

# Real-time three-dimensional speckle tracking echocardiography: a novel technique to quantify global left ventricular mechanical dyssynchrony

Christophe Thebault<sup>1,2</sup>, Erwan Donal<sup>1,2\*</sup>, Anne Bernard<sup>3</sup>, Olivier Moreau<sup>1,2</sup>, Frederic Schnell<sup>1,2</sup>, Philippe Mabo<sup>1,2</sup>, and Christophe Leclercq<sup>1,2</sup>

<sup>1</sup>Cardiologie & INSERM, CIC-IT 804, Rennes F-35000, France; <sup>2</sup>INSERM U642, Centre Hospitalier Universitaire Pontchaillou, Rennes, France; and <sup>3</sup>Cardiologie, CHU Tours, Tours, France

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## Aims

Left ventricular (LV) mechanical dyssynchrony (LVMD) has emerged as a therapeutic target using cardiac resynchronization therapy (CRT) in chronic heart failure patients. Current methods used to evaluate LVMD are technically challenging and do not assess all the components of LVMD simultaneously. We analysed real-time 3D speckle tracking (3DST) echocardiography as a novel method to assess LVMD.

## Methods and results

Three-dimensional ST was performed in 60 unselected patients ( $71 \pm 9$  years old; 39% with ischaemic cardiomyopathy) who were referred to optimize and to control of a CRT device; implanted according to current guidelines (9 added to be excluded from the protocol). Two standardized conditions [right ventricular (RV) versus an optimized biventricular (BiV) pacing modality] were tested. These two pacing modalities lead to two distinct electrical activation patterns. We sought to test the capability of 3DST to distinguish these two patterns. The LV ejection fraction was  $24 \pm 9$  in the RV mode and  $29 \pm 10\%$  in BiV. By 3DST, we measured global end-systolic LV deformation and dyssynchrony (standard deviation of the time to peak/16 LV-segment). The 3D radial strain increased from  $13.8 \pm 5.7$  in the RV to  $15.9 \pm 6.5\%$  in the BiV mode, and the dyssynchrony index decreased from  $15.1 \pm 5.0$  to  $11.8 \pm 4.1\%$ . 3D longitudinal strain increased from  $-6.9 \pm 2.8$  in the RV to  $-7.8 \pm 3.2\%$  in the BiV mode, and the dyssynchrony index decreased from  $14.2 \pm 4.8$  to  $11.5 \pm 5.0\%$  ( $P < 0.01$  for all). The 3D area strain (AS) increased from  $-15.4 \pm 6$  in the RV to  $-18.3 \pm 7.0\%$  in the BiV mode, and the dyssynchrony index decreased from  $12.2 \pm 5.1$  to  $9.5 \pm 4.5\%$  ( $P < 0.001$  for all).

## Conclusion

When image quality is optimal, 3DST might offer a new rapid method to quantify global LVMD in CRT candidates. In a comparison of the utility of various 3D strain measurements, the 3D AS appears to be closed to the ideal parameter that we are looking for.

## Keywords

Three-dimensional speckle tracking imaging • Dyssynchrony • Heart failure

## Introduction

Heart failure remains a complex clinical syndrome. While optimal medical therapy improves survival, biventricular pacing (CRT) has been established as an effective adjuvant treatment for patients with moderate-to-severe systolic heart failure and wide QRS.<sup>1</sup> However, 20–30% of the patients who meet the criteria for CRT implantation do not experience any improvement in symptoms.<sup>2</sup> While the precise mechanisms responsible for the benefits from CRT are not fully understood, the reduction of ventricular

dyssynchrony following biventricular (BiV) pacing has been shown to produce favourable acute haemodynamic and neurohormonal changes as well as ventricular remodelling with concomitant symptomatic improvement.<sup>2</sup>

Consequently, imaging-based methods for the assessment of dyssynchronous myocardial contraction have been intensively investigated with the ultimate goal of predicting response to CRT.<sup>3</sup> The ideal parameter or index for the selection of patients for CRT should be simple and practical, and it should not require an elaborate off-line analysis with poor reproducibility.<sup>4</sup>

Several echocardiographic parameters of dyssynchrony have been proposed based on results from small, single-centre studies, but in a large multi-centre study these parameters had a modest predictive value and a large intra-observer and inter-observer variation ranging from 10 to over 30%.<sup>5</sup>

Real-time three-dimensional echocardiography (3D), coupled with a speckle tracking (ST) capability to assess deformations, is a novel approach that might become a powerful method for the assessment of dyssynchrony.<sup>6</sup> In the study, we sought to test the capability of the very new 3D speckle tracking (3DST) echocardiographic technique to distinguish acutely two different left ventricular (LV) pacing modalities. We looked for the different component of the LV regional 3D deformation and their alteration by this acute change in LV electrical activation. One of the parameters that we especially sought to evaluate is the 'area strain' (AS), a potentially useful index combining different components of LV myocardial deformation and LV mechanical dyssynchrony.

