Core Lab Analysis of Baseline Echocardiographic Studies in the STICH Trial and Recommendation for Use of Echocardiography in Future Clinical Trials

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Background: The Surgical Treatment for Ischemic Heart Failure (STICH) randomized trial was designed to identify an optimal management strategy for patients with ischemic cardiomyopathy. Baseline echocardiographic examinations were required for all patients. The primary aim of this report is to describe the baseline STICH Echocardiography Core Laboratory data. The secondary aim is to provide recommendations regarding how echocardiography should be used in clinical practice and research on the basis of the experience gained from echocardiography in STICH.

Methods: Between September 2002 and January 2006, 2,136 patients with ejection fractions (EFs) $\leq$ 35% and coronary artery disease amenable to coronary artery bypass grafting were enrolled. Echocardiography was acquired by 122 clinical enrolling sites, and measurements were performed by the Echocardiography Core Laboratory after a certification process for all clinical sites.

Results: Echocardiography was available for analysis in 2,006 patients (93.9%); 1,734 (86.4%) were men, and the mean age was 60.9 $\pm$ 9.5 years. The mean left ventricular end-systolic volume index, measureable in 72.8%, was 84.0 $\pm$ 30.9 mL/m^2, and the mean EF was 28.9 $\pm$ 8.3%, with 18.5% of patients having EFs > 35%. Single-plane measurements of left ventricular and left atrial volumes were similar to their volumes by biplane measurement (r = 0.97 and r = 0.92, respectively). Mitral regurgitation severity by visual assessment was associated with a wide range of effective regurgitant orifice area, while effective regurgitant orifice area $\geq$ 0.2 cm^2 indicated at least moderate mitral regurgitation by visual assessment. Deceleration time of mitral inflow velocity had a weak correlation with EF (r = 0.25) but was inversely related to estimated pulmonary artery systolic pressure (r = $-$0.49).

Conclusions: In STICH patients with ischemic cardiomyopathy, Echocardiography Core Laboratory analysis of baseline echocardiographic findings demonstrated a wide spectrum of left ventricular shape, function, and hemodynamics, as well as the feasibility and limitations of obtaining essential echocardiographic measurements. It is critical that the use of echocardiographic parameters in clinical practice and research balance the strengths and weaknesses of the technique. (J Am Soc Echocardiogr 2012;25:327-36.)

Keywords: Ischemic, Cardiomyopathy, Echocardiography

The Surgical Treatment for Ischemic Heart Failure (STICH) trial, supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health (Bethesda, MD), is an international randomized trial designed to test two specific hypotheses in patients with left ventricular (LV) dysfunction and coronary artery disease.[1] Hypothesis 1 (H_1) tested whether coronary artery bypass grafting

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This study was supported by grant UO5-HL-69010 from the National Institutes of Health (Bethesda, MD).

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0894-7317/$36.00

doi:10.1016/j.echo.2011.12.002

Abbreviations

CABG = Coronary artery bypass grafting

DT = Deceleration time

EF = Ejection fraction

EROA = Effective regurgitant orifice area

H_1 = Hypothesis 1

H_2 = Hypothesis 2

LA = Left atrial

LV = Left ventricular

LVEDV = Left ventricular end-diastolic volume

LVESV = Left ventricular end-systolic volume

LVOT = Left ventricular outflow tract

MR = Mitral regurgitation

PASP = Pulmonary artery systolic pressure

STICH = Surgical Treatment for Ischemic Heart Failure

SV = Stroke volume

SVR = Surgical ventricular reconstruction

(CABG) would result in improved long-term survival compared with intensive medical therapy alone. Hypothesis 2 (H_2) tested whether combining a surgical ventricular reconstruction (SVR) procedure with CABG would improve survival free from cardiac hospitalization in comparison with CABG alone in patients with reduced LV ejection fraction (EF) and dysfunctional anterior segments. The STICH protocol required that all patients undergo baseline, 4-month follow-up, and 2-year follow-up echocardiography and that measurements be performed by an echocardiography core laboratory. The primary outcomes data in H_2 patients (499 assigned to CABG vs 501 to CABG plus SVR) showed no overall benefit from the addition of SVR to CABG despite a more significant reduction in LV volumes and an increase in EF with SVR.[2] The outcomes in H_1 patients (602 assigned to medical therapy vs 610 to CABG) showed no statistically significant benefit for CABG in the primary outcome of all-cause mortality. However, patients assigned to CABG compared with those assigned to medical therapy alone had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes.[3] Knowledge of LV structure, function (volumes, EF, and diastolic function), and hemodynamics in STICH patients would help us better understand the outcomes of tested treatment strategies in future subgroup analyses. Because the STICH trial was conducted at 122 clinical sites in 26 countries, we made a substantial effort to standardize and maintain the quality of echocardiograms of study patients. Our experience in operating the Echocardiography Core Laboratory in this large clinical trial provided insights into how echocardiography should be used in clinical trials and subsequent implementation of trial data in our clinical practice.

Therefore, the aims of this report are (1) to provide the feasibility of obtaining quality baseline echocardiographic data for the entire STICH trial cohort as well as for H_1 and H_2 separately, (2) to provide pertinent baseline echocardiographic data analyzed by the Echocardiography Core Laboratory in these patients, and (3) to provide recommendations for the use of echocardiography in clinical practice and trials.

