Myocardial hibernation: a noninvasive physician's point of view

Robert O. Bonow

Division of Cardiology, Northwestern University Medical School, Chicago, IL, USA

Key words:
Coronary artery disease; Heart failure; Left ventricular insufficiency; Myocardial ischemia.

In a large subset of patients with coronary artery disease and left ventricular (LV) dysfunction, LV performance is reduced on the basis of regionally ischemic or hibernating myocardium rather than irreversibly infarcted myocardium. The detection of reversibly dysfunctional myocardium is clinically relevant, as regional and global LV function in such patients may improve substantially after revascularization. Noninvasive imaging methods to assess myocardial metabolic activity, membrane integrity, and inotropic reserve are ideally suited for this assessment. Among these are the unique potential of nuclear cardiology techniques to distinguish viable regions on the basis of perfusion, cell membrane integrity, and metabolic activity and the ability of dobutamine echocardiography to assess regional inotropic reserve. Contrast-enhanced magnetic resonance imaging has also emerged as important method for viability assessment. Patients with LV dysfunction and extensive regions of hibernating myocardium appear to have the potential not only for improved left ventricular function after revascularization, but also for improved symptoms and improved survival. Thus, assessing myocardial viability may provide important information regarding the selection of patients with LV dysfunction for myocardial revascularization procedures.

(Ital Heart J 2002; 3 (5): 285-290)

Address:

Robert O. Bonow, MD

Division of Cardiology
Northwestern University
Medical School
201 East Huron Street
Suite 10-240
Chicago, IL 60611
USA
E-mail: r-bonow@
northwestern.edu

The incidence and clinical significance of left ventricular (LV) dysfunction have increased dramatically in the past several decades. Coronary artery disease (CAD) is in large part responsible for the rise in morbidity and mortality related to LV dysfunction, as CAD is now the leading cause of impaired LV function and heart failure in the developed countries of the world[1]. Moreover, the mortality rate of patients with LV dysfunction caused by CAD is significantly greater than that of patients with LV dysfunction stemming from non-ischemic etiologies[2,3].

Conversely, patients with CAD and LV dysfunction have significantly greater mortality rates compared to patients with preserved LV function, as LV function remains among the most important determinants of long-term prognosis in patients with ischemic heart disease[4-7]. Thus, among patients with LV dysfunction, those with CAD have the worst outcome, and among patients with CAD, those with LV dysfunction have the worse outcome.

This has important diagnostic and therapeutic implications. First, it is critically important to identify those patients with symptomatic heart failure (as well as those with asymptomatic LV dysfunction) who have CAD, as these patients require aggressive secondary prevention strategies[8]. In addition, a large subset of patients with CAD and LV dysfunction should be considered candidates for myocardial revascularization procedures. These procedures are associated with high periprocedural morbidity and mortality in patients with LV dysfunction, many of whom have already undergone a previous bypass operation. However, this is the same population that ultimately may benefit the most from revascularization.

Proper selection of patients for revascularization includes selection of those with the potential for clinical improvement or survival benefit in whom the risks of revascularization procedures are justified. Thus, diagnostic testing has a role to identify those patients with LV dysfunction who have underlying CAD, and also to identify those with established CAD who are suitable candidates for myocardial revascularization.

The role of noninvasive testing to identify the presence and magnitude of inducible myocardial ischemia is well established, as patients with LV dysfunction and inducible ischemia (especially in the setting of multivessel CAD) clearly represent a high risk group in whom survival and quality of life is enhanced by revascularization. During the

past decade, noninvasive imaging to determine the presence and magnitude of dysfunctional but viable myocardium has also become an important component of the evaluation of patients with depressed LV function. It is now apparent that LV dysfunction stemming from CAD is not always an irreversible process related to previous myocardial infarction, as LV function may improve substantially in many patients, and may even normalize, after myocardial revascularization[9-15] The percentage of patients with LV dysfunction who manifest a substantial improvement in LV function after myocardial revascularization varies among reported series, related in part to patient selection factors and adequacy of the myocardial revascularization procedures. This percentage, however, is not inconsequential as it has been estimated that 25 to 40% of patients with chronic CAD and LV dysfunction undergoing revascularization have the potential for significant improvement in LV function[15-19]. The available evidence indicates that this improvement in LV function also translates into improved survival[20-26], although this concept has not yet been tested prospectively in a randomized clinical trial.

