Heart rate reduction after ivabradine might be associated with reverse electrical remodeling in patients with cardiomyopathy and left bundle branch block

Andrea Kučerová, Petr Doškář, Libor Dujka, Veronika Lekešová, Petr Volf, Katarina Koščová, Petr Neužil and Filip Málek

Abstract
Left bundle branch block increases the risk of death in patients with chronic heart failure. We herein report four clinical cases of patients with chronic heart failure caused by nonischemic cardiomyopathy with left bundle branch block that occurred when adding ivabradine to optimal medical therapy, resulting in reverse electrical and mechanical remodeling. This phenomenon might be explained by the effect of ivabradine on reverse remodeling of the left ventricle with improvement of intraventricular conduction.

Keywords
Electrical remodeling, ivabradine, left bundle branch block, cardiomyopathy, chronic heart failure, intraventricular conduction

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Introduction
The Ivabradine and Outcomes in Chronic Heart Failure (SHIFT) study showed that the presence of left bundle branch block (LBBB) increased the risk of death in patients with chronic heart failure (CHF) and a heart rate of ≥70 beats per minute (bpm) with
sinus rhythm. Ivabradine was safe in patients with LBBB, and its effect was similar to that in patients without LBBB.1

We herein report four clinical cases of patients with CHF characterized by nonischemic cardiomyopathy, sinus rhythm, and LBBB at baseline. The addition of ivabradine to optimal medical therapy was associated with a reduction in the heart rate, narrowing of the QRS complex duration, and loss of the LBBB pattern on electrocardiography (ECG). The aim of this study was to assess the potential indirect effect of ivabradine on intraventricular conduction in patients with cardiomyopathy.

**Patients**

Four patients (one man, three women; age range, 28–76 years) were followed at a tertiary care heart failure clinic after diagnosis of heart failure with a reduced left ventricular ejection fraction (LVEF) caused by nonischemic cardiomyopathy.

The patients were chosen from the database of the tertiary care heart failure clinic. ECG was recorded at each clinic visit and stored in a personal computer database. Chronic LBBB was defined as a permanent LBBB morphology on 12-lead ECG at each clinic visit before initiation of ivabradine therapy. The heart rate was recorded from the resting 12-lead ECG recorded at each clinic visit.

Three patients had idiopathic cardiomyopathy and one patient had a history of myocarditis. The patients were undergoing optimal medical therapy including maximal tolerated doses of beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and mineralocorticoid receptor antagonists.

Ivabradine was started at a dose of 5 mg twice daily and titrated to 7.5 mg twice daily when the heart rates remained at >75 bpm despite the maximal tolerated beta blocker dose. Heart failure symptoms were mild [New York Heart Association (NYHA) class II in all patients].

**Observation**

After a mean of 866 days (range, 538–1211 days) of follow-up, a heart rate reduction

| Table 1. Effect of ivabradine on parameters of patients with LBBB and CHF. |
|---------------------------------------------|-----------------|---------------|------------|-----------------|---------------|
| Case number (sex, age) | Follow-up days | HR, bpm | QRS width, ms | LVEF | LVEDD, mm | NT-proBNP, pmol/l |
|-------------------------|----------------|--------|--------------|------|----------|------------------|
| 1 (M, 76 y) Before IVA | 924           | 87     | 134          | 26%  | 63       | 224              |
| 1 (M, 76 y) After IVA  | 59            | 104    |              | 46%  | 52       | 21               |
| 1 (M, 76 y) Change     | –28           | –30    |              | +20% | –11      | –203             |
| 2 (F, 45 y) Before IVA | 1211          | 84     | 154          | 25%  | 57       | 407              |
| 2 (F, 45 y) After IVA  | 67            | 106    |              | 43%  | 43       | 22               |
| 2 (F, 45 y) Change     | –17           | –48    |              | +18% | –12      | –415             |
| 3 (F, 28 y) Before IVA | 791           | 86     | 168          | 25%  | 61       | 139              |
| 3 (F, 28 y) After IVA  | 72            | 114    |              | 44%  | 55       | 47               |
| 3 (F, 28 y) Change     | –14           | –54    |              | +19% | –6       | –92              |
| 4 (F, 44 y) Before IVA | 538           | 75     | 140          | 31%  | 63       | 76               |
| 4 (F, 44 y) After IVA  | 58            | 104    |              | 43%  | 55       | 11               |
| 4 (F, 44 y) Change     | –17           | –36    |              | +12% | –8       | –65              |

LBBB: left bundle branch block, CHF: chronic heart failure, M: male, F: female, IVA: ivabradine, HR: heart rate, bpm: beats per minute, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, NT-proBNP: N-terminal B-natriuretic peptide.
after ivabradine therapy was associated with clinical improvement from NYHA class II to I. We observed an increase in the LVEF, a decrease in the LV end-diastatic diameter, and a reduction in the N-terminal B-natriuretic peptide level. We also observed a reduction in the QRS duration with loss of the LBBB pattern on ECG. The changes in parameters before and after ivabradine are shown in Table 1.

An example of the ECG changes before and after ivabradine is shown in Figures 1 and 2.

This study was approved by the local ethics committee of Na Homolce Hospital (2017). The patients participating in the study provided verbal informed consent.

**Discussion**

Ivabradine is a selective inhibitor of a specific If channel in the sinoatrial node and
causes dose-dependent heart rate reduction. Ivabradine has no effect on conduction, blood pressure, or inotropy of the heart. Experimental studies have shown that ivabradine treatment is associated with reverse mechanical remodeling in animal models of heart failure.\textsuperscript{2,3} These experimental results were confirmed in the SHIFT echocardiography substudy.\textsuperscript{4} Reverse electrical remodeling as a shortening of the intrinsic QRS interval has been described in patients receiving optimal medical therapy, including beta blockers and angiotensin-converting enzyme inhibitors; in patients receiving cardiac resynchronization therapy; and in patients with LV assist devices.\textsuperscript{5–7} Reverse electrical remodeling after ivabradine in humans has not yet been described.

Our study is limited by the fact that it was a retrospective analysis. Holter ECG monitoring and exercise stress tests were not performed in all patients. The LBBB pattern at baseline might be heart rate-dependent. This fact does not decrease the possible indirect role of ivabradine on reverse electrical cardiac remodeling.

**Conclusion**

Heart rate reduction after ivabradine might be associated with shortening and a change of the morphology of the QRS complex in patients with CHF characterized by non-ischemic cardiomyopathy and LBBB at baseline. This phenomenon might be explained by the effect of ivabradine on reverse remodeling of the left ventricle with improvement of intraventricular conduction.

**Declaration of conflicting interest**

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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