

[ ORIGINAL ARTICLE ]

## Implications of Doppler Echocardiography-guided Heart Rate Modulation Using Ivabradine

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### Abstract:

**Objective** Heart rate modulation therapy using ivabradine reduces both morbidity and mortality in patients with systolic heart failure. However, the target heart rate for this patient population remains to be elucidated.

**Methods** In this prospective observational study, we included patients with heart failure and a reduced ejection fraction who received 5.0 mg/day of ivabradine for three days. At baseline and three days later, the overlap length between E-wave and A-wave using trans-mitral Doppler echocardiography, as well as the cardiac output using AESCLONE mini, were simultaneously measured. The associations between  $\Delta$  overlap length and  $\Delta$  cardiac output were then investigated.

**Results** Eight patients [77 (53, 87) years old, 2 men] were included. The heart rate decreased from 81 (69, 104) bpm down to 64 (57, 79) bpm ( $p=0.012$ ). The overlap length increased in four patients and decreased in the other four patients. During the time period of ivabradine therapy, patients who had a greater decrease in overlap length had a greater increase in cardiac output ( $r=0.84$ ,  $p=0.009$ ).

**Conclusion** Decreases in the overlap length between E-wave and A-wave by Doppler echocardiography were associated with an increase in the cardiac output while on ivabradine therapy. The implications of Doppler echocardiography-guided heart rate modulation therapy targeting a minimal overlap length therefore require further evaluation in larger, prospective studies.

**Key words:** hemodynamics, echocardiography, arrhythmia

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### Introduction

Heart rate (HR) modulation therapy using ivabradine, an I<sub>c</sub> channel blocker that decreases the heart rate without affecting the sympathetic nerve activity (1), reduces both morbidity and mortality in patients with systolic heart failure (2). Rate control in patients with heart failure with a reduced ejection fraction is associated with increased diastolic filling and decreased myocardial oxygen demand. However, the optimal heart rate target to improve both survival as well as patient symptomology has yet to be established.

Chronotropic control may improve the cardiac output in patients who otherwise are tachycardic (3), while allowing for greater reverse remodeling and improved clinical outcomes (4). We hypothesized that the cardiac output is maximized at a HR where diastolic filling occurs without any

overlap between E-wave and A-wave as measured by Doppler echocardiography (5). In this study, we investigated the association between the overlap length and changes in the cardiac output during ivabradine therapy in patients with heart failure with a reduced ejection fraction.

### Materials and Methods

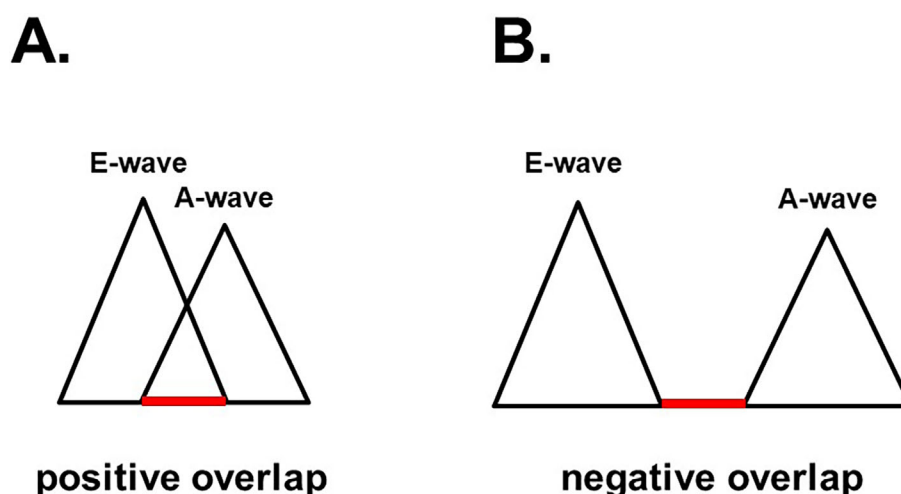
#### Patient selection

Consecutive patients with heart failure with a reduced ejection fraction, who received HR modulation therapy using 5.0 mg/day of ivabradine for three days (the observational period) and underwent both echocardiographic assessment and noninvasive cardiac output measurement, were included in this prospective observational study. All patients had a baseline HR above 75 bpm and were in sinus rhythm

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**Figure 1.** Trans-mitral Doppler echocardiography showing the positive overlap between the two waves (A) and the negative overlap between the two waves (B). The overlap length is represented as a red line. When there was no overlap between the two waves, the overlap length was shown as a negative value of the length between the two waves.

during the screening period. All patients were in stable clinical condition during the index hospitalization without any significant volume overload; baseline medications were not changed during the three-day ivabradine therapy. The study protocol was approved by the local institutional review board. All participants gave their written informed consent before the enrollment.

