Detection and Quantification of Myocardial Scars using Contrast-Enhanced 3D-Echocardiography

Running Title: Infarct size by 3D-Echo

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ABSTRACT

Background—Myocardial infarct scars are usually imaged using delayed-enhanced cardiac magnetic resonance (DE-cMR). In this study, we tested the hypothesis that the detection and the quantification of myocardial scars can be evaluated by 3D-Echo.

Methods and Results—Fifty patients with a healed myocardial infarction (>3 months) and 10 controls underwent 3D-Echo and DE-cMR within 2 weeks. 3D-Echo images were acquired using different settings, in the presence or absence of contrast. The highest contrast-to-noise ratio was obtained using second harmonic imaging (1.6/3.2 MHz), at an MI of 0.5, in the presence of contrast. Using this modality, the sensitivity and specificity for the 3D-Echo detection of cMR scars on a segmental basis were 78% and 99%, respectively. On a per patient basis, they were of 96% and 90%, respectively. Good correlation and limits of agreement were found between the assessment of scar mass by 3D-Echo and DE-cMR (r=0.93, p<0.001, bias: 1.4±3.6g), and the concordance between both techniques for the assessment of scar transmurality was good. Intraobserver, interobserver and day-to-day reproducibility was comparable between 3D-Echo and DE-cMR for both the detection and the quantification of scars.

Conclusions—Contrast-enhanced 3D-Echo is a promising new tool for the detection and the quantification of myocardial infarct scars.

Key Words: echocardiography, magnetic resonance imaging, myocardial infarction.

List of abbreviations:

AU: arbitrary unit
CE-3D-Echo: contrast-enhanced 3D-Echocardiography
cMR: cardiac magnetic resonance
CNR: contrast-to-noise ratio
DE-cMR: delayed-enhanced cardiac magnetic resonance
DE-CT: delayed-enhanced computerized tomography
EDV: end-diastolic volume
ESV: end-systolic volume
ICC: intraclass correlation coefficient
LV: left ventricle
MI: mechanical index
ROI: region of interest
SD: standard deviation
VI: videointensity
3D-Echo: 3D Echocardiography
INTRODUCTION

In patients with coronary artery disease and chronic left ventricular dysfunction, the distinction between reversible and irreversible myocardial injury is of paramount clinical importance, as only patients with reversibly injured or viable myocardium can experience increased LV ejection fraction and improved survival after revascularization.

Noninvasive methods for assessing myocardial viability include positron-emission tomography, single-photon-emission computed tomography, and dobutamine echocardiography. These techniques have proven clinical utility, but each has limitations that may reduce its diagnostic accuracy. For example, they only interpret myocardial viability as an all-or-none phenomenon within a given myocardial region, and none of them does assess the transmural extent of viability across the ventricular wall. Because gadolinium accumulates in scar tissue, delayed-enhanced cardiac magnetic resonance (DE-cMR) has been proposed to delineate the transmural extent of infarction and to distinguish reversible from irreversible myocardial injury. Both experimental and clinical studies have validated this concept, allowing DE-cMR to progressively become the reference method for assessing the transmural extent of necrosis and by inference myocardial viability.

Several previous studies have shown that, in patients with prior myocardial infarction, myocardial scar tissue usually appears brighter than normal myocardium on diagnostic echocardiographic images, the intensity of the backscattered echo signals being proportionate to the amount, orientation and compactness of the underlying collagen fibers. Although both m-mode and 2D-echocardiography allow for the detection of the presence of myocardial scar, the information provided by these modalities is seldom used clinically, owing probably to their inability to delineate the 3-dimensional extent of the pathological process.
Recently, 3D-echocardiography was introduced as a promising new method for assessing LV morphology, volumes and mass in patients with structural heart disease. When used in combination with computerized endocardial contour tracking algorithms, it indeed permits faster, more accurate, and less operator dependent quantification of LV volumes and mass than 1D-Echo or 2D-Echo. In this study, we sought to determine if 3D-Echo could be used to evaluate the presence and extent of myocardial scars.

**METHODS**

**Patients.** We prospectively recruited 63 subjects in sinus rhythm to undergo DE-cMR and 3D-Echo in random order within 2 weeks. Subjects with constant arrhythmia or any contraindication to cMR were not considered for inclusion. Of the initial 63 subjects, 3 could not complete the cMR study (2 because of claustrophobia, 1 because of an adverse reaction to the gadolinium contrast agent) and were therefore excluded from the analysis.

