Editorial

Quantitative Assessment of the Coronary Microvasculature
New Tools for the Black Box

Bernard De Bruyne, MD, PhD; Emanuele Barbato, MD, PhD

Epicardial coronary arteries are called conductance arteries (or macrocirculation) because their normal intrinsic resistance is close to zero and their main function is to transport blood. They are visible at invasive coronary angiography with an unsurpassed spatial and temporal resolution. Coronary arteries <500 µm are usually referred to as resistance arteries (or microvasculature) because, by continuously modifying their resistance, they match blood flow to the requirements of the myocytes.

Microvascular dysfunction can be isolated and then called primary, as is most disease about which we do not have the slightest clue. However, during the past decades, microvascular dysfunction has admittedly been associated with almost all cardiovascular pathologies and risk factors one might think of: diabetes mellitus, smoking, hyperlipidemia, hypertension, dilated cardiomyopathies, aortic stenosis, remote myocardial infarction, infiltrative heart disease, coronary atherosclerosis, acute coronary syndromes, stable coronary obstructive disease, and more. Although in some of these conditions, microvascular dysfunction represents a marker of the disease, it might become a therapeutic target in others. Nevertheless, the microvasculature has remained the poor cousin of the coronary tree.

Because it is not visible and it is difficult to access, the microvasculature is often considered the heart’s black box: not seeing is not believing. The difficulty of quantifying microvascular function in humans discourages research of potential therapies that, in turn, spurs a relative lack of interest. In clinical practice, microvascular dysfunction is considered an unavoidable bystander, or a convenient excuse for treatment failure. “It must be microvascular disease” sounds like a resigned, stoical shrug of the shoulders, and one can be confident that this statement can neither be confirmed nor contradicted and convinced that this condition cannot be treated. This might change.

Fearon et al6 developed a new, invasive approach to quantitatively assess the function of the microcirculation by using the index of microvascular resistance (IMR). Much as fractional flow reserve was developed to quantify the impact of epicardial stenoses, IMR is based on an unmet clinical need, namely the absence of a quantitative measurement of microvascular resistance. IMR is based on the thermodilution principle applied to the coronary arteries.7,8 By using a combined pressure/temperature wire and by injecting a small amount of saline at room temperature through the coronary guide catheter, it is possible to obtain an indicator–dilution curve, the decrease in temperature being the indicator. This principle is similar to the thermodilution-derived cardiac output measurements obtained by using a Swan Ganz catheter. Yet, rather than obtaining an absolute value of flow, coronary thermodilution after bolus administration of saline allows the determination of an index of flow, the mean transit time ($T_{mn}$). $T_{mn}$ is the average time needed for a red blood cell to travel from the ostium to the distal part of the epicardial artery. Therefore, $T_{mn}$ is inversely proportional to flow. Because resistance is the ratio of driving pressure to flow, the resistance index is calculated by the product of distal coronary pressure and $T_{mn}$. In patients with stable coronary atherosclerosis an IMR >25 to 30 indicates an abnormal microvascular resistance.10 IMR is reproducible11,12 little influenced by systemic hemodynamics,13 and independent of epicardial stenosis severity.13 Thus, it provides specific and quantitative information on the microvasculature.

In the present issue of Circulation, Fearon et al14 report 3-year clinical follow-up in 253 patients with ST-segment elevation myocardial infarction, in whom IMR was obtained immediately after primary percutaneous coronary intervention (PCI). The authors show that mortality or rehospitalization for congestive heart failure was significantly higher when IMR was >40. IMR >40 was the single independent prognosticator of death, whereas other methods for invasively assessing microvascular function are not. More detailed clinical characteristics that are known to influence post–myocardial infarction outcome (time to reperfusion, left ventricular diastolic pressure, volume and ejection fraction, the presence of mitral regurgitation) would have been useful to better evaluate the truly independent predictive value of IMR. In addition, high-risk patients have not been included because their clinical

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From the Cardiovascular Center Aalst, OLV-Clinic, Aalst, Belgium. Correspondence to Bernard De Bruyne, MD, Cardiovascular Center Aalst, OLV-Clinic, Moorelsebaan, 256, B-9300 Aalst, Belgium. E-mail Bernard.de.bruyne@olvz-aalst.be (Circulation, 2013;127:2378-2379.) © 2013 American Heart Association, Inc.

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status made it impossible to obtain consent or to perform the measurements. It is likely, however, that the prognostic value of IMR would have been even higher had these patients have been included.

The present data are important for several reasons. Methodologically, this study indicates that IMR resists the wind tunnel of clinical outcomes after myocardial infarction; IMR distinguishes patients with ST-segment elevation myocardial infarction who have a favorable long-term outcome from those who have an unfavorable long-term outcome after primary PCI. Yet, acute myocardial infarction is a clinical condition in which acute changes in microvascular resistance are presumably the most dramatic. Therefore, one of the next steps will be to investigate whether IMR is also useful to predict outcome in conditions associated with more subtle forms of microvascular dysfunction. More importantly, IMR will gain full respectability when its figures trigger a change in practice to improve patients’ outcomes.

Mechanistically, Fearon’s study confirms that microvascular dysfunction is likely one of the main culprits of poor long-term outcome after recanalization of the occluded segment. This opens the possibility of evaluating new potential treatment specifically targeting the microcirculation. For example, in a small pilot study, the administration of intracoronary streptokinase immediately after primary PCI resulted in less microvascular damage as assessed by IMR. The effect of thrombus aspiration on microvascular resistance in patients with ST-segment elevation myocardial infarction is currently being investigated in a prospective randomized trial. Also, in patients with ST-segment elevation myocardial infarction due to plaque erosion as assessed by optical coherence tomography, it has recently been proposed that revascularization be limited to thrombus aspiration without balloon dilation or stenting to minimize the risk of embolization of the microcirculation. Evaluating this new approach will require new tools to measure outcome. Besides the setting of myocardial infarction, Mangiacapra et al recently reported an acute beneficial effect of angiotensin-converting enzyme inhibitors on microvascular resistance as assessed by IMR immediately after PCI in stable patients.

From a daily practice diagnostic point of view, IMR has the advantage of being readily available in the catheterization laboratory. It could therefore be envisaged that, in patients admitted for an acute myocardial infarction, the complete diagnostic workup and risk stratification would be performed in the catheterization laboratory, at the time of the primary PCI, obviating the need for additional invasive and noninvasive testing. When recorded properly, left ventricular angiography and left ventricular pressures provide an outstanding assessment of global and regional wall motion and filling status. When present, nonculprit lesions can be evaluated by fractional flow reserve, even during the acute stage. Why not add IMR to this information? This report by Fearon et al suggests that this quantitative index of microvascular function provides incremental, prognostic information for patients undergoing primary PCI.

Disclosures
Dr De Bruyne reports Institutional Consultancy Fees from St Jude Medical.

References

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