

Troubles of Atrial Mechanical Recovery after Electrical Cardioversion in Patients with Persistent or Long-Lasting Persistent Atrial Fibrillation

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Abstract: *Background:* In the present retrospective cohort study we have evaluated the missed or delayed atrial mechanical recovery in a population of patients with persistent or long-lasting persistent atrial fibrillation (AF) who achieved restoration of sinus rhythm on the ECG by electrical cardioversion (ECV).

Methods: The endpoint of our study was the failure to recover the normal mechanics of the left atrium. Inclusion criterion was the persistent or long-lasting persistent AF successfully treated by means of ECV, provided that a pertinent documentation was made available, comprising ECG, conventional 2D echo-color-Doppler and speckle tracking echocardiography (STE) evaluation, with also a STE assessment of the atria at the days 1, 30 and 90 from the ECV freely available within the clinical record of the patient.

Results: Out of a total of 80 patients with persistent or long-standing persistent AF, retrospectively enrolled, as many as 22.5% of them did not achieve the normalization of their atrial STE profile, even though they had been converted to sinus rhythm on the ECG by means of ECV. The building of ROC curves allowed us to establish that early measurements of global atrial strain could serve to predict both the risk of failure to recover the atrial mechanical function and the one of AF relapses over a 12 month follow-up. The values of 18% and 17% were also calculated to serve as cut off values, respectively, for the risk of atrial mechanical dysfunction and for the risk of AF relapses over a 12 month follow-up.

Conclusions: Failure to recover the atrial reservoir function can accompany a restoration of sinus rhythm on the ECG in patients with long-standing persistent AF. In this case a serial STE evaluation could be useful to evaluate the atrial hypofunction over time.

Keywords: Atrial fibrillation, electrical cardioversion, atrial mechanical recovery, speckle tracking echocardiography, outcome.

INTRODUCTION

If atrial fibrillation (AF) persists for a long time - for more than 48 hours, persistent AF, or for more than twelve months, long-lasting persistent AF - the method adopted for converting AF to sinus rhythm is usually the ECV, although, in the most of the dedicated centers, an initial attempt at pharmacological cardioversion with the use of intravenous amiodarone or propafenone is generally implemented [1].

Unlike recent onset atrial fibrillation (≤ 48 hours, paroxysmal AF), the persistent or long-lasting persistent AF requires a minimum period of three weeks of full anticoagulation, carried out by means of warfarin, in the case of valvular AF, i.e., associated with mitral stenosis or mitral prosthesis, or, in the case of non-valvular AF, carried out by means of a non-vitamin K antagonist oral anticoagulant.

A not completely clarified issue is the fact that a post-cardioversion very prolonged stunning might take place in a certain number of patients. In the case of persistent or long-lasting persistent AF, it is well-known that an atrial both anatomic and electrical remodeling takes place usually. Moreover, in the patients converted to sinus rhythm, it is known that a certain timeframe has to pass before this unfavorable remodeling can regress or disappear.

In short, in the period immediately following the ECV, a reduction of global atrial strain (GSA+) in the reservoir phase of the atrial cardiac cycle is detected usually using speckle tracking echocardiography (STE). The acronym adopted is GSA+, which stands for global strain of the left atrium, while the sign + represents the percentage increase in left atrial volume that occurs at this stage. In patients with persistent AF or long-lasting persistent AF, low values of GSA+, detected at the hours immediately subsequent to the ECV, are a relatively frequent finding [2]. Moreover, in about 75% of patients, there is a recovery of the atrial global strain over the course of the days, with

