The echocadiografic assessment of left atrium size and functions in patients with heart failure undergoing cardiac resynchronization therapy

Scientfic coordinator: Prof. Dan Dobreanu, MD, PhD

PhD candidate: Silvia-Elisabeta Lupu

During the last decade, cardiac resynchronization therapy has become an excellent and widely used procedure for the treatment of a specific category of heart failure patients. Current heart failure guidelines released by the European Society of Cardiology in 2016 firmly recommend cardiac resynchronization therapy for the treatment of patients with heart failure (class II NYHA or higher) who are on optimal medical therapy, have left bundle branch block, wide QRS ≥130 msec and decreased left ventricular ejection fraction (≤35%) (Class I indication). Guidelines recommendations also extend to patients with similar characteristics who have non-left bundle branch block QRS morphology, provided that QRS width is at least 150 msec (class IIa recommendation, level of evidence B).

The echocardiographic assessment of such patients is currently challenging, as pooled evidence on different parameters is either insufficient or conflicting. The single echocardiographic parameter mentioned by the guidelines for cardiac resynchronization therapy patients selection is the left ventricular ejection fraction, despite the fact that many other parameters have been tested for this purpose. Besides patient selection, echocardiography has previously been used for optimizing atrio-ventricular and inter-ventricular delays, monitoring patient evolution and assessing prognosis, with variable results.

Currently, cardiac resynchronization therapy patients evaluation by echocardiography mainly implies the assessment of left ventricular dimensions, systolic and diastolic functions, right chambers quantification, including the probability of pulmonary hypertension, and the evaluation of mechanical dyssynchrony, although the utility and accuracy of the latter are debatable. Some authors suggested that left atrium dimensions and functions assessment by echocardiography may provide additional information regarding patient status and prognosis, mainly based on the previously proven connection between left atrium parameters and left ventricular diastolic dysfunction.

The topic was then approached by Yu et al., who suggested that the measurement of maximum, minimum and preA left atrial volumes indexed to body surface and the assessment of left atrium function by strain and strain rate imaging using speckle tracking might be useful for monitoring patient evolution and for prognostic purposes. Their research yielded positive results, showing left atrium dimensions and function improvement at three months after the implant procedure. D'Andrea et al. conducted a similar study, the main difference being the use of tissue Doppler-based techniques instead of speckle tracking for strain and strain rate assessment and of conventional echocardiography for volume-based atrial function parameters, as well as the fact that the first assessment after cardiac resynchronization therapy was performed 6 months after the implant procedure. None of these studies focused, however, on left atrium assessment in the acute phase, within a couple of days after device implant, nor is there any published data regarding the contribution of acute changes in cardiac mechanics to left atrium size and functions.

The current PhD thesis has been endorsed by a research project which focused on the echocardiographic study of left atrial size and function by conventional, previously described and validated methods, based on two-dimensional echocardiography. Currently, the guidelines recommend the evaluation of left atrial size by volumetric measurements indexed to body surface. The three main left atrial functions – the reservoir, conduit and pump function – can also be assessed by left atrium volumes-derived parameters, such as the global, passive and active left atrial emptying fractions.

The aims of the current study were to provide data on acute changes in the previously mentioned left atrial parameters following the improvement of cardiac mechanics immediately after device implantation; to assess possible correlations between left atrium parameters and parameters of atrio-ventricular, intra-ventricular and intra-ventricular dyssynchrony; to provide an extensive follow-up of patients who benefited from cardiac resynchronization therapy by conventional echocardiography techniques.

The main hypothesis behind the current study was that left atrium parameters might be influenced by acute changes in cardiac mechanics following resynchronization therapy, as well as by myocardial reverse-remodelling occurring during mid- and long-term evolution.

In order to test this hypothesis and accomplish the aims of this study, we enrolled patients who had a firm indication for cardiac resynchronization therapy. Patients were not admitted to the study if they were not in sinus rhythm at each evaluation, or if they had hemodynamically significant organic mitral valve disease, very low life expectancy (less than a year) due to heart failure and/or co-morbidities, and poor echocardiographic window. Patients were only admitted to the study provided that they agreed to sign the informed consents. The current research has been conducted according to the principles set out in the Declaration of Helsinki and approved by the Research Ethics Committee of the University of Medicine and Pharmacy by Decision no. 8/14.02.2014.

