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Clinical Investigation

Slope of the Anterior Mitral Valve Leaflet:

A New Measurement of Left Ventricular Unloading for Left Ventricular Assist Devices and Systolic Dysfunction

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Left ventricular assist device (LVAD)-supported patients are evaluated routinely with use of transthoracic echocardiography. Values of left ventricular unloading in this unique patient population are needed to evaluate LVAD function and assist in patient follow-up.

We introduce a new M-mode measurement, the slope of the anterior mitral valve leaflet (SLAM), and compare its efficacy with that of other standard echocardiographically evaluated values for left ventricular loading, including E/e′ and pulmonary artery systolic pressures. Average SLAM values were determined retrospectively for cohorts of random, non-LVAD patients with moderately to severely impaired left ventricular ejection fraction (LVEF) (<0.35, n=60). In addition, pre- and post-LVAD implantation echocardiographic images of 81 patients were reviewed.

The average SLAM in patients with an LVEF <0.35 was 11.6 cm/s (95% confidence interval, 10.4–12.8); SLAM had a moderately strong correlation with E/e′ in these patients. Implantation of LVADs significantly increased the SLAM from 7.3 ± 2.44 to 14.7 ± 5.01 cm/s (n=42, P *<0.0001). The LVAD-supported patients readmitted for exacerbation of congestive heart failure exhibited decreased SLAM from 12 ± 3.93 to 7.3 ± 3.5 cm/s (n=6,* P*=0.041). In addition, a cutpoint of 10 cm/s distinguished random patients with LVEF <0.35 from those in end-stage congestive heart failure (pre-LVAD) with an 88% sensitivity and a 55% specificity.*

Evaluating ventricular unloading in LVAD patients remains challenging. Our novel M-mode value correlates with echocardiographic values of left ventricular filling in patients with moderate-to-severe systolic function and dynamically improves with the ventricular unloading of an LVAD. ***(Tex Heart Inst J 2014;41(3):262-72)***

Key words: *Echocardiography, Doppler/methods/trends; health status indicators; heart failure/classification/physiopathology/therapy; heart-assist devices; models, theoretical; predictive value of tests; reference values; sensitivity and specificity; severity of illness index; ventricular function/physiology*

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Therapy with an implanted continuous-flow left ventricular assist device (CF-LVAD) has improved survival rates and quality of life in patients with end-stage heart failure by increasing cardiac output and decreasing left ventricular (LV) preload.[1-3] In non-LVAD–supported patients with heart failure, multiple transthoracic echocardiographic (TTE) methods exist for evaluating LV filling pressures, including chamber dimensions, mitral valve inflow Doppler measurements, pulmonary venous Doppler measurements, and tissue Doppler velocities.[4-6] In patients with nonphysiologic unloading of the LV by a CF-LVAD, acquisition and interpretation of the Doppler and echocardiographic images required for many of these accepted methods might be challenging. Even in circumstances in which accurate Doppler evaluation is possible, some studies in CF-LVAD patients have revealed that, although E/e′ ratio decreases after LVAD implantation, it correlates poorly with invasive measurements of pulmonary capillary wedge pressure (PCWP).[7,8] Other guidelines are therefore needed to supplement current knowledge toward evaluating LV unloading and clinical status in CF-LVAD–supported patients.

The mitral valve is a fast-moving structure, the motion of which is best detected with the superior temporal resolution of M-mode echocardiography in the parasternal views.[9] In the presence of elevated filling pressures, the anterior mitral leaflet tracing in M-mode displays gradual closure after the peak of the A-wave in cardiac diastole, as compared with brisk closure in patients with normal filling pressures.[9] In extreme cases, this closure process slows to the point where there is a recognizable "B-bump" after atrial contraction, which for more than 40 years has been known to correlate with significantly elevated LV end-diastolic pressure (LVEDP)— greater than 20 mmHg.[10] Until now, the slope of the anterior mitral leaflet (SLAM) in end-diastole has never

been measured or quantified. In the present study, we examined the clinical usefulness of this phenomenon by evaluating SLAM in randomly selected patients with systolic heart failure, and in LVAD-implanted patients before and after LVAD implantation. We hypothesized that the SLAM would indicate relative LV filling pressures, and that it would increase in patients with end-stage heart failure after CF-LVAD support.

Patients and Methods

Our echocardiographic database was queried randomly for 60 non-intensive care unit patients with moderate-to-severe systolic dysfunction (LV ejection fraction [LVEF], <0.35) on studies performed from January through March 2010. In addition, the clinical records and echocardiograms of 81 adult recipients of the HeartMate II® LVAD (Thoratec Corporation; Pleasanton, Calif) from January 2007 through December 2010 were evaluated in a single-center, retrospective review. The retrospective study was approved by the institutional review board of the Washington University School of Medicine.

Echocardiographic Data

We reviewed parasternal and apical views, including 2-dimensional (2D), Doppler, and M-mode data obtained with use of the iE33 (Koninklijke Philips N.V.; Best, The Netherlands) or the GE Vivid 7® ultrasound system (GE VingMed Ultrasound AS; Horten, Norway). Doppler and 2D measurements included: LVEF by means of the Simpson method, E point-septal separation (EPSS) in triplicate, LV end-diastolic and end-systolic diameters, peak early (E) transmitral filling velocity in diastole, early tissue septal and lateral annular velocities (E′), pulmonary artery pressure estimates by tricuspid regurgitation velocity and inferior vena cava size, and right ventricular outflow tract (RVOT) volume thickness index (VTI).[4,11,12]

The SLAM closure after the atrial phase of LV diastolic filling was obtained from 2D-guided M-mode TTE images of the mitral valve in parasternal views obtained at either a 66-mm/s or 100-mm/s sweep speed. With use of ProSolv® software (FUJIFILM Medical USA, Inc.; Stamford, Conn), the slope was calculated in cm/s between a point of inflection at which the anterior mitral valve leaflet begins a downward descent and another point at which it meets the posterior mitral valve leaflet, closing the mitral valve. Figure 1 shows an illustration of the methodology and actual image measurements. The slope was obtained at the underside of the valve for thickened anterior mitral valve leaflets, at which the image contrast between the valve space and valve tissue is greatest. If the downward descent of the A wave contained a "B-bump," the slope remained calculated from the inflection of the A-wave descent to mitral valve closure. We included only patients for whom at least 3 cardiac cycles were available, in order to generate a mean SLAM for each patient's study. Our LVAD analysis of SLAM was obtained only on those patients for whom we had paired before- and after-implantation data. After-implantation data were obtained in patients in the ambulatory setting or who were readmitted for reasons other than exacerbation of congestive heart failure (CHF) . Patients were excluded for atrial fibrillation or flutter, mechanical mitral valves, excessive artifact from bioprosthetic valve struts, and poor image quality that precluded slope analysis. The slope is negative; however, for clarity, the slope in this article is expressed as an absolute value with SD, obviating the need for a preceding negative sign (–).

