Three-dimensional echocardiography for left ventricular quantification in heart failure

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Chapter 5

Early identification of left ventricular remodelling after myocardial infarction, assessed by transthoracic 3D echocardiography

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Abstract

Aims: The usefulness of three-dimensional echocardiography (3DE) for accurate evaluation of left ventricular (LV) remodelling after acute myocardial infarction (AMI), and early identification of remodelling in the subacute phase, was assessed.

Methods and results: Thirty-three AMI patients (21 anterior AMIs) underwent 3DE prospectively at baseline (6 ± 4 days) and at 3, 6, and 12 months post-AMI. Remodelling was defined as > 20% increase in end-diastolic volume (EDV) at 6 or 12 months in relation to baseline. In patients with remodelling (n=13) at baseline, EDV and end-systolic volume (ESV), but not ejection fraction (EF), were significantly increased compared to patients without subsequent remodelling (n=20). At 12 months, EDV and ESV increased further and significantly, and EF was unchanged in patients with remodelling, whilst LV volumes were unchanged and EF slightly increased in patients without remodelling. Clinical, electrocardiographic, and echocardiographic variables were analysed for the early identification of LV remodelling. Of these, at baseline the 3D sphericity index (EDV divided by the volume of a sphere, the diameter of which is the LV major end-diastolic long axis) was, by far, the most predictive variable with a sensitivity, specificity, and positive and negative predictive value for a cutoff value of > 0,25 of 100%, 90%, 87% and 100%, respectively.

Conclusions: 3DE can differentiate patients with and without subsequent development of LV remodelling accurately and early on the basis of the 3D sphericity index, a new and highly predictive variable.

Introduction

Left ventricular (LV) remodelling after acute myocardial infarction (AMI) comprises infarct expansion, LV dilatation, and hypertrophy. It can begin very soon after AMI and, if not attenuated or reversed by intervention, has a poor prognosis [1]. Several diagnostic modalities have been used in large trials to identify LV remodelling. In this respect, transthoracic two-dimensional echocardiography (2DE), for obvious reasons, has played an important role. Calculation of LV volume by three-dimensional echocardiography (3DE), however, is up to three times more accurate than 2DE [2]. Volumetry by 2DE depends on geometric assumptions and is subject to image-plane positioning errors. Hence, it is not accurate in LVs that are distorted in shape, such as after AMI [2]. The aim of the present study was to measure prospectively serial changes in LV volumes and ejection fraction (EF) after AMI and to identify clinical, electrocardiographic (ECG), and (3D) Doppler-echocardiographic criteria in the subacute phase that could predict the subsequent development of LV remodelling.

Methods

Patient population

Consecutive patients who met the following inclusion criteria were eligible to enter the study: patients with ST-elevation AMI, as evidenced by history, ECG changes, and serial enzyme concentrations (creatine kinase [CPK] > 2 times the upper limit, CPK-MB fraction above normal and equivalent to at least 5% of total CPK). Patients had to be 18-75 years old and give informed consent. Patients were excluded on the basis of poor acoustic windows, atrial fibrillation, frequent extrasystoles or other significant arrhythmias, failure to give informed consent, coronary/haemodynamic instability, cardiac surgery scheduled in the near future, pre-existing haemodynamically significant valvular heart disease, cardiomyopathy, serious non-cardiovascular disease, and probable difficulties for follow-up. The study was approved by the institutional committee on human research. After the diagnosis of AMI, patients were treated with thrombolysis, primary percutaneous coronary intervention (PCI), or conservatively, depending on the time window after the onset of AMI, estimated infarct size (using ECG or 2DE criteria), contraindications for thrombolysis, and logistics for the interventional procedure. We set out to include all

consecutive and eligible post-AMI patients in 1 year, after which an interim analysis was planned. Therefore, no formal sample size calculations were made for this part of the study.