Of the 60 remaining subjects (46 men, mean age 63±14 years, range 25-84 years), there were 50 patients with coronary heart disease and a prior myocardial infarction (40 men, mean age: 66±11 years, range 41-84 years) and 10 volunteers (6 men, mean age: 50±19 years, range 25-72 years). Patients with prior myocardial infarction were selected using the SPECT database of our institution. Inclusion criteria were the presence of a fixed perfusion defect and a clinical diagnosis of a previous myocardial infarction of at least 3-months of age, in the same anatomical distribution as the SPECT perfusion defect. Inclusion criterion for normal volunteers was the absence of heart disease, based on history, ECG, rest echocardiography and maximal exercise test. The study protocol was approved by the ethical committee of our Institution and all patients gave informed consent prior to inclusion into the study.

**3D-Echocardiography.** 3D-Echo was performed using an IE33 echocardiographic system (Philips,
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Andover, Massachusetts) equipped with a broadband, wide angle, matrix array transducer. 3D-Echo datasets were acquired from the apical window using an ECG-triggered wide-angled acquisition (93°x80°) mode in which 4 wedge-shaped subvolumes were obtained over 4 consecutive cardiac cycles during a short breath hold. Care was taken to include the entire LV within the pyramidal scan volume.

Delayed-enhanced cardiac magnetic resonance. cMR was performed in a 1.5 Tesla magnet (Philips, Eindhoven, The Netherlands) using a phased array coil wrapped around the chest. After localization of the heart, patients received an intravenous bolus of 0.1 mmol.kg⁻¹ of Gadobenas Dimeglumin (Bracco Altana Pharma GmbH, Konstanz, Deutschland). Fifteen minutes later, delayed images were acquired in the apical 4-, 3-, 2-chamber and short-axis orientations (end-diastolic images, 10 mm slice width) as previously described.¹⁶

Design of the study. We first sought to evaluate which imaging modality would permit optimal differentiation between scar tissue, normal myocardium and LV cavity. For this purpose, 10 patients and 5 normal volunteers were studied. In each subject, 84 3D-Echo full-volumes were acquired, each investigating a different combination of image acquisition settings. Among the tested parameters, we investigated 7 different mechanical indexes (MI, 0.1-0.7), 4 different pulse emission frequencies (1.4, 1.6, 2.0, and 2.6 MHz), 2 different pulse cycle lengths (2 cycles in fundamental mode, 4 cycles in harmonic mode) and 2 different pulse repetitions (harmonic and power modulation). Gain control and time gain compensation were adjusted at noise floor during 3D-imaging. Finally, all modalities were also tested in the presence (enhanced 3D-Echo) or in the absence (unenhanced 3D-Echo) of the contrast agent SonoVue (Bracco Diagnostics, Inc., Geneva, Switzerland), administered as a continuous intravenous infusion, at a rate adjusted to obtain a homogeneous LV cavity opacification without attenuation of the basal segments (mean infusion rate of 1.0±0.1 mL.min⁻¹).

Once the optimal settings were defined, the remaining 45 subjects were studied using the chosen
modality.

**Data analysis.** All images, irrespective of their quality, were blindly analyzed by 2 observers with at least 2 years of experience in reading 3D-Echo and cMR studies (PM and FC). For this purpose, the images were first anonymized. Image analyzes were then randomly performed, in separate sessions for 3D-Echo and cMRs, to avoid recalling the patients’ images. The main results were generated by one single observer (PM). The second observer (FC) analyzed a subset of data for assessment of the interobserver reproducibility.

