

Reduction in Sample Size for Studies of Remodeling in Heart Failure by the Use of Cardiovascular Magnetic Resonance

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ABSTRACT

Fast breathhold cardiovascular magnetic resonance (CMR) has become a reference standard for the measurement of cardiac volumes, function, and mass. The implications of this for sample sizes for remodeling studies in heart failure (HF) have not been elucidated. We determined the reproducibility of CMR in HF and calculated the sample size requirements and compared them with published values for echocardiography. Breathhold gradient echo cines of the left ventricle were acquired in 20 patients with HF and 20 normal subjects. Sample size values were calculated from the interstudy standard deviation of the difference. The percentage variability of the measured parameters in our HF group of intraobserver (2.0–7.4%), interobserver (3.3–7.7%), and interstudy (2.5–4.8%) measurements was slightly larger than for our normal group (1.6–6.6%, 1.6–7.3%, and 2.0–7.3%, respectively) but remained comparable with previous studies in normal subjects. The calculated sample sizes in patients with HF for CMR to detect a 10-ml change in end-diastolic volume ($n = 12$) and end-systolic volume ($n = 10$), a 3% change in ejection fraction ($n = 15$), and a 10-g change in mass was ($n = 9$) were substantially smaller than recently published values for two-dimensional echocardiography (reduction of 81–97%). Breathhold CMR is a fast comprehensive technique for the assessment of cardiac volumes, function, and mass in HF that is accurate but also highly reproducible. This allows a considerable reduction in the patient numbers required to prove a hypothesis in research studies, which suggests a potential for important research cost savings.

KEY WORDS: Heart failure; Magnetic resonance imaging; Remodeling; Reproducibility; Sample size.

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INTRODUCTION

The assessment of cardiac volume, mass, and function is fundamental to the understanding and treatment of many heart diseases (1,2). As well as providing important information at a single point in time, serial assessments can document progressive cardiac remodeling (3). There is growing interest in treatments designed to moderate or reverse pathologic remodeling (4), but this requires measures of cardiac volumes, mass, and function that are both accurate and reproducible. The reproducibility of a technique determines the sample size required to demonstrate a clinical change (5), which is a major cost in pharmaceutical trials.

Several techniques are used to assess remodeling. Echocardiography is widely available, but image acquisition is operator and acoustic window dependent (6). Reproducibility is reasonable in normal ventricles (7), but the quantification of volumes and mass is limited by geometric assumptions that do not hold true in ventricles undergoing cardiac remodeling (8,9). Radionuclide ventriculography is reproducible (10), but volumes are more difficult to measure. Although gated single photon emission computed tomography looks promising (11), ventricular mass still remains problematic, and for both nuclear techniques, repeated studies for research purposes are limited by the radiation exposure. Cardiovascular magnetic resonance (CMR) is a new noninvasive method of assessing remodeling that addresses these problems without exposure to ionizing radiation (12). Cine CMR has been shown to be an accurate (13–17) and reproducible (18–22) technique, but conventional techniques have been limited by the long acquisition times required, which have been up to 45 min.

Faster techniques that can be acquired within breathhold have now made CMR more clinically acceptable, providing fast and accurate results in the normal population (23–26). Despite the widespread use of breathhold CMR, there are very limited data on the application of these fast techniques to patients undergoing cardiac remodeling. These patients present the most technical challenges for CMR because of a higher prevalence of arrhythmias, orthopnea, and the presence of slow-moving blood with poor signal, all of which affect image quality. We hypothesized that fast CMR would retain high reproducibility even in patients with heart failure (HF) and that this would result in only small sample sizes being required to detect statistically significant changes by CMR in comparison with published data from echocardiography. Therefore, we compared the reproducibility of a breathhold fast low angle shot (FLASH) cine sequence

in patients with chronic stable HF and in a normal population and determined interstudy reproducibility of the technique.