METHODS

Patients

Between September 2002 and January 2006, 2,136 patients with EFs $\leq$ 35% and coronary artery disease amenable to CABG were enrolled in STICH. The qualifying LV EF for enrollment was determined by clinical sites using any of available imaging modalities within 3 months of enrollment. More detailed inclusion and exclusion criteria have been published elsewhere.[1,2]

Design and Quality Assurance of the Echocardiography Core Laboratory

The Echocardiography Core Laboratory team that analyzed echocardiographic studies for STICH (Appendix) consisted of experienced physician echocardiographers (with level 3 training and >5 years of practice) and sonographers (with >3 years of clinical sonography). They were instructed in the goals of the STICH trial and measurement standards. A manual of operation for echocardiography was produced to standardize the sequence, duration, and technique of echocardiographic studies at all clinical sites in 26 countries. Each site was asked to submit one to three echocardiographic studies that demonstrated all of the required components of echocardiography to be certified before patient enrollment began. When the initial echocardiographic studies did not meet minimal criteria for measurements of LV volumes, LV EF, mitral regurgitation (MR) severity, diastolic function, and tricuspid regurgitation velocity, additional studies were requested until the requirements were met.

Once an echocardiographic study arrived at the Echocardiography Core Laboratory, it was transferred directly, if in digital format, to the Echocardiography Core Laboratory's workstation (Digiview; Digisonics Inc., Houston, TX) for measurement and archiving; if the study was in an analog format, it was digitized first and then transferred. Echocardiographic measurements were performed by Echocardiography Core Laboratory sonographers and were approved by Echocardiography Core Laboratory physician staff members. The qualitative assessments, including MR severity, regional wall motion abnormalities, and grading of diastolic function severity, were performed primarily by a physician member.

Echocardiographic Measurements

All measurements and analyses were performed without knowledge of clinical or other laboratory data. An average of three cardiac cycles was used for sinus rhythm, and an average of three to five cardiac cycles was used for atrial fibrillation. If arrhythmia or poor image quality prevented quantitative measurements, LV EF was estimated visually. Interobserver variability in measuring LV volumes was determined in a subset of patients. The following parameters were measured mostly according to the recommendation of the American Society of Echocardiography.[4]

LV Dimensions. LV dimensions were measured from the two-dimensional parasternal long-axis view of the left ventricle at the junction of the head of the papillary muscle and chordae. The long-axis dimension of the left ventricle was measured from the apical four-chamber view. The LV sphericity index was calculated as the ratio of the LV short-axis dimension and the maximum long-axis dimension.

LV Volume and LV EF Measurement. LV EF was measured primarily using Simpson's volumetric method whenever possible. Either a combination of apical four-chamber and two-chamber views (preferentially) or a combination of apical four-chamber and long-axis views was used. If two apical views were not available, only one apical view was used for Simpson's single-plane method. The LV endocardial border was traced contiguously from one side of the mitral annulus to the other, excluding the papillary muscles and trabeculations. LV end-diastolic volume (LVEDV) was measured at the time of QRS, when the LV cavity was largest, and LV end-systolic volume

(LVESV) when the left ventricle was smallest. Both were indexed to body surface area. When the definition of the LV endocardial border was not satisfactory from any apical view, LV EF was determined by visual estimation.

LV Regional Wall Motion. LV regional wall motion was analyzed visually using the standard 16-segment model. On the basis of the contractility of each segment, a wall motion score was assigned: 1 = normal, 2 = hypokinesis, 3 = akinesis, and 4 = dyskinesis. The wall motion score index was calculated as an average of the individual wall motion scores of each visualized segment. If more than two segments were not visualized or wall motion abnormalities were global, wall motion analysis was not performed.

Left Atrial (LA) Volume

LA volume was measured using the area-length method ($[A_1 \times A_2]$/length) using the apical four-chamber view and the apical long-axis or two-chamber view. A_1 is LA area from the apical four-chamber view, A_2 is LA area from the apical two-chamber or long-axis view, and length is LA long-axis dimension of the line drawn from the center of the mitral annulus to the posterior wall of the left atrium from an apical view. LA volume was also calculated from the apical four-chamber view only using the following modified area-length method: $(A_1 \times A_1)$/length.

Stroke Volume (SV) and Cardiac Output. SV was calculated using two methods: one from the LV outflow tract (LVOT) using the formula SV = LVOT area × LVOT time-velocity integral,[3] and another from the LV volumes measured by the single-plane or biplane Simpson's method as SV = LVEDV − LVESV. Cardiac output was calculated as the product of SV and heart rate.

MR Severity. The severity of MR was primarily determined by the physician's visual assessment of the width, depth, and area of the MR jet. In addition, effective regurgitant orifice area (EROA) was determined using the proximal isovelocity surface area method, as previously described,[4,5] whenever possible.

Pulmonary Artery Systolic Pressure (PASP). PASP was estimated from the peak tricuspid regurgitation velocity, obtained by continuous-wave Doppler echocardiography, and estimated right atrial pressure, as previously described.[6,7]

Determination of Diastolic Function. Mitral inflow velocities were recorded by placing a small sample volume at the tip of the mitral valve during diastole. Early diastolic velocity (E), late diastolic velocity with atrial contraction (A), and deceleration time (DT) of E velocity were measured from the inflow velocity recording.[4,8] A velocities were not available for patients with atrial fibrillation. Mitral annular velocities were measured using Doppler tissue imaging by placing a sample volume over the medial and/or lateral annulus to determine early diastolic velocity (e′) and late diastolic velocity with atrial contraction (a′). In patients with sinus rhythm, diastolic function was graded as follows: grade 1 = relaxation abnormality (no elevation of filling pressure), E/A < 0.8, and DT > 240 msec; grade 2 = pseudonormalized filling (relaxation abnormality and mild elevation of filling pressure), E/A of 0.8 to 1.5, and DT of 160 to 240 msec; and grade 3 = restrictive filling (relaxation abnormality and marked elevation of filling pressure), E/A > 1.5 and DT < 160 msec. Diastolic function was regarded normal if medial or lateral e′ velocity was >8 or >10 cm/sec, respectively. If there was discrepancy among diastolic parameters in grading, function was classified as "indeterminate." Diastolic function was not graded in patients with atrial fibrillation.