Serum Pro-Brain Natriuretic Peptide Measurement

Serum pro-brain natriuretic peptide (BNP) levels (pg/mL) were obtained retrospectively for LVAD patients during the patients' hospital admission before LVAD implantation, and either before discharge from the hospital or at a follow-up hospital admission or outpatient appointment. All samples were analyzed by the institutional core laboratory.

Diuretic Requirement

The diuretic requirement for each patient was collected before and after LVAD surgery. Furosemide intravenous (IV)-equivalent dosing was calculated in such a manner that 40 mg of IV furosemide was equivalent to 80 mg of oral furosemide, 20 mg of IV torsemide, or 1 mg of IV bumetanide.[13-16]

SLAM in the Presence of Acute Heart Failure Exacerbation

We next sought to examine the usefulness of SLAM as an indicator of clinical status in CF-LVAD–supported patients. Through detailed chart reviews, we analyzed the SLAM of patients readmitted for CHF during the study period who had suitable echocardiographic images before LVAD implantation, after LVAD implantation in an ambulatory setting, and during the CHF readmission for analysis, according to discharge diagnosis.

Statistical Methods

All tests for significance were conducted at the 5% error rate (P=0.05). Analysis was conducted with use of SAS software version 9.3 (SAS Institute Inc.; Cary, NC). Change in the M-mode slope from before LVAD implantation to after-implantation and upon readmission for heart-failure symptoms was determined by means of a paired t test. Only LVAD patients for whom we had paired measurements and 3 cycles per condition were included in this part of the analysis. Reproducibility was analyzed for inter- and intraobserver reliability by means of the intraclass correlation coefficient

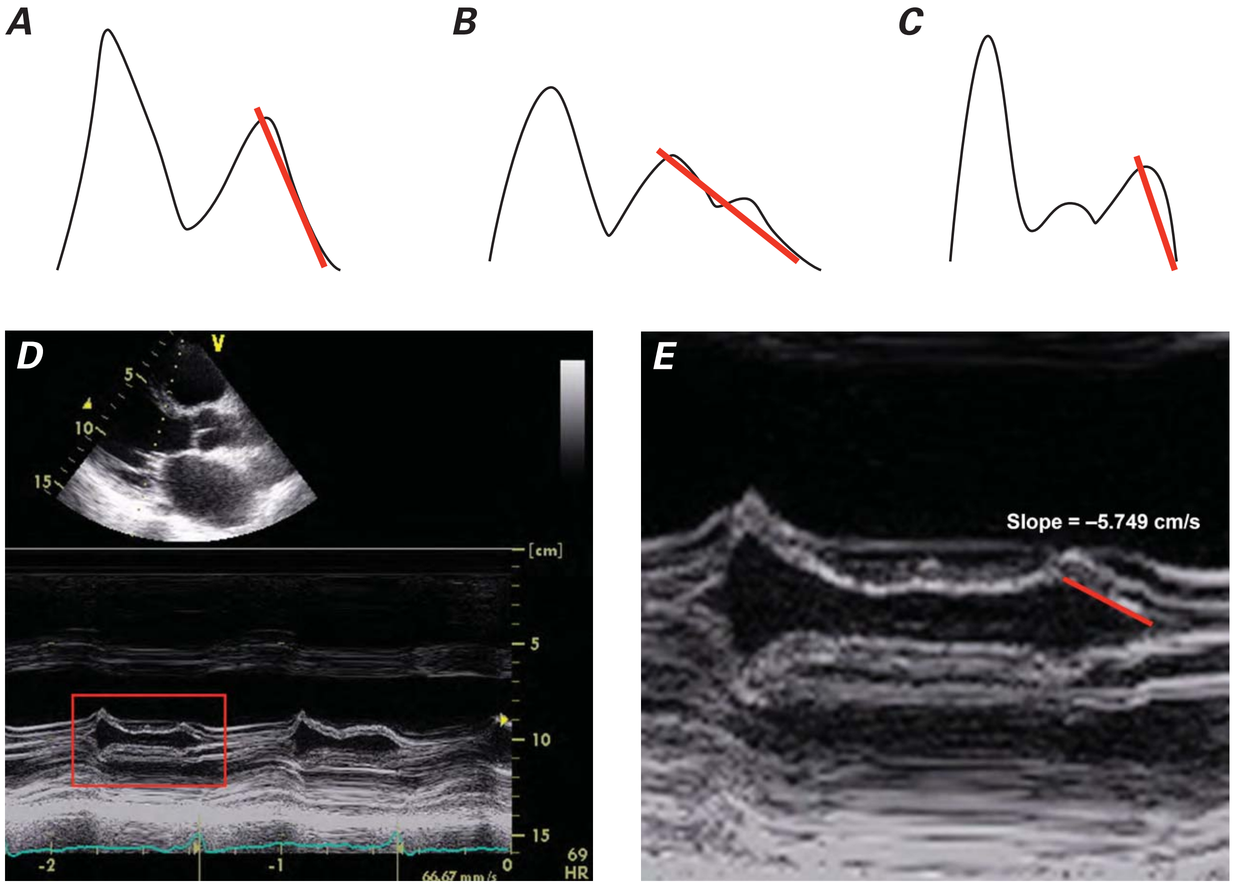


Fig. 1 Slope measurement methodology. ***A***) The slope of the anterior mitral valve leaflet (SLAM) is measured at the point of inflection of the A-wave descent in diastole. ***B***) Example of the SLAM measured in a patient with increased left ventricular end-diastolic pressure, including the "B-bump." ***C***) Example of a steep SLAM. ***D***) Two-dimensional–guided M-mode transthoracic echocardiogram of the mitral valve (parasternal long-axis view) at 66-mm/s sweep speed. The SLAM is identified in red. ***E***) The SLAM measurement at the point of inflection, from the underside of the leaflet to the point of valve closure, as shown by the red line.

(ICC) and the Bland-Altman method.[17] Before-to-after LVAD changes for RVOT-VTI, BNP, diuretic requirement, pulmonary artery pressure, EPSS, and LV end-diastolic and end-systolic diameters were calculated by means of the Student paired *t* tests. The correlation between PCWP and SLAM before LVAD implantation was examined by means of the Pearson correlation coefficient. The Fisher exact test was used for categorical variables in demographic categories.

