Case Report

Long-term follow-up of ‘‘reversible’’ dilated cardiomyopathy with improvement of cardiac sympathetic nerve activity after cardiac resynchronization therapy (CRT)

Do ‘‘CRT superresponders’’ have ‘‘dyssynchrony-induced cardiomyopathy’’?

Kazuya Ishibashi (MD, PhD)a,*, Tomoko Osamura (MD)a, Hirokazu Shiraishi (MD)b, Takeshi Shirayama (MD, PhD)b, Yasuhiro Yamahara (MD, PhD)a, Hiroaki Matsubara (MD, PhD)b

a Department of Cardiology, Saiseikai Kyoto Hospital, Kyoto, Japan
b Department of Cardiovascular Medicine, Kyoto Prefectural University School of Medicine, Kyoto, Japan

Received 11 May 2009; received in revised form 22 June 2009; accepted 27 July 2009

KEYWORDS
Dilated cardiomyopathy; Cardiac resynchronization therapy; Beta-blocker; 123I-metaiodobenzylguanidine; Superresponder; Carvedilol

Summary We report a case of idiopathic dilated cardiomyopathy with severe heart failure and complete left bundle branch block (CLBBB) which exhibited an excellent response to cardiac resynchronization therapy (CRT). A 71-year-old male had been treated for 9 years with medication for chronic heart failure. He was referred to hospital with a complaint of dyspnea. An electrocardiogram showed CLBBB, with a QRS-width of 200 ms. Markedly dilated left ventricular (LV) chamber with a low ejection fraction (EF) of 18% and severe mitral regurgitation were registered by echocardiogram. Myocardial neuronal 123I-metaiodobenzylguanidine uptake was reduced, with a heart-to-mediastinum (H/M) ratio of 1.88. Immediately after the introduction of CRT, clinical improvement was observed. At 1-year follow-up, LV chamber size and cardiac function were almost normalized, with an EF of 53%. Cardiac sympathetic nerve activity (CSNA) was simultaneously normalized, with an H/M ratio of 2.32 and a washout rate of 14.7%. However, after the cessation of carvedilol administration, CSNA and LV systolic function were slightly aggravated, with an H/M ratio of 2.20, a washout rate of 15.9%, and an EF of 44%. In
Introduction

Cardiac resynchronization therapy (CRT) for idiopathic dilated cardiomyopathy (DCM) with severely impaired cardiac function [New York Heart Association (NYHA) functional class III/IV] and complete left bundle branch block (CLBBB) is well established. However, approximately 30% of the patients who fulfill the CRT selection criteria are regarded as ‘‘nonresponders’’, who do not clinically benefit after CRT [1]. On the other hand, it has recently been reported that some cases exhibit excellent responses to CRT [2—4]. In these cases, cardiac function was almost normalized by CRT (EF > 50%) and they were called ‘‘superresponders’’ (or ‘‘hyperresponders’’). We assessed the cardiac sympathetic nerve activity in the case of a ‘‘superresponder’’ to CRT, who had been followed up over a long-term of 9 years. Moreover, we considered whether it was valid to regard ‘‘superresponders’’ as having ‘‘dyssynchrony-induced cardiomyopathy.’’

Case report

A 71-year-old male was first informed that he had intermittent left bundle branch block and left ventricular (LV) dysfunction with dyssynchrony during a complete physical checkup at the age of 61, when he was asymptomatic (Fig. 1). He had no habits of excessive alcohol drinking. Moreover, he had no history of tachyarrhythmia. At the age of 62, he was admitted to our hospital because of exertional dyspnea. Coronary angiography showed normal coronary arteries and left ventriculography revealed diffusely severe hypokinesis of LV, with an ejection fraction (EF) of 30%. He was then diagnosed with DCM. Conventional medical treatment including beta-blocker (carvedilol), diuretic (furosemide), and angiotensin-converting enzyme inhibitor (ACEI) (enarapril) was initiated. Since he was 63 years’ old, 1.2-metabolobenzylguanidine (MIBG) scintigraphy was conducted to evaluate the degree of cardiac sympathetic nerve activity in the case of a ‘‘superresponder’’ to CRT, who had been followed up over a long-term of 9 years. Moreover, we considered whether it was valid to regard ‘‘superresponders’’ as having ‘‘dyssynchrony-induced cardiomyopathy.’’