Tei Index. The LV Tei index, or LV index of myocardial performance, was derived from the mitral inflow and LVOT velocity time-intervals, as previously described.[9]

Statistical Analysis

Continuous variables are summarized as mean ± SD and categorical variables as percentages of the group total. Two-sample *t* tests were used to compare echocardiographic continuous variables, and χ^2 tests were used to compare categorical data. Because there was some overlap between the H_1 and H_2 patient groups and the statistical tests we used require independent samples, 74 patients included in both groups were excluded from the statistical analysis. Pearson's correlation coefficients are presented when describing relationships among echocardiographic parameters.

RESULTS

Of the total of 2,136 patients, baseline echocardiograms were available for analysis in 2,006 patients (93.9%). The mean age was 60.9 ± 9.5 years, and 86.4% were men. Atrial fibrillation was present in 85 patients (5%). Table 1 shows echocardiographic variables and their values measured by the Echocardiography Core Laboratory as well as the number of patients in whom each variable could be measured.

LV Dimensions and Sphericity Index

The mean LV end-diastolic dimension and LV long-axis dimension were significantly longer in H_2 patients than the dimensions in H_1 patients ($P = .03$ for end-diastolic dimension and $P = .007$ for long-axis dimension). The sphericity index was similar in H_1 and H_2 patients ($P = .26$). There was no significant difference between H_1 and H_2 patients in LV end-systolic dimension ($P = .84$).

LV Volumes and EF

In 873 of 2,006 patients (43.5%), reliable delineations of the LV endocardial border were feasible from two apical views; in 587 patients (29.3%), border detection was possible from a single apical view only. Therefore, in 1,460 patients (72.8%), LVEDV and LVESV (and hence EF) were measured using Simpson's method. When those 1,460 patients with volume measurement were compared with 546 patients without volume measurement, the latter group was older and heavier, with more patients with hypertension or diabetes (Table 2).

Interobserver variability for measuring LV volumes was assessed in 67 patients (approximately one in 20 patients in whom LV volumes could be measured) and was determined to be good ($r = 0.92$), with a mean difference and a mean percentage difference of 8.9 ± 24.8 mL and 4.6 ± 11.6%, respectively, for LVEDV, and of 7.6 ± 23.3 mL and 6.8 ± 17.9% for LVESV. Table 1 shows LV volumes, their indexes, and EF in H_1 and H_2 patients separately as well as their mean values in all patients. LV volumes were measured by both the biplane and single-plane Simpson's method in 182 randomly selected patients and were highly correlated, as shown in Figure 1 (LVESV, $r = 0.97$; LVEDV, $r = 0.96$). When LV volumes were correlated with LV EF, LVESV had a better correlation with LV EF than LVEDV (Figure 2). Although LV EF ≤ 35% was an enrollment criterion, LV EFs measured by the Echocardiography Core Laboratory were > 35%

Table 1 Baseline echocardiographic parameters and their values

Measurement	Overall (n = 2,006)		H_1 (n = 1,144)		H_2 (n = 936)		P*
	Number of patients	Value	Number of patients	Value	Number of patients	Value	
LVEDD (cm)	1,432	6.3 ± 0.8	804	6.3 ± 0.8	680	6.4 ± 0.8	.027
LVESD (cm)	1,352	5.4 ± 0.9	767	5.3 ± 0.9	635	5.3 ± 0.9	.842
LV long-axis dimension (cm)	1,506	9.2 ± 1.0	846	9.2 ± 1.0	721	9.3 ± 1.0	.007
Sphericity index (diastole)	1,154	0.69 ± 0.09	648	0.69 ± 0.09	551	0.68 ± 0.09	.264
LVEDV (mL)	1,460	222.4 ± 68.8	806	220.4 ± 67.3	710	225.0 ± 69.4	.167
LVESV (mL)	1,460	160.7 ± 60.4	806	160.2 ± 60.1	710	161.0 ± 60.3	.766
LVEDV index (mL/m^2)	1,460	116.3 ± 34.6	806	115.6 ± 33.8	710	117.0 ± 35.5	.417
LVESV index (mL/m^2)	1,460	84.0 ± 30.9	806	84.1 ± 30.7	710	83.8 ± 31.2	.854
LV EF (%)	1,460	28.9 ± 8.3	806	28.5 ± 8.5	710	29.5 ± 8.1	.016
LA volume index (mL/m^2)	1,237	41.9 ± 15.2	696	41.7 ± 14.7	596	42.1 ± 15.6	.500
Global hypokinesis	1,985	227 (11%)	1,130	149 (13%)	929	88 (9%)	.006
Wall motion score index	1,758	2.2 ± 0.3	981	2.3 ± 0.3	841	2.2 ± 0.3	.020
DT (msec)	1,492	186.2 ± 56.2	842	189± 58.2	708	183.3 ± 53.4	.028
MV E velocity (m/sec)	1,635	0.73 ± 0.25	920	0.72 ± 0.26	778	0.73 ± 0.25	.198
MV A velocity (m/sec)	1,535	0.67 ± 0.24	860	0.67 ± 0.24	736	0.68 ± 0.24	.562
E/A ratio	1,532	1.3 ± 1.1	859	1.4 ± 1.3	734	1.3 ± 0.9	.473
e′ or Ea septal velocity (m/sec)	1,002	0.05 ± 0.02	592	0.04 ± 0.02	450	0.05 ± 0.02	<.001
e′ or Ea lateral velocity (m/sec)	971	0.06 ± 0.03	573	0.06 ± 0.03	436	0.06 ± 0.03	.934
Septal E/Ea or E/e′ ratio	920	17.6 ± 9.6	544	18.1 ± 9.7	413	16.8 ± 9.3	.041
Diastolic function	1,992		1,132		934		.882
Normal		5 (0.3%)		3 (0.3%)		2 (0.2%)	
Grade 1		604 (30%)		362 (32%)		268 (29%)	
Grade 2		590 (30%)		304 (27%)		311 (33%)	
Grade 3		433 (22%)		253 (22%)		194 (21%)	
Grade 4		2 (0.1%)		1 (0.1%)		1 (0.1%)	
Indeterminate		358 (18%)		209 (18%)		158 (17%)	
MR grade	1,990		1,138		926		.851
0		514 (26%)		316 (28%)		227 (24%)	
1		871 (44%)		465 (41%)		437 (47%)	
2		306 (15%)*		174 (15%)*		142 (15%)*	
3		110 (6%)*		58 (5%)*		52 (5%)*	
4		51 (3%)*		30 (3%)*		24 (3%)*	
Indeterminate		138 (7%)*		95 (8%)*		44 (5%)*	
TR velocity (m/sec)	596	2.9 ± 0.5	342	2.9 ± 0.5	274	2.8 ± 0.5	.186
PASP (mm Hg)	430	42.8 ± 15.5	241	43.4 ± 15.8	205	41.7 ± 15.0	.241

