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Different effects of cardiac resynchronization therapy on left atrial function in patients with either idiopathic or ischaemic dilated cardiomyopathy: a two-dimensional speckle strain study

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Aims In dilated cardiomyopathy (DCM), attenuation of left atrial (LA) booster pump function has been observed, and attributed both to altered LA loading conditions owing to left ventricular (LV) diastolic dysfunction and to LA involvement in the myopathic process. The aim of the present study was to detect LA systolic dysfunction in DCM using speckle-tracking two-dimensional strain echocardiography (2DSE), and to assess the effects of cardiac resynchronization therapy (CRT) on LA myocardial strain during 6 month follow-up.

Methods and results A total of 90 patients (aged, 52.4 $\pm$ 10.2 years) with either idiopathic ($n = 47$) or ischaemic ($n = 43$) DCM underwent standard Doppler echo and 2DSE analysis of atrial longitudinal strain in the basal segments of LA septum and LA lateral wall, and in LA roof. The two groups were comparable for clinical variables (NYHA class: III in 72.2%; IV in 27.8%). LV volumes, ejection fraction, stroke volume, and mitral valve effective regurgitant orifice were similar between the two groups. No significant differences were evidenced in Doppler transmitral inflow measurements. LA diameter and maximal volume were also similar between the two groups. Conversely, LA active emptying volume and fraction were both lower in patients with idiopathic DCM. Peak systolic myocardial atrial strain was significantly compromised in patients with idiopathic DCM compared with ischaemic DCM in all the analysed atrial segments ($P < 0.001$). At follow-up, 64 patients (71.1%) (37 idiopathic and 27 ischaemic) were responders, and 26 (28.9%) (10 idiopathic; 16 ischaemic) were non-responders to CRT (responder: decrease of LV end-systolic volume >15%). A significant improvement in LA systolic function was obtained only in patients with ischaemic DCM responders to CRT ($P < 0.001$). By multivariable analysis, in the overall population, it was found that ischaemic aetiology of DCM (β-cofficient = 0.62; $P < 0.0001$) and positive response to CRT (β-cofficient = 0.42; $P < 0.01$) were the only independent determinants of LA lateral wall systolic strain.

Conclusions Two-dimensional strain represents a promising non-invasive technique to assess LA atrial myocardial function in patients with DCM. LA pump and reservoir function at baseline and after CRT are more depressed in idiopathic compared with ischaemic DCM patients. Future longitudinal studies are warranted to understand further the natural history of LA myocardial function, the extent of reversibility of LA dysfunction with CRT, and the possible prognostic impact of such indexes in patients with congestive heart failure.

Cardiac resynchronization therapy (CRT) has become an attractive therapeutic option for patients with end-stage chronic heart failure (HF), left ventricular (LV) dilatation, and left bundle branch block (LBBB) with wide QRS duration.[1–2] Currently, patients are selected for CRT on the

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basis of clinical and ECG criteria and of standard LV echocardiographic indexes.[3–4]

Among various echocardiographic techniques, Doppler myocardial imaging (DMI) and strain rate imaging have gained their acceptance by virtue of their ability to define myocardial timing, contractility, and deformation in patients with LBBB and HF, and are highly feasible and easy-repeatable.[5–12] Although DMI and Doppler strain measures have been used most often in clinical practice, they are limited by Doppler angle of incidence. A novel approach to quantify regional LV function from routine gray-scale 2D echocardiographic images, known as speckle-tracking two-dimensional strain echocardiography (2DSE), calculates myocardial strain independent of angle of incidence, and has been recently validated against sonomicrometry and tagged magnetic resonance imaging.[13–16]

Augmentation of left atrial (LA) systolic function and active LA contribution to LV filling (booster pump function) is a common finding in conditions associated with LV diastolic dysfunction.[17] Conversely, in dilated cardiomyopathy (DCM), attenuation of LA booster pump function has been observed, and attributed both to altered LA loading conditions owing to LV diastolic dysfunction and to LA involvement in the myopathic process.[18–19] By the use of standard echocardiography, previous authors have showed a LA systolic function more depressed in idiopathic compared with ischaemic DCM.[20–22] To date, no previous report analysed the potential effects of CRT on LA myocardial function.

On these grounds, aims of the present study were: (i) to detect by speckle-tracking 2D strain underlying LA myocardial dysfunction in patients with either idiopathic or ischaemic DCM with comparable atrial mechanical overload; (ii) to assess possible different effects of CRT on LA myocardial strain during the 6 month follow-up.

Methods

Study population

From January 2005 to April 2006, 455 ambulatory HF patients with known LV systolic dysfunction were referred to our echocardiographic laboratory. Patients with QRS value of $<$120 ms (n = 92), atrial fibrillation (n = 69), inducible myocardial ischaemia (n = 25), poor echocardiographic window (n = 11) and mildly impaired LV ejection fraction (EF) ($>$40%) (n = 36) were ineligible for our study. Among the remaining 222 patients (120 with idiopathic DCM and 102 with ischaemic DCM), 90 patients were prospectively studied and selected for CRT for severe HF despite optimal pharmacological therapy, and were followed up for at least 6 months after the implantation.

The final study population, therefore, included 90 patients (mean age, 52.4 $\pm$ 10.2 years) with either idiopathic (47 patients) or ischaemic (43 patients) DCM. Inclusion criteria for CRT were: NYHA class III–IV refractory HF, LV end-diastolic diameter value of $>$55 mm, LV EF of $<$35%, QRS interval of $>$120 ms, and sinus rhythm.[1–2] Exclusion criteria were: acute HF, coronary artery by-pass graft surgery, or myocardial infarction within the previous 3 months, valvular stenosis, and previous valve replacement or reconstruction. The study was approved by the local Ethics Committee. All gave their informed consent.

Since 2DSE represents a novel technique with few clinical applications, we also studied LA myocardial function in 25 age- and sex-matched subjects without detectable cardiovascular risk factor. Volunteer controls were all recruited in Naples (Italy), were selected from our departments of Cardiology amongst subjects investigated for work eligibility, and were examined in a single centre (Monaldi Hospital, Naples, Italy). None of the control subjects had cardiovascular structural or functional abnormalities and received any medication.

Implantation technique

Cardiac resynchronization therapy was initiated with implantation of a biventricular pacing system (CONTAK CD H115, CD II H119, RENEWAL H135, or III H170, H175, H177, Guidant Corp; InSync ICD 7272, Marquis 7277, or InSync ICD II Marquis 7289, Medtronic). Three transvenous pacing leads were inserted: one in right atrium and another in the high interventricular septum or in the right ventricular apex. A coronary sinus lead was positioned on the LV free wall through a coronary sinus tributary veins. LV leads were positioned as follows: posterior–lateral or lateral in 72 patients, and anterior or anterior–lateral in 18 patients.

