Three-dimensional echocardiography for left ventricular quantification in heart failure

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Chapter 7

Contrast-enhanced versus Non-Enhanced Three-dimensional Echocardiography ofLeft Ventricular Volumes

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Abstract

Background: In three-dimensional echocardiography (3DE), individual endocardial trabeculae are not clearly visible necessitating left ventricular (LV) volumes to be measured by tracing the innermost endocardial contour. Ultrasound contrast agents aim to improve endocardial definition, but may delineate the outermost endocardial contour by filling up intertrabecular space. Although measurement reproducibility may benefit, there may be a significant influence on absolute LV volume measurements.

Methods: Twenty patients with a recent myocardial infarction and good ultrasound image quality underwent 3DE using the TomTec Freehand method before and during continuous intravenous contrast infusion. LV volumes were measured off-line using TomTec Echo-Scan software.

Results: The use of contrast enhancement increased end-diastolic (110 ± 35 versus 144 ± 53 ml; $p < 0,01$) and end-systolic volume measurements (68 ± 31 versus 87 ± 45 ml; $p < 0,01$) significantly compared to non-contrast; the ejection fraction remained unchanged (40 ± 13 vs 41 ± 14%, p = NS). Measurement reproducibility did not improve significantly, however.

Conclusion: Volumes measured by 3DE are significantly larger when ultrasound contrast is used. Possibly, intertrabecular space comprises a substantial part of the LV cavity. In the presence of an adequate apical acoustic window, ultrasound contrast does not improve LV volume measurement reproducibility.

Introduction

In clinical cardiology, left ventricular (LV) volume and ejection fraction are widely used parameters, as they carry important diagnostic and prognostic information, particularly when evaluated quantitatively rather than qualitatively. Traditionally, LV volume and ejection fraction are evaluated using quantitative two-dimensional echocardiography (2DE), radionuclide angiography or LV angiography. These modalities have been extensively validated and show a reasonable correlation with each other [1], yet it should be noted that they are not simply interchangeable due to the fundamentally different principles they are based on [2]. Although magnetic resonance imaging (MRI) has progressed to the reference method for LV volume measurements over the last few years, its limited availability, longer examination times and higher cost preclude routine clinical use [3]. Currently, 2DE is the most frequently applied method to assess LV volumes and ejection fraction in daily clinical practice. 2DE, like LV angiography, relies on geometric assumptions of LV shape however, and is therefore not ideal. Three-dimensional echocardiography (3DE) however, does not rely on geometric assumptions, and promises to provide more narrow limits of confidence, while a better correlation between 3DE and MRI has been reported [4-10].

In quantitative echocardiographic studies, it is customary to consider the endocardial wall to be a reasonably smooth surface that may be traced manually with a computer mouse. It was not appreciated fully that the endocardium consists of trabeculae because these are usually too small to be seen by echocardiography, and therefore the innermost endocardial contour has been called the endocardial wall. To improve LV endocardial definition in the substantial amount of patients with limited echogenicity, administration of intravenous ultrasound contrast agents is increasingly advocated, with a reported success rate of > 95% [11-17]. Besides improved endocardial border definition, several studies observed larger LV volumes following ultrasound contrast administration [11-21, 29]. This may be explained by the fact that the LV contrast fills up the intertrabecular space, thereby delineating the outermost rather than the innermost endocardial contour. Although ultrasound contrast agents have the potential to improve LV volume measurement reproducibility, the question arises where the LV cavity boundaries should be drawn: i.e. either the innermost endocardial contour in the absence of contrast enhancement, or the outermost contour, when ultrasound contrast is present? The present study aimed to

compare measurements of end-systolic and end-diastolic LV volume and ejection fraction using 3DE without and with ultrasound contrast enhancement, and to evaluate the effect of contrast enhancement on measurement reproducibility.