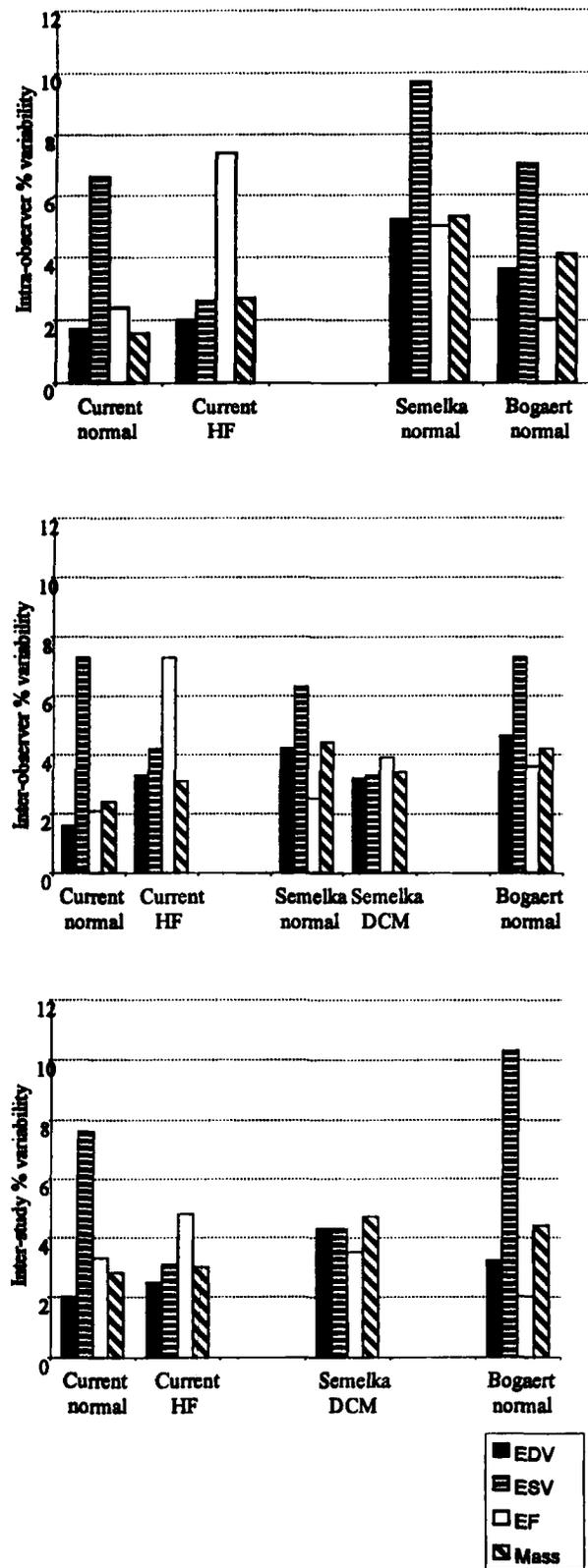
METHODS

Patients

Forty subjects were included in the study from two groups: 20 healthy adult volunteers and 20 patients with chronic stable HF (New York Heart Association class II–III) of ischemic origin with dilated ventricles and left ventricular systolic dysfunction (mean ejection fraction [EF], $31 \pm 10\%$). All patients were recruited from a dedicated HF clinic. For the intraobserver and interobserver variability studies, one scan per subject was required for analysis, and this was undertaken by 15 subjects in each group. For the interstudy variability analysis, however, two scans were required with standardized conditions that were separated by 7 days and at the same time of day to minimize variations from simple physiologic changes. In both the adult volunteer and the patient group, five subjects failed to attend the second study at the required time for a variety of logistic reasons, and a further five subjects in each group were recruited. Therefore, the interstudy variability results are based on 15 subjects in each group, of which only 10 are common with the subjects from the intraobserver and interobserver analyses. The study was approved by the institutional Ethics Committee, and all subjects gave written consent.

