Optimal Heart Rate Modulation Using Ivabradine

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Summary

Heart rate modulation therapy using ivabradine improves mortality and morbidity in patients with systolic dysfunction. However, a target heart rate remains uncertain. Echocardiography-guided ivabradine therapy, in which we attempt to approach zero overlap between two diastolic filling inflow waves, has recently been proposed to maximize cardiac output, facilitate reverse remodeling, and reduce mortality and morbidity, instead of using an absolute value for the target heart rate. Prospective studies are needed to validate the clinical implication of these therapeutic strategies. Also, this concept should be expanded to other clinical scenarios.

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Key words: Heart failure, Hemodynamics, Deceleration time, Echocardiography

Despite guideline-directed medical therapy including beta-blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists, morbidity and mortality in patients with heart failure is not satisfactorily low.¹⁾ A meta-analysis of the AT-TEND, WET-HF, and REALITY-AHF registries demonstrated a slight decrease in in-hospital mortality but unchanged one-year mortality and readmission rates in patients with acute heart failure between 2007 and 2015.²⁾

Heart rate has been one of the untreated clinical parameters that affect the progression of heart failure via multifactorial pathways.³⁾ The CHART-2 study demonstrated that the higher tertile heart rate group (78-130 bpm) had significantly higher all-cause mortality than the lower tertile heart rate group (40-66 bpm).⁴⁾ In the ASCEND-HF trial that included 2906 acute heart failure patients, a heart rate above 70 bpm at index discharge was associated with higher mortality.⁵⁾

Heart Rate Modulation Using Ivabradine

In 2010, the SHIFT trial demonstrated that heart rate modulation using ivabradine, an I_f channel blocker that reduces heart rate without affecting hemodynamics,⁶⁾ improved cardiovascular mortality and heart failure recurrence in patients with a left ventricular ejection fraction ≤ 35% and resting heart rate ≥ 70 bpm.⁷⁾ In a sub-analysis, 8-month ivabradine therapy decreased left ventricular size. Those with a left ventricular end-systolic volume index < 59 mL/m² enjoyed a better clinical outcome.⁸⁾ In the same manner, the J-SHIFT trial, which included patients with a left ventricular ejection fraction ≤ 35% and resting heart rate ≥ 75 bpm, also demonstrated an advantage in ivabradine therapy in improving the incidence of cardiovascular death and heart failure recurrence.⁹⁾

Given these findings, ivabradine is recommended for the management of heart failure with reduced ejection fraction in various guidelines. In the ESC guidelines, ivabradine is recommended for those with a left ventricular ejection fraction ≤ 35% and heart rate ≥ 70 bpm despite optimal medical therapy including beta-blockers.¹⁰⁾ In the AHA/ACC guidelines, ivabradine is recommended as an almost similar indication to the ESC guidelines.¹¹⁾ The Japanese Circulation Society guideline published in March 2021 focused its update on the diagnosis and treatment of acute and chronic heart failure,¹²⁾ in which ivabradine is recommended for those with a left ventricular ejection fraction < 40% and heart rate ≥ 75 bpm despite optimal medical therapy including beta-blockers.

Target Heart Rate

One of the unsolved issues is target heart rate. In the sub-group analysis of the SHIFT trial, those with a baseline heart rate < 77 bpm did not have a significant advantage in the primary endpoint over the placebo (hazard ratio 0.93, 95% confidence interval 0.80-1.08).⁷⁾ In another sub-group analysis of the SHIFT trial, a > 10 bpm of heart rate reduction was required to achieve statistical significance in the primary endpoint for those with a baseline heart rate ≥ 75 bpm.¹³⁾ Patients with a baseline heart rate < 75 bpm could not show statistical significance irrespective of the degree of heart rate reduction. Cardiovascular mortality rather tended to increase by ivabradine therapy for them.

The J-SHIFT trial set a heart rate ≥ 75 bpm as an inclusion criterion given these findings.⁹⁾ Too much heart rate reduction seems to be rather harmful. Thus, a target heart rate to achieve the greatest reverse remodeling and prognosis remains unknown.

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Figure 1. Trends in the overlap length between early rapid filling flow (E-wave) and an atrial contraction flow (A-wave) in patients with systolic dysfunction at heart rate of 54 bpm (A), 65 bpm heart rate (B), and 87 bpm heart rate (C). Red bars indicate the overlap length between the two waves. At lower heart rate (A), both waves stand apart and there is no overlap (we express the overlap length as negative in this situation). At higher heart rate (C), both waves stand overlapped.

Ideal Heart Rate and Cardiac Output in Theory

Heart rate reduction, in general, increases end-diastolic volume, resulting in incremental stroke volume via Frank-Starling's law.¹⁴⁾ Increased stroke volume compensates for heart rate reduction and cardiac output would be maintained or rather enhanced. Potential energy per minute would be decreased due to heart rate reduction.¹⁵⁾ As a result, cardiac reverse remodeling is achieved, accompanying heart failure prevention and prognostic improvement.¹⁶⁾ This could be a mechanism by which ivabradine improves clinical outcomes.

