Left atrial strain: a new predictor of thrombotic risk and successful electrical cardioversion

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Abstract

Background: Left atrial deformation (LAD) parameters are new markers of atrial structural remodelling that seem to be affected in atrial fibrillation (AF) and atrial flutter (AFL). This study aimed to determine whether LAD can identify patients with a higher risk of thrombosis and unsuccessful electrical cardioversion (ECV).

Methods: Retrospective study including 56 patients with AF or AFL undergoing ECV, with previous transthoracic (TTE) and transoesophageal echocardiography (TEE) studies. Echocardiographic parameters analysed were as follows: left ventricle function, left atrium (LA) dimensions, LAD parameters (positive and negative strain peaks), left atrial appendage (LAA) filling and emptying velocities and the presence of thrombi. Strain values were analysed according to thrombotic risk and success of ECV.

Results: Lower mean values of peak-positive strain (PPS) in patients with prothrombotic velocities (<25 cm/s) and a higher incidence of thrombi in LAA were observed compared with those with normal velocities. Multivariate analysis revealed PPS normalised by LA maximum volume indexed by body surface area (BSA) to be associated with prothrombotic risk (odds ratio 0.000 (95% CI: 0.000–0.243), P = 0.017), regardless of CHADs2VASC score. Peak-negative strain normalised by LA volumes indexed by BSA were associated with unsuccessful ECV.

Conclusions: Atrial deformation parameters identify AF and AFL patients with a high risk of thrombosis and unsuccessful ECV. Therefore, these new parameters should be included in anticoagulation management and rhythm vs rate control strategies.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the general population and is associated with significant cardiovascular morbidity (1, 2, 3, 4, 5, 6, 7, 8). Left atrium (LA) structural changes play a major role in the process of initiation and maintenance of the arrhythmia together, with fibrosis and myofibre disarray (1, 2, 9). Although LA size appears to be a factor for AF recurrence, it is, however, determined by many other factors such as age, cause and AF duration (2, 6).

LA function modulates left ventricle (LV) filling through its three components: the reservoir phase during ventricular systole, conduit phase during early ventricular...
diastole and pump phase at end ventricular diastole (1, 6). In AF, the reservoir and conduit functions are believed to be impaired and pump function is lost (6, 7).

New markers of atrial structural remodelling and myocardial deformation properties, measured as strain and strain rate by two-dimensional speckle-tracking techniques, have recently been proposed (1, 2, 3, 6, 8, 10, 11, 12). These parameters have the advantage of being angle-independent (2, 10, 11). Several studies conducted in recent years found that patients with AF have lower LA strain values compared with healthy controls (2, 3, 5, 7, 8). LA wall fibrosis, as part of structural remodelling occurring in AF, seems to be inversely related to LA strain and strain rate (13). These parameters of myocardial deformation could thus identify patients at increased risk of developing AF and predict, in those with diagnosed arrhythmia, the success of therapeutic interventions (2), one of which is external electrical cardioversion (ECV), considered to be the most effective for restoring sinus rhythm (SR) (4, 6, 7).

This study aimed to ascertain whether atrial deformation parameters can: (1) identify individuals with higher thrombotic risk, defined as low LAA velocities <25 cm/s or LAA thrombus; and (2) foresee unsuccessful ECV, in a population of patients with AF and atrial flutter (AFL).

### Methods

#### Study population

One hundred and thirty-three consecutive patients with AF or AFL undergoing a first ECV between 2010 and 2014 at the Hospital Vall d’Hebron, Barcelona, were retrospectively evaluated. Transthoracic (TTE) and transoesophageal echocardiography (TEE) studies were conducted before cardioversion in all patients. Exclusion criteria were presence of organic valvular disease (n=15), prosthetic valves (n=2), pericarditis or acute myocardial infarction (n=3), or a recent history of heart surgery or pacemaker implantation (n=7) and without minimum requirements for LAD analysis (n=50).

