The Additive Value of Combined Assessment of Myocardial Perfusion and Ventricular Function Studies*

Trip J. Meine, MD[1]; Michael W. Hanson, MD[1,2]; and Salvador Borges-Neto, MD[1,2]

[1]Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina; and [2]Division of Nuclear Medicine, Department of Radiology, Duke University Medical Center, Durham, North Carolina

In addition to providing quantitative ventricular function information, gated SPECT and radionuclide angiocardiographic studies can evaluate regional wall motion and ventricular volumes. This review focuses on the combined assessment of myocardial perfusion and left ventricular function. Two clear roles for nuclear imaging in clinical practice include the diagnosis of coronary artery disease and assessment of prognosis in patients with known coronary artery disease. Ventricular function information can help differentiate an attenuation artifact from an infarct and is helpful in diagnosing 3-vessel coronary disease. Additionally, several studies have highlighted the prognostic benefit to combined assessment of myocardial perfusion and ventricular function. Several new modalities have recently been reported that promise to continue to solidify the place of nuclear imaging in the diagnosis and prognosis of coronary artery disease.

Key Words: clinical cardiology; SPECT; myocardial perfusion; nuclear cardiology; ventricular function

J Nucl Med 2004; 45:1721–1724

Early cardiac nuclear imaging studies were hampered by an inability to integrate myocardial perfusion imaging with studies of ventricular function. Though myocardial perfusion imaging (*1*) and radionuclide cineangiography (*2*) have been possible since the 1970s, it was not until the subsequent decade that the 2 modalities were used simultaneously (*3*). Since those early reports, other investigators have successfully related the results of using electrocardiogram-gated images to evaluate left ventricular function by comparing their findings with equilibrium-gated blood pool measurements (*4*), conventional radionuclide measurements (*5*), and echocardiographic ejection fraction assessments (*6–8*).

This review focuses on the combined assessment of myocardial perfusion imaging and left ventricular function. Two clear roles for nuclear imaging in clinical practice include the diagnosis of coronary artery disease (CAD) and assessment of prognosis in patients with known CAD. Combined nuclear imaging can play a role in both these areas, and in fact, the addition of left ventricular function data to myocardial perfusion imaging can enhance the clinician's ability to both diagnose CAD and assess prognosis.

DIAGNOSIS

Assessment of ventricular function has long been recognized as a sensitive means by which to diagnose the presence of CAD, as shown in early studies of first-pass radionuclide angiocardiography (*9,10*). More recently, studies have evaluated the diagnostic benefit of adding ventricular function information to myocardial perfusion imaging. Borges-Neto et al. studied 167 patients with suspected CAD who underwent myocardial perfusion imaging, radionuclide angiocardiography, and cardiac catheterization. They found that combined nuclear perfusion and functional studies contributed 31% of the diagnostic information beyond that provided by clinical and electrocardiographic data alone when evaluating for the presence of severe CAD; that is, functional studies had an incremental value of 16% and myocardial perfusion imaging provided an additional value of 15% above functional studies (*11*). Other studies have confirmed the benefit of ventricular function assessment. Flamen et al. evaluated 52 patients undergoing cardiac catheterization after a recent myocardial infarction. All received perfusion imaging as well as first-pass radionuclide angiocardiography. The authors found that ejection fraction, wall motion score, and myocardial perfusion score were all associated with the presence of severe CAD. However, on multivariate analysis, only wall motion score was an independent predictor of severe CAD (*12*). Similarly, an evaluation of 70 patients undergoing exercise treadmill as well as myocardial perfusion imaging and radionuclide angiocardiography found that stepwise addition of scintigraphic data—perfusion followed by ejection fraction—to the tread-

Received Feb. 3, 2004; revision accepted Jul. 1, 2004.
For correspondence or reprints contact: Salvador Borges-Neto, MD, Duke University Medical Center, Box 3949, Durham, NC 27710.
E-mail: borge001@mc.duke.edu
*NOTE: FOR CE CREDIT, YOU CAN ACCESS THIS ACTIVITY THROUGH THE SNM WEB SITE (http://www.snm.org/ce_online) THROUGH OCTOBER 2005.

mill score provided significant incremental value in predicting the extent of CAD (*13*).