## Methods

### Study population and protocol

The study population consisted of 60 consecutive heart failure patients implanted with a CRT device; referred to our University Hospital for a scheduled visit from January to May 2009. An informed consent was obtained for every patient.

Exclusion criteria were the presence of a bad acoustic window ( $n = 4$ ) or atrial fibrillation ( $n = 5$ ). A total of 51 patients were finally included in the statistical analysis.

Clinical variables including age, gender, QRS duration, clinical status, CRT-related duration of implantation, and CHF aetiology were recorded from each patient's medical file.

All patients were examined lying on their left side, and the CRT device was alternatively programmed for a BiV or right ventricular (RV) pacing mode at the same heart beat. Echocardiographic setting was done 3 min following the new pacing mode.

All these patients were paced according to the usual practice of our group. The RV lead tip position was targeted as the inter-ventricular septum. The LV lead was implanted according to the coronary sinus anatomy but always trying to get the shortest QRS duration at the end of the procedure.<sup>7</sup> The quality of the BiV stimulation was checked by the QRS duration and morphology.

The study was performed in accordance with the ethics rules (observational study in patients scheduled for echocardiography and having provided informed consent) of our institution.

### Real-time three-dimensional echocardiography

Patients were imaged with a commercially available system (Artida, Toshiba Medical Systems, Tokyo, Japan) by means of a 3D transthoracic probe (PST-25SX 1 to 4 MHz phased array matrix transducer), using the same protocol and performed by an experienced echocardiographer (C.T.).

Five apical full-volume data sets were recorded within one breath-hold, combining four real-time sub-volumes during four cardiac cycles. The mean frame rate was 20 volumes/s.

Three-dimensional data sets were stored in raw data format for off-line analysis and exported to the UltraExtend workstation (Toshiba Medical Systems) using a semi-automated contour-tracing algorithm.<sup>8,9</sup>

### LV borders (endocardial and epicardial) setting

Each 3D data set was displayed in a five-plane view: (i) an apical four-chamber view; (ii) a second apical view orthogonal to plane A; and (iii) three short-axis planes: plane C1 in the apical region, plane C2 in the mid-ventricle, and plane C3 at the basal portion of the left ventricle.

In the A plane, three reference points are set by the user: two at the base of the LV at the mitral valve level and one at the apex. The same three points are fixed on plane B. The epicardial border can be entered manually or by setting a default 'thickness' for the myocardium. After detection of the myocardium borders at the end-diastolic reference frame, the user can correct the shape of the LV reference at the starting image.

The 3D wall motion tracking is then automatically performed through the entire cardiac cycle, making LV volumes and left ventricular ejection fraction (LVEF) calculation easy and robust (no assumption on the LV shape).

At that time, the investigator can appreciate the quality of the images and loops. The quality of their tracking was controlled and if the border detection was incorrect or if  $\geq 3$  segments were not adequately seen, then the acquisition could not be used for the study. The quality of the tracking could be estimated from the whole LV volume.

### Strain measurements

The same process is applied for all directional strain measurements: longitudinal strain (LS), circumferential strain (CS), and radial strain (RS).

A strain parameter using 3D wall motion tracking was recently developed by the Toshiba Company, and named the AS. AS is based on interface (endocardium or epicardium) tracking, reflecting the deformation of a box during contraction and relaxation. The area is the product of length and width. Thus, AS can be considered a combination of the total vector resultant based on radial, circumferential, and longitudinal vectors. Conversely, the RS has only the radial vector (perpendicular to the endocardium) (Figure 1).