CE-3D-Echo. All 3D-Echo datasets were analyzed using a prototype version of the QLab software (version 6.0, Philips Medical Systems, Eindhoven, The Netherlands) which allows for the manual contouring of the endocardial and epicardial borders as well as that of any hyperechoic area. As with DE-cMR, myocardial scar tissue were identified as areas of increased subendocardial or transmural brightness. Briefly, the 3D volume dataset was first displayed in 3 different cross sections that can be modified interactively. For the detection algorithm to work properly, the anatomically correct 4- and 2-chamber views need to be displayed simultaneously. Markers were then placed onto the mitral annulus and the apex, both in end-diastole and end-systole. Using these markers, the software program first creates truncated ellipsoid end-diastolic and end-systolic 3D meshes of the LV. The vertices of these meshes are then automatically attracted to the image borders (3D gradient of image intensity) while respecting pre-specified surface smoothing constraints (in order to minimize local curvature on the surface). The end-diastolic and the end-systolic 3D meshes deform until equilibrium is reached between closeness to the borders and minimal curvature. If needed, manual adjustments were applied. The end-diastolic epicardial contours were next automatically estimated, by adding a fixed myocardial wall thickness of 8.8 mm to the endocardial mesh. Manual corrections were applied, if needed. These epicardial contours are used to delineate and calculate the volume of the myocardium. Finally, the software program automatically contoured the hyperechoic areas within the end-diastolic myocardial
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volume to delineate myocardial scars. Here also, manual corrections were applied, if needed. From these contours, the mass of scar tissue was computed and expressed either in absolute terms (assuming a density of 1.05 g.mL\(^{-1}\)) or as a percentage of the total LV mass. The software also allows for the computation of the transmural extent of the scar tissue on a segmental basis (using the ASE 16 segment model), either as a percentage of the segmental mass or as a fraction of the regional wall thickness.

For determination of CNR, end-diastolic datasets were first cropped in QLab to obtain 10 mm thick slices in the apical 2-, 3- and 4-chamber projections. In patients with a prior myocardial infarction, the cropped planes were carefully chosen to pass through the infarct area. The so-obtained cropped 2D-images were then saved as uncompressed files onto the hard drive and were subsequently analyzed using the ImageJ software (version 1.38, National Institutes of Health, Bethesda, MD, USA). This software allows for the measurement of video-intensity in manually traced regions of interest (ROIs). ROIs were positioned onto the scar area, the normal myocardium, the LV cavity, the pericardium, and the septal stripe if present. CNRs were calculated as the differences in video-intensity between 2 ROIs, divided by 256 and expressed in percentages.

DE-cMR. DE-cMR datasets were transferred on a computer workstation and analyzed using the Segment software (version v1.691, Einar Heiberg), which allows for the semi-automatic detection of hyperenhanced areas. Briefly, the endocardial and epicardial LV contours were first manually traced on each consecutive short-axis slice. The software program then divided the myocardial volume into 6 segments per slice. Manual adjustments were applied, if needed. The images were then binarized to a threshold of 2 standard deviations of the mean value obtained in 9 remote normal segments without hyperenhancement. The transmural extent of hyper-enhancement was then computed within each segment on these thresholded images and reported as the percentage of the segmental area that is hyperenhanced. The scar mass, expressed in absolute term (assuming a density of 1.05 g.mL\(^{-1}\)) or as a percentage of the total LV mass was computed using the Simpson’s method. The transmural extent of
hyper-enhanced areas was computed on a segmental basis (using the ASE 16 segment model), as a fraction of the segmental wall thickness. Finally, the software also allowed computation of LV volumes and ejection fraction.

**Statistical analysis.** Statistical analyses were performed using the SPSS (version 12.0) software (Chicago, Illinois). Values are reported as mean ± 1 standard deviation (SD). Measurements of myocardial scar mass and its transmural extent by cMR and CE-3D-Echo were compared by the Bland Altman method. Differences in mean measurements between the two modalities were compared by Student’s t-test. Intraobserver, interobserver and test-retest reproducibility of scar quantification was assessed by using two-way random single-measure intraclass correlation coefficients (ICC) and the Bland Altman method. For this purpose, 20 datasets were randomly chosen at the end of the recruitment period to assess intra- and interobserver reproducibility. Test-retest reproducibility was investigated using the data of the first 10 patients who accepted to undergo CE-3D-Echo and DE-cMR twice on two consecutive days. The transmural extent was compared using t-statistics. All tests were 2-sided, and p<0.05 was considered to indicate statistical significance.

**RESULTS**

In the 50 patients with prior myocardial infarction, infarct age was 6±7 years (median 2.7 years, range 3 months to 34-years). The area of necrosis involved the anterior wall in 18 (36%), the lateral wall in 3 (6%) and the inferior and/or posterior wall in 29 (58%). Mean LVEF was 44±13% by CE-3D-Echo and 43±14% by cMR. CE-3D-Echo slightly, albeit non significantly underestimated EDV and ESV as compared to cMR (180±60 mL vs 191±67 mL and 106±55 mL vs 116±66 mL, respectively). Body mass index was 25±5 kg.m⁻² (range 18-43 kg.m⁻²).