To optimize the benefit from CRT, in the overall population of DCM patients, we performed an echo-guided positioning of the LV pacing lead, determining by use of DMI the site of latest mechanical activation.[3] In addition, among the 43 patients with ischaemic cardiomyopathy, pre-implantation evaluation of myocardial thickness of the region targeted for LV pacing was assessed. As reported by others, we considered the presence of myocardial scar tissue in case of measurement of end-diastolic wall thickness ($\leq$0.6 cm).[23] In particular, end-diastolic wall thickness was assessed at the centre of each myocardial segment from the leading endocardial edge to leading epicardial edge using the echocardiographic window that best identified the endocardial and epicardial borders. In our population, myocardial scar was observed in the anterior/antero-lateral position in 29 ischaemic patients, in the posterior/postero-lateral position in eight patients. In addition, in six ischaemic DCM patients, a normal myocardial thickness ($>$0.6 cm) was observed, and contrast-enhanced cardiac magnetic resonance was used to localize and measure the extent of the myocardial scar. As a consequence, in 27 of 29 patients with anterior/antero-lateral scar, LV lead was implanted in the posterio-lateral position, whereas in six of eight patients with posterior/postero-lateral scar LV lead was implanted in anterio-lateral position. Only in four patients, patient-tailored LV lead positioning was not possible as a result of the limited number of suitable branches of the coronary sinus.

The pacing leads were connected to a dual-chamber biventricular device with programmable inter-ventricular delay. The device was programmed in DDD mode and the atrio-ventricular (AV) delay was adjusted during simultaneous pacing. Optimal AV delay was determined first using Ritter's method[24] followed by optimization of interventricular (VV) delay. According to Ritter *et al.*,[24] the longest filling time without truncation of the A wave was chosen by means of pulsed Doppler analysis of transmitral flow. Readjustment of AV delay was done again after VV optimization. LV pre-excitation of 4–50 ms and right ventricular pre-excitation of 4–40 ms were tested in each patient. Post-optimization mean atrio-ventricular delay was 120 $\pm$ 55 ms, with a wide variability in optimized AV delay intervals (60–180 ms) among the patient cohort, whereas post-optimization mean VV delay was 35 $\pm$ 15 ms.

Study protocol

One week before and 6 months after implantation, all the patients underwent a clinical examination, 12-lead ECG, standard Doppler echo, and two-dimensional strain by Vivid 7 ultrasound system (GE Vingmed Ultrasound). The patients were considered as responders to CRT if LV end-systolic volume decreased by 15% and as non-responders in all other cases.[2]

Standard echocardiography

Standard Doppler echocardiography and 2DSE were performed with the subjects in partial left decubitus. A variable frequency phased-array transducer (2.5–3.5–4.0 MHz) was used for 2DSE and

Doppler imaging. Doppler echocardiographic tracings were recorded on magneto-optical disk. All the measurements were analysed by two experienced readers blinded to the aetiology and responder status of DCM patients, on the average of ≥ 3 cardiac cycles. Stroke volume was obtained by LV outflow Doppler method as the product between outflow tract area and LV output time–velocity integral.[25] LV EF was measured using a commercially available software program that applied modified Simpson's rule on the two- and four-chamber views. Tricuspid annular plane systolic excursion (TAPSE) was calculated as index of right ventricular global systolic function by the difference between end-diastolic and end-systolic measurement (in millimetres). The early (E_a) and late (A_a) diastolic annular velocities were measured at the lateral corner of the mitral annulus by pulsed DMI, in accordance with the method proposed by Nagueh *et al.*[26] Mitral E_a, corrected for the influence of relaxation (i.e. the E/E_a ratio), was calculated to estimate LV filling pressures.

The proximal flow convergence (PFC) technique has been validated as a quantitative Doppler method to calculate regurgitant volume (RV) of flow and orifice area [effective regurgitant orifice (ERO)]. The regurgitant flow is measured as $2\pi r^2 \times Vr$, where r is the radius of the hemispheric PFC region and Vr is the aliasing velocity. The following parameters are calculated: ERO = regurgitant flow/maximal regurgitant velocity, and RV = ERO × RTVI, where RTVI being the regurgitant time–velocity integral. At least three consecutive beats of sinus rhythm were measured and the average value was taken.[27]

According to American Society of Echocardiography guidelines, M-mode measurement of LA diameter was performed in parasternal long-axis view at end-systole, measured at the maximum dimension from the leading edge of the posterior wall of the aorta to the dominant line of posterior wall of LA.[17] LA volumes were obtained as described previously.[17,20–22] In brief, LA volumes were calculated using the biplane area–length method as follows: LA volume = 8 × (LA area in four-chamber view) × (LA area in two-chamber view)/ 3Π (LA length). Left atrial length was defined as the longest line that could be drawn between the posterior LA wall and the mid-portion of the mitral annulus and was similar in the six-chamber views, which are perpendicular to each other. Left atrial maximal volume was measured at the point of mitral valve opening, whereas LA minimal volume was measured at the point of mitral valve closure. Left atrial volume at onset of atrial systole was considered the volume corresponding to the onset of the P wave in the simultaneously recorded ECG. All LA volume values were obtained as the mean of three consecutive beats and were corrected for body surface area. Left atrial systolic (active emptying) function was assessed with the use of the following parameters[17,20–22]:

$$\text{LA active emptying volume} = \text{LA volume at onset of atrial systole} - \text{LA minimal volume} \quad (1)$$

$$\text{LA active emptying fraction} = \frac{\text{LA active emptying volume}}{\text{LA volume at onset of atrial systole}}. \quad (2)$$

