Exercise or pharmacological stress has long been a mainstay of diagnostic testing aimed at identifying the presence of a flow-limiting coronary stenosis. The basis for this is the well-known clinical observation that even severe coronary artery atherosclerosis does not usually cause angina or ischemia at rest. Sir William Osler observed that angina pectoris is commonly precipitated by “muscular exertion, violent mental states, stomach upsets, or cold weather.” However, in Osler’s time, the mechanism whereby resting myocardial perfusion was maintained despite a hemodynamically significant coronary stenosis, namely coronary autoregulation, was unknown.

Coronary Autoregulation

Myocardial oxygen consumption and perfusion are tightly coupled. Because the myocardium extracts most of the oxygen delivered to it, increases in oxygen demand (e.g., exercise, tachycardia) require a prompt increase in myocardial perfusion. For example, maximal exercise can easily cause a 4-fold increase in myocardial oxygen consumption, which is matched by a 4-fold increase in myocardial perfusion. Such hyperemic flow is typically mediated by vasodilation of precapillary arterioles to provide increased nutrient flow at the capillary level. Under normal conditions, 40% to 50% of total coronary resistance resides at the level of these precapillary arterioles (those <100 μm in diameter). These vessels respond rapidly to complex neural and metabolic control mechanisms to maintain myocardial perfusion over a wide range of driving pressures, a process known as autoregulation.

Autoregulation is able to maintain nearly constant myocardial perfusion over a pressure range of 40 to 130 mm Hg in conscious dogs. A similar autoregulatory pressure range has been reported in humans with an intracoronary pressure wire. In the healthy dog, resting coronary flow does not decrease significantly until a fixed stenosis of >85% diameter reduction, a point at which the distal coronary perfusion pressure drops below the autoregulatory range. During maximal hyperemia, the precapillary arterioles are already maximally dilated, such that maximal or hyperemic coronary flow begins to decline at a 40% diameter stenosis. Thus, during exercise or pharmacologically induced hyperemic flow, it is possible to detect a moderate coronary stenosis, particularly by perfusion imaging techniques.

An aspect of microvascular autoregulation that is unique to the heart is the effect of extravascular compressive forces, specifically left ventricular intracavitary pressure and systolic contraction. Left ventricular intracavitary pressure is fully transmitted to the subendocardium and negligible at the subepicardium. Likewise, myocardial contraction is greater in the subendocardium than in the subepicardium; this helps explain why the subendocardium is more vulnerable to ischemia. In addition, systolic contraction causes compression of precapillary arterioles and postcapillary venules but not the capillaries themselves. This results in continuous perfusion of the capillary bed during both systole and diastole, which importantly, allows oxygen extraction throughout the cardiac cycle. It also causes retrograde displacement of flow into the arterioles during systole, a fact that has been clearly demonstrated by advanced microvascular imaging techniques and in vivo velocity measurements.

Imaging the Coronary Microcirculation by Myocardial Contrast Echocardiography

In this issue of Circulation, Wei et al take advantage of the unique capabilities of myocardial contrast echocardiography (MCE) to assess the presence of a coronary stenosis without the need for exercise or pharmacological stress by imaging retrograde arteriolar flow in systole. MCE uses gas-filled microbubbles, which are ultrasound contrast agents that behave like red blood cell tracers within the myocardial circulation. Various imaging techniques can be used to detect the microbubble contrast agents. Real-time imaging uses low acoustic power to cause microbubbles to resonate, producing a harmonic signal, albeit with a fairly low signal-to-noise ratio. At high acoustic powers, most microbubbles are destroyed, yielding a robust signal with a high signal-to-noise ratio. Because of microbubble destruction, high-power methods require ECG triggering to allow replenishment of the myocardial capillary bed with microbubbles before the next ultrasound pulse. Capillary red blood cell velocity is slow, typically <1 mm/s, and the ultrasound beam elevation is roughly 4 to 5 mm, so it takes 4 to 5 seconds for capillaries to refill with microbubbles after a destructive ultrasound.

