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Assessing myocardial ischemia, hibernation, and viability: stress echocardiography and nuclear imaging

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DO NUCLEAR IMAGING techniques offer advantages over stress echocardiography in detecting the location and degree of ischemia and in determining the viability of myocardial tissue in patients with angina or myocardial infarction? How should the information from these modalities be used in deciding whether a patient should undergo revascularization?

In this installment of *Cardiology Dialogues*, George A. Beller, MD, a pioneer in the field of nuclear cardiology and Chief of the Cardiovascular Division at the University of Virginia, reviews two challenging cases with Thomas H. Marwick, MD, Director of Cardiac Stress Imaging, Cleveland Clinic Department of Cardiology. The cases illustrate the importance of testing for viable myocardium and the relative merits of these two modalities.

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■ This series is based on the Cleveland Clinic Heart Center's "Controversies in Cardiology" conferences, at which a visiting clinician-professor and a Cleveland Clinic Heart Center clinician give contrasting perspectives on the application of a current technology or the management of a cardiologic disease.

CASE 1

DR. MARWICK: A man with non-Hodgkin's lymphoma (for which he is receiving chemotherapy) and insulin-dependent diabetes came to his local hospital with chest pain and anterior wall infarction. Owing to chemotherapy and resultant severe anemia, he did not undergo thrombolysis. Several weeks later, he was referred to the Cleveland Clinic. Angiography performed at the local hospital within a few days of the infarction showed a proximal occlusion of the left anterior descending (LAD) coronary artery, a small left circumflex artery, an occlusion in the posterior descending artery, and akinesis of the anterior wall. There were a few collateral vessels leading to the LAD territory. Electrocardiography showed new anterior Q waves and recurrent episodes of ventricular tachycardia, but the patient was not in heart failure and did not have angina.

Dr. Beller, what would you do next?

DR. BELLER: Given the Q waves and akinesis of the anterolateral wall, one might assume that the area of the anterior wall is irreversibly injured, especially if there was a large rise in the creatine kinase concentration at the time of the infarction. Recurrent ventricular tachycardia is not unusual after a large infarction like this. He may need only electrophysiologic evaluation for a transvenous defibrillator or to begin amiodarone therapy.

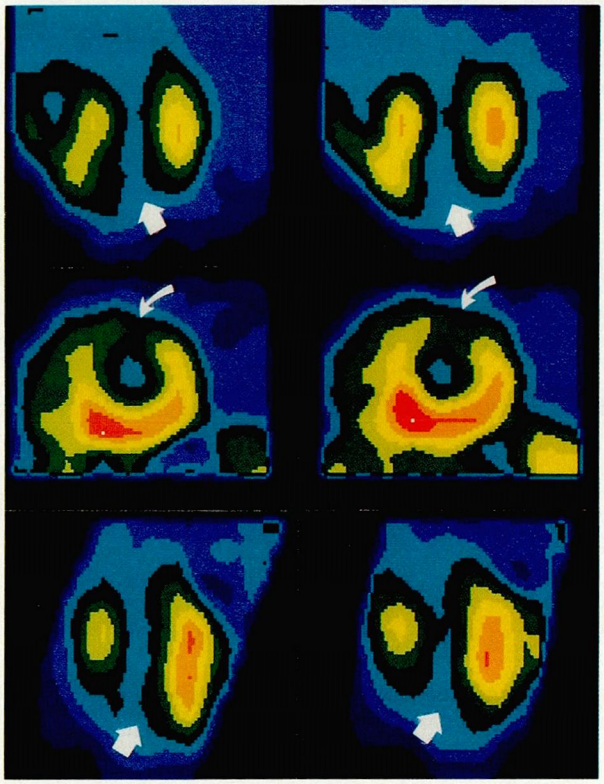

FIGURE 1. Myocardial perfusion images in coronal (top), transverse, and sagittal (bottom) views using rubidium-82 positron-emission tomography. The perfusion defects in the apex (broad arrow) and anterior (curved arrow) walls are similar at rest (right image) and during stress (left image).

DR. MARWICK: Would you look further for viable myocardium, and how likely is it that you would find this?

DR. BELLER: Five years ago, everyone would have concluded that this area was all infarcted. Today we know there is a 40% to 50% chance that revascularization could improve this patient's left ventricular function by enhancing blood flow to viable "hibernating" myocardium.

