Editorial Comment

Myocardial Viability
What Does It Mean and How Do We Measure It?

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The paper by Bonow et al1 in this issue of Circulation reports important empirical observations on measuring myocardial viability in humans with the potassium analogue thallium-201. After obtaining standard \(^{201}\)TI exercise and redistribution images, a second dose of \(^{201}\)TI was injected and a third (reinjection) image was obtained beginning 10–15 minutes later. The reinjection images identified viable and necrotic myocardium with the same accuracy as perfusion/metabolic imaging by positron emission tomography (PET) using cyclotron-produced \([^{18}F]\)fluorodeoxyglucose (FDG) and water labeled with oxygen 15.

The observations in their paper1 have implications about how we measure myocardial viability, what we mean by it, how it relates to perfusion imaging, and about the imaging technology; each of these issues is briefly addressed here.

Definition of Viability

Myocardial cells are considered dead when some basic aspect of cell behavior no longer functions. That cell function may be intermediary metabolism as reflected by FDG uptake2 or cell membrane integrity as reflected by the cell’s ability to retain intracellular components such as creatine phosphokinase, inosine, phosphate, or the potassium ion.

Leak of one or more of these components out of myocardium has been used as a marker of myocardial necrosis. In particular, leak of potassium from myocardial cells has been extensively studied in relation to cell injury and necrosis.3,4 \(^{201}\)TI and rubidium-82 are potassium analogues that were developed as perfusion tracers reflecting initial myocardial uptake in proportion to blood flow delivery. However, as potassium analogues, they are also markers of viability because only viable cells with intact membranes retain the tracer, reflecting the potassium space of viable tissue. In myocardial scar tissue, these potassium analogues are not taken up to the same extent as normal myocardium because of low blood flow to scar tissue associated with a corresponding fixed defect. In acutely injured myocardium these potassium analogues leak back out of necrotic cells after initial uptake, leaving an image defect reflecting loss of the potassium space and interpreted as necrosis. The kinetics of this ion leak as a measure of viability have been most clearly elucidated for \(^{82}\)Rb5,6 but in principle apply equally to \(^{201}\)TI.

FDG Versus Potassium Analogues

Which is the better measure of myocardial viability—intermediary metabolism, reflected by FDG uptake, or cell membrane integrity, reflected by uptake of \(^{201}\)TI or \(^{82}\)Rb? Under the right conditions and by the right protocol, the two approaches are equivalent, as shown in the paper by Bonow et al1 comparing imaging using FDG with that using \(^{201}\)TI and by our clinical study6 comparing the kinetics of FDG with those of \(^{82}\)Rb in patients with evolving myocardial infarction. This equivalency makes sense because both intermediary metabolism and cell membrane integrity are necessary for cell viability.

However, the proviso must be that the measures are taken under the right conditions and with the right protocol. Myocardial FDG uptake is highly dependent on substrate availability and on conditions of fasting, glucose loading, catecholamine and hormone levels, and diabetes.6–12 The accuracy of judging viability with FDG may therefore be variable, with viable myocardium failing to take up FDG under some conditions and necrotic myocardium taking up FDG under others.5,7,10–12 In the study by Bonow et al1 the conditions were chosen appropriately for using FDG as a standard for viability. However, under the broad range of conditions seen in clinical practice, FDG imaging may be difficult to interpret as a measure of viability in up to 20% of patients who need myocardial viability studies,6,7,10 particularly in diabetics or in patients tested after fasting. These limitations of FDG are due to its uptake (or lack thereof) being affected by factors unrelated to viability or necrosis.
The integrity of cell membranes for the potassium analogues $^{201}$Tl and $^{82}$Rb is not dependent on these physiological and metabolic variables affecting intermediary metabolism as long as the cells are viable. Cell membrane integrity for potassium or its analogues is therefore a simpler, more basic, and more reliable measure of cell viability than intermediary metabolism. However, using a potassium analogue to assess myocardial viability requires the right imaging protocol because it is also a perfusion tracer. The report by Bonow et al. indicates that the standard stress–redistribution protocol may be the wrong one for assessing viability with a potassium analogue. The conceptual error of assessing viability by the standard stress–redistribution approach becomes understandable if considered in terms of coronary flow reserve and the kinetics of potassium or the potassium analogues $^{201}$Tl and $^{82}$Rb; the infarct size determinations by these methods match infarct size determination by FDG images in clinical studies of patients with evolving myocardial infarction. Thus, the kinetics of potassium analogues provide a rationale or basis for the $^{201}$Tl reinjection protocol.