The benefit of ventricular function information is not limited to first-pass radionuclide angiocardiography. An evaluation of 99 patients with suspected CAD who were undergoing gated SPECT in addition to myocardial perfusion imaging found that postexercise wall motion abnormalities added significant incremental value over stress myocardium perfusion alone for the identification of severe CAD in patients with normal resting myocardial perfusion findings. The sensitivity for identifying severe CAD by wall motion abnormality was 78%, versus 49% for myocardial perfusion imaging ($P < 0.0001$), and specificity was not significantly different. The authors suggested that decreases in subendocardial blood flow, as might be seen in severe CAD, could result in severe impairment of myocardial function without causing an observable perfusion defect (*14*).

Much of the benefit of the addition of ventricular function data to myocardial perfusion imaging may relate to the ability of gated SPECT and radionuclide angiocardiography to help differentiate attenuation from infarct. This finding was confirmed by DePuey et al., who performed myocardial perfusion imaging and gated SPECT on 551 patients. Thirty-three percent of these patients had isolated fixed defects on myocardial perfusion imaging. By using gated SPECT to evaluate these areas of decreased perfusion, the percentage of patients with "unexplained fixed defects," that is, no clinical myocardial infarction, was decreased from 14% to 3%. About half of these unexplained defects were anterior abnormalities in women, which were believed to be related to breast attenuation. The authors thus concluded that gated SPECT could potentially improve specificity (*15*). Another evaluation of 285 patients undergoing gated SPECT found that the addition of ventricular function information to myocardial perfusion data decreased the number of "borderline" interpretations from 89 to 29 (*16*). Similarly, Taillefer et al. studied 115 with known coronary anatomy. They performed thallium myocardial perfusion imaging as well as gated SPECT and found that specificity for coronary stenoses improved by greater than 50%, from 86% to 94%, and that specificity for stenoses improved by greater than 70%, from 84% to 92% (*17*).

Another potential use of this additional technology is in identifying patients with multivessel CAD who might otherwise be missed by myocardial perfusion imaging. A recent study attempted to evaluate this question. Yamagishi et al. found that the sensitivity for detecting multivessel CAD was increased (from 26.9% to 43.4%, $P < 0.05$) by the addition of ejection fraction by gated SPECT to myocardial perfusion imaging. The authors concluded that the worsening of ventricular function by exercise had the potential to increase the sensitivity of patients with multivessel CAD among those without multivessel patterns of reversible defects (*18*).

Thus, the diagnostic benefits of nuclear modalities that determine ventricular function cannot be overstated. These benefits encompass enhanced sensitivity and specificity for significant coronary artery stenoses. Furthermore, the addition of ventricular function information to myocardial perfusion imaging can aid in the interpretation of clinically complex studies, such as those involving multivessel disease and attenuation artifacts.

PROGNOSIS

An equally, if not more, useful role for the adjunctive use of myocardial perfusion and ventricular function studies is in determining cardiac prognosis. The prognostic value of SPECT alone has long been recognized. Machecourt et al. evaluated the prognostic information gleaned from SPECT myocardial perfusion imaging and found that cardiovascular survival was related to the number of perfusion abnormalities present, with a cumulative 32-mo survival of 83% in patients with 4 or more abnormal cardiac segments (*19*). Similarly, another group of investigators found that the extent of reversible defects on SPECT added information to clinical and catheterization data (*20*). Hachamovitch et al. studied 2,200 patients without known CAD and found that SPECT added prognostically even after clinical and exercise variables had been utilized (*21*).

As with myocardial perfusion imaging, ventricular function assessment has been found—in numerous studies of both radionuclide angiocardiography and gated SPECT—to provide prognostic value. Several early studies provided evidence that evaluation of left ventricular function, specifically by radionuclide angiocardiography, adds significantly to the prognostic value of clinical variables. Pryor et al. at Duke University followed 386 patients for up to 4.5 y. The investigators examined 6 variables, including rest and exercise ejection fraction by radionuclide angiocardiography, change in ejection fraction with exercise, left ventricular wall motion abnormalities, and exercise time and found that exercise ejection fraction was the variable most associated with future cardiac events ($P < 0.01$) (*22*).