However, as discussed in the above section, such an ideal mechanism might not necessarily be processed when a target heart rate is inappropriate.¹³⁾ For the incremental end-diastolic volume, heart rate reduction should increase diastolic filling. We focus on the trans-mitral inflow waves in Doppler echocardiography to seek an ideal heart rate.¹⁷⁾

The trans-mitral diastolic filling inflow consists of an early rapid filling flow (E-wave) and an atrial contraction flow (A-wave) in patients with normal sinus rhythm (Figure 1A). At incremental heart rate, both waves come close and overlap (Figure 1A-C).¹⁸⁾ Given that the inflow volume during the diastasis phase (the period between E-wave and A-wave) is only 5%,¹⁹⁾ we hypothesized that the optimal heart rate should be the one when the two waves stand adjacent without any overlap.¹⁷⁾ In short, when there is an overlap between the two waves (Figure 1C), a heart rate reduction is recommended until the overlap just disappears. When there is no overlap and instead both waves stand apart (Figure 1A), further heart rate reduction is not recommended. Of note, we do not propose any absolute values as a target heart rate, which would vary in each in-

dividual.

Ideal Heart Rate and Cardiac Output in Clinical Situations

Nguyen and colleagues demonstrated that IV ivabradine maintained cardiac output in patients with systolic heart failure.²⁰⁾ Bakkehaug and colleagues also observed preserved cardiac output following administration of ivabradine in an animal model with systolic dysfunction.²¹⁾ Of note, they did not assess the overlap between diastolic filling waves.

Our team demonstrated that cardiac output was maximized when the overlap length between the two waves was minimized during the 3-day ivabradine therapy (Figure 2).²²⁾

Estimation of Ideal Heart Rate Using Doppler Echocardiography

Heart rate optimization, based on our hypothesis, requires repeated Doppler echocardiography to observe the overlap between the diastolic filling waves.²²⁾ If the lengths of both waves remain unchanged during the heart rate modulation (most of heart rate change is translated into the diastolic time),²³⁾ ideal heart rate, at which the overlap length is zero, would be theoretically calculated at baseline and can be applied during the follow-up period.

Our team found that deceleration time (approximately equal to the length of E-wave) and heart rate were the dominant determinants of the overlap length among those with systolic heart failure in a multivariate analysis.¹⁷⁾ Given the linear regression analysis including these vari-

Figure 2. Changes in overlap length and cardiac output during the 3-day ivabradine therapy.²²⁾ HR indicates heart rate. When two waves are overlapped (positive overlap length), ivabradine therapy tended to decrease the overlap length and increase cardiac output (dotted green line). Extreme heart rate reduction let two waves go apart (negative overlap length), and cardiac output rather decreased (dotted purple line).

ables, we proposed a formula to calculate ideal heart rate, at which the overlap length was zero: (ideal heart rate [bpm]) = $93 - 0.13 \times (\text{deceleration time [msec]})$. For example, when a patient has 200 msec of deceleration time, the ideal heart rate is calculated as 67 bpm. Again, this formula is an alternative to repeated measurement of the overlap length based on the hypothesis that the deceleration time is constant in each individual.

Ideal Heart Rate and Clinical Outcomes

Ideal heart rate may be associated with maximum diastolic filling and cardiac output as well as greatest reverse remodeling and clinical outcomes. Among those with systolic dysfunction, optimal heart rate, which was defined as a heart rate within 10 bpm of calculated ideal heart rate, was associated with greater reverse remodeling than the sub-optimal heart rate groups.²⁴⁾ Heart failure recurrence rate was not statistically stratified by the optimal heart rate, probably due to the small event number.

This concept might be expanded to other clinical scenarios such as systolic dysfunction following transcatheter aortic valve replacement, at which optimal heart rate was associated with greater reverse remodeling and a lower incidence of heart failure recurrence.²⁵⁾ Furthermore, optimal heart rate was associated with a lower incidence of heart failure recurrence in patients with diastolic dysfunction due to constrictive pericarditis.²⁶⁾

Heart Rate Optimization Using Ivabradine and Clinical Outcome

The implication of echocardiography-guided heart rate optimization using ivabradine, targeting zero overlaps, has not been validated thus far, except for several case reports (Figure 3).²⁷⁾ We are currently conducting a prospective randomized control trial, in which echocardiography-guided ivabradine therapy is performed versus a conventional treatment arm to investigate any advantages in improving clinical outcomes in patients with systolic dysfunction (CRB4180013).

Similar studies should be performed shortly to validate the implication of echocardiography-guided heart rate optimization in other clinical scenarios including acute heart failure,^{28,29)} heart failure with preserved ejection fraction,³⁰⁾ hypertrophic cardiomyopathy,³¹⁾ and acute coronary syndrome.³²⁾ We believe that target heart rate would vary depending on each patient's physiological scenario, and any absolute heart rates might not be proposed as a target.

Conclusions

Heart rate modulation using ivabradine improves morbidity and mortality in patients with systolic dysfunction. However, a target heart rate remains unknown. Recently, echocardiography-guided heart rate modulation using ivabradine has been proposed. Here, the overlap between two diastolic filling inflow waves is attempted in order to approach zero to maximize cardiac output, facilitate reverse remodeling, and prevent heart failure recur-

Figure 3. A patient with systolic dysfunction who received echocardiography-guided ivabradine therapy.²⁷⁾ HR indicates heart rate; DcT, deceleration time; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; and SV, stroke volume. On admission (A), two waves were overlapped with 104 bpm heart rate. The trend remained unchanged before ivabradine therapy (B). Following the initiation of ivabradine (C), the overlap between two waves diminished and two waves stood almost adjacent with incremental cardiac index. Cardiac index was calculated using AESCLONE mini (Osypka Medical, Berlin, Germany).³³⁾

rence. A prospective randomized control trial to validate this strategy is now ongoing.

Disclosure

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