Echocardiographic Predictors of Survival and Response to Early Revascularization in Cardiogenic Shock

Michael H. Picard, MD; Ravin Davidoff, MBBCh; Lynn A. Sleeper, ScD; Lisa A. Mendes, MD; Christopher R. Thompson, MD; Vladimir Dzavik, MD; Richard Steingart, MD; Ken Gin, MD; Harvey D. White, DSc; Judith S. Hochman, MD; for the SHOCK Trial

Background — Although echocardiography is used in diagnosis and management of myocardial infarction, it has not been established whether specific features of cardiac structure or function early in the course of cardiogenic shock provide prognostic value. The purposes of this substudy of the SHould we emergently revascularize Occluded Coronaries for cardiogenic shock (SHOCK) trial were to describe the echocardiographic features of cardiogenic shock, identify findings on early echocardiograms associated with outcome, examine the interaction of such features with treatment, and determine whether these features could provide insights into the survival benefit observed with early revascularization and guide selection of patients for this strategy.

Methods and Results — One hundred seventy-five echocardiograms performed within 24 hours of randomization to the early revascularization (ERV) or initial medical stabilization (IMS) arms of the trial were submitted for quantitative assessment, and 169 were suitable for analysis. The 2 groups were similar in terms of clinical and early echocardiographic characteristics. Mean left ventricular ejection fraction (LVEF) was 31%, and moderate or greater mitral regurgitation (MR) was noted in 39.1%. On multivariate analysis, the only independent predictors of survival were MR severity and LVEF. A survival benefit for the ERV strategy was observed at all levels of LVEF and MR.

Conclusions — A wide range of cardiac structural and functional abnormalities exists in patients presenting with acute cardiogenic shock. Both short- and long-term mortality appear to be associated with initial left ventricular systolic function and MR as assessed by echocardiography, and a benefit of ERV is noted regardless of baseline LVEF or MR.

Key Words: shock ■ echocardiography ■ myocardial infarction ■ regurgitation

Despite advances in treatment of myocardial infarction (MI), the incidence of cardiogenic shock after MI remains relatively unchanged, and it remains a major cause of death in patients hospitalized with acute MI. 1-4 Although predictors of cardiogenic shock have been determined, 5 there are limited data on early markers of outcome in this disease. Although echocardiographic evaluation is widely used in MI, assessing its value acutely in cardiogenic shock has been more challenging, and thus it has not been established whether specific features of cardiac structure or function early in the course of cardiogenic shock provide prognostic value.

The SHould we emergently revascularize Occluded Coronaries for cardiogenic shock (SHOCK) trial, an international, randomized trial of acute treatment in cardiogenic shock, demonstrated a 6-month and 1-year survival benefit for patients who were assigned to early emergency revascularization compared with initial medical stabilization. 6-7 Echocardiograms were performed both on entry and again later, thus offering a unique opportunity to assess their value and better understand the pathophysiology of this disease. The purposes of this prospectively designed substudy of the SHOCK trial were to identify the echocardiographic features of cardiogenic shock, identify findings on early echocardiograms that are associated with mortality after cardiogenic shock, assess the interaction of such findings and treatment, and determine whether any of these echocardiographic features could provide insights into the survival benefit observed with early revascularization and guide the selection of patients for this strategy.

Methods

Trial Design

The trial design has been described in detail elsewhere. 6,8 Briefly, from 1993 to 1998, 302 acute MI patients at 30 sites were
randomized within 12 hours of cardiogenic shock diagnosis to either early emergency revascularization (ERV) or initial medical stabilization (IMS). The trial focused on shock due to left ventricular (LV) failure. Cardiogenic shock was strictly defined on both a clinical and hemodynamic basis. Those with shock due to predominant severe mitral regurgitation (MR), isolated right ventricular (RV) shock, or other mechanical complication were prospectively excluded from the trial, because management of these conditions differs from LV shock. For the ERV, PTCA or CABG had to be performed within 6 hours of randomization; intra-aortic balloon counterpulsation (IABP) was recommended. For patients randomized to IMS, intensive medical therapy was required, and IABP and thrombolytic therapy were recommended. Delayed revascularization at a minimum of 54 hours after randomization was recommended for IMS patients if clinically appropriate. The study was designed and powered to detect an absolute 20% difference in overall mortality at 30 days. One-year mortality was a secondary end point.

