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Epicardial coronary stenosis severity and myocardial perfusion

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Abstract: Patients suspected of having epicardial coronary disease are often investigated with noninvasive myocardial ischemia tests to establish a diagnosis and guide management. However, the relationship between myocardial ischemia and coronary stenoses is affected by multiple factors, and there is marked biological variation between patients. The ischemic cascade represents the temporal sequence of pathophysiological events that occur after interruption of myocardial oxygen delivery. The earliest part of the cascade is examined via perfusion imaging, and fractional flow reserve (FFR) is a corresponding index which is specific to the coronary artery. Whereas FFR has come to be regarded a clinical reference standard against which other newer invasive and noninvasive tests are validated, the diagnostic FFR threshold for detecting ischemia was established against a combination of noninvasive ischemia tests that assessed different stages of the ischemic cascade. Moreover, the validity of invasive pressure-derived indices of stenosis severity are contingent on the assumption that pressure is proportional to flow if microvascular resistance is constant, a condition induced by pharmacological intervention or by examining specific segments of the cardiac cycle. Furthermore, myocardial perfusion reserve depends on dynamic modulation of microvascular resistance, and dysfunction of the microvasculature can lead to ischemia even in the absence of epicardial coronary disease. ■ *Heart Metab*. 2020;81:12-16

Keywords: coronary physiology; fractional flow reserve; myocardial perfusion; obstructive coronary artery disease; percutaneous coronary intervention

Introduction

Ischemia occurs due to supply and demand imbalance and in the heart corresponds to the pathophysiological state in which there is insufficient blood flow to the myocardium. In stable coronary artery disease (CAD), this occurs when there is increased workload in the face of diminished ability to increase flow to meet this demand (exhausted flow reserve), whereas in acute coronary syndromes, it is usually the result of reduced resting flow even with a relatively fixed workload. Patients suspected of having underlying stable CAD routinely undergo clinical assessment that incorporates myocardial ischemia testing, as recommended by international guidelines.[1-3] However, given that the relationship between myocardial ischemia and the severity of the underlying CAD is multifactorial and nonlinear and the fact that each noninvasive test examines a different part of the ischemic cascade with variable accuracy, ischemia test results are often discordant with the extent of coronary disease. Furthermore, the contribution of the coronary microcirculation and how this affects indices of myocardial ischemia have become increasingly appreciated in recent years. In this review, we provide an overview of the ischemic

cascade, myocardial perfusion imaging modalities and the role of the microcirculation in myocardial ischemia, and how these relate to the link between coronary stenosis severity and myocardial perfusion, imaging.

Myocardial ischemic cascade

The ischemic cascade is a temporal sequence of pathophysiological events occurring with increasing myocardial oxygen supply–demand imbalance.[4] Ischemia can occur without the accompaniment of angina and if significant enough may even cause left ventricular dysfunction with nonspecific or complete lack of symptoms. The cascade has been described as following a sequence of steps (*Figure 1*):

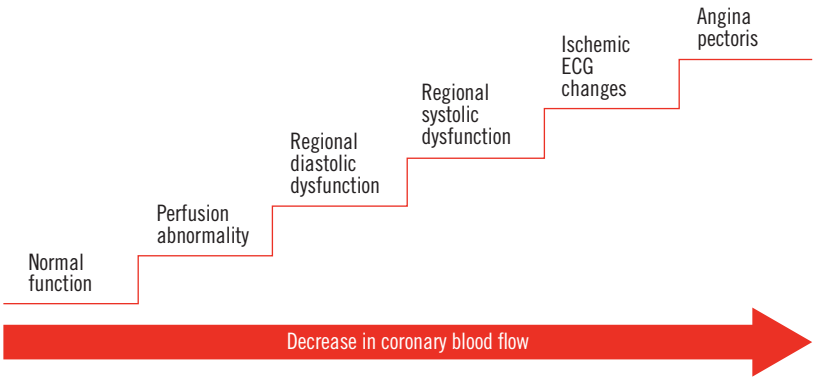

Figure 1 *Ischemic cascade.*
Abbreviation: ECG, electrocardiogram.

i) normal function; ii) perfusion abnormalities; iii) regional diastolic dysfunction; iv) regional systolic wall motion abnormalities; v) ischemic electrocardiogram (ECG) changes; and vi) angina pectoris.[4] Each pathophysiological abnormality progresses in a cascade, conditional on the preceding dysfunction. Although it is rarely observed in its entirety in clinical practice, its appreciation is essential in the understanding of ischemia.

The earliest abnormality in the ischemic cascade is decreased perfusion secondary to metabolic alterations, which can be indirectly observed by both positron emission tomography (PET)[5] and cardiac magnetic resonance (CMR) imaging.[6,7] Hence, perfusion imaging makes possible the detection of ischemia at its earliest point in the ischemic cascade, whereas other noninvasive modalities detect ischemia at later stages of the ischemic cascade. The diagnostic accuracy of noninvasive ischemia tests for detection of obstructive CAD was initially established on the likelihood of finding CAD of at least 50% diameter stenosis on coronary angiography. However, coronary angiography is inaccurate in assessing the functional significance of a coronary stenosis—this is not only in the 50% to 70% but also in the 70% to 90% angiographic severity range.[8] Hence, the basis for treatment of CAD has moved from an anatomical to a physiological hemodynamic-based evaluation of epicardial coronary artery stenosis severity. This has been principally driven by fractional flow reserve (FFR)—the ratio of distal coronary to aortic pressure during maximal hyperemia in a stenosed coronary artery. FFR is linearly and strongly correlated to flow in the diseased artery in relation to hypothetical flow in an entirely disease-free artery supplying the same myocardial territory.[9,10] Studies have demonstrated that of various techniques both CMR and PET have the best diagnostic correlation for hemodynamically significant CAD on both a per-patient and per-vessel basis, compared directly with FFR as the reference standard[11,12] CMR has greater spatial resolution and can determine quantitative myocardial perfusion without the need for ionizing radiation,[13] and it has been shown that CMR-derived fully quantitative myocardial perfusion imaging provides additional prognostic benefits in CAD patients.[14]

