Improvement of Left Ventricular Ejection Fraction by Baroreflex Activation Therapy in a Young Man with Dilated Cardiomyopathy

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Summary

The progression of heart failure with reduced ejection fraction is promoted by sympathovagal imbalance. Baroreflex activation therapy (BAT) by the electrical stimulation of baroreceptors at the carotid sinus significantly improved exercise capacity and NT-proBNP levels in a randomized trial; however, no significant difference in left ventricular ejection fraction (LV-EF) between groups was found. Here, we report the case of a 30-year-old man with a long history of dilated cardiomyopathy and severely reduced LV-EF despite optimal medical therapy, who was treated with BAT since October 2014 and showed a remarkable improvement in both symptoms and LV-EF under this treatment.

Case Report

The diagnosis of dilated cardiomyopathy was established in 2004 and was attributed to an infection with Mycoplasma pneumoniae. LV-EF was mildly reduced at first and deteriorated in recent years reaching a minimum of 28% in August 2014 (Figure). Concomitantly, left ventricular end-diastolic diameter increased (Table). While the patient was in NYHA class I early after initial diagnosis, functional status subsequently worsened, and the patient was reclassified as NYHA III since 2012 (Figure). Maximal oxygen uptake assessed by spiroergometry was 15.9 mL/minute/kg at a maximal load of 135 W (Table) before BAT was started.

The patient was obese (see Table for body weight) and had a history of smoking (10 pack years, cessation in 2010). He had no hypertension at initial presentation, and blood pressure was mostly in the normal range under heart failure medication during follow-up (Table). Diabetes mellitus was excluded by repetitive HbA1c measurements. Serial blood sampling revealed an intermittent moderate increase in non-fasting triglycerides, whereas LDL cholesterol was in the normal range. In October 2014, a polygraphy detected mild obstructive sleep apnea. In addition, the patient had a history of the osteochondrosis of the left knee.

The patient received optimal heart failure medication,
including maximal doses of ramipril (10 mg/day), metoprolol (237.5 mg/day), spironolactone (50 mg/day), ivabradine (15 mg/day), and an appropriate diuretics dose (torasemide, 50 mg/day and hydrochlorothiazide, 25 mg/day); prescribed heart failure medication was quite stable over a long follow-up period before and after the initiation of BAT. Coronary artery disease had been excluded by angiography in 2012; iron deficiency had also been ruled out several times at last in September 2014. QRS complex was narrow (Supplemental Figure); thus, cardiac resynchronization therapy was not indicated. The implantation of an implantable defibrillator (ICD) had been discussed with the patient several times but has been rejected by him so far. Heart transplantation had also been discussed a number of times; however, the patient was not listed due to obesity and his personal decision.

As ultima ratio, the option of BAT was discussed, which received approval for the treatment of HFrEF in October 2014 in Europe. After careful consideration, the patient gave his consent for the implantation of BAT device and the simultaneous implantation of an ICD. The implantation of the BAT device (Barostim neo, CVRx
Inc., Minneapolis, MN, USA) in the right subclavicular or cervical regions and the left-sided implantation of an ICD (Origen Mini, Boston Scientific, Marlborough, MA, USA) were performed without complications on October 16, 2014. Intraoperative and subsequent interrogations showed a normal function of both the devices. BAT was activated on October 31, 2014 and was well tolerated.

During subsequent follow-up visits, functional status improved considerably, and the patient was classified as NYHA I since June 2015 (Figure, Table) because he described no restrictions in every day activity any more. Concurrently, LV-EF was improved to 43% in January, 49% in July, and 50% in October 2015 (Figure, Table). Left atrial area, mitral regurgitation grade, NT-proBNP, and heart rate were reduced (Table). The maximal oxygen uptake slightly increased to 17.7 mL/minute/kg at a maximal load of 165 W, which was limited by the pain in the left knee due to osteochondrosis but not by dyspnea. No symptoms of hypotension occurred. ICD interrogations showed no arrhythmias.

**Discussion**

Although the activation of the sympathetic nervous system is known to deteriorate systolic function in patients with HFrEF, the application of BAT in patients with HFrEF and LV-EF ≤ 35% did not show a significant benefit on LV-EF in the only randomized trial. The case reported here indicates that BAT may have the potential to considerably improve LV-EF in a subset of patients. A subgroup analysis of the randomized trial suggested a more pronounced effect of BAT, including a significant increase in LV-EF of 4.4 ± 2.0%, in patients not treated by cardiac resynchronization therapy, which may be one explanation for the good response to BAT in this case. The patient had a heart rate ≥ 75/minute despite treatment with a high dose of metoprolol and ivabradine before BAT and showed a clear decrease in heart rate after BAT, which may indicate a high sympathetic tone before BAT and a relevant sympathoinhibition by BAT, providing another possible explanation for the good response. Considering the characteristics of this case, younger patients, obese patients, and patients with dilated cardiomyopathy may respond better to BAT, which has not been evaluated in the previous trials. The characteristics of patients that are likely to show, such a sustained benefit, should be a scope of the future studies. Besides patient characteristics, the influences of the implantation procedure or programmable device parameters may also affect the therapeutic effect on LV-EF, which too deserves further evaluation in the future.

Of course, the case described here is subject to the known limitations of case reports. The temporal correlation between the initiation of BAT and improvement in LV-EF suggests a causal link; however, it cannot be excluded that factors unknown to the authors led to the observed improvement in cardiac function. However, the course of the disease, particularly the progressive decline of LV-EF during 9 years before BAT, argues against a spontaneous reconstitution, which is similar to that frequently seen in acute myocarditis. Moreover, there were no changes in the prescribed medications and no obvious non-medical treatments that may explain the improvement after initiation of BAT.

In summary, we report the case of a young man with a 10 year history of dilated cardiomyopathy that was worsening despite optimal guideline-directed treatment. After the initiation of BAT, both functional capacity and objective parameters such as LV-EF considerably improved. While the available data on BAT in HFrEF have shown a positive effect on functional capacity but not on LV-EF, this case demonstrates that the benefit of BAT in the treatment of HFrEF may include the enhancement of systolic cardiac function in a subset of patients.

**Disclosures**

**Conflict of interest:** MH, NM, and HR are investigators of the trials sponsored by CVRx and received speaker or consultant honoraria.

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**Supplemental Files**

Supplemental Figure.
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