Three-dimensional simultaneous strain–volume analysis describes left ventricular remodelling and its progression: a pilot study

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Aims	Three-dimensional (3D)-echocardiography speckle imaging allows the evaluation of frame-by-frame strain and volume changes simultaneously. The aim of the present investigation was to describe the strain–volume combined assessment in different patterns of cardiac remodelling.
Methods and results	Fifty patients received a 3D acquisition. Patients were classified as follows: healthy subjects (CNT), previous AMI, and normal ejection fraction (EF; group A); ischaemic cardiomyopathy with reduced EF (group B); hypertrophic/infiltrative cardiomyopathy (group C). Values of 3D strain were plotted vs. volume for each frame to build a strain–volume curve for each case. Peak of radial, longitudinal, and circumferential systolic strain ($R\varepsilon p$, $L\varepsilon p$, and $C\varepsilon p$, respectively), slopes of the curves ($R\varepsilon Sl$, $L\varepsilon Sl$, $C\varepsilon Sl$), and strain to end-diastolic volume (EDV) ratio ($R\varepsilon/V$, $L\varepsilon/V$, $C\varepsilon/V$) were computed for the analysis. Strain–volume curves of the CNT group were steep and clustered, whereas, due to progressive dilatation and reduction of strains, progressive flattening could be demonstrated in groups A and B. Quantitative data supported visual assessment with progressive lower slopes ($P < 0.05$ for $R\varepsilon Sl$, $C\varepsilon Sl$, $P = 0.06$ for $L\varepsilon Sl$) and significantly lower ratios ($P < 0.01$ for $R\varepsilon/V$, $L\varepsilon/V$, and $C\varepsilon/V$). Group C showed an opposite behaviour with slopes and ratios close to those of normal subjects. Correlation coefficients between EDV and slopes of the curves were significant for all the directions of strain ($C\varepsilon Sl$: $r = 0.891$; $R\varepsilon Sl$: $r = 0.704$; $L\varepsilon Sl$: $r = 0.833$; $P < 0.0001$ for all).
Conclusion	We measured left ventricular volumes and strain by 3D-echo and obtained strain–volume curve to evaluate their behaviour in remodelling. A distinctive and progressive pattern consistent with pathophysiology was observed. The analysis here shown could represent a new non-invasive method to assess myocardial mechanics and its relationship with volumes.
Keywords	Remodelling • Speckle strain • 3D-echocardiography

Introduction

Left ventricular (LV) remodelling is the process that involves shape, volume, and function rearrangement secondary to acute or chronic myocardial injury.[1,2] It is a main feature of the heart failure (HF) syndrome and it is strongly related to the progression of the disease and finally to prognosis.[1–3] Furthermore, it has become evident that reversing the mechanism of LV remodelling changes the natural history of HF in turn representing a therapeutic target.[4,5] Ischaemic LV maladaptation represents the most studied form of remodelling[6] and it has been demonstrated that its progression and/or regression is strongly linked to the alteration

of regional myocardial contraction.[7] In this scenario, the assessment of cardiac mechanics in relation to the structural (size and shape) changes would represent a cornerstone for the management of HF patients. Despite this central role and complex relation with myocardial function,[8] remodelling is still merely described as changes of LV volumes and shape (sphericity) with respect to normal hearts.[9] The use of echocardiography represents the standard practice and by means of three-dimensional (3D) technique, it becomes extremely accurate and reproducible.[10–15] Besides those to obtain volume reconstructions, several efforts have been made to provide quantitative and non-subjective methods to express contractility status in injured heart. In this context, LV strain has been validated as a powerful method to quantify myocardial shortening/lengthening.[16–19] Its use has grown also in the detection of subclinical stages of diseases[20] or in complex evaluation of cardiac mechanics[21] but data on LV remodelling are lacking. Recently, LV volume reconstruction and myocardial strain assessment have been integrated and a single 3D-echocardiographic acquisition of myocardial function and LV volume can be extrapolated from a single cardiac cycle.[22–24] In our study, we applied the simultaneous 3D acquisition of volume and strain to the evaluation of LV remodelling. We hypothesized that combining data from function and structure in a simultaneous volume–strain analysis could be a sensible approach to the evaluation of cardiac maladaptation.