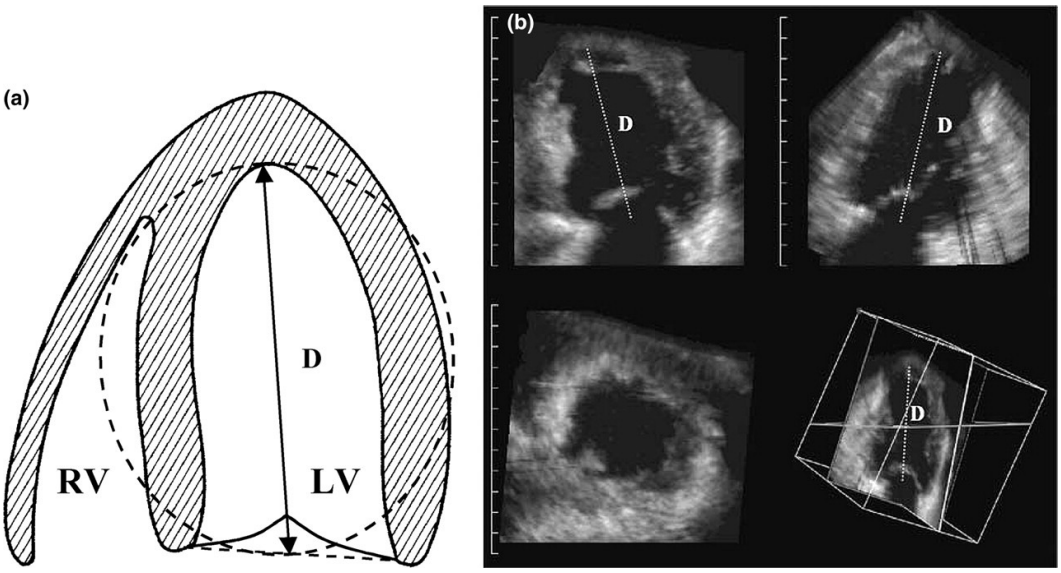
Clinical, electrocardiographic, and echocardiographic data

Serial cardiac enzymes were assessed every 6 h after admission until the corresponding peaks were reached. The ECG data used were, among others not mentioned in table 1, the number of Q waves and cumulative ST elevation in the admission ECG. The incidence of paroxysmal atrial fibrillation and of early (< 48 h after the onset of AMI) sustained ventricular tachycardia (VT) or early ventricular fibrillation (VF) was noted. In patients who underwent acute or subacute coronary angiography, with or without subsequent PCI, the thrombolysis-in-myocardial-infarction (TIMI) flow before and after revascularisation was assessed.

Baseline 3DE was recorded in the subacute phase before hospital discharge and repeated at 3, 6, and 12 months using a commercially available 2-4 MHz broadband phased-array transducer connected to a Hewlett-Packard Sonos 5500 or ATL HDI 5000 system (Philips Medical Systems, Eindhoven, The Netherlands). These echocardiographic imaging systems were interfaced with TomTec EchoScan 4.2 software (TomTec Imaging System, Munich, Germany). The 3DE Freehand acquisition has been described previously.2 In summary, the 3DE dataset was acquired via the apical acoustic window by a fan-like sweep with the 2DE transducer from the epicardial anterior wall to the epicardial posterior wall or vice versa. A spatial locator was mounted on top of the transducer and second harmonic imaging was used. The patient was instructed not to move and to hold his breath in inspiration or expiration for 10-12 s, during which part of the fan-like acquisition was acquired with ECG triggering. Afterwards, patients took air and another breath-hold acquisition was performed. Thus, by repeated breath-holding, a dynamic pyramidal 3DE dataset was generated within a total acquisition time of 3 min and stored on hard disk for subsequent analysis. Afterwards, data were post-processed and analysed off-line by tracing the endocardial contours of nine equidistant long axes. Thus, LV end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) were obtained. The 3D sphericity index was calculated by dividing EDV by the volume of a sphere whose diameter was derived from the major end-diastolic LV long axis. The LV long axis was obtained from the 3DE dataset as the longest distance between the centre of the mitral

annulus and the endocardial apex (figure 1). In the cubical display, the two near-orthogonal cutplanes, in conjunction with going back and forth through the cardiac cycle, were helpful in assessing the exact location of the endocardial apex in end-diastole. LV remodelling was defined as an increase of more than 20% in EDV at 6 or 12 months in relation to baseline [3,4]. By slicing the 3D dataset, multiple short and long axes can be obtained (at the basal-, mid-, and apical levels) and analysed to obtain the 3DE wall motion score index (3D WMSI) based on a 16-segment model [5].

Figure 1.



(a) Schematic drawing of calculation of the 3D sphericity index. The LV cavity is shown, of which D is the LV end-diastolic major long axis. With the formula: $4/3*\pi*(D/2)^3$ a spherical volume in mL can be calculated, of which D is the diameter (cm). The 3D sphericity index is calculated as $EDV/(4/3*\pi*(D/2)^3)$. (b) Four-tile image display of the dynamic 3D dataset with two near perpendicular long axes (top panels), a short axis (lower left), and a cubical display with the corresponding cutplanes (lower right). The measurement of D is shown. A prominent trabecula is present in the LV apex.

