Ejection Fraction by Radionuclide Ventriculography and Contrast Left Ventriculogram

A Tale of Two Techniques

PEDRO E. UREÑA, MD,* GERVASIO A. LAMAS, MD, GARY MITCHELL, MD,† GREG C. FLAKER, MD,‡ SIDNEY C. SMITH, JR., MD, CHD, DPHIL.§ FRANS J. WACKERS, MD,¶ PATRICIA MCEWAN, MD,¶ MARC A. PFEFFER, MD, PHD,† FOR THE SAVE INVESTIGATORS

Miami, Florida; Boston, Massachusetts; Columbia, Missouri; Chapel Hill, North Carolina; and New Haven, Connecticut

Objectives. We assessed the abilities of two methods to measure ejection fraction (EF)—radionuclide ventriculography (RVG) and contrast left ventriculography (Cath-EFa) to predict cardiovascular events.

Background. Both RVG and Cath-EFa are commonly used methods to measure left ventricular performance and assess prognosis. Their comparative abilities to predict clinical events have not been reported.

Methods. Both RVG EF and Cath-EFa were measured within 16 days of myocardial infarction (MI) in 688 patients. The results were divided into terciles. Prognosis by terciles was assessed for each technique. A multivariate analysis was performed to determine which EF measurement was a better predictor of prognosis.

Results. Average RVG–EF was 32% ± 7, while Cath-EFa was 42% ± 10. Both RVG and Cath-EFa were poorly correlated (R = 0.42). Event rate declined across terciles with increasing EF for both techniques (events in lowest to highest tercile of Cath-EFa 40.7%, 25.9%, 11.6%, p < 0.001; and RVG-EF 39.9%, 26.1%, 15.6%, p < 0.001). There was concordance of terciles in 303 of 688 patients (44%). When patients in the highest RVG terciles were in the highest Cath-EFa tercile, the event rate was 7%. However, when patients in the highest RVG terciles were in the lowest Cath-EFa tercile, the event rate was 19%. Both Cath-EFa (p < 0.001) and RVG-EF (p < 0.001) were independent predictors of cardiovascular events.

Conclusions. Ejection fraction measured by RVG or during catheterization is a valuable tool in the risk stratification of postinfarct patients. When disagreement is present between clinical impression and measurement by either method, the use of an alternative measurement is warranted and complementary.

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The presence of left ventricular (LV) dysfunction in the postmyocardial infarction period has been recognized as an important determinant of subsequent morbidity and mortality (1–3). The degree of impairment of LV function can be assessed using a variety of methods. End-diastolic volume, end-systolic volume and ejection fraction (EF) have all been described as important predictors of outcome in patients with coronary artery disease (2–4). However, EF is the most widely used clinical descriptor of LV function because of ease of measurement and excellent reproducibility in patients with a broad range of diagnoses. Ever since its description by Dodge et al. in 1956 (5), LV function measured with contrast ventriculography has remained the gold standard against which other techniques are judged. However, noninvasive techniques for cardiac imaging are now in widespread use. One of the most commonly used noninvasive techniques for measuring EF is radionuclide ventriculography (RVG). In the time since its initial application in the detection of wall-motion abnormalities, RVG has become an important method for the quantification of LV systolic function and its relation to future cardiovascular events (6,7). The purpose of this study was to determine the relationship and prognostic significance of two methods of measuring EF in postmyocardial infarction (MI) patients with LV dysfunction: RVG and contrast left ventriculography.

Methods

All patients in this study were participants in the Survival and Ventricular Enlargement (SAVE) study. Both the protocol and the results of SAVE have been published previously (8,9). Eligible patients between the ages of 21 to 79 years, with
an EF ≤40% by RVG, and who were between 3 to 16 days’ post-MI were randomly assigned to receive captopril or placebo. Patients were enrolled at 50 centers encompassing 110 hospitals. Out of 2,231 patients enrolled, 1,301 underwent cardiac catheterization within 16 days of their MI. Out of this group, 990 angiograms were submitted to the Cardiac Catheterization Core Laboratory for analysis. Left ventriculograms had been performed in 743 patients, but only 688 studies were technically acceptable for quantitation of EF. Thus, the present study is based on the final cohort of 688 SAVE study patients who underwent technically acceptable contrast left ventriculograms that were analyzed by the SAVE Cardiac Catheterization Core Laboratory (G.L., G.F., S.S., G.M.).