Fifty-six patients were included in the study. Demographics, medical history including the type of arrhythmia (AF or AFL), duration of the arrhythmia episode classified as paroxysmal (if it lasted less than 48 h) and as persistent (lasting days or months) and other co-morbidities (hypertension, diabetes, history of stroke and body mass index) are given in Table 1.

Echocardiographic parameters by TTE and TOE study were LV dimensions and ejection fraction, LA dimensions and deformation parameters, left atrial appendage (LAA) filling and emptying velocities, and the presence of thrombi in patients with atrial fibrillation. All variables were compared to a control group of 200 healthy volunteers, with a mean age of 65 years.

### Table 1 Clinical and echocardiographic characteristics of patients.

| Demographic characterization | Co-morbidities |
|------------------------------|----------------|
| **Sex**                      |                |
| Male                         | Hypertension   |
| 36 (64%)                     | 39 (69.6%)     |
| Female                       | Diabetes       |
| 20 (36%)                     | 14 (25%)       |
| Age (years)                  | History of stroke |
| 67 (59–74)                   | 2 (3.6%)       |
| **Arrhythmia characterization** | Body mass index (kg/m²) |
| Type of arrhythmia           | 28.8 (25.4–31.6) |
| Atrial fibrillation          | 39 (69.6%)     |
| Atrial flutter               | 17 (30.4%)     |
| Paroxysmal (<48 h)           | 100 (80–125)   |
| Persistent (days)            | 4 (8.9%)       |
| Persistent (months)          | 9 (16.1%)      |

| Echocardiographic characterization | LA |
|-----------------------------------|----|
| LV                                | LAMV (mL) |
| EDD (mm)                          | 49 (45–55) |
| ESD (mm)                          | 37 (30–42) |
| EDV (mL)                          | 108 (82–135) |
| ESV (mL)                          | 53 (41–80) |
| EF (%)                            | 50 (33–55) |
| **LAA**                           | LAMV indexed to BSA (mL/m²) |
| FVLAA (m/s)                       | 0.32 (0.12–1.00) |
| EVLAA (m/s)                       | 0.26 (0.20–0.44) |
| Presence thrombi                  | 4 patients (7.1%) |
| **LA**                            | PPS/LAMV indexed to BSA (mL/m²) |
| LA diameter (mm)                  | 46 (43–51) |
| LA area (cm²)                     | 26 (23–31) |
| Presence thrombi                  | 4 patients (7.1%) |
of LA thrombi. Prothrombotic status was defined when emptying and filling velocities were <0.25 m/s (14).

The success of ECV was established when SR was stable at least 1 day after cardioversion.

**Echocardiography**

All patients were evaluated by TTE and TOE, immediately before ECV, using a Vivid digital ultrasound system (GE Medical Systems). The analysis was performed with a software package (EchoPac; GE Healthcare). LA diameter was measured at end-systole, in parasternal long-axis view. LV diameters were measured at end-diastole and end-systole, in the same imaging plane. LA volumes were calculated from an apical four-chamber view (maximum volume at end-systole; minimum volume at end-diastole). LV volumes were also measured in this imaging plane, and ejection fraction (LVEF) was calculated.

2D speckle tracking imaging was used to analyse LA strain values in six segments. For this purpose, a line was manually drawn along the LA endocardium at peak systole in an apical four-chamber view. The software then automatically generated tracking of the LA endocardium, which was further adjusted by the operator. The six segments of the left atrium were analysed and an average value of all segments was considered.

