Implication of Ivabradine in Up-titrating Beta-blocker in a Patient with Advanced Heart Failure

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Abstract:
Titration of beta-blockers is a gold-standard therapy in patients with heart failure and a reduced ejection fraction but is sometimes challenging to administer, given symptomatic hypotension. Ivabradine is a recently introduced selective I, channel inhibitor that purely reduces the heart rate. We encountered a patient with advanced heart failure in whom a beta-blocker could not be up-titrated given his symptomatic hypotension. Following the initiation of ivabradine, an increase in blood pressure due to heart rate optimization, probably via an improvement in the cardiac output, allowed for the further up-titration of carvedilol, followed by a successful clinical course. Ivabradine might be a novel therapeutic tool to facilitate the up-titration of beta-blockers in patients with heart failure and hypotension.

Key words: heart failure, deceleration time, hemodynamics

(Intern Med 60: 897-900, 2021) (DOI: 10.2169/internalmedicine.6061-20)

Introduction
Titration of beta-blockers up to the maximum dose is the guideline-directed gold-standard therapy in patients with heart failure with reduced ejection fraction (HFrEF) (1, 2). However, up-titration is often insufficient predominantly due to symptomatic hypotension and dizziness (3, 4).

Ivabradine, a selective inhibitor of I, channel that purely reduces heart rate (5), has been demonstrated to additively improve clinical outcomes in patients with HFrEF and sinus tachycardia (3, 4). Given the result of J-systolic heart failure treatment with the inhibitor ivabradine (SHIFT) trial, ivabradine might maintain or rather increase the systemic blood pressure, probably due to an increased cardiac output driven by heart rate reduction (4). We hypothesized that the increased systemic blood pressure following ivabradine administration might facilitate the further up-titration of beta-blockers and improve patients’ clinical outcomes.

Case Report
On admission
A 34-year-old man without any remarkable medical history was admitted to our institute complaining dyspnea and appetite loss. He was taking no medication. His blood pressure was 147/101 mmHg, heart rate at rest was 120 bpm, body weight was 63 kg, and saturation was 99% on 3 L/min of nasal oxygenation. Plasma B-type natriuretic peptide was 1,774 pg/mL. Chest X-ray showed bilateral congestion. Transthoracic echocardiography showed a left ventricular end-diastolic diameter of 66 mm, left ventricular ejection fraction of 10%, and moderate mitral regurgitation. Given the results of an endomyocardial biopsy, he was diagnosed with dilated cardiomyopathy.

Ivabradine-incorporated beta-blocker up-titration
Intravenous dobutamine and carperitide improved the systemic congestion and decreased the serum creatinine level from 2.1 to 1.5 mg/dL (Fig. 1). Tolvaptan was initiated for hypervolemic hyponatremia. We hesitated to up-titrate the 2.5 mg of carvedilol and 1.25 mg of enalapril due to his...
systolic blood pressure of approximately 90 mmHg accompanied by dizziness. We therefore decided to start administering 5 mg/day of ivabradine. His heart rate fluctuated around 80 bpm (>75 bpm).

The trends in trans-mitral Power Doppler echocardiography are shown in Fig. 2 (6). Just before starting ivabradine administration (Fig. 2A), the dobutamine dose was 1.7 μg/min/kg, and the carvedilol dose was 2.5 mg. The overlap length between the E- and A-waves (red bar) was 140 msec with an 89-bpm heart rate.

Following the initiation of 5.0 mg/day of ivabradine, his heart rate decreased to around 65 bpm, the overlap length decreased from 140 to 10 msec, and the systolic blood pressure increased from 84 to 98 mmHg (Fig. 2B). As a result, dobutamine was discontinued, and carvedilol was able to be up-titrated from 2.5 to 5.0 mg.

After 10 days of ivabradine therapy, ivabradine was discontinued, and carvedilol was further up-titrated to 10.0 mg (Fig. 2C). His heart rate remained around 60 bpm without ivabradine, and there was no overlap between the E- and A-waves. Thanks to the hemodynamic stabilization and up-titration of medications (20 mg/day of carvedilol and 2.5 mg/day of enalapril), he was discharged at day 50.

**Discussion**

**Overlap between E-wave and A-wave and cardiac output:**

Ivabradine has been shown to improve the clinical outcome in patients with HFrEF and sinus tachycardia by reducing the heart rate and likely facilitating left ventricular reverse remodeling (3, 4). However, the target heart rate remains unknown.

Our team recently focused on the overlap between E- and A-waves observed on trans-mitral Doppler echocardiography (3). We hypothesized that the cardiac output might be maximized at the ideal heart rate, where the overlap length between the two waves is “zero”. Consistently, the overlap between the two waves was minimized (from 140 to 10 msec) and the systolic blood pressure increased (from 84 to 98 mmHg) following the initiation of ivabradine therapy (Fig. 2A, B).

We speculate that the increased systolic blood pressure was caused by the enhanced cardiac output at optimized heart rate (7), and further detailed hemodynamic assessments are warranted. Our team is currently conducting a study investigating the association between the optimized heart rate and improvement in the cardiac output through a non-invasive estimation by an AESCULON mini (Osypka Medical, Berlin, Germany) (8). Consistently, the J-SHIFT trial observed a relatively increased systemic blood pressure...
during ivabradine therapy (4).

**Ivabradine-incorporated up-titration of beta-blockers**

Ivabradine is indicated to reduce the heart rate in patients receiving beta-blockers at as high a dose as tolerable in the hopes of achieving a better long-term prognosis (9). Given our case, ivabradine might stabilize the hemodynamics by increasing the systemic blood pressure and improving the tolerability to further the up-titration of a beta-blocker, which would improve the patients’ prognosis. A prospective large-scale randomized control trial is warranted to validate the implication of the ivabradine-incorporated up-titration of a beta-blocker strategy.

**Calculation of the ideal heart rate for heart rate optimization**

Our team recently proposed a formula to calculate the ideal heart rate using the deceleration time: $96-0.13 \times \text{(deceleration time)}$, at which the overlap length between the two waves is theoretically zero (6). For example, given that the deceleration time was 121 msec in this case, the ideal heart rate was calculated as 78 bpm. We discontinued ivabradine because the heart rate dropped below the ideal rate of 78 bpm due to the up-titration of a beta-blocker. We recommend calculating the ideal heart rate before initiating ivabradine therapy rather than repeating echocardiography, particularly for ambulatory cases. Owing to the up-titration of beta-blockers and sufficient heart rate reduction, ivabradine might be recommended to be terminated to avoid bradycardia in some cases like ours.

The authors state that they have no Conflict of Interest (COI).

**Financial Support**

TI receives grant support from JSPS KAKENHI: JP20K17143.

Masakazu Hori and Teruhiko Imamura contributed equally to this work.

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