

Sequential Strategy Using Multimodality Viability Tests: Does It Work?

In this issue of *The Journal of Nuclear Medicine*, Bax et al. (1) have introduced the concept of using sequential imaging with rest-redistribution ^{201}Tl imaging and low-dose dobutamine echocardiography as a clue to the management of coronary artery disease and left ventricular dysfunction. In their study, ^{201}Tl imaging alone had a high sensitivity of 84% and a relatively low specificity of 63% for predicting a left ventricular ejection fraction (LVEF) improvement of $\geq 5\%$, whereas dobutamine echocardiography was less sensitive (63%) but more specific (85%) than ^{201}Tl . More important is that sequential use of these 2 viability tests, compared with either alone, significantly improved the accuracy of predicting functional recovery after revascularization in a subset of patients with an intermediate likelihood of viability, suggesting that the tests may be complementary.

Despite recent advances in therapeutic options, heart failure caused by coronary artery disease is still one of the leading causes of mortality and morbidity in many countries. Therefore, noninvasive assessment of myocardial viability continues to represent an important issue in heart failure patients for whom coronary revascularization is under consideration. Viable myocardium is most likely to benefit from revascularization, whereas scar tissue is unlikely to show functional recovery. Nuclear imaging techniques such as ^{201}Tl scintigraphy (either a rest-re-

distribution protocol (2) or a reinjection protocol (3)) and metabolic imaging using PET (4,5) have long played a major role in the identification of such dysfunctional but viable myocardium. More recently, other imaging techniques have been introduced for clinical use as promising viability tests. These include low-dose dobutamine echocardiography (6) or MRI (7) to assess contractile reserve and contrast MRI to assess delayed hyperenhancement as a marker of scar tissue (8). In particular, dobutamine echocardiography has emerged as a competitor of nuclear imaging and has gained wide clinical acceptance because of easy accessibility for patients and physicians. To date, several reports have compared nuclear imaging and dobutamine echocardiography for the detection of viable myocardium (6,9–11). The clinical experience from these studies suggested that ^{201}Tl imaging is highly sensitive but only modestly specific for the prediction of functional recovery, whereas dobutamine echocardiography is less sensitive but more specific than ^{201}Tl . Bax et al. (1) have again confirmed this experience. Thus, neither ^{201}Tl nor dobutamine echocardiography may be optimal at present. Under most circumstances, nuclear imaging and echocardiographic procedures are performed by different physicians of different medical backgrounds. Perhaps for this reason, nuclear imaging and echocardiography are often considered to be competitive rather than complementary diagnostic modalities. The sequential use of nuclear imaging techniques proposed by Bax et al. may be more appropriate and of importance to referring physicians and nuclear medicine communities.

How the sequential strategy enhances diagnostic accuracy deserves

consideration. Perhaps, the combination of highly sensitive ^{201}Tl and highly specific dobutamine echocardiography is a key factor in the improved overall accuracy. Conversely, a combination of diagnostic tests with similar trends for sensitivity and specificity will not work in this manner. For example, the combination of ^{201}Tl and $^{99\text{m}}\text{Tc}$ -sestamibi or $^{99\text{m}}\text{Tc}$ -tetrofosmin imaging, all of which are reportedly highly sensitive but modestly specific in predicting functional recovery (12, 13), is unlikely to improve overall accuracy compared with ^{201}Tl or $^{99\text{m}}\text{Tc}$ flow tracer alone. Thus, determining which viability tests are to be used in sequence is essential to improving accuracy.

Several other issues warrant attention. First, as Bax et al. (1) nicely showed in their article, they analyzed receiver operating characteristic curves to determine how many viable segments were required for a $\geq 5\%$ LVEF improvement after surgical revascularization. On a regional basis, however, a viable segment on ^{201}Tl imaging was defined as having a ^{201}Tl uptake $\geq 50\%$ of that in the reference region. Although the 50% cutoff to define viable segments with ^{201}Tl imaging has often been used in published studies (2,6), whether this cutoff is optimal to distinguish viable from nonviable segments is still uncertain. In fact, several reports have suggested that the optimal threshold for viability on ^{201}Tl imaging may be somewhat higher than 50% (12,13). In a recent study by Pace et al. (14), the use of a higher cutoff (65% of peak activity) to define viability with ^{201}Tl , compared with dobutamine echocardiography, resulted in a higher sensitivity and a trend toward higher specificity for the prediction of LVEF improvement. It is conceivable, there-

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fore, that the use of a 50% cutoff might, at least partially, have been responsible for the relatively low specificity for LVEF improvement observed by Bax et al. for ^{201}Tl .

