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Administration of an Intravenous Perfluorocarbon Contrast Agent Improves Echocardiographic Determination of Left Ventricular Volumes and Ejection Fraction: Comparison With Cine Magnetic Resonance Imaging

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Objectives. **The purpose of this study was to determine whether contrast-enhanced transthoracic echocardiography improves the evaluation of left ventricular (LV) volumes and ejection fraction (EF).**

Background. **Echocardiographic assessment of LV volumes and EF is widely used but may be inaccurate when the endocardium is not completely visualized. Recently the intravenous (IV) administration of perfluorocarbon microbubbles has been shown to enhance opacification of the LV cavity, but the utility of these agents to improve the echocardiographic assessment of LV systolic function is unknown.**

Methods. **In 40 subjects (29 men and 11 women, aged 24 to 81 years) an assessment of LV volumes and EF was performed with a magnetic resonance imaging examination, followed immediately by a transthoracic echocardiogram before and after the intravenous administration of 2% dodecafluoropentane emulsion (EchoGen; Sonus Pharmaceuticals, Bothell, Washington).**

Results. **Contrast enhanced the echocardiographic assessment of LV end diastolic volume ($p < 0.02$), end systolic volume ($p < 0.01$) and LVEF ($p < 0.03$). The percentage of subjects in whom the correct echocardiographic classification EF was normal, mild to moderately depressed or severely reduced improved significantly after contrast enhancement (from 71% before contrast to 94% after, $p < 0.03$). These findings were most striking in the subjects with two or more adjacent endocardial segments not visualized at baseline.**

Conclusions. **Administration of an intravenous contrast agent improves the ability to accurately assess LV volumes and EF in humans. Contrast enhancement is most useful in subjects with two or more adjacent endocardial segments not seen at baseline.**

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Measurement of left ventricular (LV) volumes and systolic function provides valuable diagnostic and prognostic information in patients with cardiovascular disease. Although echocardiography is used widely to assess global and regional LV systolic function (1), inadequate definition of the endocardium may limit the accuracy of these measurements (2,3). A rapid and easily implemented method to enhance the visualization of the endocardium and therefore to improve the echocardiographic assessment of LV volumes and ejection fraction (EF) would be useful.

Recently intravenous (IV) contrast agents (composed of microbubbles that traverse the pulmonary circulation) have been used to opacify the LV cavity and improve endocardial border definition during transthoracic echocardiography (4–6). However, it is not known whether this contrast-enhanced border is the true endocardial surface or whether its visualization improves the assessment of LV systolic function. Accordingly, the purpose of this study was to determine whether contrast-enhanced echocardiography improves the evaluation of LV volumes and EF. To accomplish this, echocardiographic data acquired before and after IV contrast were compared with quantitative assessments obtained by gated cine magnetic resonance imaging (MRI). Because cardiovascular MRI assessments of LV volumes (7,8), EF (9) and regional wall motion (10) are three-dimensional, noninvasive, accurate and reproducible, they served as an ideal reference standard for this study.

Methods

Study population. The study was approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center at Dallas and the Dallas Veterans Administration Medical Center. All participants gave written informed

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Abbreviations and Acronyms

DDFP = dodecafluoropentane
ECG = electrocardiographic
EF = ejection fraction
IV = intravenous
LV = left ventricular
MRI = magnetic resonance imaging

consent. The study population consisted of 40 subjects (29 men and 11 women, aged 24 to 81 years) referred for routine transthoracic echocardiography for the assessment of LV systolic function. The original plan was to consecutively enroll at least 12 subjects in each of 3 categories: 1) normal LV shape and systolic function, 2) normal LV shape and depressed systolic function and 3) abnormal LV shape (two or more contiguous segments with dyskinesia) and depressed systolic function. However, several patients were subsequently reclassified after the MRI, leaving only nine subjects in the latter group. Patients were ineligible for the study if they had an indwelling pacemaker, intracranial clips, intraauricular or intraocular implants, a history of metal fragments in the eye, claustrophobia, marked ventricular ectopy, pregnancy, acute myocardial infarction within 3 months, atrial fibrillation, obesity (>130% of ideal body weight) with concomitant obstructive sleep apnea, obstructive or restrictive lung disease, unstable neurologic disease or an unstable medical condition that precluded transport from an intensive care unit.

