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Does 'super-responder' patients to cardiac resynchronization therapy still have indications for neuro-hormonal antagonists? Evidence from long-term follow-up in a single center

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Abstract

Background Whether cardiac resynchronization therapy super-responders (CRT-SRs) still have indications for neuro-hormonal antagonists or not remains uninvestigated. **Methods** We reviewed clinical data from 376 patients who underwent CRT implantation in Fuwai Hospital from 2009 to 2015 and followed up to 2017. CRT-SRs were defined by an improvement of the New York Heart Association functional class and left ventricular ejection fraction to ≥ 50% in absolute values at 6-month follow-up. All CRT-SRs were assigned into two groups on the basis of whether persistently receiving neuro-hormonal antagonists (NHA) (defined as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and β-blockers) after 6-month follow-up and then we compared long-term outcome. **Results** A total of 60 patients met criteria for super-response. One of thirteen (7.7%) CRT-SRs without NHA had all-cause death, which also occurred in 2 of 47 (4.3%) in CRT-SRs with NHA (P = 0.526). However, 3 of 13 (23.1%) CRT-SRs without NHA had heart failure (HF) hospitalization, 1 of 47 (2.1%) CRT-SRs with NHA had this endpoint (P = 0.040). Besides, subgroup analysis indicated that, for ischemic etiology group, CRT-SRs receiving NHA had considerably lower incidence of HF hospitalization than those without NHA (0 *vs.* 75%, P = 0.014), which was not observed in non-ischemic etiology group (2.6% *vs.* 0, P = 1.000) during long-term follow-up. **Conclusions** Our study found that for ischemic etiology, compared with CRT-SRs with NHA, CRT-SRs without NHA were associated with a higher risk of HF hospitalization. However, for non-ischemic etiology, we found that CRT-SRs with NHA or without NHA at follow-up were associated with similar outcomes, which needed further investigation by prospective trials.

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1 Introduction

Cardiac resynchronization therapy (CRT) has emerged as an important treatment for heart failure with reduced ejection fraction (HFrEF), despite optimal pharmacological therapy.[1,2] Randomized trials have demonstrated that CRT can reduces symptoms, mortality, and heart failure (HF) hospitalization.[2–4] Moreover, several studies have indicated that it even improves reduced left ventricular ejection fraction (LVEF) to normal in some patients with HFrEF, 'super-responders'.[5,6]

Optimal pharmacological therapy is considered as a prerequisite to consideration for CRT.[7] Neuro-hormonal antagonists [angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and β-blockers (BBs)] serve as the essential component of neuro-hormonal antagonists (NHA), which, however, are recommended by guidelines only for the treatment of HFrEF.[7] Therefore, whether CRT super-responders (CRT-SRs), whose reduced LVEF have been improved dramatically, still have indications for NHA or not remains uninvestigated.

In addition, long-term registry shows that the majority of patients with HFrEF does not receive the target dosage of NHA.[8] Their relatively serious conditions of heart failure result in their intolerance of target dosage. According to our speculation, there is higher possibility that CRT-SRs, bene-

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fiting from bi-ventricular pacing which improves cardiac function, can be treated with target dosage in clinical practice.

Consequently, our study aims to evaluate the state of NHA used in CRT-SRs in clinical practice. We seek to explore, most importantly, the association between long-term NHA use and all-cause mortality, together with cardiac death and HF hospitalization.

2 Methods

2.1 Study population

Our study population consisted of 376 consecutive patients with HFrEF, who successfully underwent CRT-Pacing (CRT-P) or CRT-Defibrillator (CRT-D) implantation in Arrhythmia Center of Fuwai Hospital (Beijing, China), between January 2009 to December 2015. Indication for CRT implantation was based on the latest Guidelines (symptomatic HF, LVEF ≤ 35%, QRS duration ≥ 130 ms, despite ≥ 3 months of NHA).[7] Patients were excluded if they underwent CRT for pacemaker upgrade, because they had chronic right ventricular pacing. The enrolled patients were at least 18 years old, willing to return for a follow-up visit in regular intervals. The study conforms to the Declaration of Helsinki. All patients provided written informed consent and the ethics committee of Fuwai Hospital approved this study.