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consequent restoration of the end-diastolic contractile efficiency of the atria, and normalization of their function of mechanical contribution to the ventricular filling. However, in about a quarter of patients with previous persistent or long-lasting persistent atrial fibrillation converted to sinus rhythm, the pharmacological or electrical cardioversion is not able to gain the atrial mechanical recovery, even if sinus rhythm has been achieved on ECG [3]. The due emphasis should be given to this ominous functional behavior, because of its unfavorable prognostic implications. The lack of atrial mechanical normalization can be diagnosed based on the Doppler-velocimetric profile of the mitral valve using the echo 2D Doppler or by relying on the STE, namely taking into account the GSA + [4]. Persistent low values of GSA + are irreconcilable with a good recovery of the atria. Even when not affected by AF recurrences, the atria may be more vulnerable to the risk of blood stasis, red cell stacking and left atrial appendage thrombosis. Furthermore, in these cases the emptying velocity of the left atrial appendage is lower. Besides, more often the atria which do not recover show increased volume and are associated with high circulating levels of natriuretic peptides -atrial natriuretic peptide and B-type natriuretic peptide-, an indirect proof of high left ventricular end-diastolic pressure. It is also ascertained that if the atria are involved by a prolonged or permanent "stunning", with a low GSA+, they are likely to be burdened by a greater amount of fibrosis. Both atrial fibrosis and high ventricular end-diastolic pressure, the latter testified by a high E/e' ratio [5] not only contribute to weakening or suppressing atrial mechanical contraction, even in the presence of sinus rhythm on ECG, but are risk factors for new AF episodes. Another potential implication could be that in these patients devoid of effective atrial contribute, though showing sinus rhythm on ECG, a reduced GSA+ value could strengthen the indication for loop recorder implantation, to detect possible atrial arrhythmias, and/or for anticoagulation therapy, to prevent cardioembolic events [6]. Alternatively, patients without atrial mechanical recovery, identified by means of STE, could usefully undergo pharmacological prophylaxis with amiodarone or other antiarrhythmic agents against AF relapses [7]. On this point, however, the experimental and clinical evidence is sparse or much debatable [6-7].

Aims of the Study

The studies regarding the topic of the relationship between recurrent atrial fibrillation and global left atrial

strain (GSA+) are relatively few and all characterized by rather small sample sizes. Therefore, we felt that there was still enough room to perform an assessment of diagnostic odds ratio (DOR) concerning the diagnostic accuracy of the possible values of left atrial strain measured immediately after ECV (3 hours later) to be used as predictors of the risk of failure to recover the atrial function within the subsequent follow-up period of 12 months.

Furthermore, paying attention to the values of global left atrial strain (GSA +) measured at the third hour from ECV, we searched for the cut-off value capable of better discriminating the patients who would have developed AF relapses from those who would have remained free from AF in the subsequent 12 month follow-up period.

METHODS

The endpoint of our retrospective cohort study was the failure to recover the normal mechanics of the left atrium. Inclusion criteria were the persistent or long-lasting persistent atrial fibrillation successfully treated with ECV, provided that a pertinent documentation was made available, comprising ECG, conventional 2D echo-color-Doppler and STE evaluation, with also a STE assessment of the atria at the days 1, 30 and 90 freely available within the clinical record of the patient. For this study, the Institutional Review Board Approval was not required, considering the study features (retrospective cohort study). Moreover, this study was conducted in compliance with the ethical standards of the responsible Institution on human subjects as well as with the Helsinki Declaration. This study did not involve experiments on animals.

As regards the origin of the data used for making comparisons, it is composite, due to the fact that the pertinent database collects contributions attributable to patients belonging to Cardiology Outpatient Units and Inpatient Divisions of the ASL Napoli 1 Centro (Naples, Italy), as well as to the Arrhythmology Operational Unit of the "Pineta Grande" Clinic of Castelvolturno (CE), Italy.

EQUIPMENT

Conventional Echocardiography Evaluation

All the echocardiograms were performed by the same cardiologist (RDV) with specific training and experience in cardiovascular echocardiography, by using the portable Philips Sparq ultrasound machine with a 2.5MHz transducer.

All measurements were performed according to the Recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [8].

In the subsequent analysis the following parameters were considered: left atrium indexed volume (LAVi), left ventricle ejection fraction (LVEF) and the ratio of early diastolic mitral inflow velocity to early diastolic myocardial relaxation velocity (average E/e' ratio), considered a marker of diastolic ventricular function.

Speckle Tracking Echocardiography

The global and regional LA myocardial strain was measured by 2DSTE. Grey scale imaging of the four chamber and two-chamber views was obtained with a frame rate of 60–80 Hz. Recordings were processed with acoustic-tracking software (EchoPAC, GE Healthcare), allowing off-line semi-automated speckle based strain analysis. Briefly, lines were manually traced along the LA endocardium. An additional epicardial line was automatically generated by software, creating a region of interest (ROI). After manually adjusting the ROI shape, the software divided the LA region into six segments and generated the longitudinal strain curves. Once the longitudinal atrial strain curves were obtained, the following measurements were performed: positive global atrial strain (GSA+), during the reservoir phase, plotted as a positive curve at the aortic valve closure, and negative global atrial strain (GSA-), during the left atrial systole, plotted as a negative curve with a peak after the P wave on ECG.