Echocardiography revealed marked LV dilatation [dimension of LV end-diastole (Dd)/dimension of LV end-systole (Ds) of 78/72 mm], wall thinning in the LV anteroseptal area and impaired LV contraction, with EF of 18% (Fig. 3). Dyspnea was relieved with intensive diuresis and oxygen supply. $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy was conducted to evaluate the degree of cardiac sympathetic nerve activity in the case of a ‘‘superresponder’’ to CRT, who had been followed up over a long-term of 9 years. Moreover, we considered whether it was valid to regard ‘‘superresponders’’ as having ‘‘dyssynchrony-induced cardiomyopathy.’’

The subjective symptoms were unchanged for 7 years, with NYHA functional class II, although LV remodeling gradually developed (Table 1). The serum brain natriuretic peptide (BNP) concentration was getting higher during the clinical follow-up was conducted every 2 weeks after that. Two weeks after, the ECG was unchanged, except for a slight increase in the heart rate (89 bpm) and the QRS width (120 ms) (Fig. 5). One month after the cessation of carvedilol administration, echocardiography revealed mild LV dilatation and mild aggravation of LV contractile function (Dd/Ds of 56/43 mm and EF of 44%). LV synchrony was visually corrected. No significant mitral regurgitation was detected by color Doppler imaging. The serum BNP concentration was 13.7 pg/ml (normal range: <18.4 pg/ml). MIBG scintigraphy disclosed a normal pattern, with the H/M ratio of 2.32/2.48 (early phase/delayed phase) and the washout rate of 14.7%. After informed consent was obtained, beta-blocker (carvedilol 10 mg/day) was discontinued. A thorough clinical follow-up was conducted every 2 weeks after that. Two weeks later, the ECG was unchanged, except for a slight increase in the heart rate (89 bpm) and the QRS width (120 ms) (Fig. 5). One month after the cessation of carvedilol administration, echocardiography revealed mild LV dilatation and mild aggravation of LV contractile function (Dd/Ds of 56/43 mm and EF of 44%). LV synchrony was visually corrected. CTR and BNP value slightly increased to 50% and 22.3 pg/ml, respectively. Moreover, MIBG scintigraphy disclosed slight aggravation of the parameters: the H/M ratio was 2.20/2.38 (early phase/delayed phase), and the washout rate was 15.9% (Table 2). Although he was completely free from palpitations and shortness of breath during the 1-month follow-up, beta-blocker therapy was resumed. One month after the administration of carvedilol (10 mg/day), the echocardiographic parameters returned to baseline. Moreover, carvedilol was increased to the maxi-
Figure 1  Electrocardiogram (ECG) and M-mode echocardiogram at the age of 62. The ECG showed both a wide QRS and a narrow QRS, indicating intermittent left bundle branch block at the age of 62 (A). In the narrow QRS pattern, ECG showed inverted T waves with slight ST depressions in the leads I, II, III, aVF, V4 through V6 (A). The M-mode echocardiogram revealed an asynchronous movement in the left ventricle (LV) with poor LV performance (B).

mal dosage of 20 mg/day. Under the CRT and the medical treatment with diuretics, ARB, and beta-blocker, his clinical condition remained stable in the follow-up over the next 3 months.

Discussion

This case report indicates two major findings as follows. First, even if severe heart failure persists for a long time,
Table 1  Time course of echocardiographic parameters, heart rate, blood pressure, CTR and BNP before cardiac resynchronization therapy.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>61</th>
<th>62</th>
<th>65</th>
<th>66</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dd (mm)</td>
<td>60</td>
<td>64</td>
<td>66</td>
<td>74</td>
<td>78</td>
</tr>
<tr>
<td>Ds (mm)</td>
<td>52</td>
<td>54</td>
<td>57</td>
<td>64</td>
<td>72</td>
</tr>
<tr>
<td>EF (%)</td>
<td>32</td>
<td>30</td>
<td>28</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>MR</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>70</td>
<td>85</td>
<td>75</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>140/80</td>
<td>130/86</td>
<td>130/80</td>
<td>112/70</td>
<td>98/62</td>
</tr>
<tr>
<td>CTR (%)</td>
<td>52</td>
<td>50</td>
<td>51</td>
<td>55</td>
<td>63</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>—</td>
<td>78.9</td>
<td>103.9</td>
<td>347.4</td>
<td>1091.8</td>
</tr>
</tbody>
</table>

