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Predictive value of early cardiac magnetic resonance imaging functional and geometric indexes for adverse left ventricular remodelling in patients with anterior ST-segment elevation myocardial infarction: A report from the CIRCUS study

Valeur prédictive des indices fonctionnels et géométriques évalués précocement par IRM cardiaque pour prédire le remodelage ventriculaire gauche pathologique chez les patients présentant un infarctus du myocarde antérieur avec élévation du segment ST : rapport de l'étude CIRCUS

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Abbreviations: CI, Confidence Interval; CIRCUS, Does Cyclosporine Improve Clinical Outcome in ST-Elevation Myocardial Infarction Patients; CMR, Cardiac Magnetic Resonance; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; MVO, Microvascular Obstruction; LGE, Late Gadolinium Enhancement; LV, Left Ventricle/Ventricular; LVEDV, Left Ventricular End-Diastolic Volume; LVEF, Left Ventricular Ejection Fraction; LVESV, Left Ventricular End-Systolic Volume; LVGFI, Left Ventricular Global Functional Index; OR, Odds Ratio; STEMI, ST-Segment Elevation Myocardial Infarction; TTE, Transthoracic Echocardiography.

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KEYWORDS

Myocardial infarction;
Ventricular
remodelling;
Cardiac magnetic
resonance;
Conicity index;
Sphericity index

Summary

Background. – Postinfarction adverse left ventricular (LV) remodelling is strongly associated with heart failure events. Conicity index, sphericity index and LV global functional index (LVGFI) are new LV remodelling indexes assessed by cardiac magnetic resonance (CMR).

Aim. – To assess the predictive value of the new indexes for 1-year adverse LV remodelling in patients with anterior ST-segment elevated myocardial infarction (STEMI).

Methods. – CMR studies were performed in 129 patients with anterior STEMI (58 ± 12 years; 78% men) from the randomized CIRCUS trial (CMR substudy) treated with primary percutaneous coronary intervention and followed for the occurrence of major adverse cardiovascular events (MACE) (death or hospitalization for heart failure). Conicity index, sphericity index, LVGFI, infarct size and microvascular obstruction (MVO) were assessed by CMR performed 5 ± 4 days after coronary reperfusion. Adverse LV remodelling was defined as an increase in LV end-diastolic volume of $\geq 15\%$ by transthoracic echocardiography at 1 year.

Results. – Adverse LV remodelling occurred in 27% of patients at 1 year. Infarct size and MVO were significantly predictive of adverse LV remodelling: odds ratio [OR] 1.03, 95% confidence interval [CI] 1.01–1.05 ($P < 0.001$) and OR 1.12, 95% CI 1.05–1.22 ($P < 0.001$), respectively. Among the newly tested indexes, only LVGFI was significantly predictive of adverse LV remodelling (OR 1.10, 95% CI 1.03–1.16; $P = 0.001$). In multivariable analysis, infarct size remained an independent predictor of adverse LV remodelling at 1 year (OR 1.05, 95% CI 1.02–1.08; $P < 0.001$). LVGFI and infarct size were associated with occurrence of MACE: OR 1.21, 95% CI 1.08–1.37 ($P < 0.001$) and OR 1.02, 95% CI 1.00–1.04 ($P = 0.018$), respectively. Conicity and sphericity indexes were not associated with MACE.

Conclusions. – LVGFI was associated with adverse LV remodelling and MACE 1 year after anterior STEMI.

MOTS CLÉS

Infarctus du
myocarde ;
Remodelage
ventriculaire ;
Résonance
magnétique
cardiaque ;
Indice de conicité ;
Indice de sphéricité ;
Indice fonctionnel
global ventriculaire
gauche

Résumé

Introduction. – Le remodelage ventriculaire gauche (VG) post-infarctus est fortement associé à des événements d'insuffisance cardiaque ultérieurs. L'indice de conicité, l'indice de sphéricité et l'indice fonctionnel global du VG (LVGFI) sont de nouveaux indices de remodelage du VG évalués par imagerie par résonance magnétique (IRM) cardiaque. Le but de notre étude était d'évaluer leur valeur prédictive sur le remodelage du VG à un an chez les patients ayant un infarctus du myocarde antérieur.

Méthodes. – Un examen d'IRM cardiaque a été réalisé chez 129 patients présentant un infarctus du myocarde antérieur avec élévation du segment ST (58 ± 12 ans, 78 % d'hommes) recruté au sein l'essai clinique randomisé CIRCUS et traités par intervention coronaire percutanée (ICP) primaire. Ces patients ont été suivis pour évaluer la survenue d'événements cardiovasculaires majeurs (décès ou hospitalisation pour insuffisance cardiaque). L'indice de conicité, l'indice de sphéricité, le LVGFI, la taille de l'infarctus et l'obstruction microvasculaire (MVO)

ont été évalués par IRM réalisée 5 ± 2 jours après la reperfusion coronaire. Le remodelage pathologique du VG a été défini comme une augmentation du volume télédiastolique du VG ≥ 15 % par échocardiographie transthoracique à 1 an.