Methods

Population

We screened all the consecutive patients referred to our centre from November 2009 to February 2010 for standard echocardiographic evaluation. Patients were considered suitable for the study if they met the following criteria for each group: subjects without history of cardiovascular disease or risk factor for developing subclinical dysfunction or HF, normal clinical examination and normal recent laboratory tests, were selected as the control group (CNT, $n = 12$); group A ($n = 16$): history of timely revascularized non-complicated acute myocardial infarction >6 weeks and demonstration of preserved ejection fraction (EF ≥ 55%), no symptoms or sign of HF; group B ($n = 10$): known ischaemic dilated cardiomyopathy with moderate-to-severe systolic dysfunction (EF ≤ 40%); group C ($n = 12$): non-obstructive hypertrophic or infiltrative cardiomyopathy with moderate-to-severe hypertrophy with a history of hospitalization for HF in the last 6 months and evidence of preserved systolic function (EF ≥ 55%).

Patients were excluded if they showed active sign of decompensated HF, atrial fibrillation with highly variable RR intervals, chronic pacemaker stimulation, moderate-to-severe valvular regurgitations, symptoms suggestive of active angina, and, finally, poor echocardiographic images.

Our Institutional Review Board approved the study and witnessed informed consent was obtained from each patient.

Standard and three-dimensional echocardiography

Echocardiography, including Doppler evaluation, was performed by using a 4D Artida System (Toshiba Medical Systems). The standard echocardiography examination included parasternal and apical views with pulsed Doppler evaluation of the LV inflow and outflow tract;

continuous Doppler study of each transvalvular gradient was performed to rule out inflow or outflow obstruction. Colour-Doppler was used to detect any significant regurgitation. The following parameters were computed: aortic root (Ao root), left atrial (LA) dimension, interventricular septum, posterior wall (PWd), left internal diastolic (EDD) and systolic (ESD) diameters by m-Mode in parasternal long-axis view as recommended.[9] LV mass, fractional shortening, and relative wall thickness were calculated as previously described.[9] Segmental wall motion was graded as follows: 1 = normal; 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. Wall motion score index was derived by dividing the sum of individual segment scores by the number of interpretable segments in a 17-segment model.

Real-time 3D-echo imaging was performed from the apical position with the patient in the left lateral decubitus using a fully sampled matrix array transducer (PST-25SX) in the tissue harmonic mode. Gain and TGC were optimized for the best endocardial definition in the multiplane mode simultaneously showing both apical four-chamber and two-chamber views. Sector scan and depth were adjusted to completely include LV in the scan and to maximize frame rate. Then, by the full-volume acquisition mode triggered on the QRS peak, we acquired at least six consecutive cardiac cycles during patient breath-hold. A wide acquisition 'full-volume' mode was used, in which four wedge-shaped subvolumes were acquired for six consecutive cardiac cycles during a single breath-hold.

Frame rate during acquisition varied from 15.66 to 18.75 f/s with a very low dispersion within the population here examined (mean + SD 17.32 + 0.68 f/s).

Images were stored and analyzed offline.

Strain–volume curve reconstruction

The best cardiac cycle of the full-volume 3D acquisition was chosen and line markers centred in LV cavity from apex to base in the long-axis views to allow an exact volume reconstruction. In the same manner, short-axis line markers were placed at the base, mid and apical level. 3DE data sets were analysed using the 3D wall motion tracking software (Toshiba Medical System). Endocardial and epicardial boundaries were traced including the papillary muscles in the LV cavity. A semi-automatic tracking algorithm with a frame-by-frame manual adjustment was applied to follow the endocardial and epicardial limits in 3D throughout the cardiac cycle. By protocol, epicardial boundaries could not been corrected after the first frame while the endocardial margins could be adjusted for a maximum of two segments per frame. The algorithm calculates and immediately shows the variability of the mass which should be constant in 3D image, thus providing an internal reference of quality of the LV mass data set. Patients were excluded from the analysis if there was a significant mass variability or if the visual assessment of the tracking was poor.

For each frame of the cardiac cycle, voxel count within the LV cavity is used by the software to calculate LV volumes. End-diastolic volume (EDV), end-systolic volume (ESV), and frame-by-frame volumes within the systolic phase were extrapolated and then referred to body surface area (EDVi, ESVi). Similarly, changes in myocardial wall are used to assess shortening and lengthening of a segment in three-dimension and finally compute longitudinal, radial and circumferential strain (Lε, Rε, and Cε, respectively).

Data were then exported in a datasheet and analysed for each patient. Global strain for each direction of the contraction of the whole LV was used for the analysis. The conventional 17-segment model of LV regions was used and global strain was calculated after the exclusion of the minimum and maximum values by averaging all the regional strains.

