The Role of Radionuclide Ventriculography in the Assessment of Prognosis in Patients with CAD

Steven C. Port

Cardiology Department, Mount Sinai Medical Center, Milwaukee, Wisconsin

One of the most important roles of cardiovascular nuclear medicine in evaluating patients with coronary artery disease (CAD) is predicting patient outcome. Measurements of ventricular function obtained by radionuclide ventriculography play a key role in defining a patient's prognosis. Because ventricular function correlates well with the total extent of myocardial ischemic burden, data derived from radionuclide ventriculography serve as valuable prognostic indicators. Radionuclide ventriculography provides noninvasive information that is comparable to contrast angiography for predicting subsequent cardiac events and mortality in patients with CAD.

Key Words: coronary artery disease; radionuclide ventriculography; prognosis

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One of the most important roles of cardiovascular nuclear medicine in evaluating patients with coronary artery disease (CAD) is defining prognosis. Determining a patient's risk for future cardiac events and/or death is of increasing importance in the current environment of medical economics. Measurements of ventricular function, obtained from radionuclide ventriculography, play a key role in defining a patient's prognosis.

Radionuclide ventriculography has been used to measure both left and right ventricular ejection fractions (LVEF and RVEF) at rest and during exercise. The change in ejection fraction (ΔEF) during exercise has been widely applied for diagnostic purposes. The relative importance of resting EF, exercise EF and ΔEF in assessing prognosis remains somewhat controversial.

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For correspondence or reprints contact: Steven C. Port, MD, Cardiology Department, Mount Sinai Medical Center, 950 North 12th St., Milwaukee, WI 53233.

VENTRICULAR DYSFUNCTION AT REST: A SIGNIFICANT RISK FACTOR

A review of the clinical trials designed to analyze the prognostic value of ventricular function begins in the 1970s when investigators at Duke University launched the largest single-center database project for the study of patients with CAD (*1*). Early results from the contrast angiographic portion of the database are summarized in Figure 1, which shows the mortality during a 7-yr follow-up of patients treated medically for chronic, stable, angiographically confirmed CAD. These data indicate that resting LVEF at the time of initial evaluation is highly predictive of subsequent outcome. There is a dramatic difference in outcome between patients with severe left ventricular dysfunction and those with normal left ventricular function.

The importance of resting LVEF was confirmed in the CASS study, a large multicenter trial comparing medical and surgical therapies for CAD (*2*). Figure 2 shows survival data in patients with chronic, stable CAD treated medically or surgically. The trial showed that resting LVEF was equally powerful prognostically in both medically and surgically treated patients.

The prognostic significance of resting LVEF was also substantiated in patients following myocardial infarction (MI) in the Multicenter Postinfarction Research Group database (*3*). In that study, the LVEF was measured prior to discharge from the hospital. Figure 3 shows 1-yr mortality after MI plotted against the predischarge resting LVEF. Of particular importance is that the relationship is not linear. Prognosis changes very little within the range of LVEFs from 45% to 65%; however, once LVEF drops below 40%, mortality increases exponentially. Interestingly, additional information about post-MI patients can be derived by incorporating the RVEF. The influence of RVEF on prognosis has generated recent attention, particularly in patients with inferior MI (*4,5*).

Figure 4 shows the prognostic significance of LVEF and RVEF obtained from resting gated radionuclide ventriculography in patients soon after acute MI (*5*). Nonsurvivors are clustered in the group with both low LVEF (<30%) and reduced RVEF (<40%). More recently, prognosis of pa-