Echocardiography

During the last 4 years of the trial, 2D transthoracic echocardiograms were performed on each patient within 24 hours of randomization and again at least 7 days later or within 2 days of discharge. Eighty-five percent of early echocardiograms were performed while the patient was supported with at least 1 of the following measures: IABP, dopamine, or norepinephrine. The echocardiograms were analyzed at the core laboratory in 2 stages: a qualitative and quantitative assessment. The assessments were performed by core laboratory physicians (M.H.P., R.D., L.A.M.) blinded to patient clinical status, treatment group, time of echocardiogram, and outcome.

The qualitative review included a complete evaluation of size and function of each ventricle and all valves in addition to LV regional wall motion assessment. Regional wall motion was scored by a 20-segment model with hyperkinetic segments graded as 0, normal as 1, mild hypokinesis as 1.5, moderate hypokinesis as 2.0, severe hypokinesis as 2.5, and akinesis/dyskinesis as 3. A total score for regional wall motion was calculated as the sum of all segment scores. Separate scores were calculated for infarct and remote zones. A wall-motion score index was calculated by dividing the wall-motion score by number of segments visualized. Color Doppler of MR was evaluated with the sphericity index as a ratio of the LV to mitral valve orifice area. A total score for mitral regurgitation was calculated as the sum of all segment scores. Mitral valve leaflet geometry and function were assessed for presence of leaflet prolapse, flail, and incomplete closure.

Quantitative analysis was then performed on echocardiograms of sufficient quality. Measurements included right and left atrial dimensions, LV dimensions, LV volume, LV ejection fraction (EF), LV function, extent of LV endocardium involved with wall-motion abnormality, LV sphericity index, and mitral valve annular dimensions.9,10 LV volumes were measured by the method of discs from orthogonal apical views. The sphericity index was calculated as a ratio of the LV midventricular dimension (in the apical 4-chamber view) and the long-axis dimension.11 Doppler indices of LV filling were obtained from pulse-wave Doppler at the tips of the mitral valve and included E- and A-wave peak velocities, time velocity integrals, acceleration time, and deceleration time. RV function was measured both by the descent of the base method and as an area change.12,13

In 35% of ERV patients, the initial echocardiogram, although performed within 24 hours of randomization, was performed after the revascularization procedure. These 29 cases were excluded from the analyses except where noted.

Statistical Analysis

Treatment group differences in baseline patient and echocardiographic characteristics were compared by Student’s t test and the Wilcoxon rank-sum test for continuous variables, Fisher’s exact test for categorical variables, and the Mantel-Haenszel test for linear trend for ordered categorical variables (number of diseased vessels). Descriptive statistics are presented as mean ± SD (median for skewed variables) or as percentages. Spearman correlation coefficients were used to estimate association between LVEF and other echocardiographic measures and echocardiographic measures versus timing of the echocardiogram. Logistic regression was used to examine the association of 30-day and 1-year survival with echocardiographic measures. All measures with a univariate probability value <0.20 were considered for inclusion in a multivariate model for survival. Kaplan-Meier curves were generated to demonstrate survival differences between patient subgroups defined by independent risk factors for death. One patient in the IMS group was lost to follow-up and excluded from 1-year survival analyses. Analyses were conducted with Statistical Analysis System14 and S-Plus software.15

Results

Patient Characteristics

Of the 274 echocardiograms evaluated at the core laboratory, 175 were performed within the first 24 hours of randomization. During this period of the trial, a total of 221 patients were randomized. Ninety-seven percent of the early echocardiograms were acceptable for qualitative and 73% for quantitative analysis. Among the 169 acceptable for qualitative analysis, the early echocardiograms were performed at a median 0.2 hours from randomization and the later echocardiogram at 13 days.

Of the early echocardiograms suitable for analysis, 82 were from the ERV group and 87 from the IMS patients. The characteristics of the patients with early echocardiograms were similar in terms of age, sex, rate of transfer admissions, and timing of shock and the echocardiograms (Tables 1 and 2). Although the prevalence of most risk factors was similar, diabetes was more frequently noted in the ERV group, whereas more subjects in the IMS group had prior CABG. As seen with all 302 patients in the trial, a difference in 30-day mortality was noted in favor of ERV, but this did not meet statistical significance. Similar to the entire trial population, at 6 months and 1 year, there was an absolute difference in survival between groups. However, this did not reach statistical significance in this smaller subset of patients.

