Wanted: Dead or Alive
Assessment of Myocardial Viability After Thrombolysis
James D. Thomas, MD, and Eric J. Topol, MD

The time course of absolute myocardial ischemia is rapid. With the interruption of blood flow to the myocardium, aerobic metabolism ceases within 10 seconds, and soon even anaerobic metabolism is inhibited due to the accumulation of H⁺, lactate, and other metabolites. To preserve limited in situ stores of preformed high-energy phosphate, systolic contraction is markedly inhibited, generally ceasing within 10 to 15 seconds, but ATP is gradually depleted by the ongoing activity of membrane proteins. By 40 minutes of ischemia, membrane chemogadients can no longer be maintained, and the resulting influx of calcium and sodium causes cellular and subcellular edema, which, along with accumulation of toxic metabolites, leads to cell death. However, as critical as the issue of myocardial viability is, our ability to distinguish reversibly from irreversibly damaged tissue remains imperfect. Even with electron microscopy, the precise boundary of irreversibility is not obvious. Clinically, such complete coronary occlusion produces a wave front of necrotic tissue, beginning in the subendocardium within about 40 minutes and spreading outward, so that by 6 hours the maximal infarct size is achieved. However, the presence of even a small amount of perfusion to the infarct bed, from either antegrade or collateral flow, will significantly delay necrosis and limit infarct size. In general, the likelihood that myocardium downstream from a coronary occlusion will remain viable depends on many factors, including the duration of coronary occlusion, presence of collateral vessels, and timeliness and extent of reperfusion. Interpretation of the clinical results of myocardial reperfusion therapy often hinges on the definition of regional viability. It is of importance that previous studies have demonstrated how difficult accurate assessment of viability can be after thrombolytic therapy.

Stunning Versus Hibernation
Viable but nonfunctional myocardium is often separated conceptually into two types: “stunned” and “hibernating.” Hibernating myocardium is that which is so severely ischemic that normal systolic function is impos-

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Cardiology, Cleveland Clinic Foundation, Cleveland, Ohio.

Correspondence to Department of Cardiology/Desk F-15, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195 (Dr Thomas).

Results of the Current Study
In this issue of Circulation, Smart and colleagues have used dobutamine echocardiography in an attempt to define reversibly damaged myocardium in patients after thrombolytic therapy. From a potential population of 121 patients undergoing thrombolytic therapy at their hospital, 63 patients underwent echocardiographic examination during dobutamine infusion within 7 days of the index infarct. Studies were obtained at baseline, at extremely low-dose infusions of dobutamine (4 μg·kg⁻¹·min⁻¹) and at two higher doses (14 to 40 μg·kg⁻¹·min⁻¹), and the data were stored digitally, allowing simultaneous semiquantitative assessment of wall motion at varying dobutamine doses. These dobutamine echos were compared with wall motion obtained on a follow-up echo 4 or more weeks after the infarct.

Not surprisingly, the patients who had improved wall motion on the follow-up study were more likely to have had non-Q-wave infarctions with a low level of creatine kinase–MB leakage. In contrast, there was no significant
prediction of long-term recovery by a number of traditional indexes: the duration of chest pain before thrombolytic therapy; the signs of early reperfusion on clinical, electrocardiographic, or enzymatic grounds; or the status of the infarct related artery at early angiographic follow-up. The single best predictor of late improvement in regional wall motion in this study was the response of the infarct zone myocardium to the infusion of dobutamine. The presence of wall motion enhancement with low-dose dobutamine predicted with 86% certainty the recovery of function on the follow-up echo, whereas absence of improvement with low-dose dobutamine predicted with 90% certainty those patients whose wall motion would remain stable.

There are a number of intriguing points in the results of this study. For instance, more than half of the patients who responded to dobutamine at low dose showed a deterioration in wall motion at intermediate- and high-dose dobutamine, and all of these patients had more than 70% residual stenosis in the infarct-related vessel. The combination of enhancement at low-dose dobutamine infusion with deterioration at high dose, comprising 20% of the patients in the current study, thus identifies a patient population with clearly viable myocardium but with low threshold ischemia, for whom revascularization should be considered. Three other patients enhanced at low-dose dobutamine but showed no improvement at late follow-up. All had severe stenoses in their infarct-related vessel, and one may speculate that blood flow was so low that myocardial hibernation was present chronically.

**Study Limitations**

Despite the very encouraging results of this study, a few caveats are appropriate. First, it represents the experience of a single medical center with a relatively small number of patients. Also, the improvement of wall motion by echocardiography at 4-week follow-up was used as the gold standard for judging the predictive accuracy of the dobutamine echo, rather than an independent standard such as 18FDG positron emission tomography.

Furthermore, the changes in regional wall motion identified in this study were often quite subtle (hypokinetic tissue becoming more normal or akinetic tissue developing hypokinesis), requiring both sophisticated digital processing and highly expert interpretation. The authors of this study largely developed the field of stress echocardiography and have an enormous experience in the analysis of digital echocardiographic loops. They were quite meticulous in their assessment of interobserver and intraobserver variability to demonstrate the reliability of the echo readings, but even with this care, there was some disagreement in 5% to 10% of studies. It is unrealistic for the average echocardiographer to expect to achieve these results, unless he or she has the discipline to ensure accurate interpretation of regional wall motion.