Imaging Technique

Subjects were imaged on a Picker Edge 1.5-T scanner (Picker, Cleveland, OH), using the body coil and prospective electrocardiographic triggering. The cardiac short axis was determined from three scout images. The initial transverse scout was used to align the vertical long axis connecting the left ventricular apex with the center of the mitral valve. The third horizontal long axis scout was aligned through the apex and mitral valve on the vertical long axis image. A diastolic image at end expiration on the horizontal long axis image provided the reference image on which the short-axis slices were positioned. A segmented FLASH breathhold cine was used for each of the contiguous 10-mm short-axis slices. Parameters were as follows: TE 3.8 msec, repeat time = RR interval, slice thickness 10 mm, field of view 35×35 cm, read matrix 256, phase matrix 128, frames 16 (typical temporal resolution of 45–80 msec), flip angle 35 degrees, phase encode grouping 6–10. An average of 10



short-axis segments was needed to encompass the entire left ventricle (27).

Image Analysis

This was performed on a personal computer using in-house developed software (CMRtools, ©Royal Brompton and Harefield NHS Trust). This method, the time of acquisition and analysis, together with a comparison with echocardiography and radionuclide ventriculography have been previously described (27). Manual tracing of epicardial and endocardial borders of contiguous short-axis slices allowed calculation of volumes, EF, and mass (27). Mass (g) was derived from this volume multiplied by the specific density of myocardium (1.05 g/cm³) (28). Papillary muscles were included in the mass and excluded from the volume. To provide information on intraobserver and interobserver reproducibility, analysis of a patient's scan was performed twice on all subjects by one investigator (N.G.B.) and once by a second investigator (L.C.D.). To assess interstudy reproducibility, subjects underwent a second scan 7 days later at a similar time and under similar conditions to the first scan. All analysis was performed with investigators blinded to the previous results and in random order. The overall image quality of the cines was assessed subjectively using a nine-point scale by one observer, where 1 was uninterpretable, 3 was poor, 5 was average, 7 was good, and 9 was excellent, with even scores being given when quality was between grades.

Statistical Analysis

The intraobserver, interobserver, and interstudy reproducibility were assessed by calculating the mean difference and standard deviation between results, with percentage variability equal to the mean of the absolute values of the differences between the two measurements divided by their mean. Student's paired *t*-test was used to

Figure 1. Percentage variability of end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), and left ventricular mass for (top) intraobserver, (middle) interobserver, and (bottom) interstudy reproducibility studies. Semelka et al. (18) used conventional cine MR in normal subjects and dilated cardiomyopathy (DCM), and Bogaert et al. (24) used fast breathhold MR in normal subjects only. Normal, healthy group; HF, heart failure group; DCM, dilated cardiomyopathy group.

assess any significant differences between measurements. The correlation coefficient and Bland-Altman limits of agreement were calculated to assess the strength of the relation. Differences between groups of patients were assessed using an unpaired nonparametric test (Mann-Whitney). The nature of the diagnosis meant it was not possible to blind the observers as to whether the scans were from patients with heart failure or normal subjects, but scans were presented for review in random order. Differences in proportions were analyzed using the chi-squared test. Results are shown as mean \pm SD, and $p < 0.05$ was taken as statistically significant.

The sample sizes required by CMR to show a clinical change with a power of 90% and an α error of 0.05 were calculated from the interstudy standardized difference, where the standardized difference equals the difference to be detected divided by the interstudy standard deviation of the parameter concerned, as described by Altman (29). The sample sizes required by echo to show the same clinical changes were calculated in the same way using the published interstudy standard deviation of the difference from Otterstad et al. (30).

RESULTS

CMR was well tolerated by all subjects in the study, and the average imaging time was 18 min, similar to previous reports (24). All normal subjects were in sinus rhythm, but arrhythmias were present in 53% ($p < 0.001$ vs. normal group) of the HF group (90% of which were atrial fibrillation, with a mean rate of 72 ± 11 , the rest being multiple ventricular ectopics). The average breathhold time for the normal group was 12 sec, allowing an average of 16 phases per heartbeat to be acquired.