Patients were followed for 2 to 5 years. The primary clinical end point of the present analysis is cardiovascular mortality or the first occurrence of severe heart failure during the mean follow-up period of 3.5 years. Severe heart failure is defined as a hospitalization for treatment of heart failure, or heart failure severe enough to warrant discontinuation of blinded study medication and initiation of open-label angiotensin converting enzyme inhibitor therapy.

Assessment of RVG-EF. All patients underwent RVG prior to enrollment in SAVE utilizing a standardized protocol. The patient’s own red blood cells were labelled with technetium-99. This was accomplished by intravenous injection of 50 mg of stannous pyrophosphate. Fifteen minutes later, 10 cc of blood was withdrawn into a syringe containing 30 mCi of technetium-99 pertechnetate and 1 ml of anticoagulant citrate dextrose solution. The blood was incubated in the syringe for 10 min, and then re-injected into the patient with saline flush (10).

The RVG was performed with a gamma camera equipped with a general, all-purpose, parallel hole collimator interfaced with a dedicated computer. The energy window (20%) was set over 120 keV. Image acquisition was done in the left anterior oblique projection, and the anterior projection (45° to the right of the angulation for the left anterior oblique projection). All data were acquired in 64 × 64 matrix (word mode). At least 16 frames per electrocardiographic RR interval were acquired. Each frame was <40 ms. Unsmoothed studies were stored on floppy disk or magnetic tape. The RVG-EF was determined from the left anterior oblique projection using semiautomated edge-detection algorithms, varying regions of interest throughout the cardiac cycle, and background correction. Ejection fraction was calculated in standard fashion: end-diastolic counts − minus end-systolic counts/end-diastolic counts. Radionuclide studies were analyzed in the nuclear medicine laboratories of each of the 50 SAVE clinical centers and their component participating hospitals, where a wide variety of commercially available computers and software was used to measure RVG-EF. Nevertheless, although different software was used in various laboratories, EF was determined according to similar concepts and principles. Overreading of a randomly selected group of studies for the purpose of quality control was performed at the Yale University RVG Core Laboratory.

Contrast ventriculography. The decision to perform left ventriculography as part of the catheterization procedure was based on clinical indications and local practice in each catheterization laboratory and was not mandated by the SAVE protocol. Each analysis was carried out by one of three experienced invasive cardiologists (G.L., G.F., S.S.).

The left ventricular silhouettes at end-diastole and end-systole were traced onto a transparency film and digitized at a resolution of 10 points per millimeter by using a digitizing tablet interfaced to a personal computer. When extrasystoles were present, care was taken to analyze a cardiac cycle at least two beats after the last extrasystole. Computer-assisted analysis provided LV volumes by the area-length (11) method in 358 patients in whom calibration for magnification correction was available. Thus, conventional, volume-based EF could be calculated on only 52% of the study cohort. To permit analysis of all patients who had undergone contrast left ventriculography, we analyzed a surrogate, area-based EF (Cath-EFa). Using traced systolic and diastolic areas uncorrected for magnification the simple formula for Cath-EFa is as follows:

\[
\text{Cath-EFa} = \left( \frac{\text{diastolic area} - \text{systolic area}}{\text{diastolic area}} \right) \times 100
\]

Statistical analyses. Baseline characteristics were examined with simple descriptive statistics. Validation of Cath-EFa was made by assessing its linear correlation coefficient to volumetric EF. Patients who had EF assessed by both methods were divided into terciles according to their level of EF, with the lowest level of EF corresponding to the first tercile and the highest EF to the third tercile by each method. A bivariate analysis of the predictive value of EF tercile for the combined clinical end point of severe congestive heart failure or cardiovascular mortality was carried out for each technique using one-way analysis of variance.