Furthermore, transmitral E and A waves, as well as E-wave deceleration time, were measured online. Three consecutive beats were averaged. With conventional 2D colour Doppler, the severity of mitral regurgitation, if present, was assessed semiquantitatively as grades 1-3 according to the method of Helmcke et al [6].

Statistics

Differences between patients at baseline with and without subsequent remodelling (table 1) were analysed with an unpaired t-test for continuous variables, or the Mann-Whitney test in the case of non-normal distribution. Fisher's exact test was used for dichotomous variables. Only two-sided tests were performed and a p-value < 0,05 was considered significant. To analyse the change over time in LV volumes and EF, paired t-tests were used with the Bonferroni correction. In order to predict LV remodelling in an individual patient, clinical, ECG, and echocardiographic variables that were significantly different at baseline (table 1) between patients with and without subsequent remodelling were further assessed. This was done by calculating optimal cutoff values for continuous variables by Receiver Operating Characteristic (ROC) analysis (MedCalc, version 7.1). For these and for dichotomous variables, sensitivity, specificity, and positive and negative predictive values for subsequent remodelling were calculated (table 2). Intra-observer variability was assessed for the 3D sphericity index and its components, EDV and the diameter of the LV end-diastolic major long axis, by Bland-Altman analysis [7]. This was done by a single observer who analysed the same data twice for EDV and the major end-diastolic LV long axis, 4 weeks apart, with subsequent calculation of the 3D sphericity index using the formula shown in figure 1.

Results

Thirty-three AMI patients were included and underwent 3DE prospectively at baseline (6 ± 4 days, range 1-15 days) and at 3, 6, and 12 months. A total of 43 consecutive patients with AMI were screened initially. Seven were excluded for poor image quality, one for ECG trigger problems, and two for incomplete follow-up. The analysis for LV volumes together with measurement of the 3D sphericity index took about 30-40 minutes.

At 6 or 12 months, 13 patients with remodelling and 20 without remodelling were identified. Their baseline characteristics are shown in table 1. Patients with remodelling showed significantly higher cardiac enzyme peaks and more heart failure, as well as nearly significant tendencies to be younger, have anterior MI, and receive ACE inhibitor therapy. ECG variables in these patients showed a significantly higher number of pathological Q-