Image Quality and Reproducibility

The image quality was significantly better in the normal group (7.8 ± 0.8 for normal, 4.9 ± 0.8 for HF, $p < 0.05$). The intraobserver, interobserver, and interstudy data for end-diastolic volume (EDV), end-systolic volume (ESV), EF, and mass for both groups are shown in Table 1. The mean values of these parameters were not significantly different for all three variability comparisons in both groups, with the exception of normal subject intraobserver ESV and the HF interobserver EDV measurements. The correlation between the first and second calculation of each parameter for all variability comparisons in both groups was good (0.93–0.99). The percent-

age variability results are depicted graphically in Fig. 1. In this study, the intraobserver, interobserver, and interstudy percentage variability of the normal group compared favorably with previous studies of normal groups using slower conventional cine techniques (18) and faster breathhold techniques (24). The percentage variability was in general higher for the HF group, although this was only significant for intraobserver ESV ($p < 0.001$) and EF ($p < 0.001$), the interobserver EF ($p < 0.001$), and the interstudy ESV ($p < 0.05$) and EF ($p < 0.05$). This difference is illustrated in Fig. 1. Nevertheless, the percentage variability remains comparable with previous studies in the normal population. An alternative measure of reproducibility is provided by the Bland-Altman limits of agreement for each group. This analysis showed no systematic bias in error between measurements according to the mean EF level, and in general, the limits of agreement in abnormal hearts were similar to normal subjects.

Sample Size

In patients with HF, calculations showed that for the left ventricle, CMR requires 12 and 10 patients to detect a 10-ml change in EDV and ESV, respectively; 15 patients to detect a 3% change in EF; and 9 patients to detect a 10-g change in mass (Table 2). The percentage reduction in sample size compared with recently published echocardiography data (30) was 90% for EDV, 81% for ESV, 85% for EF, and 97% for mass.

DISCUSSION

Breathhold CMR is now widely used for the assessment of left ventricular function, but the reproducibility of this technique has not been previously reported in heart failure patients. We have shown that the reproducibility of breathhold CMR is good in the HF group and compared with normal subjects. Furthermore, this high reproducibility suggests that a smaller sample size is required to detect a change in volumes, mass, and function in comparison with published values for echocardiography.

The interstudy variability determines the sample size required to demonstrate a statistically significant change in a parameter under measure. The sample sizes required for CMR to show a statistically significant change in volumes, EF, and mass have not been previously described for patients with HF. Recent data for echo in patients with abnormal left ventricular function are available from Otterstad et al. (30), who investigated two-dimensional echo using Simpson's biplane analysis in 24 subjects (12