Study design. After establishment of a 20 G IV catheter in the right antecubital fossa, each subject underwent MRI followed immediately by transthoracic echocardiography, first without and then with contrast agent. Heart rate and systemic arterial pressure were monitored and recorded during MRI and echocardiography. All data, including heart rate, blood pressure, LV volumes, EF and regional wall motion determinations were compiled, analyzed and stored without knowledge of the findings obtained during the other procedure. To ensure blinded interpretation of the data, images were not labeled with the patient's name, but rather with a number derived from a randomization table before the study.

Magnetic resonance imaging technique. Magnetic resonance imaging was performed with a 1.5-T Philips NT whole-body imaging system (Philips Medical Systems, Shelton, Connecticut). Each patient was positioned supine on the MRI table with electrocardiographic (ECG) monitoring leads attached. All MRI scans used prospective ECG gating. The apical two- and four-chamber views were positioned using the Planscan software, according to previously published techniques (8,11). The two-chamber view was parallel to the interventricular septum and intersected the cardiac apex and midmitral valve; the four-chamber view was perpendicular to the interventricular septum, maximizing right ventricular size and intersecting the apex and midmitral valve. Left ventricular volume and EF measurements were calculated from a series of multislice, multiphase gradient-echo sequences positioned perpendicular to the long axis of the left ventricle (short axis), spanning apex to base. The apical and short-axis slices were 9 mm thick (short-axis slices separated by a 1-mm gap) with a 256 × 256 matrix, a temporal resolution of 40 ms, a field of view of 35 cm (yielding voxel sizes of 1.4 × 1.4 × 9 mm), a flip angle of 40°, a repetition time of 13.7 ms and an echo time of 8.1 ms.

For LV volume measurement the endocardial border of each slice was planimetered manually at end diastole and end systole, and volumes were calculated by Simpson's rule (12). End diastole was defined as the first frame in each sequence. To determine end systole, the images were reviewed in cine format and the frame with the smallest endocardial circumference was selected. Basal slices were reviewed in cine format to resolve structures for inclusion (the aortic outflow tract) or exclusion (left atrium and mitral leaflets) from the volume measurements. Magnetic resonance images were stored on optical disks for subsequent recall and analysis.

Transthoracic echocardiography. Echocardiography was performed with a Sonos 2500 (Hewlett-Packard Company, Andover, Massachusetts) using a 2.5-MHz transducer. Each patient was positioned on the left side with ECG monitoring leads attached. Gain settings were optimized for each subject and then not changed throughout the remainder of the protocol. Apical two- and four-chamber views of the left ventricle were acquired at a rate of 30 frames/s, and a single cardiac cycle was stored as a cine loop on an optical disk. Great care was taken to avoid apical foreshortening and to maximize the length from base to apex. Echocardiographic data were analyzed by an experienced observer (P.G.) who was unaware of the MRI and clinical data. A second observer (I.A.), who was unaware of the study design and methods, also read the studies independently. Left ventricular volumes were determined using the biplane summation of disks method recommended by the American Society of Echocardiography (2). All data regarding the baseline examination were recorded before beginning the contrast portion of the study.

A weight-adjusted dose (0.5 ml/kg) of 2% dodecafluoropentane (DDFP) emulsion (EchoGen, Sonus Pharmaceuticals, Bothell, Washington) was used to opacify the LV cavity. This substance is liquid at room temperature and shifts to a gaseous phase at body temperature, producing bubbles 3 to 5 μm in diameter. After it was drawn into a polycarbonate syringe, the agent was activated by withdrawal and abrupt release of the plunger against the vacuum provided by a closed stopcock. The agent was infused intravenously at a rate of 0.5 to 1.0 ml/s followed by 5 ml of normal saline flush at a rate of 0.5 to 1.0 ml/s. During the intravenous infusion two- and four-chamber views of the left ventricle were acquired and stored as cine loops on an optical disk. Assessments of global LV systolic function were determined and recorded in the same fashion as the baseline echocardiogram. After 15 min of observation the patient was discharged.

