Atrial asynchrony and function before and after electrical cardioversion for persistent atrial fibrillation†

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Aims
The relation between left atrial (LA) electrical and mechanical activity is a challenging field of investigation. The availability of echocardiographic strain analysis techniques has enhanced our ability to non-invasively assess LA wall mechanical synchrony and performance. The aim of our study was to investigate how new strain analysis tools describe the improvement in LA mechanical function after sinus rhythm (SR) restoration as a result of electrical cardioversion (CV) and how such improvement mirrors endocrine profile changes.

Methods and results
Seventy-three patients, with persistent atrial fibrillation (AF) who underwent successful electrical CV, were prospectively studied with transthoracic echocardiography 1 week before CV and 1 month after SR. Speckle-tracking 2D-strain evaluation and asynchrony quantification were performed according to the standard deviation of time-to-peak (TP-SD) of deformation of six segments automatically located along the perimeter of the LA cavity, as imaged in an apical four-chamber view. We also calculated classic echocardiographic parameters such as mitral regurgitation (MR) jet area, LA volume, LV diastolic and systolic volumes, as well as E-wave velocity and deceleration time (DT) on transmitral pulsed wave Doppler. Specimens for plasmatic brain natriuretic peptide (BNP) were also obtained before and 1 month after CV. After 1 month of SR, we detected a significant reduction in TP-SD (from $17.5 \pm 7.4$ to $15.2 \pm 7.5\%$, $P = 0.022$), this being the expression of improved LA asynchrony, together with a marked increase in LA deformation (peak strain from $11.4 \pm 5.2$ to $17.2 \pm 7.5\%$, $P < 0.001$) and a reduction in LA volume ($4.5 \pm 36\%$, $P = 0.012$). BNP decreased by one-third (from $127 \pm 96$ to $86 \pm 89$ pg/mL, $P = 0.01$). We also noticed improved ventricular pump performance [LV ejection fraction (EF) from $53 \pm 10$ to $57 \pm 8\%$, $P = <0.001$] due to a $20 \pm 42\%$ ($P = 0.001$) increase in LV diastolic volume (without variations in LV systolic volume and mass), a better diastolic profile (DT $34 \pm 64\%$, $P = 0.003$), and a reduction in MR jet area ($1.0 \pm 2.0$ cm², $P < 0.001$). These findings are compatible with reverse LA remodelling secondary to SR maintenance, with a favourable effect on LV function that appears modulated by the atrium itself. A significant correlation ($r = 0.40$, $P < 0.001$) was demonstrated between TP-SD and peak strain data pre–post CV. At multivariate analysis, a significant capacity for the TP-SD/peak strain ratio to predict AF recurrence at 1-year follow-up ($P = 0.013$) was shown.

Conclusion
Our novel noninvasive approach appears to be able to describe the LA mechanical behaviour during AF and how this ameliorates after 1 month of SR, together with an improved endocrine profile. LA mechanical data pre-CV can predict AF recurrence 1-year post CV.

Keywords
Atrial fibrillation • Speckle tracking echocardiography • Atrial remodelling

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Introduction

Atrial fibrillation (AF) is the most frequent arrhythmia in clinical practice and its frequency is increasing along with the progressive ageing of the population. While continuous efforts are being made by investigators to adopt more definite approaches (MAZE procedure, catheter ablations, and pulmonary veins isolation), external DC cardioversion (CV) remains the most widely used and cost-effective method available to re-establish sinus rhythm (SR). Although the procedure is associated with an AF recurrence rate that can be as high as 7–25%, this rate being only partially affected by antiarrhythmic treatment. Presently, several studies have proposed either non-invasive or partially invasive methods to assess left atrial (LA) function in order to select patients candidate to electrical CV or to more invasive procedures. Unfortunately, none of the proposed indexes is reliable and easy-to-perform enough to be widely used in the clinical context.

The recent availability of speckle tracking echocardiography has enhanced our ability to assess regional ventricular function: the use of strain analysis techniques to evaluate synchrony and performance at the atrial level appears to be a timely project, testing the association between LA mechanical vs. endocrine profile changes pre–post CV. In the present study, we have used this novel tool in studying LA cavity characteristics in a group of persistent-AF patients during arrhythmia and after 1 month of re-established SR. Our aim was to assess the usefulness of the novel approach in describing LA changes and any relation, if present, between mechanical synchrony, performance, and natriuretic peptide emission pre–post CV. Furthermore, to expand the paper contribution beyond a pure phenomenological context, pre-CV predictors of maintenance of SR at 1-year follow-up, including clinical, echocardiographic and treatment characteristics were also assessed.

