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Discordance Between Fractional Flow Reserve and Coronary Flow Reserve

Insights From Intracoronary Imaging and Physiological Assessment

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the epicardial and microvascular substrates associated with discordances between fractional flow reserve (FFR) and coronary flow reserve (CFR) values.

BACKGROUND Discordances between FFR and CFR remain poorly characterized.

METHODS FFR, hyperemic stenosis resistance (HSR), and intravascular ultrasound were performed as indexes of epicardial function and CFR and hyperemic microvascular resistance (HMR) as measures of microvascular function in 94 patients with moderate coronary stenosis. Maximal plaque burden (PB_{max}), HSR, and HMR were calculated in 4 quadrants based on values of FFR ≤0.80 and CFR ≤2.0 as follows: concordant normal (preserved FFR and CFR), concordant abnormal (low FFR and CFR), discordant low FFR and preserved CFR, and discordant preserved FFR and low CFR.

RESULTS Sixty-four patients (68%) had concordant FFR and CFR findings, and 30 patients (32%) had discordant FFR and CFR. Compared with patients with preserved FFR and CFR, those with low FFR and CFR had higher PB_{max} ($p = 0.003$), higher HSR ($p < 0.001$), and similar HMR. Among patients with preserved FFR, those with reduced CFR had similar PB_{max} and HSR but a trend toward higher HMR ($p = 0.058$) compared with patients with preserved CFR. Among patients with reduced FFR, those with preserved CFR had lower PB_{max} ($p = 0.004$), a trend toward lower HSR ($p = 0.065$), and lower HMR ($p = 0.03$) compared with patients with reduced CFR. Furthermore, compared with patients with preserved FFR and low CFR, those with low FFR and preserved CFR had higher HSR ($p = 0.022$) but lower HMR ($p = 0.003$).

CONCLUSIONS In patients with moderate coronary stenosis, preserved FFR and low CFR is associated with increased microvascular resistance, while low FFR and preserved CFR has modest epicardial stenosis and preserved microvascular function. (J Am Coll Cardiol Intv 2017;10:999–1007) © 2017 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Myocardial ischemia can occur as a result of epicardial disease, microvascular disease, or a combination of both. Advances in our understanding of this disease spectrum as well as technological developments have led to greater penetration of invasive physiological indexes such as fractional flow reserve (FFR) and coronary flow reserve (CFR), as well as intravascular ultrasound (IVUS)

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ABBREVIATIONS AND ACRONYMS

APV = average peak velocity

CAD = coronary artery disease

CFR = coronary flow reserve

FFR = fractional flow reserve

HMR = hyperemic microvascular resistance

HSR = hyperemic stenosis resistance

IQR = interquartile range

IVUS = intravascular ultrasound

PB_{max} = maximal plaque burden

PCI = percutaneous coronary intervention

and optical coherence tomographic imaging to complement the diagnostic capability of coronary angiography for epicardial lesion and microvascular function assessment (1–3).

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FFR has been increasingly used in the catheterization laboratory as an evidence-based prognostic indicator of epicardial lesion severity, as well as a simple tool to guide coronary revascularization in patients with single-vessel and multivessel coronary artery disease (CAD) (4–7). FFR is measured during maximal hyperemia to optimally reduce microvascular resistance and hence render pressure an adequate surrogate of coronary flow. Although FFR is designed to be relatively independent of microvascular function, significant microvascular disease may increase the value of FFR for the same level of epicardial stenosis. Meanwhile, CFR, which represents combined epicardial and microvascular function, has also been shown to be an important prognostic indicator of adverse outcomes when reduced in patients with and those without epicardial CAD (8–10). Patients with preserved FFR but reduced CFR have been shown to experience higher incidence of adverse outcomes compared with those with preserved FFR and CFR. Conversely, compared with patients with concordantly abnormal FFR and CFR, those with abnormal FFR but preserved CFR may have favorable outcomes when treated medically (11,12). Given these observations, some have argued that combined FFR and CFR should be incorporated in making clinical decision in the catheterization laboratory. Others have pointed to the large randomized controlled trials and real-life registries that have demonstrated the efficacy and value of FFR by itself for guidance of coronary revascularization (4–7). They have also reminded us that routinely performing CFR, which does not have a clear abnormal cutoff, varies significantly with loading conditions and contractility and thus has a wide coefficient of variability would introduce added complexity to physiological lesion assessment at a time when the focus should be on wider adoption of basic physiology in the catheterization laboratory (13–16).

Clearly, greater understanding of the underlying epicardial and microvascular substrate of patients with discordant FFR and CFR would inform the debate and enhance our understanding of physiological lesion assessment. We hypothesized that in patients with moderate coronary stenosis with preserved FFR, those with low CFR would have minimal epicardial stenosis and elevated microvascular resistance, and conversely, among patients with low FFR, those with preserved CFR would have moderate epicardial stenosis with more preserved microvascular function. Accordingly, we sought to determine the anatomic and physiological characteristics of patients with moderate CAD and discordant FFR and CFR through comprehensive intracoronary imaging and coronary and microvascular physiological assessment.

METHODS

SUBJECTS AND STUDY DESIGN. We investigated 94 patients with moderate coronary lesions in the proximal 60 mm of an epicardial vessel presenting with stable angina or stabilized acute coronary syndromes. We performed detailed physiological assessment of epicardial and microvascular function as well as IVUS. Patients were excluded if they presented with ST-segment elevation myocardial infarction, cardiogenic shock, ejection fraction <30%, or significant hepatic, hematologic, or renal impairment or had histories of coronary artery bypass surgery or severe valvular heart disease. All patients had consented to enroll in a research study that was approved by the Emory University Institutional Review Board.

INVASIVE PHYSIOLOGICAL PROCEDURE AND ANALYSIS. Patients underwent angiography in a biplane cardiac catheterization system (Toshiba America Medical Systems, Tustin, California) using a standard 6-F technique. A 0.014-inch combined pressure and Doppler flow velocity monitoring guidewire (ComboWire XT Guide Wire, Philips Volcano, Del Mar, California) was advanced into the target vessel chosen to make Doppler and hemodynamic recordings. Coronary and microvascular function was evaluated from pressure and velocity responses to intravenous adenosine infusion (140 μg/kg/min) for 3 min, which were recorded for off-line analysis. Average peak velocity (APV) was assessed over a 3- to 5-beat period. FFR was defined as the ratio of distal to aortic pressure and CFR as the ratio of hyperemic to basal APV. Hyperemic stenosis resistance (HSR) index was calculated as the ratio of stenosis pressure gradient (mean aorta pressure – mean distal coronary pressure) to hyperemic APV and hyperemic microvascular resistance (HMR) index as the ratio of distal pressure to APV at maximal hyperemia and (13,17). Velocity measurements demonstrated good reproducibility, with a concordance correlation coefficient of 0.979 (95% confidence interval: 0.966 to 0.988) (18). Off-line analysis was performed at the Emory cardiovascular imaging and biomechanical core laboratory by