Table 1. Baseline characteristics post-AMI

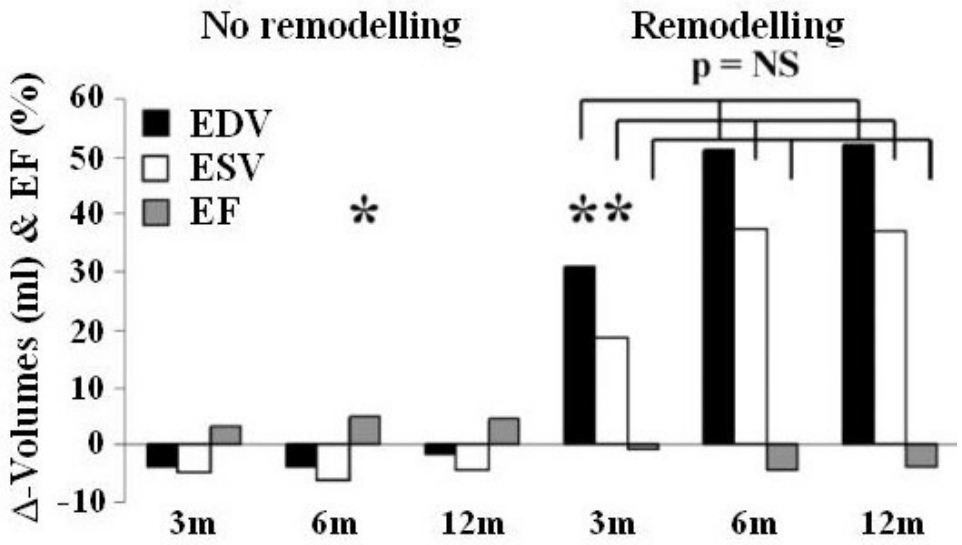
Variables	All	No remodelling	Remodelling	*p*
Number of patients	33	20	13	
Clinical				
Age (years)	58,7 ± 13,1	62,0 ± 11,1	53,7 ± 14,6	0,07
Male	28	16 (57)	12 (43)	0,63
Anterior infarction	21	10 (48)	11 (52)	0,07
Non-anterior infarction	12	10 (83)	2 (17)	0,07
Primary PCI	21	12 (57)	9 (43)	0,72
Rescue PCI	2	1 (50)	1 (50)	1,0
Thrombolysis	7	5 (71)	2 (29)	0,68
Conservative or failed primary PCI	3	2 (67)	1 (33)	1,0
Stent	18	10 (56)	8 (44)	1,0
Recurrent ischaemia	17	9 (53)	8 (47)	0,48
AMI during follow-up	1	0 (0)	1 (100)	0,39
PCI during follow-up	10	6 (60)	4 (40)	1,0
CABG during follow-up	2	2 (100)	0 (0)	0,51
Prior AMI	4	3 (75)	1 (25)	1,0
Prior PCI	4	3 (75)	1 (25)	1,0
Prior CABG	0	0 (0)	0 (0)	1,0
Peak CPK-MB fraction (U/L)	235 ± 192	156 ± 91	358 ± 243	0,001
Peak SGOT (U/L)	300 ± 322	185 ± 87	491 ± 463	0,001
Peak LDH (U/L)	1190 ± 969	836 ± 335	1750 ± 1350	0,004
ß-blockers*	33	20 (61)	13 (39)	1,0
ACE inhibitors*	16	7 (44)	9 (56)	0,08
ACE inhibitors and/or AT2 antagonist*	7	4 (57)	3 (43)	1,0
Electrocardiographic				
Heart failure (clinical/radiological)	7	1 (14)	6 (86)	0,008
No. of pathologic Q waves at admission	1,8 ± 1,9	1,1 ± 1,3	3,0 ± 2,2	0,003
Cumul. ST elevation at admission (mm)	15,3 ± 8,5	12,7 ± 7,7	19,1 ± 8,6	0,04
Early sustained VT/VF	6	1 (83)	5 (17)	0,02
3DE/Doppler				
End-diastolic volume (mL)	97,2 ± 27,2	87,8 ± 21,3	111,8 ± 29,7	0,01
End-systolic volume (mL)	54,5 ± 19,0	48,5 ± 14,3	63,9 ± 21,9	0,02
End-diastolic volume index (mL/m^2)	49,7 ± 13,5	45,2 ± 9,5	56,7 ± 16,0	0,01
End-systolic volume index (mL/m^2)	27,9 ± 10,0	25,0 ± 7,2	32,5 ± 12,1	0,03
Ejection fraction (%)	44,6 ± 8,5	45,1 ± 6,5	43,6 ± 11,1	0,67
3D WMSI	1,44 ± 0,27	1,37 ± 0,23	1,57 ± 0,28	0,04
3D sphericity index	0,26 ± 0,07	0,22 ± 0,04	0,32 ± 0,06	<0,0001
Width/length ratio	0,45 ± 0,08	0,43 ± 0,07	0,48 ± 0,09	0,11
Deceleration time (ms)	182 ± 68	186 ± 65	172 ± 77	0,62
Transitory MR (grade 2)	7	5	2	0,68
Persistent MR (grade 2)	2	0	2	0,21
Coronary angiographic				
TIMI flow pre-PCI	0,8 ± 1,2	1,1 ± 1,3	0,4 ± 0,8	0,15
TIMI flow post-PCI	2,8 ± 0,8	2,8 ± 0,7	2,8 ± 0,8	0,85
No. of patients with TIMI 3 flow**	28	16 (57)	12 (43)	1,0
1 vessel disease**	13	6 (46)	7 (54)	0,28
2 vessel disease **	11	9 (82)	2 (18)	0,13
3 vessel disease **	7	4 (57)	3 (43)	1,0

Absolute numbers with percentages in parentheses are shown (if appropriate). See text for abbreviations. VD, vessel disease. p, p-value for comparison between patients with- and without subsequent remodelling.
* at hospital discharge
** In three patients in the non-remodelling group, no coronary angiography was performed.
SGOT, serum glutamic oxalacetic transaminase; LDH, lactic dehydrogenase; MR, Mitral regurgitation

waves, higher cumulative ST elevation, and more frequent early sustained VT or VF. Furthermore, for the 3DE variables, both EDV and ESV, but not EF, were significantly higher as early as at baseline. The 3D sphericity index and 3D WMSI were significantly higher in patients with subsequent remodelling, in contrast to deceleration time. Mitral regurgitation at baseline and during follow-up was generally mild, but significant (grade 2) in nine patients: seven with transitory and two with persistent regurgitation (in the remodelling group). Mitral regurgitation did not differ at baseline or during follow-up. Coronary angiographic variables at baseline were similar in the two groups.