2.2 Device implantation and program optimization

The CRT-P (D) devised and leads used were manufactured by Medtronic (Minneapolis, MN, USA), St. Jude Medical (St. Paul, MN, USA), Biotronik (Berlin, Germany) or Boston Scientific [Natick, MA, USA, formerly CPI, Guidant (St. Paul, MN, USA)]. The coronary sinus (CS) was cannulated from left subclavian and/or cephalic entry site using a commercially available long peelable guiding sheath. The LV lead was positioned in the venous system, preferably in the lateral or posterolateral vein. The right atrial (RA) and right ventricular (RV) leads were positioned conventionally in the RA appendage and the RV apex, respectively. Leads were connected to the corresponding CRT-P (D) device. All procedures were performed under local anesthesia.

After implantation, atrioventricular delay optimization was programmed individually to reach the optimal diastolic filling using the Doppler mitral inflow before discharge.[9] V-V delay ranged from 0 to 40 ms, according to the standard of the shortest biventricular paced QRS duration.

2.3 Echocardiographic evaluation and definition of NHA and super-response

All patients underwent two-dimensional echocardiographic evaluation before and 6 months after implantation in ultrasound room. Echocardiographic parameters including left atrial diameter (LAD), interventricular septum thickness (IVS), left ventricular end-diastolic dimension (LVEDD) and left ventricular ejection fraction (LVEF) were routinely measured. LVEF was measured using the modified Simpson method.

In our study, NHA was defined as ACEIs/ARBs and β-blockers, not including mineralocorticoid receptor antagonists (MRAs). Because practical guidance from guidelines recommended that MRAs should be added when patients remain symptomatic despite treatment with ACEIs/ARBs and BBs. Super-response was defined by an improvement of the New York Heart Association functional class (NYHA) and LVEF to ≥ 50% in absolute values at 6 month after implantation.

2.4 Follow-up and data collection

Periodical follow-up visits were scheduled every 6–12 months, or more often when clinically indicated, which were told repeatedly at discharge. Besides, we made a telephone to patients or their family members at regular intervals, to remind them of next visit or to find endpoints. During visits, patients were clinically assessed and devices were interrogated. Also, medications were asked and recorded in details. The target dosage of NHA was in accordance with the latest Chinese Guidelines of HF.[10] For those CRT-SRs who had stopped NHA by themselves after discharge for certain reasons (e.g., feeling himself being cured, concerned about drug-related effects), if they had no indication (e.g., atrial fibrillation, hypertension) for NHA, we did not advise them to receive NHA again and regarded them as non-NHA patients in order to continue observation. However, for those who had indications for NHA, we advised them to continue receiving NHA at follow-up. If they did not receive NHA over half of their follow-up period for the same reasons mentioned above, we also regarded them as non-NHA patients. Patients were considered lost to follow-up if their telephone could not be connected more than three times. All enrolled patients were followed up to December 2017.

Baseline clinical data during hospitalization, including demographic characteristics, laboratory data, medications, were obtained from Fuwai Electronic Medical Record System.

Finally, we reviewed the long-term follow-up in CRT-SRs. Patients who persistently adhered to NHA after 6-month follow-up were assigned to the NHA group. In contrast, for those who did not persistently receive either or both of the neuro-hormonal antagonists over half of their

follow-up period were assigned to the non-NHA group. We compared the long-term follow-up outcomes between those two groups.

2.5 Endpoints

The primary endpoints were defined as follows: (1) all-cause death; (2) cardiac death; and (3) HF hospitalization.

2.6 Statistical analysis

Continuous variables are expressed as mean ± SD or median (interquartile range) and categorical variables as percentage. For group comparisons, the Student *t* test or Mann-Whitney *U* test for continuous variables and chi-square test or Fisher's exact test for categorical variables were used. All tests were two-tailed, and a significant difference was considered at the $P < 0.05$. Statistical analysis was performed using the SPSS 22.0 statistical software package (SPSS, Inc, IBM, Armonk, New York).

A multivariable analysis and a Kaplan-Meier were not feasible due to the limited number of events.