Patients and Methods

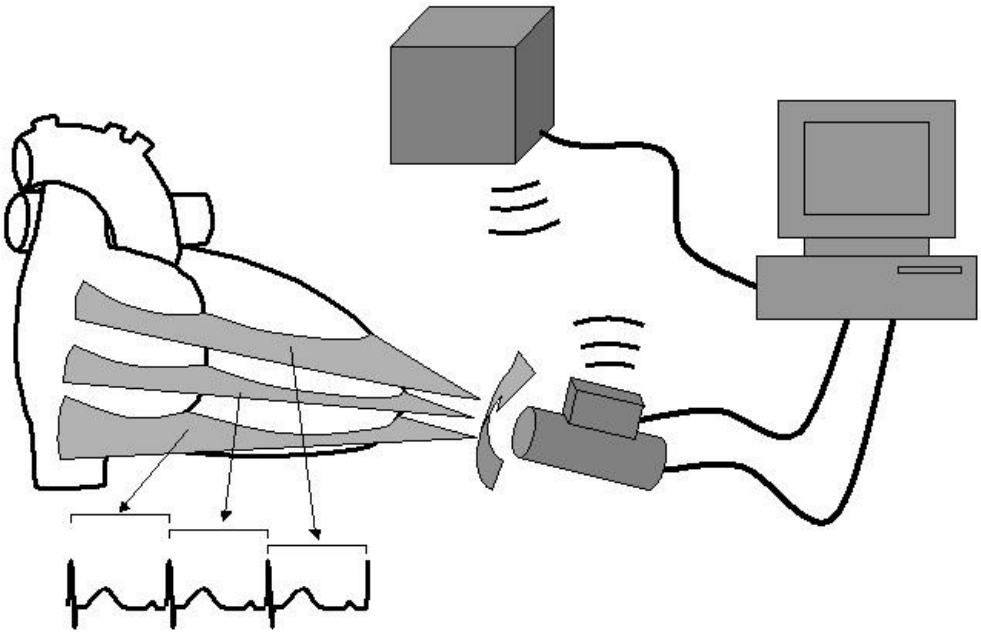
Twenty clinically stable patients with recent myocardial infarction with a good acoustic apical window and absence of known or suspected contraindications to the ultrasound contrast agent (as specified in the package insert), underwent 3DE using the TomTec Freehand method [22]. The study was approved by the medical ethics committee of our institution and all patients provided prior written informed consent. One 3DE acquisition was performed immediately before and one during continuous intravenous ultrasound contrast infusion. LV volumes, ejection fraction, and intra- and inter-observer variation were evaluated.

Three-dimensional echocardiography

The echocardiographic examinations were performed using an ATL HDI 5000 (Philips Medical Systems, Eindhoven, the Netherlands) or a HP 5500 ultrasound platform (Hewlett Packard, Andover, Massachusetts, USA). Imaging was continuous using the gray-scale second harmonic imaging (harmonic penetration) mode. During ultrasound contrast infusion, second harmonic imaging with lower mechanical indices (between 0,2 and 0,4) was used, and gain and compression settings were adjusted for optimal endocardial visualization. The ultrasound platform was interfaced with a TomTec Compact 3DTM Cardiac Imaging system (TomTec GmbH, Munich, Germany) as described earlier [22]; see figure 1. Briefly, a pyramidal 3DE data set was acquired from via the apical acoustic window by making a fan-like 120-degree sweep with the 2DE transducer from the epicardial anterior wall to the epicardial posterior wall or vice-versa, with a spatial locator mounted on top of the transducer. Using ECG triggering, consecutive imaging planes encompassing a full cardiac cycle were thus acquired at known spatial orientations along the 120-degree sweep. To circumvent artifacts caused by cardiac motion during respiration, image acquisition was performed during 6 to 10 repeated periods (of 10 to 15 seconds each) of breath holding. Thus, a dynamic pyramidal 3DE data set consisting of 60 to 80 “slices” was generated within a total acquisition time of approximately 3 min at a

temporal resolution of 40 ms. The acquired images were stored digitally for subsequent off-line analysis.

Figure 1.



The spatial locator system consists of a small antenna that can be mounted on any 2D ultrasound transducer and a larger electromagnetic transmitter that is placed on the examination table near the antenna/transducer. Combining spatial orientation data from antenna and transmitter with 2D echocardiography data from the ultrasound machine, images are acquired at known spatial orientations. Using ECG triggering, 60 to 80 full cardiac cycles are stored on computer hard disk. Three-dimensional reconstruction is then performed off-line.

