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WHY IS THE GROUP OF NON-RESPONDERS TO CARDIAC RESYNCHRONIZATION THERAPY SO LARGE? SOME ETHICAL AND MEDICAL ASPECTS OF THE TOPIC

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Abstract

The aim of this single centre study ("St. Ekaterina" Hospital) is to assess the effect of a second successful cardiac resynchronization therapy (CRT) in patients who had already had an unsuccessful implantation of a CRT system at other medical centres in Bulgaria and were defined as "non-responders". This is a prospective observational study. The patients have previously had an unsuccessful implantation of a left ventricular (LV) lead or the latter has not been placed in the target vessel. After the successful implantation of a new LV lead in another target vessel, the post-procedure criteria for echocardiographic (EchoCG) and clinical response were monitored. Over the period 2017–2019, 18 CRT systems have been implanted in 18 patients with an average age 65 ± 1 years with initial heart failure (HF) according to the Classification of the New York Heart Association (NYHA) class III. The average LV ejection fraction (LVEF) was $28 \pm 1\%$. After the successful implantation of a new LV lead, patients presented with HF class II–III and LVEF $36 \pm 1\%$. In the new "upgrading" procedure, 15 patients (83%) had a good clinical and EchoCG response, and two of those 15 patients were "super responders". The remaining three patients (17%) were "poor responders". After the good clinical and echocardiographic response to the therapy with a second successful implantation of a LV lead in another target vessel, an important question arises, whether all "non-responders" to the CRT are actually supposed to be defined as such.

Key words: cardiac resynchronization therapy (CRT), non-responders, left ventricular (LV) lead upgrade

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Introduction. Cardiac resynchronization therapy (CRT) is one of the successful therapies used in patients with symptomatic heart failure (HF) and evidence of interventricular dyssynchrony [1] and it is effective in only up to 70% of these cases [2, 3]. This raises the question why the group of non-responders is so large. A number of studies suggest that the CRT improves quality of life (QoL), reduces hospitalization and mortality in patients with heart failure, and positively affects the structural remodelling of the heart.

With the following article, we would like to provide a practical and comprehensive guidance for the clinician on how to manage the patient who does not improve after initiation of CRT and how to identify the reasons for nonresponse. However, a complete and comprehensive review of all the factors that are associated with nonresponse to CRT (e.g., baseline clinical characteristics like age, sex, ischemic etiology, atrial fibrillation, comorbidities, etc.) is beyond the scope of this manuscript and has been discussed in detail elsewhere.

The purpose of this single centre study ("St. Ekaterina" Hospital) is to assess what is the effect of the cardiac resynchronization therapy in patients who had already had an unsuccessful previous implantation of a CRT system at other medical centres in Bulgaria, (and were defined as "non-responders"), that was further followed by a second successful procedure.

Materials and methods. A prospective observational single centre study was performed at "St. Ekaterina" University Hospital in Sofia. The study monitored patients from other medical centres who had previously an unsuccessful implantation of the LV lead or the latter had not been placed in the appropriate target vessel for achieving optimal left ventricular stimulation. These patients were successfully implanted with a new left ventricular lead in another target vessel at "St. Ekaterina" Hospital. The post-procedure criteria for echocardiographic and clinical response were monitored.

Results. Over the period 2017–2019 at "St. Ekaterina" University Hospital in Sofia, new left ventricular leads were successfully implanted in 18 patients (14 male), as the primary procedure of all these patients was performed in another medical centre and they were all defined as "non-responders" or "unresponsive to therapy". The average age of these patients was 65 years, with the oldest being 84 years old and the youngest being 42 years old. They were divided by sex, respectively: female four and male 14. The initial heart failure according to the Classification of the New York Heart Association (NYHA) was Class III–IV and following the successful implantation of a left ventricular lead, the functional capacity improved to Class II–III. The initial mean left ventricular ejection fraction (LVEF) was $28 \pm 1\%$ and following the successful implantation of LV lead it was $36 \pm 1\%$. The mean ventricular complex duration (QRS) was 145 ± 1 ms and the mean stimulated ventricular complex duration (SQRS) was 128 ± 1 ms. The mean time from the primary procedure until the successful implantation of a LV lead or the upgrading with a new left ventricular lead was 11 ± 1 months, with the