3 Results

3.1 Clinical characteristics

Between January 2009 and December 2015, a consecutive cohort of 376 patients with HFrEF successfully underwent CRT implantation and were followed up to December 2017, whereas 365 were eligible for exclusion. Therefore, a total of 61 (16.7%) patients met the criteria for super-response, and 60 CRT-SRs were enrolled in the final analysis (unfortunately one CRT-SR lost in follow-up). Of this total, 47 CRT-SRs were assigned to the NHA group, while 13 CRT-SRs were assigned to the non-NHA group. Overall, the two groups were approximately balanced with respect to baseline characteristics. Baseline characteristics are summarized in Table 1.

3.2 Use of NHA in real world

The proportion of CRT-SRs without NHA in real world was unexpectedly high, about 21.3%. Figure 1 displays the reasons why enrolled CRT-SRs did not persistently adhere to NHA after 6-months follow-up. The main reason was poor compliance to drug (53.8%), followed by blood pressure intolerance and impaired renal function at follow-up (30.8% and 15.4%, respectively). In CRT-SRs with poor compliance to NHA, four patients lived in remote villages in the northwestern of China, where they could not buy the same brand of medicine as that from our hospital. They felt good and refused to take another type of ACEI, ARB or BBs from local hospitals. Another two patients believed that their heart disease had been almost cured by the implanted

Table 1. Clinical characteristics in super-responders to CRT with or without NHA at 6-month follow-up.

	Non-NHA group (*n* = 13)	NHA group (*n* = 47)	*P*-value
Basic parameters			
Age, yrs	62 ± 12	59 ± 10	0.338
Women	5 (38%)	22 (47%)	0.420
BMI, kg/m^2	24 ± 6	24 ± 4	0.434
Smoking	5 (38%)	17 (36%)	0.879
Alcohol	5 (38%)	15 (32%)	0.658
Cardiac history			
Non-ischemic etiology	9 (69.2%)	38 (80.9%)	0.450
Sinus rhythm	11 (84.6%)	45 (95.8%)	0.202
Hypertension	5 (38.5%)	25 (53.2%)	0.347
Diabetes	2 (15.4%)	9 (19.1%)	0.883
Coronary heart disease	5 (38.5%)	16 (34.0%)	0.767
Prior MI	2 (15.4%)	3 (6.4%)	0.295
Clinical parameters			
Systolic blood pressure, mmHg	110 ± 17	116 ± 19	0.205
Diastolic blood pressure, mmHg	70 ± 10	70 ± 10	0.942
Pacing QRS, ms	136 ± 7	140 ± 8	0.469
Percentage of Biv-pacing	99% ± 1%	98% ± 4%	0.645
Hemoglobin, g/L	136 ± 22	134 ± 15	0.930
Albumin, g/L	42.4 ± 2.5	42.5 ± 3.1	0.254
BUN, mg/dL	20.3 ± 7.9	19.4 ± 6.5	0.266
Creatinine, mg/dL	1.00 ± 0.38	0.95 ± 0.20	0.136
NT-proBNP level, pg/mL	685.0 (400.5, 839.5)	444.4 (211.0, 721.3)	0.157
Medications			
Diuretic	6 (46.1%)	44 (93.6%)	< **0.001**
ACEI or ARB	7 (53.8%)	47 (100.0%)	< **0.001**
β-blocker	7 (53.8%)	47 (100.0%)	< **0.001**
MRA	6 (46.1%)	44 (93.6%)	< **0.001**
Echocardiographic parameters			
LVEF, %	52.8% ± 2.9%	54.0% ± 4.2%	0.358
LVEDD, mm	53.6 ± 5.9	52.5 ± 6.1	0.582
IVS, mm	9.0 ± 1.0	10.0 ± 8.0	0.631
LA, mm	40.0 ± 7.0	38.0 ± 5.0	0.242

Data are presented as median ± SD or *n* (%) unless other indicated. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; BUN: blood urea nitrogen; CRT: cardiac resynchronization therapy; IVS: interventricular septum; LA: left atrial; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; NHA: neuro-hormonal antagonists; NT-proBNP: N-terminal pro brain natriuretic peptide.