LVEDD, LV end-diastolic dimension; *LVESD*, LV end-systolic dimension; *MV*, mitral valve; *TR*, tricuspid regurgitation.
Data are expressed as mean ± SD or as number (percentage).
*The *P* value tests differences between H_1 and H_2 patients for which there is no overlap (n = 1,044, n = 863).

in 18.5% of patients (10.6% had 35% < LV EF ≤ 40%, and 7.9% had LV EFs > 40%). The distribution of LV EF in STICH patients is shown in Figure 3.

LA Volume

There was no significant difference in mean LA volume index (41.9 ± 15.2 vs 42.8 ± 16.8 mL/m^2) whether measured by the biplane area-length method or from a single apical four-chamber image, respectively (Figure 4).

Right Ventricular Systolic Function

Right ventricular systolic function was visually assessed in 1,838 patients; 1,387 (75.5%) had normal function, 237 (12.9%) had mildly reduced function, 156 (8.5%) had moderately reduced function, and 58 (3.2%) had severely reduced function.

SV and Cardiac Output

SV from the LVOT was available for 1,028 patients, with a mean value of 64.9 ± 19.6 mL. In the 964 patients with data available, cardiac output and index were 4.5 ± 1.4 L/min and 2.3 ± 0.7 L/min/m^2, respectively. There was a statistically significant ($P < .0001$) but a weak correlation between cardiac output and LV EF ($r = 0.26$). Mean SV obtained from LVEDV − LVESV was 61.9 ± 19.6 mL. The correlation between the two methods was modest ($r = 0.37$, $P < .0001$).

MR Severity

The determination of MR severity by visual assessment of color flow imaging was feasible for 1,852 patients (92.3% of received echocardiographic studies), and the distribution of MR severity in STICH patients is shown in Table 1. There was a modest correlation between the severity of MR by visual assessment of color flow imaging and

Table 2 Comparison of patients with and without echocardiographic volume measurement

Variable	Have volume measurements (n = 1,460)	Do not have volume measurements (n = 546)	P
Age (y)	60.6 ± 9.51	61.8 ± 9.54	.0104
Women	13.6% (198)	13.6% (74)	.9960
Weight (kg)	78.3 ± 14.0	83.4 ± 19.3	<.0001
Body mass index (kg/m^2)	27.0 ± 4.19	28.6 ± 5.56	<.0001
Myocardial infarction	82.7% (1208)	78.4% (428)	.0253
Stroke	7.3% (106)	5.3% (29)	.1210
Hypertension	58.2% (849)	65.0% (355)	.0052
Atrial flutter or fibrillation	11.9% (174)	13.2% (72)	.4406
Diabetes	34.5% (504)	43.8% (239)	.0001
Previous CABG	2.5% (37)	3.7% (20)	.1757
Previous PCI	15.0% (219)	16.8% (92)	.3083
NYHA class			
I	10.4% (152)	9.7% (53)	.6469
II	46.2% (675)	49.5% (270)	
III	39.2% (573)	37.0% (202)	
IV	4.1% (60)	3.8% (21)	
Visual EF*	0.28 ± 0.08	0.29 ± 0.08	.1415
MR grade			
0	33.6% (490)	41.9% (229)	.0083
1	46.7% (682)	42.7% (233)	
2	15.8% (230)	12.5% (68)	
3	3.5% (51)	2.4% (13)	
4	0.5% (7)	0.5% (3)	

NYHA, New York Heart Association; *PCI*, percutaneous coronary intervention.
Data are expressed as mean ± SD or as percentage (number).
*EF is available for 1,453 subjects with volume measurements and 517 subjects without volume measurements.