Ultrasound contrast infusion

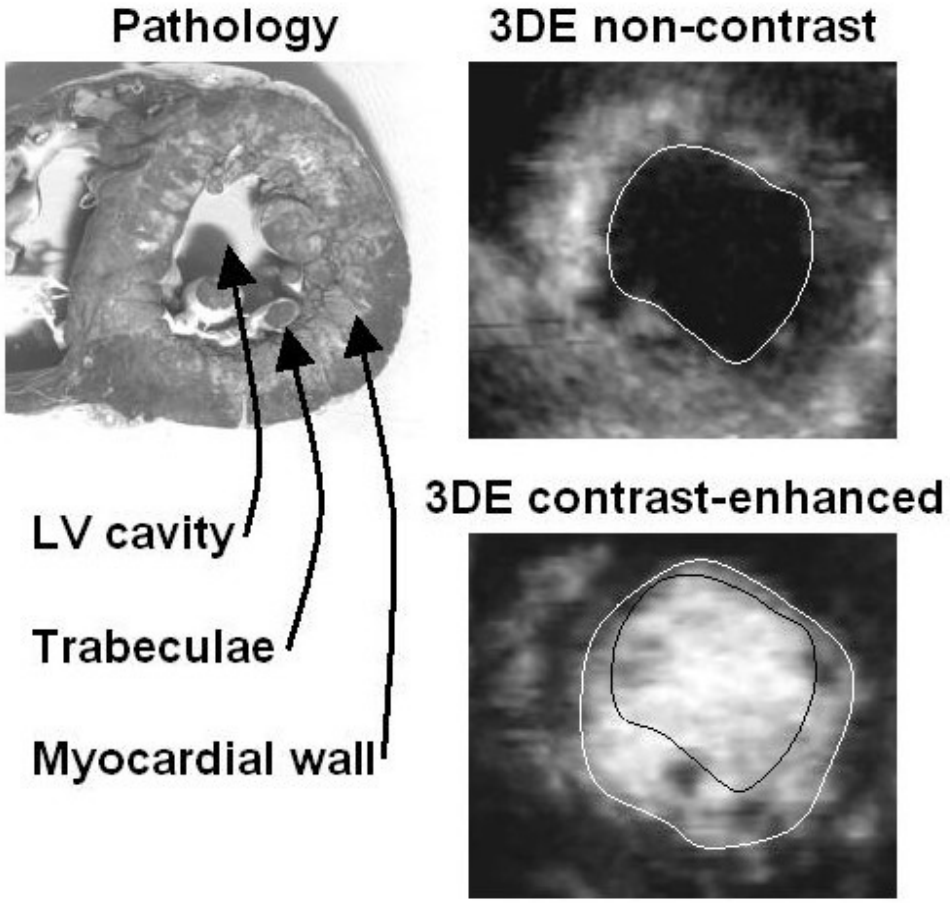
After non-contrast 3DE, patients were cannulated in the right antecubital vein and a three-way stopcock was attached to the cannula. Using the main port, a 0.9% saline infusion running at 200 ml/h was given as a carrier liquid. As intravenous ultrasound contrast agent we used Optison (Mallinckrodt Medical, St. Louis, MO, USA), a suspension of perflutren-filled albumin microbubbles with a mean diameter of 2,0 - 4,5 µm at a concentration of 5 - 8 × 108 microspheres/mL. At the side port, a bolus of 0,2 - 0,3 ml of Optison was given, followed by continuous infusion of approximately 25 ml / h, with infusion speed continuously adjusted to maintain steady-state LV opacification with no attenuation. The close proximity of the stopcock to the entry point prevented trapping of contrast microbubbles in the lines [23]. During infusion, the pump was slowly and continuously agitated manually to keep microbubbles in suspension. Steady-state LV opacification could be maintained for 4 - 6 minutes, allowing 3DE acquisitions to be repeated once or twice. Total volume administration was approximately 20 ml.

LV volume measurement

For 3DE analysis, the TomTec workstation in conjunction with TomTec EchoScan 4.1 software was used to calculate LV volumes and ejection fraction. Data were post-processed off-line and based on visual assessment of acquisition quality, e.g. presence of movement artifacts or attenuation, it was decided which acquisitions were used. The end-diastolic and end-systolic frames were determined by the moments of closure of the mitral and aortic valves, respectively. LV volumes were measured by manual tracing of the black-and-white or the white-and-black endocardial contours for non-contrast and contrast-enhanced acquisitions, respectively, using nine equidistant long axes. Papillary muscles were included into the LV cavity.