Myocardial hibernation versus repetitive myocardial stunning

The mechanism for the improvement in LV systolic function following successful revascularization remains a matter of debate, as the underlying processes responsible for reversible contractile dysfunction are often difficult to ascertain in patients, and the development of animal models of chronic reversible dysfunction has been disappointing to date. Restoration of blood flow to chronically underperfused myocardium may be lead to the functional recovery of hibernating myocardium[9-12], whereas revascularization of myocardium with adequate perfusion at rest but with recurrent ischemic episodes during stress may successfully reverse persistent contractile dysfunction caused by repetitive stunning[27-32].

It has been argued on one extreme that myocardial hibernation simply does not occur and that the clinical scenario of chronic ischemic reversible contractile dysfunction is caused solely by repetitive stunning[31,32]. Arguments raised in favor of this hypothesis are, first, the inability to reproduce the clinical situation adequately with experimental animal models and, second, the suggestion that resting regional blood flow is in the normal range in most patients in whom regional function improves after revascularization. The first argument may be countered by the observation that animal models of hibernation have not been successful because the underlying disease responsible for hibernation, namely chronic diffuse atherosclerotic disease with concomitant diffuse endothelial dysfunction, does not occur in animals and has not been reproduced in the laboratory. The second argument may be countered by the overwhelming evidence that resting regional myocardial blood flow is *not* normal in the majority of patients with reversible contractile dysfunction reported in the majority of studies, and only a few studies have reported normal blood flow in dysfunctional myocardial territories[33]. Moreover, in the patients in whom blood flow was reported in the normal range, the blood flow in the dysfunctional myocardial territories was significantly reduced relative to the flow in the normally contracting territories of the same patients[33]. Finally, numerous studies using positron emission tomography (PET) and single photon emission computed tomography (SPECT) have provided convincing evidence of reduced regional perfusion in patients with LV dysfunction in whom perfusion improves or normalizes after revascularization.

The terms "hibernation" and "stunning" represent uniquely different pathophysiologic processes with distinct definitions, but in clinical circumstances the boundaries between stunning and hibernation are often indistinct. It is likely that both hibernation and repetitive stunning do occur clinically and contribute to ischemic LV dysfunction. Moreover, it is likely that both processes occur in the same patient and even coexist in the same myocardial region. Given the critical balance between reduced perfusion, reduced function, and reduced coronary flow reserve in the hibernating myocardium, some myocardial regions that are hibernating at rest may develop ischemia during exercise with a subsequent process of postischemic stunning superimposed on the baseline hibernating state.

Thus, the clarity with which chronic LV dysfunction can be defined as hibernation, repetitive stunning, or a combination of the two processes is limited. On the other hand, regardless of the definition, it is clear from multiple clinical series that there is an important subset of patients with chronic CAD, regional LV dysfunction, and reduced regional blood flow who manifest substantial improvement in myocardial perfusion and LV function after myocardial revascularization.

Role of noninvasive imaging

Several noninvasive imaging methods have evolved during the past decade to identify physiologic markers of myocardial viability in patients with regional and global contractile dysfunction[13,15,33-35]. These include principally PET imaging to assess myocardial metabolic activity, SPECT imaging with thallium-201 or technetium-99m sestamibi to assess myocardial perfusion and membrane integrity, and dobutamine echocardiography to assess myocardial contractile reserve. In the absence of definitive trials comparing all three methods in a large series of patients undergoing revascularization, uncertainties persist regarding the relative accuracies of each method in predicting recovery of LV function and regarding whether some patient subsets are better evaluated by a particular test. However, the

rapidly expanding literature that has evolved in the past decade has helped to clarify the role of these methods in identifying viable myocardium and in selecting patients with LV dysfunction for revascularization.

In the 1980's, at a time when the limitations of standard planar thallium imaging and two-dimensional echocardiography for viability assessment were quite apparent, PET became established as an exceptional method for demonstrating viable myocardium in patients with impaired LV function, by demonstrating preserved metabolic activity in regions with contractile dysfunction[36-40]. Using ^{18}F-fluorodeoxyglucose as a marker of myocardial glucose utilization in dysfunctional myocardium, PET achieved positive and negative diagnostic accuracies in the range of 85% for predicating recovery of regional function after revascularization, and PET imaging achieved a position as the noninvasive gold standard for viability assessment.