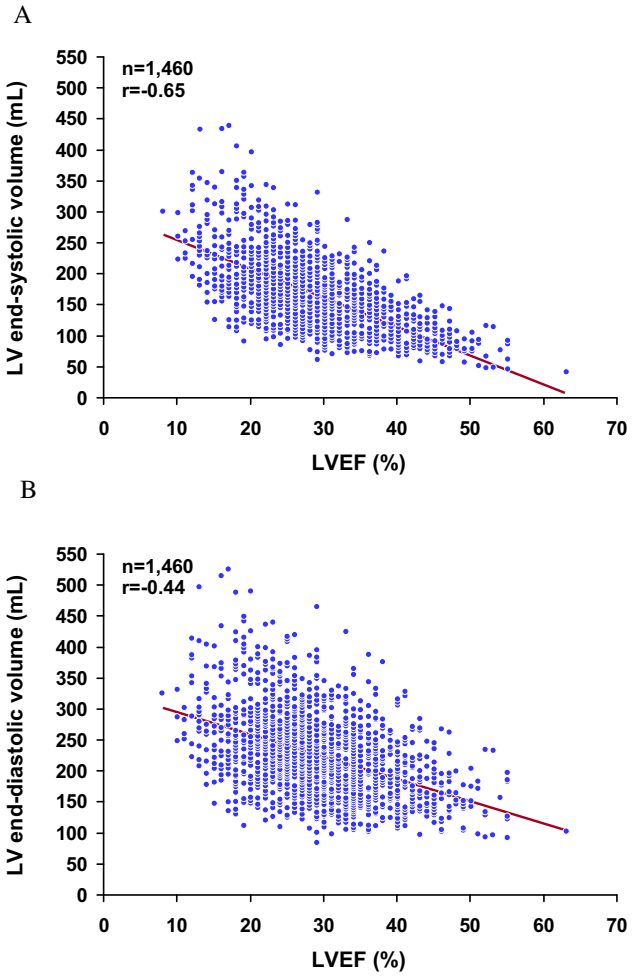

Figure 2 Correlation between LV EF and LVESV **(A)** and LVEDV **(B)**. LVESV had a better correlation than LVEDV with LVEF.

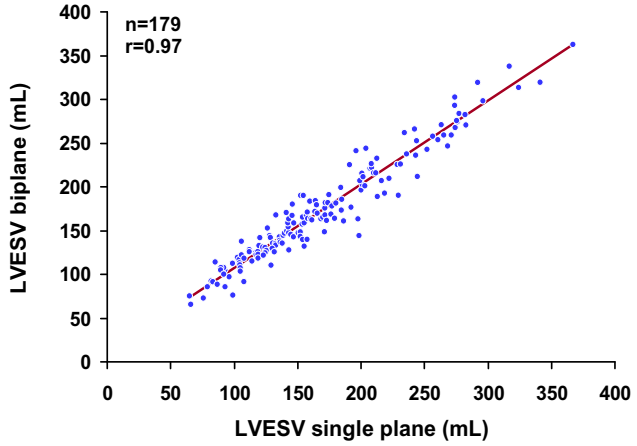

Figure 1 Correlation between LVESV measured by biplane and single-plane Simpson's method.

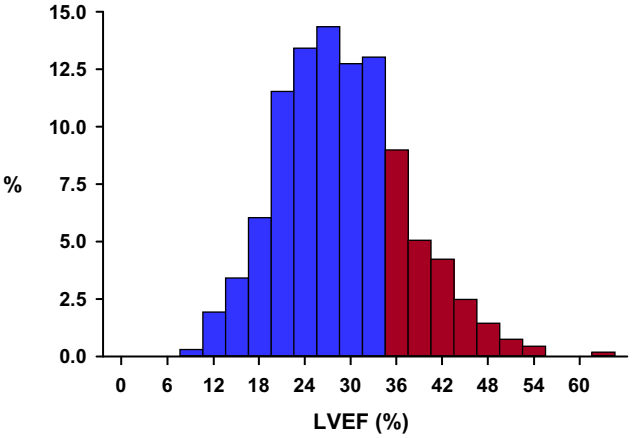

Figure 3 Distribution of LV EF measured by the Echocardiography Core Laboratory. LV EFs were >35% in 18.5% and mentioned in the text.

EROA, which was measured in 169 patients ($r = 0.67$, $P < .001$). However, there was a wide range of EROA for each grade of MR severity (Figure 5). When EROA was ≥0.2 cm^2, MR was at least moderate by visual interpretation in most patients.

Diastolic Function and Filling Pressure

Baseline diastolic function assessment was feasible in 1,634 patients, and function was found to be abnormal in almost all patients enrolled in the trial. Only five of 1,634 patients had normal diastolic function.

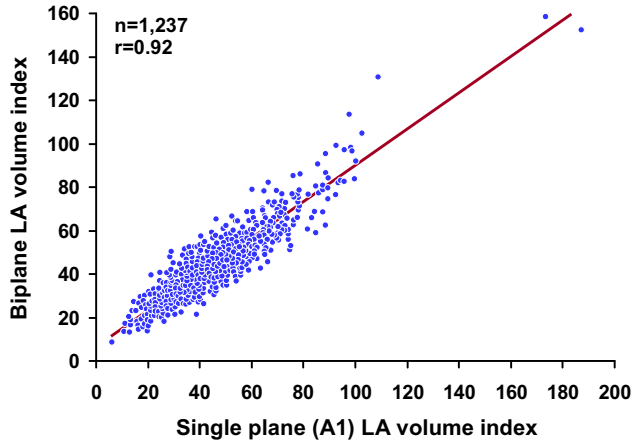

Figure 4 Correlation between biplane and single-plane LA volume index.