### Echocardiographic assessment

All patients received a standard echocardiographic assessment at baseline (day 0) and after the three days of ivabradine therapy (day 3). Of note, the overlap length between E-wave and A-wave in the trans-mitral Doppler echocardiography was measured by independent expert sonographers, who were blinded to the clinical data (Fig. 1A). If E-wave and A-waves were distinct without overlap, the length between both waves was expressed as a negative value (Fig. 1B). The overlap length was blinded to the attending physicians and it was not used for clinical management.

The  $\Delta$  overlap length was calculated as the change in the absolute value of the overlap length. For example, when the overlap length changed from 50 msec to 30 msec, then the  $\Delta$  overlap length was calculated as -20 msec. When the overlap length changed from -50 msec to -30 msec, then the  $\Delta$  overlap length was calculated also as -20 msec.

### Noninvasive cardiac output measurement

We estimated the cardiac output by using the AESCULON mini (Osypka Medical, Berlin, Germany) which was carried out simultaneously with echocardiography (i.e., day 0 and day 3) (6).

### Primary outcome

The purpose of this study was to validate the hypothesis that the cardiac output is maximized when the overlap

length between E-wave and A-wave is “zero”. The primary outcome of interest was the correlation between the  $\Delta$  cardiac output and  $\Delta$  overlap length.

### Statistical analyses

Continuous variables were expressed as the median and interquartile range. Categorical variables were expressed as a number and percentage. Trends were assessed using the Wilcoxon signed-rank test or McNemar test as appropriate. The correlation between the  $\Delta$  cardiac output and  $\Delta$  overlap length was assessed by using a Pearson’s correlation coefficient. Statistical analyses were performed using the SPSS Statistics 22 software program (SPSS, Armonk, USA). Two-sided p values <0.05 were considered to be statistically significant.

## Results

### Baseline characteristics

Eight consecutive patients [77 (53, 87) years old; 2 men] were included (Table). All patients received guideline-directed medical therapy as tolerated for their heart failure management. The median baseline systolic blood pressure was 107 (89, 114) bpm, heart rate 81 (69, 104) bpm, and cardiac output 3.2 (2.1, 4.3) L/min. The left ventricular end-diastolic diameter was 61 (57, 64) mm, the left ventricular ejection fraction was 39% (28%, 52%), and the overlap length was 81 (6, 178) ms.

### Three-day ivabradine therapy

Following the trial of ivabradine therapy, systolic blood pressure remained unchanged [110 (92, 118) mmHg at day 3, p=0.76]. The body weight also remained unchanged [51 (39, 71) kg at day 3, p=0.10]. The median heart rate de-

**Table. Baseline Characteristics.**

Demographics	
Age, years	77 (53, 87)
Men	2 (25%)
Body mass index	18.4 (17.2, 29.0)
Ischemic etiology	5 (50%)
Diabetes mellitus	3 (38%)
Atrial fibrillation	0 (0%)
Laboratory data	
Hemoglobin, g/dL	11.7 (9.5, 14.6)
Serum total bilirubin, mg/dL	0.5 (0.3, 0.6)
eGFR, mL/min/1.73m <sup>2</sup>	60.3 (43.1, 67.1)
Plasma B-type natriuretic peptide, pg/mL	252 (72, 1522)
Medications	
Beta-blocker	7 (88%)
Angiotensin-converting enzyme inhibitor	7 (88%)
Mineralocorticoid receptor antagonist	6 (75%)
Hemodynamics	
Systolic blood pressure, mmHg	107 (89, 114)
Heart rate, bpm	81 (69, 104)
Cardiac output, L/min	3.2 (2.1, 4.3)
Echocardiography	
Left ventricular end-diastolic diameter, mm	61 (57, 64)
Left ventricular ejection fraction, %	39 (28, 48)
Overlap length, msec	81 (6, 178)
Trans-mitral E wave height, cm/s	64 (39, 85)
Trans-mitral A wave height, cm/s	79 (73, 102)
Deceleration time of E wave, msec	144 (83, 291)