Résultats. – Un remodelage pathologique du VG est survenu chez 27 % des patients en un an. La taille de l'infarctus et la présence de MVO étaient statistiquement associées à un remodelage pathologique du VG (OR=1,03, IC 95 % [1,02–1,05], $p < 0,001$ et OR=1,12, IC 95 % [1,05–1,22] $p < 0,001$, respectivement). Parmi les indices nouvellement testés, seul le LVGFI était significativement associé à un remodelage pathologique du VG (OR=1,10, IC 95 % [1,03–1,16], $p = 0,001$). Dans l'analyse multivariée, seul la taille de l'infarctus est restée un prédicteur indépendant du remodelage pathologique du VG à 1 an (OR=1,05, IC 95 % [1,02–1,08], $p < 0,001$). LVGFI et la taille de l'infarctus étaient associés à la survenue d'événements cardiovasculaires majeurs (OR=1,21; IC 95 % [1,08–1,37], $p < 0,001$ et OR=1,02; IC 95 % [1,00–1,04], $p = 0,018$, respectivement). Cependant, les indices de conicité et de sphéricité n'étaient pas associés aux événements cardiovasculaires majeurs.

Conclusion. – Le LVGFI a été associé à un remodelage pathologique du VG et à la survenue d'événements cardiovasculaires majeur un an après un infarctus du myocarde antérieur avec élévation du segment ST. Cependant, cette relation et sa valeur prédictive, au-delà de la taille de l'infarctus, soulèvent certaines questions. Ainsi, d'autres études sont nécessaires pour explorer la relation de tous ces indices de remodelage avec des résultats indésirables dans des populations plus importantes de patients atteints d'infarctus du myocarde.

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Background

Left ventricular (LV) remodelling begins in the first hours after myocardial infarction (MI) [1]; it consists of all molecular, cellular and tissue processes involved in the response to infarction, leading to ventricular dilatation and further systolic dysfunction [2,3]. In time, adverse LV remodelling is associated with heart failure and sudden cardiac death [4,5].

Adverse LV remodelling has been defined with various imaging indexes, but the most common definition is an increase in LV end-diastolic volume (LVEDV) of 15–20% between baseline and follow-up measures [6–8]. Screening for patients at high risk of adverse LV remodelling in the acute phase could be of clinical interest for therapeutic management.

One hypothesis is that chronic adverse LV remodelling can be predicted by the assessment of LV geometry at the acute phase of an MI. An initial LV dilation is associated with LV geometry modifications [9]. The left ventricle (LV) changes from an ellipsoidal shape to a more spherical shape. This deformation has been described early in the postinfarction phase, and tends to increase with time [9]. Various geometrical indexes have been proposed to assess this deformation at the acute phase of MI, such as the sphericity and conicity indexes. These indexes have been suggested to be predictive of adverse LV remodelling [10] and major cardiovascular events, independent of ejection fraction [11]. Several reports have explored the association between infarct size and adverse LV remodelling [12,13].

Another index, the LV global function index (LVGFI), integrating global LV remodelling and function variables, has been shown to be related to cardiovascular events in a general population [14,15]. This index is based upon stroke volume, LV mass and diastolic and systolic volumes. Although the sphericity and conicity indexes have already

been described, the early frequency distribution and predictive value of LVGFI for chronic LV remodelling and outcomes are unknown in a population with acute MI.

The principal aim of our study was to assess the relationship of infarct size with the conicity, sphericity and LVGFI indexes, measured at the acute phase of MI by cardiac magnetic resonance (CMR) in patients with anterior MI from the CIRCUS (Does Cyclosporine Improve Clinical Outcome in ST-Elevation Myocardial Infarction Patients) trial. The secondary aim was to explore their respective relationships with adverse LV remodelling and major adverse cardiovascular events (MACE) at 1 year [16].

Methods

Study population

This study is an ancillary study from the CIRCUS trial, a large multicentre double-blind trial testing the effect of cyclosporine (given as a single intravenous bolus injection) versus placebo on adverse cardiovascular events at 1 year in an anterior ST-segment elevated myocardial infarction (STEMI) population. The trial protocol and results have already been reported [16]. There was no significant effect of cyclosporine on all-cause death, heart failure events and adverse LV remodelling at 1 year.

Briefly, patients included in the trial were men and women aged ≥ 18 years, who presented within 12 hours after the onset of symptoms, who had ST-segment elevation of ≥ 0.2 mV in two contiguous anterior leads and for whom the clinical decision was made to treat with primary percutaneous coronary intervention. The culprit coronary artery was the left anterior descending coronary artery, with a Thrombolysis In Myocardial Infarction flow grade of 0 or 1 at the time of diagnostic coronary angiography.

Our patient population included all patients from the CIRCUS trial who underwent an acute CMR study within the first week (7 days) of admission, only in centres that had access to a CMR scanner. Patients without contraindication to CMR were selected and included if they agreed to CMR being performed.