The degree of collateralization detected at angiography is not a good guide to the presence of residual viable tissue. A recent study showed no correlation between the presence of collaterals or collateral grade and fluorine-18-labeled deoxyglucose (FDG) uptake in patients with totally occluded arteries and left ventricular dysfunction.[1] Surgeons always tell me that the flow assessed in the operating room is better than we estimate it to be when there is a very high-grade lesion, so one can be misled by the appearance of the coronary angiogram.

We might want to look at some index of viability in that anterior wall. We could obtain a resting thallium image and look at 4-hour uptake to see how much of the anterior wall might really still be viable, but very hypoperfused with collaterals we cannot see. The greater the thallium activity on the 4-hour resting scan, the higher the likelihood that the anterior wall is viable. If there were enough viable myocardium, anastomosis of a distal vessel could be performed. But if the anterior wall were nonviable, we would want to reduce the risk of sudden death and cardiac remodeling by giving angiotensin-converting enzyme (ACE) inhibitors, beta blockers, warfarin, and possibly amiodarone.

DR. MARWICK: From our experience, there are three reasons to look for viability in this situation. First, if there is viable tissue but the patient does not undergo revascularization, we have found there to be a high mortality rate—approximately 40% to 50% per year.[2] Second, if there is an extensive area of viable or ischemic tissue (about 25% of the myocardium), revascularization may improve functional capacity.[3] Third, several studies have shown an improvement in ejection fraction when hibernating segments are revascularized, though the degree of improvement is clearly related to the extent of viability.

DR. BELLER: I agree. Di Carli et al[4] reported an 88% survival rate at 1 year for patients with revascularized hibernating myocardium, compared with a 50% rate in patients who did not undergo revascularization. In addition, of patients with symptomatic New York Heart Association class III heart failure, 40% to 50% converted to class I heart failure after revascularization.

DR. MARWICK: For all these reasons, this patient underwent a positron-emission tomography (PET) scan with rubidium, to examine myocardial perfusion (*Figure 1*). This showed a large area of reduced uptake near the apex, a fair amount of septal uptake, and reduced perfusion to the anterior wall.

DR. BELLER: Rubidium has a very short half-life—75 seconds. Therefore, one cannot detect rubidium ions that may accumulate over time in areas of hypoperfusion. Rubidium scanning will show per-

fusion defects during stress or rest. Thallium scanning will show the same information at rest, within 2 or 3 minutes of injection, but at 4 hours one might also see slow circulation through collaterals. Rubidium is good for looking at ischemia, where there is more of a defect with stress than with rest, but it does not tell us as much about viability. While some believe we can assess viability by taking rapid, sequential rubidium images, as necrotic tissue has a faster clearance rate, most cardiologists use PET perfusion imaging with rubidium only in conjunction with a metabolic image (FDG or carbon-11-labeled acetate) and look for either a mismatch pattern or the absolute uptake of FDG.

DR. MARWICK: But you might expect the chance of residual viable tissue being present to correlate with the amount of residual myocardial perfusion after an infarct. Isn't there some evidence that viability might be predicted on the basis of absolute flow?

DR. BELLER: You could certainly expect there to be no viable myocardium if the flow were less than 25% of normal. But what about between 25% and 50%? A rubidium image may look like this patient's if there were a 40% reduction in flow, for example, because of a partial volume effect. In that situation, the absence of systolic wall thickening might exaggerate a mild reduction of perfusion.

DR. MARWICK: What about the theory that one can use perfusion imaging to predict viability if the regional thallium (or perhaps rubidium) activity is more normal—say, more than 50% of that in normal segments?

DR. BELLER: I think that is fairly reliable, but for a flow deficit of 60%, thallium and PET scanning have only an 80% predictive value. In other words, 20% of segments judged to be nonviable by noninvasive testing still improve function after revascularization. Again, the partial volume effect may be very important—a subendocardial scar tremendously influences epicardial thickening, even though the epicardium is viable.

We conducted an experiment in animals in which we reduced the flow in the endocardium to 0.45 mL/minute per gram while leaving the epicardial flow completely normal.[5] We found that myocardial thickening was mainly dependent on endocardial flow and not epicardial flow. I believe this is one explanation for hibernation: when subendocardial flow declines to about 50% without necrosis, transmural akinesis results. If that area of subendocardial hypoperfusion is scar tissue, the FDG "lights up" in the epicardium, but function does not improve after revascularization because the epicardial segment is tethered to the akinetic endocardium in systole. That is why some "viable" segments do not improve function after revascularization: you are perfusing a subendocardial scar, and the epicardium was healthy to begin with.