Volumes (x-axis) and global strain (y-axis) of each frame were plotted in a Cartesian system and the volume–strain curve of a cardiac cycle was build for each component of the strain (Lє, Rє, and Cє) (*Figure 1*). For this analysis only, the systolic phase of the curve was considered and a mean of 6.98 volume/strain data (i.e. frame) per patients was processed. After the visual assessment of the curves, the following quantitative parameters were extrapolated for each direction of the strain: peak systolic strain (LεP, RεP, and CεP) as the nadir or the zenith of the trace at end-systole; strain/volume ratio (Lε/V, Rε/V, and Cε/V) which represents the slope of the curve given an ESV and an end-diastolic strain equal to zero (i.e.

influenced by slope and position of the curve in the Cartesian axis); slope of the systolic phase of the curve (LεSl, RεSl, and CεSl) as the difference of maximum and minimum strain divided by the difference of EDV and ESV (i.e. stroke volume) (absolute slope of the curve).

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation (SD). Baseline categorical data were compared by means of the Chi-square test. Statistical comparison between groups was performed by the Mann–Whitney test due to non-normal distribution of data. Bivariate correlation was performed between EDVi and peak of ε in CNT and ischaemic patients (groups A and B) and r was presented.

Slope of the curves were plotted (y-axis) against EDVi (x-axis) for each component of strain and correlation between the two parameters was evaluated. Due to nonlinear relation in the various plots and after curve estimation analysis, quadratic model was chosen as the best model that fit data. Multiple R was presented. For all tests, a *P*-value < 0.05 was considered significant.
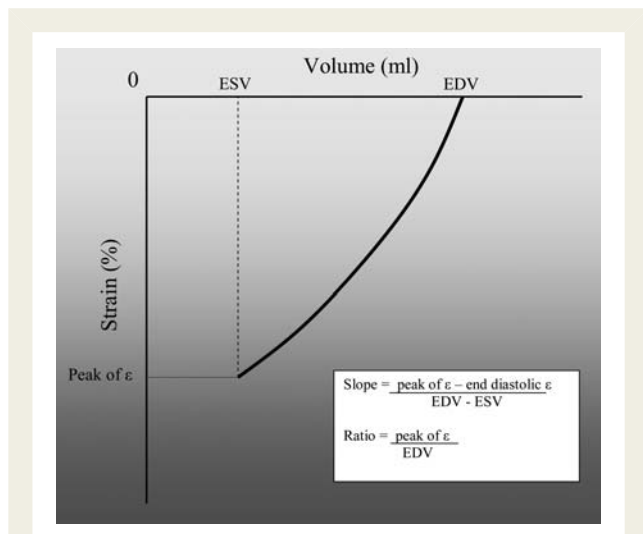

Figure 1 Schema of strain/volume curve. Values of strain (y-axis) and volume (x-axis) of each frame were plotted and curve were derived for the systolic phase. For each patient, absolute slope of the curve was calculated as the differences between peak of strain (ε) and end-diastolic ε divided by stroke volume. Ratio of peak of ε and EDV was also computed: ratio represents slopes of the curve considering ESV and basal ε equal to 0.

Results

Population

We screened 56 patients for the study in the reference period: four had poor echocardiographic images and full volume acquisition was not achievable, two were initially included and images stored but subsequently excluded due to poor endocardial or epicardial definition. Feasibility was thus possible in 89% of cases and the population included 40 patients (61.1% male, mean age 64.05 ± 14.65 years) and 10 healthy controls (64.9% male, mean age 64 ± 14.09 years, $P =$ NS) (*Table 1*). Time from acute myocardial infarction in groups A and B ranged from 9 to 23 months. Within the group C, eight patients (66.6%) had an asymmetrical HCM with a non-significant basal LV outflow tract obstruction. Two patients had a biopsy proven cardiac AL amyloidosis, one of them were in NYHA class 2 and the other in NYHA 3 with a mean time from

Table 1 Standard echocardiographic data

	CNT	EF > 50%	*P* vs. CNT	EF < 40%	*P* vs. CNT	*P* vs. EF > 50%	ECC	*P* vs. CNT
Age (years)	53.00 ± 18.80	67.43 ± 9.61	0.106	66.00 ± 13.28	0.130	0.765	71.89 ± 11.77	0.027
BSA (mq)	1.81 ± 0.21	1.92 ± 0.13	0.187	1.85 ± 0.42	1.000	0.263	1.82 ± 0.26	0.935
Aortic root (mm)	32.40 ± 4.70	37.15 ± 4.45	0.019	32.00 ± 3.39	0.805	0.020	35.00 ± 3.65	0.141
LA (mm)	37.33 ± 4.03	42.00 ± 4.19	0.027	50.80 ± 5.67	0.002	0.001	45.29 ± 4.23	0.007
IVSd (mm)	10.00 ± 1.89	11.23 ± 2.11	0.176	11.80 ± 3.35	0.317	0.739	18.56 ± 4.34	<0.001
EDD (mm)	48.80 ± 2.25	52.08 ± 4.74	0.078	60.20 ± 16.53	0.063	0.057	41.25 ± 10.95	0.117
PWd (mm)	9.94 ± 1.07	10.00 ± 2.26	0.567	11.40 ± 3.58	0.950	0.789	14.25 ± 3.41	0.014
FS (%)	48.73 ± 7.36	38.52 ± 9.45	0.027	13.50 ± 5.19	0.006	0.005	33.41 ± 9.62	0.041
Mass (g)	98.90 ± 19.72	111.58 ± 19.40	0.113	158.40 ± 53.43	0.085	0.058	169.00 ± 67.32	0.012
RWT	0.40 ± 0.06	0.41 ± 0.09	1.000	0.45 ± 0.34	0.270	0.290	0.83 ± 0.25	<0.001
WMSI	1.00	1.33 ± 0.31	0.003	2.43 ± 0.56	0.003	0.002	1.00	1.000