Second, as mentioned in the article (1), functional recovery may not have been completed within the observation period for some patients, possibly contributing to the relatively low specificity for predicting functional improvement with ^{201}Tl imaging. Chronically dysfunctional but viable myocardium may represent hibernation (15), intermittent stunning (16), or both. Hibernating myocardium represents impaired contractile function coupled with reduced perfusion at rest that recovers after restoration of blood flow. Stunning, on the other hand, represents impaired contractile function that persists after an ischemic episode despite restoration of blood flow. Differentiating between these states is complex because they may often coexist clinically. Prior studies by Bax et al. (17) and others (18) have suggested that stunned myocardium is likely to show early functional recovery after revascularization, whereas hibernating myocardium may take longer to recover. Also noteworthy is that contractile reserve to dobutamine infusion is more common in normally perfused (stunned) myocardium than in hypoperfused yet viable (hibernating) myocardium (19). In addition, the timing of revascularization after the onset of hibernation may influence the degree of recovery after cardiac surgery, because progressive cellular degeneration in hibernating myocardium may reduce the chance for complete structural and functional recovery after restoration of blood flow (20). These factors need to be considered when one is interpreting the results.

Third, the choice of endpoint is almost always an issue in viability studies. Studies in the literature have used many endpoints for viability tests, including myocardial ^{18}F -FDG uptake on PET (7), histologic examination of biopsy samples at cardiac surgery (21), regional functional recovery (2,3,12,13), global improvement of left ven-

tricular function (as in the study of Bax et al. (1)), improvement of symptoms (22), and improvement of survival (23). What is the optimal endpoint for such viability studies? From a pathophysiologic point of view, biologic signals by PET or histologic findings from biopsy certainly provide important insight into viability at the cellular or molecular level. Regional or global functional recovery after restoration of blood flow is also relevant because of the direct association with the definition of stunned or hibernating myocardium. From a clinical standpoint, improved survival and symptoms after revascularization would be the optimal endpoint of a viability test, because these are the main goals of revascularization procedures. In this regard, more clinical studies with prognostic data are needed before the sequential concept proposed by Bax et al. is transferred to clinical decision making. However, such prognostic information is not always available, because some patients may drop out during follow-up. Furthermore, improvement of symptoms is sometimes difficult to measure objectively. As an alternative, the use of global improvement of left ventricular function as an endpoint by Bax et al. was of worth because of the likely association with improved prognosis.

Fourth, Bax et al. (1) stated that the choice of which test is to be used first in the sequence can be determined through local expertise and experience, because the order of testing does not alter the overall accuracy. Perhaps, in the current era of Medicare- or Medicare-like systems in many countries, the choice should be determined in light of the cost-effectiveness of a test. The sequence, although confined to patients with an intermediate likelihood of tissue viability, is obviously more expensive than ^{201}Tl or echocardiography alone. The question is therefore whether the additional cost, which may differ from country to country depending on its medical economics, is offset by the improved accuracy of the sequence. An additional consideration is the prevalence of patients who are not eligible for echocardiographic

examination because of a poor acoustic window.

Finally, although both ^{201}Tl imaging and dobutamine echocardiography are established and widely used viability tests, they warrant further attention because of recent technical advances. Promising results have been reported for nitrate-enhanced perfusion scintigraphy (24), attenuation-corrected SPECT (25), gated SPECT (26), and ^{18}F -FDG SPECT (27). In particular, dobutamine stress gated SPECT using a $^{99\text{m}}\text{Tc}$ -labeled flow tracer provides information on both perfusion and contractile reserve in a single study. In this setting, dobutamine echocardiography may add little information on tissue viability to that provided by the nuclear technique (28). On the other hand, intravenously injectable contrast agents to opacify myocardium and to assess perfusion and microvascular integrity are now available for echocardiography (29). The combination of myocardial contrast agents and dobutamine echocardiography may provide information on both perfusion and contractile reserve similar to that obtained by dobutamine stress gated SPECT. In addition, cyclic variation in ultrasonic integrated backscatter has recently been proposed as a new echocardiographic marker of tissue viability (30). Furthermore, contrast-enhanced MRI is emerging as another promising tool for viability assessment (31). Thus, whether nuclear imaging and other diagnostic techniques work competitively or complementarily will change depending on future technical advances.