At 12 months, the EDV, ESV, and EF in patients with remodelling were 163,8 ± 44,3 mL, 101,1 ± 42,1 mL, and 39,8 ± 12,4% ($p < 0,001$, $p < 0,001$, and $p = 0,20$ from baseline), respectively, and in patients without remodelling, 86,2 ± 24,5 mL, 44,1 ± 17,7 mL, and 49,5 ± 8,1% ($p = 0,92$, $p = 0,27$, and $p = 0,05$ from baseline), respectively. There was no significant further increase in EDV and ESV between 3 and 12 months in patients with remodelling (figure 2). No patients died during the 1-year follow-up period.

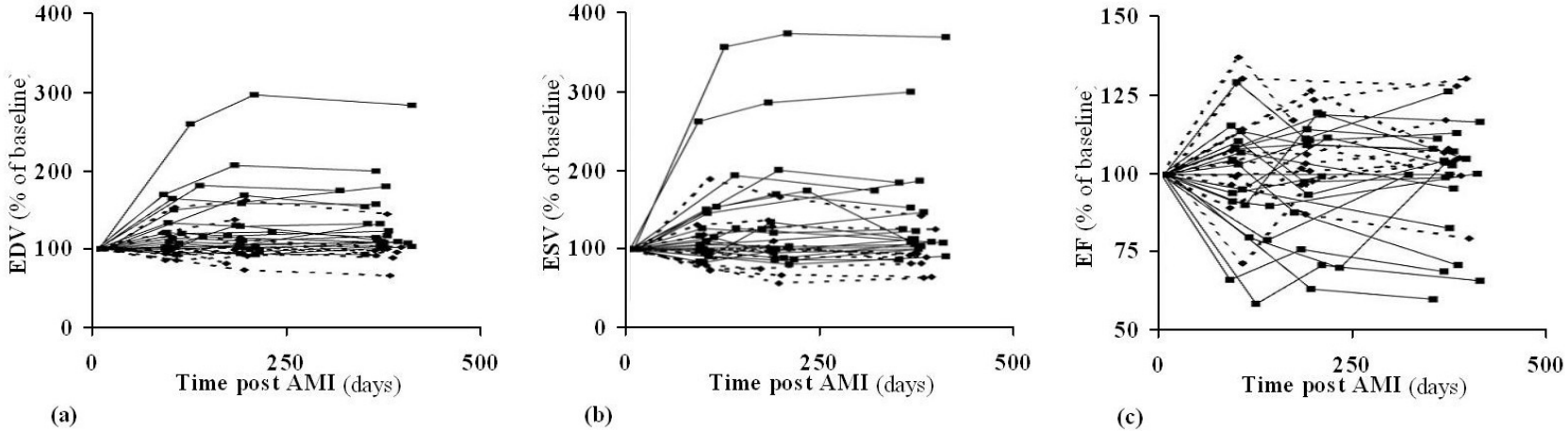
Figure 2.



Mean absolute changes in LV volumes and EF at 3, 6, and 12 months after MI, relative to their corresponding baseline values. The black bars correspond with EDV, the white bars with ESV, and the grey bars with EF. The asterisks (*) denote a significant change from baseline. m, months; NS, not significant. See text for abbreviations.

The individual changes in EDV, ESV, and EF for all 33 patients are shown in figure 3.

Figure 3.



Relative individual percent changes in time from baseline (set at 100%) for EDV, ESV, and EF. The dark lines represent anterior infarction, the dashed lines non-anterior infarction (see figure 1 and text for abbreviations).

The results of ROC analysis of the most predictive variables, which were significant in table 1 (except for EF), are shown in table 2. For the 3D sphericity index and baseline EDV, ESV, and EF results are also shown in figure 4. Figure 5 shows the Bland-Altman plot for the reproducibility of the 3D sphericity index, which was reasonable (the bias ± 2SD was 0,00 ± 0,06). The bias ± 2SD for EDV was –2,9 ± 11,2 mL, and for the LV major end-diastolic long-axis length, -0,05 ± 0,49 cm. If the second set of calculated values of the 3D sphericity index (obtained from the second set of measurements by the same observer) was used in the ROC analysis, sensitivity, specificity, and positive and negative values hardly changed (respectively, 92%, 90%, 86%, and 95%; area under the curve 0.965 (95% confidence limits 0.835-0.995).