Methods

We evaluated 130 consecutive subjects who underwent successful elective electrical CV (one to three biphasic shocks with energy from 100 to 200 J) for persistent AF (arrhythmia duration 3.5 ± 2.5 months, range 1–12 months) between January 2005 and June 2007 and then we studied the 73 patients (40 males, age 71.6 ± 8.3 years, range 47–84 years) who were still in SR 1 month after being cardioverted (Table 1). The CV success rates, in this consecutive patient population, were not related to duration of prior AF, LA cavity volumes, or BNP levels.

All patients had been evaluated at baseline (1 week before CV) and 1 month after by means of: (i) standard 12-leads ECG and physical examination; (ii) transthoracic echocardiography according to a standard protocol using a Vivid Seven digital ultrasound system (GE Medical Systems, Horten, Norway) with at least two cardiac cycles stored in digital cineloop format for off-line analysis performed with a dedicated software package (EchoPac PC, BT06 version; GE Healthcare). In particular, in AF patients, we waited for a moment of relatively rhythmic atrioventricular conduction, then we acquired from two to four clips (each composed of two cardiac cycles) and analysed the most regular one; (iii) collections of blood specimens as clinically required, besides a specimen for evaluation of BNP with immunoenzymatic assay (ELISA). Blood specimens (for BNP evaluation) were collected in EDTA tubes, immediately stored in a −80 °C refrigerator and processed within a week with chemiluminescence method (Siemens Centaur, normal values 0.0–18.0 pg/mL).

We defined AF recurrence as a self-reported symptomatic episode of arrhythmia with ECG documentation of AF, or as an asymptomatic AF detected by means of 24 h Holter recording (performed at 1 month follow-up and in case of symptoms without clear documentation of AF) or routine ECG (performed at 1, 3, and 6 months visits). Patients were called by phone between follow-up visits and asked about AF-related symptoms (palpitations, syncope, dizziness, dyspnoea, and chest pain); they were invited to perform an unscheduled visit if AF was suspected.

Echocardiographic measurements

All echocardiographic studies were performed with the subject lying in the left lateral decubitus position, obtaining complete 2D-echocardiographic colour Doppler examination with a 3.5 MHz variable-frequency harmonic phased-array transducer. The LA volume was calculated according to the formula: 8/3π[(LA area in apical 4 – chamber-LA area in apical two-chamber)/LA length]. LV global systolic function was calculated ventricular volumes (end-diastolic volume, EV; end-systolic volume, ESV), obtained using real-time three-apical longitudinal planes and then by manually tracing the endocardial border with built-in software. LV EF was computed as usual. LV mass was assessed with the area-length formula. Both LA area and volume, together with LV EDV, ESV, and mass, were indexed to body surface area.

Mitrail regurgitation (MR) was graded quantitatively according to the area of the regurgitant jet in four-chamber view using the colour Doppler data and expressed as regurgitation jet area/LA area ratio. Mitral deceleration time (DT) was also measured as the time interval between peak E wave and the zero intercept of the deceleration profile.

Left atrial asynchrony quantitation

LA asynchrony was quantified using a two-dimensional strain speckle tracking approach. Speckle tracking echo is a novel non-Doppler method to evaluate strain from standard two-dimensional greyscale...
acquisitions.24 By tracing the endocardial contour on an end-diastolic/systolic cavitary frame and after defining the thickness of the region to be considered, the software will automatically track the atrial wall on subsequent frames. Adequate tracking can be real-time verified and corrected by adjusting the region of interest or the contour (Figure 1). A minimum frame rate of 30 Hz is required for reliable operation, but we used the highest possible frame rate available (30–80 Hz acquisitions). Using this technique, we analysed regional deformation of six segments located along the septum, the roof, and the lateral wall of the LA cavity, as represented in a four-chamber apical view. For each segment, during LV systole, LA wall lengthening (positive strain value) is observed due to the filling of the atrial cavity by blood coming from the pulmonary veins, while the mitral valve is closed; wall shortening (negative strain value) occurs during LV diastole because the atrium empties into the underneath ventricular cavity. A curve plotting the average of the six segments’ strain curves was also automatically generated: we called the integral of such curve global strain (as an expression of the total amount of LA deformation) and the maximum value of the curve peak strain (as an expression of the maximum global amount of LA deformation).