Patients with moderate-to-severe systolic dysfunction were combined with before- and after-LVAD patients, to examine differences in mean SLAM between each group. Analysis of covariance (ANCOVA) was conducted to adjust for age and sex. Group means and all paired comparisons were on the basis of model results. A correction for multiple comparison tests was applied. Two different ANCOVA models were built: one with LVAD pre-implant SLAM values and one with LVAD post-implant SLAM values. Changes in SLAM and E/e′ from post-LVAD status to readmission were evaluated by means of paired *t* tests. Only patients for whom we had post-implant and readmission data were included in this analysis.

The ability of SLAM to distinguish accurately between groups was evaluated by means of the area under the receiver operating characteristic curve. Comparisons were made between random patients with an LVEF <0.35 and pre-LVAD patients. Sensitivity and specificity were determined, and an optimal cutpoint was chosen on the basis of the Youden index. The correlation between SLAM, E/e′, and LVEF values was examined by means of the Pearson correlation coefficient. Deviation from linearity was examined by means of scatter plots and a regression model, including the quadratic term for E/e′.

Results

SLAM in Patients with Moderate-to-Severe Systolic Dysfunction

The SLAM, LVEF, and E/e′ were first evaluated in cohorts of patients who had at least moderately im-

paired LVEF (<0.35). The median SLAM was 11.6 ± 5.27 cm/s for patients with LVEF <0.35 (Table I). Linear regression analysis revealed no significant correlation between SLAM and LVEF. Figure 2A shows a representative M-mode TTE image of the SLAM in a patient with an LVEF <0.35, and Figure 2B shows a selected line for SLAM determination. To evaluate the correlation of SLAM with estimated filling pressures in these patients, the ratios of early transmitral velocity (E) to the average of medial and lateral annular early myocardial tissue Doppler velocities (e′) were plotted against the SLAM values (Fig. 2C). The median E/e′ of patients with moderate-to-severe LV dysfunction was 16.3 ± 7.74 and correlated significantly with the SLAM in a linear fashion (r= –0.473, P=0.0001) (Fig. 2C). Unsupported, randomly selected patients with moderately to severely depressed LVEFs therefore display a correlation between SLAM and E/e′ measurements, and E/e′ is well validated in this population to correlate closely with LV filling pressures.[5]

Demographic Characteristics of the LVAD Study Population

We identified 81 LVAD patients who had undergone HeartMate II implantation at our institution. They were predominantly male (79%) and white (72%), with a median age of 53.8 ± 13.05 years (Table II). Approximately one third had diabetes mellitus at the time of implantation, and the cause of heart failure was nonischemic cardiomyopathy in 54%. We were unable to obtain the SLAM for 39 of these patients because of atrial fibrillation (n=7), lack of before-implantation TTE studies (n=5), lack of after-implantation TTE studies (n=8), mechanical mitral valves (n=3), uninterpretable images of the mitral valve in 2D or M mode (n=7), and fewer than 3 cardiac cycles for the before- or after-LVAD windows (n=9).

TABLE I. Random Patients with LVEF <0.35

Variable	**LVEF <0.35** (N=60)
Age (yr)	54.3 ± 15.74
Male sex	32 (53)
LVEF	0.22 ± 0.53
SLAM (cm/s)	11.6 ± 5.27
E/e′ ratio	16.2 ± 7.74
Calculated PCWP (mmHg)	22 ± 9.59

E = Early diastolic mitral velocity; e′ = mitral annular tissue velocity; LVEF = left ventricular ejection fraction; PCWP = pulmonary capillary wedge pressure; SLAM = slope of the anterior mitral valve leaflet

Values are expressed as mean ± SD or as number and percentage.

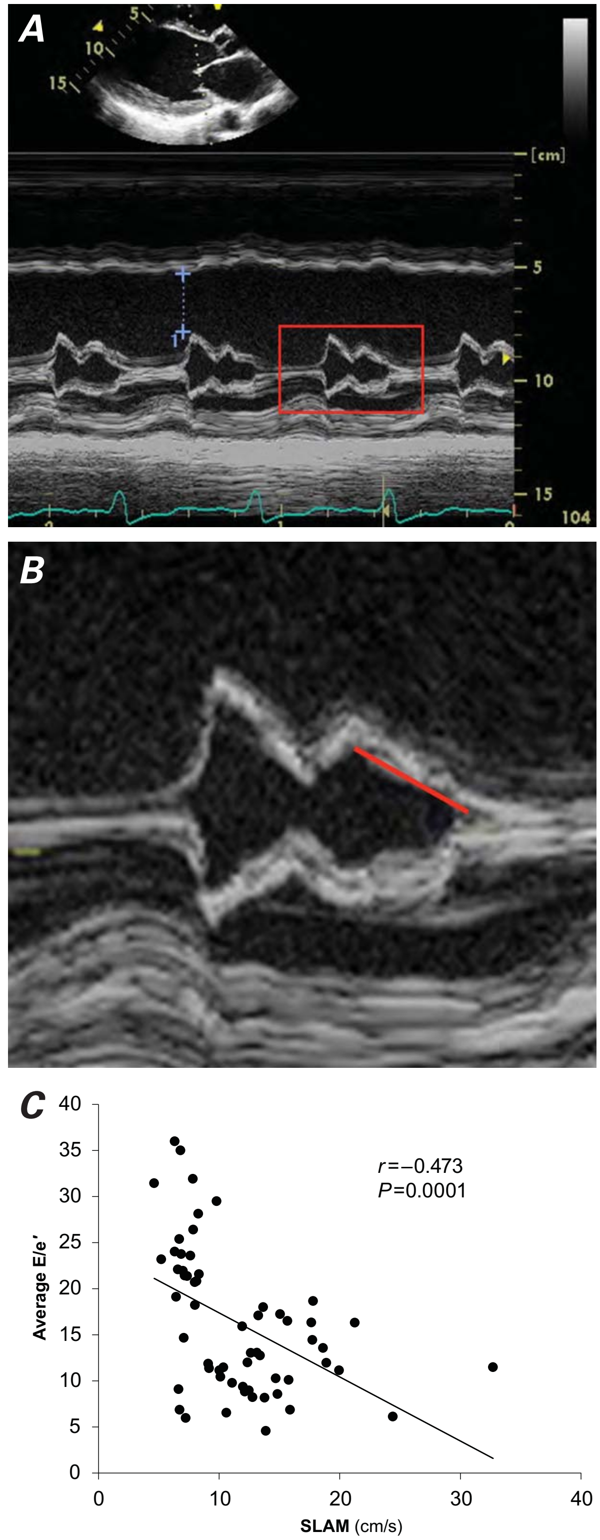


Fig. 2 *Slope of the anterior mitral leaflet (SLAM): LVEF <0.35 and correlation with E/e′.* ***A****) M-mode transthoracic echocardiographic image of the mitral valve in a patient with a left ventricular ejection fraction (LVEF) <0.35.* ***B****) One diastolic cycle of the same M-mode image of the mitral valve with the visualized SLAM.* ***C****) Plot of E/e′ and SLAM in patients with an LVEF <0.35, (r= –0.473,* P*=0.0001).* P *<0.05 was considered statistically significant.*