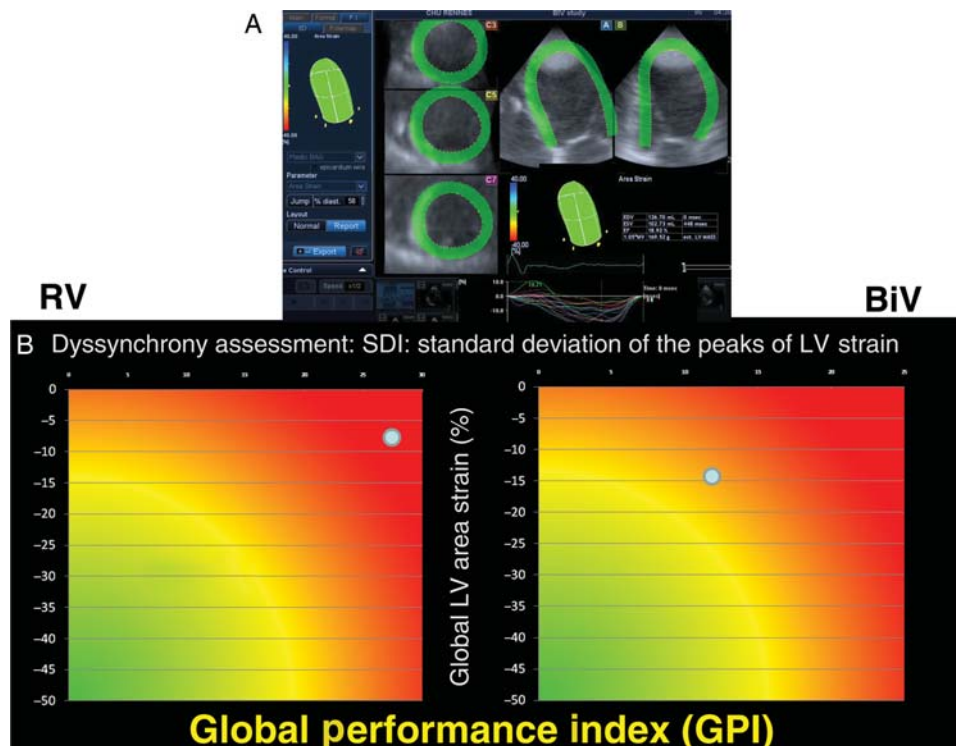
The software analysis is semi-automatic and is able to display all the components of the ST analysis. Radial components are related to an axis perpendicular to the endocardium at that specific sample position. Longitudinal vectors are perpendicular to the radial direction.

All these myocardial deformation parameters were exported as text-files for further statistical analysis on Excel (Microsoft Office 2007).

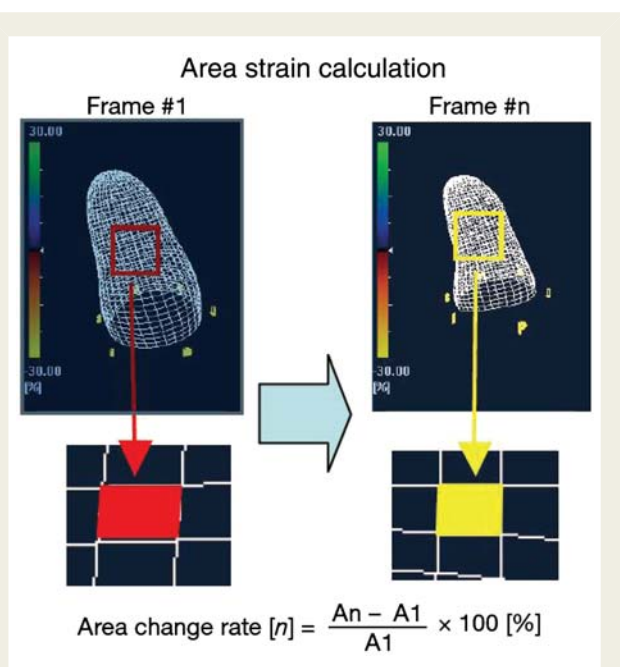
### LV dyssynchrony assessment

The standard 16-segment model of the LV anatomy was used. Considering the longitudinal and the circumferential one direction strain, the time to first negative peak (Min 1) was considered. The time to first positive peak (Max 1) was looked for in each segment for the radial component of LV deformations. That was done for each segment in every direction. The LV dyssynchrony was evaluated by the standard deviation of the Min 1 (or Max 1 for the radial component) for 16 segments related to the heart cycle, defining the standard deviation index (SDI) as described by Kapetanakis *et al.*<sup>6</sup> for each of the components of the LV regional volume changes, instead of the regional deformation that we looked for.

