Matrix Metalloproteinase-9 (MMP-9) and Myeloperoxidase (MPO) Levels in Patients with Nonobstructive Coronary Artery Disease Detected by Coronary Computed Tomographic Angiography

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Rationale and Objectives: The aim of this study was to evaluate whether matrix metalloproteinase–9 (MMP-9) and myeloperoxidase (MPO) are elevated in patients with nonobstructive coronary artery disease.

Materials and Methods: Eighty-four patients with nonobstructive coronary artery disease (group A) and 90 patients with no coronary plaques (group B) were enrolled. MMP-9 and MPO levels were compared between the two groups. The relationships between these biomarkers and Framingham risk score were analyzed. Receiver-operating characteristic curves were used to evaluate the ability of these biomarkers to predict the presence of coronary artery plaques.

Results: The MMP-9 and MPO values in group A were significantly higher than in group B ($P < .001$). The levels of MMP-9 and MPO showed significant correlations with Framingham risk score ($r = 0.796$, $P < .001$, and $r = 0.409$, $P < .001$, respectively). The areas under the receiver-operating characteristic curves for MMP-9 and MPO were 0.80 (95% confidence interval, 0.74–0.87) and 0.74 (95% confidence interval, 0.66–0.81), respectively.

Conclusions: Levels of MMP-9 and MPO are positively correlated with Framingham risk score. Additionally, in patients with nonobstructive coronary artery disease, elevated levels of MMP-9 and MPO may identify patients at risk for future myocardial infarction or sudden cardiac death.

Key Words: Matrix metalloproteinase–9; myeloperoxidase; nonobstructive plaque; 64-slice CT.

Early reports have revealed that obstructive coronary artery disease (CAD), as identified by coronary computed tomographic angiography (cCTA) and defined by coronary plaques causing ≥50% reductions in luminal diameter, is valuable for the prognosis of individuals at risk for major adverse cardiovascular events (1,2). Nevertheless, individuals undergoing cCTA commonly exhibit nonobstructive plaques. Prior invasive ultrasound and autopsy studies have implicated nonobstructive plaques as central to the pathophysiologic processes of sudden cardiac death and myocardial infarction (3,4). But percutaneous or surgical revascularization is performed only in patients with >50% luminal stenosis. Nonobstructive plaques cannot be detected by traditional coronary angiography and may be considered normal.

Matrix metalloproteinases (MMPs), a family of structurally and functionally related zinc endopeptidases, degrade extracellular matrix proteins and have been implicated in connective tissue destruction and remodeling (5). MMP-9, a significant member of the MMP family, has been found to degrade a

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wide range of extracellular matrix proteins, including gelatin, type IV collagen, and other basement membrane proteins (6). Increased levels of MMP-9 have been found in human atherosclerotic plaques involved in plaque rupture (7). Myeloperoxidase (MPO) is the most abundant component of primary azurophilic granules in neutrophils and is promptly discharged after activation by different agonists (8). First identified within human atherosclerotic plaques nearly a decade ago, MPO has emerged as an important factor in the development and progression of atherosclerotic disease (9). In clinical studies conducted in patients with acute coronary syndromes, an elevated level of MPO was associated with an adverse prognosis and the occurrence of major cardiovascular events (10).

We hypothesized that serum levels of MMP-9 and MPO are elevated in patients with nonobstructive coronary plaques.