Data analysis. Without knowledge of the LV function data, we excluded patients from analysis a priori if heart rate or mean arterial pressure varied by >10% between MRI and

Table 1. Summary of Patient Data

	Demographics		Two or More Segments Not Visualized		Quantitative Measures								
					End Diastolic Volume			End Systolic Volume			Ejection Fraction		
Patient	Patient Condition	Sex/Age	Echo	Cont.	MRI	Echo	Cont.	MRI	Echo	Cont.	MRI	Echo	Cont.
Group I (normal LV systolic function)													
1	Hypertension; dyspnea	F/55	No	No	64	62	55	21	27	20	0.67	0.56	0.64
2	Hypercholesterolemia; dyspnea	M/39	No	No	86	79	91	26	20	35	0.70	0.75	0.62
3	Mitral valve prolapse	M/44	Yes	No	85	102	89	26	49	31	0.69	0.52	0.65
4	Hypertension; dyspnea	M/65	Yes	No	103	97	96	40	40	45	0.61	0.59	0.53
5	Mitral valve prolapse	F/59	Yes	Yes	92	109	93	30	41	28	0.67	0.62	0.70
6	Hypertension; dyspnea	M/60	No	No	79	107	95	29	30	32	0.63	0.72	0.66
7	Mitral regurgitation	M/46	No	No	203	170	171	71	63	57	0.65	0.63	0.67
8	Mitral regurgitation	M/55	Yes	No	109	139	87	35	48	36	0.68	0.65	0.59
9	Hypertension; dyspnea	M/46	No	No	84	100	89	33	27	23	0.61	0.73	0.74
10	Mitral regurgitation	F/29	No	No	114	98	99	45	30	30	0.61	0.69	0.70
11	Hypertension; dyspnea	M/43	Yes	No	118	148	122	54	48	47	0.54	0.68	0.61
12	Mitral regurgitation	F/24	No	No	113	96	118	42	33	35	0.63	0.66	0.70
13	Mitral regurgitation	M/75	Yes	No	127	106	84	56	27	34	0.56	0.75	0.60
14	Effusive/constrictive pericarditis	M/75	No	No	67	69	70	33	38	33	0.51	0.45	0.53
15	Coronary atherosclerosis	F/53	No	No	96	124	110	46	73	50	0.52	0.41	0.55
Group II (abnormal LV systolic function)													
16	Ischemic cardiomyopathy	M/65	No	No	174	199	177	132	151	136	0.24	0.24	0.23
17	Dilated cardiomyopathy	F/34	Yes	No	154	119	113	100	64	71	0.35	0.46	0.37
18	Ischemic cardiomyopathy	M/50	No	No	349	336	372	301	257	308	0.14	0.24	0.17
19	Hypertensive cardiomyopathy	F/71	Yes	No	88	110	101	58	54	67	0.34	0.51	0.34
20	Ischemic cardiomyopathy	M/56	Yes	No	156	149	116	99	98	75	0.37	0.34	0.35
21	Ischemic cardiomyopathy	M/66	Yes	No	155	175	141	111	87	93	0.28	0.50	0.34
22	Ischemic cardiomyopathy	F/63	Yes	No	283	247	226	221	177	183	0.22	0.28	0.19
23	Hypertensive cardiomyopathy	M/33	No	No	134	159	126	90	106	87	0.33	0.33	0.31
24	Ischemic cardiomyopathy	M/58	No	No	67	99	84	36	55	52	0.46	0.44	0.38
25	Coronary atherosclerosis	M/49	No	No	113	169	132	67	99	65	0.41	0.41	0.51
26	Coronary atherosclerosis	M/47	Yes	No	110	104	110	57	48	61	0.48	0.54	0.45
Group III (abnormal LV systolic function with dyskinesia)													
27	Ischemic cardiomyopathy	M/57	Yes	No	201	193	199	138	125	123	0.31	0.35	0.38
28	Ischemic cardiomyopathy	M/61	Yes	No	182	212	172	139	124	113	0.24	0.42	0.34
29	Ischemic cardiomyopathy	M/78	No	No	219	236	244	154	183	179	0.30	0.22	0.27
30	Ischemic cardiomyopathy	M/64	No	No	131	111	128	94	80	84	0.28	0.28	0.34
31	Ischemic cardiomyopathy	M/60	Yes	No	186	163	165	140	105	116	0.25	0.36	0.30
32	Ischemic cardiomyopathy	M/51	No	No	155	147	150	104	113	107	0.33	0.23	0.29
33	Ischemic cardiomyopathy	M/81	No	No	216	159	205	165	122	146	0.24	0.23	0.29
34	Ischemic cardiomyopathy	M/49	No	No	118	113	110	76	70	59	0.36	0.38	0.46
35	Ischemic cardiomyopathy	M/56	Yes	No	136	143	149	79	68	89	0.42	0.52	0.40