Two-dimensional echocardiographic left atrial strain

Two-dimensional strain uses gray scale (B-Mode) sector image and is based on frame by frame tracking of small rectangular image blocks with stable speckle pattern.[16] A minimum frame rate of 30 Hz was required for reliable operation of this program and frame rates of 30–90 Hz were used for routine gray-scale imaging.[13–15] Apical four-chamber view value (the same of the LA volume measurement) was obtained using the same ultrasound system and probe used for standard echocardiography; end-systole was chosen as the single frame for the endocardial to epicardial region of interest to include maximal wall thickness for strain calculation. The 'Zoom/RES' feature on the echocardiographic machine was used to improve the accuracy of atrial measurements. A circular region of interest was traced on the endocardial cavity interface of the apical four-chamber view at the LA systole (minimum cavity area) using point-and-click approach. Then a second larger concentric circle was automatically generated that was near the epicardium with a default width of 15 mm. The region of interest then included the entire LA myocardial wall, and a click feature increased or decreased the width of the two circles for thicker or thinner walls, respectively. The tracking algorithm followed the endocardium from this single frame throughout the cardiac cycle. The image-processing algorithm automatically subdivided the region of interest into blocks of ~20–40 pixels containing stable patterns of speckles. Subsequent frames were then analysed automatically by searching for the new location of each of the blocks with correlation criteria and the sum of the absolute differences. The location shift of these acoustic markers from frame to frame, which represents tissue movement, provides the spatial and temporal data used to calculate velocity vectors. Temporal alterations in this stable speckle patterns are identified as moving further apart or closer together, and a series of regional strain vectors are calculated as change in length/initial length. Accordingly, for atrial longitudinal strain, myocardial thickening was represented with a positive value, colour coded as red; myocardial thinning was represented with a negative value, colour coded as blue; and then these were superimposed to conventional two-dimensional images.[28–30] The software then automatically divided the image into six standard segments and provided an automated tracking score, similar to statistical standard deviation, as feedback of the stability of the regional speckle tracking, ranging from 1.0 to 3.0 in arbitrary units. A tracking score value of <2.5 was determined as acceptable as previously described, and slight adjustments were made to the placement of the region of interest in regions with greater SDs to attempt to improve the tracking stability.[16]

The tracking process and conversion to Lagrangian strains were performed offline using a dedicated software (EchoPAQ PC 2D strain, GE Healthcare, Milwakee). The analysis was performed for atrial longitudinal strain from the four-chamber apical view for the basal segments of LA septum and LA lateral wall, and for LA roof. Atrial radial strain was not calculated from the parasternal short- and long-axis views because the atrial wall is too thin to be properly analysed in these views, as demonstrated by our previous pilot studies.[31–32] Continuous care was taken to keep the sample volume out of the pulmonary veins and of oval fossa.

Statistical methods

All the analyses were performed using a commercially available SPSS software (SPSS, Rel 11.0 2002, Chicago, SPSS Inc.). Variables are presented as mean ± SD. Two-tailed *t*-test for paired and unpaired data, and analysis of variance by Newman–Keuls *post hoc* test for multiple comparisons were used to assess changes between groups. Linear regression analyses and partial correlation test by Pearson's method were performed to assess univariate relations.

To identify significant, independent determinants of LA myocardial strain in patients with DCM, their individual association with clinical relevant and echocardiographic variables was assessed by multivariable Cox regression analysis. The following variables were included into the analysis: clinical data (age, sex, BSA, mean blood pressure, and etiology of HF), standard echocardiographic indexes (LV volumes, LA volumes, Doppler transmitral inflow measurements, mitral valve ERO, and response to CRT). These variables were selected according to their clinical relevance and potential impact on LA function, as shown by earlier studies.[17] Variable selection was performed in the multivariable Cox regression as an interactive stepwise backward elimination method, each time excluding the one variable with the highest *P*-value according to Wald's statistics. The assumption of linearity was checked graphically by studying the smoothed martingale residuals from the null model plotted against the covariate variables.[33] The linearity

assumptions were satisfied. The Hosmer–Lemeshow goodness-of-fit test was used to check that the model adequately fit the data.[34] The model also underwent bootstrap validation (200 runs). To decrease the inflation of the Type 1 error rate because of multiple testing, the statistical significance was defined as two-sided *P*-value of <0.01.

Reproducibility of 2DSE measurements was determined in all the subjects. Inter- and intra-observer variability was determined using both Pearson's bivariate two-tailed correlations and Bland–Altman analysis. Relation coefficients, 95% confidence limits, and percentage errors were reported.

Results

Study population

Clinical features of the 90 patients enrolled in the study are shown in *Table 1*. At the time of CRT system implantation, 72.2% patients were in NYHA functional class III and 27.8% in NYHA class IV. QRS duration ranged from 120 to 220 ms (mean, 134.8 ± 28 ms). The two groups were comparable for most of the clinical variables. However, patients with ischaemic DCM were more frequently smokers and diabetics.

Standard echocardiography at baseline

Left ventricular volumes, EF, stroke volume, as well as mitral valve ERO and right ventricular TAPSE were comparable between the two groups. No significant differences were evidenced in Doppler transmitral inflow measurements and in E/E_a ratio (*Table 2*).

Left atrial dimension and function at baseline

Left atrial diameter and maximal volume were similar between the two groups. Conversely, LA active emptying

Table 1 Demographic and clinical characteristics of the study population ($n = 90$)

Variable	Idiopathic DCM ($n = 47$)	Ischaemic DCM ($n = 43$)	*P*-value
Age (years)	51.3 ± 8.3	53.6 ± 11.3	NS
Male/female	25/22	23/20	NS
Heart rate (b.p.m.)	75.2 ± 12.3	76.1 ± 11.5	NS
Systolic blood pressure (mmHg)	132.2 ± 11.1	131.8 ± 10.2	NS
Diastolic blood pressure (mmHg)	79.4 ± 8.1	77.4 ± 7.8	NS
Body surface area (m^2)	1.85 ± 0.15	1.87 ± 0.14	NS
Diabetes mellitus (%)	30	45	<0.01
Smoking (%)	35	55	<0.01
Systemic hypertension (%)	33	35	NS
Hypercholesterolaemia (%)	52	58	NS
NYHA functional class III/IV	35/12	30/13	NS
ACE-inhibitors (%)	93	95	NS
β-Blockade (%)	82	86	NS
Loop diuretics (%)	96	94	NS
Spironolactone (%)	58	53	NS
Symptoms duration (years)	6.1 ± 3.1	5.9 ± 5.1	NS

DCM, dilated cardiomyopathy; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; NS, not significant.

