Optimal Heart Rate Modulation Using Ivabradine
Teruhiko Imamura,1 MD and Koichiro Kinugawa,1 MD

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.

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 If 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).13) 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.
**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. 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. As a result, cardiac reverse remodeling is achieved, accompanying heart failure prevention and prognostic improvement. 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. 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.

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. At incremental heart rate, both waves come close and overlap. Given that the inflow volume during the diastasis phase (the period between E-wave and A-wave) is only 5%, we hypothesized that the optimal heart rate should be the one when the two waves stand adjacent without any overlap. In short, when there is an overlap between the two waves, a heart rate reduction is recommended until the overlap just disappears. When there is no overlap and instead both waves stand apart, 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 individual.

**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. Bakkehaug and colleagues also observed preserved cardiac output following administration of ivabradine in an animal model with systolic dysfunction. 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.

**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. If the lengths of both waves remain unchanged during the heart rate modulation (most of heart rate change is translated into the diastolic time), 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. Given the linear regression analysis including these vari-
Advancing Publication 3

OPTIMAL HR MODULATION USING IVABRADINE

Figure 2. Changes in overlap length and cardiac output during the 3-day ivabradine therapy. 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).

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). 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, heart failure with preserved ejection fraction, hypertrophic cardiomyopathy, and acute coronary syndrome. 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-
A patient with systolic dysfunction who received echocardiography-guided ivabradine therapy. 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).

Disclosure
Conflicts of interest: TI receives grant support from JSPS KAKENHI: JP20K17143 and the INAMORI Foundation.

References
1. Tsutsui H, Isobe M, Ito H, et al. JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure- Digest Version. Circ J 2019; 83: 2084-184.
2. Shiraishi Y, Kohsaka S, Sato N, et al. 9-Year Trend in the Management of Acute Heart Failure in Japan: A Report From the National Consortium of Acute Heart Failure Registries. J Am Heart Assoc 2018; 7: e008687.
3. Bohm M, Reil JC. Heart rate: surrogate or target in the management of heart failure? Heart 2013; 99: 72-5.
4. Takada T, Sakata Y, Miyata S, et al. Impact of elevated heart rate on clinical outcomes in patients with heart failure with reduced and preserved ejection fraction: a report from the CHART-2 Study. Eur J Heart Fail 2014; 16: 309-16.
5. Kitai T, Grodin JL, Mentz RJ, et al. Insufficient reduction in heart rate during hospitalization despite beta-blocker treatment in acute decompensated heart failure: insights from the ASCEND-HF trial. Eur J Heart Fail 2017; 19: 241-9.
6. Bucchi A, Tognati A, Milanesi R, Baruscotti M, DiFrancesco D. Properties of ivabradine-induced block of HCN1 and HCN4 pacemaker channels. J Physiol 2006; 572: 335-46.
7. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010; 376: 875-85.
8. Tardif JC, O’Meara E, Komajda M, et al. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy. Eur Heart J 2011; 32: 2507-15.
9. Tsutsui H, Momomura S, Yamashina A, et al. Heart Rate Control With If Inhibitor, Ivabradine, in Japanese Patients With Chronic Heart Failure- A Randomized, Double-Blind, Placebo-Controlled Phase II Study. Circ J 2016; 80: 668-76.
10. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-200.
11. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017; 70: 776-803.
12. Tsutsui H, Ide T, Ito H, et al. JCS/JHFS 2021 guideline focused update on diagnosis and treatment of acute and chronic heart failure. Circ J 2021 (in press).
13. Bohm M, Swedberg K, Komajda M, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between...
heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010; 376: 886-94.
14. Yamanaka T, Onishi K, Tanabe M, et al. Force- and relaxation-frequency relations in patients with diastolic heart failure. Am Heart J 2006; 152: 966.e1-7.
15. Ceconi C, Cargnoni A, Francolini G, Parinello G, Ferrari R. Heart rate reduction with ivabradine improves energy metabolism and mechanical function of isolated ischaemic rabbit heart. Cardiovasc Res 2009; 84: 72-82.
16. Ide T, Ohtani K, Higo T, Tanaka M, Kawasaki Y, Tsutsui H. I-V ibradine for the Treatment of Cardiovascular Diseases. Circ J 2019; 83: 252-60.
17. Izumida T, Imamura T, Nakamura M, Fukuda N, Kinugawa K. How to consider target heart rate in patients with systolic heart failure. ESC Heart Fail 2020; 7: 3231-4.
18. Chung CS, Afonso L. Heart Rate Is an Important Consideration for Cardiac Imaging of Diastolic Function. JACC Cardiovasc Imaging 2016; 9: 756-8.
19. Chung CS, Kovacs SJ. Consequences of increasing heart rate on deceleration time, the velocity-time integral, and E/A. Am J Cardiol 2006; 97: 130-6.
20. Nguyen LS, Squara P, Amour J, et al. Intravenous ivabradine versus placebo in patients with low cardiac output syndrome treated by dobutamine after elective coronary artery bypass surgery: a phase 2 exploratory randomized controlled trial. Crit Care 2018; 22: 193.
21. Bakkehaug JP, Naesheim T, Torgersen Engstad E, Kildal AB, Myrnel T, How OJ. Reversing dobutamine-induced tachycardia using ivabradine increases stroke volume with neutral effect on cardiac energetics in left ventricular post-ischaemia dysfunction. Acta Physiol (Oxf) 2016; 218: 78-88.
22. Hori M, Imamura T, Narang N, Kinugawa K. Implications of optimal heart rate on left ventricular reverse remodeling and functional improvement in patients with systolic heart failure. Heart Vessels 2021 (in press).
23. Imamura T, Tanaka S, Ushijima R, et al. The implication of optimal heart rate in patients with systolic dysfunction following TAVR. J Card Surg 2021; 36: 1328-33.
24. Izumida T, Imamura T, Ueno Y, et al. Impact of optimal heart rate on left ventricular reverse remodeling and functional improvement in patients with systolic heart failure. Heart Vessels 2021 (in press).
25. Imamura T, Narang N, Besser S, Kinugawa K. Chronotropic assessment in patients with constrictive pericarditis. Int Heart J 2021 (in press).
26. Hori M, Imamura T, Kinugawa K. Implication of heart rate optimization in patients with heart failure. J Cardiol Cases 2021; 23: 163-5.
27. Su Y, Ma T, Wang Z, et al. Efficacy of early initiation of ivabradine treatment in patients with acute heart failure: rationale and design of SHIFT-AHF trial. ESC Heart Fail 2020; 7: 4465-71.
28. Nakayama A, Iwama K, Makise N, et al. Use of a Non-invasive Cardiac Output Measurement in a Patient with Low-output Dilated Cardiomyopathy. Intern Med 2020; 59: 1525-30.