

Accurate and Reproducible Measurement of Left Ventricular Volume and Ejection Fraction by Contrast Echocardiography

A Comparison With Magnetic Resonance Imaging

Siri Malm, MD,* Sigmund Frigstad, MSc,† Einar Sagberg‡, Henrik Larsson, MD, PhD,*
Terje Skjaerpe, MD, PhD*

Trondheim, Norway

OBJECTIVES	We evaluated the accuracy and reproducibility of contrast echocardiography versus tissue harmonic imaging for measurements of left ventricular (LV) volumes and ejection fraction (EF) compared to magnetic resonance imaging (MRI).
METHODS	Digital echo recordings of apical LV views before and after intravenous contrast were collected from 110 consecutive patients. Magnetic resonance imaging of multiple short-axis LV sections was performed with a 1.5-T scanner. Left ventricular volumes and EF were calculated offline by method of discs. Thirty randomly selected patients were reanalyzed for intraobserver and interobserver variability.
RESULTS	Compared with baseline, contrast echo increased feasibility for single-plane and biplane volume analysis from 87% to 100% and from 79% to 95%, respectively. The Bland-Altman analysis demonstrated volume underestimation by echo, but much less pronounced with contrast. Limits of agreement between echo and MRI narrowed significantly with contrast: from -18.1% to 8.3% to -7.7% to 4.1% (EF), from -98.2 to -11.7 ml to -59.0 to 10.7 ml (end-diastolic volume), and from -58.8 to 21.8 ml to -38.6 to 23.9 ml (end-systolic volume). Ejection fraction from precontrast echo and MRI differed by $\geq 10\%$ (EF units) in 23 patients versus 0 after contrast ($p < 0.001$). At intraobserver and interobserver analysis, limits of agreement for EF narrowed significantly with contrast.
CONCLUSIONS	The two-dimensional echocardiographic evaluation of LV volumes and EF in non-selected cardiac patients was found to be more accurate and reproducible when adding an intravenous contrast agent. (J Am Coll Cardiol 2004;44:1030-5) © 2004 by the American College of Cardiology Foundation

Measurements of left ventricular (LV) ejection fraction (EF) by two-dimensional echocardiography (2D-echo) has been marred by significant observer variability and poor agreement with reference methods (1-3). This has been improved by left ventricular opacification (LVO) by second-generation intravenous ultrasound contrast agents (4,5), the main effect being seen in difficult-to-image patients compared with fundamental imaging (4). Limited data have been reported comparing tissue harmonic to contrast-enhanced imaging with adequate reference methods.

The aim of this study was to evaluate whether LVO with intravenous contrast has superior accuracy and reproducibility in 2D-echo assessment of LV volumes and EF compared to state-of-the-art tissue harmonic imaging in non-selected

cardiac patients. Multislice magnetic resonance imaging (MRI) was used as reference standard (6,7).

METHODS

Study population. A total of 110 consecutive patients referred to the cardiologic department for known or suspected heart disease were enrolled (age above 18 years, stable clinical condition, and sinus rhythm). No screening for image quality was performed. The exclusion criteria were generally accepted contraindications for MRI (metallic implants), pregnancy or lactation, known allergy to the contrast agents, significant valve diseases or shunts, and severe extracardiac disease. All subjects gave written informed consent. The study conformed to the Declaration of Helsinki, and the Regional Committee of Medical Ethics approved the protocol.

Echocardiography. Two second-generation ultrasound contrast agents were used; 55 patients received Definity (Bristol-Myers Squibb, North Billerica, Massachusetts), the other half SonoVue (Bracco, Milan, Italy). All studies were performed by an experienced physician using Vivid 7 (GE Vingmed Ultrasound, Horton, Norway) with the M3S transducer. The subjects were lying in the left lateral

From the *Department of Circulation and Medical Imaging and †Medical Student, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; and ‡GE Vingmed Ultrasound, Trondheim, Norway. The study was supported in part by a Research Fellowship grant from the Norwegian Council for Cardiovascular Diseases. Bracco (Italy) and Bristol Myers Squibb (U.S.) provided some of the contrast agent used; GE Vingmed Ultrasound (Norway) provided the research ultrasound machine and software.