The independent predictive value of each technique for the combined end point of each technique was assessed using the Cox proportional hazards method (12). A model was constructed using Cath-EFa, RVG-EF, and previously reported clinical (2,13,14) and coronary anatomic predictors of postinfarct outcome as independent variables, and the combined end points as the dependent variable. Finally, a 3 × 3 table was constructed showing the clinical outcomes of patients in whom there was a disagreement between techniques used to measure EF.
**Table 1.** Demographic and Clinical Characteristics of Patients Enrolled

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>57 ± 11 years</td>
</tr>
<tr>
<td>Gender (males)</td>
<td>82%</td>
</tr>
<tr>
<td>Race (white)</td>
<td>89%</td>
</tr>
<tr>
<td>Smoking</td>
<td>44%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>34%</td>
</tr>
<tr>
<td>Triple vessel disease</td>
<td>22%</td>
</tr>
<tr>
<td>Anterior-wall MI</td>
<td>63.5%</td>
</tr>
<tr>
<td>RVG-EF</td>
<td>32% ± 7</td>
</tr>
<tr>
<td>Cath-EFa</td>
<td>42% ± 10</td>
</tr>
</tbody>
</table>

Cath-EFa = EF area by contrast ventriculography; RVG-EF = EF by radionuclide ventriculography; SD = standard deviation.

**Results**

**Baseline characteristics.** The average age of the study cohort was 57 ± 11 years (Table 1), and 83% of the cohort was male. A history of prior MI was present in 34% of the patients enrolled. Coronary angiograms were available on all 688 patients studied, and triple-vessel disease was present in 22%. The average RVG-EF of the group was 32% ± 7. Most (63.5%) patients had sustained an anterior-wall MI.

**Validation of Cath-EFa.** The linear correlation coefficient of Cath-EFa with volumetric Cath-EF in 358 patients with available LV volumes was 0.96 (p < 0.001) (Fig. 1). In contrast, the correlation between Cath-EF and RVG-EF was 0.46 (p < 0.001) in 358 patients; and between Cath-EFa and RVG-EF 0.42 (p < 0.001) in all 688 patients (Fig. 2).

**Validation of RVG-EF measured at the clinical units.** The linear correlation coefficient of RVG-EF with RVG-EF (core) was calculated in 326 studies that had undergone measurement at the clinical site, and the core lab. The correlation coefficient was 0.73 p < 0.001.

**Correlation with clinical events.** The RVG-EF was divided into terciles. The first tercile was comprised of patients with an RVG-EF of 30% or less (n = 236). The second tercile included patients with an RVG-EF between 31% and 36% (n = 220). The third tercile included patients with an RVG-EF over 36% (n = 232). There was a stepwise decrease in the incidence of the combined endpoint in patients with higher RVG-EF (RVG-EF tercile 1, 39.9%; tercile 2, 26.1%; and tercile 3, 15.6%; (p < 0.001).

Likewise, Cath-EFa was divided into terciles. The first tercile included patients with Cath-EFa 38% or less (n = 233), and had an incidence of the combined endpoint of 40.7%. The second tercile included patients with Cath-EFa between 38% and 46% (n = 238), and had an incidence of the combined end point of 25.9%. The third tercile included patients with Cath-EFa greater than 46% (n = 256). This group had an incidence of the combined end point of 11.6% (p < 0.001) (Fig. 3).

Patients whose RVG-EF was in the first tercile of RVG-EF, but in the third tercile of Cath-EFa; or whose RVG-EF was in the third tercile of RVG-EF, but in the first tercile of Cath-EFa were labelled as discordant by 2 terciles, and comprised 11.1% of the cases. In this small group of patients, the incidence of the combined clinical end point was intermediate (19.5%) between the highest EF tercile and lowest EF tercile clinical event rates (Table 2).