Cont. = echocardiogram performed with contrast; Echo = standard echocardiogram; MRI = magnetic resonance imaging examination.

echocardiography. The primary end point was quantitation of LV volumes and EF. We also analyzed semiquantitative assessment of regional wall motion as a secondary end point.

Left ventricular volumes and EF obtained by echocardiography with and without contrast agent were compared with those measured by MRI using linear regression analysis. The limits of agreement (defined as ±2 SDS from the mean difference) between echocardiographic and MRI measurements of global LV function were compared using the analysis of Bland and Altman (13). In addition, the absolute differences between MRI and echocardiographic assessment of LV volumes and EF (before and after contrast agent administration) were compared using a paired *t* test. The EF for each patient was grouped into one of three categories: normal (≥50%), mildly to moderately reduced (35% to 49%) or severely depressed (<35%). McNemar's test (14) was used to evaluate the agreement between both echocardiographic tests (with and without contrast agent) and MRI for the classification of the subjects into the proper EF subset. Unless stated otherwise, data for heart rate, systemic pressure, wall motion assessment, LV volumes and EF were expressed as mean ± 1 SD. For all statistical analyses a p value of <0.05 was considered significant.

Results

Clinical data. Magnetic resonance imaging and echocardiographic studies were completed in all but three subjects;

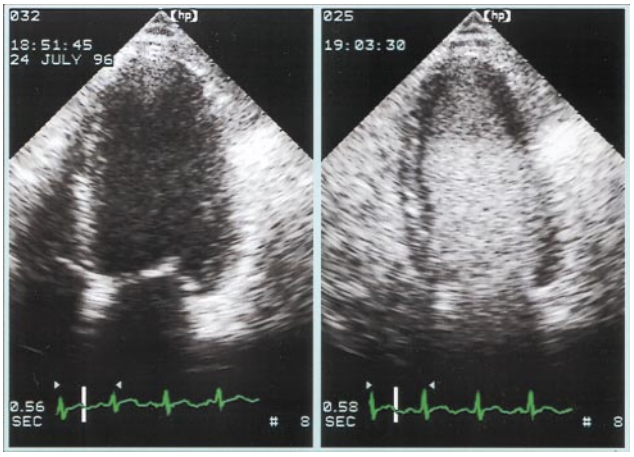


Figure 1. Transthoracic echocardiographic images of the apical four-chamber view obtained from a patient before **(left)** and after **(right)** the administration of contrast agent. The endocardial border is not well seen at baseline but becomes readily apparent with contrast enhancement.

one had no acoustic window to obtain the apical views with echocardiography, and two did not receive contrast agent because IV access was not maintained throughout the MRI and baseline echocardiographic examinations. Two additional subjects were excluded from further analysis because heart rate changed by >10% during echocardiography and MRI. The remaining 35 subjects formed the study population; their detailed data are listed in Table 1. The patients' mean height was 174 cm (range 152 to 193 cm) and the mean weight was 78 kg (range 61 to 108 kg). In seven subjects the apical two-chamber view was determined to be foreshortened, and only data from the four-chamber view were used for global LV function assessments. After receiving contrast agent, two subjects reported mild side effects lasting <1 min with no other sequelae: one noted a headache and the other noted paresthesias. Representative precontrast and postcontrast echocardiograms from a subject in this study are shown in Figure 1.