BSA, body surface area; LA, left atria; IVSd, interventricular septum diastole; DTD, PWd, posterior wall diastole; EDD, end-diastolic diameter; FS, fractional shortening; RWT, relative wall thickness; WMSI, wall motion score index.

Table 2 Left ventricular volumes, function, strains and quantitative data from strain–volume curves

	CNT	EF > 50%	P vs. CNT	EF < 40%	P vs. CNT	P vs. EF > 50%	ECC	P vs. CNT
Volumes								
EDV (mL)	88.27 ± 22.43	122.83 ± 34.06	0.005	197.23 ± 73.06	<0.001	0.007	80.13 ± 37.18	0.410
ESV (mL)	32.49 ± 11.84	55.15 ± 17.02	<0.001	158.81 ± 57.17	<0.001	<0.001	36.52 ± 18.69	0.757
EF (%)	63.82 ± 5.65	55.09 ± 5.00	0.001	19.40 ± 6.72	<0.001	<0.001	54.10 ± 10.19	0.008
SV (mL)	55.78 ± 12.26	67.68 ± 18.81	0.057	38.43 ± 20.85	0.035	0.004	43.61 ± 21.74	0.136
EDVi (mL/mq)	48.90 ± 10.86	63.41 ± 16.47	0.014	108.12 ± 43.37	<0.001	0.004	44.14 ± 17.61	0.504
ESVi (mL/mq)	17.84 ± 5.45	28.44 ± 8.06	<0.001	87.54 ± 34.76	<0.001	<0.001	19.93 ± 8.58	0.681
SVi (mL/mq)	31.05 ± 6.67	34.96 ± 9.38	0.458	20.59 ± 11.68	0.014	0.007	24.21 ± 11.22	0.064
Peak of strain								
Radial ε P (%)	30.51 ± 8.36	27.07 ± 9.12	0.486	4.37 ± 3.92	<0.001	<0.001	20.40 ± 8.75	0.018
Circumferential ε P (%)	−32.42 ± 3.34	−25.90 ± 4.77	<0.001	−6.29 ± 3.17	<0.001	<0.001	−27.15 ± 6.48	0.013
Longitudinal ε P (%)	−17.74 ± 1.79	−15.46 ± 2.93	0.027	−6.33 ± 2.22	<0.001	<0.001	−11.39 ± 4.88	0.002
Slope of curves								
R ε Sl	0.56 ± 0.17	0.43 ± 0.18	0.036	0.16 ± 0.13	<0.001	<0.001	0.54 ± 0.24	0.877
C ε Sl	0.61 ± 0.15	0.41 ± 0.10	0.001	0.19 ± 0.11	<0.001	<0.001	0.69 ± 0.41	0.959
L ε Sl	0.30 ± 0.08	0.24 ± 0.06	0.063	0.19 ± 0.07	0.004	0.082	0.30 ± 0.16	0.471
Strain/volume ratio								
R ε/V	0.65 ± 0.21	0.44 ± 0.17	0.018	0.05 ± 0.06	<0.001	<0.001	0.49 ± 0.21	0.209
C ε/V	−0.70 ± 0.19	−0.43 ± 0.12	<0.001	−0.08 ± 0.09	<0.001	<0.001	−0.64 ± 0.30	0.123
L ε/V	−0.35 ± 0.10	−0.26 ± 0.07	0.018	−0.07 ± 0.06	<0.001	<0.001	−0.24 ± 0.10	0.013

EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; SV, stroke volume; i, values indexed to the BSA; ε P, peak of strain; RεSl, CεSl, LεSl, slope of the curves in radial, circumferential and longitudinal direction, respectively; Rε/V, Cε/V, Lε/V, strain/volume ratio in radial, circumferential, and longitudinal direction, respectively.

diagnosis that ranged from 4 to 13 months. The acquisition time and analysis of 3D was 3 ± 1 min.