**Multivariate analyses.** A multivariate model then was constructed to determine the independent predictors of the combined clinical end point in this cohort. The results of a a Cox regression analysis revealed that age (p < 0.001), hypertension (p < 0.001), number of diseased vessels (p < 0.001), use of beta-blockers (p = 0.05), RVG-EF (p < 0.001), Cath-EFa (p < 0.001) and captopril therapy (p = 0.06) independently predicted outcome. Gender, aspirin therapy, use of thrombolitics, prior MI and diabetes mellitus were not found to be significant predictors of the combined end point during the average follow-up period of 3.5 years (Table 3).
Discussion

The LV function is the principal determinant of outcome in the post-MI period (13,15,16), and EF is one of the most widely and clinically applicable measures of LV function. The predominant modality used for the determination of ejection fraction varies by institution. However, although the measurement of EF initially was described using contrast left ventriculography (17), noninvasive techniques have come into widespread use. Nevertheless, regardless of the method, the importance of an accurate estimation of the degree of LV dysfunction in the post-MI period is of paramount importance in the postthrombolytic era owing to its prognostic and therapeutic implications (18).

Among noninvasive techniques to measure EF, RVG is of particular interest vis-a-vis its comparability to contrast ventriculography. The measurement of EF with contrast ventriculography requires geometric assumptions of ellipsoidal LV

- RVG Terciles: 1st EF \leq 30, 2nd Tercile EF > 30 or \leq 36, 3rd EF > 36. 
  p < 0.001
- CATH-EF \text{a} Terciles: 1st EF \leq 38, 2nd EF > 38 or \leq 46, 3rd EF > 46. 
  p < 0.001

Figure 2. Scattergram of area-based EF (Cath-EFa) and radionuclide ventriculographic EF (RVG-EF); R = 0.42, p < 0.001.

Figure 3. Bar graphs showing the relationship between EF tercile measured by either RVG (RVG-EF) or catheterization (Cath-EFa) and the first occurrence of severe congestive heart failure (CHF) or death. See text for EF boundaries defining terciles.
Table 2. Agreement Between Techniques (RVG-EF and Cath-EFa) With Clinical End Points

<table>
<thead>
<tr>
<th></th>
<th>1st Tercile</th>
<th>2nd Tercile</th>
<th>3rd Tercile</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Tercile Cath-EFa</td>
<td>46% n = 56</td>
<td>45% n = 31</td>
<td>19% n = 9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd Tercile Cath-EFa</td>
<td>34% n = 22</td>
<td>21% n = 21</td>
<td>24% n = 21</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3rd Tercile Cath-EFa</td>
<td>20% n = 6</td>
<td>15% n = 13</td>
<td>7% n = 8</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Cath-EFa = EF area by contrast ventriculography; RVG-EF = EF by radionuclide ventriculography. *Development of congestive heart failure or cardiovascular mortality.

Table 3. Cox Regression Analysis Dependent Variable: CHF or Mortality

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Wald Chi-Square</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01</td>
<td>1.90–1.03</td>
<td>4.43</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.78</td>
<td>1.32–2.40</td>
<td>14.58</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Killip class</td>
<td>1.48</td>
<td>1.10–2.00</td>
<td>6.66</td>
<td>0.05</td>
</tr>
<tr>
<td>No. of Diseased Vessels</td>
<td>1.51</td>
<td>1.26–1.81</td>
<td>20.24</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cath-EFa</td>
<td>0.95</td>
<td>0.92–0.96</td>
<td>20.99</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RVG-EF</td>
<td>0.96</td>
<td>0.94–0.97</td>
<td>15.28</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Gender, prior MI, use of thrombolytics and diabetes were not statistically significant.

shape. However, the measurement of EF by RVG is count-based and may be less dependent on geometric assumptions. Thus, the correlation of RVG to catheterization EF is of clinical importance. Validation studies of EF by RVG have reported correlations with Cath EF ranging from 0.80 to 0.92 (19–21,23). However, all reports have not been quite so positive. For example, Manish et al. (22) reported a series of cases in which agreement among echocardiographic EF, RVG-EF, and angiographic EF ranged from 23% to 42%. An important potential source of error when comparing the techniques stems from the preferential contribution to the overall counts of tracer nearest the chest wall. Because of lower attenuation, patients with large akinetic anterolateral walls or apices may have greater contribution to overall counts from diseased areas, and hence an underestimation of EF.