LA function can be evaluated through 2D speckle tracking imaging by analysing its three curve strain components. In sinus rhythm, a QRS-timed analysis identifies the reservoir phase by peak ventricular systolic value ($\varepsilon_R$), which corresponds to the maximum atrium filling; the contractile phase by peak late diastole ($\varepsilon_{CT}$) and the conduit phase by peak early diastole ($\varepsilon_{CD}$), corresponding to the difference between peaks $\varepsilon_R$ and $\varepsilon_{CT}$ (Fig. 1). In AF, it is believed that the reservoir and conduit function are impaired and pump function is lost. Thus, in these patients, only peak-positive systolic strain (PPS) and peak-negative diastolic strain (PNS) of the curves were analysed, as there was no accurate way of identifying the different stages of atrial function (Fig. 2). An average of different measurements of LA strain curves was taken (in five consecutive cycles) in each case. All patients included in the study fulfilled the minimum requirements for analysis by speckle tracking imaging.

**Statistical analysis**

Continuous variables were expressed as medians and interquartile range (IQR) in line with their non-normal distribution. Normality was tested with the Kolmogorov–Smirnov test. Categorical variables were expressed as frequencies and percentages. Statistical comparisons were made using the chi-square test or Fisher’s exact test, as appropriate, for categorical variables, and the Mann–Whitney test for continuous variables. Spearman's correlation test was used to compare associations between parameters. Variables associated in the univariate analysis, or clinically significant in the investigator's opinion, were entered into a forward stepwise logistic regression model to identify variables independently associated with higher...
thrombotic risk (odds ratio (95% confidence interval (CI) for $\exp (B)$ %)).

To predict the discriminatory effect of the peak-positive strain in prothrombotic risk and cardioversion success, ROC curves were performed with its sensitivity and specificity values. The interobserver variabilities of peak-positive and -negative strains were assessed with the intraclass correlation coefficient (ICC). A $P$ value $\leq 0.05$ was considered significant. All analyses were performed with SPSS version 20.0 for Windows.

## Results

### Clinical and echocardiographic characteristics of the patients

Patients were predominantly male (64%) with a median age of 67 years. Most patients had atrial fibrillation (69.6%), with a persistent character (91.1%). Duration of the arrhythmia was <48 h in only 5 patients (9%). Of the 51 patients with persistent arrhythmia, 42 (75%) had the arrhythmia <30 days (median 24 days; range: 14–31 days) and 9 patients had the arrhythmia >30 days (median 115 days; range: 46–280 days).

The majority of patients had hypertension (69.6%) and only two had a history of stroke (3.6%). LA size and LAD parameters are given in Table 1. LV systolic function was normal or slightly depressed in 36 patients (64.3%), and with moderate-to-severe dysfunction (LVEF <45%) in 20 (35.7%). In 27 patients (48.2%), emptying and filling LAA velocities were <0.25 m/s and normal in 29 (51.8%). Thrombi in LAA were observed in 4 (7.1%) patients.

### Correlation between LA size dimension and strain parameters

Both PPS and PNS correlated with all LA size parameters as given in Table 2. Correlation was better with LA maximum (LAMV) and minimum (LAmV) volumes indexed to body surface area (BSA) than with absolute LA diameter or area.

The PPS correlated with heart rate (HR) (Spearman correlation 0.291; $P = 0.030$), as opposed to the PNS (Spearman correlation 0.149; $P = 0.275$). A linear regression model applied verified that HR interferes with approximately 8.5% of the PPS value. The interobserver variability of strain parameters was excellent: ICC was 0.97 for PPS (0.96–0.99; $P < 0.001$) and 0.93 for PNS (0.89–0.96; $P < 0.001$).

### Atrial deformation parameters and thrombotic risk

The sample was divided into two groups according to LAA velocities: the first with normal velocities and the second with emptying and filling velocities <0.25 m/s. The second group had higher LA volumes and lower PPS values, absolute and indexed by BSA (Table 3). In addition, the four patients with thrombi had LAA velocities <0.25 m/s. The CHADs2VASC score was similar between groups ($P = 0.71$).