For the planned analysis, GSA+ was considered, because it has been recognized to be the most important index of left atrium mechanical function [9]. All data were digitally stored and analyzed off-line with customized software.

Statistical Analysis

All statistical tests were performed with a commercially available statistical analysis program (SPSS 15.0 for Windows, SPSS Inc., Chicago, IL, USA). The distribution of the data was assessed using the one-sample D'Agostino-Pearson test. Continuous variables displaying normal distribution were expressed as mean \pm SD, while values with asymmetric distribution were expressed as medians with interquartile ranges. Categorical variables were presented as percentages. One-way ANOVA test was

used, in order to generate the pertinent graph, showing the splitting of the values of GSA+ -measured after three hours from ECV – across the three identified categories:

a) failure to recover the atrial function, b) relatively early restoration of the atrial reservoir function- detected from one week to one month after the ECV- c) relatively late restoration of the atrial reservoir function, identified not sooner than three months from the ECV. Besides, two Receiver Operating Characteristic (ROC) curves were built. The first ROC curve was built to identify among the GSA+ values taken 1 to 3 hours after the ECV the most accurate cut-off value capable of discriminating with the best balance of sensitivity and specificity the patients who would have gained the atrial mechanical recovery from those unable to retrieve the atrial mechanical function during a 3 month follow-up. Additionally, a second ROC curve was planned concerning the GSA+ values taken 1 to 3 hours after the ECV in order to detect the best cut-off value able to separate the patients who would have suffered from AF relapses from those who would have remained free from AF recurrences during a 12 month follow-up.

RESULTS

Patients who did not achieve the normalization of the atrial reservoir phase of the atrial mechanical cycle were 18/80 (22.5%). Their mean GSA+ measured from one to three hours after ECV was $16.44 \pm 4\%$. On the contrary, patients whose left atrial mechanical recovery was identified from one week to one month after cardioversion were 37/80 (46.2%). Their mean GSA+ measured from one to three hours after ECV was $22.45 \pm 3\%$. Moreover, patients whose left atrial recovery was identified at measurements performed three months after cardioversion were 25/80 (31.2%). Their mean GSA+ measured from one to three hours after ECV was $20.20 \pm 2.82\%$ (Figure 1).

Based on the results of the analysis of the ROC curves, the value of "basal" global atrial strain (GSA+), that is the GSA+ measured 1 to 3 hours after ECV, was associated with a significantly decreased risk of failure to recover the atrial reservoir function in the event that it was higher than + 18% (sensitivity: 83.2%; specificity: 76.7%) (Figure 2). Likewise, the value of "basal" global atrial strain (GSA+), that is the GSA+ measured 1 to 3 hours after ECV, was associated with a significantly decreased risk of AF relapse over a follow-up of 12 months in the event that it was higher than + 17%