However, access to PET technology and radiotracers remained limited in the 1990's, and during that decade modifications in myocardial perfusion imaging and echocardiographic techniques achieved results that approached the predictive accuracies of PET. SPECT imaging emerged as a method in which localization and quantification of perfusion defects was enhanced compared to planar imaging, and viability-specific imaging protocols resulted in improved detection of dysfunctional but viable myocardium. These protocols include stress-redistribution-reinjection and rest-redistribution imaging with thallium-201[41-44] and rest imaging with technetium-99m sestamibi[44-49], particularly with nitrate enhancement[49-54]. Similarly, low-dose dobutamine stress echocardiography has emerged as a method to elicit inotropic reserve, which is a characteristic feature of myocardium that is stunned and/or hibernating, with excellent clinical results[55-59]. The cumulative evidence suggests that SPECT protocols have higher sensitivity but lower specificity than echocardiography in predicting recovery of function, whereas the demonstration of contractile reserve by dobutamine echocardiography is highly specific in predicting recovery of function after revascularization[15,60]. In terms of enhanced survival after revascularization, SPECT and dobutamine echocardiography appear to have similar potential, with results that are roughly equivalent to those achieved with PET[20-26,61].

The emerging role of magnetic resonance imaging

In the past few years, viability-specific protocols have been developed for cardiac magnetic resonance imaging (MRI). These protocols have enormous potential and have generated tremendous excitement.

First, cardiac MRI provides enhanced image resolution, improved endocardial border delineation, and the potential for accurate quantitation of regional and global LV function. Thus, one would anticipate that cardiac MRI performed during low-dose dobutamine administration would identify dysfunctional myocardium with contractile reserve with an accuracy that is at least equivalent to that of echocardiography. The potential of dobutamine cardiac MRI has been demonstrated in a few small series[62-65], but the experience to date is too limited in patients with LV dysfunction in terms of predicting recovery of function or enhanced survival after revascularization to permit definitive comparisons with the large database that is now available for dobutamine echocardiography.

Second, contrast-enhanced MRI has emerged as a powerful tool for viability assessment. It has been well demonstrated that standard gadolinium-based MRI contrast agents have delayed washout and are retained in irreversibly damaged myocardium, whether acutely necrotic or chronically fibrotic, compared to viable myocardium[66,67]. Thus, late contrast enhancement is a means of identifying *nonviable* myocardium, with an excellent correlation with thallium-201 SPECT imaging and dobutamine echocardiography[68]. In addition, MRI provides improved spatial resolution that permits, for the first time, noninvasive delineation of the transmural extent of viable versus nonviable tissue and the identification of even small subendocardial infarcts that are undetected by SPECT or echocardiography[69,70]. It has been demonstrated that the transmural extent of contrast-enhanced myocardium in dysfunctional territories may be used to predict the likelihood of recovery of regional and global LV function after revascularization[71].

Perfusion imaging with cardiac MRI is currently limited to first pass imaging with gadolinium, an agent with rapid washout rates from normal myocardium and viable but ischemic myocardium. Nonetheless, modeling of contrast wash-in and wash-out rates may provide semiquantitative information regarding relative regional perfusion[72,73]. It is anticipated that the future development of specific MRI myocardial perfusion agents that are retained in the myocardium (like sestamibi) or exhibit delayed, differential wash-out (like thallium) will result in protocols that evaluate regional subendocardial ischemia.

Thus, MRI has the potential to assume a role in the comprehensive evaluation of regional function, contractile reserve, perfusion, and viability in patients with LV dysfunction. Whether these MRI protocols will achieve sufficient ease and efficiency for routine testing, with results that are as definitive, accurate, and cost-effective as the current and future SPECT and echocardiographic methods, will require extensive evaluation. In the interim, it is clear that the identification of viable myocardium will continue to play a pivotal role in clinical decision making in patients with LV dysfunction, and for the foreseeable future nuclear cardiology and echocardiographic techniques will continue to be called upon for evaluating the hibernating myocardium.