Manuscript received January 17, 2004; revised manuscript received May 6, 2004, accepted May 10, 2004.

Abbreviations and Acronyms

APLAX	= apical long-axis
ASE	= American Society of Echocardiography
EDV	= end-diastolic volume
EF	= ejection fraction
ESV	= end-systolic volume
LV	= left ventricle
LVO	= left ventricular opacification
MRI	= magnetic resonance imaging
2CH	= two-chamber
2D-echo	= two-dimensional echocardiography
4CH	= four-chamber

recumbent position. Recordings of standard apical four-chamber (4CH), two-chamber (2CH), and long-axis (APLAX) views were obtained in baseline tissue harmonic imaging with single and double focus, thereafter with contrast using a single-pulse harmonic mode. Power was adjusted to minimize contrast destruction (mechanical index 0.22 to 0.31). The contrast agents were administered by a trained nurse as repeat slow bolus injections of 0.2 (Definity) and 0.5 ml (SonoVue) through a 20-G vial in a proximal forearm vein, followed by flushing with at least 5 ml of 0.9% saline at a speed adjusted to optimize cavity opacification. This imaging protocol was preferred to multipulse technology with continuous contrast infusion because of simpler setup, shorter procedure time, and wider availability. Overall gain, depth, and tissue gain compensation were optimized initially and thereafter kept constant. Special care was taken to avoid foreshortening of the LV long axis. Cine-loops of three cardiac cycles per imaging view and modality were digitally stored in raw-data format.

All patients fulfilling the imaging protocol were considered for volume analysis. Echocardiographic image quality, based on endocardial "traceability" at baseline, was graded as: 1) very poor (insufficient for volume analysis), 2) poor (analysis possible but difficult), or 3) good (analysis possible with confidence).

All cine-loops were assigned random numbers and analyzed by an experienced physician unaware of MRI results and patient identity using the modified biplane Simpson's rule in EchoPacPC (GE Vingmed Ultrasound). End-diastole was defined as the frame closest to the R-wave and end-systole as the minimal cavity area just before mitral valve opening. The inner contour of the LV cavity was manually traced according to the recommendations of the American Society of Echocardiography (ASE), leaving the papillary muscles and trabeculations within the cavity (8). The end-diastolic volume (EDV) and end-systolic volume (ESV) from three cardiac cycles were averaged, avoiding ectopic and post-ectopic beats. Ejection fraction was calculated as: $([EDV - ESV]/EDV) \times 100\%$. The APLAX rather than 2CH view was used in combination with 4CH view because of its better acoustic availability and reproducibility (9,10). If the APLAX view was not available or the

Table 1. Patient Characteristics (n = 100)

Age (yrs)	59 ± 11 (30-83)
Men	89
Height (cm)	175 ± 7 (159-194)
Body weight (kg)	80 ± 11 (50-105)
Previous myocardial infarction	57
Dilated cardiomyopathy	16
Hypertension	36
Diabetes mellitus	11
LV dilation	23
LV hypertrophy	34
Regional LV dyssynergy	60

Values are mean ± SD (range), or number of patients.
 LV = left ventricle.

2CH image was clearly of better quality, the 2CH image was used to maximize feasibility of biplane analysis.

Thirty randomly selected patients were analyzed by another less experienced observer who was blind to all other data. The experienced observer reanalyzed 30 echocardiograms in a new random order after a minimum interval of eight weeks.

MRI. Two experienced operators performed the MRI studies using a 1.5-T Symphony whole-body system with Quantum Gradients and Syngo 2002B software (Siemens, Erlangen, Germany). Long-axis reference views were used for positioning the necessary 8 to 12 perpendicular LV short-axis slices. Images were collected during breath-hold (8 to 10 s) with prospectively ECG-gated TrueFISP (Fast Imaging with Steady-State Precision) sequences. No magnetic resonance contrast agent was needed. Section thickness was 6 mm with intersection gaps of 4 mm. Acquisition time was 90% of the RR-interval, image matrix 256 × 150 (read/phase), field of view 380 mm, repetition time 52.05 ms, echo time 1.74 ms, flip angle 70°, and 12 to 17 heart phases were acquired per repetition time interval. The images were stored and transferred digitally. Echo and MRI exams were performed within the shortest possible time interval. No change in patient medication or clinical condition between the two studies was accepted.