Later studies continued to evince the predictive benefits of radionuclide angiocardiography over clinical variables. The Duke group studied 571 patients with symptomatic CAD and followed them for a median of 5.4 y. The investigators found that the most important radionuclide angiocardiography predictor of mortality was the exercise ejection fraction ($P < 0.00001$) and that, when compared with noninvasive clinical data, radionuclide angiocardiography variables were more predictive of mortality. In fact, the strength of the relationship of the radionuclide angiocardiography variables to mortality was equivalent to a set of cardiac catheterization variables studied (*23*). A year later, these authors published a further study of 2,042 patients with CAD, examining the relationship of clinical and radionuclide angiocardiography variables to cardiac mortality. They again found that exercise ejection fraction by radionuclide angiocardiography was the single most important predictor of cardiac death (*24*). The results of the 2 previous studies were confirmed in 1998, when the Duke investigators found, in a study of 863 patients with CAD, that radionuclide angiocardiography was a key predictor of cardiac death when compared with both clinical and catheterization data (*25*).

Recently, other investigators have examined the ability of radionuclide angiocardiography to add information to myocardial perfusion imaging. Mast et al. studied 240 patients undergoing pharmacologic perfusion studies with adjunctive first-pass radionuclide angiocardiography and found that clinical information, myocardial perfusion data, and radionuclide angiocardiography ejection fraction were all significant predictors of the combined endpoint of death and myocardial infarction. Interestingly, though, they found that the addition of radionuclide angiocardiography ejection fraction to myocardial perfusion imaging data and clinical information added incremental prognostic value but that when the ejection fraction was added first, myocardial perfusion imaging had no incremental prognostic value (*26*). The predictive power of ejection fraction as determined by radionuclide angiocardiography was also evaluated by Heiba et al., who studied 101 patients undergoing vascular surgery. They found that extent of both ischemic myocardium on perfusion imaging and left ventricular ejection fraction on radionuclide angiocardiography had independent and complementary power to predict cardiac events in this population (*27*).

The prognostic information gleaned from radionuclide angiocardiography also is available from gated SPECT images. This has been confirmed in 2 separate studies from Cedars-Sinai Medical Center. In the first study, involving 1,680 patients, the authors found that both poststress ejection fraction and end-systolic volume, as determined by gated SPECT, were independent predictors of overall coronary events and provided incremental prognostic information over prescan clinical and myocardial perfusion data in predicting cardiac death and the combination of death and myocardial infarction. They concluded that an ejection fraction of less than 45% and an end-systolic volume of greater than 70 mL placed patients in a "high-risk" category (*28*). In a second study, the same research group evaluated 2,686 patients with myocardial perfusion imaging and gated SPECT. They found that, whereas the best predictor of nonfatal myocardial infarction was the amount of ischemia present on perfusion imaging, the most powerful predictor of cardiac death was poststress ejection fraction. By integrating the perfusion data with the poststress ejection fraction, they were able to separate patients into tertiles of risk (*29*).

Finally, it is important to note that valuable prognostic data can be gleaned from negative scan findings as well. Berman et al. reported a 0.2% rate of myocardial infarction or cardiac death in 1,131 patients with normal or equivocal SPECT findings. Of interest, in patients with a high (>85%) prescan likelihood of CAD, the event rate was 0% (*30*).

Thus, the value of prognostic information gained from myocardial perfusion imaging and radionuclide evaluation of left ventricular ejection fraction cannot be overstated, as these data are additive to clinical, exercise, and even cardiac catheterization variables in predicting risk.

VIABILITY

Combined assessment of function and perfusion can also play a role in determining myocardial viability. Levine et al. performed rest gated SPECT before and after revascularization on 50 patients with CAD and found that the addition of ventricular function information to perfusion data alone increased the accuracy of the test from 85% to 91% (*31*). This same group also found that rest gated SPECT was equivalent to rest-redistribution thallium studies in the prediction of myocardial viability (*32*).