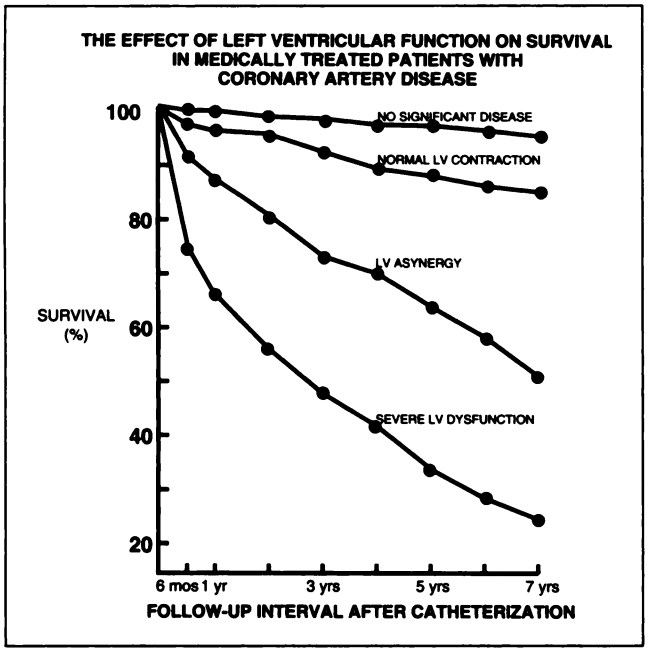

FIGURE 1. Survival during medical treatment of patients with CAD is plotted against the contrast angiographic LVEF at the time of initial evaluation. Note the marked difference in survival between patients with relatively normal systolic function and those with reduced systolic function.

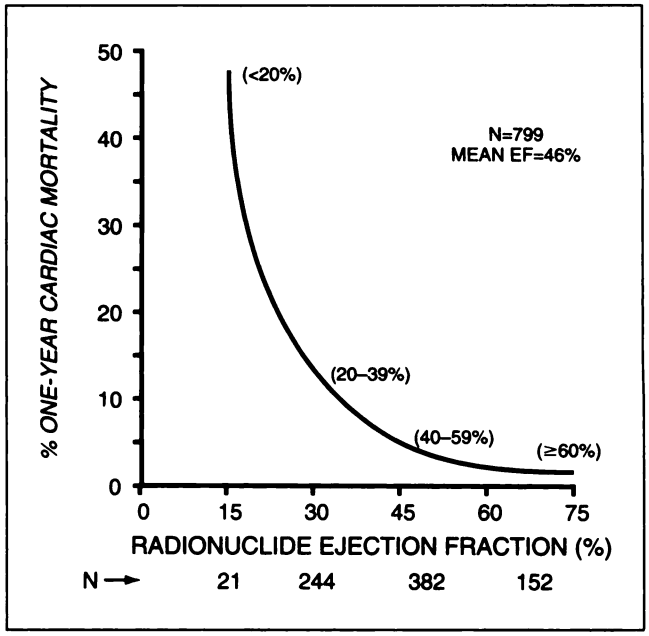

FIGURE 3. In the Multicenter Postinfarction Research Group trial, survival following acute MI was shown to be predicted by the LVEF measured prior to hospital discharge. Survival is plotted for four levels of ejection fraction. Reprinted with permission from the *New England Journal of Medicine* 1983;310:331–336.

tients with inferior MI accompanied by right ventricular infarction has been shown to be significantly worse than the prognosis in the absence of right ventricular infarction (*6*). Since LVEF and RVEF may change over time following an acute MI, the data in Figure 4 could change if these measurements were obtained some period of time after the acute event.

More recent multicenter trials, including the GISSI-2 trial (*7*), have studied the prognosis of patients following thrombolytic therapy. These studies show that, even in the thrombolytic era, resting left ventricular function, post-MI, remains an important prognostic indicator.

Figure 5 shows the relative risk of dying within 6 mo of randomization in the GISSI-2 trial. The most significant risk factor is the patient's inability to perform an exercise test. The second most important risk factor is left ventricular dysfunction, detected in this study by echocardiography. Evidence of ventricular dysfunction at rest increased