Echocardiographic and Laboratory Values Before and After LVAD Implantation

We next evaluated currently accepted echocardiographic and clinical values of heart failure in the CF-LVAD–supported patient group both before and after LVAD implantation (Table III). Consistent with the medical literature,[18,19] the LV end-diastolic and end-systolic dimensions and estimated pulmonary artery pressures decreased by approximately 20% to 30% after LVAD implantation (P <0.001). The EPSS decreased an average of 28.5% (from 2.5 to 1.8 cm) after LVAD implantation (P <0.0001). The RVOT-VTI significantly increased after LVAD implantation (P <0.0001), which was similar to increases in prior studies.[20] In addition, our patient population showed a reduction in BNP similar to that in other institutional populations after LVAD surgery, from an average of 1,715 to 305 pg/mL (P <0.0001).[8] Concomitant with a decrease in BNP, diuretic dosing (expressed as roughly equivalent to IV furosemide) decreased from approximately 70 mg/d to 22 mg/d, at a documented outpatient visit. These results indicate that, after LVAD implantation, our patients experienced an expected improvement in cardiac output and a decrease in congestion.

We next sought to validate the SLAM value in the sicker group of CHF patients who later received an LVAD. Invasive hemodynamic data were available for 23 patients before LVAD implantation within 48 hours of the TTE and SLAM measurement. The median before-implantation PCWP was 26 ± 5.9 mmHg. In these patients, the average SLAM was 7 cm/s, which was significantly lower than the average SLAM in moderate-to-severe native heart failure (SLAM, 11.6 cm/s; P ≤0.0001). Upon LVAD implantation, the E/e′ value significantly decreased from 19.4 ± 8.72 to 13.3 ± 10.91 (P=0.0042), which was similar to a published observation in hemodynamically stable outpatients.[19] The before-LVAD E/e′ ratio correlated significantly with the SLAM (r= –0.409, P=0.0119), although the after-LVAD E/e′ did not (r= –0.249, P=0.1631). After LVAD implantation, the mean SLAM of patients increased in steepness from 7.3 ± 2.44 to 14.7 ± 5.01 cm/s (n=42; P <0.0001) at a mean of 11 months after implantation (range, 5 d–47 mo) (Fig. 3). Interobserver ICC values ranged from 0.864 to 0.932, and intraobserver ICC values ranged from 0.881 to 0.908 (Table IV). The Bland-Altman graphs suggested few to no differences between observer measurements, and insignificant results were found upon testing for linearity (P >0.2 in all) (Fig. 4). Taken together, the ICC and Bland-Altman analyses indicate that inter- and intraobservations are equally precise.

TABLE II. Characteristics of the 81 Patients with LVADs

Variable	Value
Age (yr)	53.8 ± 13.05
Male sex	64 (79)
White	59 (73)
Black	22 (27)
Diabetes mellitus	26 (32)
Ischemic cardiomyopathy	37 (46)

LVADs = left ventricular assist devices

Values are expressed as mean ± SD or as number and percentage.

SLAM in LVAD Patients Admitted for Congestive Heart Failure Exacerbation

During the study period, 13 patients with CF-LVADs were readmitted for CHF exacerbation (Table V). Of

TABLE III. Comparison of Variables Before and After LVAD Implantation

Variable	N	Before LVAD	After LVAD	*P* Value*
M-mode SLAM (cm/s)	42	7.3 ± 2.44	14.7 ± 5.01	<0.0001
RVOT-VTI (cm)	54	6.5 ± 3.07	9.8 ± 2.75	<0.0001
BNP (pg/mL)	45	1,758.2 ± 1,286.17	350.4 ± 245.4	<0.0001
PASP (mmHg)	48	53.4 ± 14.21	33.4 ± 10.13	<0.0001
EPSS (cm)	43	2.6 ± 0.59	1.8 ± 0.76	<0.0001
LVEDD (cm)	54	6.8 ± 1	5.5 ± 1.46	<0.0001
LVESD (cm)	54	6.1 ± 0.96	5 ± 1.45	<0.0001
Furosemide IV requirement (mg/d)	60	69.8 ± 54.16	21.7 ± 21.41	<0.0001

BNP = pro-brain natriuretic peptide; EPSS = E-point septal separation; IV = intravenous; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; PASP = pulmonary artery systolic pressure; RVOT-VTI = right ventricular outflow tract-volume thickness index; SLAM = slope of the anterior mitral valve leaflet

*On the basis of paired t test

Values are expressed as mean ± SD. P <0.05 was considered statistically significant.

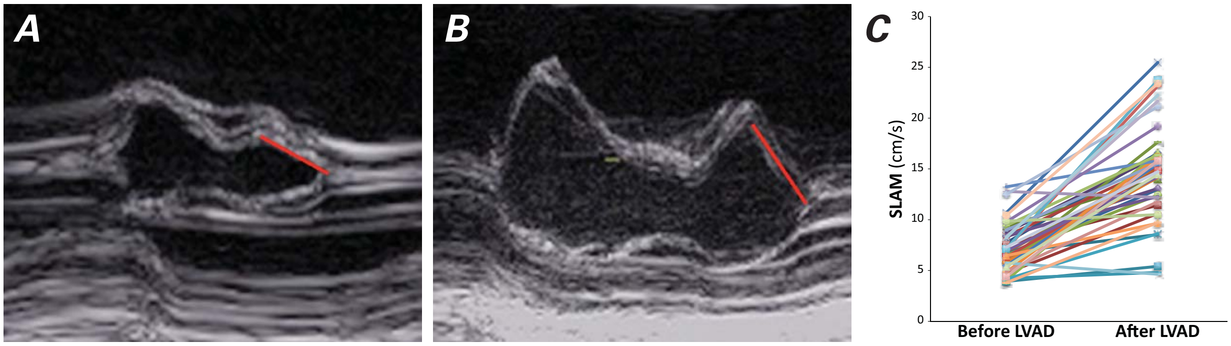


Fig. 3 *Two-dimensional guided M-mode transthoracic echocardiograms show the mitral valve **A**) before left ventricular assist device (LVAD) implantation and **B**) a steeper descending slope of the anterior mitral valve leaflet (SLAM) after implantation. **C**) Graph shows raw SLAM data from 42 patients before LVAD implantation (7.3 ± 2.44 cm/s) and after implantation (14.7 ± 5.01 cm/s;* P *<0.0001).* P *<0.05 was considered statistically significant.*