CONCLUSION

The role of myocardial perfusion imaging in the diagnosis of CAD and determination of its prognosis is irrefutable. However, perfusion imaging alone has several inherent drawbacks. In the diagnosis of CAD, perfusion imaging often suffers from suboptimal differentiation of infarct from soft tissue or diaphragmatic attenuation artifacts. Additionally, multivessel CAD, with its concomitant global decrease in perfusion, is a well-known Achilles' heel of nuclear imaging. The addition of ventricular function data—both overall ejection fraction and segmental wall motion—offers potential solutions to both of these vexing problems. At the same time, the data provided by radionuclide cineangiography or gated SPECT can greatly enhance the already additive prognostic information provided by myocardial perfusion imaging.

REFERENCES

1. Zaret BL, Strauss HW, Martin ND, Wells HP Jr, Flamm MD Jr. Noninvasive regional myocardial perfusion with radioactive potassium: study of patients at rest, with exercise and during angina pectoris. *N Engl J Med.* 1973;288:809–812.
2. Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE, Johnston GS. Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary-artery disease. *N Engl J Med.* 1977;296:839–844.
3. Narahara KA, Mena I, Maublant JC, Brizendine M, Criley JM. Simultaneous maximal exercise radionuclide angiography and thallium stress perfusion imaging. *Am J Cardiol.* 1984;53:812–817.
4. Nichols K, DePuey EG, Rozanski A. Automation of gated tomographic left ventricular ejection fraction. *J Nucl Cardiol.* 1996;3:475–482.
5. Germano G, Kiat H, Kavanagh PB, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med.* 1995;36:2138–2147.
6. Choragudi NL, Prakash AM, Sun Y, Prasad P, Chiaramida SA, Lucariello RJ. Comparison of echocardiography with technetium 99m-gated single photon emission computed tomography as diagnostic tools for left ventricular ejection fraction. *Echocardiography.* 2001;18:627–632.
7. Fleming RM. A tete-a-tete comparison of ejection fraction and regional wall motion abnormalities as measured by echocardiography and gated sestamibi SPECT. *Angiology.* 2002;53:313–321.
8. Nichols K, Lefkowitz D, Faber T, et al. Echocardiographic validation of gated SPECT ventricular function measurements. *J Nucl Med.* 2000;41:1308–1314.