Multivariate analysis showed peak-positive strain/LA maximum volume indexed by BSA to be associated with LAA velocities <25 cm/s (odds ratio 0.44; (95% CI: 0.003–0.658), $P = 0.024$), regardless of CHADs2VASC score (Table 4). When we applied the same analysis but with LA minimum volume indexed to BSA, and this parameter was also related significantly to LAA velocities ($P = 0.009$) but with less significant odds ratio, a measure of association was observed between an exposure and an outcome (OR 0.007).

Values of peak-positive strain in relation to LA maximum volume indexed to BSA <0.08 determined the prothrombotic risk (area under the curve (AUC) 0.72, sensitivity 81.5% and specificity 62.1%).

### Atrial deformation parameters associated with successful cardioversion

Fifty-two of 56 patients underwent ECV since thrombi in LAA, detected in four patients, formally contraindicated

| Table 2 | Correlation between heart rate and atrial dimension with peak-positive and -negative strains. |
|---------|---------------------------------------------------------------|
|         | **PPS** | **PNS** |
|         | Pearson correlation | $P$ | Pearson correlation | $P$ |
| LA diameter | -0.274 | 0.041 | 0.421 | 0.001 |
| LA area | -0.308 | 0.021 | 0.310 | 0.020 |
| LAMV | -0.295 | 0.027 | 0.280 | 0.037 |
| LAMV indexed to BSA | -0.375 | 0.004 | 0.267 | 0.047 |
| LAmV | -0.469 | <0.001 | 0.394 | 0.003 |
| LAmV indexed to BSA | -0.507 | <0.001 | 0.374 | 0.004 |

BSA, body surface area; LA, left atrium; LAMV, left atrial maximum volume; LAmV, left atrial minimum volume; PNS, peak-negative strain; PPS, peak-positive strain. Statistically significant values are given in bold.
the procedure. Forty-six converted to SR (88%) while six failed converting to SR (12%). The success of ECV-obtaining SR was maintained at 3 months of ECV in 44 patients (95%).

PNS, in absolute value and in relation to LA volumes indexed to BSA, showed lower values in patients who did not convert to SR (Table 5). However, other clinical and echocardiographic parameters such as duration of the arrhythmia, atrial volumes and left ventricle ejection fraction were not related to the efficacy of ECV.

Values of peak-positive strain in relation to LAMV indexed to BSA >0.08 determined cardioversion success (AUC 0.74; sensitivity 70% and specificity 70%) (Fig. 3).

### Discussion

The present study shows LA strain to be useful in identifying patients with AF or AFL with high thrombotic risk, and a good predictor of ECV efficacy.

Some of these findings concur with the study of Azemi and coworkers (15), which, in a series of 57 patients showed the relationship between low LAD values with high risk of stroke or TIA in patients with low CHADS2.

Both positive and negative strain peaks correlated with all the parameters of LA dimensions. This correlation was moderate regarding LA volumes (maximum and minimum indexed to BSA), a finding already described by Vianna-Pinton and coworkers in a preliminary study of 84 normal subjects (11). Those authors also verified that the correlation with LA volumes was higher than with LA diameter or area. This can be explained by the fact that LA enlargement is often asymmetrical and occurs predominantly in the medial–lateral and superior–inferior axes, while being limited in the anteroposterior axis by the thoracic cavity (10). Therefore, LA volumes are considered superior to LA diameter as a measurement of LA dimensions (10). Thus, in our study, the adjustment of strain values to LA dimensions was accomplished by considering its volumes rather than diameter. Nevertheless, in our retrospective series, we only systematically obtained the four-chamber view.

The thrombotic risk of this population of patients with supraventricular arrhythmias is a crucial issue. This study revealed a significant association between lower PPS values and the presence of prothrombotic velocities in LAA. The peak-positive strain in relation to LA maximum volume was associated with higher thrombotic risk, by multivariate analysis, regardless of the CHADS2VASC score. This association between LA deformation parameters and LAA velocities and higher thrombotic risk has been described previously (5, 15, 16). Kaya and coworkers, in their prospective study of 22 patients with AF who underwent cardioversion, showed an association between LA strain values and LAA velocities and observed a progressive improvement over time after ECV (5). Azemi and coworkers also mentioned a relationship between lower LA strain values (also measured as PPS and PNS) and a higher thrombotic risk, when evaluating the occurrence of cerebrovascular events in patients with AF (15).