A graphical tool can be used. It consists of plotting the global LV AS peak value and the SDI of this combined strain on the same graph. This 'global performance index (GPI)' provides multi-parametric information made of multi-directional strain (area strain = longitudinal + circumferential) and a dyssynchrony index (SDI) (Figures 2 and 3).



**Figure 1** (A) Example of a 3D speckle tracking image provided by the echo-machine (the 3D shape of the left ventricle with a semi-automatic tracing of the endocardial and epicardial borders and a colour map of the regional deformation is displayed as well as the regional curves of deformation). (B) Example of the parametric image generated from the echo-machine displaying the global performance index in the same patient in biventricular (ON) and in single right ventricular pacing (OFF) configurations. The blue circle represents the position of the patient on the graph according to the modality of stimulation. It is much better in ON than in OFF (right ventricle only) (x-axis: standard deviation of the time to peaks of deformation; y-axis: average deformation of the 17 segments of the left ventricle).



**Figure 2** Representation of the approach used to measure the area strain.

### Reproducibility

Intra- and inter-observer reproducibility were assessed by calculating the difference between the values of 20 randomly selected patients measured by one observer twice and by a second observer. Furthermore, Bland and Altman graphs<sup>10</sup> were shown in Figure 3.

### Statistical analysis

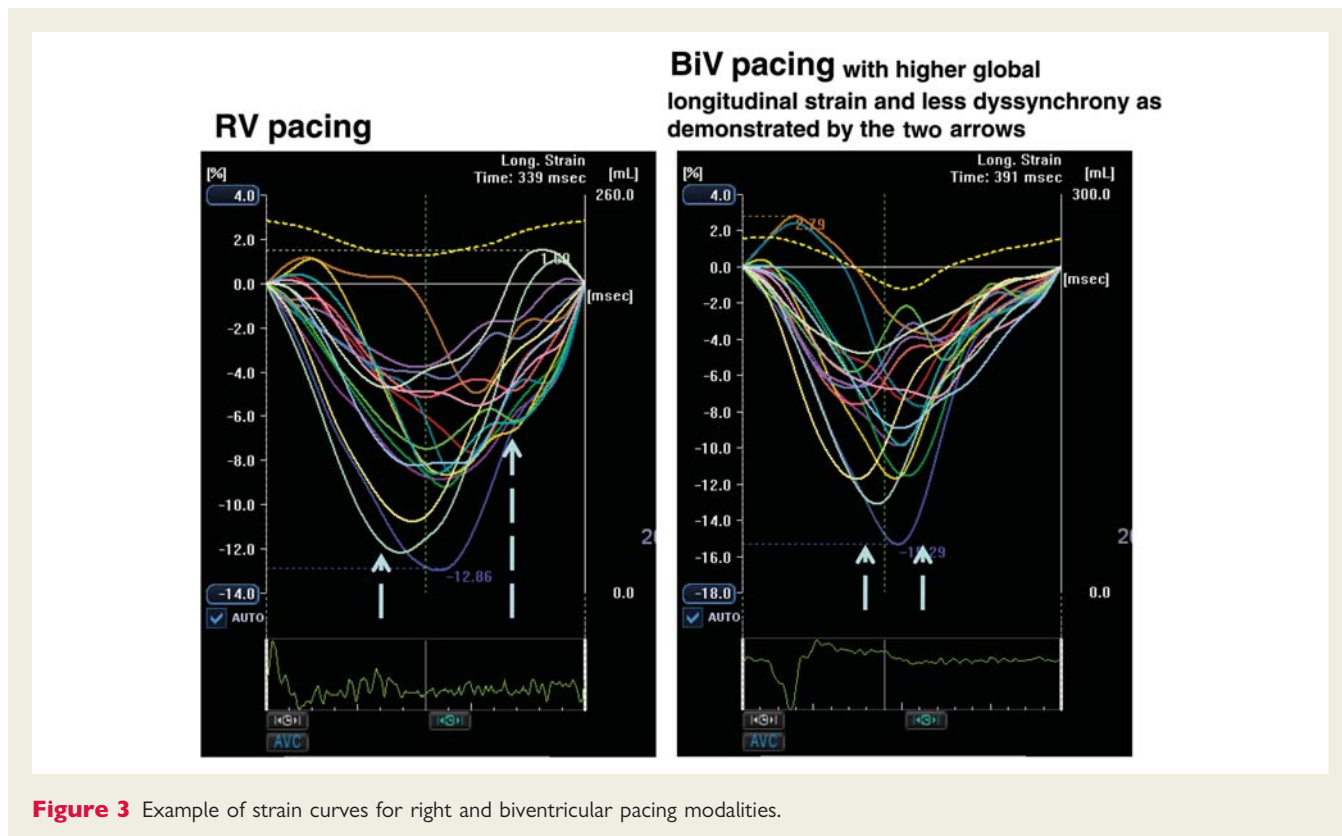
Continuous variables are expressed as the mean ± standard deviation. Nominal variables are expressed as percentages. BiV pacing and RV pacing data were compared using the Wilcoxon test. The data were analysed by Statistica software, version 8 (Statsoft, Tulsa, OK, USA). A value of  $P \leq 0.05$  was considered significant.