Comparison of echocardiography and MRI. The correlation coefficients between echocardiographic and MRI values for end diastolic volume, end systolic volume and EF were all >0.92 (Fig. 2). However, the Bland–Altman plots (Fig. 3) show that the limits of agreement (95% confidence intervals) between MRI and echocardiographic measurements of LV end diastolic volume, end systolic volume and EF narrowed significantly after IV contrast. This is illustrated in Table 2, which compares the absolute differences between echocardiographic and MRI measurements of LV volumes and EF before and after contrast agent. Before contrast echocardiographic and MRI EF differed by >0.10 in 11 patients (31%); after contrast only one patient (3%) with normal LV function had an absolute difference of >0.10 (chi-square = 6.75, $p < 0.04$).

Compared with MRI, contrast echocardiography was superior to standard echocardiography for the classification of subjects with EFs <35%, 35% to 49% and ≥50% (Fig. 4). Twenty-five subjects (71%) were correctly classified into appropriate EF subsets with precontrast echocardiography com-

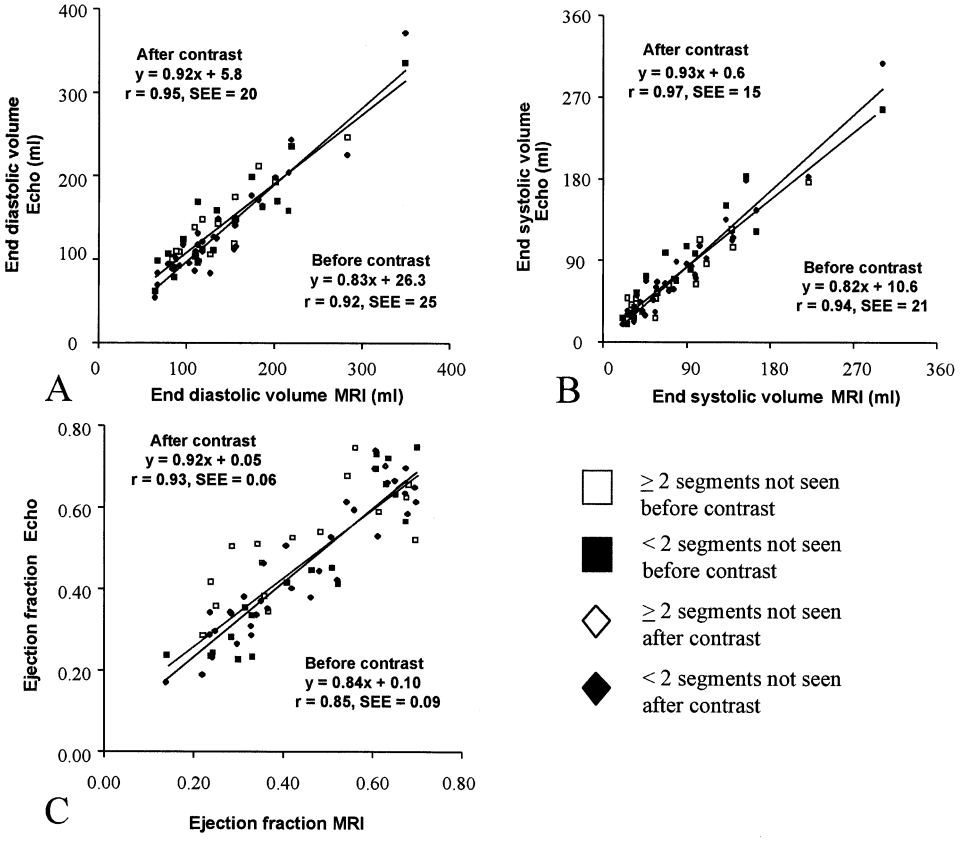


Figure 2. Regression plots showing the correlation between MRI **(horizontal axis)** and echocardiography **(vertical axis)** for LV end diastolic volumes **(A),** end systolic volumes **(B)** and EF **(C).** Data points for individual patients are displayed as precontrast values **(black squares)** or postcontrast values **(black diamonds). Open symbols** = patients in whom two or more segments were not seen on the precontrast echocardiogram.