MATERIALS AND METHODS

Patient Recruitment

We retrospectively analyzed subjects who underwent cCTA using a 64-slice multidetector computed tomographic scanner at our center between January 2010 and May 2010. All patients were referred for cCTA by their cardiologists. The cCTA was performed because of symptoms of chest pain to exclude coronary disease in patients carrying one or more risk factors or electrocardiographic abnormalities. After excluding patients with significant coronary artery stenoses (≥50%), low-quality images preventing accurate diagnosis, or factors that would affect the accurate measurement of biomarkers (fever, severe heart failure, inflammatory diseases, malignancies, impaired liver function, renal failure, or recent surgery), 101 patients with nonobstructive plaques (stenosis < 50%) and 112 patients with no plaques were contacted and asked to undergo blood tests. Finally, the blood tests, including conventional biochemical analysis and measurement of serum levels of MMP-9 and MPO, were completed in 84 subjects with nonobstructive plaques (group A) and 90 subjects with no plaques (group B). Informed consent was obtained from all 174 enrolled subjects on the basis of a protocol approved by the ethics committee.

Data Acquisition

Scans were performed using a 64-row spiral computed tomographic scanner (LightSpeed VCT; GE Healthcare, Milwaukee, WI). Patients with prescan heart rates ≥70 beats/min were given 25 to 50 mg of metoprolol (Selokeen; AstraZeneca, Zoetermeer, The Netherlands) orally 1 hour before scanning. A double-head power injector (Stellant; Medrad, Inc, Pittsburgh, PA) was used to inject contrast media through a 20-gauge intravenous catheter into an antecubital vein. A test bolus (10 mL of contrast agent followed by a 20-mL saline flush) with an injection rate of 5 mL/s was used to determine the timing of scan delay and image acquisition time. Depending on patient weight, iohexol 350 mg I/mL (Omnipaque 350; GE Healthcare) or iopromide 370 mg I/mL (Ultravist 370; Bayer Schering Pharma AG, Berlin, Germany) was injected at a speed of 4 to 5.5 mL/s. Contrast medium was injected in three phases: 50 to 60 mL of contrast medium only in the first phase, a 30-mL mixture of contrast medium (9 mL) and saline (21 mL) in the second phase, and 40 mL of saline in the final phase. The main scanning parameters were as follows: 64 detectors; individual detector width, 0.625 mm; gantry rotation time, 350 ms; tube voltage, 120 kV; electrocardiographically modulated tube current, 200 or 550 mA (tube current was 550 mA during 40%–80% RR interval, when diagnostic image quality was required, and remained at 200 mA during the other phases of the RR interval); pitch, 0.16 to 0.22; table feed per rotation, 400 mm; and field of view, 200 to 250 mm. The images were transferred to a stand-alone workstation (Deep Blue, ADW 4.3; GE Healthcare) and evaluated using dedicated analysis software.

Image Analysis

Maximum intensity projection, curved planer reconstruction, and volume-rendering images were reconstructed to analyze the presence of coronary plaques and the degree of stenosis. Coronary atherosclerosis was defined as tissue structures that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself (11). The degree of stenosis was classified as nonobstructive if the plaques caused <50% reductions in luminal diameter (12).

CAD Risk Assessment

The conventional coronary risk factors, such as obesity, cigarette smoking, hypertension, hypercholesterolemia, diabetes mellitus, and family history, were assessed. Obesity was defined as body mass index >30 kg/m^2. Smoking was defined as any cigarette smoking within 1 year of cCTA. Hypertension was defined as a previously established diagnosis, systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or antihypertensive medication use. Hypercholesterolemia was defined according to National Cholesterol Education Program guidelines or by the current use of lipid-lowering medication (13). Diabetes mellitus was defined as a previously established diagnosis, insulin or oral hypoglycemic therapy, fasting glucose >126 mg/dL, or nonfasting glucose >200 mg/dL. Family history of CAD was defined as myocardial infarction, coronary revascularization, or sudden cardiac death in the father at <55 years of age or the mother at <65 years of age. The Framingham risk score (FRS), per the National Cholesterol Education Program guidelines, was also calculated (12). All subjects were assigned to one of three different risk groups according to the revised National Cholesterol Education Program guidelines: a high-risk group (CAD risk equivalent or 10-year risk ≥ 20%), a moderate-risk group (10-year risk of 10%–19%), and a low-risk group (10-year risk < 10%).