References

1. Gheorghiade M, Bonow RO. Heart failure in the United States: a manifestation of coronary artery disease. Circulation 1998; 97: 282-9.
2. Bart BA, Shaw LK, McCants CB Jr, et al. Clinical determinants of mortality in patients with angiographically diagnosed ischemic or nonischemic cardiomyopathy. J Am Coll Cardiol 1997; 30: 1002-8.
3. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000; 342: 1077-84.
4. Hammermeister KE, DeRouen TA, Dodge HT. Variables predictive of survival in patients with coronary disease: selection by univariate and multivariate analysis from the clinical, electrocardiographic, exercise, arteriographic, and quantitative angiographic evaluations. Circulation 1979; 59: 421-30.
5. Harris PJ, Harrel FE, Lee KL, et al. Survival in medically treated coronary artery disease. Circulation 1979; 60: 1259-69.
6. Mock MB, Ringqvist I, Fisher LD, et al. Survival of medically treated patients in the Coronary Artery Surgery Study (CASS) registry. Circulation 1982; 66: 562-8.
7. Emond M, Mock MB, Davis KB, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. Circulation 1994; 90: 2645-57.
8. Smith SC, Blair SN, Bonow RO, et al. AHA/ACC Scientific Statement: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation 2001; 104: 1577-9.
9. Rahimtoola SH. Coronary bypass surgery for chronic angina - 1981. A perspective. Circulation 1982; 65: 225-41.
10. Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for "hibernating" myocardium. J Am Coll Cardiol 1986; 8: 1467-70.
11. Rahimtoola SH. The hibernating myocardium. Am Heart J 1989; 117: 211-3.
12. Ross J Jr. Myocardial perfusion-contraction matching: implications for coronary artery disease and hibernation. Circulation 1991; 83: 1076-83.
13. Dilsizian V, Bonow RO. Current diagnostic techniques of assessing myocardial viability in hibernating and stunned myocardium. Circulation 1993; 87: 1-20.
14. Rahimtoola SH. From coronary artery disease to heart failure: role of the hibernating myocardium. Am J Cardiol 1995; 75: 16E-22E.
15. Bonow RO. Identification of viable myocardium. Circulation 1996; 94: 2674-80.
16. Rozanski A, Bernard D, Gray R, et al. Preoperative prediction of reversible myocardial asynergy by postexercise radionuclide ventriculography. N Engl J Med 1982; 307: 212-3.
17. Brundage BH, Massie BM, Botvinick EH. Improved regional ventricular function after successful surgical revascularization. J Am Coll Cardiol 1984; 3: 902-8.
18. Bonow RO. The hibernating myocardium: implications for management of congestive heart failure. Am J Cardiol 1995; 75: 17A-25A.
19. Elefteriades JA, Tolis G Jr, Levi E, et al. Coronary artery bypass grafting in severe left ventricular dysfunction: excellent survival with improved ejection fraction and functional state. J Am Coll Cardiol 1993; 22: 1411-7.
20. Eitzman D, Al-Aouar Z, Kanter HL, et al. Clinical outcome of patients with advanced coronary artery disease after viability studies with positron emission tomography. J Am Coll Cardiol 1992; 20: 559-65.
21. Di Carli MF, Davidson M, Little R, et al. Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction. Am J Cardiol 1994; 73: 527-33.
22. Gioia G, Powers J, Heo J, et al. Prognostic value of rest-redistribution tomographic thallium-201 imaging in ischemic cardiomyopathy. Am J Cardiol 1995; 75: 759-62.
23. 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: 60-8.
24. Afridi I, Grayburn P, Panza J, Oh JK, Zoghbi WA, Marwick TH. Myocardial viability during dobutamine echocardiography predicts survival in patients with coronary artery disease and severe left ventricular systolic dysfunction. J Am Coll Cardiol 1998; 32: 921-6.
25. Chaudhry FA, Tauke JT, Alessandrini RS, Vardi GM, Parker MA, Bonow RO. Prognostic implications of contractile reserve in patients with coronary artery disease and severe left ventricular dysfunction. J Am Coll Cardiol 1999; 34: 730-8.
26. Pagley PR, Beller GA, Watson DD, Gimple LW, Ragosta M. Improved outcome after coronary artery bypass surgery in patients with ischemic cardiomyopathy and residual myocardial viability. Circulation 1997; 95: 793-800.
27. Bolli R. Myocardial "stunning" in man. Circulation 1992; 86: 1671-91.
28. Vanoverschelde JLJ, Wijns W, Depre C, et al. Mechanisms of chronic regional postischemic dysfunction in humans: new insights from the study of noninfarcted collateral-dependent myocardium. Circulation 1993; 87: 1513-23.
29. Buxton DB. Dysfunction in collateral-dependent myocardium: hibernation or repetitive stunning? Circulation 1993; 87: 1756-8.
30. Gerber BL, Vanoverschelde JLJ, 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: 651-9.
31. Camici PG, Wijns W, Borgers M, et al. Pathophysiological mechanisms of chronic reversible left ventricular dysfunction due to coronary artery disease (hibernating myocardium). Circulation 1997; 96: 3205-14.
32. Wijns W, Vatner SF, Camici PG. Mechanisms of disease: hibernating myocardium. N Engl J Med 1998; 339: 173-81.
33. Bax JJ, Poldermans D, Alhendy A, Boersma E, Rahimtoola SH. Sensitivity, specificity, and predictive accuracy of various noninvasive tests for detecting hibernating myocardium. Curr Probl Cardiol 2000; 26: 141-88.
34. Hendel RC, Chaudhry FA, Bonow RO. Myocardial viability. Curr Probl Cardiol 1996; 21: 145-224.
35. Beller GA. Comparison of thallium-201 scintigraphy and low-dose dobutamine echocardiography for the noninvasive assessment of myocardial viability. Circulation 1996; 94: 2681-4.
36. Marshall RC, Tillisch JH, Phelps ME, et al. Identification and differentiation of resting myocardial ischemia and infarction in man with positron computed tomography, ^{18}F-labeled fluorodeoxyglucose and N-13 ammonia. Circulation 1983; 67: 766-78.
37. Tillisch JH, Brunken R, Marshall R, et al. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. N Engl J Med 1986; 314: 884-8.
38. Schelbert HR, Buxton D. Insights into coronary artery disease gained from metabolic imaging. Circulation 1988; 78: 496-505.