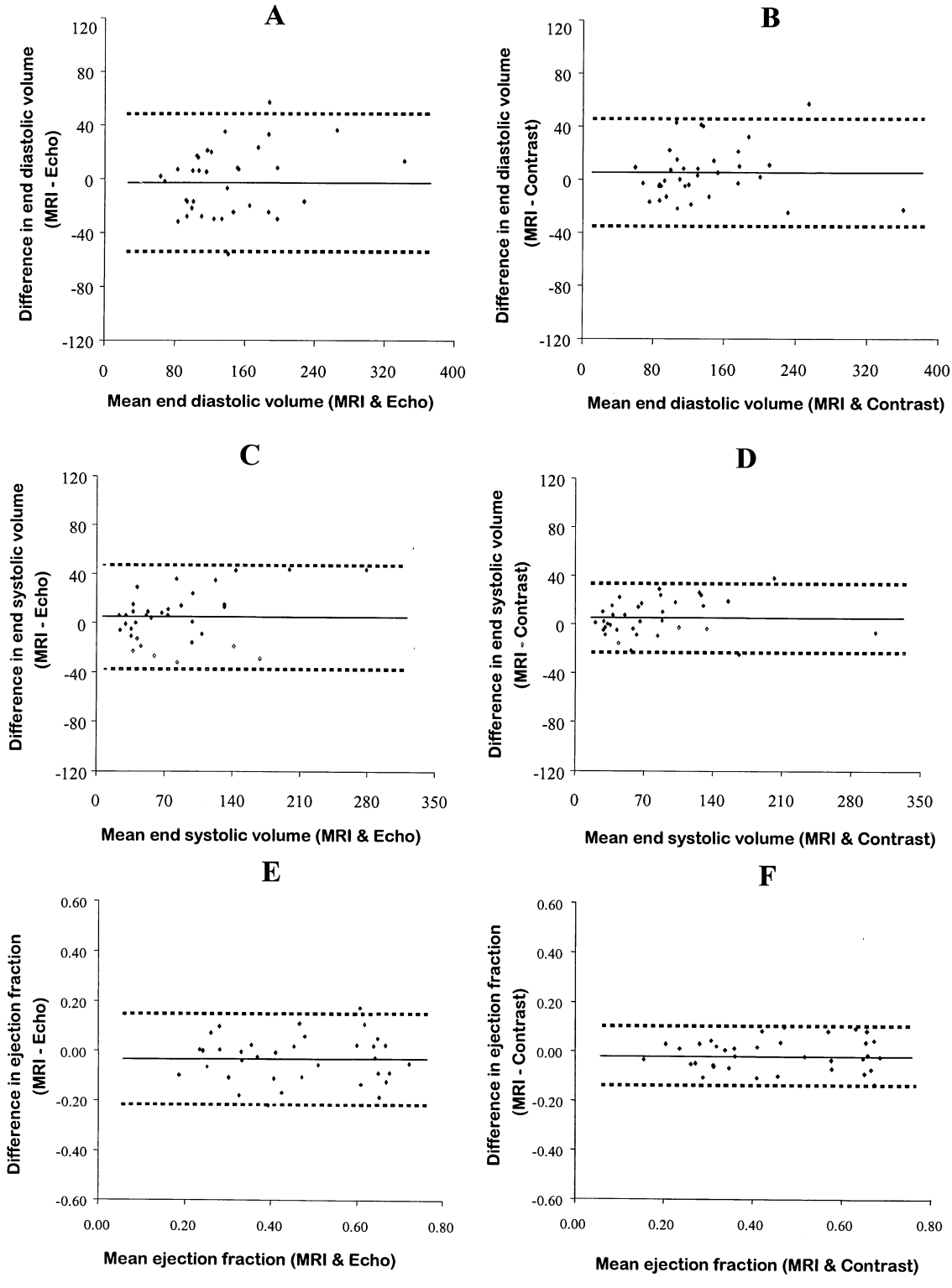


Figure 3. Bland–Altman plots showing the mean difference (**solid lines**) and the limits of agreement (**dashed lines**) between echocardiographic and MRI measurements of LV end diastolic volume (**A** and **B**), end systolic volume (**C** and **D**) and EF (**E** and **F**). **Left** = baseline echocardiography; **right** = postcontrast echocardiography. The value for each patient is represented by a **diamond.** For each variable the limits of agreement become more narrow after contrast agent administration.

pared with 33 subjects (94%) after contrast (chi-square = 4.0, $p < 0.03$). These findings were more striking in the patients with two or more adjacent segments not seen on the baseline echocardiogram.