Cardiac Structure and Function in Acute Cardiogenic Shock

Table 3 depicts findings from the early echocardiogram. As expected, on presentation with cardiogenic shock, patients in...
both treatment arms exhibited significant degrees of global and regional LV dysfunction, but there was a wide range in the LVEF. Mean LVEF was 31±11%. No significant differences in LV size or function were noted between the 2 groups. RV function was diminished in both groups.

The wall-motion scores reflect significant regional dysfunction in both groups. No differences were observed between treatments. Regional function in the infarct zone was markedly impaired, with a mean segmental score approaching 3 (representative of akinesis/dyskinesis).

MR of grades 2 or 4 was noted in 39.1% of patients. The degree of MR did not differ between treatment groups (ERV mean MR grade 1.4±0.9 versus IMS 1.3±0.9). Apical displacement of mitral leaflet coaptation, also known as incomplete mitral leaflet closure pattern, was noted in 40% of those with grade 2+ to 4+ MR.

### Echocardiographic Variables Associated With Survival

The significant echocardiographic univariate predictors of 30-day or 1-year mortality were MR severity (MR ≥2 vs <2: 1-year odds ratio for death=6.64, \( P=0.0003 \)) and LVEF (LVEF <28%: 1-year odds ratio for death 4.04, \( P=0.005 \)). Figure 1 displays the survival curves for the 4 combinations of MR and LVEF. Regardless of treatment, an important survival difference was noted for those with no or mild MR and LVEF ≥28% (70% 1-year survival) compared with patients with 2+ to 4+ MR and LVEF <28% (10% 1-year survival).

### Table 4. Univariate Predictors of 1-Year Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Dead</th>
<th>Alive</th>
<th>Odds Ratio (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic volume, mL</td>
<td>100</td>
<td>122±42</td>
<td>103±43</td>
<td>1.26 (1.02, 1.54)</td>
<td>0.029</td>
</tr>
<tr>
<td>End-systolic volume, mL</td>
<td>99</td>
<td>88±34</td>
<td>70±36</td>
<td>1.38 (1.08, 1.78)</td>
<td>0.012</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>99</td>
<td>28±11</td>
<td>34±11</td>
<td>0.79 (0.65, 0.96)</td>
<td>0.015</td>
</tr>
<tr>
<td>MR &lt;2 vs ≥2</td>
<td>114</td>
<td>2/3/4 MR: 31% survival</td>
<td>0/1 MR: 58% survival</td>
<td>3.05 (1.38, 6.74)</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEF &lt;28%</td>
<td>99</td>
<td>&lt;28%, 24% survival</td>
<td>≥28%, 56% survival</td>
<td>3.86 (1.63, 9.19)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Per 20-mL increase.
†Per 5% increase.
Severity of MR appeared related to factors that influenced mitral leaflet closure geometry and the presence of the incomplete mitral leaflet closure pattern ($P=0.026$). In addition, MR was associated with LV end-diastolic volume, because 63% of those with LV end-diastolic volume $\geq 140$ mL had at least moderate MR, whereas 65% of those with LV end-diastolic volume $<140$ mL had MR graded as mild or less.

Effect of ERV

Although both MR and LVEF were predictive of survival in both the IMS and ERV groups, a treatment effect or benefit of ERV was observed regardless of baseline LVEF and MR. Figures 2 and 3 display the treatment effect of ERV on survival.

Twenty-nine of the 82 baseline echocardiograms in the ERV group were performed after revascularization and thus were not used in the initial analyses. When all echocardiograms, regardless of timing, were examined in relation to the timing of revascularization (ie, hours before or after revascularization), LVEF ($r=-0.34, P=0.011$), end-diastolic volume ($r=-0.28, P=0.03$), and end-systolic LV volume ($r=-0.33, P=0.016$) correlated with this timing. Specifically, the end-systolic and end-diastolic volumes tended to be smaller and the LVEF higher on the baseline echocardiograms done after the revascularization procedure. Mean LVEF on ERV echocardiograms done before revascularization was $29\pm12\%$, whereas it was $39\pm13\%$ after revascularization.

Discussion

The SHOCK trial is the first large-scale randomized trial of treatment of cardiogenic shock in which 2D echocardiograms were systematically performed early in the presentation. The results of this study demonstrate a wide range of cardiac structural and functional abnormalities in patients presenting with acute cardiogenic shock. Both short- and long-term mortality appear to be associated with initial LV systolic function and the severity of MR as assessed by echocardiography. These findings occurred regardless of treatment strategy. In addition, a survival benefit was observed for those randomized to ERV regardless of the LVEF or degree of MR on entry. Thus, although each of these findings on the early echocardiogram can help judge a patient’s risk, they should not be used to deny the aggressive treatment strategy.