Volumes and strain

Patients with previous AMI and normal EF (group A) had a significantly higher mean LV end-diastolic (122.83 ± 34.06 vs. 88.27 ± 22.43 ml, $P < 0.01$) and ESVs (55.15 ± 17.02 vs. 32.49 ± 11.84 ml, $P < 0.01$) than controls (*Table 2*). Mean EF of group A was quite normal but significantly lower than CNT (55.09 ± 5 vs. 63.82 ± 5.65%, $P < 0.01$) with non-significant different SVi (*Table 2*). Of note in group A, all but two patients could be classified as non-dilated according to the recommended reference values[9] (*Table 2*, *Figure 2*).

Patients in group C had a significantly higher LV mass (169 ± 67.32 vs. 98.9 ± 19.72 g, $P < 0.01$ vs. CNT) with volumes and EF closed to normal (*Table 1*).

Peaks of strains are reported on *Table 2*. Patients of group A showed preserved systolic RεP but a significant reduction in global CεP ($P < 0.0001$) and LεP ($P < 0.05$). Group B, as expected, showed a strong and unequivocally reduction of strains regardless of the direction considered ($P < 0.001$ for all). Rεp, Lεp, and Cεp showed significant correlation with ESV ($r = −0.590$, $r = 0.582$, $r = 0.813$, respectively, $P < 0.00001$ for all) and with EF ($r = 0.774$; $r = −0.855$; $r = −0.979$, respectively, $P < 0.00001$ for all).

Group C showed a significant reduction in strain in all directions ($P < 0.05$ for all). In *Figure 2*, values of EDVi and CεP are plotted for CNT, groups A and B. Mean values are also shown. Progression

of remodelling is underlined by the simultaneous dilatation and progressive reduction of strain. As previously demonstrated, in our population, function and volumes were found to be linked together ($r = 0.666$; $P < 0.0001$ for correlation between EDVi and CεP, *Figure 2*; $r = −0.537$; $P < 0.001$ for EDVi and RεP; $r = 0.625$; $P < 0.0001$ for EDVi and LεP).

Volume–strain curves by 3D echocardiography

The curves of circumferential ε for each patient are reported in *Figure 3*. Healthy subjects showed globally steep curves, indicating a good contraction during the ejection phase. Group A showed behaviour close to CNT with some curves overlapped. However, the curves were found to be less steep due to the simultaneous presence of subclinical dilatation (rightward shift of the curves) and global reduction of CεP (upward shift). This aspect became evident and unequivocal in group B who had severe myocardial dysfunction and dilatation. Quantitative data derived from the patients confirmed the visual assessment. The slope of the curves was significantly lower in group A than in CNT with a borderline value of significance in the longitudinal direction ($P < 0.05$ for RεSl and CεSl, $P = 0.06$ for LεSl). In group B, slopes were significantly lower for any direction of strain considered ($P < 0.001$ for RεSl, CεSl, and LεSl). Strain/volume ratios (slope and position of the curves) were significantly lower in both group A ($P < 0.01$ for Lε/V, Rε/V, and Cε/V) and group B ($P < 0.0001$ for Lε/V, Rε/V, and Cε/V) (*Table 2*).

In group C, according to normal or reduced LV volumes, curves were largely overlapped with those of CNT; in the most restrictive case (AL amyloidosys), we found a markedly leftward shift with a reduced peak of strain. Due to the simultaneous and consensual reduction of the two parameters, the slope of the curves and strain/volume ratios were not significantly different from CNT (*Table 2*, P = NS).

