Microvasculature in Acute Myocardial Ischemia: Part I
Evolving Concepts in Pathophysiology, Diagnosis, and Treatment

Sanjiv Kaul, MD; Hiroshi Ito, MD

The microcirculation is generally defined as vessels <200 μm in diameter, which are not visualized on coronary angiography. Flow through the microvasculature is therefore generally measured using noninvasive techniques. One of these techniques is myocardial contrast echocardiography (MCE), which has provided important new pathophysiological insights into acute myocardial ischemia. In this article, we shall discuss these insights in both stress-induced ischemia and spontaneously occurring ischemia. We shall also discuss other important issues such as collateral blood flow, myocardial viability, ischemia-reperfusion–induced myocardial injury, and evolving treatment strategies aimed at preserving microvascular flow and function in acute myocardial ischemia.

There is \( \sim 45 \text{ mL} \) of blood in the adult human coronary circulation (termed coronary blood volume), of which about one-third resides in the arterial, venous, and capillary networks each. At baseline, \( \sim 8\% \) of the left ventricular (LV) mass is constituted by blood present in the microcirculation, 90% of which is in the capillaries—termed myocardial blood volume (MBV) (Figure 1). The velocity of blood in the coronary vessels is related to the size of the vessels, and at the level of the capillary (mean length 0.5 mm and mean diameter 7 μm), the mean red cell velocity at rest is \( \sim 1 \text{ mm} \cdot \text{s}^{-1} \). There are \( \sim 8 \text{ million} \) capillaries in the human heart, and it takes 1 mL of blood \( \sim 1 \text{ year} \) to travel through a single capillary.

The microcirculation not only consists of a channel of passive networks through which blood is transported through the myocardium, but is an active site of blood flow control as well as metabolic activity. Indeed, the regulation of flow through these networks is complicated and depends on a number of metabolic, myogenic, and other control mechanisms. The capillary hydrostatic pressure is held constant within the myocardium at all times at \( \sim 30 \text{ mm Hg} \), with the pre- and postcapillary pressures at \( \sim 45 \) and 15 mm Hg, respectively. The coronary arterioles (ranging in size from 150 to 300 μm) act as resistance vessels so that the aortic pressure (mean 90 mm Hg) is brought down to a precapillary pressure constant (autoregulation).

Coronary venules also have weak myogenic responses, and they also control local resistance by changing the rheological properties of blood. In addition, the venules are the site of leukocyte adhesion during inflammation. Their endothelial surfaces express a number of adhesion molecules, whose production is upregulated at different times after the onset of tissue injury.

Myocardial Contrast Echocardiography
MCE is ideal for measuring microcirculatory flow because of its good spatial and temporal resolutions and because it utilizes tracers that have an intravascular rheology similar to that of red blood cells (RBC). These consist of gas-filled microbubbles that are very effective scatterers of ultrasound and therefore can be used to track the passage of RBC through tissue. Microbubbles are administered as a constant infusion, and \( \sim 2 \) to 3 minutes later, steady state is achieved when their concentration in any blood pool (LV cavity, myocardium, etc) is constant and proportional to the blood volume fraction of that pool. For example, during normal conditions, for every 100 microbubbles within a sample volume in the LV cavity, there will be 8 microbubbles within a similar-sized sample volume in the myocardium. The acoustic intensity measured from the myocardium after background subtraction (to eliminate native backscatter from myocardial tissue), when normalized to that from the LV cavity, provides a measure of myocardial MBV fraction (because LV cavity is 100% blood). Because 90% of MBV fraction comprises capillary blood, a single MCE image provides an assessment of capillary density in the different myocardial regions.

At steady state, the microbubbles within the myocardium are destroyed with high-energy ultrasound pulse(s), so that there are no microbubbles seen any longer in the myocardium. Then imaging is performed to measure the rate of microbubble reappearance, which reflects RBC velocity (Figure 2). Because flow constitutes a volume of blood moving at a certain mean velocity, the product of MBV fraction and myocardial blood velocity reflects myocardial microvascular...
flow. This value can also be represented per gram of tissue by knowing the sample volume size and specific gravity of the myocardium, although for most clinical applications it is not necessary to do so.