### Table 3  Correlation between LAA velocities and other parameters.

|                                | With normal velocities in LAA (n = 29) | With prothrombotic velocities in LAA (n = 27) | P     |
|--------------------------------|---------------------------------------|-----------------------------------------------|-------|
| Type of arrhythmia (atrial flutter) | 14 (48.3%)                            | 3 (11.1%)                                     | 0.003 |
| LAMV indexed to BSA (mL/m²)     | 40 (34–43)                             | 44 (38–61)                                    | 0.021 |
| LAmV indexed to BSA (mL/m²)     | 23 (18–27)                             | 35 (25–43)                                    | 0.001 |
| PPS (%)                        | 8.52 (7.48–13.88)                     | 7.13 (5.23–8.59)                              | 0.015 |
| PPS/LAMV indexed to BSA (%/mL/m²) | 0.25 (0.14–0.36)                     | 0.16 (0.11–0.20)                              | 0.003 |
| PPS/LAmV indexed to BSA (%/mL/m²) | 0.46 (0.23–0.60)                     | 0.22 (0.14–0.29)                              | 0.001 |
| Presence of thrombi in LAA (number patients) | 0                                    | 4                                             | 0.048 |
| On anticoagulant therapy (number patients)    | 6                                             | 8                                             | 0.44  |
| CHADS2VASC score               | 2 (1–4)                                | 2 (2–3)                                       | 0.71  |

BSA, body surface area; LAA, left atrial appendage; LAMV, left atrial maximum volume; LAmV, left atrial minimum volume; PPS, peak-positive strain. Statistically significant values are given in bold.

### Table 4  Variables included in multivariate analysis of prothrombotic risk.

|                                | Odds ratio | 95% CI        | P     |
|--------------------------------|------------|---------------|-------|
| Type of arrhythmia             | 6.813      | 1.459–34.506  | 0.012 |
| PPS/LAMV indexed to BSA        | 0.80       | 0.792–0.974   | 0.014 |
| CHADS2VASC score              | 0.928      | 0.544–1.582   | 0.783 |

BSA, body surface area; Dic, dichotomous variable; LAMV, left atrial maximum volume; PPS, peak-positive strain. Statistically significant values are given in bold.
Providência and coworkers also found a correlation between increased left atrial stasis, assessed through various parameters (including LAA velocities), and LA mechanical dysfunction assessed with speckle tracking imaging (16). Therefore, the myocardial deformation parameters appear to be potential non-invasive parameters associated with a higher risk of thrombus in LAA (a contraindication for electrical cardioversion) and may, therefore, in the future, hypothetically replace invasive techniques such as TOE for their evaluation, and be determinants of how long patients should be kept under anticoagulation after cardioversion. The peak-positive strain atrial volume ratio seems to be stronger when its components are separated. The LA maximum volume indexed to BSA seems to be a more practical parameter to use in daily practice and was associated with a more significant odds ratio compared with the minimum atrial volume.

Our data suggest that left atrial mechanical dysfunction, assessed through negative peak longitudinal strain, was associated with the poor success of effective cardioversion, a fact not previously described in the literature. Peak-negative strain in this setting of atrial fibrillation can correspond to the residual capacity of myocardial fibres shortening in the absence of an effective atrial contractile function, as part of the LA remodelling process. Few studies have attempted to assess factors that may predict the success of cardioversion. Wang and coworkers studied 42 patients and found the early diastolic peak strain rate of the basal segment of the LA wall to be a possible predictor of successful cardioversion and maintenance of SR (17). In our study, the PNS variable isolated or in relation to LA volumes was associated with cardioversion failure. Remarkably, no other variables such as arrhythmia duration, atrial volumes or left ventricle ejection fraction were associated with ECV success.