For reproducibility analyses, the volume measurements were performed twice by one experienced observer (JvdH) at a four-week interval, and were repeated once by a second, blinded observer (LY).

Figure 2



The LV is depicted as a pathology specimen and as seen by 3DE operators. Trabeculae may be appreciated clearly in the pathology specimen. The endocardial contours as drawn by the different operators are depicted as well. Because trabeculae are more easily appreciated on a short axis cut, short axis images are shown. For 3DE analysis however, long axis images were used.

Biostatistical analysis

For LV volumes and ejection fraction measured by 3DE with and without ultrasound contrast infusion, values were expressed in ml or % ± standard deviation. A two-sided paired t-test was performed for comparison. Intra- and inter-observer variability was calculated by Bland-Altman analysis and expressed as bias ± 2 x standard deviation, with the percentual intra- and inter-observer variability expressed relative to the mean volume. All statistical calculations were performed using Microsoft Excel 2003 software (MicroSoft Corporation, Seattle, Washington, USA). Differences with a p-value of <0,05 were considered statistically significant.

Results

Study population

The study population consisted of 20 patients (18 male / 2 female), with an average age of 56 ± 13 years (range 25-82). Infarct location was anterior in 15 patients, inferior in 1 and inferoposterior in 4. At the time of the study, the patients were at a mean of 7,1 ± 4,9 months after their index myocardial infarction; all were in a clinically stable condition.

Volume measurements

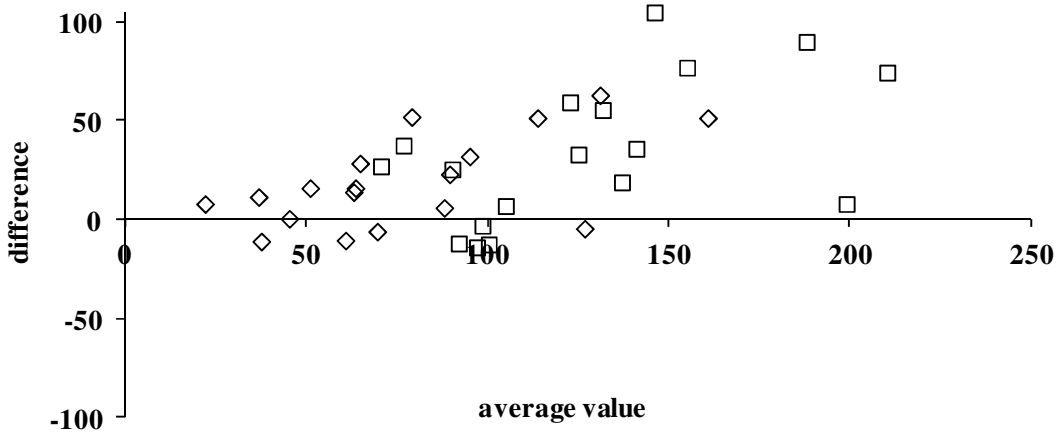
In two patients, contrast 3DE image quality was insufficient for analysis because of strong attenuation. The results of LV volume measurements in the remaining 18 patients are summarized in table 1. When compared to non-contrast 3DE measurements, the use of ultrasound contrast caused a significant increase in end-diastolic (110 ± 35 vs. 144 ± 53 ml, $p < 0,01$) and end-systolic volumes (68 ± 31 vs. 87 ± 45 ml, $p < 0,01$), but not in ejection fraction (40 ± 13 vs. 41 ± 14%, $p = 0,42$).

Table 1: non-contrast vs contrast-enhanced 3DE

	non-contrast	contrast-enhanced	p-value
End-diastolic volume (ml)	110 ± 35	144 ± 53	< 0,01
End-systolic volume (ml)	68 ± 31	87 ± 45	< 0,01
Ejection fraction (%)	40 ± 13	41 ± 14	0,42

Figure 3 shows a Bland-Altman plot comparing non-contrast to contrast-enhanced measurements. A gradual increase in difference with increasing volumes can be clearly appreciated.

Figure 3.



Bland-Altman plot comparing contrast to non-contrast enhanced measurements of end-diastolic volumes (squares) and end-systolic volumes (diamonds). On the horizontal axis, the average of the two measurements and on the vertical axis, the difference between the two measurements is shown. A gradual increase in difference with increasing volumes can be clearly appreciated.