**Stress-Induced Ischemia**

Although resting blood flow through a coronary artery remains normal despite an up to 85% luminal diameter stenosis of the vessel, flow during maximal hyperemia is lower when luminal diameter stenosis severity exceeds 50%.

It has always been assumed that during maximal hyperemia, the resistance vessels are maximally dilated and the decrease in hyperemic flow is due to resistance offered by the epicardial coronary stenosis. Because they do not have smooth muscle, capillaries are thought to be only passive conductors of flow.

With MCE, it has been realized that MBV fraction decreases during hyperemia in the presence of a stenosis and that this decrease is proportional to the severity of stenosis. Because the majority of the MBV fraction is resident in capillaries, it follows that the capillary volume decreases. The length of a single capillary remains constant, and because capillaries do not have smooth muscle, they cannot dilate or constrict. Consequently, the only way capillary volume can decrease is if capillary units functionally shut off, resulting in a lower number of microbubbles in the myocardium and a resultant perfusion defect on MCE. The same mechanism is responsible for the occurrence of reversible perfusion defects with other noninvasive imaging methods.

The lower number of functioning capillaries precludes entry of MRI contrast agents as well as radionuclides, resulting in perfusion defects during stress.

Figure 3 shows the distribution of resistances across the normal coronary circulation at baseline. As stated earlier, the mean aortic pressure of 90 mm Hg is reduced to a precapillary pressure of 45 mm Hg because of resistance offered by coronary arterioles. There is a further 30-mm drop in pressure across the capillary bed. The capillaries are very small and offer high resistance, but because they are arranged in parallel, the total capillary resistance decreases with an increasing number of capillaries. The drop across the venous bed is only 15 mm, because these are high capacitance vessels, which nevertheless have some smooth muscle. Thus, at rest, ~60% of total myocardial vascular resistance is offered by the arterioles, 25% by the capillaries and 15% by the venules.

**Importance of Capillary Resistance During Hyperemia**

When hyperemia is induced in the normal coronary circulation, smooth muscle vasodilation results in dilatation of the arterioles and venules with no change in the capillaries. The total myocardial vascular resistance decreases by 68%, and compared with rest, the arterial and venular resistances decrease by 86% and 98%, respectively (Figure 4). Because of a similar decrease in arterial and venular resistances, the capillary hydrostatic pressure remains unchanged. The arteriolar and capillary resistances now comprise 25% and 75% of the total myocardial vascular resistance. Thus, capillaries offer the most resistance to coronary blood flow (CBF) during hyperemia and provide a ceiling to hyperemic CBF. Because they are laid in parallel, the more the capillaries the higher the hyperemic CBF, and the fewer the capillaries the less the hyperemic CBF. Conditions that are associated with lesser capillaries (either anatomically or functionally), such as myocardial infarction, hypertension, or diabetes, are associated with reduced CBF reserve despite the absence of coronary stenosis. These conditions may lead to acute ische-
Several studies have shown abnormal CBF correlation has been noted between increased blood viscosity exercise-induced ischemia, which may ultimately have a hyperlipoproteinemia may lead to repeated episodes of artery morphology. Reduced CBF reserve associated with malize abnormal CBF reserve without affecting coronary of CAD on angiography. Furthermore, it has been shown that the use of lipid-lowering drugs (especially statins) can nor-

The total resistance within the circulation equals the product of vascular resistance and viscosity. In large vessels (>30 μm in diameter), vascular resistance is the major determinant of total resistance, with viscosity playing a minor role. In vessels <30 μm in diameter, however, viscosity assumes a greater role, with relative effective viscosity increasing 6- to 7-fold at the level of the capillaries. Because the effect of vascular resistance and viscosity are multiplicative, small changes in viscosity produce a large difference in total resistance. Furthermore, it has also been demonstrated that unlike glass tubes, resistance in the same-sized capillaries is almost 2-fold higher for blood than isotonic fluid probably because of the interaction between the vessel lining and blood components.