Table 2 Echocardiographic ventricular and Doppler measurements in the overall study population

Variable	Idiopathic DCM ($n = 47$)	Ischaemic DCM ($n = 43$)	*P*-value
LV end-diastolic volume (mL)	227.7 ± 34.3	219.8 ± 28.2	NS
LV end-systolic volume (mL)	156.6 ± 27.2	149.3 ± 26.4	NS
LV ejection fraction (%)	30.1 ± 4.1	31.1 ± 3.2	NS
LV stroke volume (mL/beat)	67.7 ± 19.2	73.3 ± 18.2	NS
dP/dt (mmHg/s)	628.7 ± 193.5	668.7 ± 173.4	NS
Mitral valve ERO (mm^2)	11 ± 7	12 ± 18	NS
Mitral regurgitant volume (mL)	13.2 ± 12.1	14.4 ± 15.6	NS
Transmitral E wave (cm/s)	61.1 ± 14.3	59.3 ± 12.3	NS
Transmitral A wave (cm/s)	36.1 ± 12.1	34.1 ± 12.1	NS
Transmitral E/A ratio	1.7 ± 1.2	1.8 ± 1.3	NS
Deceleration time (ms)	161.2 ± 33.1	164.3 ± 28.1	NS
IVRT (ms)	67.1 ± 12.4	66.3 ± 11.3	NS
E/E_a ratio	7.6 ± 2.1	8.1 ± 3.1	NS
A_a wave (cm/s)	5.1 ± 2.2	5.8 ± 3.1	NS
TAPSE (cm)	1.8 ± 0.3	1.9 ± 0.3	NS
Tricuspid regurgitation velocity (m/s)	2.2 ± 0.4	2.4 ± 0.5	NS

DCM, dilated cardiomyopathy; LV, left ventricle; ERO, effective regurgitant orifice; IVRT, isovolumic relaxation time; TAPSE, tricuspid annular plane systolic excursion; NS, not significant.

volume and fraction were both lower in patients with idiopathic DCM (*Table 3*).

Overall, atrial speckle tracking was possible in 96.5% of 270 attempted segments from the 90 subjects with technically adequate images, with only 3.5% of segments eliminated with tracking variation scores of >2.5. Overall tracking variation scores were <2.0 in 77% segments.

Peak systolic myocardial atrial strain was significantly compromised in patients with idiopathic DCM compared with ischaemic DCM in all the analysed atrial segments (*Table 3*; *Figures 1* and *2*). Comparing standard echo indexes with 2DSE values, we found a significant linear correlation between LA emptying fraction peak and systolic myocardial atrial strain in LA lateral wall ($r = 0.71$, $P = 0.001$), atrial septum ($r = 0.68$, $P = 0.002$), and LA roof ($r = 0.63$, $P = 0.005$).

Twenty-five age- and sex-matched healthy subjects (15 males; mean age: 52.1 ± 4.2 years), without history of cardiovascular disease, with normal ECG (mean QRS duration, 81 ± 12 ms), and normal EF (mean EF, 67.2 ± 8.1%) were selected as control group for LA myocardial function analysis. The mean values of LA peak systolic strain (in percentage) in the

Table 3 Left atrial standard echo and two-dimensional strain baseline measurements in the overall study population

Variable	Left atrium		
	Controls ($n = 25$)	Ischaemic DCM ($n = 43$)	Idiopathic DCM ($n = 47$)
LA diameter (cm)	3.7 ± 5.2	4.5 ± 0.8[a]	4.6 ± 1.2[b]
LA maximal volume (cm^2/m^2)	27.3 ± 3.1	47 ± 14.3[c]	51.1 ± 12.1[d]
LA active emptying volume (cm^2/m^2)	6.3 ± 2.1	9.1 ± 1.8[a]	8.6 ± 2.5[b]
LA active emptying fraction (%)	28.1 ± 9.2	31.1 ± 9.3	22.4 ± 10.2[d,e]
LA lateral wall strain (%)	59.3 ± 13.8	36.2 ± 19.6[c]	23.5 ± 13.2[d,e]
Atrial septum strain (%)	56.2 ± 14.4	34.2 ± 18.6[c]	22.4 ± 14.2[d,e]
LA roof strain (%)	52.3 ± 14.8	33.8 ± 14.8[c]	21.4 ± 13.2[d,e]

DCM, dilated cardiomyopathy; LA, left atrial.
[a]Ischaemic DCM vs. controls, $P < 0.01$.
[b]Idiopathic DCM vs. controls, $P < 0.01$.
[c]Ischaemic DCM vs. controls, $P < 0.00001$.
[d]Idiopathic DCM vs. controls, $P < 0.00001$.
[e]Idiopathic vs. ischaemic DCM, $P < 0.0001$.

