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Diagnostic and Prognostic Implications of Coronary Flow Capacity

A Comprehensive Cross-Modality Physiological Concept in Ischemic Heart Disease

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ABSTRACT

OBJECTIVES The purpose of this study is to evaluate whether coronary flow capacity (CFC) improves discrimination of patients at risk for major adverse cardiac events (MACE) compared with coronary flow reserve (CFR) alone, and to study the diagnostic and prognostic implications of CFC in relation to contemporary diagnostic tests for ischemic heart disease (IHD), including fractional flow reserve (FFR).

BACKGROUND Although IHD results from a combination of focal obstructive, diffuse, and microcirculatory involvement of the coronary circulation, its diagnosis remains focused on focal obstructive causes. CFC comprehensively documents flow impairment in IHD, regardless of its origin, by interpreting CFR in relation to maximal flow (hyperemic average peak flow velocity [hAPV]), and overcomes the limitations of using CFR alone. This is governed by the understanding that ischemia occurs in vascular beds with substantially reduced hAPV and CFR, whereas ischemia is unlikely when hAPV or CFR is high.

METHODS Intracoronary pressure and flow were measured in 299 vessels (228 patients), where revascularization was deferred in 154. Vessels were stratified as having normal, mildly reduced, moderately reduced, or severely reduced CFC using CFR thresholds derived from published data and corresponding hAPV percentiles. The occurrence of MACE after deferral of revascularization was recorded during 11.9 years of follow-up (quartile 1: 10.0 years, quartile 3: 13.4 years).

RESULTS Combining CFR and hAPV improved the prediction of MACE over CFR alone ($p = 0.01$). After stratification in CFC, MACE rates throughout follow-up were strongly associated with advancing impairment of CFC ($p = 0.002$). After multivariate adjustment, mildly and moderately reduced CFC were associated with a 2.1-fold (95% confidence interval: 1.1 to 4.0; $p = 0.017$), and 7.1-fold (95% confidence interval: 2.9 to 17.1; $p < 0.001$) increase in MACE hazard, respectively, compared with normal CFC. Severely reduced CFC was identified by FFR ≤0.80 in 90% of cases, although ≥40% of vessels with normal or mildly reduced CFC still had an FFR ≤0.80.

CONCLUSIONS CFC provides a cross-modality platform for the diagnosis and risk-stratification of IHD and enriches the interpretation of contemporary diagnostic tests in IHD. (J Am Coll Cardiol Intv 2015;8:1670–80) © 2015 by the American College of Cardiology Foundation.

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Although ischemic heart disease (IHD) is a complex multilevel process that originates from a combination of focal obstructive, diffuse, and microcirculatory causes of myocardial flow impairment (1), contemporary clinical practice remains focused on focal epicardial coronary artery obstruction. However, the presence of a strong link between myocardial blood flow impairment and adverse clinical outcome regardless of its origin urges a comprehensive diagnostic approach toward IHD not restricted to the epicardial coronary stenosis (2–4).

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The coronary flow reserve (CFR) (5) is a well-validated index that allows the assessment of blood flow impairment originating from obstructive, diffuse, or microcirculatory involvement of the coronary circulation. However, its use has been limited due to a reported sensitivity toward resting hemodynamics. As a result, the coronary pressure-derived fractional flow reserve (FFR) is considered the preferred surrogate for blood flow impairment in the catheterization laboratory (6). Nonetheless, FFR is an invasive tool that was introduced to identify significant epicardial coronary artery obstruction by means of trans-stenotic pressure drops, which by definition do not occur in the presence of pure microcirculatory involvement in IHD, can be very limited in the presence of diffuse coronary artery disease, and can be concealed when obstructive, diffuse, and microcirculatory causes coincide (7). Therefore, both CFR and FFR alone seem insufficient to comprehensively diagnose IHD (4,7–10).

An alternative approach toward the diagnosis of IHD can be found in the concept of coronary flow capacity (CFC), which integrates both CFR and maximal hyperemic flow to depict myocardial blood flow impairment due to a combination of obstructive, diffuse, and microcirculatory involvement of the coronary vasculature (11). First derived from positron emission tomography (PET), CFC may potentially provide a comprehensive physiological platform, likely applicable to all invasive and noninvasive modalities aiming to detect myocardial blood flow impairment, and which may overcome many of the limitations of using CFR or FFR alone. However, the complementarity of CFR and hyperemic flow in terms of risk stratification in IHD has not been documented, nor has it been compared with other contemporary invasive and noninvasive diagnostic tests in IHD. In the present study, we aimed to document: 1) the applicability of the CFC concept to invasive measurements; 2) whether the physiological complementarity of CFR and hyperemic flow translates into an improved discrimination of patients at risk for adverse outcome; and 3) the diagnostic and prognostic implications of CFC in relation to contemporary diagnostic tests for IHD.

METHODS

DATA SOURCE. Between April 1997 and September 2006, we evaluated patients with stable IHD referred for evaluation of ≥1 coronary artery stenosis (40% to 70% diameter stenosis at visual assessment). Patients were enrolled in a series of study protocols (10,12–14), and data were entered in a dedicated database. These protocols excluded patients with renal function impairment (calculated glomerular filtration rate <30 ml/min/1.73 m^2), significant left main disease, atrial fibrillation, recent myocardial infarction (<6 weeks prior to screening), and prior coronary artery bypass graft surgery, as well as vessels with ostial stenosis, serial stenoses, or visible collaterals. The institutional ethics committee approved the study procedures, and all patients gave written informed consent.

MYOCARDIAL PERFUSION SCINTIGRAPHY. Myocardial perfusion scintigraphy (MPS) was performed prior to coronary angiography using ^{99m}Technetium sestamibi or ^{99m}Technetium tetrofosmin, according to a 2-day stress/rest protocol. A blinded expert panel evaluated the scintigraphic images. Perfusion defects were classified as dubious, mild, moderate, or severe. Improvement at rest of >1 grade was considered a "reversible" perfusion defect, and improvement of ≤1 grade a "persistent" perfusion defect. The result was considered positive when a reversible perfusion defect was allocated to the perfusion territory of interest.

CORONARY ANGIOGRAPHY AND PHYSIOLOGICAL MEASUREMENTS. Coronary angiography was performed according to standard practice. Quantitative

ABBREVIATIONS AND ACRONYMS

bAPV = basal average peak flow velocity

CFC = coronary flow capacity

CFR = coronary flow reserve

FFR = fractional flow reserve

hAPV = hyperemic average peak flow velocity

HMR = hyperemic microvascular resistance index

HSR = hyperemic stenosis resistance index

IHD = ischemic heart disease

MACE = major adverse cardiac event(s)

MPS = myocardial perfusion scintigraphy

PET = positron emission tomography

sHR = standardized hazard ratio

Drs. Meuwissen and Piek have served as speakers at educational events organized by Volcano Corporation. Dr. Escaned has served as a consultant and as a speaker at educational events for Volcano Corporation and St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. van de Hoef and Echavarría-Pinto contributed equally to this work.

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