The MRI volumes and EF were calculated by a blinded investigator using a custom-made software programmed in MatLab (The MathWorks, Natick, Massachusetts). Short-axis endocardial contours were manually traced in end-diastole (start of R-wave) and in end-systole (smallest cavity area). Papillary muscles and trabeculations were, according to the ASE criteria, included in the LV cavity. The end-diastolic and end-systolic cavity surface areas were summed up and volumes estimated by multiplying with interslice interval.

Statistics. Continuous variables were expressed as mean ± SD. Limits of agreement between imaging methods and between readings were estimated as mean difference (bias) ± 2 SD of the differences, as described by Bland and Altman (11). Interobserver and intraobserver variability were also expressed as the standard deviation of difference between two readings in percent of the mean. McNemar's

Table 2. Left Ventricular Volumes and EF by MRI, Baseline Echocardiography, and Contrast Echocardiography

	MRI	Baseline Echo	Contrast Echo
EDV (ml)	177.0 ± 60.5 (90.3–395.0)	126.1 ± 52.2 (48.7–324.0)	152.2 ± 55.1 (80.8–360.7)
ESV (ml)	78.7 ± 56.4 (22.9–298.1)	63.0 ± 43.8 (9.5–227.3)	71.1 ± 48.7 (18.1–252.5)
EF (%)	59 ± 14.6 (21–78)	54 ± 12.5 (18–80)	57 ± 13.3 (22–79)

Mean ± SD (range).

EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; MRI = magnetic resonance imaging.

test was performed to compare the difference between paired proportions due to the dependent data samples. A significance level of 0.05 was selected.

RESULTS

A total of 110 patients completed echo studies. Ten patients were excluded: four because of a percutaneous coronary intervention being performed and six because of interrupted or inadequate magnetic resonance examinations. The re-

maining patient population (n = 100) spanned a wide variation of LV shapes, sizes, and function (Table 1). In 67 patients the MRI was performed within 1 h, in 20 within 2 days, and in the remaining within 1 week. A time interval exceeding 24 h was accepted only with normal LVs and no recent myocardial infarction. There were no significant differences in heart rate between echo and MRI studies (66 ± 12 beats/min vs. 68 ± 13 beats/min, p = 0.42). Mean values of LV volumes and EF are presented in Table 2. Representative precontrast and postcontrast echocardiograms are shown in Figure 1.

The patients received a mean total dose of 1.48 ml of SonoVue or 0.63 ml Definity. With contrast, procedure time was increased by up to 10 min. Except for two patients experiencing transient taste disturbances, no side effects from contrast injection were observed.

Feasibility. In 13 patients baseline echo image quality was very poor in all apical views, precluding volume analysis. By adding contrast, all these studies were converted to diagnostic. In 75 of the 87 patients analyzable at baseline, the combination of 4CH and APLAX views was adequate for biplane analysis. In 4 of the remaining 12 patients, the 2CH