In order to quantify atrial asynchrony, strain curves were exported as digital matrix data to a custom-made, open source analysis software. Time-to-peak standard deviation (TP-SD) was computed as the standard deviation of the time to maximal positive deformation of each curve and expressed as a percentage of the R–R interval (Figure 2). Time-to-peaks in opposite phase to the expected direction of strains were not included in the final computation. Values of strain for these segments counted as 100 in averaging strain. High grade of asynchrony was identified by larger values of TP-SD.

Interobserver variability, expressed as coefficient of variation, was assessed by analysing on the same clips diastolic and systolic LV volume and mass, LA area, TP-SD, and average peak strain for 10 patients, before and after CV, randomly chosen within the patients’ population by two independent investigators on two different occasions. For the atrial strain data, correlation coefficients and plots of the difference between the two measurements against their means were also computed, according to Bland and Altman.25

**Statistical analysis**

Data are expressed as mean ± SD. Differences in means were assessed by two-tailed t-tests for paired data. Regression analysis

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**Figure 1** Evaluation of atrial deformation according to the speckle-tracking technique. Left atrial endocardial contour is traced in a four-chamber view. The thickness of the region of interest to be considered is then defined. The software automatically tracks atrial wall, allowing real-time fine adjustments, and in-motion verification.

**Figure 2** Strain curves of the same patient as in Figure 1, examined during atrial fibrillation (left) and after 1 month of sinus rhythm persistence (right). Each curve represents one of the six left atrial wall segments; the dotted line is the mean strain (global strain). Peaks of each curve are marked with a white cross; the peak of the global strain curve (PS) is marked with a red cross. Times-to-peak are normalized to R–R’ interval. During sinus rhythm, a lower time-to-peak standard deviation (TP-SD) and a greater PS are observed (see values in figure).
Results are reported in Table 2. After 1 month of SR, a statistically significant reduction of TP-SD in absolute terms (−2.3 ± 8.4%, P = 0.02) was observed. Such improvement in atrial asynchrony was accompanied by a doubling in global strain (3.5 ± 4.6%, P < 0.001) and an increase of more than 70% in peak strain (5.8 ± 8.1%, P < 0.001). There was a significant inverse relation between TP-SD and both peak strain (Figure 3) (r = −0.40, P < 0.001) and global strain (r = −0.36, P < 0.001). A reduction in atrial volumes (−4.5 ± 35.7%, P = 0.012) was also observed, together with a relevant decrease in MR jet area (from 2.6 ± 2.4 to 1.7 ± 2.0 cm², P < 0.001) and the jet area/LA area ratio (from 0.11 ± 0.1 to 0.7 ± 0.7, P < 0.001). BNP decreased as well by one-third (from 127 ± 96 to 86 ± 89 pg/mL, P = 0.01), concordant with atrial volume shrinkage (from 41 ± 13 to 38 ± 13 mL/m², P = 0.012), while LV function improved significantly (EF 4.6 ± 9.8%, P < 0.001), due to a meaningful increase in LV EDV²⁶ (19.5 ± 41.8%, P < 0.001) and a better diastolic profile (34 ± 64% lengthening in DT, P = 0.003).

Follow-up information was available for 70 patients. Fifty-five of them (79%) were at 1 year in SR. A multivariate analysis, testing the effects of pre-CV clinical and echocardiographic variables in predicting recurrence of AF post CV, did reveal that atrial TP-SD/peak strain ratio was the most important independent predictor of the arrhythmia recurrence (P = 0.013, Table 3). Among the other variables, only LA volume did demonstrate some predictive capacity (P = 0.09, Table 3). None of the drugs listed in Table 1 affected the recurrence of AF at 1 year. The same was true when only the effects of amiodarone, propafenone, and flecainide were taken into account in regard to recurrence of AF independently of the measured TP-SD/peak strain ratio. Furthermore, AF recurrence rate did not differ between patients with