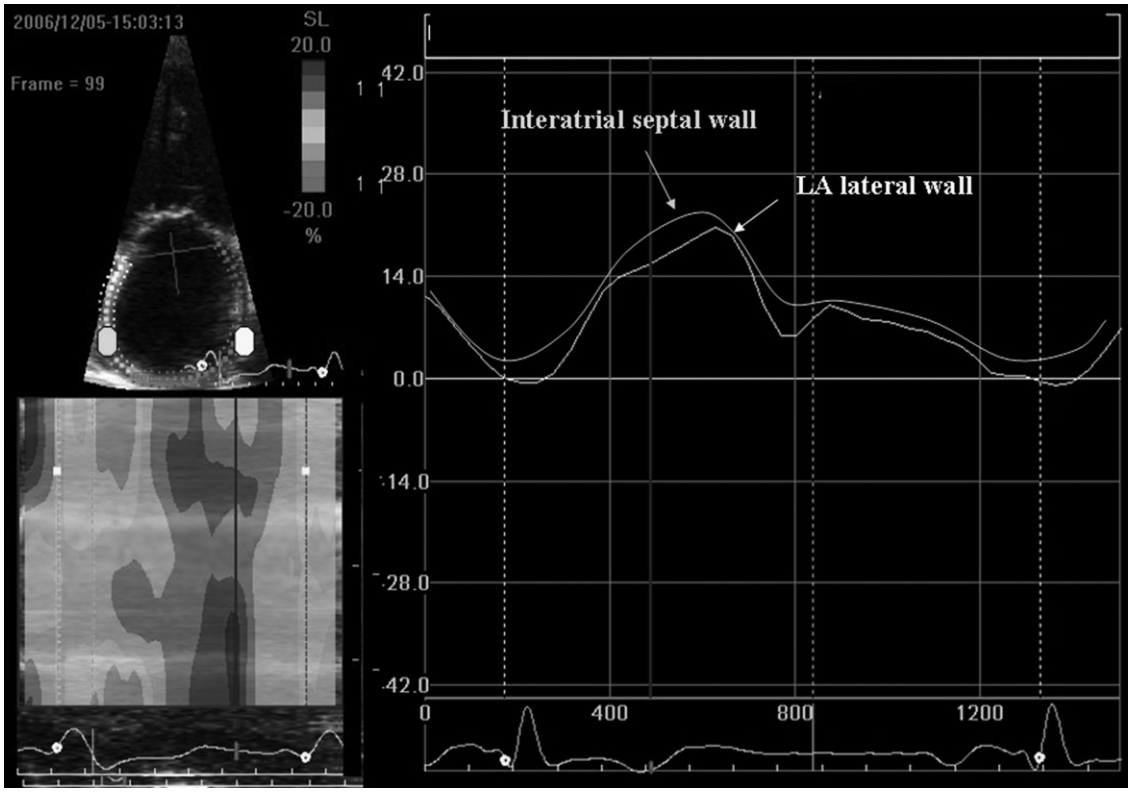

Figure 1 Two-dimensional strain curve of basal left atrial lateral wall and basal interatrial septal wall in a patient with idiopathic dilated cardiomyopathy from an apical four-chamber view. The curve is colour coded by the defined myocardial segment as depicted in the figure (yellow, basal lateral wall; green, interatrial septal wall). Note the severe impairment of LA deformation, with a peak of systolic strain of 19%. See Supplementary material online for a coloured version of this figure.

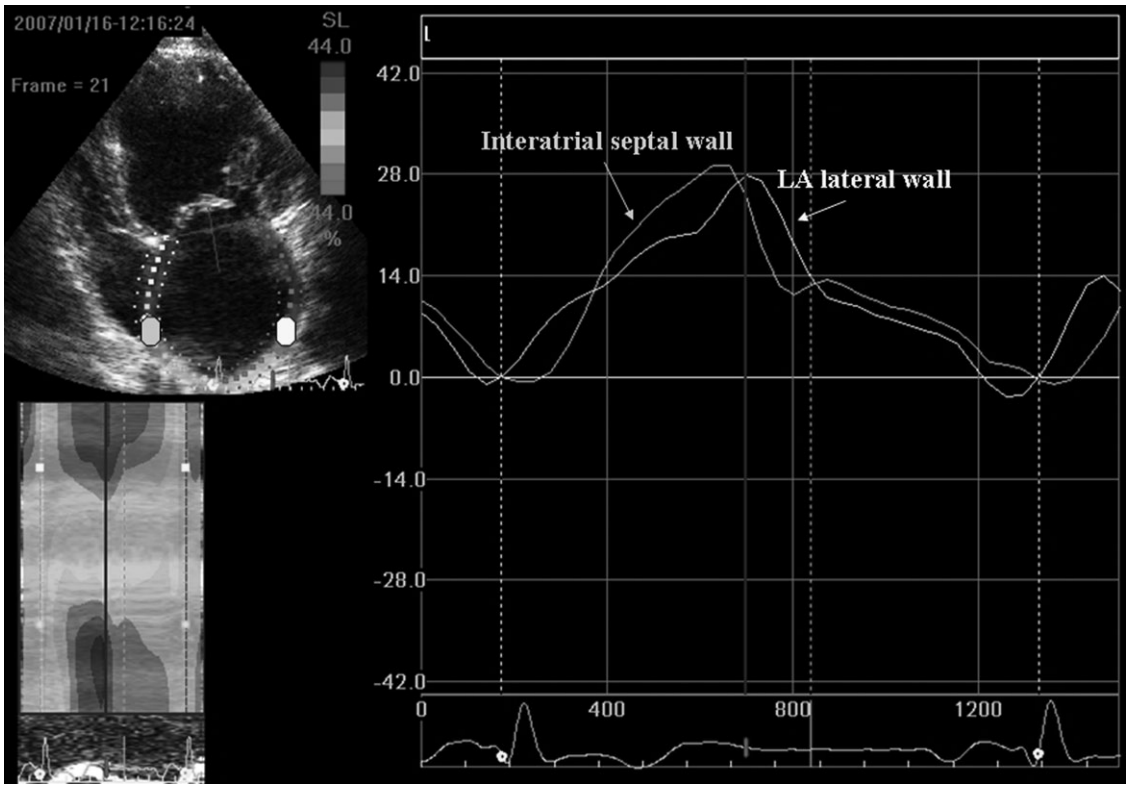

Figure 2 Longitudinal two-dimensional strain curves of basal left atrial lateral wall and basal interatrial septal wall in a patient with ischaemic dilated cardiomyopathy from an apical four-chamber view. The curves are colour coded by the defined myocardial segment as depicted in the figure (yellow, basal lateral wall; gray, basal interatrial septal wall). Note that the impairment of LA deformation is less severe than in the idiopathic patient (peaks of systolic strain of 32% and of 28%, respectively). See Supplementary material online for a coloured version of this figure.