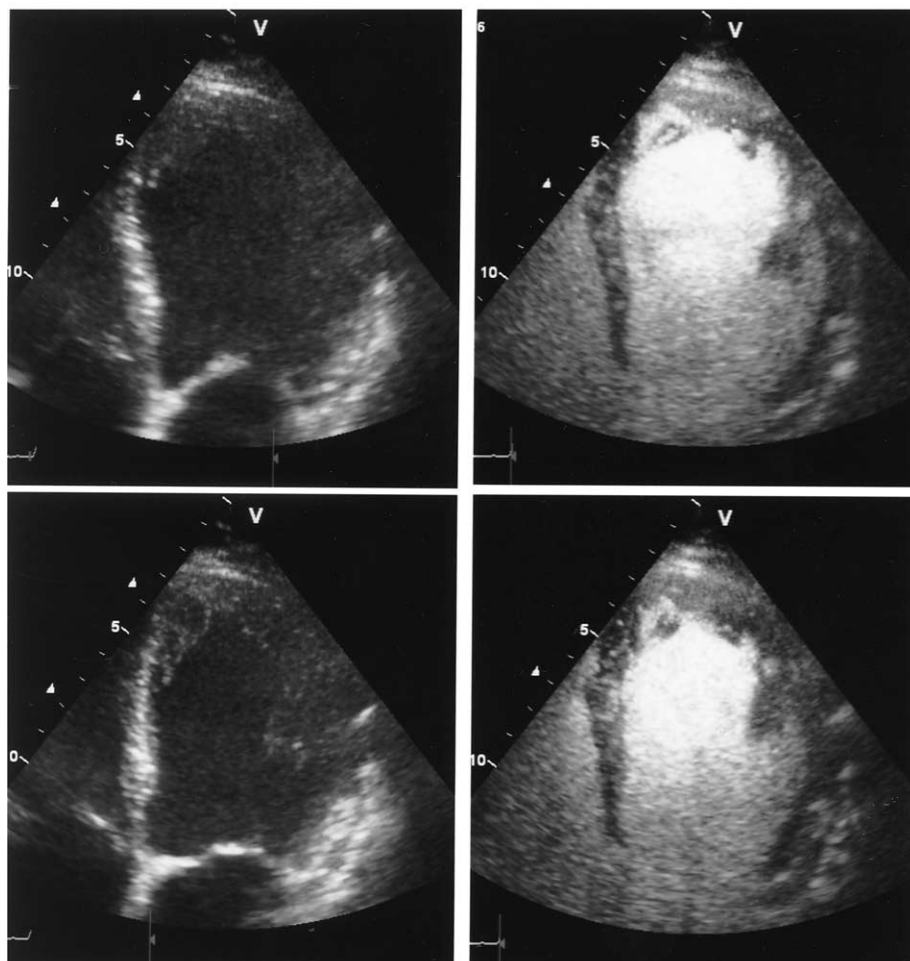


Figure 1. Echocardiographic end-diastolic (top) and end-systolic (bottom) images of the apical four-chamber view from a patient before (left) and after (right) intravenous contrast.