Table 2. ROC analysis of selected variables predictive of subsequent LV remodelling

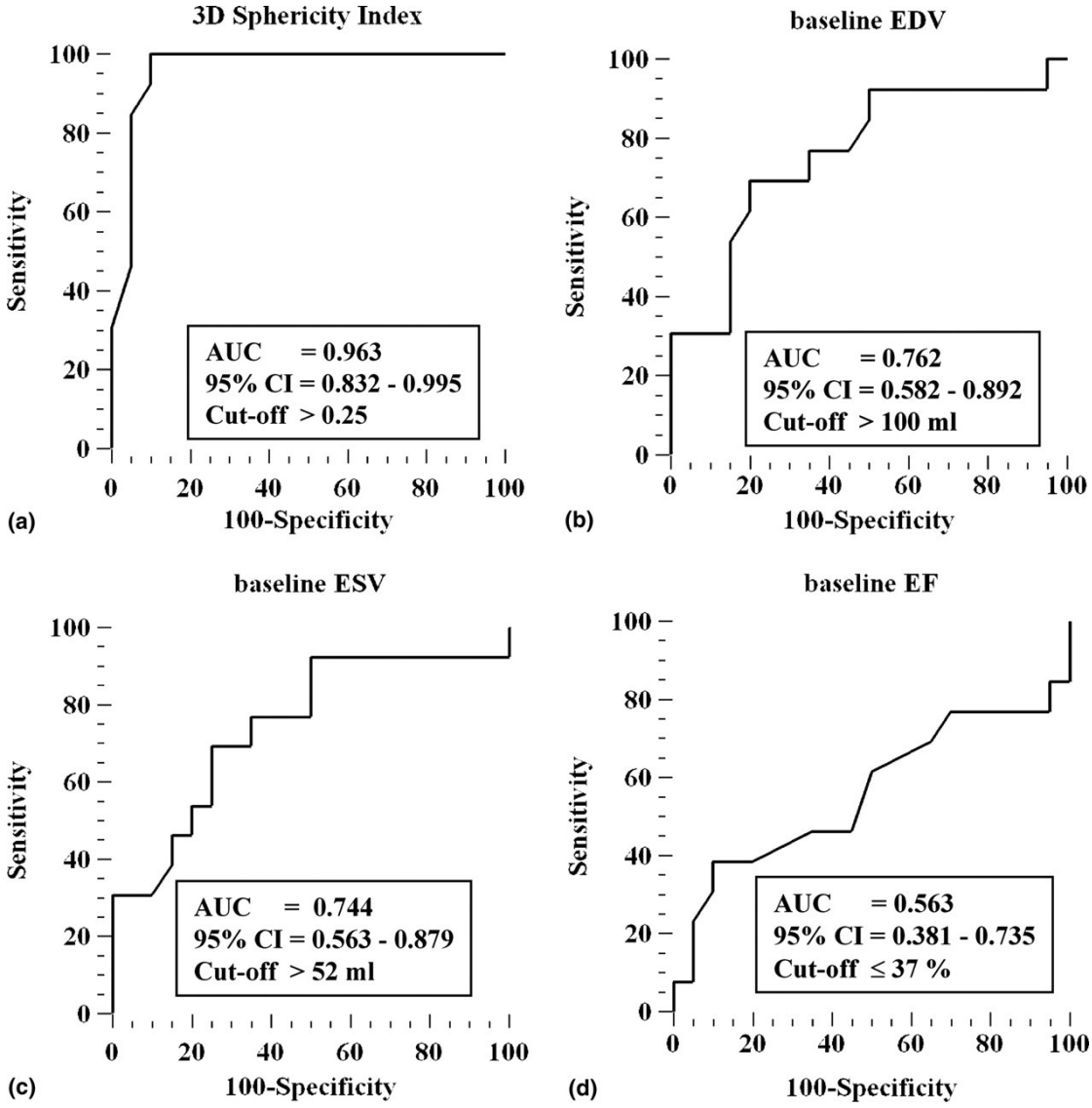
Variable	Cutoff	Sens (%)	Spec (%)	PPV(%)	NPV(%)	AUC(95%CI)
3D sphericity index	> 0,25	100	90	87	100	0,96 (0,83-1,0)
3D WMSI	> 1,25	92	55	55	92	0,23 (0,54-0,87)
EDV	> 100 mL	69	80	69	80	0,76 (0,58-0,89)
ESV	> 52 mL	69	75	64	79	0,74 (0,56-0,88)
EF	≤ 37%	39	90	71	69	0,56 (0,38-0,74)
Width/length ratio	> 0,53	42	95	83	73	0,68 (0,49-0,83)
Heart failure *	Present	46	95	86	73	NA
Peak CPK-MB fraction	> 170 U/L	92	70	67	93	0,83 (0,66-0,94)
Peak SGOT	> 328 U/L	58	100	100	80	0,83 (0,65-0,94)
Peak LDH	> 1521 U/L	58	100	100	79	0,81 (0,63-0,93)
No. of pathologic Q waves**	> 1	77	70	63	82	0,77 (0,59-0,90)
Cumulative ST elevation**	> 1,4 mV	69	79	69	79	0,73 (0,55-0,87)
Early sustained VT/VF	Present	39	95	83	70	NA