## Results

### Study population

A total of four patients were excluded from the analysis because of the image quality altering the ability of the software to correctly track at least 15/17 myocardial LV segments (feasibility 85%). Baseline characteristics of the remaining 51 patients are summarized in Table 1. The mean patient age was  $71 \pm 9$  years, 78% were male and 39% presented with ischaemic cardiomyopathy.

Most of the patients were in NYHA Class III upon inclusion. The mean QRS recorded at the time of the visit was  $146.7 \pm 18.8$  ms



**Figure 3** Example of strain curves for right and biventricular pacing modalities.

(BiV-pacing QRS duration shorter than the RV-pacing one,  $P < 0.05$ ) and the mean LVEF was  $29 \pm 10\%$ .

### LV volumes and LVEF measurements

A significant decrease in the LVESV in the BiV pacing mode ( $170 \pm 68$  mL in BiV versus  $181 \pm 73$  mL in RV,  $P < 0.01$ ) coupled with a non-significant change in the left ventricular end-diastolic diameter between the BiV and RV pacing ( $234 \pm 77$  versus  $233 \pm 77$  mL,  $P = \text{NS}$ ) resulted in a significant increase in the LVEF in the BiV mode ( $29 \pm 10$  versus  $24 \pm 9\%$ ,  $P < 0.0001$ ).

### Comparative strain measurements

Global LS, RS, CS, and AS during BiV and RV pacing are presented in Figures 4 and 5.

As expected, global LS, RS, AS, and CS are markedly improved when the patient is placed on the optimal BiV pacing mode. RS improved from  $13.0 \pm 5.7$  to  $15.9 \pm 6.5\%$  ( $P < 0.05$ ), CS improved from  $-8.9 \pm 3.8$  to  $-11.2 \pm 4.8\%$  ( $P < 0.001$ ), LS improved from  $-6.9 \pm 2.8$  to  $-7.8 \pm 3.2\%$  ( $P < 0.001$ ), and AS improved from  $-15.4 \pm 6$  to  $-18.3 \pm 7\%$  ( $P < 0.001$ ).

### LV dyssynchrony according to each directional deformation parameter

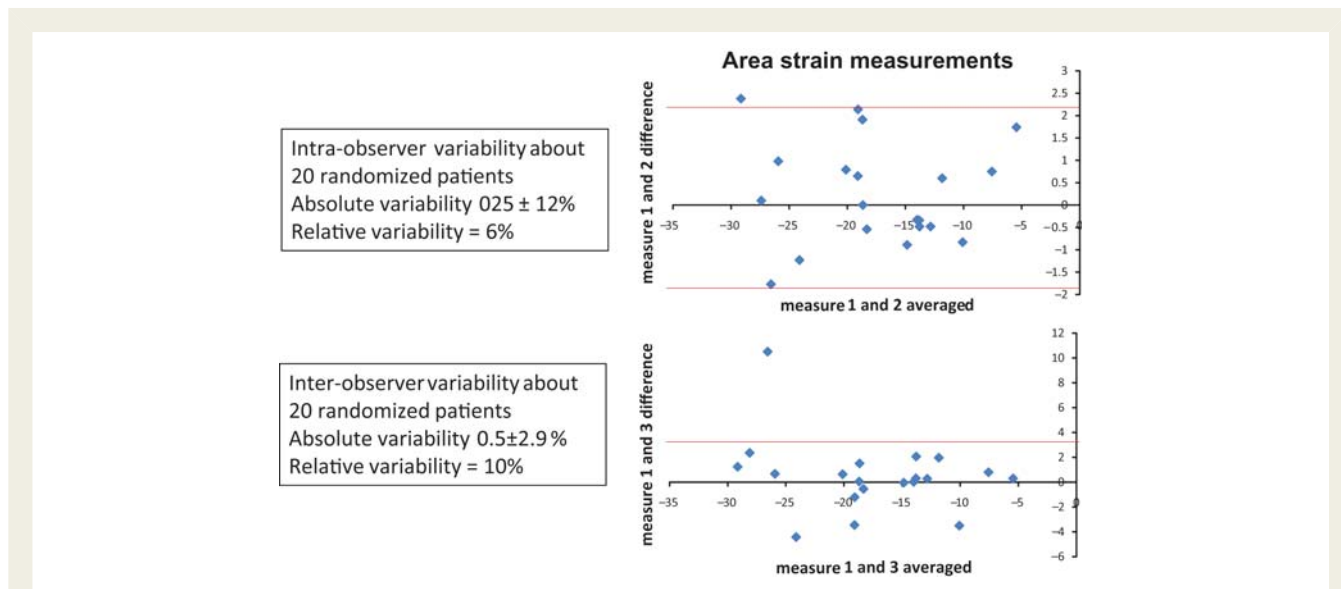
The SDI derived from the 16-segment strain curves was calculated from each 'directional' strain exploring a 3D deformation parameter, such as longitudinal or circumferential, reflecting the dimensional mechanical dyssynchrony.