CMR imaging protocol

Imaging was performed on 1.5T CMR scanners (multivendor: Siemens; Philips) within the first week of admission. All sequences were performed using vectocardiogram monitoring and multielement phased-array cardiac receiver coils. Long-axis (two- and four-chamber) and short-axis cine CMR images encompassing the LV from base to apex were obtained with a retrospectively gated fast-imaging balanced steady-state free precession sequence: repetition time/echo time 39/1.3 ms; acceleration factor 2; field of view 360×280 mm; matrix 192×156 ; and reconstructed voxel size $1.7 \times 1.7 \times 8$ mm for short-axis views (gap 2 mm) and $1.7 \times 1.7 \times 6$ mm for long-axis views. Then, a bolus of gadolinium contrast (Dotarem®; Guerbet, Aulnay, France; 0.2 mmol/kg) was injected at a rate of 4.0 mL/s with concomitant first-pass myocardial perfusion imaging, using a saturation-recovery balanced steady-state free precession sequence. The following typical parameters were: repetition time/echo time 287/1.2 ms; acceleration factor 2; field of view 370×314 mm; matrix 224×180 ; reconstructed voxel size $1.7 \times 1.7 \times 8$ mm; and slice thickness 8 mm. Five slices were acquired every two heartbeats: three short-axis (basal, median and apical); and two long-axis (two- and four-chamber). Ten minutes after contrast injection, a breath-hold contrast-enhanced three-dimensional segmented T1-weighted inversion-recovery gradient-echo sequence was acquired with the same orientations as the cine images, to detect late gadolinium enhancement (LGE): repetition time/echo time 208/1.9 ms; field of view 360×340 mm; matrix 256×120 ; and reconstructed voxel size $1.4 \times 1.4 \times 4$ mm. Sequences and parameters were similar for all CMR scanners.

CMR image analysis

LV functional assessment

Postprocessing was performed from the same CMR image data, but with two independent observers blinded to clinical data, on a dedicated postprocessing workstation (Argus [Siemens Medical Solution, Germany] and OsiriX [OsiriX Foundation, Geneva, Switzerland]). The interobserver concordance coefficient was calculated to compare these two observers.

LV volumes and function were quantified on the short-axis cine stack. LV contouring was done carefully at the most basal and apical slices, following the guidelines [17]. Indeed, when the most basal slice contains only a small crescent of basal lateral myocardium and no discernible ventricular blood pool (when < 50% of the blood volume is surrounded by myocardium), it is excluded from the analysis. Similarly, when the most apical slice contains only a circle of myocardium without cavitory blood pool, it is excluded from the analysis.

The LVGFI was calculated by CMR as previously published, using the LVEDV, LV end-systolic volume (LVESV), stroke volume and LV mass, according to the following formula [14]: $LVGFI = (\text{stroke volume} / [\text{mean cavity volume} + \text{myocardial volume}]) \times 100$.

The mean cavity volume was defined as the mean volume between the LVEDV and LVESV. The myocardial volume was defined as the myocardial mass divided by the myocardial density on CMR (1.05 g/mL of the myocardium) [14].

Infarct zone assessment

The infarct zone was defined by subendocardial or transmural LGE [18]; it was measured quantitatively using the "full width at half maximum" method as published previously [19]. The total number of LGE segments was calculated for each patient using the American Heart Association 17-segment model [20].

Microvascular obstruction (MVO) was defined as areas of hyposignal on the LGE images within a hyperenhanced myocardium, on LGE sequences measured 10 minutes after injection of gadolinium [21]. The extent of infarcted myocardium and MVO was measured by semiquantitative planimetry on consecutive slices, and is expressed in grams of tissue and percentage of LV mass [21]. All MVO areas were included in the total infarct mass estimation.

Geometric factor assessment

The LV geometric indexes were assessed on four-chamber (long horizontal axis) and two-chamber (vertical long axis) views using the cine CMR imaging sequences.

The sphericity index was defined as the ratio (as a percentage) between the LVEDV and the volume of the sphere [22], the basis of which was the mitral annulus and the height of which was the longitudinal axis of the LV in the apical two- and four-chamber views at end-diastole (Fig. 1A) [23,24].

The conicity index was defined as the ratio (as a percentage) between the LVEDV of the cone the basis of which was the mitral annulus and the height of which was the longitudinal axis of the LV in the apical two- and four-chamber views at end-diastole (Fig. 1B) [25].

Echocardiography image analysis

LV adverse remodelling

In the CIRCUS study protocol, all patients underwent conventional transthoracic echocardiography (TTE) during initial hospitalization (baseline echocardiogram) and at 12 months (± 8 weeks) after MI. Images were obtained using a 3.5 MHz transducer [16]. Three cardiac cycles of the apical four-, three- and two-chamber views were captured in conventional two dimensions. TTE data were stored digitally and sent to a centralized core laboratory for subsequent blinded offline analysis. LV volumes were measured, and the biplane Simpson's rule was applied to assess LVEDV at each time point. LV remodelling was measured as an absolute value according to the formula [6–8]: $LV \text{ remodelling} = ([\text{final LVEDV} - \text{initial LVEDV}] / \text{initial LVEDV}) \times 100$.

Adverse LV remodelling was defined as an increase of $\geq 15\%$ in the initial LVEDV, as already described [6–8].