TABLE IV. Inter- and Intraobserver Agreement for Before- and After-LVAD Measurements of SLAM

	Bland-Altman				Intraclass Correlation	
		95% Limits				
Variable	**Bias**	**Lower**	**Upper**	***P* Value**	**Coefficient**	**95% CI**
Interobserver						
Before	0.25	–1.66	2.18	0.24	0.932	(0.842–0.971)
After	–1.03	–6.92	4.85	0.53	0.864	(0.709–0.939)
Intraobserver						
Before	–0.09	–1.63	1.45	0.3	0.881	(0.65–0.963)
After	0.79	–2.11	3.69	0.96	0.908	(0.721–0.972)

CI = confidence interval; LVAD = left ventricular assist device; SLAM = slope of the anterior mitral valve leaflet

P <0.05 was considered statistically significant.

these, 6 had correlative echocardiographic data before and after LVAD implantation and after LVAD implantation with CHF-exacerbation symptoms with a SLAM value, and 7 had echocardiographic data in these 3 conditions for E/e′. Comparison between echocardiograms obtained after LVAD placement without an admission diagnosis of CHF, and at readmission for a CHF exacerbation, revealed a significant decrease in SLAM from 12 ± 3.93 to 7.3 ± 3.5 (*P*=0.041). Figure 5 shows representative findings in one patient who had a suspected pump thrombosis. The E/e′ ratio of these 13 patients displayed marked variability, and an increase in E/e′ from 15.9 ± 11.04 to 19.04 ± 14.42 was not statistically significant (*P*=0.112).

Distinguishing between Systolic Dysfunction and Advanced Heart Failure (before LVAD Placement)

Finally, we sought to identify a cutoff SLAM value to distinguish between randomly selected systolic CHF patients with an LVEF <0.35 and advanced-CHF patients who needed LVAD support. After adjusting for age and sex, we found that the SLAM of the before-LVAD patients was significantly lower (7.1 cm/s; *P* <0.0001) than that of randomly selected patients with an LVEF <0.35 (Fig. 6A). A separate analysis of the after-LVAD implantation patients also yielded a significant difference in SLAM between patients after LVAD placement (14.5 cm/s; 95% CI, 13–16) and those with LVEF <0.35 (11.6 cm/s; 95% CI, 10.4–12.8) (*P*=0.008). A receiver operating characteristic analysis indicated that SLAM could distinguish before-LVAD patients in end-stage heart failure from the randomly selected patients with an LVEF <0.35 at an area under the curve (AUC) of 0.7742 (95% CI, 0.6853–0.8631). An AUC of 1.0 would suggest perfect accuracy, whereas an AUC of 0.5 would indicate that SLAM is no better than chance (Fig. 6B). An optimal SLAM cutpoint of 10 cm/s, determined by means of Youden index analysis, had an 88% sensitivity and a 55% specificity at distinguishing patients with end-stage CHF in the before-LVAD category from all patients with LVEF <0.35 (Table VI).

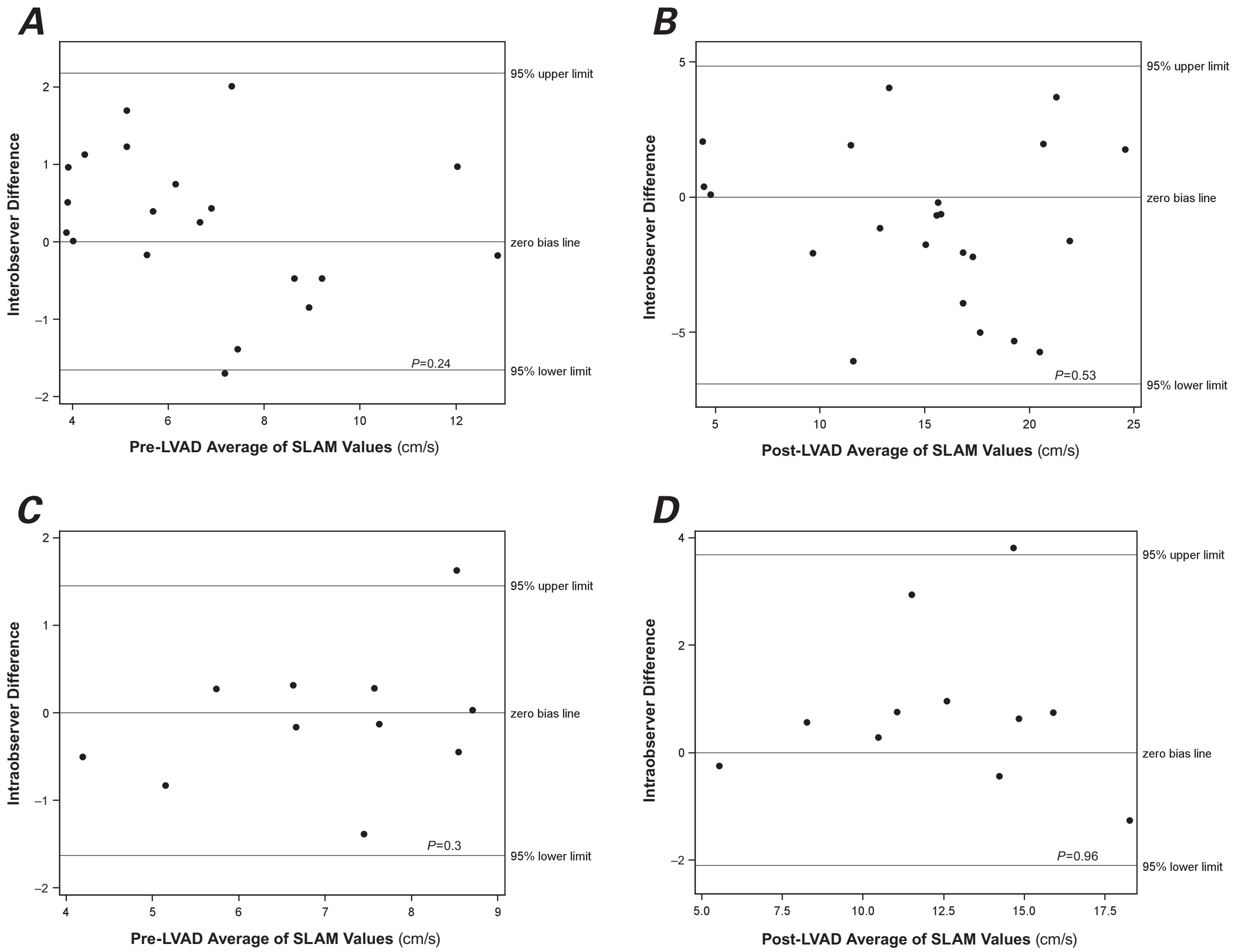


Fig. 4 *Graphs, showing Bland-Altman plots of interobserver agreement* ***A****) before and* ***B****) after left ventricular assist device (LVAD) implantation, and intraobserver agreement* ***C****) before and* ***D****) after implantation, suggest few to no differences between observer measurements; insignificant results were found upon testing for linearity.* P *≤0.05 was considered statistically significant.*