Table 1
Reproducibility Data in Normal and Heart Failure Groups

	Normal				Heart Failure			
	EDV (ml)	ESV (ml)	EF (%)	Mass (g)	EDV (ml)	ESV (ml)	EF (%)	Mass (g)
Intraobserver								
Mean ± SD	172 ± 38	46 ± 14	73 ± 5	162 ± 32	288 ± 69	201 ± 65	31 ± 10	194 ± 41
Mean diff ± SD	-0.1 ± 4.0	2.2 ± 2.8	-1.1 ± 1.8	-1.4 ± 3.0	-3.1 ± 6.2	0.5 ± 6.3	-0.9 ± 2.2	1.3 ± 5.9
Corr coef	0.99	0.98	0.96	0.99	0.99	0.99	0.98	0.99
<i>t</i> -test <i>p</i>	Ns	<0.05	Ns	Ns	Ns	Ns	Ns	Ns
% Variability ± SD	1.7 ± 1.5	6.6 ± 3.8	2.4 ± 1.5	1.6 ± 1.2	2.0 ± 1.9	2.6 ± 1.7	7.4 ± 4.6	2.7 ± 0.9
BA limits	-8.1:7.8	-3.4:7.8	-4.5:2.4	-7.4:4.6	-15.3:9.1	-11.9:12.8	-5.2:3.4	-10.2:12.8
Interobserver								
Mean ± SD	169 ± 41	44 ± 15	74 ± 4	161 ± 31	278 ± 69	193 ± 70	32 ± 12	201 ± 44
Mean diff ± SD	1.3 ± 3.8	1.7 ± 3.8	-0.7 ± 2.1	-0.7 ± 5.1	5.0 ± 12.2	2.7 ± 9.6	0.2 ± 3.3	-0.6 ± 7.7
Corr coef	0.99	0.97	0.93	0.99	0.99	0.99	0.95	0.99
<i>t</i> -test <i>p</i>	NS	Ns	Ns	NS	<0.05	Ns	Ns	Ns
% Variability ± SD	1.6 ± 2.6	7.3 ± 6.9	2.1 ± 2.4	2.4 ± 2.2	3.3 ± 3.3	4.2 ± 5.3	7.3 ± 5.4	3.1 ± 3.0
BA limits	-6.1:8.6	-5.8:9.2	-4.8:3.5	-10.7:9.3	-18.9:28.9	-16.0:21.5	-6.4:6.7	-15.9:14.6
Interstudy								
Mean ± SD	157 ± 46	46 ± 12	70 ± 7	148 ± 39	276 ± 82	190 ± 69	33 ± 10	178 ± 67
Mean diff ± SD	2.5 ± 3.5	0.9 ± 4.7	-0.1 ± 2.4	-0.7 ± 6.4	-1.2 ± 7.4	-0.8 ± 6.5	-0.1 ± 2.5	-0.7 ± 6.4
Corr coef	0.99	0.93	0.94	0.99	0.99	0.99	0.99	0.99
<i>t</i> -test <i>p</i>	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns
% Variability ± SD	2.0 ± 2.2	7.6 ± 5.6	3.3 ± 4.2	2.8 ± 2.7	2.5 ± 1.3	3.1 ± 1.9	4.8 ± 2.9	3 ± 1.5
BA limits	-4.5:9.4	-8.3:10.1	-4.8:4.7	-9.7 to 6.3	-15.8:13.4	-13.6:12	-3.8:3.6	-13.3:11.9

Mean diff, mean difference; Corr coef, correlation coefficient; BA limits, Bland-Altman limits of agreement; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction.

Table 2
Sample Size Required to Detect the Same Change by Echo, CMR with a Power of 90%, and $p < 0.05$

Clinical Change	Echo		CMR		% Reduction in Sample Size
	SD	N	SD	N	
EDV, 10 ml	23.8	121	7.4	12	90
ESV, 10 ml	15.8	53	6.5	10	81
EF, 3% (abs)	6.6	102	2.5	15	85
Mass, 10 g	36.4	273	6.4	9	97

EDV, ESV, EF, and left ventricular mass use a 90% power and an α error of 0.05. Sample size is derived from the interstudy SD of the difference as described by Altman (29). Echo, echocardiography interstudy SD from Otterstad et al. (30); CMR, cardiovascular magnetic resonance interstudy SD from this study; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction. Note that for studies comparing active vs. placebo, these sample size numbers must be doubled.

normal, 12 after myocardial infarction, mean EF 47 ± 11). Comparison of the interstudy standard deviation between our results and those of Otterstad et al. are shown in Fig. 2. Table 2 shows that the improved reproducibility of CMR results in a considerable reduction in sample sizes of between 81 and 97%. Similar findings have been demonstrated for left ventricular mass measurement in hypertensive patients (5). This reduction in sample size would potentially enable a faster more cost-effective assessment of therapeutic interventions by CMR. The rather small increment in cost of performing fast CMR