The correlation between EDVi and CϵSl for CNT, group A and group B are shown in *Figure 4*. A non-linear correlation was visible between the two variables with a highly significant coefficient (r = 0.891; P < 0.00001). The correlation with the same quadratic model was significantly also for RϵSl (r = 0.704; P < 0.0001) and LϵSl (r = 0.833; P < 0.0001).
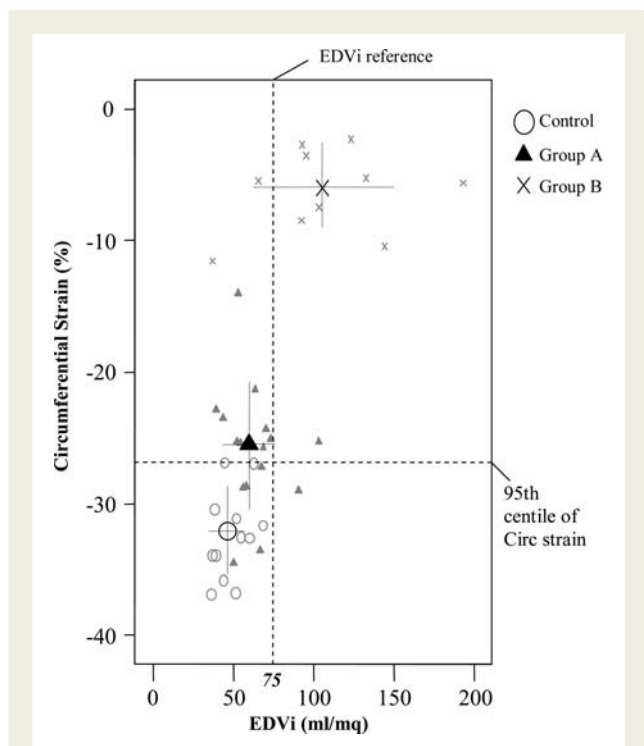

Figure 2 End-diastolic volume (EDVi) and circumferential peak of strain (Cϵp) with mean values (larger marker) within each group. Bar represents standard deviation. Progression of dilatation is coupled with reduction of strain (r = 0.666, P < 0.001).
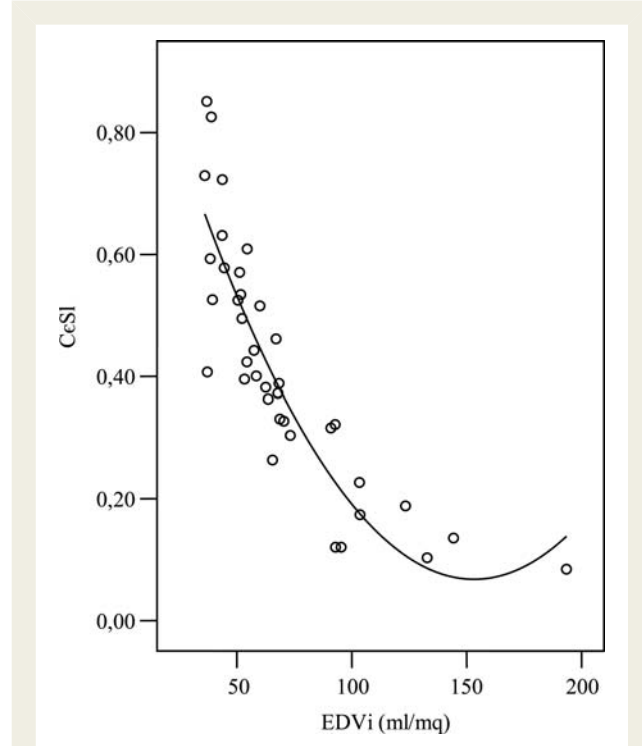

Figure 4 Relation between and end-diastolic volume and slope of curves for circumferential ϵ in CNT and ischaemic patients. Non-linear relation has been observed with a high coefficient value (r = 0.891, P < 0.0001).
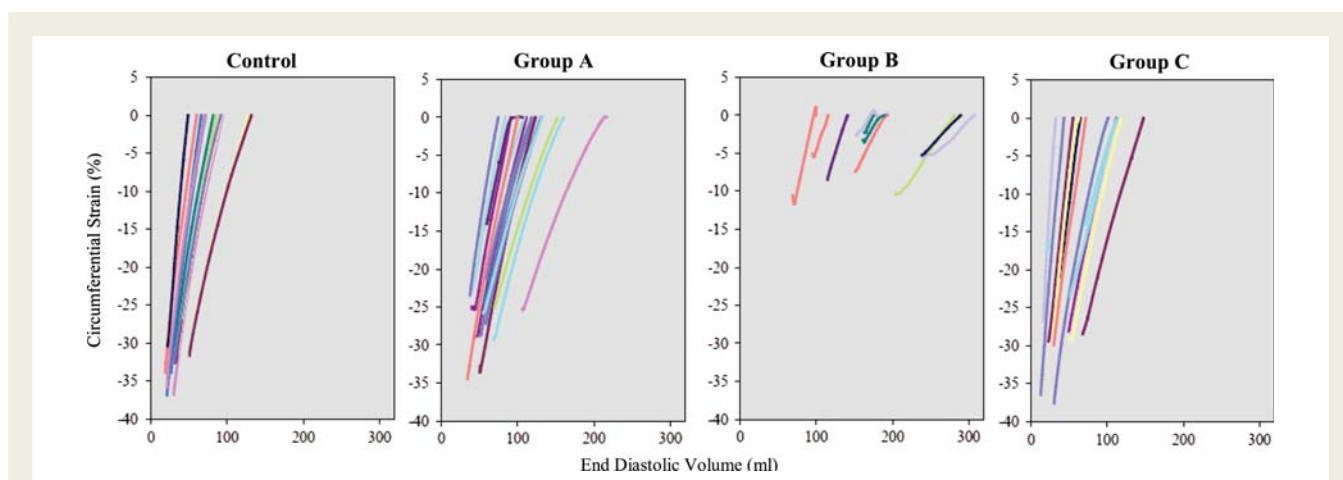