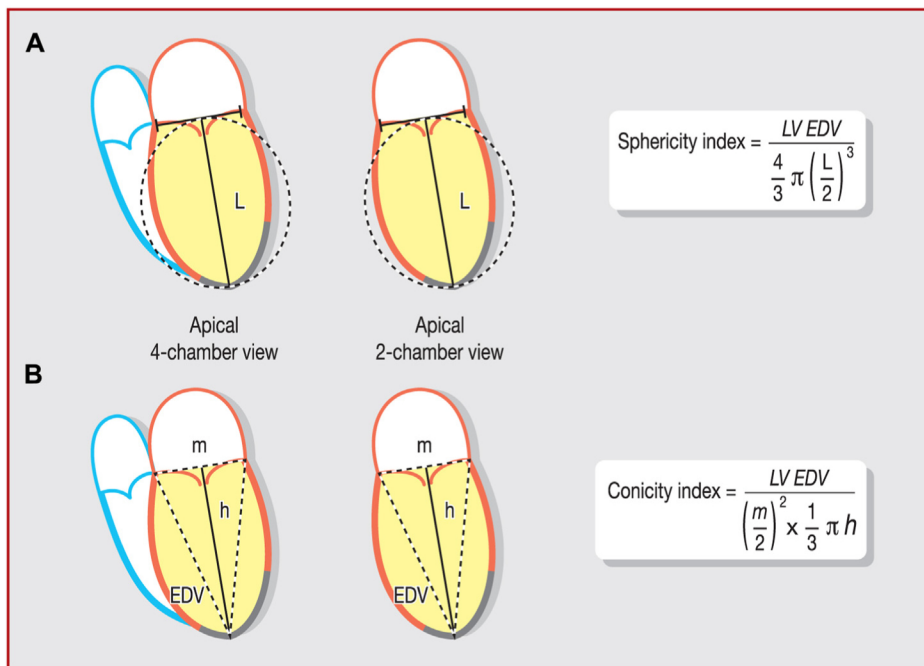


Figure 1. Illustration of left ventricular (LV) sphericity index (A) and conicity index (B) assessment, with the corresponding formulae. A. Measurement of sphericity index from the ratio between the LV end-diastolic volume (EDV) and the volume of a sphere, the base of which was the mitral annulus diameter and the height of which was the longitudinal axis of the LV in the apical two- and four-chamber views at end-diastole. B. Measurement of conicity index from the ratio between the LV EDV and the volume of a cone, the basis of which was the mitral annulus and the height of which was the longitudinal axis of the left ventricle in the apical two- and four-chamber views at end-diastole. L: LV long axis; m: mitral annulus diameter; h: height of the cone, represented by the LV long axis.

Clinical outcomes

As described in previous reports [7,16], all patients were followed up prospectively for 1 year by telephone interviews and clinical visits at 1 year, performed in each participating centre.

The clinical outcome was the occurrence of at least one of the combined MACE, defined as all-cause mortality or worsening of heart failure, defined by the use of intravenous diuretics during initial hospitalization (i.e. the index STEMI hospitalization for each patient) and rehospitalization for heart failure. All events were adjudicated by an independent adjudication committee.

Statistical analysis

Continuous variables are expressed as means \pm standard deviations or medians (interquartile ranges) depending on the type of distribution. The interobserver agreement for the different shape indexes was assessed using Lin's correlation coefficient. We used the Pearson correlation test to assess the correlation between studied variables and infarct size. Univariate and multivariable logistic regressions were used to assess the predictive value of the different indexes on adverse LV remodelling. Multivariable analyses were performed using stepwise regression (cut-off *P*-values for entry and removal were 0.05 and 0.1, respectively). To compare the predictive value of the different CMR indexes for adverse remodelling, receiver operating characteristic curves were established. In an exploratory analysis, we assessed the relationship of LV variables with MACE using

Cox univariate analysis. All tests were two-sided, and a *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using R software, version 3.3.1 (R Project for Statistical Computing, Vienna, Austria).

Results

Population characteristics

Of the 969 patients included in the CIRCUS trial, 129 patients were included in the CMR substudy. Clinical and echocardiography characteristics of patients are reported in Table 1 and Table 2. The mean age was 58.2 ± 12.1 years, 101 (78.3%) patients were male and mean left ventricular ejection fraction (LVEF) was $45.3 \pm 9.5\%$. For TTE data, the proportion of patients with poor acoustic windows was very low (< 3%).

CMR studies were performed 5 ± 4 days after admission. Conicity and sphericity indexes were measured in 110 (85.3%) patients because of insufficient quality in the bidimensional analysis, and LVGFI was measured in all patients.

CMR results

LVGFI and geometric factor distributions from our study sample are reported in Fig. 2. The median sphericity index was 0.36 (interquartile range 0.30–0.39). The median conicity index was 4.69 (interquartile range 4.13–5.43) and the mean LVGFI was $29.3 \pm 7.5\%$. The mean infarct size was 40.8 ± 24.0 g.

Table 1 Study population characteristics (n = 129).

Age (years)	58.2 ± 12.1
Male	101 (78.3)
Body mass index (kg/m ²)	26.1 ± 3.9
Diabetes mellitus	15 (11.6)
Hypertension	43 (33.3)
Dyslipidaemia	44 (34.1)
Current smoker	44 (34.1)
Time from symptom onset to PCI (hours)	3.4 (2.3–4.9)
Killip class at admission	
I	114 (88.3)
II	13 (10.1)
III	2 (1.6)
IV	0 (0)
Multivessel disease	22 (17.1)
Area at risk ^a (%)	36.3 ± 8.9
TIMI flow grade before PCI	
0	102 (79.1)
1	14 (10.9)
2	8 (6.2)
3	5 (3.8)
Thrombectomy	83 (64.3)
Stent implantation	127 (98.4)
TIMI flow grade after PCI	
0	2 (1.6)
1	2 (1.6)
2	10 (7.7)
3	115 (89.1)
Glomerular filtration rate (MDRD) (mL/min)	100.2 ± 27.9
Creatine kinase peak (IU/L)	3915 ± 2607
Medication at discharge	
DAPT	125 (96.9)
Beta-blockers	117 (90.7)
Statins	123 (95.3)
ACE inhibitors or ARBs	113 (87.6)
Potassium canrenoate/eplerenone	33 (25.6)

ACE: angiotensinogen-converting enzyme; ARB: angiotensin II receptor blocker; DAPT: dual antiplatelet therapy (three possible combinations: aspirin and clopidogrel; aspirin and prasugrel; aspirin and ticagrelor); MDRD: Modification of Diet in Renal Disease; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction. For quantitative values, data are expressed as mean ± standard deviation or median (interquartile range), depending on the type of distribution. For qualitative values, data are expressed as number (%).