Consequently, we enrolled 28 consecutive patients who were hospitalized in the 1st Adult Cardiology Department of the Emergency Cardiovascular Disease and Transplant Institute of Targu Mures from February 2014 to February 2016. Each patient was submitted to a thorough evaluation protocol, which included accurate history taking, physical examination, recording of a 12-lead ECG, a detailed echocardiographic assessment, as well as device interrogation. The six minute walk test was performed to assess functional capacity and patients were also invited to respond to the Minnesotta Living with Heart Failure Questionnaire to help assess quality of life. Patients were examined before and within two to three days, then at three and 12 months after the procedure.

25 out of the 28 patients have been examined before and within two to three days after the procedure. In these patients, left ventricular end-systolic and end-diastolic indexed volumes were significantly reduced – 111,5 (89,9-138,8) ml/m^2 vs. 106,4 ml/m^2 (81,7-132,2), p<0,01 and 83,9 ml/m^2 (64,5-111,0) vs. 78,1 (53,9-95,1), p< 0,0001, respectively, while the left ventricle ejection fraction was considerably improved - 22,0% (19,5-25,0) vs. 28,0% (26,0-30,5), p=0,0001. Maximum left atrial indexed volumes were significantly diminished after the procedure, by comparison with the baseline evaluation – 45,5 ml/m^2 (38,2-56,7) vs. 42,9 ml/m^2 (32,1 to 56,2),p <0,05, as were minimum atrial indexed volumes - 27,1 ml/m^2 (22,9-41,9) vs. 25,9 ml/m^2 (17,8-38,1), p <0,05, and indexed preA left atrium volumes - 40,0 ml/m^2 (31,3-53,0) vs. 35,5 ml/m^2 (25,8-49,1), p <0,05. Mitral regurgitation has also significantly reduced. Interestingly, no significant changes occurred in terms of diastolic function severity, or any of the left atrium function parameters.

At three months, left atrial volumes remained significantly reduced by comparison with the baseline evaluation, and a significant improvement of diastolic function was also recorded. The degree of diastolic dysfunction was diminished (p <0,01), as was the E/A ratio – 0,96 (0,70-1,65) vs. 0,66 (0,46-0,81), p<0,05, while the E wave deceleration time was increased – 145 msec (126-210) vs. 242 msec (173-278), p <0,001. The total emptying fraction of the left atrium has also considerably improved, from 30,3% (25,5-39,0) before device implant, to 39,5% (30,0-47,9) at three months, p <0,05, suggesting an improved reservoir function. The other parameters of left atrium function – namely the left atrium active and passive emptying fractions showed a trend towards improvement which did not reach statistical significance.

At 12 moths, 14 of the 28 patients were examined, and the resulting data was used for a sub-group analysis. Left ventricular end-systolic and end-diastolic indexed volumes were diminished by comparison with the baseline evaluation, and the left ventricle ejection fraction also increased. Among left atrial parameters, only the minimum left atrial indexed volume and the total emptying fraction were significantly improved at 12 months after the procedure – 26,9 ml/m^2 (21,9-42,0) vs. 20,3 (14,2-27,7) ml/m^2, p <0,05, and 33,2% (25,4-40,9) vs. 39,7% (32,4-58,3), p <0,05, respectively. However, neither of these parameters showed acute improvements within days after CRT. Notably, in this sub-group

the overall percentage of patients with ischemic dilated cardiomyopathy and restrictive diastolic dysfunction, both proven predictors of worse outcomes after cardiac resynchronization therapy, was higher than in the main group.

Based on these results, we concluded that cardiac resynchronization therapy may have an acute effect on left atrium dimensions in patients with favourable characteristics for the response to cardiac resynchronization therapy, and that this effect is justified by the immediate improvement in cardiac mechanics and the acute reduction of mitral regurgitation. Further improvement, at three months after the implant procedure can be justified by atrial and ventricular remodelling, which is consistent with the results of previously studies.

Given the lack of published studies on the topic, the current research provides a new outlook on the serial assessment of patients with cardiac resynchronization therapy, emphasizing the importance of left atrial size and function evaluation in the acute phase, within a couple of days after the implant procedure.