Figure 3 Curve of each patient for Cϵ in normal subjects, ischemic patients with normal (group A), markedly reduced ejection fraction (group B), and hypertrophic/infiltrative cardiomyopathy (group C).

Reproducibility

Reproducibility of strain and volumes was performed in 12 randomly chosen subjects/patients by the Bland—Altman method across a broad range of values. Mean $\pm$ standard deviation of differences of strains between two measurements of the same operator were $-0.49 \pm 1.95\%$ for CεP, $2.53 \pm 4.86\%$ for RεP, and $-0.02 \pm 1.1\%$ for LεP. Variations of LV volumes were 0.62 ± 12.04 mL for EDV and 0.1 ± 9.52 mL for ESV.

Differences of strains between two independent operators were $-1.6 \pm 5.1\%$ for CεP, $2.9 \pm 6.9\%$ for RεP, and $-1.6 \pm 2.97\%$ for LεP. Variations of LV volumes were 3.57 ± 7.48 mL for EDV and 4.8 ± 13.4 mL for ESV.

Discussion

The main finding of our study is that the simultaneous assessment of LV volumes and myocardial function can effectively describe the well-known process of remodelling and could represent a useful and robust approach to this issue.

Structural changes of volumes and shape induced by cardiac injury represent the final pathway of several molecular modifications and the basis of the HF syndrome.[1–3,6,8] For the clinical purpose, LV remodelling assessment and its progression or regression represent nowadays the cornerstone of HF patient management.[1,4,5] It was initially described as a consequence of post-ischaemic damage and particularly as a result myocardial infarction that promotes progressive LV dilatation and myocardial contractility alterations also in the remote myocardium initiating the vicious cycle of remodelling.[2,6,8] Few years ago, the group of Ambrosio and co-authors[7] firstly demonstrated that the loss of regional contractile function *per se* promotes LV dilation and that restoration of contractility endorsed reverse remodelling process. Furthermore, regional function and dilatation were proportionally linked in a linear manner: the higher was the dysfunctional area, the larger was the ventricle.[7] In our study, we have confirmed and extended the relationship described by these authors using a quantitative approach by 3D reconstruction of the LV volumes and myocardial contractility measurement by strain. The latter was previously validated as an effective measure of myocardial shortening/lengthening and after the initial experience with TDI-derived curves, its clinical value has been recently highlighted due to the development of speckle tracking-based analysis that allows an angle-independent evaluation.[16,19] In our study, strain has been assessed with good reproducibility by 3D-echocardiography. Compared with standard two-dimensional methods, the 3D technique allows frame-by-frame quantification and simultaneous 3D volume reconstruction within the same cardiac cycle.[22] Reproducibility of LV volumes assessment by 3D-echocardiography has been largely validated,[10–15] and 3D strain has been very recently compared with tagging-CMR by Kleijn et al.[24] obtaining similar values and variations.

To validate the hypothesis that a simultaneous evaluation of myocardial function and volumes could better describe LV remodelling, we plotted data of each patient in a Cartesian axis to develop a curve of the systolic phase during which myocardial deformation (i.e. strain) was constantly related to the resultant volumes changes. As expected, the healthy subjects show that the normal myocardial shortening/lengthening is coupled to the simultaneous progressive reduction of volume finally determining the LV stroke volume. The curves of subjects within the control group are clustered with a very low dispersion, suggesting a good performance of the parameters. In patients with CAD and previous MI, we observed a significantly reduction in global strain. It should be noted that a slightly loss of function (i.e. reduction of strain in the y-axis) was related to LV dilatation resulting in a rightward shift and a flattening of the strain—volume curve. This finding is concordant with previous observations.[7] Since the two parameters move in the opposite direction from the normal curves, we can show significant alterations of the slope also in non-dilated patients with normal EF (group A). The strain/volume ratio (considering ESV and basal strain equal to zero) reflects the slope of the curve and the distance from the origin (i.e. position) in the Cartesian axis. As expected, this parameter resulted to be more sensitive than absolute slope for the quantification of the LV remodelling because this index considers also the rightward shift of the curves linked to LV dilatation.