**Perfusion Versus Viability Imaging**

How does perfusion imaging relate to determination of viability using potassium analogues? Stress $^{201}$Tl images show the relative distribution of elevated perfusion during exercise or relative flow reserve modified by flow-dependent extraction. A reversible defect on stress–redistribution $^{201}$Tl scans indicates the zone of reduced coronary flow reserve at risk. An enlarging stress defect around a defect on the redistribution scan defines the area of reduced flow reserve around an infarction. It does not provide information about viability in the redistribution defect, as confirmed empirically by Bonow et al. The $^{201}$Tl reinjection image is essentially a resting image superimposed on the stress image. However, because the stress–redistribution images do not reliably predict viability, the resting reinjection image contains the viability information.

The correlation between necrosis of myocardium and severely reduced myocardial uptake of a potassium analogue like $^{201}$Tl or $^{82}$Rb is due to two processes: 1) low $^{201}$Tl delivery at low flows for more than a few hours, as in chronic coronary artery disease, is associated with necrotic myocardium or scar tissue; 2) even with adequate flow and radionuclide delivery after reperfusion, the radionuclide is not trapped or leaks out from necrotic tissue after initial uptake, leaving a “washout” defect on the 10–15 minute reinjection image. By either of these mechanisms, those myocardial areas with less than 50% of peak normal activity on the $^{201}$Tl reinjection image fail to take up FDG and are therefore necrotic, as defined by the absence of intermediary metabolism. Both of these mechanisms have been well defined for potassium experimentally and clinically, in comparison with FDG in patients with recent or old myocardial infarction.

The relative contribution of these two mechanisms (i.e., low flow/low tracer delivery and failure to retain $^{201}$Tl [washout]) to the final defect severity on the resting or reinjection image depends on whether reperfusion has occurred and on the acuteness of the infarction. For fixed myocardial scar tissue in chronic stable coronary heart disease, the defect severity is probably associated primarily with low flow/low tracer delivery, as observed by Bonow et al. For acutely infarcted, reperfused myocardium, in which flow and delivery of tracer may be normal, the washout phenomenon and failure to retain the delivered tracer is probably the primary cause of the defect, as demonstrated by clinical studies with $^{82}$Rb.

**PET Versus SPECT Technology**

There is a common misunderstanding about the technological advantages of PET over single photon emission computed tomography (SPECT) in determining severity of disease. The paper by Bonow et al demonstrates that with the correct protocol, $^{201}$Tl SPECT is qualitatively comparable to PET with cyclotron-produced FDG for imaging myocardial viability. The question is how can that be true given the better attenuation correction and technical imaging characteristics of PET?

Imaging myocardial necrosis involves high image contrasts between normal and abnormal areas, that is, detection of very low activity in one area as a small percent of the normal maximum activity. In its defense, such high contrast can be adequately imaged qualitatively by SPECT. However, the technical advantages of PET, particularly attenuation correction, become most apparent when quantitative size or quantitative intensity of defect severity must be measured and when lesser contrasts between normal and abnormal must be differentiated, as in detection and quantification of more graded differences in radionuclide distribution reflecting the spectrum of reduced flow reserve due to coronary artery stenosis over a range from mild to severe narrowing.

The essential clinical question often is, when deciding on a definitive intervention, how much myocardium is viable? In our early experience, although 70–80% of postinfarction left ventricular regions may be viable by $^{201}$Tl SPECT or PET, the total amount of viable myocardium adds up to a large enough size to warrant intervention in only 30% to 40% of patients. Therefore, sizing the myocardial infarction and/or viable areas as a percent of the zone of impaired flow reserve at risk becomes the real clinical issue that determines the value of a clinical methodology. The study by Bonow et al does not address this question.

However, their paper returns $^{201}$Tl imaging for determining of myocardial viability to the mainstream of our knowledge about the behavior of potassium and potassium analogues from the conceptual wilderness of 4- and 24-hour stress–redistribu-
tion protocols. Although explanations or mechanisms are not proved, the paper by Bonow et al. provides important empirical support for the concept of assessment of cell membrane integrity for a potassium analogue as a measure of myocardial viability or infarction, comparable to imaging intermediary metabolism using FDG.

References
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