**Video-intensity and contrast-to-noise ratios.** Figure 1 shows the changes in VI in normal myocardium and scar segments using second harmonic mode at increasing MI. As illustrated, the increase in VI was
larger in scar segments than in normal myocardium, reaching saturation around a MI of 0.5. Similar results were obtained for each of the pulse emission frequencies and pulse cycle lengths tested and were independent of the use of power modulation. Use of contrast markedly increased VI in the LV cavity, increased VI at only high MIs in normal myocardium, and did not modify VI in infarcted myocardium.

Figure 2 shows the effects of changing the MI, the pulse emission frequency, the pulse cycle length or the pulse repetition on contrast-to-noise ratios (CNRs) between scar tissue and surrounding structures (i.e. normal myocardium and LV cavity). As illustrated, in both unenhanced and contrast-enhanced (CE) datasets, the highest CNRs were obtained using harmonic imaging. Although the use of contrast was associated with significant decreases in CNRs, it allowed for a better delineation of endocardial contours and hence for a better appreciation of the transmural extent of the scar tissue. This is illustrated in Figure 3. Accordingly, we opted both for the use of contrast in the second part of our study, and imaging in second harmonic mode, using an emission frequency of 1.6 MHz at an MI of 0.5, as this imaging modality was associated with the highest CNRs in the presence of contrast (Figure 2).

CNRs obtained using this modality were not significantly different from those obtained with DE-cMR (CNR between scar and normal myocardium: 60±6% vs 63±20% respectively, \( p=0.8 \); CNR between scar and LV cavity: 29±11% vs 20±13% respectively, \( p=0.065 \)).

**Detection of myocardial scars by CE-3D-Echo.** Figure 4 shows representative CE-3D-Echo and DE-cMR images in 3 patients with areas of hyperenhancement by DE-cMR in the anterior, inferior and lateral walls, respectively.

As shown in Table 1, on a segmental basis, CE-3D-Echo allowed for the identification of DE-cMR scars with a sensitivity of 78% (95% CI:73-84%), a specificity of 99% (95% CI:98-100%) and an...
overall accuracy of 94% (95% CI: 92-95%). There were a total of 51 false negative segments, among which 44 presented with subendocardial scars (86%, mean transmural extent of 26±13%), and 35 (69%) were located in the anterior or lateral segments. There were also 9 false positive segments, all located in the septum. Figure 5 shows representative false positive and false negative CE-3D-Echo results. When data were analyzed on a per vascular territory basis, the sensitivity and specificity of CE-3D-Echo for the identification of DE-cMR scars were respectively 95% (95% CI: 91-99%, 113/119 segments) and 100% (181/181 segments) in the inferior and posterior walls, 68% (95% CI: 58-78%, 57/84 segments) and 98% (95% CI: 96-99%, 387/396 segments) in the anterior, antero-septal and septal walls, and 48% (95% CI: 31-66%, 16/33 segments) and 100% (147/147 segments) in the lateral wall.

On a per subject basis, 2 patients (with small subendocardial scars of 2.7 and 5 g, respectively) were missed by CE-3D-Echo. False positive results were found in only 1 subject, yielding a sensitivity of 96% (95% CI: 91-99%, 48/50 patients), a specificity of 90% (95% CI: 71-99%, 9/10 control subjects), and an overall accuracy of 95% (95% CI: 91-99%, 57/60 subjects).

**Septal Wall.** As all false positive segments were located within the septum and potentially related to the presence of septal stripes, we further investigated all bright septal areas (BSAs). For this purpose, both CE-3D-Echo end-diastolic (ED) and end-systolic (ES) frames were analyzed and compared to the corresponding DE-cMR images. BSAs were identified on CE-3D-Echo ED images in 37 subjects (62%). Two different patterns were observed. In 19 subjects, these BSAs were found in the middle of the septum and were surrounded by hypoechoic bands on both their right and left sides (Type 1). During systole, all 3 layers significantly thickened (from 2.6±0.6 to 5.1±0.8 mm for the bright septal area, from 3.4±0.9 to 4.7±1.3 mm for the right-sided hypoechoic band, and from 3.3±0.4 to 5.1±1.3 mm for the left-sided hypoechoic band, all p<0.001). None of the type 1 BSAs showed DE-cMR enhancement and were equally prevalent in patients (32%) and controls (30%). In the remaining 18 subjects, BSAs were located in the LV subendocardium, without any hypoechoic band on their left side.
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(Type 2). In 7 subjects (9 segments), the subendocardial BSAs thickened during systole (from 3.8±0.9 to 5.2±0.7 mm, p<0.001), became located in the middle of the septum and surrounded by 2 hypoechoic bands. On DE-cMR, none of these segments showed hyperenhancement (Type 2A). In the remaining 11 subjects, BSAs did not thicken (from 5.2±1.4 to 5.3±1.5 mm, p=0.9), remained located in the subendocardium at end-systole, and always exhibited subendocardial DE-cMR hyperenhancement (Type 2B).