^a The area at risk was assessed by means of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) score [21]. The APPROACH score is a scoring system in which the left ventricle is divided into regions defined by the distribution of perfusion of each coronary artery, and the estimated amount of myocardium in each region is used to calculate the amount of jeopardized myocardium for a given site of vessel occlusion. The area at risk is expressed as the percentage of the left ventricular mass.

Table 2 Echocardiography characteristics (n = 129).

Baseline	
LVEDV (mL/m ²)	105.6 ± 29.6
LVESV (mL/m ²)	56.1 ± 22.7
LVEF (%)	45.3 ± 9.5
1 year of follow-up	
LVEDV (mL/m ²)	124.4 ± 42.3
LVESV (mL/m ²)	63.3 ± 33.3
LVEF (%)	50.5 ± 10.4

LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction. Data are presented as mean ± standard deviation.

Correlation plots between the different geometric indexes and infarct size are presented in Fig. 3. There was a significant correlation between LVGFI and infarct size ($R = -0.70$; $P < 0.001$), as well as between LVEF and infarct size ($R = -0.71$; $P < 0.001$). However, there was no significant correlation between infarct size and the conicity and sphericity indexes: $R = 0.17$ ($P = 0.12$) and $R = 0.10$ ($P = 0.37$), respectively.

Relationship between acute CMR indexes and adverse LV remodelling

Among the 129 patients in our study, 35 (27%) had adverse LV remodelling defined by TTE at 1 year. The relationship of each CMR variable with adverse LV remodelling is summarized in Table 3. Infarct size and MVO were significantly associated with adverse LV remodelling at 1 year: odds ratio [OR] 1.03, 95% CI 1.01–1.05 ($P < 0.001$) and OR 1.12, 95% CI 1.05–1.22 ($P < 0.001$), respectively. Among the new indexes tested, only LVGFI was significantly associated with adverse LV remodelling (OR 1.10, 95% CI 1.03–1.16; $P = 0.001$).

In the multivariable model including clinically relevant characteristics (infarct size, MVO, LVEF and LVGFI), infarct size was the only remaining independent predictor of adverse LV remodelling (OR 1.05, 95% CI 1.02–1.08; $P < 0.001$).

The receiver operating characteristic curves were established only for LV indexes associated with adverse LV remodelling upon univariate analysis; they are reported in Fig. 4. The best predictive performance for adverse LV remodelling was found with infarct size (area under the curve 0.76; $P < 0.001$). The different areas under the curve with MVO, LVEF and LVGFI were, respectively, 0.73, 0.72 and 0.70 ($P < 0.001$ for all).

Relationship between acute CMR indexes and clinical events

The median time to follow-up was 1 year, and no patient was lost to follow-up. In the entire cohort, there were 15 MACE (12%), including six deaths and nine cases of acute heart failure at 1 year.

In the univariate Cox analysis, LVEF, LVGFI, infarct size and MVO were significantly associated with MACE (Table 4). Indeed, a lower value of LVEF and LVGFI was associated with

The interobserver concordance coefficient for the sphericity index was 0.98 (95% confidence interval [CI] 0.95–1.00). For the conicity index, the concordance was 0.87 (95% CI 0.72–1.01).