Dd, Dimension of left ventricular end-diastole; Ds, dimension of left ventricular end-systole; EF, ejection fraction; MR, mitral regurgitation; HR, heart rate; BP, blood pressure; CTR, cardio-thoracic ratio; BNP, brain natriuretic peptide.

Figure 2  Chest radiograph and electrocardiogram on admission.

Figure 3  M-mode echocardiogram before and after cardiac resynchronization therapy (CRT). Dd, Dimension of left ventricular end-diastole; Ds, dimension of left ventricular end-systole; EF, ejection fraction.
Table 2 ¹²³I-metaiodobenzylguanidine scintigraphic parameters.

<table>
<thead>
<tr>
<th></th>
<th>Pre-CRT</th>
<th>Post-CRT beta-blocker (+)</th>
<th>Post-CRT beta-blocker (−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/M ratio (early phase)</td>
<td>1.88</td>
<td>2.32</td>
<td>2.20</td>
</tr>
<tr>
<td>H/M ratio (delayed phase)</td>
<td>—</td>
<td>2.48</td>
<td>2.38</td>
</tr>
<tr>
<td>Washout rate</td>
<td>—</td>
<td>14.7</td>
<td>15.9</td>
</tr>
</tbody>
</table>

CRT, Cardiac resynchronization therapy; H/M ratio, heart-to-mediastinum ratio.

Figure 4  Chest radiograph and electrocardiogram after a year following cardiac resynchronization therapy.

Figure 5  Trend of electrocardiograms. CRT, cardiac resynchronization therapy.
certain cases show excellent response to CRT. Second, our case of "superresponder" to CRT is not equivalent to dyssynchrony-induced cardiomyopathy from the viewpoint of the response to the cessation of beta-blocker therapy.

Although CLBBB has been well known as an accelerating factor for heart failure, it is still controversial which comes first, electrical or mechanical failure [5]. According to the Framingham study, 28% of asymptomatic patients developed heart failure after the appearance of CLBBB [6]. This study suggests that certain CLBBB may mainly contribute to a deterioration of cardiac function.

CRT has been generally accepted for drug-refractory advanced heart failure with intraventricular conduction delay and LV dyssynchrony. However, approximately 30% of the patients who fulfill the CRT selection criteria do not benefit from CRT [1]. On the other hand, recent reports indicate the presence of excellent responders to CRT. Blanc et al. reported that 5 among the 29 patients (17%) with DCM and CLBBB exhibited both complete normalization of the LV function following CRT (EF from 19% to 55%) and clinical improvement [2]. They proposed a new concept of LBBB-induced or dyssynchrony-induced cardiomyopathy with the normalization of the LV function after the disappearance of LBBB. In addition, Castellani et al. reported later that these cases were observed in 11 patients (13%) among 84 patients with DCM with LBBB and were called "hyperresponders", although no patients with ischemic cardiomyopathy belonged to the "hyperresponders" group [3]. In Japan, Fujii and Takami described two similar cases as "superresponders" [4]. In the present case, the patient was diagnosed with DCM and intermittent LBBB 9 years previously, on the evidence of intact coronary arteries and poor LV performance with an EF of 30%. LV dyssynchrony had already been pointed out by echocardiography and left ventriculography. After CRT, the LV performance was synchronized visually, which resulted in normalization of the cardiac function. Therefore, the present case is considered to be a "superresponder" to CRT.