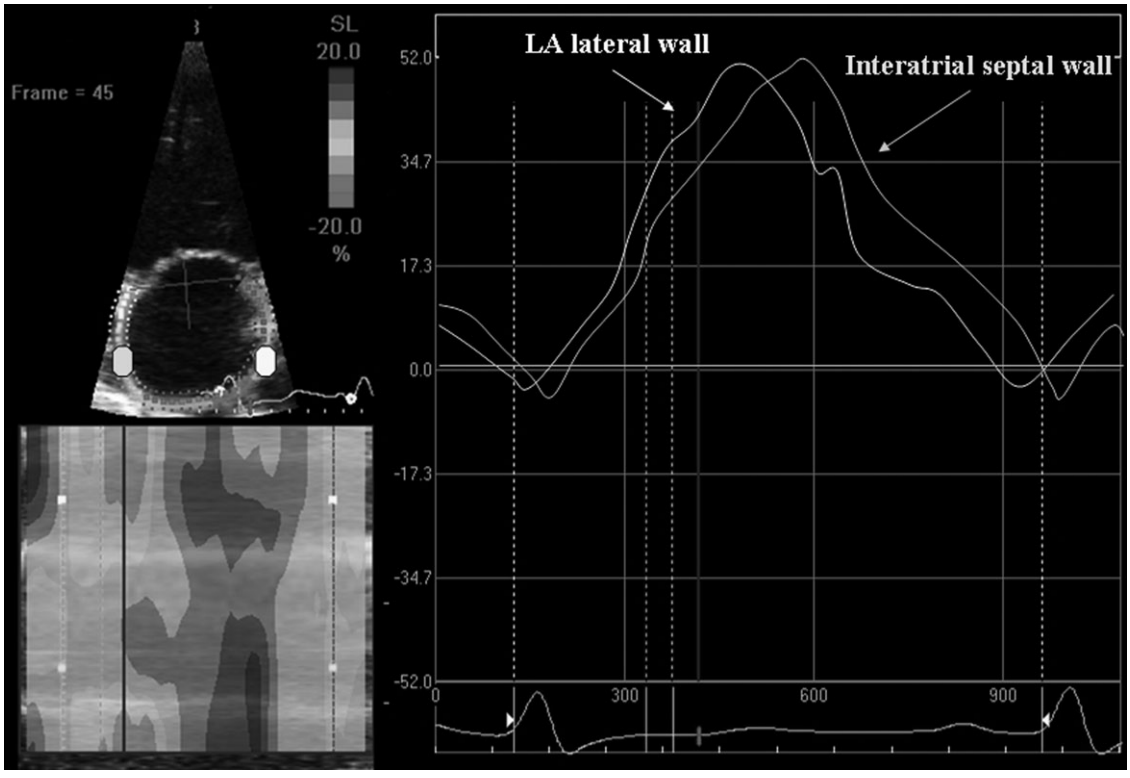

Figure 3 Example of longitudinal two-dimensional strain curve of basal left atrial lateral wall and basal interatrial septal wall in a control subject from an apical four-chamber view. The curve is colour coded by the defined myocardial segment as depicted in the figure (yellow, basal lateral wall; green, interatrial septal wall). Peaks of systolic strain were both >50%. See Supplementary material online for a coloured version of this figure.

control group were significantly higher than those in HF patients in all the analysed atrial segments (*Table 3*; *Figure 3*).

Effects of 6 month cardiac resynchronization therapy

All the patients had echocardiographic studies 6 months after CRT to determine long-term response. When LV end-systolic volume was used as the principal outcome marker for response to CRT, 64 patients (71.1%) (37 with idiopathic DCM and 27 with ischaemic DCM) were long-term responders, and 26 (28.9%) (10 with idiopathic DCM; 16 with ischaemic DCM) were non-responders.

Overall, significant changes in the entire CRT group were observed. A significant increase in LV EF and LV stroke volume was detected; however, mitral regurgitation decreased. In addition, standard and 2DSE indexes of LA systolic function increased. Individual responses, however, were variable.

In particular, among the responders to CRT, patients with ischaemic DCM showed a significant improvement in both LA active emptying volume and fraction, as well as in LA peak systolic strain in all the analysed myocardial segments (*Table 4*). Significant inverse correlation between changes in myocardial LA lateral strain and both changes in mitral valve ERO ($r = -0.58$, $P < 0.001$) and changes in transmitral E/A ratio ($r = -0.52$, $P < 0.005$) were observed. Conversely, in patients with idiopathic DCM, no significant differences were found before and after CRT for both standard and 2DSE indexes of LA systolic function (*Table 4*).

On the other hand, in patients non-responders to CRT, no improvement in LA function was evidenced both in patients with idiopathic and with ischaemic aetiology of DCM (*Table 5*). In addition, no significant correlation was found between changes in LA myocardial strain and changes in either mitral valve ERO ($r = -0.2$, $P = 0.23$) and in transmitral E/A ratio ($r = -0.22$, $P = 0.25$).

By multivariable analysis, after adjusting for potential determinants such as age, heart rate, BSA, mean blood pressure, LV and LA volumes, in the overall population of patients, ischaemic aetiology of DCM (β-coefficient = 0.62; $P < 0.0001$) and positive response to CRT (β-coefficient = 0.48; $P < 0.001$) are emerged as the only

Table 4 Left ventricular and atrial echo and two-dimensional strain measurements in patients responders to cardiac resynchronization therapy at baseline and after 6 month follow-up

Variable	Idiopathic DCM ($n = 37$)			Ischaemic DCM ($n = 27$)		
	Baseline	CRT	*P*-value	Baseline	CRT	*P*-value
LV ejection fraction (%)	31.1 ± 4.1	38.5 ± 5.1	<0.005	30.1 ± 5.2	37.8 ± 4.1	<0.005
LV stroke volume (mL/beat)	69.7 ± 17.2	82.3 ± 19.3	<0.001	71.3 ± 7.2	89.3 ± 9.4	<0.001
Transmitral E/A ratio	1.6 ± 0.9	0.8 ± 0.8	<0.001	1.7 ± 0.9	0.7 ± 1.1	<0.001
Mitral valve ERO (mm^2)	10.3 ± 4	5.1 ± 3.1	<0.001	12.7 ± 5.3	6.1 ± 4.1	<0.001
E/E_a ratio	7.5 ± 2.3	5.6 ± 1.6	<0.01	8.3 ± 2.8	5.8 ± 1.8	<0.001
LA maximal volume (cm^2/m^2)	53.1 ± 11.1	49.3 ± 8.1	NS	46.4 ± 13.3	42 ± 4.4	NS
LA active emptying volume (cm^2/m^2)	9.6 ± 2.5	9.1 ± 3.4	NS	12.1 ± 1.9	15.5 ± 2.2	<0.01
LA active emptying fraction (%)	24.4 ± 8.2	26.3 ± 9.4	NS	33.1 ± 7.3	38.7 ± 7.9	<0.01
LA lateral wall strain (%)	25.5 ± 11.2	27.2 ± 11.3	NS	36.2 ± 16.6	52.4 ± 16.4	<0.001
Atrial septum strain (%)	23.7 ± 15.2	25.4 ± 10.3	NS	33.2 ± 16.6	48.3 ± 15.2	<0.001
LA roof strain (%)	22.4 ± 15.2	23.2 ± 9.3	NS	34.8 ± 13.8	47.4 ± 12.3	<0.001

DCM, dilated cardiomyopathy; LV, left ventricle; LA, left atrial; ERO, effective regurgitant orifice; NS, not significant.