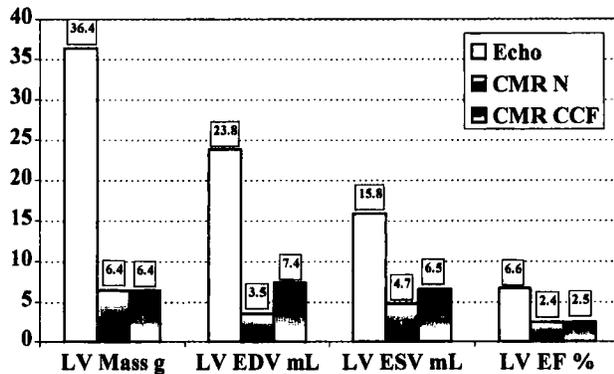


Figure 2. Comparison of the interstudy standard deviation between the results from this article for CMR and those most recently published for two-dimensional echocardiography by Otterstad et al. (30). Although these results are from different patient populations, it is clear that CMR appears to offer a marked improvement in reproducibility, which translates into reduced sample sizes for remodeling studies that require repeated volume and mass parameter assessments.

as opposed to echocardiography would be heavily outweighed by the savings from substantial reductions in the number of patients in a study, each of which costs many thousands of dollars. These differences between CMR and echocardiography are reflected in other studies looking at the variability of results between functional imaging techniques in examining parameters of cardiac function in HF (31) and after cardiac transplantation (32), which suggest that the results from different techniques are not interchangeable in individual patients (31).

Although the percentage variability of both our normal and HF groups remain comparable with slower conventional CMR (Fig. 1), the Bland-Altman limits of agreement are wider in our HF group than in our normal group. The reasons for this include the poorer image quality, which is probably due to dyspnea, causing a worse breathhold technique, and the high prevalence of arrhythmias. Nevertheless, the reproducibility of CMR is shown in this study to be quite robust to these problems. The reproducibility of MR might be improved further by using a smaller slice thickness, but this leads to reduced signal-to-noise ratios and potentially a greater imaging and analysis time, unless an interslice gap is used. This thinner slice approach is not uncommonly used in centers with the latest coil technology, which compensates for the loss in signal. It is worth noting that the percentage variability of the HF intraobserver, interobserver, and interstudy ESV appears less than that of the normal group. This is because the difference is expressed as a percentage of a much larger ESV in the HF group. Nevertheless, the percentage variability for intraobserver, interobserver, and interstudy ESV and EF is statistically greater than the equivalent normal group, and all the HF groups

have wider limits of agreement than the equivalent normal group.

Limitations of Study

The main limitation of this study is that CMR and echocardiography were not performed in the same patients to determine the interstudy variability of measurements. However, Otterstad's group had a mean EF of 47% and our study group had a mean EF of 31%, which suggests that CMR has performed better in this group of patients where typically imaging would be expected to be more difficult because of a higher incidence of arrhythmias and poor endocardial contrast due to impaired wall motion.

The temporal resolution varied in the CMR scans according to the duration of breathhold tolerated by the patient, because this defines the number of phases in each phase encode group, and ranged typically from 45 to 80 msec. In general this is a lower temporal resolution than with echocardiography (typical frame rate is 20/sec) and radionuclide ventriculography (typically 16 frames per cycle, although longer imaging for diastolic function with 32 frames per cycle is also used in research studies). However, recent techniques have been developed that resolve any issues associated with poor breathholding by using a navigator pulse to gate to the breathing cycle during free breathing (33). In addition, with faster gradient systems coming on the market now, temporal resolutions in the order of 30 msec or less are easily achievable with considerably improved image quality using true FISP sequences, which can also be run in real time (34).

CONCLUSION

In summary, breathhold CMR provides highly reproducible assessments of cardiac volumes, function, and mass in HF. This allows a considerable reduction in the patient numbers compared with echocardiography required to prove a hypothesis in research involving changes in remodeling parameters and thereby the cost of studies. The technique is fast and can be implemented on current MR scanners.

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