Serial Quantitative Assessment of Absolute Coronary Flow and Flow Reserve With CAD Progression to Events

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A LARGE ATHEROSCLEROTIC PLAQUE BURDEN AND SEVERE LUMINAL STENOSIS ARE ASSOCIATED WITH UNFAVORABLE OUTCOMES IN CORONARY ARTERY DISEASE (CAD). On the one hand, critical luminal obstruction has remained the gold standard for clinical decisions on coronary revascularization. On the other hand, expansion of plaque volume has been proposed as a prerequisite for acute coronary syndrome (ACS) events, including sudden death and acute myocardial infarction (MI) (1). In this iPIX, we discuss serial assessment of absolute coronary flow and coronary flow reserve, demonstrating the relationship between plaque progression by positron emission tomography (PET) perfusion imaging and major adverse coronary events.

Traditional belief holds that plaques resulting in ACS are generally subcritically occluded. PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), a large, multicenter serial imaging study, recently demonstrated substantial plaque expansion before the occurrence of ACS. The fateful lesions evolved from 32 ± 21% diameter stenosis to 65 ± 16% over a follow-up period of 3.4 years; intravascular ultrasound–verified cross-sectional plaque area burden (>70%) and minimum luminal area (<4 mm²) were 2 (of the 3) most important determinants of outcomes. Histopathological comparison of a large number of stable, vulnerable, and disrupted plaques revealed that plaque rupture was associated with significant luminal stenosis (1). In this study, the plaques that ruptured were substantially more occlusive than the plaques vulnerable to rupture. The authors therefore proposed that the high-risk plaques would need to expand further before they ruptured.

For stable coronary disease, a critical severity threshold of luminal stenosis identifies patients with improved outcomes by revascularization (2). In this context, percutaneous coronary intervention (PCI)
A patient had normal findings on a rest/stress rubidium-82 positron emission tomography (PET) scan in 2004 when he was 52 years of age. He had sought medical advice for atypical chest pain in the presence of numerous risk factors, including diabetes, hypertension, hypercholesterolemia, and a family history of premature coronary artery disease. He did not return for follow-up or risk factor management until 2011. During routine follow-up, with the patient experiencing no angina or cardiovascular symptoms, a PET scan performed in 2011 showed mild progression on relative tracer uptake on stress PET images. However, quantitative absolute coronary flow reserve (CFR) was severely reduced to 1.4, below the low-flow threshold causing ischemia in the distribution of the left anterior descending coronary artery (LAD). CFR in the rest of the heart averaged 2.3, indicating diffuse coronary atherosclerosis above the threshold for ischemia in addition to localized stenosis of the proximal LAD. A computed tomography scan done for attenuation correction of PET images showed dense coronary calcification throughout the coronary tree. He declined invasive procedures due to a lack of symptoms and did not undertake recommended risk factor control. Eight months later, he sustained a myocardial infarction, and angiography showed severe multivessel disease, for which he underwent 4-vessel coronary bypass surgery. A single illustrative anterior view of 2 sequential relative stress images is shown. The color bar shows absolute CFR based on rest stress myocardial perfusion in milliliters per minute per gram for the second PET scan. A generalized arterial map is superimposed on the initial images for orientation. D1 = 1st diagonal branch; D2 = 2nd diagonal branch; LCx = left circumflex artery; RI = ramus intermedius.

Exertional angina developed in a 53-year-old patient with positive results on an exercise tolerance test. The angiogram showed multiple mild to moderate stenoses. He chose strict risk factor management by diet, body weight, regular exercise, and lipid medications, with resolution of angina without invasive intervention. Risk factors included hypertension and lipids of total cholesterol of 246 mg/dl, low-density lipoprotein level of 168 mg/dl, and high-density lipoprotein level of 50 mg/dl. After starting statin therapy, the high-density lipoprotein level fell to 40, intermediate low-density lipoprotein particle size, for which nicotinic acid was added; lipids were maintained at total cholesterol 142 mg/dl, low-density lipoprotein at 70 mg/dl (type A), high-density lipoprotein 59 mg/dl to the present. At 61 years of age, routine PET relative uptake images using rubidium-82 showed no significant regional stress-induced perfusion defects. The patient, without symptoms, underwent a routine follow-up PET scan 3 years later that showed mild progression. Further routine PET follow-up at 6 years in the absence of angina showed more severe progression associated with recurrent ventricular tachycardia during dipyridamole stress. Angiography showed significant LAD stenosis, which was successfully stented, after which the patient had an uneventful course. Strict risk factor control stabilized severe coronary atherosclerosis for 14 years before revascularization was needed based on PET follow-up associated with stress-induced ventricular tachycardia. A single illustrative anterior view of stress images is shown. The color bar shows relative uptake. A generalized arterial map is superimposed on the initial images for orientation. Abbreviations as in Figure 1.
based on routine measurement of fractional flow reserve (FFR) in patients with multivessel CAD improved outcomes compared with PCI based on the angiogram. In the original FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial, the patients randomly assigned to FFR-guided PCI had a lower 2-year rate of death, MI, and need for repeat revascularization than patients with angiographically guided PCI. In the logical extension of this study, the FAME II trial established the superiority of an FFR-guided PCI strategy over optimal medical therapy in patients with an FFR ≤0.8. Although designed for a follow-up of 2 years, enrollment in the FAME II trial was terminated early due to substantial treatment difference. The difference in the composite endpoint was predominantly driven by a significantly lower rate of urgent revascularization in the PCI arm (hazard ratio: 0.13; 95% confidence interval: 0.06 to 0.30; p < 0.001). The need for an urgent revascularization was not based on demonstration of ischemia or an increase in serum biomarkers, and there were very few hard endpoints.
The facts presented here are based on a 1-time-point invasive assessment, serial intravascular imaging, or postmortem analysis. It is reasonable to propose that a noninvasive imaging strategy should provide prognostic information to help decide on timely interventions. For this iPIX, several cases of serially assessing absolute coronary flow and flow reserve or relative stress perfusion by PET show progression of CAD to an adverse event and/or indication for revascularization (Figs. 1 to 3).

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