Delineation of the transmural extent of myocardial scar by CE-3D-Echo. As shown in Table 1, the agreement between CE-3D-Echo and DE-cMR for the assessment of the transmural extent of scar was good. Only 16 segments were misclassified by CE-3D-Echo. In 14 of these segments, the transmural extent of scar was close to 50% by both techniques (CE-3D-Echo: 46±12% vs DE-cMR: 52±13%).

Quantification of scar mass by CE-3D-Echo. Absolute scar mass was 12±9 g (median 12 g) by CE-3D-Echo and 13±9 g (median 15 g) by DE-cMR. Expressed as a percent of LV mass, scar mass was 9±7% (median 9%) by CE-3D-Echo and 10±7% (median 10%) by DE-cMR. Good correlation and limits of agreement were found between quantitative measures of scar mass by CE-3D-Echo and DE-cMR, both in absolute (mean difference of 1.4±3.6 g, 95% CI [-5.7 - 8.5 g], Figure 6), and relative terms (mean difference of 0.6±3.0%, 95% CI [-5.3 - 6.5 %]).

Intraobserver, interobserver and test-retest reproducibility. Table 2 summarizes the results of these comparisons, using intraclass correlation coefficients and limits of agreement.

DISCUSSION

Clinical studies have shown that the transmurality of myocardial scars is critical in determining the recovery of function after revascularization: the more transmural the extent of scar tissue, the lower the
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likelihood of recovery in function.18,19,20

Until recently, DE-cMR was the only available imaging modality allowing for the identification and separation of subendocardial and transmural scars. On imaging, the scar tissue appears white (hyperenhanced) whereas normal myocardium appears dark.6 Because of its high spatial resolution, its excellent contrast-to-noise ratio and its intrinsic 3-dimensional nature, DE-cMR has progressively become the most popular method for assessing the presence and extent of myocardial scars. Because myocardial scar tissue appears much brighter than normal myocardium on diagnostic echocardiographic images,10,11 we tested the hypothesis that 3D-Echo would also be able to detect the presence and quantitate the extent of myocardial scars. Our results can be summarized as follows:

1. Myocardial scars reflect ultrasound more effectively than normal myocardium. At any MI, the VI measured in myocardial scars is higher than in normal myocardium. When the MI is progressively increased, the increase in VI is also greater in myocardial scars than in normal myocardium.

2. CNRs between myocardial scars and normal myocardium are the highest when imaging in second harmonic mode, using an emission frequency of 1.6 MHz and a MI of 0.5.

3. The use of contrast reduces CNRs between myocardial scars and normal myocardium but facilitates endocardial and epicardial border recognition and hence determination of the transmural extent of the scar process.

4. CE-3D-Echo allows identifying myocardial scars with good sensitivity and specificity as compared to DE-cMR, and also allows for a reasonably accurate quantification of scar tissue (mass and transmural extent). Results are nonetheless better in the inferior/posterior walls than in the anterior/lateral walls.

_Delineation of scar tissue by echocardiography._ The daily clinical experience in echocardiographic
laboratories indicates that the hearts of patients with a prior myocardial infarction not only demonstrate abnormalities of LV wall motion and thickening but also enhanced intensity of the reflected echo signals. Back in 1976, Rasmussen et al. were the first to report on the presence of areas of increased echo density on M-mode echocardiograms and to demonstrate a high degree of correlation with the presence or absence of scar at surgery or autopsy. Subsequently, in vitro and in vivo experiments have shown that the acoustic reflectivity of infarcted myocardium and its transmural extent are a function of time. In 26 dogs undergoing left anterior descending coronary artery occlusion, Parisi et al. reported that infarcted segments exhibited a progressive increase in echo intensity that became maximal 6-8 weeks after coronary ligation. Histopathologic and histochemical studies verified that these increases in echo amplitude correlated with the evolution of healing and myocardial scar formation. At 6-8 weeks, the mean collagen content of infarcted myocardium had increased by a factor of 4; concurrently, the echo amplitude in the infarcted segments had increased 2- to 3-fold. More recently, Tabel et al. demonstrated that the intensity of the echo signals reflected by the infarcted myocardium depended not only on collagen content but also on collagen fiber morphology. Specifically, these authors observed that infarcted segments containing mainly thick collagen fibers were much more echogenic than those containing predominantly thin collagen fibers. This probably explains why recently infarcted segments usually appear normoechoic whereas older infarctions appear much brighter. During the complex repair process that is initiated after myocardial infarction, the development of scar indeed begins with the production of thin collagen fibers. Over the course of several weeks, these fibers mature, becoming thicker and more densely packed.

