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Ischemia-based Coronary Revascularization: Beyond Anatomy and Fractional Flow Reserve

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ABSTRACT

Treatment strategies for patients with coronary artery disease (CAD) should be based on objective evidence of inducible ischemia in the subtended myocardium to improve clinical outcomes, symptoms, and cost-effectiveness. Fractional flow reserve (FFR) is the most verified index to-date for invasively evaluating lesion-specific myocardial ischemia. Favorable results from large clinical trials that applied FFR-guided percutaneous coronary intervention (PCI) prompted changes in coronary revascularization guidelines to emphasize the importance of this ischemia-based strategy using invasive coronary physiology. However, the frequency of functional evaluations is lacking in daily practice, and visual assessment still dominates treatment decisions in CAD patients. Despite recent efforts to integrate functional and anatomical assessments for coronary stenosis, there is considerable discordance between the 2 modalities, and the diagnostic accuracy of simple parameters obtained from current imaging tools is not satisfactory to determine functional significance. Although evidence that supports or justifies anatomy-guided PCI is more limited, and FFR-guided PCI is currently recommended, it is important to be aware of conditions and factors that influence FFR for accurate interpretation and application. In this article, we review the limitations of the current anatomy-derived evaluation of the functional significance of coronary stenosis, detail considerations for the clinical utility of FFR, and discuss the importance of an integrated physiologic approach to determine treatment strategies for CAD patients.

Keywords: Coronary artery disease; Coronary angiography; Intravascular ultrasonography; Fractional flow reserve

INTRODUCTION

Coronary revascularization should be determined, based on objective evidence for inducible ischemia in the subtended myocardium, to improve symptoms and outcomes of coronary artery disease (CAD).[1-3] Recent advances in the invasive assessment of coronary physiology have resulted in large-scale clinical trials to verify this important concept and have allowed interventional cardiologists to gain useful insights into optimal treatment strategies for CAD and improve cost-effectiveness.[4-7] In particular, fractional flow reserve (FFR) measured by pressure-wire technology provides useful guidance for determining treatment in patient subsets for various coronary lesions. Therefore, FFR is now recommended as an approach for detecting ischemia-producing lesions when objective evidence of inducible ischemia is not available.[8-11]

However, in daily practice, there is a significant gap between the guidelines and the frequency of invasive functional evaluations, and visual assessment still dominates treatment decisions in CAD patients.[12)13)] Despite many attempts to predict the functional significance of coronary stenosis using angiographic or intravascular imaging parameters, the discordance between the 2 modalities is considerable, and the diagnostic accuracy of anatomical measurements for lesion-specific ischemia is not sufficient for clinical practice.[14-18)] Coronary lesion characteristics and some clinical or demographic factors are possible reasons for the underlying rationale of the "anatomical-functional" discordance. A recent study demonstrated the impact of microvascular dysfunction on discordant findings.[19)] In this review, we discuss the limitations of the anatomical parameters derived from current coronary imaging in evaluating the functional significance of coronary stenosis, as well as factors that are associated with discordance between anatomical stenosis and functional ischemia, based on FFR. This review will also discuss detailed considerations about the clinical utility of FFR, the importance of an integrated physiologic approach, and the role of multimodality imaging for functional evaluations in CAD patients.