In these patients, LV systolic function appears to depend on the degree and severity of regional LV function, whereas LV dilation and the ability of the MV leaflets to close appropriately affect MR. Thus, prognostic factors in acute cardiogenic shock mirror those for less complicated MI $^{17-20}$

The prognostic importance of LVEF may not appear surprising in light of the prior studies of post-MI patients. $^{18-20}$ However, in most reports examining the significance of LVEF after MI, LVEF assessment occurred later during the healing process, and the mean LVEF was higher than in the present trial. In our SHOCK population, mean LVEF was $31\%$ at entry, and we found that mortality was higher when the LVEF determined by echocardiography at entry was lower than the median LVEF of 28%. A recent smaller, nonrandomized, retrospective review of shock patients,

Figure 1. Kaplan-Meier estimates of survival up to 1 year after randomization for 4 combinations of LVEF and MR (log-rank test $P=0.0001$). Total n=90; MR 0/1 and LVEF $\geq 28\%$, n=33; MR 0/1 and LVEF $<28\%$, n=20; MR 2/3/4 and LVEF $\geq 28\%$, n=16; MR 2/3/4 and LVEF $<28\%$, n=21.

Figure 2. Estimated 1-year survival by treatment assignment. LVEF measured within 24 hours of randomization (before any revascularization attempt) is significantly associated with 1-year survival ($P=0.025$). Tick marks at top and bottom of plot indicate raw data values for ERV and IMS groups, respectively.

Figure 3. Association between MR grade, treatment assignment, and 1-year survival.
treated with a variety of interventions has also shown that a similar LVEF cutpoint derived from echocardiograms performed after revascularization procedures is predictive of mortality.21 Our initial LVEFs demonstrate a wide range, which may relate to the fact that many of the echocardiograms were performed with the patient on pharmacological or mechanical support. The large variation in LV size and function suggests that the pathophysiology of shock is complex and varied and requires further investigation.

Another important observation is the role of MR at entry as a predictor of death. Significant MR is not uncommon in the failing and/or large ventricle, and our clinical echocardiographic findings support prior experimental studies relating MR in the setting of ischemia/infarction to incomplete leaflet closure.22 This apical displacement of the closure point of the leaflets can be due to displacement of the papillary muscles caused by LV enlargement and/or altered LV geometry23,24 or inadequate closure forces generated in systole by the failing ventricle.25 Although it is difficult to directly compare our patients in shock to more stable post-MI populations, angiographic studies of patients both early26 and late27 after MI have shown that significant MR is an independent predictor of poorer outcome. In the SAVE trial, MR detected days after MI was associated with larger LV volumes and more extensive coronary artery disease, and the poorer outcome with MR was independent of ACE inhibitor treatment.27

The findings of the importance of LV size, LVEF, and MR in the present study support a strategy of aggressive maneuvers to enhance forward LV stroke volume, reduce MR, improve regional and global LV systolic function, and attenuate LV remodeling in patients with cardiac shock caused by extensive LV dysfunction. Because the echocardiograms in the ERV cohort were performed at a range of times both before and after the revascularization, a comparison of the prerevascularization to postrevascularization echocardiograms allows us to speculate on potential effects of the intervention. The end-diastolic and end-systolic LV volumes were lower and the ejection fractions higher in patients whose echocardiograms were delayed until after revascularization. Although the echocardiograms in the present analysis were not paired for individual patients, these data suggest that acute revascularization results in relief of ischemia and recovery of ischemic myocardium without a prolonged stunning effect. The higher survival of the ERV group at 6 months and 1 year may relate to this rapid recovery of function resulting in reduced chronic pump failure and late arrhythmia.

In conclusion, in addition to its value in identifying causes for shock, echocardiography early in the course of cardiogenic shock can be used for risk stratification. Predictors of short- and long-term mortality from cardiogenic shock relate to LVEF and MR at presentation. The more extensive the regional dysfunction, the greater the adverse effect on global LV function. These abnormalities in function are associated with altered MV geometry that results in increased MR. ERV appears to rapidly enhance recovery of LV dysfunction, resulting in the potential for improved outcome. The improvement in survival with revascularization seen at all levels of LVEF and MR suggests that systolic function and valve dysfunction alone should not be used as reasons to withhold acute revascularization therapy.