Variables were stated as median and interquartile or number and percentage.

creased to 64 (57, 79) bpm ( $p=0.012$ ). The cardiac output remained unchanged [3.1 (2.3, 4.4) L/min at day 3,  $p=0.57$ ]. The overlap length also remained unchanged [72 (-33, 122) msec at day 3,  $p=0.54$ ]. The E-wave increased to 82 (54, 98) cm/s at day 3 ( $p=0.017$ ) and the A-wave remained unchanged [77 (56, 89)] cm/s at day 3,  $p=0.21$ ).

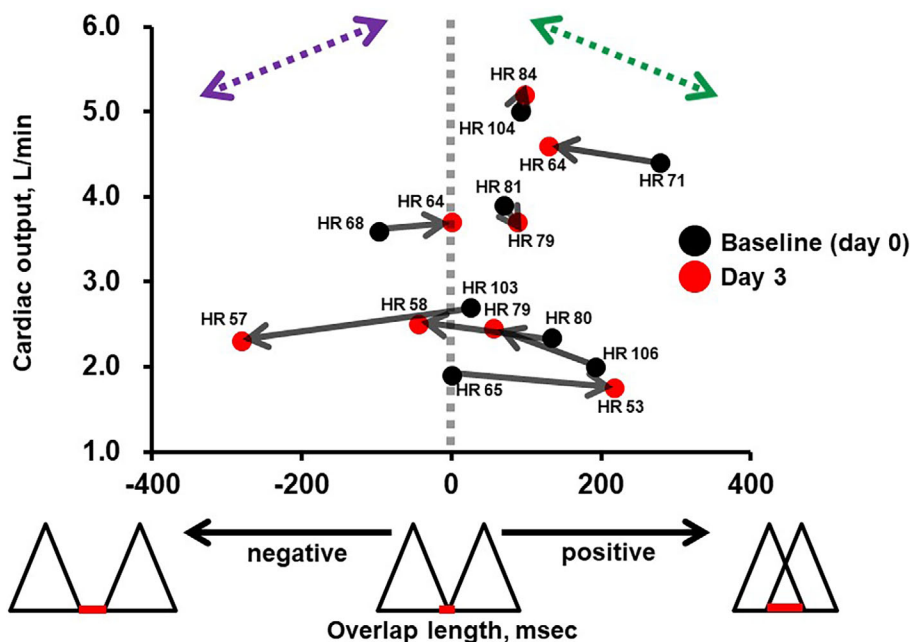
### Association between the overlap length and cardiac output (primary endpoint)

The association between the overlap length and cardiac output at baseline (black circles) and after the 3-day ivabradine therapy (red circles) are shown in Fig. 2. There are two trends (dot arrows) (1). When the degree of a positive overlap length decreases (i.e., direction toward “zero overlap”), then the cardiac output tended to increase (green dot arrow) (2). When the degree of negative overlap length increases (i.e., both waves move further apart from each other), then the cardiac output tended to decrease (purple dot arrow).