### Table 2 Values of analysed parameters in atrial fibrillation and after 1 month of sinus rhythm

<table>
<thead>
<tr>
<th></th>
<th>Atrial fibrillation</th>
<th>Sinus rhythm</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP-SD (%)</td>
<td>17.52 ± 7.44</td>
<td>15.20 ± 7.54</td>
<td>0.022</td>
</tr>
<tr>
<td>Global strain (%)</td>
<td>4.63 ± 2.74</td>
<td>8.16 ± 4.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak strain (%)</td>
<td>11.36 ± 5.19</td>
<td>17.15 ± 7.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LA area in apical four-chamber view (cm²/m²)</td>
<td>12.58 ± 2.64</td>
<td>11.94 ± 2.91</td>
<td>0.038</td>
</tr>
<tr>
<td>LA volume (mL/m²)</td>
<td>41.12 ± 12.92</td>
<td>37.56 ± 12.60</td>
<td>0.012</td>
</tr>
<tr>
<td>MR jet area (cm²)</td>
<td>2.64 ± 2.40</td>
<td>1.68 ± 2.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MR jet area/LA area</td>
<td>0.11 ± 0.10</td>
<td>0.07 ± 0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV EDV (mL/m²)</td>
<td>45.16 ± 15.93</td>
<td>50.66 ± 14.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ESV (mL/m²)</td>
<td>21.97 ± 12.09</td>
<td>22.69 ± 11.24</td>
<td>0.488</td>
</tr>
<tr>
<td>EF (%)</td>
<td>0.53 ± 0.10</td>
<td>0.57 ± 0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass (g/m²)</td>
<td>77.48 ± 32.14</td>
<td>80.85 ± 30.52</td>
<td>0.365</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>127.02 ± 96.73</td>
<td>85.57 ± 89.54</td>
<td>0.014</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>198.20 ± 58.54</td>
<td>238.12 ± 80.34</td>
<td>0.003</td>
</tr>
</tbody>
</table>

### Table 3 Multiple logistic regression analysis of 1-year recurrence of atrial fibrillation with pre-CV clinical and echocardiographic variables (likelihood ratio test P = 0.025, Hosmer–Lemeshow statistic P = 0.160)

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>SE</th>
<th>Wald statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>−6.278</td>
<td>5.444</td>
<td>1.330</td>
<td>0.249</td>
</tr>
<tr>
<td>Patients age (years)</td>
<td>−0.0694</td>
<td>0.0642</td>
<td>0.167</td>
<td>0.280</td>
</tr>
<tr>
<td>AF duration (months)</td>
<td>−0.0416</td>
<td>0.174</td>
<td>0.0571</td>
<td>0.811</td>
</tr>
<tr>
<td>TP-SD/peak strain</td>
<td>0.820</td>
<td>0.331</td>
<td>6.132</td>
<td>0.013</td>
</tr>
<tr>
<td>LV ESV (mL/m²)</td>
<td>0.0681</td>
<td>0.0401</td>
<td>2.887</td>
<td>0.089</td>
</tr>
<tr>
<td>MR jet area/LA area</td>
<td>2.846</td>
<td>4.987</td>
<td>0.326</td>
<td>0.568</td>
</tr>
<tr>
<td>EF (%)</td>
<td>0.0598</td>
<td>0.0555</td>
<td>1.161</td>
<td>0.281</td>
</tr>
<tr>
<td>LV mass (g/m²)</td>
<td>−0.00145</td>
<td>0.0191</td>
<td>0.00583</td>
<td>0.939</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>0.0103</td>
<td>0.00688</td>
<td>2.228</td>
<td>0.136</td>
</tr>
</tbody>
</table>

CV, cardioversion; EF, ejection fraction; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; SD, standard deviation; TP-SD, time-to-peak standard deviation.
antiarrhythmic treatment and patients without (21 vs. 13%, respectively, \(P = \text{ns}\)).

Interobserver variability is reported in Table 4. For the atrial strain data, correlation coefficients and plots of the difference between the two measurements against their means are also provided in Figure 4. The mean absolute (i.e. without ± sign) percentage difference between two measurements of strain (performed 8 months apart by two operators) averaged 3.6 ± 3.2%. The equivalent value for TP-SD was 3.6 ± 3.3%. Alternatively, the correlation coefficient between the two measurements was 0.87 for TP-SD and 0.77 for peak strain (\(P < 0.001\) for both, Figure 4).

## Discussion

The results of our study suggest that (i) is currently available a non-invasive tool to quantify atrial asynchrony and cavity wall deformation; (ii) the atrium asynchrony and strain contribute to a better definition of the mechanical characteristics of the cavity as is known for the ventricle; (iii) the process of LA reverse remodeling can be easily tracked and associated with the evolving endocrine profile detectable in the month after electrical CV. (iv) Finally, TP-SD/peak strain ratio pre-CV can identify those patients that will revert to AF during 1-year follow-up post CV.