**Table 1** Characteristics of the studied population of 51 patients

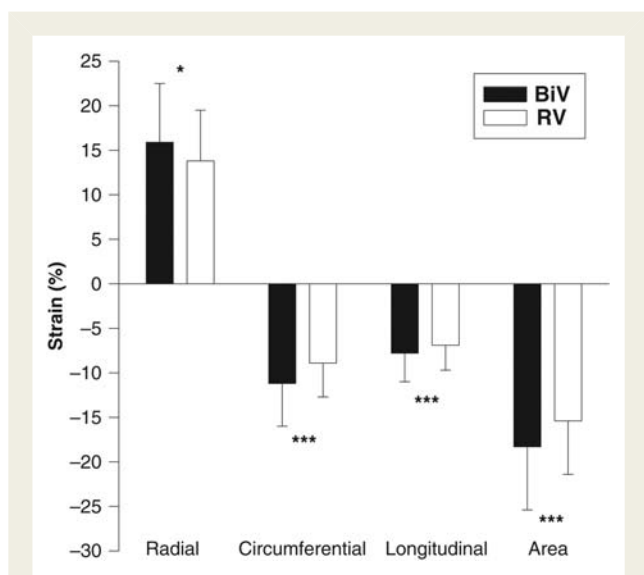
Variable	Mean	Standard deviation
Age (years)	71.2	9.9
Mean (%)	78.4	
Heart rate (bpm)	71.7	12.1
NYHA	2.9	0.6
LVEF (%) at implantation	24.9	5.5
LVEDD (mm) at implantation	67.3	9.6
Ischaemic cardiomyopathy (%)	39	
QRS width BiV OFF (ms)	163.7	28.8
QRS width BiV ON (ms)	146.7	18.8
Length time of CRT device (days)	744.9	650

LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; BiV, biventricular pacing; CRT, cardiac resynchronization therapy.

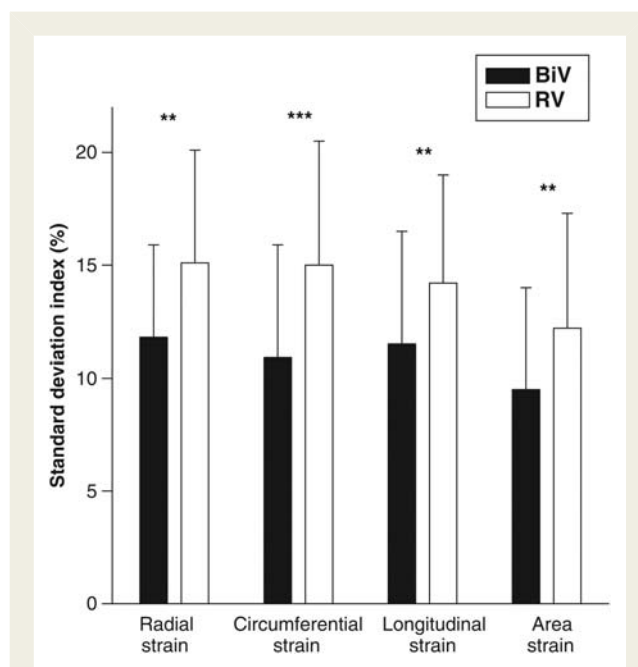
During optimal BiV pacing, the SDI was significantly lower when compared with the RV pacing in all strain components, as shown in Figure 6: the RS SDI decreased from  $15.1 \pm 5\%$  during RV pacing to  $11.8 \pm 4.1\%$  during BiV pacing ( $P < 0.01$ ), the CS SDI decreased from  $15 \pm 5.5$  to  $11.2 \pm 4.8\%$  ( $P < 0.001$ ), the LS SDI decreased from  $14.2 \pm 4.8$  to  $11.5 \pm 5\%$  ( $P < 0.01$ ), and the AS SDI decreased from  $12.2 \pm 5.1$  to  $9.5 \pm 4.5\%$  ( $P < 0.01$ ).