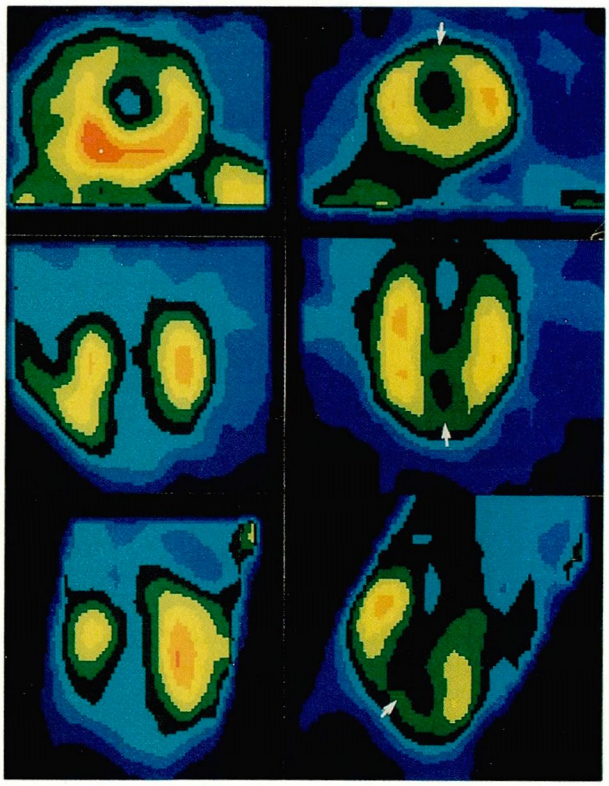

FIGURE 2. Myocardial resting perfusion and "metabolic" images in transverse (top), coronal, and sagittal (bottom) views using fluorine-18-labeled deoxyglucose (FDG) positron-emission tomography. The perfusion defects (left) are matched by areas of low FDG uptake (right) in the apex and anterior walls (small arrows).

AUDIENCE: Is the endocardium actually contracting on a myocyte basis?

DR. BELLER: Subendocardial hypoperfusion causes transmural akinesis because of the load placed on the epicardium. When the endocardium is unable to contract, there is enormous wall stress on the epicardium.

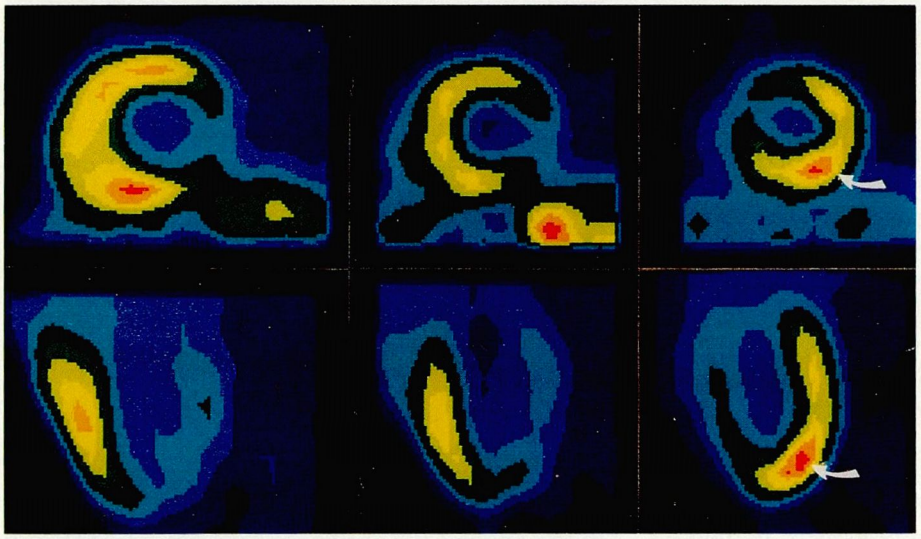

FIGURE 3. Myocardial perfusion with stress (left) and at rest (center) and "metabolic" images (right) in transverse (top) and coronal views using rubidium-82 and fluorine-18-labeled deoxyglucose (FDG) positron-emission tomography. There is no ischemia. However, the resting perfusion defect demonstrates a "mismatch" pattern of FDG uptake (curved arrows), denoting the presence of viable myocardium.