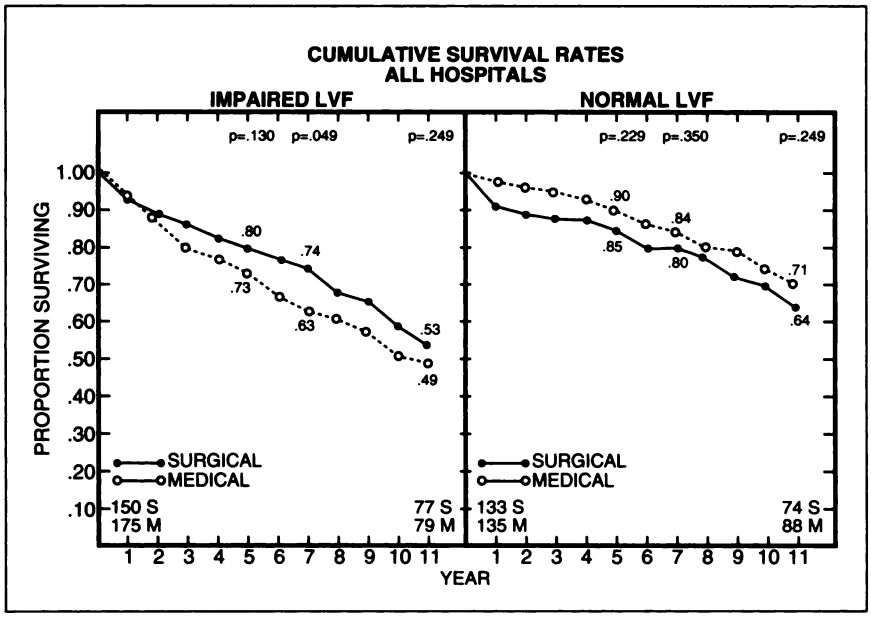

FIGURE 2. In the Coronary Artery Surgery Study, survival was influenced by the systolic function at the time of entry into the trial. Of note is the finding that the LVEF was equally predictive of subsequent survival in both medically and surgically treated patients. Reprinted with permission from the *New England Journal of Medicine* 1984;311: 1333–1339.

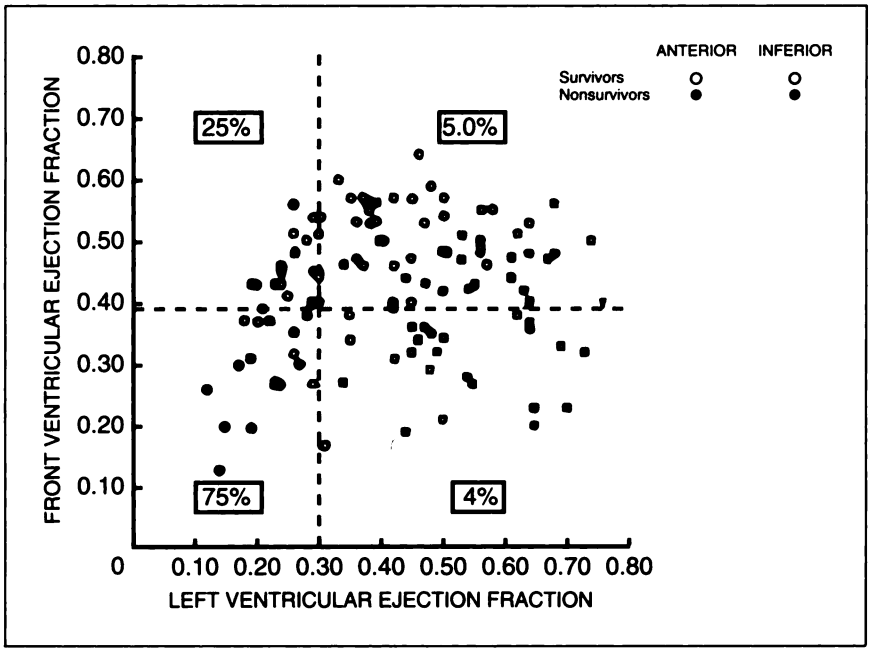

FIGURE 4. For post-MI patients, survival appears to be influenced by both LVEF and RVEF. The solid circles represent nonsurvivors and are clustered in the group of patients with reduced RVEF and LVEF. Reprinted with permission from the American College of Cardiology (*Journal of American Cardiology* 1986;58:387–393).

the relative risk of dying 2.5 times, even after thrombolytic therapy.

This trend appears in every clinical trial spanning the 1970s, 1980s and early 1990s that analyzed prognostic indicators in patients with CAD. Resting ventricular function is a potent predictor of outcome in these patients.

ROLE OF END-SYSTOLIC VOLUME

There may be an independent role for the measurement of end-systolic volume (ESV) in predicting outcome in patients with CAD. In an angiographic study by White et al. (*8*), patients were stratified into three categories of resting LVEF: >50%, 40% to 49%, and <40%. The data indicated that ESV, which varied widely among patients with similar LVEFs, could be used to further stratify patients into lower- and higher-risk groups for subsequent death. These investigators suggested that ESV may be useful to "fine-tune" the influence of LVEF on prognosis.