SLAM = slope of the anterior mitral valve leaflet

TABLE V. Comparison of 13 Patients after LVAD Implantation and at Hospital Readmission

Variable	No. Pts.	After LVAD	Readmission LVAD	*P* Value*
SLAM	6	12 ± 3.93	7.3 ± 3.5	0.0409
E/e′	7	15.9 ± 11.04	19.04 ± 14.42	0.1124

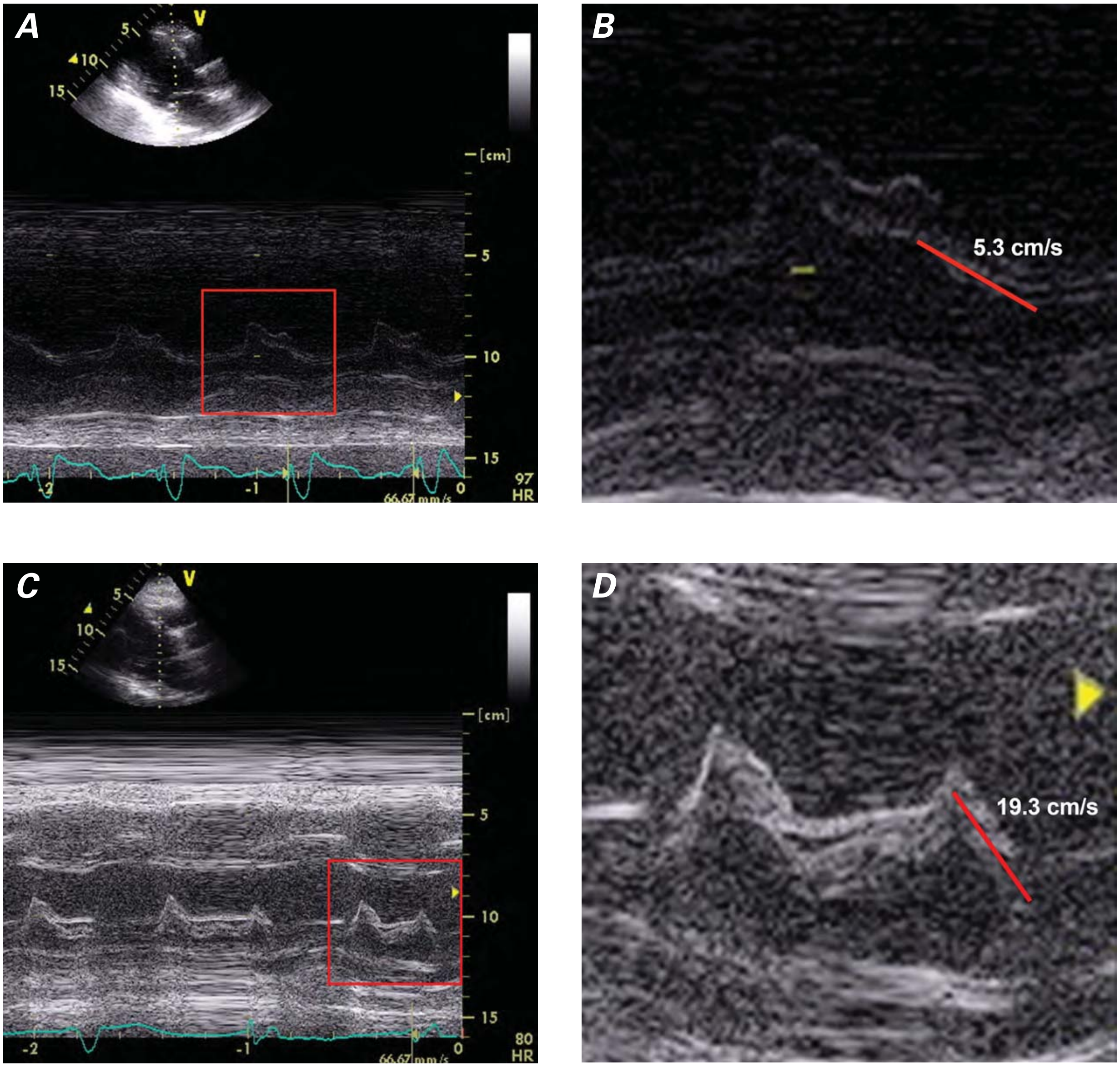
E = early diastolic mitral velocity; e′ = mitral annular tissue velocity; LVAD = left ventricular assist device; Pts = patients; SLAM = slope of the anterior mitral valve leaflet

*On the basis of paired *t* test

Values are expressed as mean ± SD. *P* <0.05 was considered statistically significant.

Discussion

Noninvasive evaluation of LV filling values in LVAD-supported patients is a vexing clinical problem. Continuous-flow LVADs unload the LV by pumping blood from the LV apex to the ascending aorta. The consequences of apical surgical LVAD implantation and near-pulseless LVAD-driven blood flow with variable output through the native aortic valve pose new challenges in evaluating circulatory hemodynamic status with use of noninvasive imaging. Currently accepted methods for evaluating LV filling pressures, such as E/e′, might at times be difficult to obtain or be unreliable because of an acoustic artifact consequent to positioning the transducer at the cardiac apex.[20] In the present study, we introduce the quantified SLAM—a novel echocar-