FUNCTIONAL EVALUATIONS: CORONARY ANGIOGRAPHY (CAG) AND INTRAVASCULAR IMAGING

Invasive coronary angiography (CAG) is the standard for diagnosing patients with suspected CAD, and is always performed before coronary revascularization procedures, such as percutaneous coronary intervention (PCI). However, there are several limitations to the use of angiographic measurements in evaluating the severity of coronary stenosis. One of the biggest limitations is translating these results into functional significance. These limitations are being increasingly observed in the literature and are more evident in patients with intermediate coronary artery stenosis.[20-23)] The importance of ischemia-based treatment has been emphasized by clinical evidence and guidelines. However, despite recommendations in current guidelines to assess the functional severity of a coronary lesion, the frequency of non-invasive stress tests before PCI or invasive physiologic evaluations after CAG remain low (13.9 and 3.72% from the Korean PCI [K-PCI] registry,[13)] respectively). Although technological advances have allowed interventional cardiologists to more readily gain on-site functional information, visual assessment still dominates treatment decisions in CAD patients.[12)] With expanded use of adjunctive invasive imaging to anatomically measured CAD to compensate for the shortcomings of "luminogram," which is the critical limitation of CAG, many efforts have recently been made to integrate functional and anatomical assessments of coronary stenosis, using intravascular imaging such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT).[24)] However, "anatomical-functional" discordance persists, and the diagnostic accuracy of angiographic stenosis or minimum lumen area (MLA) by IVUS or OCT is insufficient for determining lesion-specific ischemia based on FFR.[14)15)17)24)25)]

DISCORDANCE OF ANATOMICAL STENOSIS AND LESION-SPECIFIC ISCHEMIA BASED ON FFR

The diameter stenosis based on CAG or MLA measured by intravascular imaging, is the major determinant of coronary flow limitations and provides the functional significance of coronary stenosis; these parameters are used to measure anatomical severity in most studies that compare anatomy vs. function. However, other anatomical features (i.e., lesion

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length, diffuseness, amount of myocardial mass, lesion location, and target vessel) also influence the ischemic potential of a coronary lesion.[26)27)] In intermediate coronary artery stenosis, lesion length and plaque volume, which reflect the extent of atheromatous plaques, are related to functional significance.[27)] Accordingly, Jin et al.[28)] demonstrated that the volumetric quantification of the atherosclerotic extent of CAD, expressed as IVUS-derived total atheroma volume (TAV), was strongly correlated with FFR. In addition, the diagnostic accuracy for functional significance was greater in IVUS-TAV than IVUS-MLA. The study revealed that both segmental luminal narrowing and total plaque burden of a target vessel are important determinants for inducible ischemia of the subtended myocardium.[28)] Yoon et al.[29)] demonstrated that the amount of myocardial mass subtended by a lesion, based on its location, was a significant determinant of the FFR value and contributed to the discrepancy between the MLA and FFR. In addition, some demographic or clinical factors such as sex, diabetes, hypertension, and left ventricular hypertrophy may also be associated with the functional relevance of epicardial stenosis.[30-33)] These factors can alter end-diastolic pressure, development of collaterals, vascular compensatory capacity, and microvascular function, all of which affect the trans-stenotic pressure gradient.[34)]

FFR AND MICROVASCULAR DYSFUNCTION

The value of FFR is determined by assuming a linear relationship between pressure and flow under an ability to minimize coronary circulation resistance.[35-37)] Theoretical evidence suggests that an increase in microvascular resistance decreases the trans-stenotic pressure gradient, which subsequently results in a higher FFR. Therefore, measurement of FFR is not recommended in culprit vessels of acute myocardial infarction where microvascular resistance could not be minimized due to variable degrees of coronary microcirculation transient dysfunction.[38-40)]

Our investigation supports this theoretical evidence, which suggests that an increase in microvascular resistance decreases the trans-stenotic pressure gradient, since a positive relationship was observed between microvascular resistance and FFR.[19)] We investigated whether microvascular resistance could explain the discordance between anatomical and FFR assessments of lesion severity. The main strength of this study was to reinforce the concept that "anatomical-functional" mismatch occurs and that intravascular imaging should not be used in lieu of physiologic assessment, when considering coronary revascularization.

