What controls the magnitude and distribution of blood flow in the heart is unknown. Since the early adenosine hypothesis, investigators have continued to look for metabolites or signaling pathways involved in the regulation of coronary perfusion. The trends have run through adenosine, neuronal influences, CO₂, O₂, pH, lactate, K⁺, myogenic responses, growth factors, nitric oxide, and others. No consensus has emerged with regard to a feedback or feedforward model for coronary perfusion regulation despite decades of research.

What is becoming clear is that a simple regulatory system on the basis of one metabolite or signaling pathway is unlikely. This is supported by many lines of experimental evidence, demonstrating complex interactions among most of the putative regulatory processes. To complicate this additionally, evidence has emerged that the coordinated functions of contraction, flow, and energy metabolism are highly heterogeneous. This heterogeneity, along with the assumed regional control processes, makes the mechanistic interpretation of mean flow data from the large veins and arteries difficult, even though this has been the major form of analysis in the past.

Labeled microspheres have documented heterogeneity of myocardial perfusion with 6- to 10-fold variations between regions. The heterogeneity is apparently not random; regions trend together with a similarity in the spatial correlation as a function of distance that has fractal characteristics. Most importantly, the magnitude of flow variation increases with decreasing sample size, suggesting a highly localized form of regulatory control. One factor contributing to the flow heterogeneity could be the branching network of the coronary vasculature. However, most studies suggest that the most important factor is the tissue itself, modifying flow to meet the metabolic need. Local metabolic activity correlates with regional flow. This is almost a requirement because of the near-complete extraction of oxygen from the vascular supply in the heart, suggesting little luxuriant flow. Because the major ATP-consuming process in the myocyte is muscle contraction, it is logical to speculate that the contraction work (J/sec) within the heart wall is proportional to the regional flow. Thus, an understanding of the regulation of regional flow may lead to a better understanding of regional function and the overall mechanical performance of the heart. Clearly, no model of cardiac mechanics has developed that fully explains these highly localized phenomena.

One issue in this area of investigation is what spatial scale would be the most appropriate for study. Because the regulation of blood flow in the heart is dominated by the resistance arterioles controlling capillary bed perfusion, it could be argued that studying this process on the spatial scale that is being regulated is appropriate. What volume of heart is perfused by a single arteriole? After a review of the literature and discussions with colleagues, we found little consensus on this basic functional perfusion unit. The complicated geometry of the vessels and disagreement about what diameter of arteriole is the important regulatory site contribute to this discussion. The diameter of the cardiac arterioles in the branching blood supply vary in such a way that the larger the vessel, the more tissue it supports. The data from Kassab et al in the pig heart can be used to provide an estimate of the relationship between vessel diameter and number of capillaries supported. Using a close-packing model with 6-μm diameter, 700-μm-long capillaries uniformly spaced every 20 μm, one obtains a volume supported by a capillary of 3×10⁻⁷ mm³. The capillaries and volumes supported by different arterial diameters are shown in the Table. Note that the difference in supported volume between an arteriole of 150 and 10 μm is 50 fold. If one picks a diameter of 150 μm, below which most of the regulatory resistance is found, a functional perfusion unit of 0.13 mm³ or 130 μg or a 500-μm isotropic imaging voxel (ie, 500×500×500 μm) is obtained. This volume is taken as the resolution target for imaging perfusion events in the heart for this discussion.

Despite the technical challenge of monitoring perfusion at the resolution and field of view specified, the equivalent task of imaging single arterioles with this field of view is more difficult. This is because a small change in arteriole cross-sectional area is amplified in the much larger perfusion bed that should be easier to measure. The optical imaging of individual epicardial arterioles has been and will continue to be a very useful approach in working out mechanisms. However, it is restricted to a limited field of view of the epicardial tissues or surgically exposed endocardium and is technically challenging. Finally, a dynamic tool that can make regional flow measurements as well as functional and metabolic measurements during various physiological states would be extremely useful in working out physiological mechanisms.

In the study by Bauer et al in this issue of Circulation Research, a magnetic resonance imaging (MRI) method of...
Estimates of volumes of tissue supported by different sized arterioles

<table>
<thead>
<tr>
<th>Order</th>
<th>Diameter, μm</th>
<th>Capillaries, No.</th>
<th>Volume, mm³</th>
<th>Weight, μg</th>
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<td>3</td>
<td>0.001</td>
<td>1</td>
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</table>

Diameters are means from the left anterior descending coronary artery (LAD) perfusion field.