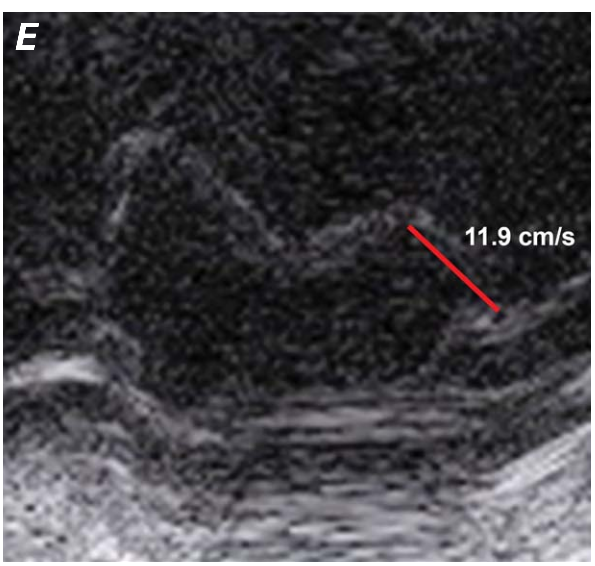


Fig. 5 *M-mode transthoracic echocardiograms of the mitral valve in a patient with congestive heart failure symptoms show **A**) a view before left ventricular assist device implantation with **B**) an associated slope of the anterior mitral valve leaflet (SLAM) of 5.3 cm/s; and **C**) a view after device implantation with **D**) an associated SLAM of 19.3 cm/s. **E**) M-mode image shows a SLAM of 11.9 cm/s in the same patient after readmission to the hospital with congestive heart failure symptoms.*

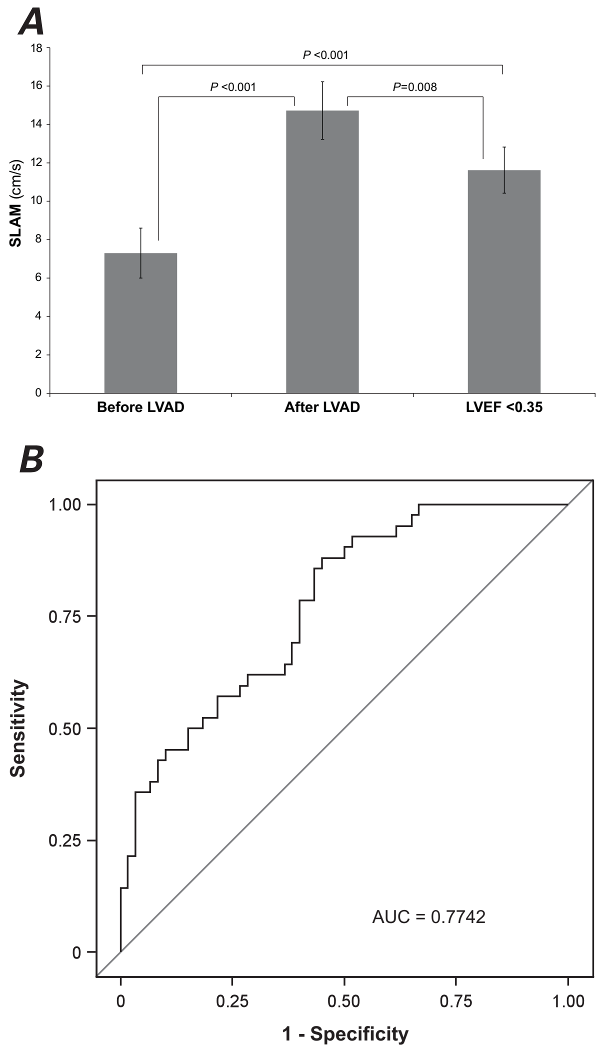


***Fig. 6 A**) Graph shows comparisons in slope of the anterior mitral valve leaflet (SLAM) in 42 patients before left ventricular assist device (LVAD) insertion, in the same 42 patients after LVAD insertion, and in 60 different, randomly selected patients without an LVAD but with left ventricular ejection fraction (LVEF) <0.35.* P *<0.05 was considered statistically significant. **B**) Receiver operating characteristic analysis indicates that the SLAM can distinguish patients in end-stage heart failure and before LVAD implantation from randomly selected patients with an LVEF <0.35 at an area under the curve (AUC) of 0.7742 (95% confidence interval, 0.6853–0.8631).*

TABLE VI. Sensitivity and Specificity Analysis of SLAM in Predicting Pre-LVAD Status versus LVEF <0.35

SLAM Cutpoint*	Sensitivity	Specificity	Youden Index
5	0.2143	0.9833	0.1976
6	0.3571	0.9667	0.3238
7	0.5238	0.8	0.3238
8	0.619	0.65	0.269
9	0.7857	0.6	0.3857
10	0.881	0.55	0.431
11	0.9286	0.4833	0.4119
12	0.9286	0.4333	0.3619
13	0.9762	0.35	0.3262
14	1	0.25	0.25
15	1	0.2167	0.2167
16	1	0.15	0.15
17	1	0.15	0.15
18	1	0.1	0.1
19	1	0.0667	0.0667
20	1	0.05	0.05
21	1	0.05	0.05
22	1	0.0333	0.0333
23	1	0.0333	0.0333
24	1	0.0333	0.0333
25	1	0.0167	0.0167

LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; SLAM = slope of the anterior mitral valve leaflet

*The cutpoint of 10 cm/s distinguished random patients with LVEF <0.35 from those in end-stage congestive heart failure (pre-LVAD) with an 88% sensitivity and a 55% specificity.

diographic measurement that in paired analyses appears to correlate with LV unloading by an LVAD and is an indicator of heart-failure clinical status both in native heart failure and in patients with an implanted CF-LVAD.

Our data suggest an inverse relationship between the SLAM and LV filling pressures in LVAD-supported and -unsupported hearts. The physiologic mechanisms underlying this observation necessitate further investigation; however, we currently hypothesize the following potentially contributory mechanisms. First, concomitant diastolic and moderate-to-severe systolic dysfunction (LVEF <0.35) has been shown in patients to result in an increased LV end-diastolic pressure (LVEDP).[10] In those patients who have an elevated left atrial pressure, a longer time would then be required for the ventricle to generate a pressure greater than that in the atrium and would thereby affect mitral valve closure. Investigators who conducted prior invasive and hemodynamic studies have reported a qualitatively prolonged transmitral flow and delayed closure of the mitral valve in patients with an elevated LVEDP, evidenced with use of M-mode echocardiography.[21] Poor LV contractile function correlates with a decreased rate of developed LV pressure during systole (dP/dt) through the increase in time for the ventricle to produce the Doppler jet of mitral regurgitation.[22] Similar to SLAM, dP/dt has been shown to improve by increasing upon CF-LVAD implanta-

tion.[8] Regardless of the cause of cardiomyopathy, a high LVEDP and weak contractile function culminate in ineffective unloading, which is consistent with the delayed-closure physiology of the mitral valve observed in M-mode echocardiography, and which in this study was quantified as the SLAM.