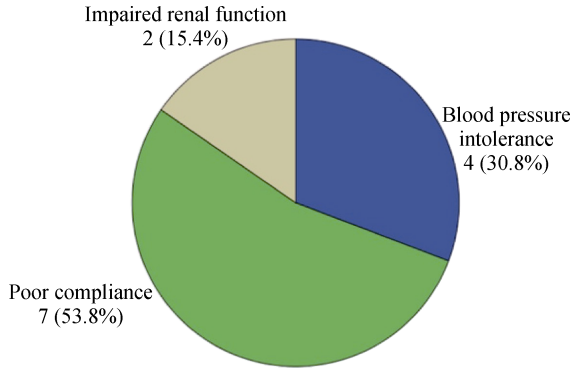

Figure 1. Pie chart showing the proportion of causes in CRT-SRs without NHA. CRT-SRs: cardiac resynchronization therapy super-responders; NHA: neuro-hormonal antagonists.

device, so they refused to take long-term medicine in fear of the drug-related effects. The last patient was a local elderly woman, with a poor memory. She lived alone since her daughter domiciled abroad, and always forgot to take medicine.

3.3 Follow-up and outcomes

The median follow-up was 56.9 months (interquartile range, 45.3–84.6 months). The shortest and longest follow-up period was 26.3 months and 109.2 months, separately. Compared to non-NHA group, LVEF (54.0% ± 4.2% *vs.* 52.8% ± 2.9%; $P = 0.358$) and LVEDD (53 ± 6 *vs.* 54 ± 6 mm; $P = 0.582$) at 6-month follow-up were approximately balanced with NHA group, but at last follow-up, LVEF (56.4% ± 6.6% *vs.* 49.8% ± 5.9%; $P = 0.002$) and LVEDD (51 ± 5 *vs.* 55 ± 5 mm; $P = 0.008$) in NHA group were significantly greater than those in non-NHA group (Figure 2).

With respect to the target dosages of the neuro-hormonal antagonists, only 11 (23.4%) CRT-SRs were on the target dosages of ACEI/ARB suggested by the current Chinese guidelines among those who persistently took these antagonists.[10] The number of patients on the target of BBs were relatively higher, 16 (34.0%).

For primary outcome, three CRT-SRs died from malignant tumor. The rates of all-cause death were not significantly different between the NHA group and the non-NHA group (4.3% *vs.* 7.6%; $P = 0.526$). The rate of cardiac death was 0 in CRT-SRs during this long-term period, while HF hospitalization occurred in three CRT-SRs (23.1%) in the non-NHA group and in one CRT-SR (2.1%) in the NHA group ($P = 0.040$). The description of those CRT-SRs suffered HF hospitalization are shown in Table 2.

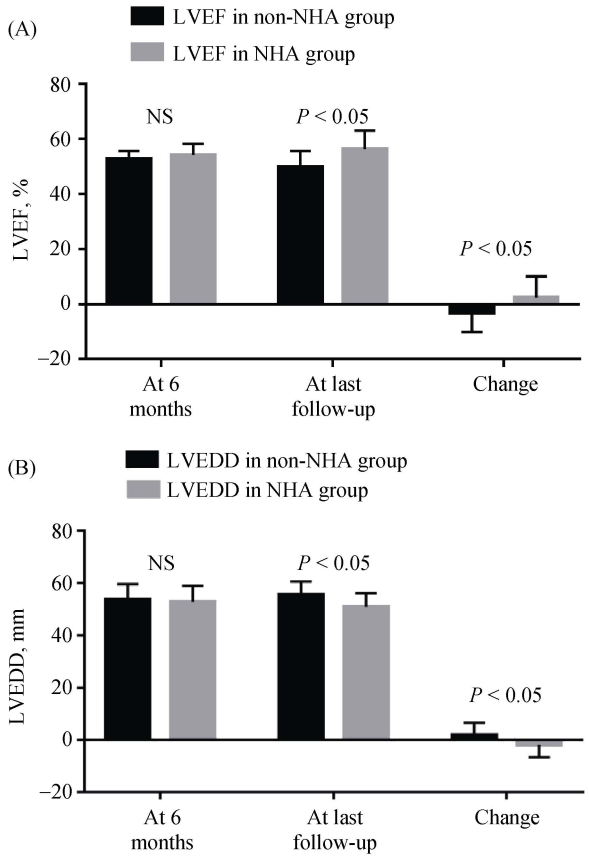

Figure 2. Changes in LVEF (A) and LVEDD (B) during follow-up. Both LVEF and LVEDD at last follow-up ($P < 0.05$), and change from 6-month follow-up to last follow-up ($P < 0.05$) were significantly different between the NHA group and the non-NHA group. LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; NHA: neuro-hormonal antagonists.