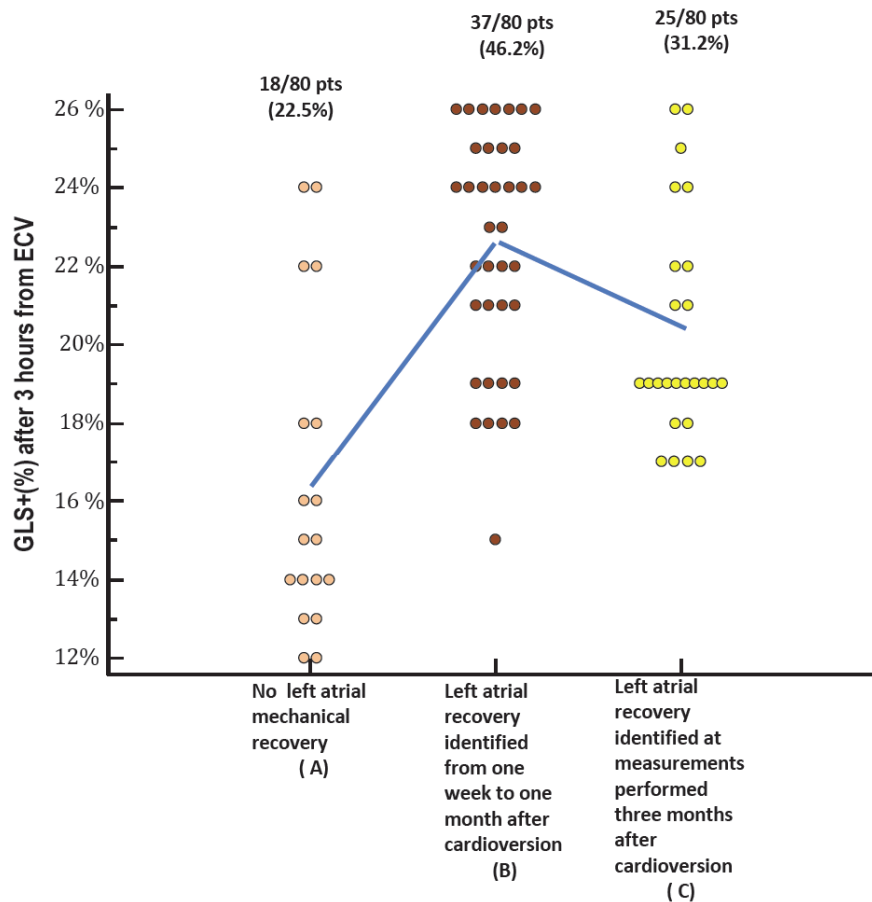


Figure 1: In this plot the global left atrial strain (GSA +) values after 3 h from the ECV are represented with regard to their distribution across the 3 categories corresponding to the different behavior in the short-medium term of the left atrial reservoir function : failure to recover the atrial function (GSA +: <18%) still persisting after 3 months (A); relatively early restoration of the atrial reservoir function (GSA +: > 18%), detected from one week to one month after the ECV (B); relatively late restoration of the atrial reservoir function, identified not sooner than three months from the ECV (C). The graph provides a visual representation of the fact that low GSA + values at the third hour are associated with increased probability of post- cardioversion failure to recover the reservoir function of the left atrium. The blue connecting lines conjoin the mean values of GSA + of the three groups.

Legend: pts, patients; ECV, electrical cardioversion.

(sensitivity: 73,7 %; specificity: 95,1%) (Figure 3). In addition, in Figure 1 the global left atrial strain (GSA +) values measured 1 to 3 hours after the ECV are represented with regard to their distribution across the 3 categories corresponding to the different behavior in the short-medium term of the left atrial reservoir function: failure to recover the atrial function (GSA +: <18%) still persisting after 3 months (A); relatively early restoration of the atrial reservoir function (GSA +: > 18%), detected from one week to one month after the ECV (B); relatively late restoration of the atrial reservoir function, identified not sooner than three months from the ECV (C). The graph provides a visual representation of the fact that low GSA + values at the third hour are associated with increased probability of post-cardioversion failure to recover the reservoir function of the left atrium.

DISCUSSION

Our study has outlined the problem of recovering atrial efficiency after ECV. Currently the increasing use of radiofrequency ablative therapy for AF has raised some doubts especially in the case of ablation applied to persistent or long-lasting persistent AF in patients with heart failure with reduced ejection fraction (HFREF)(10). Moreover, the CABANA trial (11), that used the composite end point of all cause-death, disabling stroke, major bleeding events and cardiac arrest, was not able to document with the method of the intention to treat a superiority of trans-catheter ablation compared to conventional therapy possibly integrated by the addition of antiarrhythmic drugs. Our study in turn raises the question that in persistent or long-lasting persistent AF the rhythm control strategy is