The major difficulty with ESV is that it is the least reliable measurement of ventricular function that can be made noninvasively; ESV is derived from LVEF and end-diastolic volume (EDV) and thus incorporates the errors of both of these measurements. Contrast angiographic measurement of ESV is subject to error since the mathematical assumptions about ventricular geometry are least applicable at end-systole, especially in the regionally infarcted ventricle. Those limitations may be the reasons that ESV has not emerged as a clinically practical predictor for CAD patients.

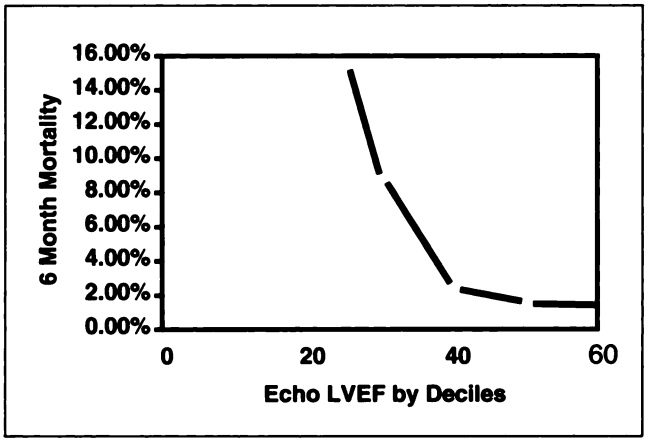

FIGURE 5. In the large GISSI-2 trial, 6-mo survival post-MI was shown to be related to LVEF, plotted here in deciles. Note the very similar shape of this curve to that in Figure 3, suggesting that this fundamental relation is maintained in the thrombolytic era. Reprinted with permission from the American Heart Association (*Circulation* 1993;88:416–429).

ROLE OF EXERCISE LEFT VENTRICULAR FUNCTION

Toward the end of the 1970s, the application of exercise radionuclide angiography for the assessment of left ventricular function became increasingly popular. As the exercise results were added to the large follow-up databases of patients with CAD, it became possible to evaluate the relative roles of resting LVEF, exercise LVEF and ΔLVEF in predicting outcome in CAD. In the first major publication on the subject, all three variables were univariate predictors of death and total cardiac events, but exercise LVEF proved to be the most powerful predictor and ΔLVEF was the least important (*1*). Perhaps of greater interest was the comparison of radionuclide variables to coronary arteriographic results. Taken alone, the number of diseased coronary vessels had previously been shown to be predictive of CAD outcome. As a univariate predictor of

TABLE 1
Coronary Artery Anatomy and Ventricular Function Data as Predictors of Outcome in Patients with CAD

Analysis	Outcome*	
	Survival	Total events
Anatomy alone	26.7 (<0.001)	19.1 (<0.001)
Adjusted for rest EF	11.6 (<0.001)	8.8 (0.003)
Adjusted for exercise EF	4.3 (0.04)	3.3 (0.07)

*Multivariate chi square and p values.
EF = ejection fraction.
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TABLE 2
Clinical, Catheterization and Radionuclide Data as Predictors of Outcome in Patients with CAD

Data	Outcome*	
	CV death	CV events
Clinical	71	48
Catheterization	102	64
Radionuclide	104	66
Clinical + radionuclide	120	78
Clinical + catheterization	124	82
Clinical + catheterization + radionuclide	138	93

*Total model chi square.
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outcome, the number of coronary arteries with ≥75% stenosis was very significant, with a chi square value of 27 (Table 1). However, when the value was adjusted for the resting radionuclide LVEF, the chi square dropped to 12; when it was adjusted for exercise LVEF, it dropped to 4, barely achieving significance (p = 0.04) for predicting death and was no longer significant for predicting other cardiac events.