Data from Reference 15.

imaging myocardial perfusion is described that begins to meet some of these criteria. Using simple methodology, the authors imaged myocardial perfusion in an isolated perfused rat heart at a spatial scale significantly below previous reports. Two basic approaches are available for perfusion imaging with MRI: following the motion of a contrast agent or water itself through the tissue. Bauer et al. have developed a rapid water-tracking approach. Simply viewed, this approach sensitized the slice of interest to inflowing or water itself through the tissue. Bauer et al. have developed a rapid water-tracking approach. Simply viewed, this approach sensitized the slice of interest to inflowing water from out-of-slice regions, permitting the estimate of tissue perfusion. Perfusion data were collected in a single short-axis slice in 40 seconds, with an in-plane resolution of 140×140 μm, with a slice thickness of 1.5 mm. These spatial diameters are not uncommon in small mammal or perfused organ MRI experiments. This corresponds to ~0.029 mm³ of tissue, well within the estimate of tissue supplied by a 150-μm arteriole (Table). This is well beyond the typical volume resolution of microspheres that approach 200 mm³. Smaller volumes are possible with microspheres using molecular spheres, but the data handling and sampling of these small volumes remain difficult. Indeed, the authors had difficulty finding a gold standard at this spatial resolution. The lack of a gold standard is a weakness that is difficult to overcome and will require many controls to additionally quantitatively validate this approach. It is important to note that ~3200 samples were collected over 40 seconds and analyzed in the slice to estimate perfusion. MRI clearly provides a rapid and simple method of collecting large amounts of data with no tissue handling. The fact that these measurements and analyses probably took only minutes to complete is in sharp contrast to destructive microsphere-counting techniques.

The authors found that the fractal behavior of perfusion heterogeneity is maintained at this near-microscopic scale, as observed in previous studies in much larger regions of the heart. The fractal behavior seemed to be dependent on the active regulation of the microvascular tone and not geometry alone, on the basis of the effects of vasodilation. However, it is still unclear what the fractal behavior means with regard to the physiological regulation of coronary blood flow. Additional studies on the physiological basis of this fractal behavior of flow in the heart need to be conducted. Hopefully, this type of high-resolution flow data coupled with appropriate experimental designs will shed some light on this persistent problem in cardiac physiology.

Recent developments in MRI methods provide high spatial resolution of more than just flow, as discussed by Bauer et al. Aletras et al. recently described high-resolution muscle displacement measurements of each voxel in the MRI image in human and canine hearts. This method is similar to the high-resolution velocity measurements previously reported but is less prone to artifacts. These high-resolution functional methods should provide information on the timing and magnitude of contractile activity, which are both critical in the determination of the metabolic demand.

Metabolism is more difficult to measure on this spatial scale but may provide a good integrated measure of work. Nuclear magnetic resonance methods have proven to be useful on tissue extracts. However, the signal to noise is too low to yield high spatial resolution and is likely limited to being used on in vitro samples like microspheres. More promising might be the use of capillary oxygen tension using the T2 relaxation-rate dependence of hemoglobin oxygenation coupled to measures of flow and blood volume to determine local metabolic rates. However, the extrapolation of T2 to metabolic rates is complicated by many factors.

It is particularly promising that flow, function, and metabolism can all be determined in the same preparation nearly simultaneously using MRI. Clearly one of the major advantages of MRI will be the registration of high spatial resolution functional data with flow and some marker of metabolic activity. The difficulty of correlating tissue extract data (ie, microspheres) to in vivo strain/stress data will increase with decreasing voxel size. Indeed, Bauer et al. encountered this difficulty in the present study. Naturally, molecular imaging of the putative molecular markers of metabolism, transducers, and signaling molecules, such as Ca²⁺, NADH, and mitochondrial membrane potential, along with measures of the electrical activity will also be needed to complete the evaluation of this complex process.

Toward the future, the spatial resolution of physiological parameters measured is essentially the same as the MRI experiment itself. Thus, any improvement in the basic MRI imaging resolution via higher magnetic fields or receiver coils will be reflected in improved resolution. Great progress is being made in these areas. Bauer et al. extrapolated their results to in vivo conditions. In vivo studies are generally conducted at lower magnetic fields that reduce signal to noise as well as the net effects of flow on the relaxation rate. The flow rate in blood-perfused organs is also much lower than saline-perfused organs. In addition, most in vivo preparations will not have the same receiver-coil sensitivity because of the poor geometry of the chest and heart. In general, we believe that these extrapolations are optimistic, and accomplishing comparable high-resolution studies in the intact animal or clinically is going to be very challenging.

In summary, the study by Bauer et al demonstrates that MRI is capable of monitoring the distribution of coronary perfusion within the heart at spatial resolutions approaching the tissue volume fed by a single arteriole capillary volume. This is a significant achievement that does not require technology beyond what is available for imaging animals.
today. One of the most exciting aspects of this development is the potential correlation of this kind of data with function and metabolism directly using other MRI approaches. This kind of multiparameter evaluation of cardiac function, at the spatial scale that flow is regulated, should help unravel the signaling network that controls coronary perfusion.

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References
Function, Metabolic, and Flow Heterogeneity of the Heart: The View Is Getting Better
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