Echocardiography

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

A Comparison With Magnetic Resonance Imaging

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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 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
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 (De-Flushing with at least 5 ml of 0.9% saline at a speed adjusted to optimize cavity opacification). The APLAX views were obtained in baseline tissue harmonic chamber (4CH), two-chamber (2CH), and long-axis views. Recordings of standard apical four-chamber (4CH) were digitally stored in raw-data format. Loops of three cardiac cycles per imaging view and modality were taken to avoid foreshortening of the LV long axis. Cine-loops were assigned random numbers and analyzed by an experienced physician unaware of MRI results. 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 perpendicularly 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
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 remaining 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

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

<table>
<thead>
<tr>
<th>MRI</th>
<th>Baseline Echo</th>
<th>Contrast Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV (ml)</td>
<td>177.0 ± 60.5</td>
<td>126.1 ± 52.2</td>
</tr>
<tr>
<td></td>
<td>(90.3–395.0)</td>
<td>(48.7–324.0)</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>78.7 ± 56.4</td>
<td>63.0 ± 43.8</td>
</tr>
<tr>
<td></td>
<td>(22.9–298.1)</td>
<td>(9.5–227.3)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>59 ± 14.6</td>
<td>54 ± 12.5</td>
</tr>
<tr>
<td></td>
<td>(21–78)</td>
<td>(18–80)</td>
</tr>
</tbody>
</table>

Mean ± SD (range).

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

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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Poor Baseline Image Quality</th>
<th>Good Baseline Image Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Echo</td>
<td>Contrast Echo</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>−56.4 ± 47.8</td>
<td>−24.4 ± 23.8</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>−16.2 ± 31.8</td>
<td>−6.5 ± 15.6</td>
</tr>
<tr>
<td>EF (%)</td>
<td>−6.0 ± 13.9</td>
<td>−1.9 ± 6.5</td>
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</tbody>
</table>

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

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.

REFERENCES