TOTAL ISCHEMIC BURDEN

Why is ventricular function a stronger predictor of prognosis than the number of diseased vessels? The number of diseased vessels is a fairly simplistic way of describing the extent of CAD. It is usually assessed visually, not quantitatively. There is a large interobserver variability in the measurement, and it does not correlate with measured coronary flow reserve. A somewhat more sophisticated approach to the description of coronary anatomy is the Gensini score, which relates the location and severity of stenoses to the amount of myocardium supplied by the respective stenoses, and is more reflective of the total ischemic burden of the ventricle. Using such a score, Iskandrian et al. showed that exercise LVEF was linearly related to the coronary score (*9*). In this study, ΔLVEF showed no significant correlation with the coronary score.

INFLUENCE OF END-DIASTOLIC VOLUME AND HEART RATE

The group at Duke University has expanded its database to include more than 2,000 patients (*10*). The high number of hard endpoints, 90 deaths and 57 nonfatal MIs, establish statistical power in the data and serve as a benchmark for other databases. As shown in earlier work, the strongest radionuclide predictor of outcome is exercise LVEF. New findings were the statistical significance of resting EDV and the change in heart rate (ΔHR) during exercise. The latter was particularly interesting because for any given exercise LVEF, the outcome was better if the ΔHR during exercise was greater.

PREDICTING OUTCOME WITHOUT CATHETERIZATION

When all clinical variables such as age, sex, type of chest pain, previous MI, radiographic cardiomegaly, etc. are analyzed together with available catheterization and radionuclide ventriculographic data, multivariate analysis shows that the radionuclide results (exercise LVEF, resting EDV and ΔHR) have the same prognostic power as the catheterization data, and much more than clinical data (*10*). Furthermore, when the clinical data are added to the radionuclide data, almost all events are correctly predicted by the model (Table 2). These results form the basis of a rational approach to prognosis and therefore to patient management. The clinical and noninvasive data can act as a surrogate for the invasive data so that the decision to treat either medically or by myocardial revascularization could be made theoretically without cardiac catheterization.

ROLE OF ΔLVEF IN PREDICTING OUTCOME

Although no other available study meets the statistical power of the data described above, there are studies that suggest that ΔLVEF may be important prognostically in certain patient groups. Bonow et al. showed that in patients with triple-vessel CAD who were mildly symptomatic, ΔLVEF could be used to dichotomize patients into higher- and lower-risk groups (*11*). Early work by Corbett et al. suggested that ΔLVEF could be used to risk-stratify patients soon after MI (*12*). However, others have found that the exercise LVEF is more powerful in predicting post-MI outcome (*13*).

Preliminary work from Yale University suggests that ΔLVEF measured during mental stress could help stratify CAD patients into high- and low-risk groups for subsequent events (*14*). In preliminary work from other investigators, ΔLVEF ≤ −8% identified a group of stable CAD patients with a ninefold increase in event rate as compared with patients with an increasing LVEF (*15*). It is important

to recognize that all of these studies purporting to show the importance of ΔLVEF are fairly small and have very few hard endpoints for analysis. Furthermore, it is possible that the importance of ΔLVEF may depend upon resting LVEF: i.e., when studies include patients whose resting LVEF is more toward the normal range, then ΔLVEF may be most important; but when patients with low resting LVEFs or patients with all levels of LVEF are included, the exercise LVEF may be the most important variable.

RELATIONSHIP TO MYOCARDIAL PERFUSION IMAGING

To date, there are no large databases that can compare the prognostic information from radionuclide ventriculography to that of myocardial perfusion imaging. The availability of ^{99m}Tc-labeled perfusion agents, which permit measurement of exercise and resting LVEF as well as perfusion imaging, now makes such a comparison possible. Preliminary data from one laboratory suggests that at least one important prognostic variable from perfusion imaging, the lung uptake of the radionuclide, correlates with exercise LVEF (*16*). However, whether left ventricular function and myocardial perfusion results provide similar or unique prognostic information remains to be seen.

CONCLUSION

Radionuclide measurements of ventricular function provide important prognostic information in patients with CAD. Compared with angiography, radionuclide ventriculography provides comparable information noninvasively. Combined with clinical information, the radionuclide ventriculogram can be used to predict accurately future events in patients with stable CAD or recent MI. The relative value of radionuclide ventriculography versus myocardial perfusion imaging in the assessment of prognosis is currently under study.

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