**Figure 4** Intra-observer and inter-observer reproducibility for the global area strain are shown in the Bland and Altman plots.



**Figure 5** Strain data reflecting the pacing of the patient in the two ventricles (BiV) or only in the right ventricle (RV). \* $P < 0.05$ ; \*\*\* $P < 0.001$ .



**Figure 6** Standard deviation of the dispersion of the regional peaks of deformation (assessment of dyssynchrony). BiV, biventricular pacing; RV, only right ventricular pacing. \*\* $P < 0.05$ ; \*\*\* $P < 0.001$ .

## Discussion

We demonstrate, for the first time, the capacity of 3DST to assess the mechanical changes induced by RV pacing in comparison with BiV pacing. We were also able to show that under good image quality conditions, 3DST is a robust and reproducible method. It appears, thus, reasonable to consider a technique for quantifying intra-ventricular mechanical dyssynchrony.

While CRT is a well-established therapeutic approach in mild-to-severe (NYHA class III or IV) heart failure patients with reduced LVEF (<35%) and wide QRS (>120 ms),<sup>1</sup> one-third of

patients fail to improve clinically or according to remodelling parameters such as echocardiographic LVESV after the implantation of a CRT device. The use of the QRS duration as the sole assessment of dyssynchrony and for a selection of patients eligible for CRT can certainly be improved upon.<sup>5,11,12</sup> Extensive research has been carried out with the aim of finding echocardiographic parameters to best select patients and predict response to CRT.<sup>4,6,13,14</sup> As a

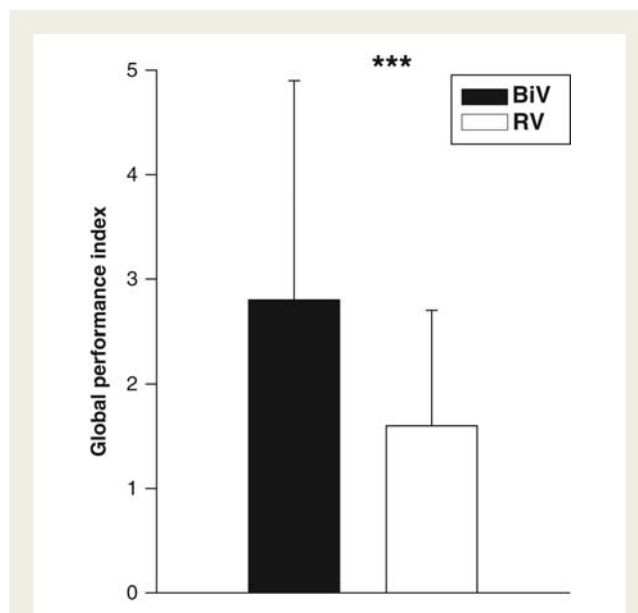
consequence of the negative outcome of the PROSPECT trial, the use of echocardiography in the selection of patients for CRT is not considered a strong choice or recommended by current guidelines.<sup>15</sup> However, new approaches and the development of new technologies, like the one we tested, might help in finding a simple, robust parameter to add to the current criteria proposed by guidelines to decide upon or not to propose to a patient a BiV pacing device.<sup>15</sup>

