a well-established marker of CAD and clearly risk stratifies asymptomatic subjects (3), the observation that coronary calcium content is lower in culprit lesions of patients with acute coronary syndromes compared to those with stable coronary artery disease (CAD), suggests that calcification may represent a healing response to injury (4). However, data from several large prospective studies demonstrating a stepwise increase in coronary risk with increasing calcium scores have challenged the notion that calcified coronary disease represents a scenario of clinical stability (3,5–10).

Post-mortem studies have shown that there are many noncalcified plaques for every calcified plaque (1). Thus, it is unclear whether CAC itself increases risk of adverse coronary outcomes or whether CAC deposition serves as a proxy

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for the extent and magnitude of noncalcified atherosclerosis and its functional consequence of coronary vascular dysfunction. Our objective was to test the hypothesis that coronary vascular dysfunction, reflecting the adverse effect of widespread atherosclerosis on coronary epicardial and microvascular function, is a key determinant of adverse prognosis irrespective of the magnitude of coronary artery calcifications.

Methods

Study population and design. A total of 1,240 consecutive patients underwent both stress myocardial perfusion positron emission tomography (PET) and CAC computed tomography (CT) at the Brigham & Women's Hospital (Boston, Massachusetts) between January 9, 2006, and June 30, 2010, for investigation of symptoms suspicious of CAD. In order to avoid the confounding effect of obstructive CAD, patients with abnormal PET myocardial perfusion imaging (MPI) studies (n = 292, 23.5%) were excluded, as were those with a history of prior myocardial infarction and/or revascularization (n = 78, 6.3%), a left ventricular ejection fraction <40% (n = 9, 0.7%), known valvular heart disease (n = 18, 1.5%), or atrial fibrillation (n = 0, 0%). The remaining 901 patients comprised the study cohort for the analysis. The study was approved by the Partners Healthcare Institutional Review Board and all study procedures were in accordance with institutional guidelines.

Clinical and historical data. Clinical histories elicited at the time of exam ascertained the patients' symptoms, coronary risk factors, and medication use at the time of the index study. Height and weight were measured and recorded, and body mass index was calculated. The Duke clinical risk score was calculated for each patient as previously described (11).

Hybrid PET/CT study. MYOCARDIAL PERFUSION PET SCAN. Patients were studied using a whole-body PET-CT scanner (Discovery RX or STE LightSpeed 64, GE Healthcare, Milwaukee, Wisconsin) after an overnight fast. Patients were instructed to avoid caffeine for at least 12 h and methylxanthine containing substances for 24 h.

Myocardial blood flow (MBF) was measured at rest and during peak hyperemia using ^{82}Rubidium as a perfusion tracer. Following a scout CT scan (120 kVp, 10 mA) used for proper patient positioning, a CT transmission scan was acquired (140 kVp, 10 mA) for subsequent correction of photon attenuation. Beginning with the intravenous bolus administration of ^{82}Rubidium (1,480 to 2,220 MBq), list mode images were acquired for 7 min as previously described (12). Then, intravenous dipyridamole (0.142 mg/kg/min for 4 min, n = 465 [52%]), adenosine (0.142 mg/kg/min for 4 min, n = 50 [5%]), regadenoson (0.4 mg bolus, n = 344 [38%]), or dobutamine (10 to 50 μg/kg/min, n = 42 [5%]) was infused. At peak hyperemia, a second dose of ^{82}Rubidium (1,480 to 2,220 MBq) was injected and images were recorded in the same manner. A second CT transmission scan was acquired (140 kVp, 10 mA) after vasodilator stress for attenuation correction of the stress emission data. The heart rate, systemic blood pressure, and 12-lead electrocardiogram were recorded at baseline and every minute during and after the infusion of the stress agent. The rate pressure product was calculated by multiplying heart rate and systolic blood pressure measured at rest and during peak hyperemia, respectively.

Abbreviations and Acronyms

- **CAC** = coronary artery calcium
- **CAD** = coronary artery disease
- **CI** = confidence interval
- **CFR** = coronary flow reserve
- **CT** = computed tomography
- **MACE** = major adverse cardiac event(s)
- **MBF** = myocardial blood flow
- **MPI** = myocardial perfusion imaging
- **NRI** = net reclassification index
- **PET** = positron emission tomography

CORONARY ARTERY CALCIUM CT SCAN. After myocardial perfusion imaging, all patients underwent CT scan for CAC scoring during breath-hold on the integrated 64-slice multidetector CT scanner (collimation 64 × 0.625 mm, gantry rotation time 350 ms, effective temporal resolution 175 ms, 120 kV, 300 mA). CAC scans were performed using axial acquisition with prospective electrocardiographic triggering at 70% of the R-R interval. Subsequently, 3-mm images were reconstructed using filtered back projection and a standard convolution kernel with a 512 × 512 matrix and a fixed 25-cm field of view. No beta-blockers were administered and the average heart rate during the study was 70 beats/min (range: 62 to 80 beats/min). Estimated radiation exposure for the integrated PET/CT study was 5.46 mSv (range: 5.00 to 5.98 mSv).

Results

PET imaging data. LEFT VENTRICULAR SYSTOLIC FUNCTION. Rest and stress left ventricular ejection fraction were calculated from gated myocardial perfusion images using commercially available software (Corridor4DM; Invia, Ann Arbor, Michigan). Left ventricular ejection fraction reserve was considered present when LVEF increased from rest to stress.

QUANTITATIVE MYOCARDIAL BLOOD FLOW AND FLOW RESERVE. Absolute MBF (in ml/g/min) was computed from the dynamic rest and stress images using commercially available software (Corridor4DM, Invia) and previously validated methods (13). Automated factor analysis was used to generate blood pool (arterial input function) and tissue time-activity curves. Regional and global rest and peak stress MBF were calculated by fitting the ^{82}Rubidium time-activity curves to a 2-compartment tracer kinetic model as described previously (13). Per-patient global coronary flow reserve (CFR) was calculated as the ratio of