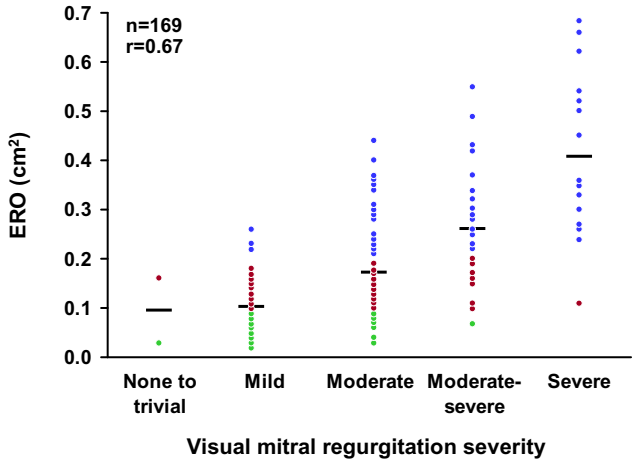

Figure 5 Effective regurgitant orifice area (ERO) versus visual determination of MR severity using color flow imaging.

Diastolic function parameters, including early diastolic mitral inflow (E) and annular (e′) velocities and E/e′ ratio as well as the number of patients in each diastolic dysfunction category, are shown in Table 1. There was only a weak correlation ($r = 0.25$) between LV EF and the DT of mitral inflow velocity, a noninvasive surrogate for pulmonary capillary wedge pressure, as shown in Figure 6. However, there was a gradual increase in LVESV (150 ± 60, 154 ± 55, and 180 ± 60 mL; $P < .001$) and a decrease in LV EF (30.8 ± 8.2%, 30.6 ± 7.9%, and 25.6 ± 7.4%; $P < .001$) as diastolic dysfunction worsened from grade 1 to 2 to 3, respectively.

PASP

PASP was elevated, with a mean value of 42.8 ± 15.5 mm Hg, and correlated best with noninvasive estimates of diastolic filling pressure, E/e′ ($r = 0.54$) and DT of early diastolic mitral inflow velocity ($r = -0.49$). It was found to have a moderate correlation with LA volume ($r = 0.34$) and a weak correlation with LV EF ($r = -0.21$) and LVESV ($r = 0.17$) but no correlation with the Tei index ($r = -0.06$).

DISCUSSION

The STICH trial is the largest cardiac surgery trial assessing different treatment strategies in patients with ischemic cardiomyopathy and

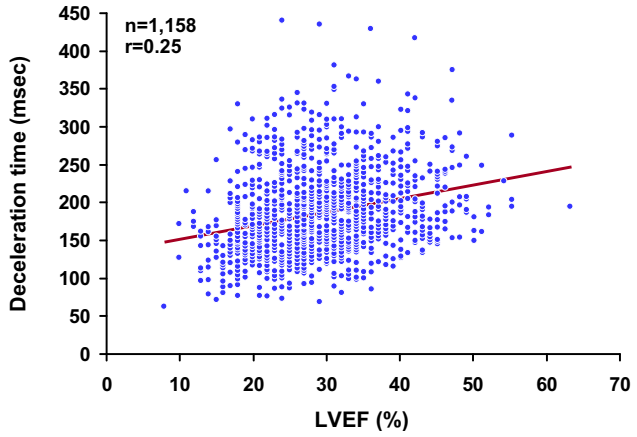

Figure 6 Correlation between LV EF and mitral inflow DT.

provided a unique opportunity to study the cardiac structural, functional, and hemodynamic characteristics in this common, high-risk population. The baseline echocardiographic studies in >2,000 STICH patients demonstrated that there is a wide spectrum of cardiac structure, systolic and diastolic function, and hemodynamic parameters in patients with ischemic cardiomyopathy. There was a weak correlation between LV EF and noninvasively derived diastolic filling pressure, and echocardiographic parameters for diastolic filling pressure were closely related to PASP. These data will be helpful in understanding the clinical outcomes of medical treatment versus CABG with or without SVR treatment strategies in STICH patients. Although LV volume has been one of most important prognostic variables in patients with myocardial infarction or dilated cardiomyopathy, patients with smaller LV volumes created by SVR did not have improved outcomes compared with CABG without SVR in either the composite of death or cardiac hospitalization or in total mortality.[2] Understanding of this paradox and the relationship between systolic and diastolic function among patients with ischemic cardiomyopathy will be critical for optimizing medical and surgical management strategies and defining clinical expectations for this growing patient population.

Echocardiography is commonly used in clinical trials because it is widely available and provides functional as well as structural information of the heart essential for clinical trials. However, many factors affect the quality and completeness of echocardiography, which may have a profound impact on the interpretation of the trial. From our experience of performing Echocardiography Core Laboratory measurements in the STICH trial with a large number of patients with ischemic cardiomyopathy, clinically relevant insights into the use of echocardiography in clinical practice as well as in clinical trials are provided.

LV Volume Measurement

LV volume and LV EF are the basic parameters for defining LV structure and systolic function, used commonly as components of inclusion criteria as well as secondary end points for cardiovascular or heart failure trials. The ability of echocardiography to provide reliable LV volume and LV EF depends on how well the LV endocardial border is defined. In STICH, the LV endocardial border could be traced in 72.8% of patients. The proportion of STICH patients in whom LV volume measurement by Simpson's method was feasible is similar to that (67.5%–79.2%) obtained in >2,000 subjects for Olmsted County diastolic function studies.[10,11] Inability to measure