The described variations were progressive and continuous and in group B the more remodelled ventricle showed an extreme rightward and upward shift of the curve.

Visual trend of the phenomenon is quantitatively documented by the significantly correlation between EDVi and slope of curves: the smaller are the LV volumes, the steeper are the strain—volume curves.

The different behaviour of radial, circumferential, and longitudinal strain in the described relation goes beyond the aim of the present study, but this finding is not unexpected. In our study, circumferential strain had the better performance probably due to its intrinsic low variability and to the fact that myocardial contraction is mainly circumferential (e.g. fibre direction) with a great dynamic range (twice of longitudinal strain).[25]

For the purposes of this study, we included in our study a group of patients with hypertrophic/infiltrative cardiomyopathy. As known in this scenario, volumes are initially normal and then progressively decrease due to an increase in myocardial mass.[26] Strain has been found reduced in these subjects despite a normal global EF.[20,26,27] According to this observation, we detected a large overlap of the curves between control and group C with an evident leftward and downward shift of the curves only in patients with advanced cardiac amyloidosis. This lack of differences of group C from controls was confirmed by the slopes of the curves and was due to simultaneous changes of volumes and function. In this scenario, other parameters such as LV mass should be considered instead of the volume to discriminate pathological subjects from CNT. In spite of this limitation, the addition of volumes gives further information about pathophysiology of reduction in strain in two different conditions: in ischaemic patients, myocardial dysfunction is coupled with LV dilatation, while in hyperthrophic/infiltrative patients it is accompanied by the reduction of volumes.

Our preliminary findings may have some new important implications concerning the use of 3D echocardiography in patients with CAD. Beyond the recommended acquisition of volumes and EF (3D mode), we can now automatically achieve the assessment of regional function by a quantitative analysis of wall motion

abnormalities and our proposed indexes of strain—volume relation. If confirmed in larger studies, strain—volume analysis can be used to detect and grade the continuous changes of LV secondary to ischaemic injury and response to the therapy. Nevertheless, strain—volume relation can be proposed also for patients eligible for cardiac resynchronization therapy since the consequence of synchronism, when efficient, determines a simultaneous positive change of global strain (due to coordination of segments)[28] and lower LV volumes. Three-dimensional strain simultaneously provides information about the most delayed wall, thus favouring both the site of implantation and device optimization.[29,30]

Limitations

Some limitation should be acknowledged in this study. First, temporal resolution of the employed 3D acquisition for speckle tracking analysis is still low. Maximum frame-rate available at best is 19 fr/s and this can theoretically affect a good tracking of speckles compared with 2D methods. However, strain studies with 3D speckle tracking by our and other groups showed a good correlation with previous data or with other technique (i.e. CMR): in our opinion, these results with such low frame rate could be due to the fact that the 3D acquired speckles can be followed in every spatial plane partly overcoming the issue of frame rate. With the 2D technique, some speckles leave the plane of scanning (out-of-plane phenomenon) and cannot be followed for the tissue tracking.

Secondly, we decided to exclude the diastolic phase. The temporal resolution in fact limits the frames available for this analysis. Diastolic phase is a complex phase of the cardiac cycle and strain rate (not available with low temporal resolution) rather than strain should be used as known to characterized relaxation. In fact, some well-known event such post-systolic shortening and diastolic asynchrony[21] determine multifaceted variation of volume—strain relation which can represent a future direction for research.

Thirdly, spatial resolution in 3D-mode acquisition can be affected by single vs. multibeat acquisition. These aspects have been evaluated by other groups with discordant results.[31,32] In atrial fibrillation, single beat acquisition may perform well with low LV volumes and EF variability. Nevertheless, Macron *et al.* stated that two-beat modality provides a better accuracy of both EF and LV volumes than single beat modality. At the best of our knowledge, there is no study that evaluated the impact of 3D acquisition in speckle tracking strain. In this context despite this potential source of error, one should remember that 3D speckle imaging with technology and algorithm employed in our study seems to perform well since it has been validated previously against CMR for both volumes[10] and strain.[24]

Conclusion

We have demonstrated that the combination of LV volume and myocardial contraction of the entire cardiac cycle in a volume—strain curve can be performed in humans by 3D echocardiography with good reproducibility. This approach can provide a more complete report of the pathophysiology of LV reaction to injuries as we verified by the different behaviour of the two principal expression of cardiac remodelling (eccentric and concentric) consistent with the different underlying pathophysiology. Changes of the curves are progressive and can be quantified by slope and strain/volume ratio. This behaviour designate, if confirmed in a larger population, a quantitative and comprehensive measure of LV remodelling.

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