A number of studies have shown an increase in blood viscosity with hyperlipoproteinemia. A strong positive correlation has been noted between increased blood viscosity and CAD. Several studies have shown abnormal CBF reserve even in patients with CAD risk factors in the absence of CAD on angiography. Furthermore, it has been shown that the use of lipid-lowering drugs (especially statins) can normalize abnormal CBF reserve without affecting coronary artery morphology. Reduced CBF reserve associated with hyperlipoproteinemia may lead to repeated episodes of exercise-induced ischemia, which may ultimately have a detrimental effect on microvascular and myocyte integrity. Similar effects could occur from hyperglycemia and may explain the higher cardiac morbidity in patients with uncontrolled diabetes. Thus, it in terms myocardial ischemia from microvascular abnormalities, the effect of whole blood viscosity and its association with RBC charge, deformability, and electrophoretic mobility is very important.

When a noncritical stenosis is present, its resistance is offset by a decrease in arteriolar resistance due to autoregulation, with the result that total vascular resistance remains unchanged, as does resting CBF. Now, when hyperemia is induced, although the total myocardial vascular resistance decreases compared with the resting state without stenosis, it increases compared with the nonhyperemic state with stenosis. During hyperemia, arteriolar and venular resistances are already minimal, so the increase in resistance occurs mostly from an increase in capillary resistance due to capillary derecruitment in an effort to keep the capillary hydrostatic pressure from rising. Thus, the major reason for attenuation of CBF reserve caused by a stenosis is also capillaries rather than the stenosis itself (Figure 4). The same mechanism operates even during dobutamine infusion, although the relative MBV of the entire myocardium increases because of the increase in myocardial oxygen demand and functional capillary recruitment.

Capillary derecruitment combined with a lesser increase in RBC velocity forms the basis for stenosis detection in CAD. During hyperemia, the normal myocardium fills very fast after microbubble destruction (1 to 1.5 seconds), while in regions sub served by stenoses, the rate of filling is slower depending on the severity of stenosis. The filling abnormalities are frequently seen to be more marked in the endocardium and, in the case of milder stenoses, may be localized only within the endocardium. It is for this reason that MCE has been shown to be more sensitive than single-photon emission computed tomography (SPECT) for the detection of coronary stenoses in patients with normal regional function and only moderate CAD. Because of its poorer spatial resolution (order of magnitude) compared with MCE, SPECT cannot detect defects located only in the endocardium. MCE is also superior in identifying multivessel CAD because each myocardial segment at stress is compared with itself at rest (Figure 5), whereas on SPECT the comparison is across segments, so that left main or “balanced” multivessel CAD can be missed. Figure 5 is an example in which a reversible defect was seen both by MCE and SPECT in a patient with a moderate mid-left anterior descending artery stenosis.

**Figure 4.** Distribution of coronary resistances at rest and during hyperemia in a coronary artery with a non-critical stenosis. Abbreviations as in Figure 3. See text for details. Reprinted from Jayaweera et al, with permission of the American Physiological Society.

**Figure 5.** MCE and SPECT images at rest and during dipyridamole stress in a patient with normal resting function and a moderate mid-left anterior descending artery stenosis. Note the endocardial perfusion defect during stress on MCE not seen on SPECT. 1s, 3s, and 5s represent the intervals (in seconds) after microbubble destruction. Arrows indicate regions with reversible decrease in MBV. Modified from W. Lepper et al, Am J Cardiol. 2003;91:445–448, with permission.

**Acknowledgments**
This work is supported in part by NIH grants 3RO1-HL48890, 1RO1-HL-65704, and 1RO1-HL66034 (to Dr Kaul).
References