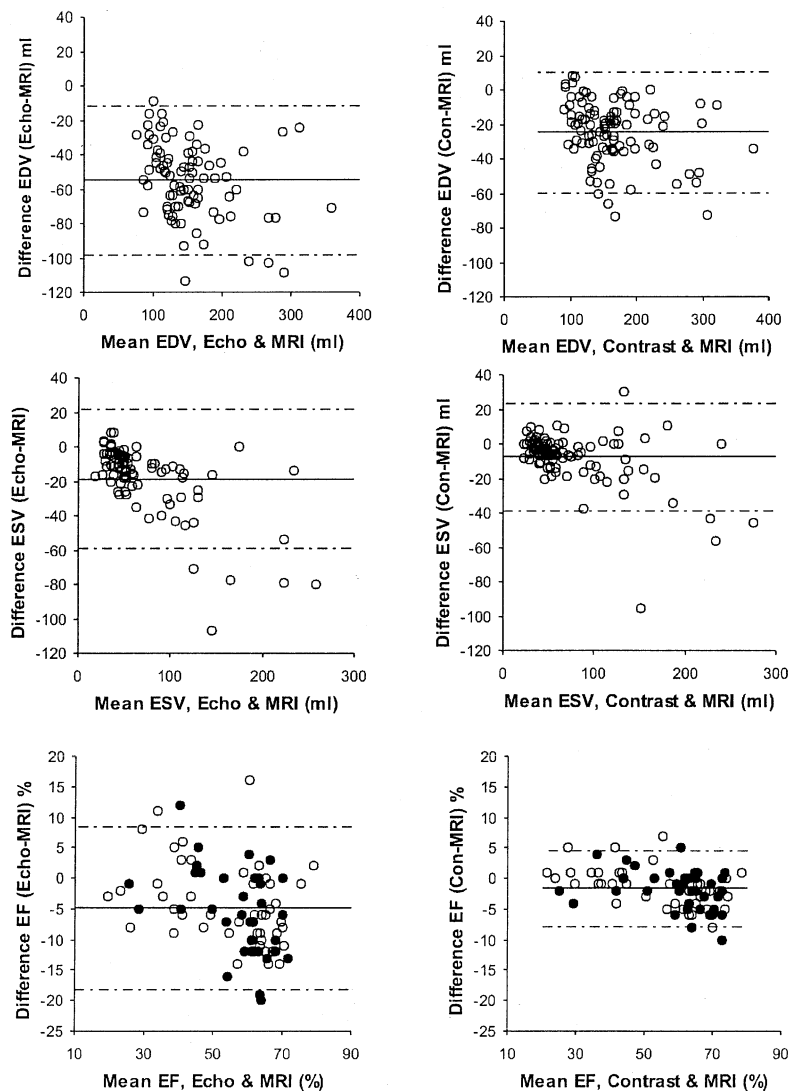


Figure 2. Bland-Altman diagrams of end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF), demonstrating mean difference (solid lines) and limits of agreement (dashed lines) between baseline echocardiography and magnetic resonance imaging (MRI) (left column), and contrast echocardiography and MRI (right column). (Bottom panels) closed circles = poor baseline image quality (n = 36); open circles = good baseline image quality (n = 51).

substituted the APLAX view, and in 8 patients only 4CH single-plane analysis was feasible. Corresponding numbers after contrast were two and five patients. With contrast, feasibility of single-plane and biplane volume analysis in the total population increased from 87% to 100% and from 79% to 95%, respectively.

Accuracy. In the 87 patients in whom comparisons could be performed, Bland-Altman analysis of LV volumes and EF from contrast echocardiograms showed significantly closer agreement with MRI measurements than precontrast studies (Fig. 2). Limits of agreement without and with contrast were -98.2 to 11.7 ml and -59.0 to 10.7 ml (EDV), -58.8 to 21.8 ml and -38.6 to 23.9 ml (ESV), and -18.1% to 8.3% and -7.7% to 4.1% (EF, absolute units), respectively.

Baseline echo and MRI EF differed by $\geq 10\%$ (EF units) in 23 patients (26%) versus 0 with contrast (chi-square = 24.2, $p < 0.001$). Seventy-five patients (86%) were correctly classified by baseline echo in the appropriate EF group (EF $< 35\%$, 35% to 54%, or $\geq 55\%$) based on MRI, whereas classification was correct in 86 patients (99%) with contrast (chi-square = 8.3, $p = 0.002$).

Baseline image quality was judged as poor in 36 and as good in 51 of the 87 analyzable patients. For the "poor" subgroup, limits of agreement for EF were -19.9% to 7.9% at baseline, narrowing to -8.3% to 4.6% after contrast. Corresponding limits of agreement for patients with good baseline image quality were -16.7% to 9.0% and -7.3% to 4.5% (Fig. 2). Between baseline and contrast, the reduction in mean differences (bias) for EDV and ESV compared with

Table 3. Subgroup Differences in LV Volumes and EF Between MRI and Echocardiography (n = 87)

Subgroup	Poor Baseline Image Quality		Good Baseline Image Quality	
	Baseline Echo	Contrast Echo	Baseline Echo	Contrast Echo
EDV (ml)	-56.4 ± 47.8	-24.4 ± 23.8	-56.3 ± 41.8	-25.7 ± 24.4
ESV (ml)	-16.2 ± 31.8	-6.5 ± 15.6	-21.8 ± 47.2	-9.0 ± 20.2
EF (%)	-6.0 ± 13.9	-1.9 ± 6.5	-3.8 ± 12.9	-1.4 ± 5.9

Values are mean differences (bias) ± 2SD of the differences (= limits of agreement).
 Abbreviations as in Table 2.

MRI was 32.0 and 9.7 ml for the “poor” and 30.6 and 12.0 ml for the “good” subgroup, respectively (Table 3).