Acknowledgments
This study was supported by grants from the National Heart, Lung, and Blood Institutes (R01-HL-50020 and R01-HL-49970). We thank the SHOCK trial sonographers, as well as Julia Nisbet-Brown, John Lim, and Rebecca Orfaly of the SHOCK Data Coordinating Center for their tireless efforts.

Appendix
Collaborating Echocardiographers
A. Mogtader, R. Hahn, and N. Konecny (deceased), St. Luke’s Roosevelt Hospital Center (New York, NY); J. Strom, O. Raju, T. Kishore, and S. Jamshid, J.D. Weiler Hospital of the Albert Einstein College of Medicine (Bronx, NY); J.L. Van Overschelde and D. Raphael, Cliniques Universitaires St. Luc (Brussels, Belgium); L. Mendes and R. Davidoff, Boston University Medical Center (Boston, Mass); J.L. Peters, O. Vanderperren, E. Leccog, and C. Chevolet, Centre Hospitalier Regional Citadelle (Liege, Belgium); E. Brickner, University of Texas Southwestern Medical Center (Dallas, Tex); D. Shindler, R. Hilkert, and S. Palmeri, University of Medicine & Dentistry of New Jersey (New Brunswick, NJ); M. Goldberger, Montefiore Medical Center, Albert Einstein College of Medicine (Bronx, NY); C. Caldwell, T. Dietz, H. Dinh, S. Lawhorn, M. Mullens, H. Patel, R. Rayford, B. Robinson, G. St. John, M. St. Pierre, and M. Velusamy, University of Arkansas for Medical Sciences (Little Rock, Ark); R. Rikfink and D. Tighe, Baystate Medical Center (Springfield, Mass); R.B. Devereux, R. Hahn, and M. Roman, The New York Hospital (New York, NY); M. Goldman, Mount Sinai Medical Center (New York, NY); M. Kiess, I. MacDonald, R. Gillis, K. Perry, C. Thompson, and B. Munt, St. Paul’s Hospital (Vancouver, British Columbia, Canada); K. Gin, J. Coburn, and S. McCorvile, and S. Phillips, Vancouver General Hospital (Vancouver, British Columbia, Canada); M.C. Herregods, G. Odent, and B. Denef, Gasthuisberg Universitaire Hospital (Leuven, Belgium); R. Minson, R. Hassam, T. Hecker, and H. Koutsournis, Finders Medical Center (Adelaide, S.A., Australia); M. Leggett and S. Greaves, Green Lane Hospital (Auckland, New Zealand); W. Mathias, Jr, U.B. Stella, and A.M. Arruda, Unicor Hospital (Sao Paulo, Brazil); D. Arani, J. Conley, and W. Beneke, Buffalo General Hospital (Buffalo, NY); S. Goldson, C. Herzog, and C. Dick, Hennepin County Medical Center (Minneapolis, Minn); R. Smith, S. Zeldis, G. Macina, and J. Lazar, Winthrop University Hospital (Mineola, NY); J. Katz, H. Novotny, and S. Simandl, State University of New York at Stony Brook (Stony Brook, NY); P. Stylianos, New York Hospital-Queens (Flushing, NY); K. Baran, P. Rusterholz, C. Alexander III, R. Guthrie, and P. Koller, United Hospital-St. Paul Heart Clinic (St. Paul, Minn); D. Human and D. Taylor, University of Alberta Hospital (Edmonton, Alberta, Canada); A. Mehra and P. Ataii, University of Southern California School of Medicine (Los Angeles, Calif); and M. Pfisterer, University Hospital Basel (Basel, Switzerland).

References
15. Statistical Sciences, Inc. S-Plus for Windows. Seattle, WA.
Echocardiographic Predictors of Survival and Response to Early Revascularization in Cardiogenic Shock

Michael H. Picard, Ravin Davidoff, Lynn A. Sleeper, Lisa A. Mendes, Christopher R. Thompson, Vladimir Dzavik, Richard Steingart, Ken Gin, Harvey D. White and Judith S. Hochman

for the SHOCK Trial

Circulation. 2003;107:279-284; originally published online December 16, 2002;
doi: 10.1161/01.CIR.0000045667.11911.F6
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/2/279

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

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

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