The results of the present study confirm those of these prior reports and extend them to the use of 3D-Echo. Like previous investigators, we observed that the intensity of the reflected echo signals was larger in infarcted than in normal myocardium. We also observed that the response of infarcted and normal myocardium to increasing MI was different, the intensity of the reflected echo signals increasing much faster in infarcted myocardium to reach saturation around an MI of 0.5. As the MI-
dependent increase in echo signal intensity was much flatter in normal myocardium, the CNRs between infarcted and normal myocardium progressively improved when increasing MIs from 0 to 0.5, and declined thereafter. These observations thus suggest that intermediate MI levels (i.e. 0.5) should be used for optimal delineation of infarcted and normal myocardium when imaging the heart in 3D. However, at such low MI levels, the intensity of the echo signals reflected by normal myocardium is very low and limits our ability to appropriately delineate endocardial and epicardial contours and hence to appreciate the transmural extent of infarction (Figure 2). To overcome this limitation, one can either modestly increase the MI in order to better visualize the tissue or use ultrasound contrast agents to improve border definition. As at an MI of 0.5, the presence of contrast did not significantly modify the signal intensity in normal myocardium but greatly enhanced border definition, we elected to use contrast in the validation experiments.

Comparison between CE-3D-Echo and DE-cMR in patients with old myocardial infarctions. In the present study, we used DE-cMR as the reference method to which CE-3D-Echo was compared. Our results show that the agreement between the 2 methods was quite good. On a segmental basis, the ability of CE-3D-Echo to identify DE-cMR scars was high, with positive and negative predictive values well above 90% (95±1% and 93±1%, respectively). Fifty-one infarcted segments by DE-cMR were nonetheless missed by CE-3D-Echo. These false negative segments were more likely to be found in the anterior and lateral walls, where dropout artifacts are frequent, and most often presented with small transmural extent of scars (26±13%). Accordingly, the segmental sensitivity of CE-3D-Echo was less in anterior and lateral segments (68 and 48%, respectively) than in inferior and posterior segments (95%). On a per patient basis, the agreement between the 2 methods was nonetheless high, with only 2 patients with very small infarcts missed by CE-3D-Echo.

As all false positive segments were located within the septum, we further investigated features of bright septal areas (BSAs). We showed that the assessment of both the location and thickening of BSAs
allows differentiating normal “septal stripes” from fibrotic septal scars. We observed two different patterns. In some patients, these BSAs were located in the middle of the septum, were surrounded by hypoechoic bands, and significantly thickened on the ES frame. None of these showed DE-cMR enhancement. This pattern, which was prevalent in patients (32%) and controls (30%), probably corresponds to the so-called “septal stripes”, and presumably represent the location of the circumferential fibers that run perpendicular to the echo scan plane. In the remaining 18 patients, the BSAs were found in the subendocardium on the ED frame and were therefore considered as myocardial scars in our study. In 9 patients, however, no late enhancement was found on DE-cMR. In each case, these “false positive BSAs showed significant systolic thickening and became more midseptal on the ES frame. These BSAs probably correspond to septal stripes as well. Finally, in the 9 last patients, the subendocardial BSAs did not thicken during systole and remained subendocardial on the ES frame. All showed significant delayed enhancement on DE-cMR.

CE-3D-Echo also permitted assessment of the transmural extent of scar tissue across the LV wall. Here again the ability of CE-3D-Echo was quite good, with positive and negative predictive values to predict >50% transmural extent by DE-cMR of 91±7% and 98±1%, respectively. Only 16 segments were misclassified by CE-3D-Echo. Fourteen of these segments had transmural extents ranging between 45 and 55% by both methods. Their misclassification was thus more related to the dichotomous nature of our analysis rather than to intrinsic inaccuracies in either of the 2 methods. Finally, CE-3D-Echo also permitted accurate quantification of the total mass of scar tissue and hence of infarct size.