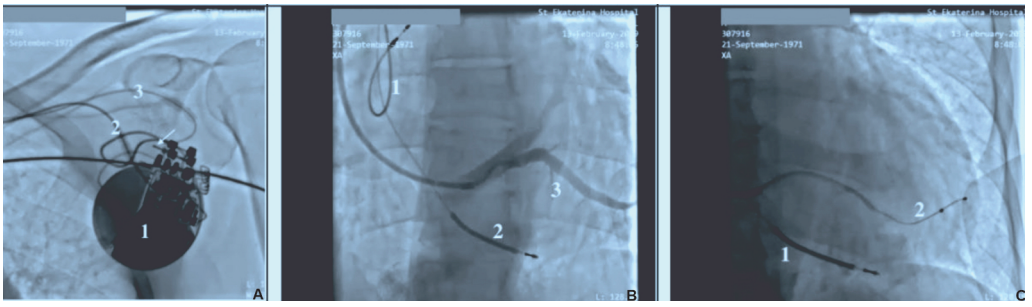


Fig. 1. **A:** CRT-D; 2. DF lead; 3. RA lead; 4. Arrow – Missing LV lead (the type of fluoroscopic projections – AP – antero-posterior)
B: 1. RA lead, 2.DF lead, 3. Postero-lateral lead
C: 1. DF lead, 2. Left ventricular quadripolar electrode

longest period being 36 months and the shortest being 4 months. In the primary procedure, a CRT-D device was implanted in six patients (33%) and a CRT-P device was implanted in 12 patients (67%). In five of the patients (28%), LV lead was not found in the implanted system, (Fig. 1) and for the other 13 patients (72%) the left ventricular stimulation lead was implanted in a non-target vessel.

In our study, we had five patients whose LV lead had not been implanted. We had other 13 patients whose LV lead had not been optimally stimulating the left ventricle. The LV lead was placed in the anterior branch of the coronary sinus in five patients (38%), of those 13 clinical cases (Fig. 2).

The LV lead was placed in the lateral and posterolateral branch in suboptimal position without reaching the optimal LV stimulation zone in six patients (46%) (Fig. 3).

The LV lead was in a posterior branch in one patient (8%); and was in a large cardiac vein in one patient (8%).

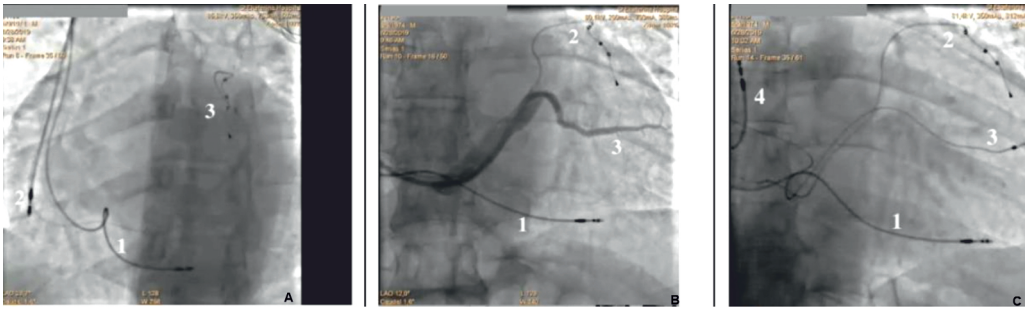


Fig. 2. **A:** 1. RV lead; 2. Dislocated RA lead; 3. Quadripolar LV lead placed in an anterior branch of CS (the type of fluoroscopic projections – left anterior oblique – LAO −40°)
B: 1. RV lead; 2. Quadripolar LV lead placed in the anterior branch of CS; 3. Lateral branch of CS (the type of fluoroscopic projections – AP – antero-posterior)
C: 1. RV lead; 2. Old quadripolar LV lead placed in an anterior branch of CS; 3. New LV lead placed in a lateral branch of CS; 4. New RA lead (the type of fluoroscopic projections – AP – antero-posterior)