Limitations of the study

One of the most significant limitations was the patient population, since small samples may lack statistical power to demonstrate the presence of significant statistical differences. Peak-negative longitudinal strain was found to correlate with successful cardioversion, even when the number of patients in the sample was low. Therefore, LAD may become an important echocardiographic parameter in the clinical decision to perform cardioversion or not in AF patients (18).

Another consideration is that the data were obtained using software designed for LV assessment and not specific for LA evaluation. Nevertheless, this tool permitted the

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**Table 5** Correlation between several parameters and cardioversion success.

|                          | Successful cardioversion (n=46) | Unsuccessful cardioversion (n=6) | P    |
|--------------------------|---------------------------------|----------------------------------|------|
| Persistent arrhythmia (months duration) | 7 (15.2%)                       | 1 (16.7%)                        | 0.926|
| LVEF                     | 50 (35–55)                      | 40 (32–50)                       | 0.241|
| LAMV indexed to BSA (mL/m²) | 41 (34–54)                      | 43 (37–54)                       | 0.685|
| LAmV indexed to BSA (mL/m²) | 26 (21–34)                      | 31 (26–38)                       | 0.230|
| PNS (%)                  | −1.02 (−2.44 to −0.67)          | −0.55 (−0.78 to −0.35)           | 0.038|
| PNS/LAMV indexed to BSA (%/mL/m²) | −0.026 (−0.058 to −0.016)      | −0.011 (−0.015 to −0.009)        | 0.030|
| PNS/LAmV indexed to BSA (%/mL/m²) | −0.042 (−0.111 to −0.022)      | −0.018 (−0.023 to −0.012)        | 0.033|
| PPS (%)                  | 8.25 (6.56–12.60)               | 6.56 (4.88–8.29)                 | 0.128|
| PPS/LAMV indexed to BSA (%/mL/m²) | 0.20 (0.14–0.34)               | 0.15 (0.11–0.19)                 | 0.160|
| PPS/LAmV indexed to BSA (%/mL/m²) | 0.32 (0.22–0.56)               | 0.19 (0.14–0.28)                 | 0.089|

BSA, body surface area; LAMV, left atrial maximum volume; LAmV, left atrial minimum volume; LVEF, left ventricle ejection fraction; PNS, peak-negative strain; PPS, peak-positive strain. Statistically significant values are given in bold.

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**Figure 3**

ROC curve to show sensitivity and specificity of PPS to predict cardioversion success.
definition and tracking of speckles in the LA with a quality of tracking we believe would not improve much further with other software. We chose to evaluate only the six segments of an apical four-chamber view owing to the lack of good LA endocardial border definition in the two-chamber view in a considerable number of patients. Overall assessment of the various segments of the LA in apical two- and four-chamber views may provide more accurate data. We did not perform multivariate analysis given the low number of patients, which would render its interpretation difficult. These findings could have a major clinical impact in the future if confirmed by larger studies.

We believe that prospective studies of larger dimensions are required to evaluate myocardial deformation parameters in patients with supraventricular arrhythmias since they seem to provide important information for clinical decision-making regarding the best treatment strategy in this patient population, particularly concerning anticoagulation and cardioversion to sinus rhythm.

**Conclusion**

This study showed that in the near future, atrial deformation parameters could constitute complementary echocardiographic data in the management of patients with atrial fibrillation and atrial flutter. These parameters seem to be able to identify patients who have a higher thrombotic risk and should, therefore, undergo anticoagulant therapy. The parameters also appear to be a good predictor of unsuccessful electrical cardioversion and could be useful in the clinical management strategy of rhythm versus rate control in this patient population.

**Declaration of interest**
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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