Another difficulty with this technique is the extremely fleeting nature of the improved wall motion in some patients. That wall motion frequently degrades after initial improvement makes detection of the initial improvement all the more uncertain, especially with the semiquantitative categorical grading system used in most echocardiographic analyses.

Finally, one must acknowledge the difficulty of obtaining echocardiograms of diagnostic quality in the intensive care setting. In the current study, 6% of patients were excluded for technically inadequate images, a number that would surely increase among technicians and echocardiographers with less experience than the authors of this study.

**Possible Enhancements to Dobutamine Echocardiography**

Acknowledging these limitations, one may imagine several enhancements to the technique of dobutamine echocardiography that would improve its diagnostic accuracy and ease of interpretation. First, transesophageal echocardiography provides high-quality images in virtually all patients studied and has been used in conjunction with inotropic stimulation to predict successful withdrawal from mechanical ventricular assistance. Although one would never use transesophageal echocardiography if transthoracic images were of diagnostic quality, the availability of this approach, especially in patients who are intubated, might significantly increase the yield of the examination.

Second, instead of the semiquantitative categorical scoring used in this study to grade left ventricular wall motion, a continuous variable of global and regional function might allow detection of more subtle improvements in regional wall motion as well as facilitate the use of a continuously escalating dose of dobutamine so that idiosyncratic improvements in function at non-standard doses might be detected. Recently, automatic boundary detection of endocardial borders has been possible, with beat-by-beat calculation of systolic and diastolic volumes. This has shown good correlation with other measures of global ventricular function, but the utility of this approach in assessing regional wall motion has not been demonstrated.

Another possible variable to follow is the cyclical variation in the integrated ultrasonic backscatter from the myocardium. This technique is based on the quantification of the ultrasonic power scattered by the myocardium. Returning echo signals are digitized in the radiofrequency range and integrated over approximately 3-μs intervals (corresponding to about 2-mm samples in the myocardium) and the integrated power displayed as a two-dimensional image, similar to a standard echocardiogram. The intensity of this signal falls significantly during systole, presumably due to the wider separation of the fundamental scattering elements. There typically is a 6 dB (fourfold) variation in integrated backscatter throughout the cardiac cycle, a normal variability that is largely lost in ischemic and infarcted tissue. Although the reduction in cyclic backscatter relates predominantly to the loss of wall thickening, there some data to suggest that cyclic backscatter changes may return earlier than visible wall thickening, perhaps reflecting patchy return of systolic function within the myocardium. If borne out, such an approach could provide a more objective method to quantifying the improvement in wall motion under infusion of dobutamine.

**Clinical Implications**

Dobutamine echocardiography has thus emerged as one of several functional tests available to assess the
results of thrombolytic therapy. These include exercise treadmill testing, radionuclide perfusion imaging with $^{201}$TI or $^{99m}$Tc-Sestamibi, and metabolic imaging with $^{18}$FDG positron emission tomography, usually with pharmacological vasodilation by dipyridamole or adenosine. Factors that should be considered in selecting a particular test include the precise clinical question being asked, the local expertise in functional testing at a particular medical center, and the cost to benefit trade-off. For example, in many patients the critical issue is whether the infarct vessel residual stenosis is associated with provokable ischemia, for which stress testing (exercise or pharmacological) coupled or not with perfusion (eg, thallium) or functional (eg, echocardiographic) imaging is most appropriate. In other circumstances, it may be most important to assess myocardial salvage with thrombolyis. This may be accomplished with $^{99m}$Tc-Sestamibi imaging, a perfusion marker that does not redistribute; injected before thrombolysis, it outlines the threatened infarct zone, which can then be compared with subsequent injections after reperfusion. In still other patients, particularly those with compromised ventricular function, the more pressing question is viability of hypofunctional myocardium, best assessed with positron emission tomography scanning or low-dose dobutamine echocardiography. It should be recognized that neither approach will make the important distinction between stunning and hibernation; demonstrating hibernation has therapeutic implications, whereas the presence of stunned myocardium primarily has prognostic implications for spontaneous recovery.

To date, dobutamine echocardiography has been prospectively compared with positron emission tomography metabolic and perfusion imaging in only a limited way. However, if findings are found to be generally concordant, dobutamine echocardiography clearly would be a more cost-effective approach to the assessment of viability, costing less than half of a comprehensive positron scan. In considering these sophisticated imaging techniques, however, one must be careful not to neglect highly predictive data available clinically on all infarction patients. For example, findings from the current study coupled with a previous one with scintigraphic evaluation underscore the value of the peak creatine phosphokinase-MB for a rapid, economical, and seemingly precise method for estimating provokable ischemia and viability. Comparing the different techniques for objective assessment of viability clearly will be an important direction for future investigation. In the meantime, the combination of pharmacological inotropic stimulation and quantitative echocardiography provides a promising strategy for use in selected patients after reperfusion therapy.

References

Key Words • Editorials • thrombosis
Wanted: dead or alive. Assessment of myocardial viability after thrombolysis.

J D Thomas and E J Topol

Circulation, 1993;88:797-799
doi: 10.1161/01.CIR.88.2.797

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/88/2/797.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/