Reproducibility

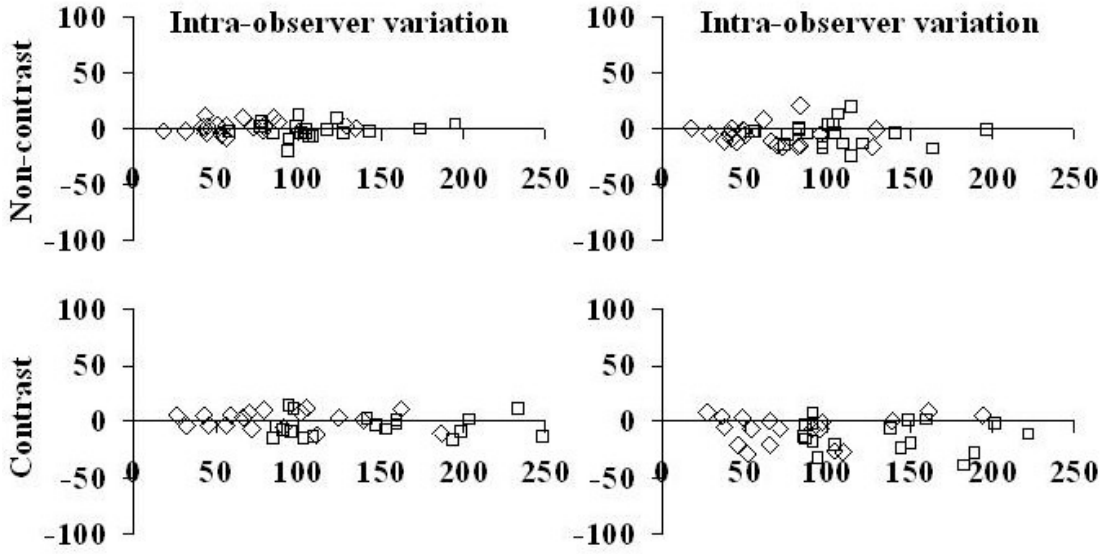
The use of contrast enhancement did not improve either intra- or interobserver variation of volume measurements, as depicted in table 2.

Table 2: Reproducibility of non-contrast and contrast-enhanced 3DE

	non-contrast	contrast-enhanced	p-value
Intraobserver variation			
End-diastolic volume (%)	-1,3 ± 13,0	-2,7 ± 13,3	0,56
End-systolic volume (%)	1,8 ± 16,2	1,7 ± 17,2	0,84
Ejection fraction (%)	-1,8 ± 7,1	-3,2 ± 15,8	0,67
Interobserver variation			
End-diastolic volume (%)	-4,4 ± 10,1	-8,9 ± 9,3	0,2
End-systolic volume (%)	-9,1 ± 14,7	-8,7 ± 15,0	0,86
Ejection fraction (%)	3,3 ± 5,0	0,4 ± 8,4	0,11

Figure 4 shows Bland-Altman plots of intra-and inter-observer variation of non-contrast and contrast-enhanced measurements, in a 2x2 fashion. The magnitude of the reproducibility as observed in this study was comparable to earlier unenhanced studies performed by our group 22.

Figure 4.



Bland-Altman plots comparing intra-and inter-observer variation of non-contrast and contrast-enhanced measurements of end-diastolic volumes (squares) and end-systolic volumes (diamonds). Left; intra-observer variation, right; inter-observervariation, upper panel; non-contrast measurements, lower panel; contrast-enhanced measurements.

Discussion

The principal finding of the present study is that the use of ultrasound contrast enhancement results in a sizable and significant increase in both end-diastolic and end-systolic 3DE LV volumes, compared to non-contrast measurements. As the relative increases in end-diastolic and end-systolic volume were equal, ejection fraction measurements were not affected. Contrast enhancement did not significantly improve measurement reproducibility. To the best of our knowledge, the present study is the first ultrasound contrast 3DE study on LV volume measurement in patients.

