Reverse Remodeling Achieved by Combination Therapy With High-Dose Beta Blocker and Cardiac Resynchronization

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SUMMARY

Although both beta-blocker treatment and cardiac resynchronization therapy (CRT) have been established as the standard therapeutic strategy to achieve left ventricular reverse remodeling (LVRR) and improve prognosis in heart failure (HF) patients with systolic LV dysfunction, some patients do not respond to such treatments. We here report a HF patient with left bundle branch block due to nonischemic cardiomyopathy who did not respond to 20 mg/day of carvedilol in terms of LVRR. Subsequent CRT only achieved insufficient LVRR, and we further titrated carvedilol up to 40 mg/day. Marked LVRR was accomplished at a fixed 70 bpm heart rate under CRT, and therefore it was considered as heart rate-independent. Up-titration of beta-blocker after CRT may be necessary to induce optimal LVRR in some populations. (Int Heart J 2015; 56: 462-465)

Key words: Carvedilol, Heart failure, Responder, Cardiomyopathy

Pharmacological therapy such as angiotensin converting enzyme inhibitor, beta-blocker (BB), and aldosterone antagonist administration has been demonstrated to improve the quality of life or prognosis of patients suffering advanced heart failure (HF) with reduced left ventricular (LV) systolic function during the past 20 years through the accumulation of large-scale studies.1-6) Beta blockers in particular are unique agents that facilitate LV reverse remodeling (LVRR) accompanied by improvement of LV ejection fraction (LVEF) and reduction of LV dimension.7-9) Although the mechanism has not been completely elucidated, some authors stated that a reduction in heart rate (HR) and prolongation of the diastolic phase might be a key to achieve LVRR by BB treatment.10,11)

Cardiac resynchronization therapy (CRT) has recently been developed as an excellent non-pharmacological strategy to facilitate LVRR and then improve patient quality of life and prognosis through amelioration of LV dyssynchrony by biventricular pacing among those with symptomatic HF, decreased LVEF, and QRS prolongation.12)

However, there are some non-responders to these treatments in real-world practice.2,13,14) Here we describe a patient with symptomatic HF due to nonischemic cardiomyopathy. He was refractory to the standard dose BB treatment, but achieved significant LVRR by combination therapy consisting of high-dose BB treatment together with CRT during fixed HR.

CASE REPORT

A 63-year-old male patient was admitted to our hospital for the first time in 2006 complaining of dyspnea on effort [New York Heart Association (NYHA) class II], presenting sinus rhythm, complete left bundle branch block (CLBBB), and 214 msec of QRS duration at electrocardiogram (ECG), dilated and systolic LV dysfunction [LV diastolic diameter (LVDd) 85 mm and LVEF 21%] at transthoracic echocardiography (TTE), and a plasma level of B-type natriuretic peptide (BNP) of 117 pg/mL (Figure 1A). Since there was no significant coronary artery stenosis, he was diagnosed as HF due to nonischemic cardiomyopathy.

LVEF decreased down to 7% along with worsening of his HF symptom (NYHA class III) regardless of administration of carvedilol at 20 mg/day, enalapril at 5 mg/day, and spironolactone at 50 mg/day for > 6 months, and eventually CRT was initiated without any perioperative complications in May 2009. QRS duration decreased down to 169 msec, LV dyssynchrony was ameliorated, and LVEF improved partially from 7% to 18%. However, his HF symptom remained unchanged even 1 year after CRT introduction (NYHA class III) (Figure 2).

Next, the dose of carvedilol was titrated up to 40 mg/day maintaining a 70 bpm fixed heart rate (HR) by biventricular pacing. After 1-year high-dose BB treatment together with CRT, LVEF increased up to 34% along with almost normalization of LVDd down to 59 mm and improvement in the HF symptom (NYHA class I) (Figure 1B).

DISCUSSION

Although BB treatment is the established pharmacologi-
cal therapeutic strategy targeting LVRR in HF patients with reduced LVEF, some patients, such as the present patient, are refractory to the standard dose of carvedilol approved in Japan (~20 mg/day).

CRT is one of the recently-established non-pharmacological strategies to achieve LVRR by correcting LV dyssynchrony through biventricular pacing, but there are also some non-responders to CRT in real-world practice. The present patient’s profile satisfied the class I indication of CRT, ie, symptomatic HF, decreased LVEF < 35%, and QRS prolonga-
tion > 150 msec along with LBBB. 12) Although he satisfied the definition of responders to CRT after 1.5 year-CRT treatment from the viewpoint of LV motion, ie, improvement of LVEF > 10%, 13) the clinical response was limited since his HF symptom remained NYHA class III even after CRT (Figure 2).

Surprisingly, though the patient had once been considered as a non-responder to beta-blocker before CRT, the patient achieved marked LVRR with dramatic improvement of his HF symptom by the combination therapy with high-dose BB and CRT. Although the precise mechanism is unknown, both the improvement of LV dyssynchrony by CRT mechanically and the unloading of LV pharmacologically by BB treatment might have interacted synergistically and achieved significant LVRR.

We titrated the dose of carvedilol over the upper limit approved in Japan (> 20 mg/day). 16,17) Although all the HF guidelines state that BB should be titrated as much as possible considering the recent evidence supporting the dose-dependent benefit of BB, 16,18-21) there is no evidence of high-dose BB treatment thus far in Japan. 22) Our result may represent a breakthrough in terms of constructing a Japanese trial using high-dose BB.

Various studies including the SHIFT trial and meta-analysis have demonstrated that a decrease in HR itself was a key to achieve LVRR by BB treatment. 10,11,12,21) However, this patient achieved LVRR regardless of a fixed HR of 70 bpm. The result would support the hypothesis that not only the extended diastolic interval but also HR-independent effects through suppressing the sympathetic system may be underlying in the process of LVRR during the high-dose BB treatment. 16) The BEAUTIFUL study consistently demonstrated HR-independent improvement of cardiac function when patients already had a considerably slow HR, ie, < 70 bpm. 23)

Titration of BB is sometimes hindered by its adverse effect, ie, symptomatic bradycardia. We could increase the dose of carvedilol up to 40 mg/day without worrying about such events due to the back-up support of CRT pacing. Initiation of CRT in HF patients with a fear of bradycardia may be justified when we attempt high-dose BB treatment targeting significant LVRR.

Although sufficient reverse remodeling could not be achieved in the present patient after 1.5 year CRT, it sometimes takes several years. To demonstrate a pure additional effect of high-dose BB treatment on CRT, a prospective study of long-term CRT with high-dose or standard dose BB treatment is warranted.

**DISCLOSURE**

None.

**REFERENCES**