* during admission

** at admission

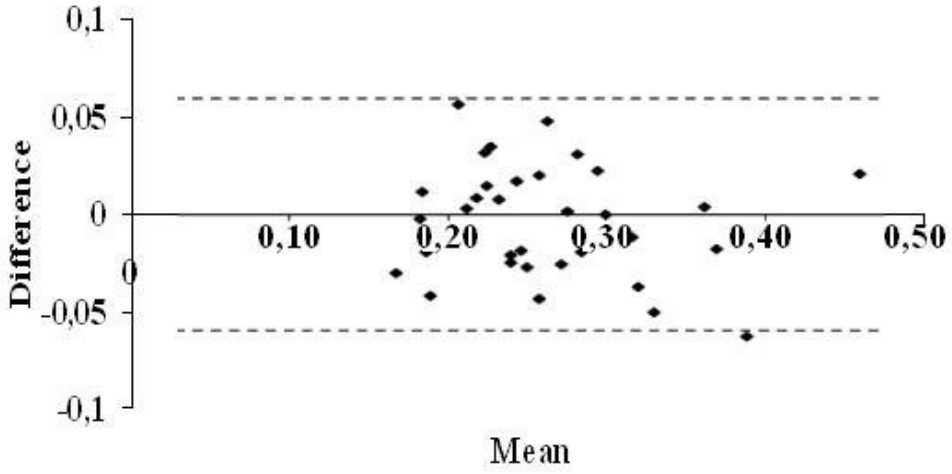
Data on sensitivity (Sens.), specificity (Spec.), positive predictive value (PPV), and negative predictive value (NPV), along with thei r cutoff values, and area under the curve (AUC) with corresponding 95% confidence interval (CI) are shown. NA, not applicable. See text and table 1 for abbreviations.

Figure 4.



ROC curves of the 3D sphericity index, baseline EDV, baseline ESV, and baseline EF are shown. AUC, area under the curve with its 95% confidence interval (CI). Cutoff values are shown.

Figure 5.



Intra-observer variability of the 3D sphericity index shown as a Bland-Altman plot with the mean of two observations on the *X*-axis and the difference on the *Y*-axis. The dashed bars represent the 95% limits of agreement.

Discussion

Quantitative changes in LV volumes and EF

To our knowledge, this is the first study to use transthoracic 3DE instead of 2DE to describe the temporal evolution of changes in LV volumes and EF following AMI. In general, with 2DE, in contrast to the present study, a substantial number of patients were required to show clinical endpoints and/or a statistically significant effect on LV volumes and EF [1,3]. With 3DE, however, due to its up to threefold better accuracy for LV volume and EF assessment [2] compared to the 2DE biplane Simpson's rule, fewer patients are required. In this respect, our 3DE method is similar to breath-hold magnetic resonance imaging, which also allows a considerable reduction in patient numbers in LV remodelling studies [8]. About one-third of our patients showed subsequent remodelling after AMI. In this respect, the present study was similar to the 2DE post-infarction remodelling study by Bolognese et al [3] after primary PCI. These authors showed, in an almost ninefold larger sample size, similar changes in EDV, ESV, and EF. This study, in contrast to the present study, was powered for clinical events. Korup et al [9] have reported that LV dilatation starts within 3 h of AMI, with no further progression in the first 6 days, which is the time period of our baseline measurements. The rate of progression may vary from slow to fast,

and LV remodelling may reverse or be absent, or may be early, late, or progressive [10] (figure 3).

Baseline characteristics and early predictors of subsequent LV remodelling
Though infarct size is reduced by primary PCI compared to thrombolysis [11], the present study was not sufficiently powered to detect differences in infarct size between patients with and without subsequent remodelling. In concordance with other studies, a significantly larger enzymatic infarct size [3,12,13] and electrocardiographic area at risk [14], as well as a higher number of pathological Q waves at admission [15], were observed in patients with subsequent remodelling. Furthermore, the incidence of subsequent heart failure [3,12] and early sustained ventricular tachyarrhythmias during admission [16] was also significantly increased. In the remodelling group there was also a strong, nearly significant, tendency for more anterior AMIs [3], which could have become significant with a larger sample. There were no significant differences in the frequency of recurrent ischaemia and subsequent revascularisation procedures, which are known to have an important effect on LV remodeling [10].