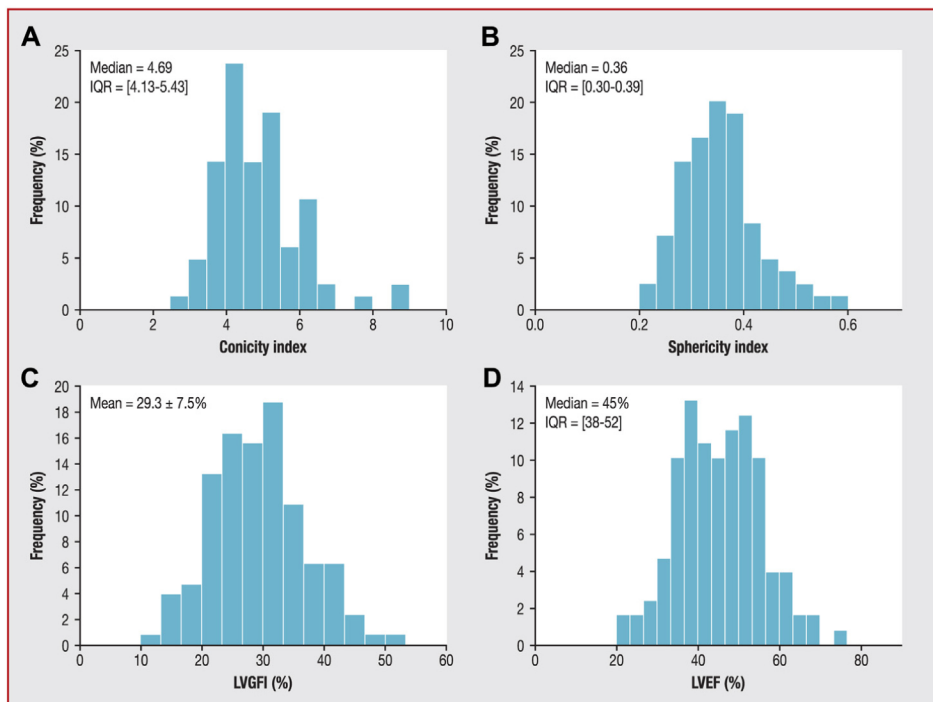


Figure 2. Distribution of the different cardiac magnetic resonance variables. A. Conicity index. B. Sphericity index. C. Left ventricular global functional index (LVGFI). D. Left ventricular ejection fraction (LVEF). Data are presented as mean \pm standard deviation or median (interquartile range [IQR]), depending on the type of distribution.

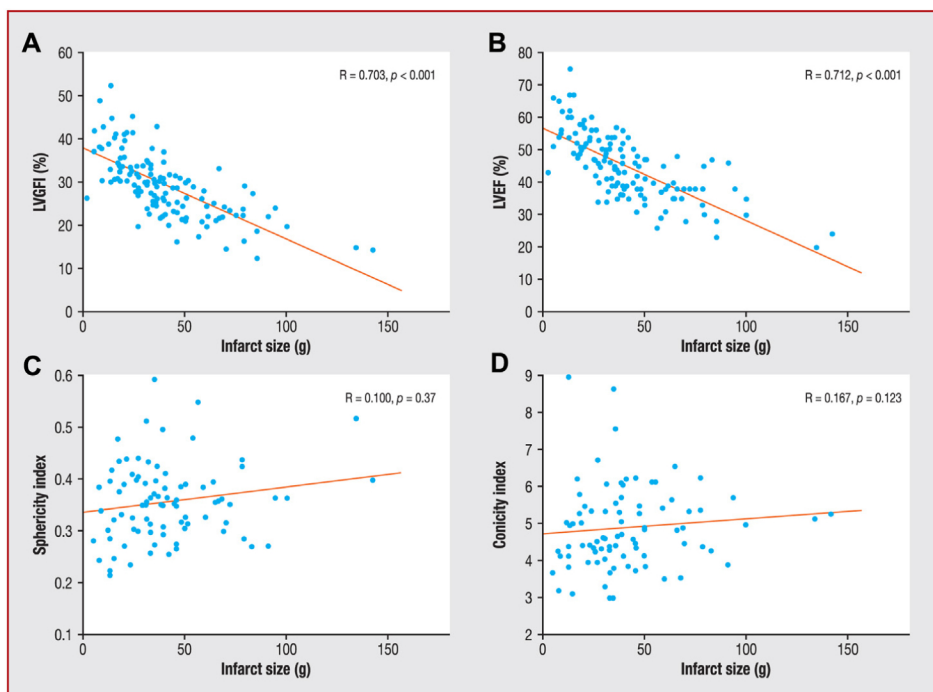


Figure 3. Linear regression between different cardiac magnetic resonance variables and infarct size. The Pearson correlation test was used to assess the correlation between the variables studied and the infarct size in grams. A. There was significant and robust correlation between left ventricular global functional index (LVGFI) and infarct size. B. There was a significant and robust correlation between left ventricular ejection fraction (LVEF) and infarct size. C. There was no significant relationship between sphericity index and infarct size. D. There was no significant relationship between conicity index and infarct size.

Table 3 Relationship between cardiac magnetic resonance variables and adverse left ventricular remodelling at 1 year.

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
Infarct size	1.03 (1.01–1.05)	< 0.001	1.05 (1.02–1.08)	< 0.001
MVO	1.12 (1.05–1.22)	< 0.001		
LVEF	1.07 (1.03–1.12)	0.001		
LVGFI	1.10 (1.03–1.16)	0.001		
Conicity index	1.28 (0.86–1.93)	0.26		
Sphericity index	1.04 (0.91–9.09)	0.59		

CI: confidence interval; CMR: cardiac magnetic resonance; LVEF: left ventricular ejection fraction; LVGFI: left ventricular global functional index; MVO: microvascular obstruction; OR: odds ratio; TIMI: Thrombolysis In Myocardial Infarction. Cox univariate analysis assessed the relationship between the different CMR variables and adverse remodelling regression. Multivariable regression was adjusted with body mass index, age, sex and final TIMI flow, and each variable factor that correlated with adverse remodelling in univariate analysis. LVGFI and LVEF were negatively correlated with remodelling, but did not provide additional information compared with infarct size alone. The geometric indexes were not correlated with remodelling.