In summary, an ideal diagnostic test for assessing myocardial viability is one that is highly accurate, easily accessible, cost-effective, and convenient for patients. Although nuclear imaging has played an important role in cardiology for decades, the goal of finding the ideal diagnostic test is still unmet. Techniques such as dobutamine echocardiography have emerged as competitors to nuclear imaging. In view of these circumstances, the results of Bax et al. (1) tell us that a sequential strategy using multimodality viability tests may work in some situations and de-

serves further prospective trials. With the advances that have occurred in both nuclear diagnostic techniques and other diagnostic techniques, the concept of sequential testing is becoming increasingly important to the appropriate use of nuclear imaging.

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REFERENCES

- Bax JJ, Maddahi J, Poldermans D, et al. Sequential ^{201}Tl imaging and dobutamine echocardiography to enhance accuracy of predicting improved left ventricular ejection fraction after revascularization. *J Nucl Med.* 2002;43:795–802.
- Ragosta M, Beller GA, Watson DD, et al. Quantitative planar rest-redistribution ^{201}Tl imaging in detection of myocardial viability and prediction of improvement in left ventricular function after coronary bypass surgery in patients with severely depressed left ventricular function. *Circulation.* 1993;87:1630–1641.
- Dilsizian V, Rocco TP, Freedman NM, et al. Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. *N Engl J Med.* 1990;323:141–146.
- Tillisch J, Brunken R, Marshall R, et al. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. *N Engl J Med.* 1986;314:884–888.
- Tamaki N, Kawamoto M, Tadamura E, et al. Prediction of reversible ischemia after revascularization. Perfusion and metabolic studies with positron emission tomography. *Circulation.* 1995;91:1697–1705.
- Amese M, Cornel JH, Salustri A, et al. Prediction of improvement of regional left ventricular function after surgical revascularization. A comparison of low-dose dobutamine echocardiography with ^{201}Tl single-photon emission computed tomography. *Circulation.* 1995;91:2748–2752.
- Baer FM, Voth E, Schneider CA, et al. Comparison of low-dose dobutamine-gradient-echo magnetic resonance imaging and positron emission tomography with [^{18}F]fluorodeoxyglucose in patients with chronic coronary artery disease. A functional and morphological approach to the detection of residual myocardial viability. *Circulation.* 1995;91:1006–1015.
- Ramani K, Judd RM, Holly TA, et al. Contrast magnetic resonance imaging in the assessment of myocardial viability in patients with stable coronary artery disease and left ventricular dysfunction. *Circulation.* 1998;98:2687–2694.
- Perrone-Filardi P, Pace L, Prastaro M, et al. Assessment of myocardial viability in patients with chronic coronary artery disease. Rest-4-hour-24-hour ^{201}Tl tomography versus dobutamine echocardiography. *Circulation.* 1996;94:2712–2719.
- Qureshi U, Nagueh SF, Afridi I, et al. Dobutamine echocardiography and quantitative rest-redistribution ^{201}Tl tomography in myocardial hibernation. Relation of contractile reserve to ^{201}Tl uptake and comparative prediction of recovery of function. *Circulation.* 1997;95:626–635.
- Bax JJ, Wijns W, Cornel JH, et al. Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left ventricular dysfunction due to chronic coronary artery disease: comparison of pooled data. *J Am Coll Cardiol.* 1997;30:1451–1460.
- Udelson JE, Coleman PS, Metherall J, et al. Predicting recovery of severe regional ventricular dysfunction. Comparison of resting scintigraphy with ^{201}Tl and $^{99\text{m}}\text{Tc}$ -sestamibi. *Circulation.* 1994;89:2552–2561.
- Matsunari I, Fujino S, Taki J, et al. Quantitative rest technetium-99m tetrofosmin imaging in predicting functional recovery after revascularization: comparison with rest-redistribution thallium-201. *J Am Coll Cardiol.* 1997;29:1226–1233.