In the present study, as well as in other studies after primary PCI, about 90% early TIMI 3 flow was reached. In patients with epicardial TIMI 3 flow after AMI, however, a substantial proportion have different degrees of microvascular no-reflow, which will lead to subsequent LV remodeling [17]. This suggests that microvascular no-reflow is also an important mechanism for subsequent LV remodelling in the present study.

There were no significant differences in the use of ß-blockers, ACE inhibitors, or angiotensin II antagonists, which attenuate LV remodeling [1]. In line with a previous study [18], mitral regurgitation did not play a major role in the LV remodelling process.

The most striking difference between patients with and without subsequent LV remodelling was a significantly higher 3D sphericity index, 3D WMSI, and indexed LV volumes at baseline in patients with subsequent LV remodelling. As shown in figure 4, the 3D sphericity index at baseline is far more sensitive than LV volumes and EF. Its reproducibility was reasonable, given the fact that it is dependent on measurement variability in both EDV and the LV major end-diastolic long-axis length. In our opinion, it is robust enough for clinical application, since the second set of 3D sphericity index

measurements yielded very similar sensitivity, specificity, and predictive values. Although different "LV shape analysis" variables have been described in the context of LV remodeling [19-22], to our knowledge this is the first description of the 3D sphericity index. Usually, the ratio of basal LV end-diastolic short-axis diameter (or area) to LV end-diastolic long-axis length (or area) was used [20-22]. In one 2DE study, a sphericity index was defined this way and was found to be weakly predictive for LV remodeling [20]. Our width/length ratio, which is an approximation of the 2D sphericity index, although derived from a 3D dataset, was also only moderately predictive. In the present study, the 3D sphericity index was a strong predictor, in contrast to the 3D end-systolic sphericity index (data not shown). Unlike 2DE shape analysis variables, the 3D sphericity index does not have the inherent limitations of image-plane positioning and foreshortening, and therefore may better reflect the remodelling process, in which the LV assumes a more globular shape, than a 1D linear width/length ratio or a 2DE area ratio. This may account for its impressive predictive value.

The finding of a restrictive filling pattern, as evidenced by a mitral E-wave deceleration time $\leq$ 125 ms in the present study, did not have clear predictive value. This is in contrast to two studies with serial 2DE, by Cerisano et al [13] and by Nijland et al [12]. Patients in the three studies mentioned were not very comparable in infarct localisation and treatment. Strikingly, the baseline EDV index and ESV index in the present study were significantly lower than in the other two studies, presumably reflecting smaller infarcts since WMSI was also lower in our study. These factors may explain the differences observed in deceleration time.

Three-dimensional WMSI showed a relatively high sensitivity with a relatively low specificity for subsequent remodelling. This may be due to transitory myocardial stunning with subsequent functional recovery. Three-dimensional WMSI may theoretically be more accurate than 2D WMSI [5]. This is due to the use of multiple long- and short axes, accurately positioned relative to anatomic markers, with avoidance of image-plane position errors and foreshortening. The cutoff values for prediction of remodelling by baseline WMSI in the present study and by 2DE in the study by Peels et al [23] (respectively, > 1.25 versus > 2) were different, since there were important differences in patient population, treatment, and ultimate infarct size between both studies.

Limitations

The present study was underpowered with respect to clinical events and not designed to assess the attenuative effects of drugs or reperfusion therapy on LV remodelling. From previous studies it is clear that LV remodelling is a predictor for major adverse clinical events, electrical instability, and sudden cardiac death [1,3,24]. The success rate of obtaining an adequate 3DE was 77%, primarily due to insufficient image quality. This number may be improved by LV opacification [25]. Rhythm disturbances can be cumbersome for 3DE acquisition. This problem may in time be solved by acquiring the dataset in a shorter time, preferably in one heart cycle, using second-generation real-time 3D scanners.

Conclusions and clinical implications

The present study shows that, even in the interventional era (with subsequently smaller infarcts), and a relatively low number of patients, 3DE can very clearly identify patients that will subsequently develop remodelling on the basis of changes in LV volumes and EF. Unlike the traditional 2D "sphericity or shape indices", the 3D sphericity index can predict, accurately and soon in the subacute phase after AMI, which patient is likely to undergo LV remodelling. Among clinical, electrocardiographic, and echocardiographic variables, it was by far the strongest predictor of subsequent remodelling.

The accuracy, speed, and predictive value of 3DE make it an ideal technique for assessment, risk stratification, and follow-up after AMI, especially with the development of second-generation real-time 3D scanners.

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