Reproducibility. Comparing the readings of two observers, the limits of agreement for baseline echo were -33.3 to 18.1 ml (EDV), -23.5 to 16.5 ml (ESV), and -16.6% to 14.2% (EF). With contrast, these limits narrowed to -18.8 to 22.6 ml (EDV), -15.6 to 14.8 ml (ESV), and -5.9% to 6.9% (EF). At intraobserver analysis, the limits of agreement for EF was -11.1% to 7.8% precontrast, improving to -2.8% to 2.4% with contrast (Fig. 3). Mean inter- and intraobserver variability for EF were reduced from 13.9% to 9.6% and from 5.4% to 2.5% without and with contrast, respectively.

DISCUSSION

Our findings indicate that measurements of LV volumes and EF in a non-selected patient population are more accurate and reproducible using a second-generation intra-

venous contrast agent, even compared to state-of-the-art tissue harmonic imaging. Contrast injections have previously been shown to improve measurement of LV volumes and EF compared to fundamental imaging (4). Tissue harmonic imaging was indeed used by Thomson et al. (5) studying patients post-myocardial infarction, but the sample size was relatively small (n = 26) and the reference method was computed tomography, which is less documented by prospective clinical EF studies. Our study is the first to show that LVO is in better agreement with MRI compared to tissue harmonic imaging results.

Echo volume underestimation before contrast was more pronounced for diastolic than systolic volumes (Fig. 2). With contrast, underestimation was reduced, especially for diastolic volumes. Accordingly, the accuracy of EF measurement improved with significant reduction in limits of agreement. This also indicates that despite tissue harmonic imaging, it is difficult to identify “true” endocardial borders.

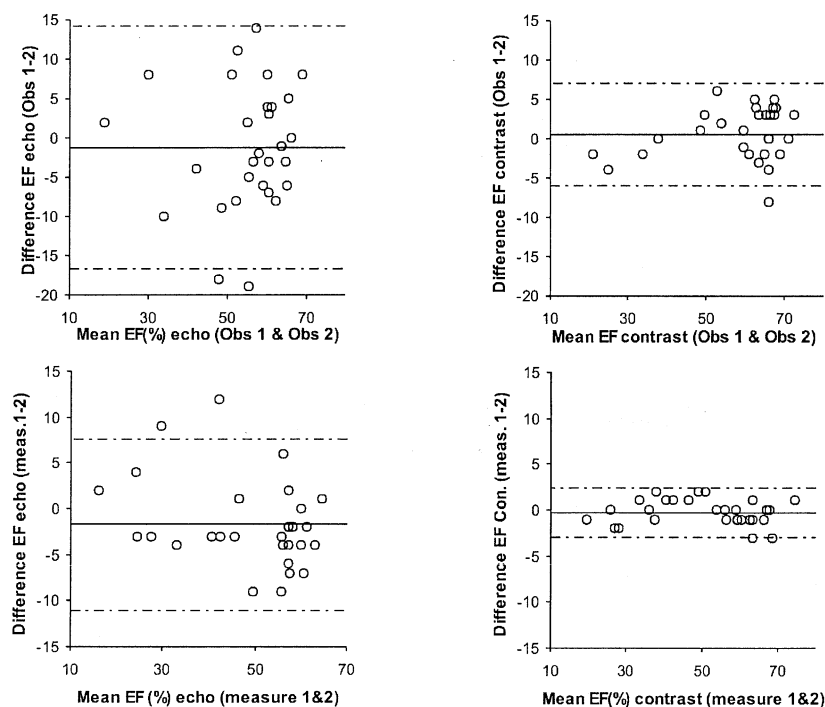


Figure 3. Bland-Altman analysis of the interobserver (upper panels) and intraobserver (lower panels) variability of ejection fraction (EF) measurements by baseline (left) compared to contrast echocardiography (right) (n = 30).

The contrast agent is filling the intertrabecular spaces, thus improving definition of the outermost endocardial lining (Fig. 1). But the addition of contrast did not eliminate volume underestimation made by echocardiography, reflecting some of the inherent limitations of transthoracic 2D-echo such as image plane positioning errors, foreshortening of the LV long axis, geometric assumptions, and cardiac translation (1,12).