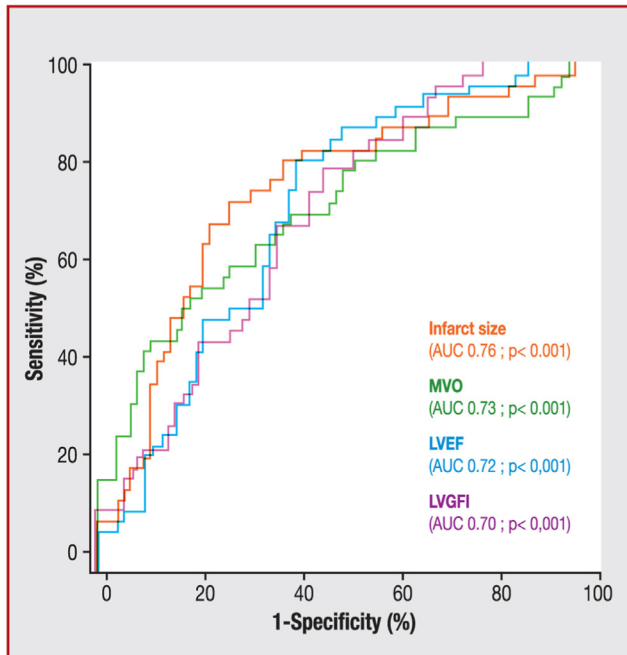


Figure 4. Receiver operating characteristic curves of the power of left ventricular global functional index (LVGFI), left ventricular ejection fraction (LVEF), infarct size and microvascular obstruction (MVO) to predict left ventricular adverse remodelling at 1 year. The best predictive performance for left ventricular adverse remodelling was found with infarct size (area under the curve [AUC]=0.76). The different AUCs for MVO, LVEF and LVGFI were, respectively, 0.73, 0.72 and 0.70 ($P < 0.001$ for all).

a higher incidence of MACE: OR 1.18, 95% CI 1.08–1.28 ($P < 0.001$) and OR 1.21, 95% CI 1.08–1.37 ($P < 0.001$), respectively. Moreover, larger infarct size and the presence of MVO were associated with a higher incidence of MACE: OR 1.02, 95% CI 1.00–1.04 ($P = 0.018$) and OR 1.13 95% CI 1.05–1.22 ($P = 0.002$), respectively. However, other LV geometric indexes were not significantly associated with MACE.

Table 4 Relationship between the different acute cardiac magnetic resonance variables and clinical events^a at 1 year.

	Univariate analysis	
	OR (95% CI)	P
Infarct size	1.02 (1.00–1.04)	0.018
MVO	1.13 (1.05–1.22)	0.002
LVEF	1.18 (1.08–1.28)	< 0.001
LVGFI	1.21 (1.08–1.37)	< 0.001
Conicity index	1.18 (0.64–2.17)	0.59
Sphericity index	1.93 (0.02–2.10)	0.26

LVEF: left ventricular ejection fraction; LVGFI: left ventricular global functional index; MVO: microvascular obstruction.

^a Clinical events were death or heart failure requiring hospitalization; conicity and sphericity were not correlated with clinical events; conversely, infarct size, MVO, LVGFI, and LVEF were correlated with clinical events.

Discussion

In our CMR substudy from the CIRCUS trial, which studied the prognostic value of the conicity, sphericity and LVGFI indexes at the acute phase of MI in patients with anterior STEMI, only LVGFI was associated with a higher incidence of adverse LV remodelling and MACE at 1 year. This relationship was not significant for the conicity and sphericity indexes. This secondary finding remains to be explored in larger groups of patients and further studies.

LVGFI is a new index, integrating structural and functional information from the LV. In a large cohort of healthy volunteers, this index showed greater performance for predicting heart failure and hard cardiovascular events than LVEF, and was comparable to LV mass [14]. This index integrates the same information as LVEF, but adds LV anatomy and mass information, which explains its superior predictive value compared with LVEF. In our study of an anterior acute MI population, the value of LVGFI was lower than normal values ($29.3 \pm 7.5\%$ vs. $40.0 \pm 7.0\%$, respectively) [14], thereby sug-

gesting anterior infarction produces an increase in LV mass as a result of myocardial oedema, and a decrease in stroke volume as a result of the decrease in LVEF. In a recent study, Eitel et al. evaluated LVGFI in a large cohort of 735 patients with STEMI using CMR studies in the postacute phase of the infarct [26]. Our results are consistent with their findings, showing a good correlation between LVGFI and infarct size ($R = -0.703$). We also found a similar correlation between infarct size and LVEF and LVGFI. However, Eitel et al. found a significantly closer correlation between LVGFI and infarct size compared with LVEF. Our cohort was smaller, and was only composed of patients who had had an anterior MI, which could explain the difference in our results. Indeed, LVGFI is closely related to the extent of myocardial damage occurring after MI. Moreover, our TTE results showed a population of severe MI with dilated LV, defined by a high mean LVEDV, probably related to the selection of only anterior STEMI.

Previous studies on LVGFI at the acute phase of STEMI did not assess the link between LVGFI and adverse remodelling. Our study is the first to report the significant relationship of acute LVGFI with LV remodelling at 1 year. This significant relationship with adverse LV remodelling seems to be similar to infarct size or MVO size ($R = 0.415$ and $R = -0.385$). Infarct size and MVO have both been reported as strong and independent predictors of adverse LV remodelling [27,28]. Considering the close relationship with infarct size, it is difficult to affirm the independent relationship of LVGFI with adverse remodelling. In our study, LVGFI was not significantly related to adverse remodelling after adjustment on infarct size. The relationship between adverse LV remodelling and LVGFI seems to be confounded by infarct size. This finding is of interest, because LVGFI has the potential to be assessed by echocardiography, a more available imaging technique in the acute phase of STEMI. In our study, MVO did not appear to be a better or independent predictive factor for remodelling, contrasting with other studies [29,30]. The absence of predictive value found in our study population may be related to a lack of statistical power. Because of this, our results should be considered at this stage only as hypothesis generating.