LV volumes by echocardiography is due to multiple factors that preclude adequate visualization of the LV endocardial border. One remedy is to use a contrast agent, which allows superior visualization of the border. The use of a contrast agent, however, requires additional cost and intravenous access, which are limiting factors in a large clinical trial. However, in clinical practice, in which LV volume and EF are the critical information needed, a contrast agent should be used whenever the LV border is not adequately visualized. Three-dimensional echocardiography also holds a promise to provide more reliable LV volume measurements than two-dimensional echocardiography[12,13] if technical expertise for three-dimensional echocardiography is more generalized and its resolution is more refined. Other cardiac imaging modalities, such as cardiac magnetic resonance imaging or radionuclide imaging, have a higher feasibility to provide LV volumes and/or EF but are less often available for a large-scale clinical trials. For that reason, in STICH, cardiac magnetic resonance and radionuclide imaging were obtained whenever feasible but not mandated. The fact that the patients in whom LV volume measurement was not possible were heavier with more hypertension and diabetes may have an impact on the interpretation and application of clinical data of a trial that uses echocardiographic LV volumes as an inclusion criterion or an end point of the study. One interesting aspect of LV volume measurement by echocardiography in STICH was that LV volumes measured using the biplane Simpson's method were very close to those measured using the single-plane method in the same patient. Therefore, at least for patients with enlarged hearts, the use of single-plane volume measurement (preferably from the apical four-chamber view) appears to be sufficient for clinical use and to be more feasible and less variable in serial volume measurements during follow-up of a specific patient. When LVEDV and LVESV were correlated with LV EF, there was a much tighter correlation with LVESV. White *et al.*[14] also demonstrated that LVESV was a more powerful predictor than LVEDV after acute myocardial infarction. Most clinical trials studying systolic heart failure also have used a change in LVESV as a means to define reverse remodeling.[15,16] In the Valsartan in Acute Myocardial Infarction Trial echocardiographic substudy,[17] both baseline end-diastolic volume and end-systolic volume were independently predictive of the combined end points of death, myocardial infarction, cardiac arrest, or stroke. Therefore, the STICH baseline data support the use of LVESV (as opposed to LVEDV) as a marker of LV remodeling extent in clinical trials of systolic heart failure.

LV EF

The patient entry criterion for STICH was a site-reported LV EF $\leq$ 35% within 3 months that could be determined using any of the following modalities: left ventriculography, radionuclide imaging, cardiac magnetic resonance imaging, or echocardiography. The baseline LV EFs measured by the Echocardiography Core Laboratory, however, were >35% in 18.5% of STICH patients. The difference in LV EF between clinical sites and the Echocardiography Core Laboratory can be related to different imaging methods, interobserver variability, different timing of imaging modalities, or interpretation error. LV EF can change drastically with an alteration in preload and/or afterload. It is possible that LV EF improved after its initial determination at the time of recruitment 2 to 3 months before baseline echocardiography. Test-retest reliability of measuring LV EF by echocardiography was shown to be $\pm$5%,[18] and a similar portion of patients were found to have LV EFs > 35% by baseline cardiac magnetic resonance imaging or radionuclide imaging studies analyzed by the respective core labs (from communication among STICH imaging core labs, but unpublished). Whether this subgroup of patients with LV EFs > 35% have a different response to treatment or outcomes compared with the group with LV EFs $\leq$ 35% will be a subject of subsequent analyses. LV EF is the single most important criterion for various drug and device therapy, which are expensive and sometimes can be harmful. It is possible that we are providing an unnecessary and potentially harmful therapy on the basis of this single measurement, which has significant variability regardless of which imaging modality is used. The medical community may consider creating clinical imaging core labs to provide more standardized measurements values when they are used for a major clinical decision.

LA Volume Measurement

LA volume has been shown to be prognostic in patients with various cardiovascular disorders and is a main component of assessing diastolic function.[19,20] Again, reliable LA volume measurement depends on the accurate detection of the LA wall border and good quality apical views of the left atrium. There are several different methods to measure its volume: prolate-ellipse, area-length, and biplane Simpson's. Most of the investigators who measured LA volumes used the area-length method, which uses a combination of the apical four-chamber view along with an apical two-chamber or long-axis view. The area-length method was used in the Echocardiography Core Laboratory for STICH. Because of the finding that LV volumes by the single-plane Simpson's method were similar to those by biplane method, we also compared LA volumes measured from two apical views with those from one apical view (the four-chamber view). The correlation was again sufficiently encouraging to suggest that a single-plane method be further considered and evaluated for use in future clinical practice and research. The similarity between the single-plane and the biplane methods in LV and LA volume measurements highlights the notion that doing more measurements may not necessarily make more accurate results.

Diastolic Function and Filling Pressures Versus Systolic Function

Many studies have shown that diastolic filling parameters are one of the most significant prognostic factors in patients with systolic dysfunction.[21-23] In this study of contemporary patients with ischemic cardiomyopathy, diastolic dysfunction was observed in nearly all patients, but the extent of dysfunction was variable, with mild, moderate, and severe dysfunction in 37%, 36%, and 26% of patients, respectively. The patients with the most severe diastolic dysfunction had larger LV volumes and lower LV EFs compared with patients with mild or moderate diastolic dysfunction. However, DT and E/e', which have been shown to correlate well with pulmonary capillary wedge pressure and to have a strong prognostic value in patients with systolic heart failure,[21-24] were found to have a weak correlation with LV EF and LV volume in the STICH population, while PASP estimated from tricuspid regurgitation velocity was correlated most closely with diastolic filling parameters among various echocardiographic parameters, including LV volumes and LV EF. Our data are consistent with those from other studies in different patient populations.[25,26] Diastolic filling pressure reflects the final hemodynamic manifestation of combined LV abnormalities, and it is possible that diastolic parameters provide incremental or even better prognostic information than systolic parameters in patients with ischemic cardiomyopathy.