Even with normal flow, it cannot contract. It is like the afterload mismatch seen with aortic stenosis. If dobutamine were infused, the epicardium would most likely thicken and flow would increase.

Some feel that hibernation is really multiple frequent episodes of transient subendocardial ischemia. In fact, a recent histological study found that hibernation was more like repetitive episodes of calcium overload and stunning than a low-flow chronic ischemic state.[6]

DR. MARWICK: I share your concerns about using relative perfusion to identify viable myocardium. In the presence of a large infarction, the normal response of the opposite (noninfarcted) wall is to develop hyperkinesis in order to compensate for the infarcted area and maintain the ejection fraction. However, when there is compensatory hyperkinesis there is compensatory hyperflow as well. If we use relative flow parameters to predict viability, we are comparing a region of interest in the infarct zone with the opposite wall which we assume to be normal. As this opposite wall has increased flow this may exaggerate the severity of the perfusion defect in the infarct zone.

DR. BELLER: That is a good point. This would cause us to underestimate viability.

DR. MARWICK: For the reasons we've discussed, we proceeded to FDG imaging (*Figure 2*). The longitudinal views show the perfusion defect in the apex to demonstrate partial mismatch, but most of the perfusion defect is matched by low FDG uptake. This implies the absence of viable tissue despite the collateralization at angiography.

The term "perfusion-metabolism mismatch" has been used to describe this pattern of preserved metabolic activity in the presence of reduced perfusion, which is highly predictive of functional recovery after revascularization. The actual criteria vary from center to center—some rely on a subjective assessment, others use a ratio of 1.2, some use a percentage change of 20% to 30%. This patient is borderline, and we felt it unlikely that this infarct zone was viable.

DR. BELLER: This certainly does not look like a significant perfusion-metabolic mismatch. Did the patient undergo surgery?

DR. MARWICK: In view of the findings at the PET scan, together with his cancer, he did not. He is being treated with ACE inhibitors and will be assessed by the electrophysiologists.

AUDIENCE: We have been describing viability as a yes-or-no question. But I would think that islands of cells are viable, and function may be a continuum.

DR. MARWICK: I agree that our appreciation of viability as a binary "dead-or-alive" phenomenon is clearly an oversimplification, and there are all sorts of degrees of damage in between. When we looked at myocardial metabolic activity after revascularization, we found it to remain abnormal in some areas in which perfusion and function were restored, suggesting that the metabolic behavior of some cells was persistently abnormal despite recovery of their

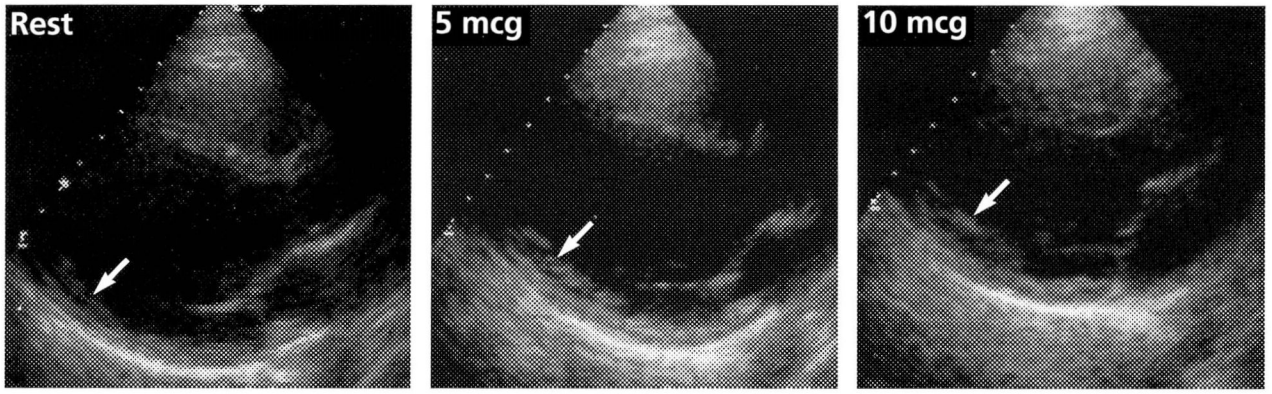

FIGURE 4. End-systolic freeze-frame images in the parasternal long-axis view at rest and during low-dose dobutamine infusion. The posterior wall thickens in response to low-dose dobutamine, indicating the presence of viable myocardium.

neighbors.[7] This is perhaps a correlate of the ultrastructural changes that Dr. Beller described. On the other hand, we do use these data to make decisions about whether to perform revascularization, which is also a binary decision—so that this simplification is unavoidable.