The postinfarct LV remodelling process is complicated and incompletely understood. It begins early after infarction, within the first hours, and is highly dynamic in the first days, with dilatation of infarcted myocardium. Compensatory hypertrophy of the remote myocardium occurs similarly soon after the infarct [31]. Finally, myocardial oedema could equally increase myocardial mass in acute postinfarction [32]. As a result of the rapid changes in infarcted and non-infarcted myocardial tissue, it is difficult to find a robust predictor of LV adverse remodelling at the acute phase, which explains the relatively low predictive performance of the CMR variables studied to predict adverse LV remodelling. Indeed, our study shows that LVGFI at the acute phase predicts adverse remodelling at 1 year. However, this prediction is limited, and is similar to that of LVEF. Further studies in larger groups of patients with acute MI, and at different time points during the LV remodelling process, are needed to confirm the clinical value of LVGFI.

In our study in an anterior acute MI population, sphericity index was slightly increased (0.36 ± 0.9 vs. 0.29 ± 0.12 , respectively) but remained within normal values with the upper limit of 0.41 [22]. Indeed, the ischaemic

cardiomyopathy following anterior infarction begins in the apical region, with secondary global dilation on a time-related basis. Our results suggested, as previously described by Di Donato et al., that there is a limitation to early analysis in acute MI of the sphericity index of the entire chamber obtained by the global axis ratio, as this single plane ratio reflects a linear alteration in the two axes of the entire ventricular chamber [25]. Consequently, it does not focus upon regional shape abnormalities in the apical region, as these changes may precede secondary global ventricular dilation. However, the conicity index was higher in our study of an anterior acute MI population than the normal value (4.69 ± 1.3 vs. 0.60 ± 0.09 , respectively) [25], indicating that the anterior infarction produced a less conical shape because of the apex abnormalities.

The geometric factors did not appear to be related to infarct size in our study. This finding contradicts two studies where sphericity and conicity indexes were strongly related to LV remodelling. Mannaerts et al. showed that the sphericity index, assessed by three dimensional TTE, was a good predictor of adverse remodelling at 1 year [33]. The sphericity and conicity indexes were independently related to adverse remodelling after adjusting with creatine kinase peak and wall motion score. Several factors can explain the differences compared with our study findings. First, there were significant differences in study populations, with only anterior MIs being included in our study, whereas other infarct locations were included in the other studies. Second, there were differences in imaging modalities; it is known that the accuracy of cardiac ultrasound in assessing LV volumes and dimensions is lower than that of CMR [34]. Finally, the other studies performed their measurements at different timings. LV remodelling is an active process that evolves rapidly in the days and weeks after infarction. If the LV tends to adopt a spherical shape early postinfarction, the spherical transformation depends on the dilatation of the non-infarcted segments [35]. This phenomenon occurs within the weeks or months following the infarction, after initial dilatation of infarcted myocardium [36,37]. So the assessment of LV sphericity within the first days after MI could be too early [38].

We studied the correlation between the stunned myocardium and our new indexes. Indeed, we thought that these new indexes could be linked to the stunning phenomenon, explaining the lack of correlation with adverse remodelling.

Our findings show that geometric indexes at the acute phase of MI are not significantly associated with adverse LV remodelling at 1 year; their assessment at later phases of infarct remodelling and scarring might provide different results. Further studies are required to assess the predictive value of these indexes at later phases of scarring for 1-year adverse LV remodelling. The early stages of LV remodelling are highly dynamic, and may explain, in part, this variability.

Study limitations

Our study has several limitations. First, only left anterior descending arteries were involved in the infarction in the CIRCUS study. Our study population was small and selected, because only centres with CMR available within 7 days of infarct participated in this study. Indeed, clinical charac-

teristics were different from the CIRCUS population [16]. Our subjects were significantly younger, with less diabetes mellitus, hypertension and dyslipidaemia. However, the main difference from the CIRCUS population was procedural characteristics, with faster admission to the catheterization laboratory (3.4 vs. 4.4 hours), which could explain the lower rate of remodelling and limited statistical power.

In addition, the assessment of adverse LV remodelling after 1 year of follow-up was defined only by TTE, and without evaluation by CMR. However, all TTE data were analysed blind by a centralized core laboratory.

The delay between the time of the STEMI and the realization of the CMR could vary by ± 4 days, which causes a risk of variations in the assessment of the infarct size and MVO, as described in the literature [39]. However, this delay remains acceptable in this study compared with in the other studies [21].

Conclusions

In conclusion, LVGFI was predictive of adverse LV remodelling and MACE at 1 year after anterior STEMI. Moreover, LVGFI was independently correlated with infarct size. For that reason, LVGFI provided no additional predictive value to infarct size alone. There was no association between conicity and sphericity indexes and the occurrence of adverse LV remodelling and MACE.

Further studies at different time points and using different non-invasive imaging techniques after infarction are needed to assess adverse LV remodelling and potentially monitor subclinical variables that could help to adjust patient management and improve patient prognosis.

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Disclosure of interest

The authors declare that they have no competing interest.

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