Our data demonstrated a clear improvement in reproducibility of EF measurements by using contrast, both between observers with different training and at repeated measurements by the same observer. The limits of agreement were reduced to one-third with contrast compared to baseline. This indicates that contrast echo has the potential to improve the confidence of less experienced investigators, making the interpretation of LV systolic function less operator dependent.

In contrast to Hundley et al. (4), we found that the advantage of contrast was also evident for patients with good image quality. According to the ASE Task Force Guidelines, contrast studies for LVO should be performed in patients with suboptimal baseline echo studies, in which at least two of six contiguous segments in a standard apical view are not visualized (13). However, according to our results, contrast should be considered whenever accurate EF or absolute volumes are required for clinical decision making. Contrast should be particularly useful in serial monitoring of smaller volume or EF changes over time, as in post-MI LV remodeling, end-stage heart failure, heart transplants, cardiotoxic chemotherapy, and timing of valve replacement in valve regurgitation. Contrast should also be considered when LV EF or volumes are used as inclusion or randomization criteria and outcome parameters in clinical trials.

Conclusions. The 2D-echocardiographic evaluation of LV volumes and EF by tissue harmonic imaging was found to be more accurate and reproducible when performed after adding intravenous contrast in non-selected cardiac patients. Our results support that contrast enhancement should be considered not only in very difficult-to-image patients, but whenever it is considered important to have precise and repeatable measurements of LV size and global systolic performance.

Reprint requests and correspondence: Dr. Siri Malm, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Medisinsk teknisk forskningscenter, N-7489 Trondheim, Norway. E-mail: siri.malm@medisin.ntnu.no.

REFERENCES

1. Erbel R, Schweizer P, Lambertz H, et al. Echoventriculography—a simultaneous analysis of two-dimensional echocardiography and cine-ventriculography. *Circulation* 1983;67:205–15.
2. Bellenger NG, Burgess MI, Ray SG. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance. Are they interchangeable? *Eur Heart J* 2000;21:1387–96.
3. Bernard Y, Meneveau N, Boucher S, et al. Lack of agreement between left ventricular volumes and ejection fraction determined by two-dimensional echocardiography and contrast cineangiography in postinfarction patients. *Echocardiography* 2001;18:113–22.
4. Hundley WG, Kizilbash AM, Afridi I, et al. Administration of an intravenous perfluorocarbon contrast agent improves echocardiographic determination of left ventricular volumes and ejection fraction: comparison with cine magnetic resonance imaging. *J Am Coll Cardiol* 1998;32:1426–32.
5. Thomson HL, Basmadjian A, Rainbird A, et al. Contrast echocardiography improves the accuracy and reproducibility of left ventricular remodeling measurements. A prospective, randomly assigned, blinded study. *J Am Coll Cardiol* 2001;38:867–75.
6. Longmore DB, Klipstein RH, Underwood SR, et al. Dimensional accuracy of magnetic resonance in studies of the heart. *Lancet* 1985;1:1360–62.
7. Sakuma H, Fujita N, Foo TK, et al. Evaluation of left ventricular volume and mass with breathhold cine MR imaging. *Radiology* 1993;88:1715–23.
8. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantification of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr* 1989;2:358–67.
9. Otterstad JE, Froeland G, St. John Sutton M, Holme I. Accuracy and reproducibility of left ventricular dimensions and function. *Eur Heart J* 1997;18:507–13.
10. Nosir YFM, Vletter WB, Boersma E, et al. The apical long-axis rather than the two-chamber view should be used in combination with the four-chamber view for accurate assessment of left ventricular volumes and function. *Eur Heart J* 1997;18:1175–85.
11. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurements. *Lancet* 1986;1:307–10.
12. Sapien PM, Schroeder KM, Gopal AS, Smith MD, King DL. Three-dimensional echocardiography: limitations of apical biplane imaging for measurements of left ventricular volume. *J Am Soc Echocardiogr* 1995;8:576–84.
13. Mulvagh S, DeMaria AN, Feinstein SB, et al. ASE position paper. Contrast echocardiography: current and future applications. *J Am Soc Echocardiogr* 2000;13:331–42.