CASE 2

DR. MARWICK: The first patient was presented in order to discuss the importance of detection of viable myocardium. We'd like to present another patient in order to provoke some discussion regarding the selection of which technique to use for this purpose.

The second patient is a 65-year-old man with mild chronic stable angina, who now presents with a probable posterior myocardial infarction. Angiography demonstrated a blocked right coronary artery and circumflex artery. We felt, in view of his history, we should look further for ischemia and viability. A PET scan demonstrated a resting perfusion defect, which did not alter during stress, with glucose images demonstrating a mismatch pattern suggesting viability in the posterolateral wall (*Figure* 3).

DR. BELLER: This image shows the greatest mismatch towards the apical region.

DR. MARWICK: We were concerned that while the presence of residual glucose uptake suggests cellular viability, not all of these segments may be robust enough to improve following revascularization. We are currently studying whether dobutamine echocardiography can be more predictive of functional recovery in this setting. The dobutamine echocardiogram showed that the lateral wall function deteriorated at peak dobutamine dose. In the inferoposterior wall, function improved (*Figure 4*)—a pattern characteristic of viable myocardium.

The role of dobutamine echocardiography for the diagnosis of hibernating myocardium is still being evaluated. However, the ability of dobutamine to detect viable tissue in the situation of stunning is convincing. What do you think, Dr. Beller?

DR. BELLER: Dobutamine echocardiography has an extremely high sensitivity for detecting stunned but viable myocardium after an acute infarction.[8] In hibernation, there are several populations of patients: some show an initial improvement and then deterioration, others start with akinesis that does not improve, even at low doses.

In order for dobutamine to improve function, it must increase the flow. And if there is some flow reserve, either by antegrade flow or by collaterals, inotropic stimulation will produce thickening. Then, as regional oxygen demand keeps increasing with increasing dose, flow becomes inadequate, and ischemia results. We showed in an animal model that if we produced ischemia to the degree that dobutamine could not increase flow, there was no increased thickening. This is a chronic low-flow state. But dobutamine will increase thickening in animals that can recruit some increased flow.

This patient's case might be an instance where inotropic stimulation gives better information than PET imaging, because there is low flow and almost no glucose uptake in that area. However, one of the weaknesses of stress echocardiography is the lack of

quantitation for an end result. Judgements are based on visual assessment of changes in wall motion or thickness. In perfusion imaging, on the other hand, we have striven to use quantitative assessments of perfusion, such as defect magnitude, and defect size. Further, the echocardiographer needs to be highly skilled to detect subtle changes after stress, particularly with treadmill exercise. The sensitivity of stress echocardiography for detection of ischemia is reduced in patients with single-vessel disease, with 50% to 70% stenoses, or submaximal exercise. Such situations may be associated with minimal wall-motion abnormalities that resolve quickly after exercise. What about quantitation for stress echocardiography?

DR. MARWICK: Obviously, this is the "Holy Grail" of stress echocardiography, and we have not found it yet. Nevertheless, for all the criticism from the nuclear community, most nuclear imaging is not quantitative either. We mostly rely on comparing redistribution between the resting and stress images by visual inspection. To apply quantitative tools to routine clinical use would require substantial time and technical support. Part of this discussion is about what is desirable vs what is practical.

With respect to your second comment about the delay, I don't think it is a major issue. Some people with single-vessel disease do get missed, but they do not have prognostically important disease. Most of the follow-up data show the frequency of events after negative echocardiograms is very low.

DR. BELLER: You showed, in one of your studies, that stress echocardiography had significantly lower sensitivity for detecting ischemia in patients who had no previous myocardial infarction than in people who did. We see the same thing in perfusion imaging. In an analysis of sensitivity of any technique, if 50% of patients had a previous myocardial infarction, that means 50% will have a positive test result from the start. What is the data on the sensitivity of stress echocardiography in patients with normal resting wall motion?

DR. MARWICK: In these patients the sensitivity is approximately 80% and the specificity is approximately 85%. The sensitivity declines in populations with mild (50% to 70%) single-vessel disease.

DR. BELLER: In general, what is being advocated is the exploration of functional testing to help make decisions with respect to outcomes. Whether we develop ultrasound techniques, PET, or thallium, it does not matter. Whatever we do, we should do it well.

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