Three-dimensional ST seems promising for several reasons:<sup>16</sup> (i) all 16 segments of the LV are evaluated in their 3D motion, and in the relationship between them, thus avoiding the 'out-of-plane' phenomenon inherent to 2D imaging; (ii) the full LV volume is assessed during a four-beat acquisition, allowing a rapid evaluation of the global and regional all-directional contractions; (iii) LV dyssynchrony based on 3D WMT can be estimated in all its components: LS, RS, CS, and a newly developed parameter named the AS.<sup>8,9</sup>

Tanaka *et al.* did a first study but they did not assess dyssynchrony in a multi-directional way despite they add the 3D capability for strain analysis. They focused on the radial component.<sup>16</sup> The AS, which describes a combination of longitudinal, radial, and circumferential tracking, reflects the deformation of the endocardial surface during LV contraction and relaxation. The inner endocardial surface decreases in systole due to longitudinal and circumferential shortening, while the myocardial thickness increases. AS is a parameter integrating all these components of LV regional deformations. It should provide a more global and complete estimation of function and dyssynchrony than the approach of Tanaka *et al.*<sup>14</sup> The AS is a rapid and comprehensive three-dimensional approach for describing the complex LV regional deformation in systole. The robustness of its calculation in routine clinical practice is still missing but we demonstrated, for the first time, the feasibility of the AS measurement in patients with severe chronic heart failure. We also showed its capability to increase when a patient is BiV-stimulated when compared with being RV-stimulated. This integrated 3D approach is in line with previous studies emphasizing the need to include several components of LV mechanics to best define mechanical dyssynchrony and predict response to CRT.<sup>17,18</sup>

Three-dimensional ST offers a comprehensive assessment of LV dyssynchrony. Using this new approach, it becomes possible, using the same volume acquisition, to assess each component of LV deformation. It has recently been stressed that each component of LV deformation can have different 'behaviour' according to the degree of alteration of LV function and according to the aetiology of the heart failure.<sup>19–22</sup> Being able to assess RS, CS, and LS and dyssynchrony within the same volume acquisition should help in describing as precisely as possible the heart disease leading to heart failure.<sup>11,23</sup>

Of note is the AS-related SDI, which reflects the dispersion of the 16-segment AS peak curves and allows a rapid and global assessment of LV dyssynchrony. The AS-related SDI could be seen as a more relevant parameter than the SDI [regional time to minimum systolic volume (Tmsv)] developed by Kapetanakis *et al.*<sup>6</sup> A comparison between them was not possible in our study as we were using different software with different algorithms and treatments of the images. Further investigation, including a healthy population as well as heart failure patients, is needed to determine the normal range of values obtained with this new AS index and to establish its accuracy for the selection, follow-up, and prediction of response in patients who are candidates for CRT (Figure 7).



**Figure 7** Global performance index for the whole population (global performance index is explained in Figure 1). \*\*\* $P < 0.001$ .

## Study limitations

The present study is a methodological one. It has looked at the feasibility and not at the clinical value of the 3DST for a better analysis of mechanical dyssynchrony. An important study limitation is the relatively low temporal resolution obtained using 3DST imaging (20 volumes/s), in particular in dilated heart failure patients; but probably, the main influence was the limited scan quality which is a usual limitation in ultrasound, and we are waiting for improvements.

The 3D transthoracic ST technology needs further validation<sup>24</sup> and would probably benefit from improvements in 3D transducer technology. Our results should therefore be interpreted in the context of the software and hardware technology that was available for our study. Several studies comparing ST technologies have demonstrated that the algorithms used by different companies are not interchangeable.<sup>4,25</sup>

We did not compare the 'new' 3DST with previous methods but rather designed the present study to assess the capability of this new 3DST. This was done in order to determine the mechanical dyssynchrony changes induced by an acute change in pacing configuration.<sup>26</sup> 2DST does not measure the translational motion of the heart, and therefore a direct comparison with 3DST was not considered relevant. However, further studies are needed to prospectively test the effectiveness of this new approach in decreasing the percentage of patients who do not respond to CRT.<sup>24</sup> That was not our purpose here; we were just researching the feasibility of the technique initially.

## Conclusion

Three-dimensional ST is a technique used in 85% of the severe chronic heart failure patients that we prospectively recruited. When the image quality was correct, this new approach appeared to be rapid and robust enough. The next step would be to test the

approach in patients before BiV pacemaker implantation to best select and predict who would be the best responders to the therapy. The recently developed AS parameter integrates longitudinal, circumferential, and radial deformation. Further studies using this 'multi-directional parameter' of function and dyssynchrony are needed as it looks promising.

**Conflict of interest:** none declared.

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