39. Tamaki N, Yonekura Y, Yamashita K, et al. Positron emission tomography using fluorine-18 deoxyglucose in evaluation of coronary artery bypass grafting. Am J Cardiol 1989; 64: 860-5.
40. Maddahi J, Schelbert H, Brunken R, Di Carli M. Role of thallium-201 and PET imaging in evaluation of myocardial viability and management of patients with coronary artery disease and left ventricular dysfunction. J Nucl Med 1994; 35: 707-15.
41. Dilsizian V, Rocco TP, Freedman NMT, Leon MB, Bonow RO. Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. N Engl J Med 1990; 323: 141-6.
42. Ragosta M, Beller GA, Watson DD, Kaul S, Gimple LW. Quantitative planar rest-redistribution 201Tl 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: 1630-41.
43. Dilsizian V, Perrone-Filardi P, Arrighi JA, et al. Concordance and discordance between stress-redistribution-reinjection and rest-redistribution thallium imaging for assessing viable myocardium. Circulation 1993; 88: 941-52.
44. Udelson JE, Coleman PS, Matherall JA, et al. Predicting recovery of severe regional ventricular dysfunction: comparison of resting scintigraphy with thallium-201 and technetium-99m sestamibi. Circulation 1994; 89: 2552-61.
45. Udelson JE. Can technetium 99m-labeled sestamibi track myocardial viability? J Nucl Cardiol 1994; 1: 571-5.
46. Medrano R, Lowry RW, Young JB, et al. Assessment of myocardial viability with 99mTc sestamibi in patients undergoing cardiac transplantation: a scintigraphic/pathological study. Circulation 1996; 94: 1010-7.
47. Maes AF, Borgers M, Flameng W, et al. Assessment of myocardial viability in chronic coronary artery disease using technetium-99m sestamibi SPECT: correlation with histologic and positron emission tomographic studies and functional follow-up. J Am Coll Cardiol 1997; 29: 62-8.
48. Dakik HA, Howell JF, Lawrie GM, et al. Assessment of myocardial viability with ^{99m}Tc-sestamibi tomography before coronary bypass graft surgery: correlation with histopathology and postoperative improvement in cardiac function. Circulation 1997; 96: 2892-8.
49. Schneider CA, Voth E, Gawlich S, et al. Significance of rest technetium-99m sestamibi imaging for the prediction of improvement of left ventricular dysfunction after Q wave myocardial infarction: importance of infarct location adjusted thresholds. J Am Coll Cardiol 1998; 32: 648-54.
50. Bisi G, Sciagra R, Santoro GM, Fazzani PF. Rest technetium-99m sestamibi in combination with short-term administration of nitrates: feasibility and reliability for prediction of postrevascularization outcome of asynergic territories. J Am Coll Cardiol 1994; 24: 1282-9.
51. Maurea S, Cuocolo A, Soricelli A, et al. Enhanced detection of viable myocardium by technetium-99m-MIBI imaging after nitrate administration in chronic coronary artery disease. J Nucl Med 1995; 36: 1945-52.
52. Bisi G, Sciagra R, Santoro GM, Rossi V, Fazzini PF. Technetium-99m-sestamibi imaging with nitrate infusion to detect hibernating myocardium and predict postrevascularization recovery. J Nucl Med 1995; 36: 1994-2000.
53. Galli M, Marcassa C, Imperato A, Campini R, Orrego PS, Giannuzzi P. Effects of nitroglycerin by technetium-99m sestamibi tomoscintigraphy on resting global myocardial hypoperfusion in stable patients with healed myocardial infarction. Am J Cardiol 1994; 74: 843-8.
54. 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: 384-91.
55. Arnese 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: 2748-52.