MR in Ischemic Cardiomyopathy

In ischemic cardiomyopathy, tenting of the apically displaced mitral leaflets and tethering of chordae tendineae result in varying degrees of MR, which is an important contributor to morbidity and mortality.[27-29] However, despite marked dilatation of the left ventricle, only 25% of patients in our study were found to have grade ≥ 2 MR. It is possible that a bias existed against patients with severe degrees of MR participating in this trial, because physicians might have opted for surgical treatment rather than randomizing the patients in this trial. However, despite the known important prognostic value of MR, surgical treatment of MR or mitral valve repair in the setting of ischemic cardiomyopathy has not been shown to improve patients' survival compared with medical therapy.[30] The STICH trial provides an opportunity to assess the impact of medical therapy, CABG, or CABG plus SVR on the natural history of functional MR in the setting of ischemic cardiomyopathy. Although measured by the proximal isovelocity surface area method in only a subset of 169 patients, there was a wide range of EROA for each grade of visually assessed MR severity, although there was a significant correlation. It has been shown that patients with EROAs > 0.2 cm^2 have reduced survival after myocardial infarction, and EROA > 0.2 cm^2 in this study was associated with at least a moderate degree of MR by visual assessment. McCully *et al.*[31] showed that visual assessment overestimates MR severity compared with EROA (or EROA underestimates compared with visual assessment) in functional MR, as shown in STICH. When there is a discrepancy between MR severity assessments, further testing such as transesophageal echocardiography and/or an integrated approach along with clinical correlation is required.

If a specific treatment strategy results in reducing MR severity and reversing the underlying determinants of MR, it is logical to expect that this treatment may correlate with a reduction in symptoms and an improvement in survival in patients with MR. Although reduction of LV volume in response to a given therapeutic modality (medical or surgical) is expected to parallel the reduction of MR, there has not been a large prospective study of patients with ischemic cardiomyopathy to monitor the immediate and long-term impact of medical or surgical treatment on the severity of MR. EROA and MR volume measurements are more objective in serial follow-up of patients. We recommend that both visual assessment and the proximal isovelocity surface area method for MR severity be performed in all patients with MR.

The impact of SVR on LV remodeling process is not well known, and even worsening of MR after SVR has been reported.[32] A more recent report, however, suggested that mitral valve repair was not found to be necessary in conjunction with SVR.[33] Comprehensive serial (4-month and 24-month follow-up) echocardiographic data in STICH patients will be able to correlate changes in structural and functional parameters with the extent of change in the severity of MR as well as to evaluate the mechanism and effects of volume reduction SVR surgery as well as of CABG on MR.

Echocardiography Core Laboratories for Clinical Trials

Echocardiography is an operator-dependent and patient-dependent imaging modality with multiple factors to influence the accuracy of its measurements, while it is the most widely available and versatile technique to provide structural, functional, and hemodynamic information of the heart. The interpretation of the trial data depends on the accuracy and the reliability of echocardiographic measurements when it is used for determination of inclusion and/or as an end point in a clinical trial. Although more costly, measurement of echocardiographic variables in a standardized way by echocardiography core laboratories minimizes measurement variability and improves the precision of study results.[34] The superiority of core lab interpretation for reducing variability and enhancing study outcome has been reported.[35-37] Moreover, the American Society of Echocardiography has published a document emphasizing the importance of high-quality imaging and measurement for clinical trials[38] and an expert consensus document regarding the responsibilities and best practices of echocardiography core laboratories participating in clinical trials.[34]

Limitations

Although vigorous efforts at standardization were made in the Echocardiography Core Laboratory, echocardiographic measurements were performed and approved by several sonographers and physician echocardiographers, resulting in potential measurement variability. However, the large scale of the STICH trial did not allow analysis by a single sonographer and a single physician. Interobserver variability in LV volume measurements was small and acceptable. An important limitation inherent to echocardiography and a large clinical trial involving a large number of clinical sites was that not all echocardiographic parameters were obtained or able to be measured in all patients. LV volumes and LV EF could not be measured quantitatively in 27% of patients because of difficulty in visualizing the entire endocardial border of the left ventricle. The use of contrast echocardiography might have improved visualization but was not performed in this trial.

The severity of MR, right ventricular dysfunction, and LV regional wall motion abnormalities were assessed visually. However, the visual assessment was done by a small group of experienced physician echocardiographers and is still the most widely accepted method of assessing MR. From the comprehensive echocardiographic data from the STICH trial, we expect to gain a better understanding of which variables have most prognostic power in patients with ischemic cardiomyopathy and how these variables change after different treatment strategies. Baseline echocardiographic data and correlations among systolic function, diastolic function, MR, RV function, and PASP reported herein will serve as a reference to answer those clinically valuable questions.

CONCLUSIONS

In this contemporary STICH trial of a large number of patients with ischemic cardiomyopathy, baseline echocardiograms analyzed by the Echocardiography Core Laboratory demonstrated a wide spectrum of LV shape, function, and hemodynamic parameters as well as the feasibility and limitations of obtaining essential echocardiographic measurements. The use of echocardiographic parameters in clinical practice and research needs to incorporate the variability and limitations of echocardiographic measurements described in this report.

ACKNOWLEDGMENTS

We acknowledge all STICH clinical sites for their excellent echocardiographic studies.

APPENDIX

STICH Echocardiography Core Laboratory Personnel

Jae K. Oh, MD, director; Barbara G. Manahan, RDCS, manager; Daniel D. Borgeson, MD; Charles J. Bruce, MD; Grace Lin, MD;

Fletcher A. Miller, Jr., MD; Patricia A. Pellikka, MD; Fredrick J. Blahnik, RDCS; Diane M. Miller, LPN, RDCS; Ronald F. Springer, RDCS; James M. Welper, RDCS.

Mayo Echocardiography Core Laboratory Statistics

Heather J. Wiste, BA.

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