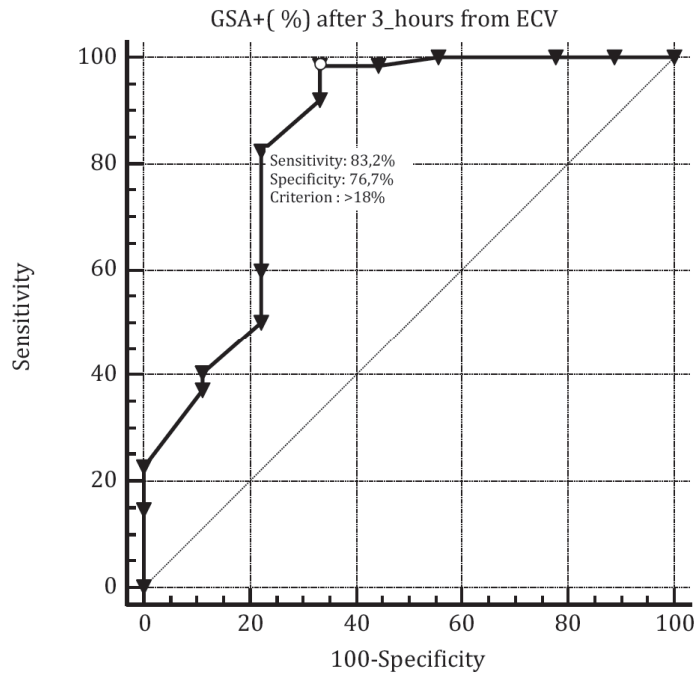


Figure 2. The value of "basal "global atrial strain (GSA+), that is the GSA+ measured after 3 hours from electrical cardioversion is associated with a significantly decreased risk of failure to recover the left atrial reservoir function when it is superior to the cut-off value of 18%.

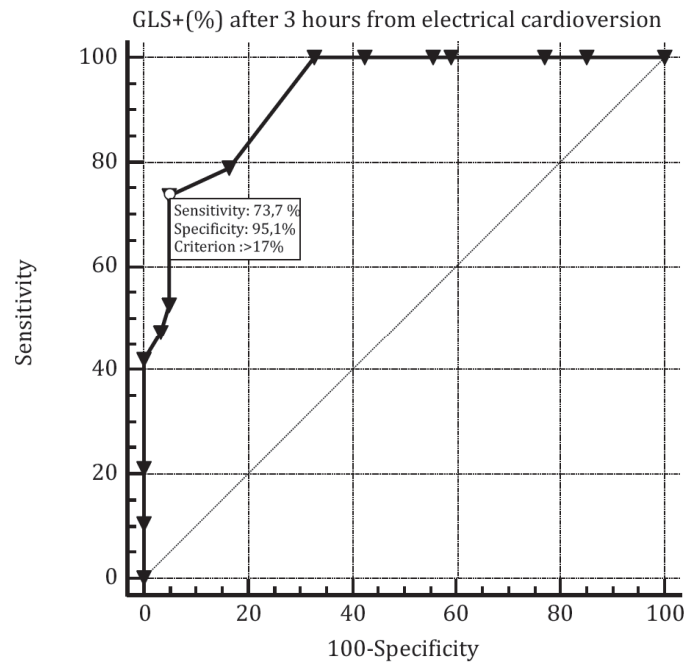


Figure 3: The value of "basal "global atrial strain (GSA+), that is the GSA+ measured after 3 hours from electrical cardioversion is associated with a significantly decreased risk of AF relapse over a 12 month follow-up when it is superior to the cut-off value of 17%.

ineffective because in about a quarter of cases it would bring about a fictitious improvement, i.e., the recovery of sinus rhythm on ECG, which does not find a mechanical equivalent due to a real atrial electromechanical dissociation. In other words, the ECG finding of sinus rhythm does not yield the benefits

that such a change should entail as the reservoir phase of the atrial mechanical cycle is indefinitely impaired or suppressed. Therefore also the end-diastolic contribution to ventricular filling is abolished in these cases. Relatively few studies have dealt with the subject [2,3,6,12,13]. However, electrocardiographic

success is not synonymous of mechanical and/or clinical success. Surveillance should not be limited to the prescription of anticoagulant therapy for 4 weeks after cardioversion. It should also include the serial STE ultrasound practice to evaluate the evolution over time of the post-procedural residual atrial mechanical hypofunction. There are patients whose atria improve slowly and others where mechanical normalization never occurs. In the latter it is legitimate to expect recurrent AF episodes. Furthermore, in these patients, even when free from AF relapses, the unsatisfactory atrial mechanical performance results in the lack of clinical benefit. Thus cardioversion has no favorable effect, for example, on a possible process already in progress towards the clinical picture of heart failure. We still lack data that allow us to affirm the possibility of differentiated pharmacological protocols of secondary prevention of AF on the basis of the STE findings, i.e., based on whether or not the patient has resumed a satisfactory atrial function. Finally, we are waiting for drugs able to improve the function of the reservoir phase of the atrial mechanical cycle. Is this an unrealistic expectation?

CONCLUSIONS

In the present retrospective cohort study as many as 22.5% of patients with persistent or long-standing persistent AF did not achieve the normalization of their atrial STE profile, even though they had been converted to sinus rhythm on the ECG by means of ECV. This finding prompts the attending physician to careful surveillance, even by executing serial STE assessment in order to evaluate the evolution of this atrial hypofunction over time.

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