Table 5 Left ventricular and atrial echo and two-dimensional strain measurements in patients non-responders to cardiac resynchronization therapy at baseline and after 6 month follow-up

Variable	Idiopathic DCM ($n = 10$)			Ischaemic DCM ($n = 16$)		
	Baseline	CRT	*P*-value	Baseline	CRT	*P*-value
LV ejection fraction (%)	29.7 ± 6.1	31.5 ± 3.1	NS	31.1 ± 4.2	32.8 ± 3.1	NS
LV stroke volume (mL/beat)	70.8 ± 13.2	74.6 ± 15-2	NS	73.2 ± 7.2	75.2 ± 8.4	NS
Transmitral E/A ratio	1.8 ± 1.1	1.5 ± 0.8	<0.05	1.7 ± 0.9	1.4 ± 1.1	<0.05
Mitral valve ERO (mm^2)	11.3 ± 4	8.5 ± 4.1	<0.05	11.9 ± 5.3	8.2 ± 2.1	<0.05
E/E_a ratio	7.7 ± 2.2	6.5 ± 1.8	<0.05	8.1 ± 3.2	6.8 ± 1.8	<0.01
LA maximal volume (cm^2/m^2)	50.1 ± 10.1	48.3 ± 8.1	NS	48.4 ± 11.3	46 ± 4.4	NS
LA active emptying volume (cm^2/m^2)	7.9 ± 2.5	8.1 ± 3.4	NS	10.1 ± 1.7	11.5 ± 2.2	NS
LA active emptying fraction (%)	23.3 ± 7.2	25.3 ± 9.4	NS	32.1 ± 6.3	33.7 ± 7.9	NS
LA lateral wall strain (%)	23.6 ± 9.2	26.5 ± 10.3	NS	35.6 ± 15.5	38.4 ± 13.4	NS
Atrial septum strain (%)	21.6 ± 12.2	23.6 ± 9.4	NS	33.2 ± 13.4	34.3 ± 15.2	NS
LA roof strain (%)	21.9 ± 11.2	23.4 ± 9.2	NS	32.8 ± 11.6	33.4 ± 10.3	NS

DCM, dilated cardiomyopathy; LV, left ventricle; LA, left atrial; ERO, effective regurgitant orifice; NS, not significant.

independent determinants of LA lateral wall systolic strain after CRT.

Reproducibility of speckle-tracking two-dimensional strain echocardiography left atrial strain

Intra-observer variability

Pearson's correlations—lateral wall: $r = 0.87$, $P < 0.00001$; atrial septum: $r = 0.88$, $P < 0.00001$; atrial roof: $r = 0.85$, $P < 0.00001$.

Bland–Altman analysis—lateral wall (95% CI ± 1.8; percent error 3.3%); atrial septum (95% CI ± 1.2; percent error 3.1%); atrial roof (95% CI ± 1.6; percent error 3.2%).

Inter-observer variability

Pearson's correlations—lateral wall: $r = 0.85$; $P < 0.00001$; atrial septum: $r = 0.86$; $P < 0.00001$; atrial roof: $r = 0.84$; $P < 0.00001$.

Bland–Altman analysis—lateral wall (95% CI $\pm$ 1.9; percent error 3.4%), atrial septum (95% CI ± 1.5; percent error 3.5%), atrial roof (95% CI ± 1.7; percent error 3.6%).

Discussion

The results of the present study demonstrate the usefulness of 2DSE in analysing LA myocardial function in patients with either idiopathic or ischaemic DCM undergoing CRT.

The main findings of our study are: (i) 2DSE detected at baseline more impaired LA systolic function in patients with idiopathic compared with ischaemic DCM; (ii) a significant improvement in LA systolic function was obtained only in patients with ischaemic DCM responders to CRT; (iii) ischaemic aetiology of DCM and positive response to CRT were powerful independent determinants of LA myocardial function after CRT.

The advantages and perspectives of speckle-tracking two-dimensional strain echocardiography in the study of left atrial function

Previous reports have documented that echocardiography with its new applications such as DMI and strain imaging may represent useful techniques to better select candidate to CRT.[3,8–12]

In particular, myocardial strain is a dimensionless index of change in myocardial length in response to an applied force, and is expressed as fractional or percent change. This technique has a theoretic advantage over DMI in that it is relatively immune to cardiac translational motion and tethering allowing differentiation between active systolic contraction and passive motion.[10] In a previous report, we have documented for the first time the feasibility of Doppler strain in analysing myocardial deformation properties of both atria during recent-onset lone atrial fibrillation, and atrial myocardial strain measurements as predictive of sinus rhythm maintenance.[31]

However, in patients with DCM and large and spherical atria and ventricles, Doppler strain estimation with its angle dependency represents an important limitation as a result of poor alignment between Doppler beam and myocardial wall.[10] Conversely, in our study, we used 2DSE, a novel approach to quantify regional myocardial deformation within a scan plane that is inherently two-dimensional and independent of interrogation angle as it tracks speckle patterns (acoustic markers) within serial B-Mode sector scans.[28–30] A recent study in patients with DCM has demonstrated that asynchrony indexes derived from the novel speckle-tracking radial 2DSE predict response to CRT.[16] To the best of our knowledge, the present paper is the first report analysing the LA function in patients with DCM at baseline and after CRT using speckle-tracking 2DSE.

Left atrial function in idiopathic vs. ischaemic dilated cardiomyopathy

Normal LA function consists of three components. Left atrium is: (i) a contractile chamber (booster pump) that actively empties immediately before the end of LV diastole and establishes final LV end-diastolic volume; (ii) a reservoir that stores pulmonary venous return during LV systole and isovolumic relaxation after the closure and before the opening of the mitral valve; (iii) a conduit that empties its contents into the LV down a pressure gradient after the mitral valve opens and during LV diastole.[17]

The LA is therefore exposed during ventricular diastole to the pressures of the LV. With increased stiffness or noncompliance of the LV, LA pressure rises to maintain adequate LV filling, and the increased atrial wall tension leads to chamber dilatation and stretch of the atrial myocardium.[17] As a result, early in HF, LA pump function is augmented but LA stiffness increases and work mismatch occurs. With further progression of LV dysfunction, LA pump function decreases as a result of increased afterload imposed on the LA myocardium. However, in idiopathic DCM, although loading conditions are same, a more depressed LA booster pump function at rest has been observed compared with ischaemic patients, and attributed both to altered LA overload and to LA larger involvement in the myopathic process.[20–22,35]

Several authors have recently demonstrated that LA peak systolic myocardial atrial strain, which is LA passive stretching during LV systole, could be used as an index of LA reservoir function.[31–32,36–39]

In our study protocol, both LA booster pump function (i.e. LA active emptying fraction) and LA passive deformation indexes (i.e. peak systolic myocardial atrial strain) in patients with DCM were significantly more impaired in patients with idiopathic DCM compared with patients with ischaemic DCM in all the analysed atrial segments.