The consideration that LA mechanical profile in SR is better than when AF is present is quite obvious, even in the post-AFFIRM era.\(^{27-32}\) Our study associates classical echocardiographic demonstration of improved cardiac performance during SR, such as

### Table 4 Interobserver variability for those parameters described below, expressed as coefficient of variation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ((\mu)) ± SD ((\sigma))</th>
<th>Coefficient of variation ((\sigma/\mu))</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EDV (mL/m²)</td>
<td>54.6 ± 16.5</td>
<td>0.30</td>
</tr>
<tr>
<td>LV ESV (mL/m²)</td>
<td>22.3 ± 7.2</td>
<td>0.32</td>
</tr>
<tr>
<td>LV mass (g/m²)</td>
<td>134.7 ± 32.9</td>
<td>0.24</td>
</tr>
<tr>
<td>LA area in apical four-chamber view (cm²/m²)</td>
<td>24.3 ± 6.8</td>
<td>0.28</td>
</tr>
<tr>
<td>Peak strain (%)</td>
<td>14.2 ± 6.7</td>
<td>0.47</td>
</tr>
<tr>
<td>TP-SD (%)</td>
<td>20.6 ± 9.3</td>
<td>0.45</td>
</tr>
</tbody>
</table>

EDV, end-diastolic volume; ESV, end-systolic volume; LA, left atrium; LV, left ventricle; SD, standard deviation; TP-SD, time-to-peak standard deviation.

![Figure 4](https://academic.oup.com/ehjcimaging/article-abstract/11/7/577/2396654)
reduction in MR, increase in LVEF, and reduction in LA volume, with novel parameters like greater LA cavity strain generation and ameliorated degree of synchrony. In our group of patients, the effect of 1-month SR conferred a detectable spin off for the process of recovery of LA function. This is particularly mirrored by the significant improvement in the ability of the cavity to deformate, accommodating and releasing blood during the cardiac cycle, as reflected by the marked improvement in the generated global and peak strain. The improved mechanical profile is well described by the recovery of LA mechanical synchrony, i.e. the reduction of dispersed atrial regional contraction as reflected by the TP-SD decrease, linked to the re-established electrical synchrony after CV.

It must be acknowledged, however, that LA strain indexes might be a reflection of ventricular rather than atrial function, although such reasoning cannot be applied to an index that quantifies asynchrony that, by definition, reflects temporal inhomogeneities within the cavity wall. This consideration is confirmed by the absence of whatsoever relation between changes in LA peak or global strain and changes in ventricular variables (Δ mitral regurgitant jet area, Δ EF, and Δ EDV) pre–post CV. There was instead a borderline statistically significant inverse relation between global strain and LA volume changes (P = 0.064), and between peak strain and TP-SD changes (P < 0.06).

The behaviour of other significant parameters must also be considered: the prolongation in DT reflects the more favourable ventricular filling profile and improved operative stiffness following electrical CV (secondary to the larger LV end-diastolic volume which improves EF). This change is substantially modulated by the LA cavity, given that no significant differences were observed in LV anatomy, either expressed as mass or systolic volume. As a consequence, reduction in BNP circulating levels can be explained solely by reduction of atrial wall stress and possibly improved LV pump performance. These findings are compatible with LA favourable remodelling due to SR maintenance, with a positive influence on LV function that appears modulated only by the atrium itself.

Predictability of AF recurrence post CV

Multiple logistic regression analysis did demonstrate that the TP-SD/peak strain ratio can predict AF recurrence post CV with a reasonable accuracy (P = 0.013, Table 3). LA volume came second (P = 0.09, Table 3), while no other instrumental, clinical, or therapeutic variable did predict the AF recurrence at 1-year follow-up. In particular, neither operative ventricular stiffness, as expressed by the E wave mitral DT, pre- and post CV, nor LV mass did predict 1-year recurrence of AF in our population. Thus, it is conceivable that pre-CV detection of different degrees of LA mechanical derangement, secondary to variable asynchrony, can affect long-term maintenance of SR post CV. The analysis we adopted can be used to describe LA behaviour in other clinical situations such as, for example, the atrial stunning condition that follows the restoration of SR, or to identify patients with a predictable poor recovery of atrial function, who would need more aggressive pharmacological therapy in order to avoid AF relapses. As shown, the reproducibility of our proposed indexes of atrial synchrony and mechanical function appears reasonable, making the technique clinically implementable. Certainly, reproducibility will be further improved by technical advances in software analysis focused on selecting more cardiac cycles than what is now possible (in order to better mediate strain values in a situation of irregular R–R intervals) and increasing the frame rate of the greyscale acquisitions.

Conclusion

In conclusion, our novel noninvasive technique appears to be able to describe LA behaviour during AF and SR, and how LA behaviour can mediate changes in the endocrine profile pre–post CV as well as predict 1-year AF recurrence post CV. If confirmed by other studies, these findings may have relevant applications in the clinical management of AF patients.

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Conflict of interest: none declared.

References