9. Jengo JA, Oren V, Conant R, et al. Effects of maximal exercise stress on left ventricular function in patients with coronary artery disease using first pass radionuclide angiocardiography: a rapid, noninvasive technique for determining ejection fraction and segmental wall motion. *Circulation.* 1979;59:60–65.
10. Austin EH, Cobb FR, Coleman RE, Jones RH. Prospective evaluation of radionuclide angiocardiography for the diagnosis of coronary artery disease. *Am J Cardiol.* 1982;50:1212–1216.
11. Borges-Neto S, Shaw LJ, Kesler KL, et al. Prediction of severe coronary artery disease by combined rest and exercise radionuclide angiocardiography and tomographic perfusion imaging with technetium 99m-labeled sestamibi: a comparison with clinical and electrocardiographic data. *J Nucl Cardiol.* 1997;4:189–194.
12. Flamen P, Dendale P, Bossuyt A, Franken PR. Combined left ventricular wall motion and myocardial perfusion stress imaging in the initial assessment of patients with a recent uncomplicated myocardial infarction. *Angiology.* 1995;46:461–472.
13. Palmas W, Friedman JD, Diamond GA, Silber H, Kiat H, Berman DS. Incremental value of simultaneous assessment of myocardial function and perfusion with technetium-99m sestamibi for prediction of extent of coronary artery disease. *J Am Coll Cardiol.* 1995;25:1024–1031.
14. Sharir T, Bacher-Stier C, Dhar S, et al. Identification of severe and extensive coronary artery disease by postexercise regional wall motion abnormalities in Tc-99m sestamibi gated single-photon emission computed tomography. *Am J Cardiol.* 2000;86:1171–1175.
15. DePuey EG, Rozanski A. Using gated technetium-99m-sestamibi SPECT to characterize fixed myocardial defects as infarct or artifact. *J Nucl Med.* 1995;36:952–955.
16. Smanio PE, Watson DD, Segalla DL, Vinson EL, Smith WH, Beller GA. Value of gating of technetium-99m sestamibi single-photon emission computed tomographic imaging. *J Am Coll Cardiol.* 1997;30:1687–1692.
17. Taillefer R, DePuey EG, Udelson JE, Beller GA, Latour Y, Reeves F. Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. *J Am Coll Cardiol.* 1997;29:69–77.
18. Yamagishi H, Shirai N, Yoshiyama M, et al. Incremental value of left ventricular ejection fraction for detection of multivessel coronary artery disease in exercise: ^{201}Tl gated myocardial perfusion imaging. *J Nucl Med.* 2002;43:131–139.
19. Machecourt J, Longere P, Fagret D, et al. Prognostic value of thallium-201 single-photon emission computed tomographic myocardial perfusion imaging according to extent of myocardial defect: study in 1,926 patients with follow-up at 33 months. *J Am Coll Cardiol.* 1994;23:1096–1106.
20. Marie PY, Danchin N, Durand JF, et al. Long-term prediction of major ischemic events by exercise thallium-201 single-photon emission computed tomography: incremental prognostic value compared with clinical, exercise testing, catheterization and radionuclide angiographic data. *J Am Coll Cardiol.* 1995;26:879–886.
21. Hachamovitch R, Berman DS, Kiat H, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. *Circulation.* 1996;93:905–914.
22. Pryor DB, Harrell FE Jr, Lee KL, et al. Prognostic indicators from radionuclide angiography in medically treated patients with coronary artery disease. *Am J Cardiol.* 1984;53:18–22.
23. Lee KL, Pryor DB, Pieper KS, et al. Prognostic value of radionuclide angiography in medically treated patients with coronary artery disease: a comparison with clinical and catheterization variables. *Circulation.* 1990;82:1705–1717.
24. Jones RH, Johnson SH, Bigelow C, et al. Exercise radionuclide angiocardiography predicts cardiac death in patients with coronary artery disease. *Circulation.* 1991;84(3 suppl):I52–I58.
25. Shaw LJ, Heinle SK, Borges-Neto S, Kesler K, Coleman RE, Jones RH. Prognosis by measurements of left ventricular function during exercise. Duke Noninvasive Research Working Group. *J Nucl Med.* 1998;39:140–146.
26. Mast ST, Shaw LK, Ravizzini GC, et al. Incremental prognostic value of RNA ejection fraction measurements during pharmacologic stress testing: a comparison with clinical and perfusion variables. *J Nucl Med.* 2001;42:871–877.
27. Heiba SI, Jacobson AF, Shattuc S, Ferreira MJ, Sharma PN, Cerqueira MD. The additive values of left ventricular function and extent of myocardium at risk to dipyridamole perfusion imaging for optimal risk stratification prior to vascular surgery. *Nucl Med Commun.* 1999;20:887–894.
28. Sharir T, Germano G, Kavanagh PB, et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. *Circulation.* 1999;100:1035–1042.
29. Sharir T, Germano G, Kang X, et al. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: risk stratification by the amount of stress-induced ischemia and the poststress ejection fraction. *J Nucl Med.* 2001;42:831–837.
30. Berman DS, Hachamovitch R, Kiat H, et al. Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: a basis for optimal utilization of exercise technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography. *J Am Coll Cardiol.* 1995;26:639–647.
31. Levine MG, McGill CC, Ahlberg AW, et al. Functional assessment with electrocardiographic gated single-photon emission computed tomography improves the ability of technetium-99m sestamibi myocardial perfusion imaging to predict myocardial viability in patients undergoing revascularization. *Am J Cardiol.* 1999;83:1–5.
32. Duncan BH, Ahlberg AW, Levine MG, et al. Comparison of electrocardiographic-gated technetium-99m sestamibi single-photon emission computed tomographic imaging and rest-redistribution thallium-201 in the prediction of myocardial viability. *Am J Cardiol.* 2000;85:680–684.