In unsupported patients with LVEF <0.35, there was a correlation between SLAM and E/e′ measurements, and E/e′ is well validated and routinely used in this population to correlate closely with LV filling pressures.[5,23] In addition, our data indicate that SLAM is able to identify, with good sensitivity and specificity, patients with a depressed LVEF who are sicker. A SLAM cutpoint value of <10 cm/s differentiates patients with end-stage CHF who are clinically determined to need LVAD support from a random cohort of patients with LVEF <0.35. Although all echocardiographic values should be analyzed within the clinical context of each individual patient, a SLAM <10 cm/s or an appreciable decrease in SLAM might trigger a change in medical therapy or accelerate referral for advanced heart-failure therapies.

The SLAM method appears to have a unique capacity to provide a metric of ventricular unloading in an LVAD-supported population. The average SLAM of patients with end-stage CHF doubled after LVAD implantation—and, in a limited subgroup analysis within our data set, appeared to detect clinical deterioration sensitively in patients with LVADs who were readmitted for CHF symptoms. The possible causes of CHF exacerbations in an LVAD population are varied and might include inadequate rotor speed and unloading of the LV, or worsening of native heart failure. Each of these complications would lead to a decrease in the left atrial and LV gradients and prolong the closure of the mitral valve. Regular evaluation of the SLAM after LVAD implantation might provide the treating physician with a sensitive, noninvasive tool for rapidly evaluating the adequacy of LV unloading in these patients who have complications. In addition, we anticipate that SLAM might be used in future studies to adjust the LVAD for clinical optimization and for long-term patient monitoring. Prospective analyses at fixed imaging intervals after LVAD implantation will result in more rigorous future validation of the SLAM method.

Study Limitations

This study has several important limitations. First, it is a single-institution, retrospective study. Because the SLAM was not prospectively collected, many patients had insufficient echocardiographic images or cardiac cycles from which to obtain the SLAM; and in some cases, M-mode TTE of the mitral valve was not available. Furthermore, echocardiograms were obtained at varying intervals postoperatively, and we were unable to categorize them into consistent time-intervals for a thorough longitudinal study. We did not evaluate the correlation between the SLAM and aortic valve opening in LVAD patients, because aortic valve opening is also variable, with an unknown mathematical correlation to unloading.[20,24] In addition, SLAM cannot be applied to patients who have atrial fibrillation or flutter, a mechanical mitral valve, or poor 2D TTE windows that preclude seeing the mitral valve in M mode.

Conclusion

We introduce the SLAM as a promising, novel, M-mode echocardiographic method of evaluating LV filling pressures, and we provide evidence to suggest that it remains valid in patients with a CF-LVAD. This method adds to an expanding panel of echocardiographic methods that are used to evaluate LV unloading in LVAD recipients. Further echocardiographic studies are needed to determine the usefulness of SLAM in other patient populations and to establish a time course of dynamic changes of echocardiographic values within the post-implantation LVAD population toward LVAD optimization, clinical status, and outcomes.

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References

1. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001; 345(20):1435-43.
2. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 2007;357(9): 885-96.
3. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009; 361(23):2241-51.
4. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. Eur J Echocardiogr 2011;12(3):167-205.
5. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30(6):1527-33.
6. Ritzema JL, Richards AM, Crozier IG, Frampton CF, Melton IC, Doughty RN, et al. Serial Doppler echocardiography and tissue Doppler imaging in the detection of elevated directly measured left atrial pressure in ambulant subjects with chronic heart failure. JACC Cardiovasc Imaging 2011;4(9):927-34.
7. Andersen M, Gustafsson F, Madsen PL, Brassard P, Jensen AS, Secher N, et al. Hemodynamic stress echocardiography

in patients supported with a continuous-flow left ventricular assist device. JACC Cardiovasc Imaging 2010;3(8):854-9.
8. Kato TS, Chokshi A, Singh P, Khawaja T, Cheema F, Akashi H, et al. Effects of continuous-flow versus pulsatile-flow left ventricular assist devices on myocardial unloading and remodeling. Circ Heart Fail 2011;4(5):546-53.
9. Feigenbaum H. Role of M-mode technique in today's echocardiography. J Am Soc Echocardiogr 2010;23(3):240-57; 335-7.
10. Konecke LL, Feigenbaum H, Chang S, Corya BC, Fischer JC. Abnormal mitral valve motion in patients with elevated left ventricular diastolic pressures. Circulation 1973;47(5):989-96.
11. Massie BM, Schiller NB, Ratshin RA, Parmley WW. Mitral-septal separation: new echocardiographic index of left ventricular function. Am J Cardiol 1977;39(7):1008-16.
12. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23(7):685-713.
13. Mielniczuk LM, Tsang SW, Desai AS, Nohria A, Lewis EF, Fang JC, et al. The association between high-dose diuretics and clinical stability in ambulatory chronic heart failure patients. J Card Fail 2008;14(5):388-93.
14. Brater DC. Update in diuretic therapy: clinical pharmacology. Semin Nephrol 2011;31(6):483-94.
15. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol 2006;97(12):1759-64.
16. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, Adams KF Jr. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail 2007;9(10): 1064-9.
17. Lachin JM. The role of measurement reliability in clinical trials. Clin Trials 2004;1(6):553-66.
18. Xydas S, Rosen RS, Ng C, Mercando M, Cohen J, DiTullio M, et al. Mechanical unloading leads to echocardiographic, electrocardiographic, neurohormonal, and histologic recovery. J Heart Lung Transplant 2006;25(1):7-15.
19. Topilsky Y, Oh JK, Atchison FW, Shah DK, Bichara VM, Schirger JA, et al. Echocardiographic findings in stable outpatients with properly functioning HeartMate II left ventricular assist devices. J Am Soc Echocardiogr 2011;24(2):157-69.
20. Rasalingam R, Johnson SN, Bilhorn KR, Huang PH, Makan M, Moazami N, Perez JE. Transthoracic echocardiographic assessment of continuous-flow left ventricular assist devices. J Am Soc Echocardiogr 2011;24(2):135-48.
21. Ambrose JA, Teichholz LE, Meller J, Weintraub W, Pichard AD, Smith H Jr, et al. The influence of left ventricular late diastolic filling on the A wave of the left ventricular pressure trace. Circulation 1979;60(3):510-9.
22. Kolias TJ, Aaronson KD, Armstrong WF. Doppler-derived dP/dt and -dP/dt predict survival in congestive heart failure. J Am Coll Cardiol 2000;36(5):1594-9.
23. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22(2):107-33.
24. Estep JD, Stainback RF, Little SH, Torre G, Zoghbi WA. The role of echocardiography and other imaging modalities in patients with left ventricular assist devices. JACC Cardiovasc Imaging 2010;3(10):1049-64.