Since heart rate, LA volumes, transmitral flow velocity profile, LV isovolumic relaxation time, LV stroke volume, and mitral valve ERO in our population were similar in the two cardiomyopathy groups, it is unlikely that the differences between the two groups were only due to differences in LA loading conditions. Therefore, it is reasonable to assume that in addition to LV diastolic dysfunction, depressed LA contractility and deformation resulting from LA involvement in the myopathic process might have contributed to the LA myocardial dysfunction in our patients with idiopathic DCM. This hypothesis is further supported by previous studies demonstrating: (i) higher degree of LA fibrotic change in autopsied heart of patients with idiopathic DCM compared with patients with old myocardial infarction[35]; (ii) more impaired LA function in patients with idiopathic DCM than in those with LV dysfunction caused by valvular abnormalities, despite comparable mechanical loads[40]; (iii) reduced LA pump function in idiopathic vs.

ischaemic DCM despite a similar LA size and tension at onset of LA systole[20]; (iv) after dobutamine infusion, absence of significant changes in the LA active emptying fraction in idiopathic DCM, in contrast to significant increase in these indexes in ischaemic DCM.[21–22]

Left atrial myocardial function after 6 month cardiac resynchronization therapy

Few reports have previously investigated the long-term effect of CRT on LA volumes and function by standard echocardiography. In a first study by Vural *et al.*[41] in 20 patients with DCM (13 idiopathic/seven ischaemic), CRT resulted in atrial reverse remodelling (reduced both maximal and minimal volume), increase in LA total emptying fraction, and reduction in both frequency and intensity of LA spontaneous echo contrast. In a subsequent study of the same group by transoesophageal echocardiography, in 18 patients (10 idiopathic/eight ischaemic), treatment of HF by CRT resulted with marked improvements in LA appendage function and increases pulmonary venous systolic velocity.[42]

In our study, a significant improvement in LA myocardial function after CRT was obtained only in patients with ischaemic DCM responders to CRT. Such reversible LA dysfunction in ischaemic patients may further confirm that the initial LA dysfunction was mainly because of LA afterload mismatch rather than intrinsic LA disease. In fact, in our patients, changes in lateral LA strain were strongly associated with changes in mitral valve ERO and in Doppler transmitral A wave after CRT. Therefore, in these patients, enhanced LA electromechanical function after CRT may result in improved LV filling, contribute to the haemodynamic improvement observed with CRT, and also has implications for reduction in the propensity for atrial fibrillation.[17]

Conversely, in idiopathic DCM, our findings detected a reduced LA systolic reserve as well as an irreversible impairment of LA deformation even after improvement of loading conditions during CRT. The lack of association between changes in LA strain and improvement in diastolic measurements may confirm the presence in idiopathic DCM patients of a larger involvement of LA structure and function in the myopathic process.[35] Since in congestive HF the loss of LA contribution to LV filling adversely affects prognosis, and a recent report has used LA strain analysis for demonstrating beneficial effects of renin–angiotensin system inhibitors on LA reservoir function,[39] our results may have important clinical implications on the evaluation long-term effects of pharmacological therapy and of CRT in patients with DCM.

Study limitations

Our study has several limitations. First, even though the biplane area–length method is a better way to assess LA dimensions compared with the M-mode evaluation,[17] it is necessary to underline that the volumes obtained with this method are estimations derived from two-dimensional datasets, and not true measurements of a three-dimensional structure.

Atrial strain is influenced by loading conditions; thus, the comparisons of atrial deformation properties between idiopathic and ischaemic patients may have been influenced by preload and by different atrial wall stress.[10] However, even though our study protocol did not include any invasive haemodynamic measurement, our patients with DCM presented similar mean heart rates, LA and LV volumes, and Doppler indexes of global diastolic function. As a result, this confounding factor should not detract from the value of atrial strain analysis.

A technical limitation is that speckle-tracking 2DSE is dependent on frame rate as well as image resolution. Low frame rate results in the speckle pattern changing too much from frame to frame, which prevents the precise characterization of regional myocardial motion and impacts the overall temporal resolution of the regional strain map. In contrast, increase in the frame rate reduces the scan line density, thereby reducing the image resolution.[28–30] Frame rate in our setting ranged from 35 to 90 frame/s; this value is lower than frame rate available with Doppler strain, however indexes of LA function used in this study did not rely on difference in the timing of contraction.

As previously specified, this is the first report analysing LA function in patients with DCM using speckle-tracking 2DSE. In particular, we used EchoPAC PC program (GE Healthcare) for two-dimensional strain analysis. Since a definite 2DSE software for LA two-dimensional strain has not yet been provided, we applied a program of 2DSE for LV to analyse also LA strain. The feasibility and the reproducibility of LA strain patterns and measurements were good. However, in future studies, changes in the software may be needed in order to improve the tracking ability of the speckle-tracking system for LA functional study.

Our analysis was limited by data collection from the apical four-chamber view as this was the only image plane that provided reliable information on longitudinal atrial deformation in a sufficient numbers of patients. It would be desirable to obtain information on left atrial deformation from the complete atrial cavity. However, in the present study, atrial radial strain was not calculated from the parasternal short- and long-axis views because the atrial wall is too thin to be properly analysed in these views, as demonstrated by our previous studies.[31–32]

In our patients with ischaemic DCM, end-diastolic myocardial thickness of the region targeted for LV pacing was measured by standard echocardiography. This is a rude but simple and largely available method to detect myocardial scar tissue in ischaemic patients, as previously showed by Cwajg JM *et al.*,[23] who reported that end-diastolic wall thickness can predict in patients with suspected myocardial hibernation recovery of function similar to T1-201 scintigraphy. Recent reports have documented that delayed contrast-enhanced magnetic resonance imaging, positron emission tomography, and gated SPECT are highly effective and more quantitative methods to define myocardial viability.[43–45] However, in our study, we limited the use of contrast-enhanced cardiac magnetic resonance imaging to patients with ischaemic DCM and normal myocardial thickness. Although these techniques may serve as 'gold standard', high costs and limited availability reduce their routine use in our country in selecting candidates for CRT.

Conclusions

This study demonstrates for the first time that a novel speckle-tracking algorithm applied to routine gray-scale two-dimensional images represents a promising and feasible non-invasive and easy-repeatable technique to assess LA

atrial myocardial function in patients with DCM. Left atrial pump function and passive deformation both at baseline and after CRT are more impaired in idiopathic compared with ischaemic DCM. Since LA enlargement has been proposed as a barometer of diastolic burden and a predictor of common cardiovascular outcomes such as atrial fibrillation, stroke, and cardiovascular death,[17] future longitudinal studies are warranted to understand further the natural history of LA myocardial function, the extent of reversibility of LA dysfunction with medical therapy and/or CRT, and the possible long-term impact of such changes on outcomes in patients with congestive HF.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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