Several previous studies have used contrast-enhanced echocardiography to assess myocardial viability. None of them, however, did report on the presence of hyperechoic signals in nonviable segments. Instead, they always identified nonviable myocardium as areas of reduced brightness or contrast intensity, which is just opposite to our findings. These apparently diverging results can readily be explained by the way the contrast echo images were acquired in these different studies. Because in
the earlier works, identification of nonviable myocardium relied on the assumption that nonviable segments are hypoperfused and hence should exhibit reduced signal intensity, the former investigators used contrast specific imaging modalities, which almost completely suppress the signals emanating from the underlying native tissue. Accordingly, these modalities also eliminated the hyperechoic signals emanating from scar tissue and made nonviable myocardium (presumably scarred) appear darker than normal or viable myocardium.

Reproducibility of CE-3D-Echo and DE-cMR assessment of scar mass and scar transmurality.

Previous studies using 3D-Echo to measure LV volumes, LV ejection fraction and LV mass have shown that this technique was more reproducible than 2D-Echo and as reproducible as cMR. The results of our study are thus in line with these previous results. Myocardial scar measurements from CE-3D-Echo images are as reproducible as those obtained by DE-cMR (Table 2), a particularly important finding for the follow-up of patients with ischemic heart disease.

Test-retest variation. In contrast with the more widely reported parameters of intra- and inter-observer variability, which relate to the repeated measurement of a single dataset, test-retest variation involves repetition of the entire acquisition and analysis. Assessment of test-retest variations is important because imaging factors contribute to variations in infarct size over time. The present study demonstrates that test-retest variations in CE-3D-Echo and DE-cMR measurements of scar mass and scar transmurality are quite similar. This is also an important finding because these measurements are often used to help make clinical decisions. Since CE-3D-Echo is far more available and less costly than DE-cMR, our findings suggest that CE-3D-Echo could become alternative to DE-cMR when DE-cMR is either unavailable or contra-indicated.

Study limitations. The present study has limitations that should be acknowledged. First, we did not study the time course of appearance of the hyperechoic signals after myocardial infarction.

Based on
previously published experimental data, which indicated that the echo intensity in the infarct zone becomes maximal 6-8 weeks after the index event, we only studied patients whose myocardial infarctions were older than 3 months. As CE-3D-Echo relies on the detection of dense tissue fibrosis, it is unlikely to allow identification of irreversible tissue damage early after acute infarction. At these earlier time points, use of contrast specific modalities might be better suited, as they specifically interrogate microvascular integrity. Second, we did not acquire 2D-Echo images because 2D-imaging is not well suited to display the full 3-dimension extent of the scarring process. Third, scar quantification by the 2 techniques was performed using 2 different softwares. For CE-3D-Echo, we used a prototype version of the QLab software which allows for a precise delineation of endocardial, epicardial and scar borders, on 3D-Echo full volumes. For DE-cMR, we used the Segment software. Although this software also allows for a precise delineation of contours on DE-cMR images, contour delineation is performed on consecutive short-axis slices and not on a 3D full volume. The resulting partial volume effects may lead to overestimation of the scar mass, particularly when it is located at the apex. Forth, the 3D-transducer used in this study was quite bulky and sometimes difficult to fit into the intercostal spaces. This resulted in a relatively high rate of dropout artifacts in the anterior and lateral walls, which probably explains the lower sensitivity of CE-3D-Echo in these regions. In the future, introduction of smaller footprints 3D-transducers should help reducing the occurrence of these artifacts and permit a better delineation of scar tissue in the anterior and lateral walls. Lastly, the 3D algorithm used to draw the endocardial, epicardial and scar contours is not yet fully automated and still requires some manual adjustments. Future development of the software should thus aim at tracking these contours automatically to further improve the robustness of the measurements.

Conclusion. Contrast-enhanced 3D-Echo is a promising new tool for the detection and the quantification of myocardial infarct scars. Future developments are nonetheless needed to improve the sensitivity of the technique, particularly in the anterior and lateral walls, where dropout artifacts are common.
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Disclosures

None.
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Table 1  Presence of subendocardial (<50% of the wall thickness) or transmural scar (>50%) on a segmental basis by CE-3D-echo, comparison with DE-cMR.