56. Haque T, Furukawa T, Takahashi M, Knioshita M. Identification of hibernating myocardium by dobutamine stress echocardiography: comparison with thallium-201 reinjection imaging. Am Heart J 1995; 130: 553-63.
57. Perrone-Filardi P, Pace L, Prastaro M, et al. Dobutamine echocardiography predicts improvement of hypoperfused dysfunctional myocardium after revascularization in patients with coronary artery disease. Circulation 1995; 91: 2556-65.
58. Vanoverschelde JJ, D'Hondt AM, Marwick T, et al. Head-to-head comparison of exercise-redistribution-reinjection thallium single-photon emission computed tomography and low dose dobutamine echocardiography for prediction of reversibility of chronic left ventricular ischemic dysfunction. J Am Coll Cardiol 1996; 28: 432-42.
59. Bax JJ, Cornel JH, Visser FC, et al. Prediction of recovery of regional ventricular dysfunction following revascularization: comparison of F18-fluorodeoxyglucose SPECT, thallium stress-reinjection SPECT and dobutamine echocardiography. J Am Coll Cardiol 1996; 28: 558-64.
60. Bax JJ, Wijns W, Cornel JH, Visser FC, Boersma E, Fioretti PM. Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left ventricular dysfunction due to coronary artery disase: comparison of pooled data. J Am Coll Cardiol 1997; 30: 1451-60.
61. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol 2002; 39: 1151-8.
62. Baer FM, Voth E, Schneider CA, Theissen P, Schicha H, Sechtem U. Comparison of low-dose gradient-echo magnetic resonance imaging and positron emission tomography with [18F]fluorodeoxyglucose in patients with chronic coronary artery disease: a functional and morphological approach to the detection of residual myocardial viability. Circulation 1995; 91: 1006-15.
63. Baer FM, Theissen P, Schneider CA, et al. Dobutamine magnetic resonance imaging predicts contractile recovery of chronically dysfunction myocardium after successful revascularization. J Am Coll Cardiol 1998; 31: 1040-8.
64. Nagel E, Lehmkuhl HB, Bocksch W, et al. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. Circulation 1999; 99: 763-70.
65. Hundley WG, Hamilton CA, Thomas MS, et al. Utility of fast cine magnetic resonance imaging and display for the detection of myocardial ischemia in patients not well suited for second harmonic stress echocardiography. Circulation 1999; 100: 1697-702.
66. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999; 100: 1992-2002.
67. Hillenbrand HB, Kim RJ, Parker MA, Fieno DS, Judd RM. Early assessment of myocardial salvage by contrast enhanced magnetic resonance imaging. Circulation 2000; 102: 1678-83.

68. 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: 2687-94.
69. Wu E, Judd RM, Vargas JD, Klocke FJ, Bonow RO, Kim RJ. Visualization of the presence, location, and transmural extent of healed Q-wave and non-Q-wave myocardial infarction. Lancet 2001; 357: 21-8.
70. Ricciardi MJ, Wu E, Davidson CJ, et al. Visualization of discrete microinfarction following percutaneous coronary intervention associated with mild CK-MB elevation. Circulation 2001; 103: 2780-83.
71. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000; 343: 1445-53.
72. Lauerma K, Virtanen KS, Sipilä LM, Hekali P, Aronen HJ. Multislice MRI in assessment of myocardial perfusion in patients with single vessel proximal left anterior descending coronary artery disease before and after revascularization. Circulation 1997; 96: 2859-67.
73. Al-Saadi N, Nagel E, Gross M, et al. Noninvasive detection of myocardial ischemia from perfusion reserve based on cardiovascular magnetic resonance. Circulation 2000; 101: 1379-83.