MIBG, an analogue of norepinephrine, is a useful myocardial tracer for detecting abnormalities in the myocardial adrenergic nervous system in patients with heart failure [7]. A large number of previous studies have shown that medical treatment of heart failure can improve cardiac sympathetic nerve activity in patients with heart failure, as demonstrated by MIBG scintigraphy. Moreover, several investigators have reported that CRT improves cardiac sympathetic nerve activity in CRT responders [8,9]. Nishioka et al. evaluated the relationship between CRT response and MIBG scintigraphic parameters [8]. They concluded that the H/M ratio was the only independent predictor of CRT response. They suggested that the optimal H/M ratio (delayed phase) cutoff point was 1.36, with 75% sensitivity and 71% specificity. Although a delayed MIBG image was not acquired before CRT in our case, the H/M ratio in the early phase was 1.88, which was one of the reasons why we chose CRT. After CRT, the H/M ratio increased from 1.88 to 2.32, and the washout rate indicated 14.7%, which implied complete recovery of cardiac sympathetic nerve activity.

In almost all reported cases of "superresponders", conventional medical treatment, including diuretic, ACEI, ARB, and/or beta-blocker, was maintained after CRT. Therefore, the influence of these drugs on the normalization of cardiac function in "superresponders" cannot be excluded. In other words, it remains unclear which contributes to the normalized LV function, a single effect of CRT (correction of intraventricular conduction delay) or the combined effects of medical treatment and CRT. There have been many previous reports that beta-blockers almost normalized cardiac function in patients with DCM. In particular, according to previous reports, carvedilol, a unique beta-blocker with alpha1-receptor blocking and antioxidant properties, improves cardiac sympathetic nerve activity and LV remodeling in patients with DCM [10—12]. Thus, we evaluated the efficacy of beta-blocker therapy in the normalization of cardiac function following CRT. Under CRT, the potential effect of carvedilol on cardiac sympathetic nerve activity was elucidated, using MIBG scintigraphy. One month after the cessation of carvedilol administration, in spite of the short-term observation, the H/M ratio in the delayed phase slightly decreased from 2.48 to 2.38 and the washout rate slightly increased from 14.7% to 15.9%. These results suggested that carvedilol therapy might have an additional effect on the improvement of cardiac sympathetic nerve activity obtained after CRT. In addition, in the present case, the cessation of carvedilol treatment led to mild aggravation of LV contractility and a mild increase in LV chamber size. It has been reported that carvedilol therapy stimulates an increase in contractile function and a reduction of intraventricular dyssynchrony in DCM with narrow QRS complex [13]. Therefore, these pharmacological effects might have partly contributed to the complete recovery of sympathetic nerve activity obtained after the combination of CRT and medical treatments. Moreover, the cessation of carvedilol administration might attenuate the potential of CRT. In the present case, however, its attenuation was considered to be quite limited in terms of influence on cardiac function because of the minimal change in the QRS-width after the cessation of carvedilol administration. In any case, we should note that cardiac function is not completely restored in CRT "superresponders", even after gaining resynchronization. However, a precise etiology of the "latent" cardiac dysfunction disclosed by the cessation of beta-blocker treatment is unclear. Several factors responsible for the "remaining" myocardial damage in "superresponders" might be possible: preexisting heart disease and/or secondary myocardial degeneration triggered by long-term dyssynchrony and/or incomplete synchrony. Thus, against the previous reports [2—4], it cannot simply be concluded that a "superresponder" to CRT would be regarded as a patient with LBBB-induced cardiomyopathy without organic myocardial disease. In the future, the relationship between the LV synchronicity and the "normalized" cardiac function in CRT "superresponders" as well as the existence of "pure" LBBB-induced cardiomyopathy should be clarified by prudent investigations. Moreover, a subset of "superresponders" should be properly selected prior to CRT and the timely introduction of CRT is also essential.

In summary, we reported a case with DCM which exhibited a dramatic reverse remodeling after CRT. In the present case, the combination of CRT and medical therapy exerted excellent effects on the long-term impaired LV function, leading to the complete recovery of cardiac...
sympathetic nerve activity. The present case warns that, despite normalization of LV performance following CRT, suboptimal medical treatment would lead to the aggravation of cardiac function.

References