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pulse. Therefore, triggering every 4 to 5 heartbeats will allow full capillary filling at normal heart rates such that the perfusion image primarily represents capillary blood volume. This is especially true for end-systolic imaging, when the extravascular compressive forces occlude arterioles and venules, so that 90% of myocardial blood volume resides in the capillaries. If the ultrasound pulses are triggered at 15 frames per second (pulsing interval of 67 ms), however, there is no time for the capillaries (or venules) to refill and the only microbubbles seen in the myocardium are those residing in the arterioles, where retrograde systolic blood velocities range from 20 to 40 mm/s. Thus, this technique provides an image of arteriolar blood volume (aBV). As noted earlier, arteriolar blood flow occurs primarily during diastole, with a small retrograde component during systole. In the setting of a flow-limiting coronary stenosis, the arterioles vasodilate at rest as part of coronary autoregulation. Therefore, Wei et al hypothesize that the retrograde systolic flow component would be larger in the presence of a flow-limiting coronary stenosis. By calculating the systolic to diastolic (S/D) ratio of aBV, the same authors were able to predict the severity of an artificially induced coronary stenosis in the dog model without the need for exercise or pharmacological stress. In the present study, Wei et al extend these findings to human atherosclerotic coronary stenosis using quantitative coronary arteriography to quantify stenosis severity.

In 44 patients who underwent coronary angiography, MCE was performed using 1 of 2 fluorocarbon-gas contrast agents, Definity (Bristol-Myers Squibb Medical Imaging) administered as a bolus, or Imagent (IMCOR Pharmaceuticals) administered as an infusion. In the patients who received a bolus injection of Definity, attenuation limited imaging to the anterior wall supplied by the left anterior coronary artery. A progressive increase in S/D aBV ratio was noted with increasing severity of stenosis by quantitative angiography. A S/D aBV ratio >0.34 predicted the presence of a 75% stenosis with a sensitivity of 80% and specificity of 71%. In the patients who received an infusion of Imagent, both anterior and posterior territories could be analyzed. Again, a progressive increase in S/D aBV ratio was observed with increasing stenosis severity. An S/D aBV ratio >0.43 predicted a 75% diameter stenosis with a sensitivity of 89% and specificity of 74%.

These findings are promising and demonstrate proof-of-principle that a flow-limiting coronary stenosis can be detected at rest by a technique specifically tailored to image myocardial aBV with sufficient temporal resolution to determine S/D flow ratio. MCE is unique in its ability to distinguish arteriolar from capillary blood volume. The potential to detect a flow-limiting coronary stenosis at rest could have important implications because it could be done in much less time than could a stress study and could be done in patients with a contraindication to exercise or pharmacological stress.

Naturally, there are limitations to the technique, and additional studies are needed. The number of patients was fairly small, and they were selected for coronary angiography. This can lead to a verification bias that favors a high sensitivity and lower specificity. Quantitative coronary angiography is an imperfect reference standard that often underestimates stenosis severity. As pointed out by the authors, tachycardia or a hypercontractile state could affect the arteriolar S/D ratio. Collateral flow could be sufficient to normalize the S/D ratio in some patients. The authors used a mid-myocardial region to measure arteriolar S/D ratios. Although this is convenient and less prone to contamination by the left ventricular cavity signal, a subendocardial region could theoretically be superior because the subendocardium is prone to ischemia and more affected by the extravascular compressive forces that result in arteriolar systolic flow reversal. Alternatively, systolic arteriolar flow reversal is not uniform throughout the myocardium but is greater in the subendocardium, a finding that may complicate the present approach. Finally, the optimal microbubble formulation and imaging methodology for accurately measuring aBV remains to be firmly established. Accordingly, the threshold value of the arteriolar S/D ratio for predicting a hemodynamically significant coronary stenosis is likely to change with future studies.

Although the present understanding of coronary microvascular physiology was beyond the science of Osler’s day, he famously observed that “medicine is an art, based on science.” Wei et al are to be congratulated for advancing the art of MCE by incorporating the science of coronary microvascular physiology with the unique ability of MCE to specifically image coronary aBV.

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References


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