Table 2. Description of the super-responders to CRT suffered HF hospitalization.

	Groups	Age (yrs)	Sex	Etiology	LVEF before CRT implantation	LVEF at 6-month follow-up	LVEF at 1-year follow-up	LVEF at 2-year follow-up	LVEF during HF hospitalization	Duration*
Patient 1	Non-NHA	73	Female	Ischemic	35%	53%	55%	-	28%	19 months
Patient 2	Non-NHA	58	Male	Ischemic	20%	51%	50%	-	25%	16 months
Patient 3	Non-NHA	73	Male	Ischemic	33%	60%	53%	-	34%	18 months
Patient 4	NHA	48	Male	Non-ischemic	30%	52%	66%	46%	35%	23 months

*From 6-month follow-up to the first hospitalization for HF. CRT: cardiac resynchronization therapy; HF: heart failure; LVEF: left ventricular ejection fraction; NHA: neuro-hormonal antagonists.

Table 3. Subgroup analysis for long-term outcome in super-responders to cardiac resynchronization therapy.

No. of patients	Ischemic		*P*-Value	Non-ischemic		*P*-Value
	Non-NHA group	NHA group		Non-NHA group	NHA group	
Total	4	9		9	37	
HF hospitalization	3 (75%)	0	0.014	0	1 (2.6%)	1.000

Data are presented as *n* (%) unless other indicated. HF: heart failure; NHA: neuro-hormonal antagonists.

Furthermore, the results of subgroup analysis are shown in Table 3. For ischemic etiology group, CRT-SRs receiving NHA had considerably lower incidence of HF hospitalization than those without NHA (0 *vs.* 75%, $P = 0.014$), which was not observed in non-ischemic etiology group (2.6% *vs.* 0, $P = 1.000$).

In the non-ischemic group, the only HF hospitalization was observed in a 48-year-old man, diagnosed with dilated-phase hypertrophic cardiomyopathy by endo-myocardial biopsy and treated with CRT (Medtronic C2TR01) on 6 May 2015. He adhered to NHA after discharge, and LVEF before CRT implantation, at 6-month follow-up and at 1-year follow-up was 30%, 52% and 66%, separately. But LVEF at 2-year follow-up was reduced to 35% and he had HF hospitalization at Fuwai emergency department in October 2017.

Multivariable analysis and Kaplan-Meier were not attempted because of the small number of endpoint events.

4 Discussion

The main result of our study was CRT-SRs in non-ischemic etiology, whether persistently adhering to NHA or not, had no significant difference in long-term outcomes. We also found the proportion of CRT-SRs, who could receive the target dosage of NHA after discharge, was actually not high in clinical practice.

4.1 Adhering to NHA and long-term outcome in CRT-SRs

Previous clinical researches have demonstrated the excellent long-term prognosis in CRT-SRs. In the MADIT-CRT, non-fatal HF events or all-cause death, the primary endpoint, occurred only in 2.6% of the CRT-SRs.[11] Zecchin, *et al*.[12] observed 62 CRT-SRs for a mean follow-up of 68 ± 30 months and found the rate of all-cause death, cardiovascular death and HF hospitalization was 6%, 1.5% and 2%, separately. More recently, a longer follow-up (a median of 5.3 years) by Ghani, *et al*.[13] showed that, among 56 CRT-SRs the all-cause mortality and the rate of HF hospitalization were 13% and 9%, respectively, but no cardiac death occurred. In our study which followed up for a median of 56.9 months, we showed the rate of all-cause death, cardiac death and HF hospitalization in 60 CRT-SRs was 5%, 0 and 6.7%, separately. The results of outcome were similar to studies mentioned above.