Interobserver variability. The interobserver variability for the precontrast echocardiographic measurements of LV end diastolic and end systolic volumes as well as EF was 4 ± 18,

Table 2. Absolute Difference Between Echocardiographic and Magnetic Resonance Imaging Measurements

	Standard Echo-MRI	Contrast Echo-MRI	p Value
Heart rate (min^{-1})	3.0 ± 2.3	2.9 ± 2.4	0.44
Mean arterial pressure (mm Hg)	4.5 ± 4.7	4.9 ± 5.0	0.30
End diastolic volume (ml)	21 ± 13	15 ± 14	0.038
End systolic volume (ml)	17 ± 13	12 ± 9	0.015
LVEF	0.08 ± 0.06	0.05 ± 0.03	0.031

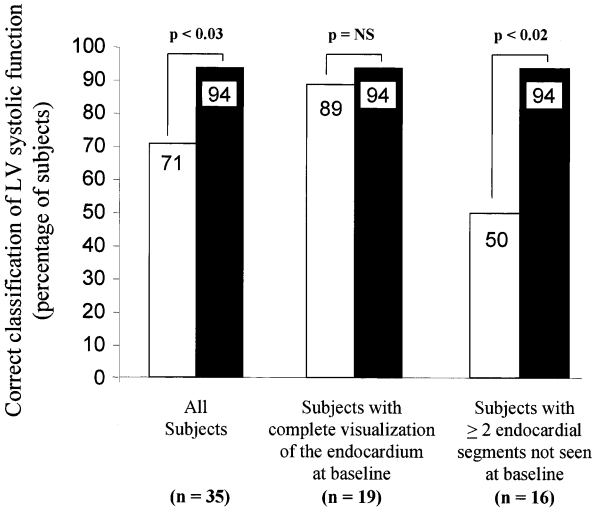
All values are mean ± 1 SD. LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging.

−6 ± 18 and 0.07 ± 0.10 ml, respectively. After contrast these values were −8 ± 20, −10 ± 15 and 0.04 ± 0.07 ml.

Discussion

Assessment of LV volume, EF and regional wall motion is valuable for risk stratification in myocardial infarction (15), coronary artery bypass grafting (16) and valvular heart disease (17,18). The use of angiotensin-converting enzyme inhibitors in patients who sustain a myocardial infarction (19) or exhibit symptoms of heart failure (20) has been shown to prolong survival in those with severely, as opposed to mildly, reduced LVEF. Thus, for patients with a variety of cardiovascular disorders, identification of reduced systolic function and quantification of the magnitude of this reduction has marked clinical importance. Although images acquired with transthoracic echocardiography may be used to assess LV volumes and EF, inadequate definition of the endocardium may limit their accuracy and utility (2). Whether required for clinical or research purposes, quantitative measures of global and regional LV systolic function in many patients often require additional forms of testing (angiography, radionuclide scintigraphy and, more recently, MRI). Thus, a rapid and relatively simple method to improve the visualization of the endocardial border with transthoracic echocardiography, resulting in a more reliable assessment of LV volumes and EF, would improve the utility of this widely used versatile imaging modality.

Figure 4. The percentage of subjects in which echocardiographic assessments of global LV systolic function were accurate for the determination of normal, mildly to moderately depressed or severely reduced LV systolic function. In subjects with complete visualization of the endocardium, contrast agent administration was of no benefit; however, if two or more endocardial segments were not visualized at baseline, contrast enhancement markedly improved classification of EF subsets. **Open bars** = standard echocardiography; **solid bars** = contrast echocardiography.