We found a correlation between RVG-EF and cath-EFa of 0.42. Although the correlation was statistically significant, the correlation coefficient is considerably lower than expected based on the preponderance of published results. This discordance may be related to the participation of many different hospitals in the acquisition of RVG and catheterization data. In general, prior studies have been reported from centers specializing in validating radionuclide techniques (20,23). The authors believe that participation in the present study by a diverse group of operators represents a strength. These findings reflect what the practicing physician is likely to encounter when interpreting EFs measured with different techniques in different hospitals.

Prior studies that have documented the importance of EF in predicting clinical outcome have generally focused on a single technique for each study, and have been unable to compare the independent prognostic information yielded by multiple techniques for measuring EF. In contrast, the SAVE database provided a unique opportunity to compare the prognostic abilities of RVG and catheterization EF in a subgroup of 688 patients. As expected, each technique alone was an excellent predictor of the primary end point of cardiovascular mortality or congestive heart failure. The evidence of an increased rate of adverse cardiovascular events in the group with the lowest levels of EF by both techniques correlates well with previous studies (24–27).

Although the combined end point of cardiovascular mortality or congestive heart failure was well predicted by both techniques, both RVG and Cath EFa were unexpectedly found to be independent predictors of outcome. An interesting corollary to this unexpected observation was present in the subgroup of patients in whom EF was in the first (or third) tercile with one technique, and in the third (or first) tercile with the other. In this small subgroup of 11% of the cohort, if one technique were less accurate than the other, then the expected result would be for the event rate to reflect that of the technique which was most accurate. This, however, was not observed.

In contrast, the outcome of patients with a 2-tercile disagreement was intermediate, more closely reflecting those patients in the middle terciles. For example, patients whose Cath-EFas and RVG-EF were both in the third tercile had an excellent outcome, with an incidence of CHF or death of 7%. However, in a patient whose RVG-EF was in the first tercile, and whose Cath-EFa was in the first tercile, prognosis was intermediate, with an incidence of the combined end point of 20%. Unfortunately, the reason for this observation is less than clear, but it may have to do with subtle differences in the measurement of EF, LV volumes, and LV geometry by each technique.

For example, the measurement of EF by RVG should carry with it little information regarding LV volume or geometry. However, catheterization EF, even when measured by the modified technique reported here, does correlate more strongly with LV volumes and geometry than does RVG-EF. Thus, the physiologic principle is correct that all EF measurements should be the same. However, in practical terms each technique might introduce additional data on LV function, which may modify its ability to predict prognosis. Although the explanation for this observation is tentative and not conclusive, the observation itself is of clinical relevance for patients whose EF has been measured by different techniques, with divergent results. It is clear from this study that these patients have an intermediate prognosis.

Study limitations. The present study has several limitations. Perhaps the most important is the shift in current practice away from RVG measurement of EF toward a frequently qualitative measurement with echocardiography. This clinical shift limits the applicability of the present study. However, the present study suggests a methodology for the future assessment of the clinical importance of EF measurement by echocardiography as compared with other techniques.
Another important limitation is a statistical consideration that likely leads an underestimation of true correlation between techniques used to measure EF. The SAVE study, by design, systematically excluded patients with an RVG EF above 40%, while not basing any exclusion criteria on catheterization EF. This narrowed range of RVG EF reduces the spread of EF measurement and, hence, diminishes the measured correlation coefficient.

Conclusions. In the postmyocardial infarction period, ejection fraction by radionuclide ventriculography and ventriculography by cardiac catheterization are valuable tools in the risk-stratification of patients. The results of the present study suggest that significant disagreement in measurements may occur when utilizing different techniques. When clinical circumstances and conditions are inconsistent with the measured ejection fraction, remeasurement by another method will allow more accurate risk stratification. The optimal utilization and interpretation of EF by RVG and contrast ventriculography offer an effective and reliable way of stratifying patients and contribute to the management of the postmyocardial infarction population.

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References