In addition, the study highlights that there are a number of variables that determine the pressure drop across a stenosis, as well as the association between FFR and microvascular dysfunction. Since the relationship between FFR and microvascular function is not widely understood, the implications of this for the assessment of stenosis in intermediate CAD is important for clinicians. In this study of 97 intermediate coronary lesions in 83 consecutive patients, coronary microvascular resistance was associated with anatomical-functional discordance, and was higher in patients with higher FFR. One might concern that the results indicate that microvascular dysfunction could lead to underestimating ischemic potential of a given epicardial stenosis by falsely increasing FFR. However, myocardial ischemia results from both epicardial narrowing and other coronary circulatory pathologies, such as microvascular abnormalities. Thus, a high FFR value does not indicate the absence of myocardial ischemia, but instead suggests that revascularization with current devices and techniques for epicardial stenosis would have little to no benefits. Revascularization can improve patient quality of life,

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based on FFR measurements, irrespective of the presence of microvascular disease.[35] Although the clinical usefulness of FFR is not compromised, except in cases with severe microvascular dysfunction, it is important to take an integrated physiologic approach for cases where small changes in FFR may alter the treatment decision, based on current dichotomous criteria, for example, in patients with intermediate lesions with borderline FFR. Accounting for pressure, flow, and resistance, rather than FFR alone, may provide a more comprehensive overview of the coronary status for clinical decision-making. This approach considers the relationship between microvascular resistance and FFR. In the patients that were assigned (due to FFR >0.8) to the registry in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial, 3.0% had a primary end-point event at 1 year.[41] This indicates that additional actions to prevent adverse cardiac events are also required for patients with negative FFR (>0.8). A recent study reported that both coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) independently showed improvements in risk stratification for patients with FFR >0.8, which supported this hypothesis. Furthermore, prognosis was poorest in cases of low CFR with high IMR, even with a negative FFR.[42]

Coronary microcirculation is currently being reviewed and evaluated actively with more reliable indices, such as the IMR or hyperemic microvascular resistance index. In combination with epicardial indices, such as FFR, which ensures epicardial coronary artery assessment, a more integrated physiologic approach for the entire coronary system may lead to better treatment strategies.

CONCLUSIONS AND FUTURE PERSPECTIVES

FFR is an index that quantitatively reflects flow limitation caused by coronary artery stenosis. As such, a dichotomous cut-off of value of 0.8 has been validated for detecting hemodynamically relevant stenosis; this value also has practical utility because of its simplicity. However, this is not an absolute indicator of myocardial ischemia. It is important to remember that FFR is an adjunctive tool that provides supplementary information for physicians to determine the most appropriate treatment strategy. For accurate interpretation and proper application of FFR, it is important to be well-informed of conditions and factors that influence FFR. In particular, when FFR is greater than 0.75 or 0.80, further considerations may be necessary to ensure that the result is not simply interpreted as a negative FFR. Despite some limitations of FFR, evidence that supports or justifies anatomy-guided PCI is more limited at this point. Estimating the functional severity of coronary stenosis using non-invasive computed tomography (CT) and imaging-derived flow simulation with computational fluid dynamics (CFD) technology has recently improved. Using coronary CT, Kim et al.[43] recently proposed that the ratio of the subtended myocardial mass by the stenosed vessel (fractional myocardial mass), to minimal luminal diameter, can accurately be used as a novel and simpler index for determining lesion-specific ischemia.

This study highlights that such non-invasive imaging techniques have a specific merit over invasive physiology parameters by providing information for both the significance of inducible ischemia and significance of the amount of myocardium, which should be considered together to maximize the benefits of revascularization. Multimodality imaging, such as a combination between CT technology, 3-dimensional reconstruction of invasive imaging, and CFD technology enables precise simulation of coronary flow in a patient-specific coronary model, and provides non-invasive hemodynamic information to overcome the current 'simple' imaging-derived parameters for predicting lesion-specific functional significance.[44-47] Further research on the role of precise imaging techniques is expected and needed. Finally, the body of clinical evidence on resting physiologic indices is rapidly growing, predominantly with instantaneous wave-free ratio (iFR). Considering the unique features of the resting index, such as microvascular resistance under resting versus hyperemic conditions, further studies are needed to directly compare the effects of clinical and hemodynamic conditions, including microvascular function, on hyperemic and resting indices.

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