Rationale for study. Because microbubbles have a high acoustic impedance and reflect ultrasonic transmissions better than blood, they can opacify the LV cavity after IV injection and traversal of the pulmonary circulation. Preliminary studies of microbubble administration indicate that their use improves endocardial border definition and reader confidence in wall motion assessment in subjects with suboptimal visualization of the LV endocardial surface (4–6,21). However, it is important to recognize that improved visualization of the LV cavity after contrast agent administration may not translate into improved measures of global and regional LV systolic function. Contrast-induced attenuation artifacts may obscure the endocardial surface. In addition, accumulation of contrast agent simultaneously in the LV myocardium and cavity may reduce visualization of the border between the blood pool and the endocardium. Perhaps more important, microbubbles may slow the velocity of ultrasound transmission through the cavity, resulting in spatial misregistration of the true endocardial surface (22). Contrast-enhanced echocardiographic assessments of LVEF have been shown to be similar to those acquired with routine echocardiography or contrast ventriculography in patients with high-quality images and preserved LV systolic function (23). However, no study has rigorously compared the utility of contrast agent administration for the assessment of LV volumes and EF in patients with a spectrum of echocardiographic image quality, LV shape and systolic performance. This study is the first to demonstrate that improved LV endocardial border definition after IV contrast translates into more accurate measurements of global and regional LV systolic function.

Clinical findings. Our data allow us to reach several conclusions. First, the correlation and limits of agreement between MRI and echocardiographic determinations of LV volumes and EF improve after contrast agent administration (Figs. 2 and 3). The more narrow limits of agreement that are noted in contrast assessments of EF appear related to two factors: 1) improved assessment of end systolic volumes (Fig. 3, B and D) and 2) a subtle tendency to draw end diastolic volumes smaller after IV contrast (Fig. 3, A). The fact that the limits of agreement between echocardiographic and MRI measurements were more narrow after the administration of contrast agent is not surprising. It is well known that structures that are parallel to the ultrasound beam, such as the endocardial border in the apical views, are difficult to resolve with echo-

cardiography. Spherical microbubbles in the LV cavity provide a surface that is perpendicular to the ultrasound beam, have a large scattering cross section (22) and therefore facilitate endocardial visualization and tracing of its contour. We did not encounter failure of the contrast agent to opacify the apex during systole, as has been seen with first-generation agents.

Second, the improved echocardiographic assessment of LV systolic function after IV contrast agent administration has clinical utility for distinguishing between mildly and severely depressed LVEF. We prospectively chose a cutoff value of EF < 0.35 because this value has important prognostic implications in heart failure (20). It is important to point out that the advantage of contrast echocardiography was most striking in the subjects with two or more nonvisualized segments on the baseline echocardiogram. Thus, these data do not support the use of IV contrast agent to improve quantitation of the left ventricle in patients in whom all segments can be clearly seen on the baseline echocardiogram.

Finally, the improved accuracy of contrast-enhanced determination of EF was most valuable in patients with EF values between 25% and 50%. We found little clinical utility when the precontrast EF was ≥60% or <25%. In no case did an EF calculation fall below 50% (our cutoff for mildly depressed LV systolic function) when the precontrast EF was ≥60%. Similarly, in patients with a precontrast EF <25%, contrast echocardiography did not raise the EF above 35%. These findings held true regardless of the number of segments seen on the baseline echocardiogram.

Study limitations. Our study has limitations. First, all our patients were in sinus rhythm. None had frequent ventricular ectopy or atrial fibrillation. We are uncertain if contrast provides reliable results in subjects with irregular rhythms. Second, contrast enhancement may reduce the ability to visualize the mitral annular plane because of marked opacification of both the left atrium and left ventricle in the apical views. Thus, both readers had to occasionally refer to the baseline images to identify the mitral annulus. This was done after all of the baseline data sets had been analyzed in blinded fashion without knowledge of the contrast-enhanced echocardiogram or the MR images. Finally, we used continuous, two-dimensional, fundamental imaging for the echocardiographic portions of the protocol. Recently it has been shown that the use of intermittent or second harmonic imaging, or both, increases the signal/noise ratio for contrast echocardiography (24). Thus, improved results may occur with such techniques. In addition, tissue harmonic imaging enables improved visualization of endocardial borders even without the use of contrast agent and may reduce the number of patients in whom contrast agent is needed for quantitation of LV function.

Conclusions. Intravenous contrast using 2% DDFP emulsion during routine echocardiography improves quantification of LV volumes and EF. These findings are most pronounced in subjects with incomplete visualization of the endocardium during precontrast echocardiography.

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