- Pace L, Perrone-Filardi P, Storto G, et al. Prediction of improvement in global left ventricular function in patients with chronic coronary artery disease and impaired left ventricular function: rest thallium-201 SPET versus low-dose dobutamine echocardiography. *Eur J Nucl Med.* 2000;27:1740–1746.
- Rahimtoola SH. The hibernating myocardium. *Am Heart J.* 1989;117:211–221.
- Gerber BL, Vanovershelde JL, Bol A, et al. Myocardial blood flow, glucose uptake, and recruitment of inotropic reserve in chronic left ventricular ischemic dysfunction. Implications for the pathophysiology of chronic myocardial hibernation. *Circulation.* 1996;94:651–659.
- Bax JJ, Visser FC, Poldermans D, et al. Time course of functional recovery of stunned and hibernating segments after surgical revascularization. *Circulation.* 2001;104:I314–I318.
- Haas F, Augustin N, Holper K, et al. Time course and extent of improvement of dysfunctioning myocardium in patients with coronary artery disease and severely depressed left ventricular function after revascularization: correlation with positron emission tomographic findings. *J Am Coll Cardiol.* 2000;36:1927–1934.
- Sawada S, Elsner G, Segar DS, et al. Evaluation of patterns of perfusion and metabolism in dobutamine-responsive myocardium. *J Am Coll Cardiol.* 1997;29:55–61.
- Elsasser A, Schlepfer M, Klovekorn WP, et al. Hibernating myocardium: an incomplete adaptation to ischemia. *Circulation.* 1997;96:2920–2931.
- Zimmermann R, Mall G, Rauch B, et al. Residual ^{201}Tl activity in irreversible defects as a marker of myocardial viability: clinicopathological study. *Circulation.* 1995;91:1016–1021.
- Bax JJ, Poldermans D, Elhendy A, et al. Improvement of left ventricular ejection fraction, heart failure symptoms and prognosis after revascularization in patients with chronic coronary artery disease and viable myocardium detected by dobutamine stress echocardiography. *J Am Coll Cardiol.* 1999;34:163–169.
- Cuocolo A, Petretta M, Nicolai E, et al. Successful coronary revascularization improves prognosis in patients with previous myocardial infarction and evidence of viable myocardium at thallium-201 imaging. *Eur J Nucl Med.* 1998;25:60–68.
- Sciagra R, Bisi G, Santoro GM, et al. Comparison of baseline-nitrate technetium-99m sestamibi with rest-redistribution thallium-201 tomography in detecting viable hibernating myocardium and predicting postrevascularization recovery. *J Am Coll Cardiol.* 1997;30:384–391.
- Matsunari I, Boning G, Ziegler SI, et al. Attenuation-corrected $^{99\text{m}}\text{Tc}$ -tetrofosmin single-photon emission computed tomography in the detection of viable myocardium: comparison with positron emission tomography using ^{18}F -fluorodeoxyglucose. *J Am Coll Cardiol.* 1998;32:927–935.
- Stollfuss JC, Haas F, Matsunari I, et al. $^{99\text{m}}\text{Tc}$ -tetrofosmin SPECT for prediction of functional recovery defined by MRI in patients with severe left ventricular dysfunction: additional value of gated SPECT. *J Nucl Med.* 1999;40:1824–1831.
- Bax JJ, Cornel JH, Visser FC, et al. Prediction of improvement of contractile function in patients with ischemic ventricular dysfunction after revascularization by fluorine-18 fluorodeoxyglucose single-photon emission computed tomography. *J Am Coll Cardiol.* 1997;30:377–383.
- Yoshinaga K, Morita K, Yamada S, et al. Low-dose dobutamine electrocardiograph-gated myocardial SPECT for identifying viable myocardium: comparison with dobutamine stress echocardiography and PET. *J Nucl Med.* 2001;42:838–844.
- Kaul S, Senior R, Dittrich H, et al. Detection of coronary artery disease with myocardial contrast echocardiography: comparison with $^{99\text{m}}\text{Tc}$ -sestamibi single-photon emission computed tomography. *Circulation.* 1997;96:785–792.
- Takiuchi S, Ito H, Iwakura K, et al. Ultrasonic tissue characterization predicts myocardial viability in early stage of reperfused acute myocardial infarction. *Circulation.* 1998;97:356–362.
- Klein C, Nekolla SG, Bengel FM, et al. Assessment of myocardial viability with contrast-enhanced magnetic resonance imaging: comparison with positron emission tomography. *Circulation.* 2002;105:162–167.