FFR is routinely referred to as the “gold” or “reference” standard in the diagnosis of myocardial ischemia, owing to two seminal randomized controlled trials that demonstrated reduction in adverse clinical cardiovascular events with FFR-guided revascularization.[15,16] However, this was principally driven by high rates of emergency revascularization, with no obvious difference in mortality or morbidity. It is worth recalling that the ischemic threshold for FFR was established against numerous noninvasive ischemia tests in 1996.[17] Therefore, although clinically and scientifically, the existence of a gold-standard ischemia test would be beneficial, it remains an entity that is elusive. Moreover, alternative invasive physiological indices that encompass both coronary pressure and flow

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have been demonstrated to have better correlation with epicardial stenosis severity.[18] The hyperemic stenosis resistance (HSR) index, defined as the ratio of hyperemic stenosis pressure gradient and hyperemic average peak-flow velocity, has the strongest diagnostic agreement with myocardial ischemia detected via single-photon emission computed tomography (SPECT) for the discrimination of functional coronary stenosis severity during cardiac catheterization.[18] Indeed, utilization of HSR to determine the physiological significance of epicardial stenosis reveals that the optimal threshold for two of the most commonly adopted pressure indices should be lower than that in contemporary practice—instantaneous flow reserve (iFR) of 0.86 and a FFR of 0.75.[19] These are more in keeping with the initial thresholds established when these indices were derived. The lack of a clear gold-standard ischemia test, an increase in the treatment thresholds from initial derivation studies, and the role of the ischemic cascade and how this impacts detection of ischemia and its correlation to stenosis severity form the complex multifactorial underlying reasons why the link between epicardial coronary stenosis severity and myocardial perfusion remains elusive.

Coronary microcirculation

Until recently, the coronary microcirculation was considered the unseen "black box" of the coronary arterial vasculature. The advent of coronary angiography and coronary angioplasty was accompanied by development of the "oculostenotic reflex" and clinical emphasis on treatment of epicardial CAD. Consequently, despite the theoretical appreciation of the importance of the coronary microcirculation, its clinical importance was inadequately established. The coronary microcirculation regulates resistance to flow and thus perfusion; hence, myocardial ischemia can be caused by abnormalities of both epicardial and downstream microcirculation. However, the impact of both these differ significantly; it is epicardial arteries that determine the total blood supply whereby a hemodynamically significant (flow-limiting) stenosis will cause regional myocardial supply-and-demand mismatch. In contrast, the microcirculation controls blood flow distribution within terminal vascular networks, safeguarding a functionally adequate supply distribution. Coronary microvascular dysfunction (MVD) typically causes increased heterogeneity of flow.[20]

Understanding the contribution of the microcirculation in myocardial ischemia assessment is imperative. Irrespective of the ischemia test modality utilized, MVD can affect results. For pressure-wire–derived indices, the scientific basis for these calculations is dependent on negating microvascular resistance by either pharmacological agents or physiological (resting) periods when resistance has been demonstrated to be minimal. However, in patients with MVD, attainment of minimal and steady microvascular resistance can be troublesome.[21,22] For myocardial perfusion testing, perfusion imaging examines both the epicardial and microvascular circulation; hence, an abnormality may arise from either of these compartments. Therefore, further assessment in a cardiac catheterization laboratory is usually mandated. The microcirculation can be examined in the cardiac catheterization laboratory with the use of thermodilution or Doppler coronary wire assessment. MVD is defined by diminished coronary flow reserve in response to pharmacological vasodilator stimuli in the absence of epicardial stenosis.[23,24] In addition, noninvasive techniques that combine anatomical and physiological stenosis evaluation have come to prominence. These include computed tomography (CT)-FFR and angiographic physiological stenosis evaluation (eg, quantitative flow ratio [QFR]). Although these have been shown to increase the sensitivity and specificity of stenosis evaluation, they are based on computational modeling calculations that make numerous assumptions to formulate measurement of stenosis significance, in particular the microvascular resistance, which is a major limitation.[25]

Recently, the ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches), with over 5000 patients, failed to demonstrate that myocardial ischemia–driven revascularization compared with guideline-directed medical therapy improved the clinical composite endpoint of cardiovascular death, myocardial ischemia, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure. Although the study excluded patients with severe or refractory anginal symptoms and half of the patients had severe ischemic burden, this landmark study did not reveal a correlation between baseline degree of ischemia and composite end point benefit from coronary revascularization. This brings us full circle to question the importance of ischemia and whether it should guide

the decision to perform coronary revascularization. Conversely, whether these results are due to a disconnect between stenosis severity, ischemia, and outcomes remains to be seen. Furthermore, in the acute setting, a recent study demonstrated that complete revascularization may be superior to culprit-lesion-only revascularization in ST-elevation myocardial infarction patients, suggesting that outcomes may relate to factors beyond the hemodynamic severity of a lesion in the acute setting.[26]

Conclusion

The ischemic cascade and the role of the microcirculation remain fundamental to understanding the limitations of myocardial perfusion imaging and its correlation to epicardial coronary artery stenosis severity. The lack of a clinically applicable gold standard makes it difficult to independently validate invasive coronary physiological and noninvasive perfusion imaging tests, as a result of which the last few decades have been dominated by debating imperfect correlations between these modalities. Finally, the role of ischemia in determining prognosis or guiding treatment has been called into question by the recent publication of the largest randomized trial in this arena. ■

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