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<th></th>
<th>DE-cMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
</tr>
<tr>
<td>CE-3D-Echo</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>715</td>
</tr>
<tr>
<td>Subendocardial</td>
<td>9</td>
</tr>
<tr>
<td>Transmural</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>724</td>
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</tbody>
</table>
Table 2  Intraobserver, interobserver and test-retest reproducibility of CE-3D-echo, as compared to DE-cMR for absolute scar size, scar size as a percent of LV mass, and segmental transmurality.

<table>
<thead>
<tr>
<th></th>
<th>Reproducibility *</th>
<th>Limits of agreement †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intra-observer</td>
<td>Inter-observer</td>
</tr>
<tr>
<td>Scar mass (g)</td>
<td></td>
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</tr>
<tr>
<td>CE-3D-Echo</td>
<td>0.94</td>
<td>0.93</td>
</tr>
<tr>
<td>DE-cMR</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>0.5 ± 2.7</td>
<td>0.0 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>0.2 ± 2.8</td>
<td>-1.3 ± 3.3</td>
</tr>
<tr>
<td>Infarct size (% LV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CE-3D-Echo</td>
<td>0.94</td>
<td>0.94</td>
</tr>
<tr>
<td>DE-cMR</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>0.4 ± 2.2</td>
<td>0.1 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>0.0 ± 2.4</td>
<td>0.9 ± 2.3</td>
</tr>
<tr>
<td>Transmurality (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CE-3D-Echo</td>
<td>0.93</td>
<td>0.90</td>
</tr>
<tr>
<td>DE-cMR</td>
<td>0.94</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>0.2 ± 6.9</td>
<td>0.3 ± 7.7</td>
</tr>
<tr>
<td></td>
<td>0.9 ± 6.6</td>
<td>0.2 ± 7.3</td>
</tr>
</tbody>
</table>

(*Datas are intraclass correlation coefficient; † Datas are mean differences ± 1 standard deviation)
Figure Legends

**Figure 1** Line plot illustrating the relationship between mechanical index and videointensity in normal (triangles) and infarcted (circles) myocardium in patients imaged using harmonic imaging at an emission frequency of 1.6 MHz. Data are mean ± 1 SD.

**Figure 2** Line plots showing the changes in contrast-to-noise ratios (CNR) between scar tissue and the LV cavity (left panels) and between scar tissue and normal myocardium (right panels). The upper panels show the data obtained without contrast, whereas the lower panels show the data obtained during contrast infusion.

**Figure 3** Comparison of unenhanced (left panel) and contrast-enhanced (right panel) 3D-echo in a patient with a 20 month-old posterior myocardial infarction. On both images, 3 areas of brightness can be identified (at 2, 5 and 9 o’clock). Only the contrast-enhanced image allows identifying these areas, respectively as the pericardium, a subendocardial scar and a midwall septal stripe.

**Figure 4** Representative CE-3D-echo and DE-cMR images in 3 patients with old myocardial infarction and 1 control subject. Panel A: 1-year old anterior myocardial infarct. Panel B: 1.5-year old inferior myocardial infarct. Panel C: 10-year old lateral myocardial infarct. Panel D: control subject.

**Figure 5** CE-3D echo and DE-cMR images illustrating possible causes of false positive and false negative using 3D-Echo. Panel A: hyperechoic signal from a septal stripe that was confused with a septal scar. Panel B: missed anteroseptal and anterior infarction in a patient with a well identified septal scar.

**Figure 6** Scatter and Bland Altman plots comparing infarct size by CE-3D-echo and DE-cMR.
Unenhanced 3D-Echo  Contrast-enhanced 3D-Echo
DE-cMR

CE-3D-Echo

DE-cMR

CE-3D-Echo
DE-cMR

CE-3D-Echo
Scar mass by 3D-echo (g) vs. Scar mass by DE-cMR (g)

$y = 0.91x - 0.27$

$r = 0.93, p<0.0001$
1. **Video-Intensity of pericardium and septal stripe.**

The following figure shows the relationship between mechanical index and videointensity in scar tissue (circles), pericardium (triangles) and septal stripes (squares), for each tested ultrasonic modality.
2. **Septal stripe illustration.**

Representative end-diastolic (left panel) and end-systolic (right panel) CE-3D-Echo 4-chamber view still frames showing thickening of a septal stripe.