The treatment of etiology of chronic heart failure is essential for patients to recover normal left ventricular function and functional state, which explains why CRT-SRs have a benign prognosis.[14] LBBB has been demonstrated as a common and important etiology of the heart failure, which causes bi-ventricular contraction disturbances that can be treated by CRT. LBBB induces abnormalities in left ventricular performance due to abnormal asynchronous contraction patterns, resulting in left ventricular systolic failure.[15,16] Previous studies have showed that in some patients the LBBB-induced abnormal LV contraction pattern could induce Non-ischemic cardiomyopathy (NICM), illustrating the concept of LBBB-induced cardiomyopathy and latent cardiomyopathy.[14,17,18] The reason why some patients can meet super response to CRT and maintain such normalcy, in our speculation, was that LBBB may be the key risk factor for chronic heart failure in these patients.

4.2 LBBB: the key etiology of chronic heart failure in CRT-SRs

The theory of CRT in the treatment of chronic heart failure is to correct mechanical desynchronization, with the reversal of LBBB by LV-based pacing, and several studies have shown that patients with LBBB morphology are more likely to respond favorably to CRT.[11,16,19] So, guidelines point out that patients with LBBB QRS morphology are specifically recommended to undergo CRT implantation.[7] However, in clinical practice, there are many adverse factors affecting how patients meet super response, such as the position of LV lead in the venous system, the co-morbidities that impair cardiac function. Admittedly, before CRT implantation, we could not guarantee patients with HFrEF and LBBB meeting super response. What we could assume is that, after CRT implantation, the results of super response show that LBBB may be the key etiology of chronic heart failure in CRT-SRs.

For non-ischemic etiology, our study found that adhering to NHA in CRT-SRs did not provide benefits in prognosis. In respect to drug therapy, for one part, there are few data

showing that, once LBBB occurs, the drug of NHA treatments can cause an electrical reverse remodeling and so restore a normal conduction.[15] But for CRT-SRs, amelioration of LBBB only achieved by bi-ventricular pacing could result in sustained reversal of severe LV dysfunction.[20–22] This is also why CRT-SRs have excellent prognosis. For another, the primary function of NHA is to antagonize disadvantageous neuro-hormonal over-activation induced by decreased cardiac output and ventricular overfilling. It cuts off the vicious circle that the over-activation of sympathetic nervous system and renin-angiotensin-aldosterone system, in turn, further contributes to myocardial fibrosis and even remodeling.[23–25] Merlo, *et al*.[26] observed LV reverse remodeling in IDCM receiving tailored medical treatment, and found that baseline predictors of LV reverse remodeling were higher systolic blood pressure and the absence of LBBB. Zou, *et al*.[27] showed that the normalization of LVEF in recent-onset cardiomyopathy was associated with a history of hypertension, higher systolic blood pressure at present, shorter electrocardiographic QRS duration at baseline. So, LV remodeling in patients with chronic heart failure can be reversed by drug therapy, mainly for those who have indications, such as reduced LVEF, hypertension. As mentioned above, CRT can treat LBBB- the main etiology of super-responders as assumed, and can also contribute to the normality of cardiac output and the alleviation of neuro-hormonal over-activation.[16,28] Besides, physicians used to deem that neuro-hormonal antagonists were essential and better benefited the patients than without it, but for those patients when their LVEF is normal before HFrEF, there is no current guidelines suggesting that any patients who may evolve into HFrEF should use NHA in advance to prevent.[7]

4.3 NHA should follow requirements in guidelines

For patients with chronic heart failure of non-ischemic etiology and LBBB who met super-responder after CRT, current guidelines show that there is no indication for them to use NHA, unless combined with other indications such as hypertension and/or atrial fibrillation.[7] Our study also supported that adhering to NHA made no difference in prognosis. On the contrary, the reason why CRT-SRs with ischemic etiology must adhere to NHA was that they have indications in guidelines.[29,30] Our study showed that CRT-SRs with ischemic etiology in non-NHA group had a higher rate of HF hospitalization than NHA group. Without indication in guidelines, additional use of ACEI, ARB or BBs, even demanding target dosage of drugs in CRT-SRs may incur more detrimental drug effects such as hypotension and/or hyperkalemia.