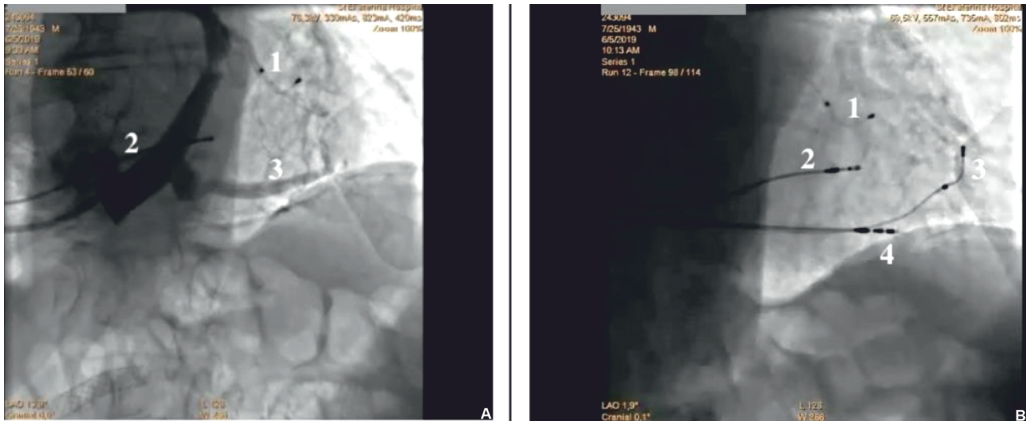


Fig. 3. **A:** 1. Old LV lead not reaching the targeted area; 2. RV lead placed in the mid-septal position; 3. Mid Cardiac Vein (the type of fluoroscopic projections – AP – antero-posterior) **B:** 1. Old LV lead not reaching the target area; 2. RV lead placed in the mid-septal position; 3. New LV lead placed in the middle cardiac vein; 4. New RV lead placed in the apex of the right ventricle (the type of fluoroscopic projections – AP – antero-posterior)

In the "upgrading" procedure at "St. Ekaterina" hospital, the LV lead was placed as follows: in a posterolateral branch in ten patients (56%) (Fig. 1B-3) in lateral branches in six patients (33%) (Fig. 2A, B), and in the middle cardiac vein in two patients (11%) (Fig. 3A, B). Patients were followed up for a period of one year (in the 3rd month, the 6th month, and the 12th month) whereby the post-procedure criteria for echocardiographic and clinical response were monitored. Fifteen of all 18 patients (83%) had a good clinical and echocardiographic response. Two patients of this group (11%) had a very good response and were defined as 'super-responders' (LVEF $47 \pm 1\%$; heart failure – ejection fraction class II according to NYHA). A poor echocardiographic and clinical response was recorded in three patients (17%) only. They were defined as 'non-responders'. At the same time the period until successful implantation of a left ventricular lead in one of the patients in this group was too long (36 months). A left ventricular assist device was implanted in this patient in the 7th month, following the second procedure.

Discussion. The use of CRT in a certain population of patients is a means of choice, even though it does not have the expected effect in every 3rd patient that has received this therapy. The expected good outcome as a result from the cardiac resynchronization therapy is determined by the successful implantation of a left ventricular lead placed in a target vessel of the coronary sinus. Coronary sinus intubation, insertion, and placement of a left ventricular lead in the target venous vessel may be a technical challenge and the therapy may fail due to various procedural or anatomical obstacles [4,5]. In recent years, the increased number of implantations of CRT has determined the growth of this procedure performance in medical centres. In clinical practice in other medical centres, there are cases of patients who had experienced unsuccessful attempts to be implanted with a left

ventricular lead, or that it had not been placed in the optimal position or in the "target vessel".

Meta-analyses have been published in which it is stated that with the greater experience of the operator the percentage of unsuccessful implantation of a LV lead decreases [6,7]. The anatomical and technical requirements may interfere with the optimal placement of the LV lead. The cases of patients with reimplantation in another target vessel, which leads to a successful procedure in the presence of appropriate but difficult coronary anatomy are analyzed [6, 7].

In all 18 patients in the study an appropriate anatomy of the coronary sinus existed and none of them required a surgical implantation of a left ventricular lead (epimyocardial lead). None of the patients were referred from another medical centre which is another topic for discussion. The need of monitoring procedure after implantation is obvious. Our experience shows that the group of responders might become larger if the LV lead was implanted in the optimal place. Very often, there are cases when the LV lead implanted is not in the optimal position for LV stimulation, instead it had been placed at the most effortless position for the operator. This procedure is challenging and quite often the final success depends on the operator's skills and experience. In this regard, if the operator is not able to implant the LV lead in the optimal position due to some reasons, it is a much better option to refer the patient to another centre instead of just leaving the lead in a non-target vessel.

Conclusion. The echocardiographic and clinical response in patients indicated for CRT with appropriate anatomy of the coronary sinus who have previously had unsuccessful procedure, and who subsequently had a successful second implantation of a left ventricular lead exceeded the expected good outcome for 'responders' and the therapy response. The appropriate implantation of a left ventricular lead is one of the main reasons for the good clinical and echocardiographic response to the therapy, and the time until the implantation of the lead determines the degree of effect. The successful implantation of a new left ventricular lead in a target venous vessel of the coronary sinus defined most of these patients as 'responders', i.e., responding to the therapy, as the level of the final effect was determined by the amount of time prior to the implantation. As a result, an important question arises, whether all "non-responders" to the CRT are actually supposed to be defined as such.

The limitation of our study is that the sample group is small and does not allow any general conclusions, but data can be used in a bigger study.

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