The concept of the endocardial wall as a smooth surface as is common to the echocardiographic mind, is challenged by the results from this study. Although it has been known since the earliest anatomic studies that the endocardium consists of sponge-like trabeculae with blood flowing in-between them, the consequence of this anatomical fact appears to be largely underappreciated in quantitative 3DE analysis. As indicated by the striking increase in both LV end-systolic and end-diastolic volume measurements following contrast enhancement, the intertrabecular space may actually comprise a large part of the true LV cavity volume - a volume that traditionally remains undetected, as the LV trabeculae are indistinguishable from the LV wall if contrast were not used. Although studies comparing ultrasound contrast 3DE and MRI have yet to be performed, Hundley et al. reported a significantly better correlation of 2DE volume measurements with MRI measurements following contrast enhancement [19].

Several earlier studies investigated the influence of contrast enhancement on LV endocardial wall visibility and volume measurements using both 2- and 3DE, as described schematically in table 4 [11-21, 28-29]. Among these, the results of two 2D studies using the ultrasound contrast agent Levovist are in line with the present study (a significant increase in LV volumes), effects that were ascribed to ultrasound contrast filling up intertrabecular space [17,19]. A similar study with EchoGen showed a small but significant decrease in LV end-diastolic volume, and no change in LV end-systolic volume and ejection fraction measurements [20]. Conceivably, the difference in LV end-systolic volume measurements between the studies, may represent relatively more destruction of ultrasound contrast agent in the intertrabecular zone in the EchoGen study.

The present study demonstrates an increase in LV volumes after administration of an ultrasound contrast agent. As the administered volume load during the contrast-enhanced studies was quite small (20 to 25 ml), this is highly unlikely to have caused the reported increase in LV volumes as obtained during contrast-enhanced imaging. Ejection fraction, however, remained unchanged, as the relative increase in end-diastolic and end-systolic volumes was equal. The effect of ultrasound contrast filling up intertrabecular space seems to be equal both in end-diastole and in end-systole. It appears that in end-systole, intertrabecular space may not be completely obliterated, as is supported by both contrast echocardiography and MRI studies [19,30]. In one contrast echocardiography study, LV end-diastolic volume showed a larger increase than LV end-systolic volume, with a

resulting increase in ejection fraction [17]. In this study however, the amount of ultrasound contrast material that was injected was very small, which might have aggravated the effects of ultrasound contrast destruction.

In previous studies, patients were either selected for suboptimal acoustic windows, or consecutive patients were included. Consistently, ultrasound contrast infusion lead to improved endocardial visibility [11-16, 18, 21, 28] and (when assessed) to improved volume measurement reproducibility [17, 19, 21, 29]. In our patient group acoustic windows were good even without ultrasound contrast enhancement, but with the 3DE method we used, image reconstruction inherently causes a slight deterioration of image quality. We therefore sought to improve image quality by the use of contrast infusion, but we were not able to demonstrate significant improvement in LV volume measurement reproducibility. Conceivably, "blurring" after reconstruction may affect non-contrast and contrast-enhanced acquisitions equally. The advent of real-time 3DE may obviate reconstruction and its deteriorating effects on image quality, but whether ultrasound contrast infusion may indeed increase volume measurement reproducibility remains to be determined [31].

Another reason for the failure of ultrasound contrast to improve reproducibility in our study may be related to a decrease in valve visibility during ultrasound contrast infusion. As noted by Kasprzak et al., visibility tends to be better at the LV apex than at the base due to attenuation [16]. We observed significant basal attenuation in two patients and subsequently excluded them from further analysis, because we felt that technically satisfying LV opacification had not been accomplished. In most other patients however, valve visibility, especially of the aortic valve, was decreased by ultrasound contrast. We did feel however, that the endocardial contour was easier to trace with contrast enhancement, which is in accordance with virtually all studies on endocardial visibility using ultrasound contrast enhancement [11-15, 18, 28]. Conceivably, the advent of real-time 3D echocardiography, in which "blurring" inherent to reconstruction algorithms is circumvented, holds new promises for increased measurement reproducibility by contrast enhancement.

Conclusion

In 3DE, the use of the ultrasound contrast agent Optison for LV cavity opacification significantly increases both enddiastolic and endsystolic LV volumes, but has no significant influence on the determination of the ejection fraction. In the presence of an adequate apical acoustic window, contrast enhancement does not further improve measurement reproducibility. Conceivably, measurement reproducibility may benefit from the advent of real-time 3D echocardiography.

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