4.4 CRT-SRs may not maintain super response

In clinical practice, there are many risk factors impairing cardiac function in patients with chronic heart failure, such as LBBB, primary myocardial disease, myocardial ischemia, or diabetes. Merlo, *et al*.[26] found that patients with LV reverse remodeling only on optimal medical treatment can worsen again their LV function in long-term follow-up, suggesting that reverse remodeling although long-lasting, can be transient, or not complete. As mentioned above, the treatment of etiology of chronic heart failure is essential for patients to recover normal LV function and maintain this situation. Although LBBB, the major risk factor, can be effectively treated by CRT in CRT-SRs, their recovered normal LV function could worsen again because of untreated minor factors. In our study, 3 CRT-SRs with ischemic etiology in non-NHA group had HF hospitalization during follow-up, indicating that coronary ischemia without the treatment of BBs may induce cardiac dysfunction. Besides, one CRT-SR with non-ischemic etiology, diagnosed with dilated-phase hypertrophic cardiomyopathy, persistently adhered to NHA but had HF hospitalization during follow-up. We speculated that the possible reason was the progression of primary myocardial disease.

Hence, for CRT-SRs or patients with LV reverse remodeling just on optimal medical treatment, other uncontrolled risk factors that may lead to cardiac dysfunction can worsen again their LV function. The function of CRT or/and NHA is limited, the only effective way may be the cardiac transplantation.

4.5 Use of NHA in CRT-SRs in clinical practice

In our center, we found that the proportion of CRT-SRs who did not stick to NHA was 21.3%, half of whom have poor compliance to NHA. CRT coordinated bi-ventricular dyssynchrony and restored cardiac function in these patients, improving their exercise capacity and quality of life. Hence, instead of Neuro-hormonal antagonists used ineffectively before, CRT-SRs instinctively felt that only implanted device controlled the process of chronic heart failure. Besides, considering the costly CRT implantation and its equally expensive generator replacement, especially in China, and the side effects of drugs, CRT-SRs tended to stop NHA by their own decisions.

Theoretically, we speculate that devices that coordinate right and left ventricular contraction can significantly improve cardiac function and enhance functional capacity in CRT-SRs. Therefore, we hypothesized that for these patients who adhere to NHA after discharge, many of them can be treated with target dosage of Neuro-hormonal antagonists.

However, our study found that far fewer than half of the CRT-SRs were on the target dosage recommended by the current guidelines: 23.4% for ACEI/ARBs, 34.0% for BBs. In addition, the ESC Heart Failure Long-Term Registry, including patients with CRT implantation, showed that the target dosage of ACEI, ARB and BBs were used merely in 29.3%, 24.1% and 17.5% of patients with heart failure, respectively.[8] Also, in a published paper by Schmidt *et al*.,[31] 59.6% and 40.4% of CRT-SRs were on the > 50% target dosage of ACEI/ARB and BBs, separately.

Thus, according to Castellant, *et al*.[20] treatment of device only brought the chronic heart failure in CRT-SRs under control, rather than leading to temporary remission or curing. The treatment was continued after recovery, CRT-SRs remained stable and treatment could be disrupted but after a certain delay the initial disease reappeared.

Consequently, chronic heart failure in CRT-SRs were not cured, so in fact, the number of patients who could be treated with target dosage was not higher.

4.6 Study limitations

Firstly, the major limitation of this study was the single-center retrospective experience, which did not provide an argument as strong as the randomized clinical trials (RCTs). Secondly, although the two groups were approximately balanced with respect to baseline characteristics, we were unable to analyze other variables affecting primary outcomes because of the small number of events. Besides, the lack of myocardial imaging further demonstrates the ameliorated bi-ventricular dyssynchrony and the degree of myocardial ischemia in CRT-SRs. Finally, the median follow-up in our study was only 56.9 months, which may not be long enough for us to observe the benefits of NHA.

5 Conclusions

Our study found that for ischemic etiology, compared with CRT-SRs with NHA, CRT-SRs without NHA were associated with a significantly higher risk of HF hospitalization. However, for non-ischemic etiology, we found that CRT-SRs with NHA or without NHA at follow-up were associated with similar outcomes, which needed further investigation by prospective trials.

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