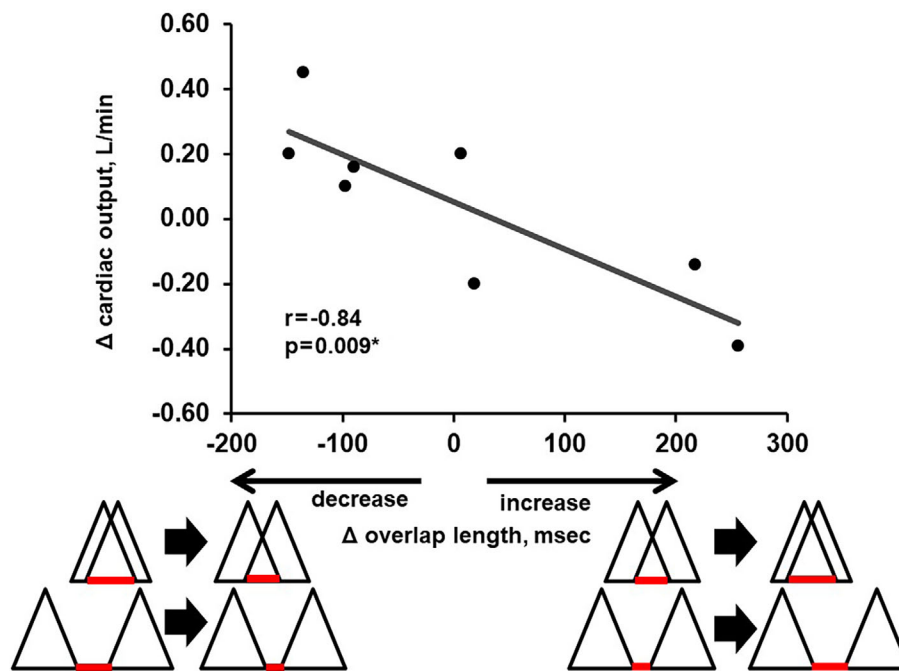
The association between  $\Delta$  overlap length and  $\Delta$  cardiac output during the 3-day ivabradine therapy is displayed in Fig. 3. The overlap length increased in four patients and decreased in the other four patients. The patients who showed a greater decrease in the overlap length tended to have a greater increase in the cardiac output ( $r=-0.84$ ,  $p=0.009$ ).

## Discussion

In this prospective observational study, we investigated the association between the overlap length between E-wave



**Figure 2.** Association between the overlap length and cardiac output at baseline (black circle) and three days (red circle) following the initiation of ivabradine therapy. There was a trend that the cardiac output became higher when the overlap length went towards “zero”.



**Figure 3.** Association between the  $\Delta$  overlap length and the  $\Delta$  cardiac output during the three-day ivabradine therapy. \* $p < 0.05$ .

and A-wave in the trans-mitral Doppler echocardiography and cardiac output during the three-day ivabradine therapy in patients with systolic heart failure. The heart rate decreased in all patients following ivabradine therapy, whereas the cardiac output did not increase in all patients (median value remained unchanged). The patients who achieved a greater decrease in the overlap length tended to have a greater improvement in the cardiac output following the trial of ivabradine therapy.

### Optimal heart rate and clinical outcomes

Based on the concept that the cardiac output should be maximized at an optimal heart rate, where the overlap length between E-wave and A-wave is “zero” (5), data from smaller studies in patients with systolic heart failure have demonstrated that reverse remodeling is maximized in patients with optimized rate control (7). Another study observed that the optimized heart rate was associated with a reduced rate of heart failure readmissions in patients with constrictive pericarditis (8). In this study, we specifically observed that patients with systolic heart failure may have an improved cardiac output with an optimized heart rate, at which the diastolic inflow overlap length between E and A waves was “zero”.

### Association between overlap length and cardiac output

All patients experienced a reduction in heart rate with ivabradine therapy. Nevertheless, the entire cohort did not have an observed improvement in the cardiac output. When there was residual overlap between E and A waves, (Fig. 1A), improvements in the cardiac output were mar-

ginal. Heart rate reduction using ivabradine improve the chance of E and A wave separation, which subsequently may lead to an increase in the cardiac output (green dot arrow in Fig. 2) (9). When wave overlap occurs, cardiac efficiency may be reduced due to inefficient diastolic filling.

Both waves remained apart in some patients (Fig. 1B). Aggressive heart rate reduction using ivabradine might not be recommended in these specific patients due to the association with a lower cardiac output, irrespective of the absolute heart rate levels (purple dot arrow in Fig. 2) (9). In these scenarios, there may be some potential energy reserve due to lower myocardial oxygen consumption, though extremes of bradycardia may be detrimental for maintaining an adequate physiologic cardiac output.

As observed in this study, the optimal heart rate varies in each individual, with a strong association with deceleration time (5). For example, when a patient has a very short deceleration time, as often observed in patients with diastolic dysfunction (8), a relatively higher heart rate would be optimal to achieve “zero” overlap. This is a rationale why we recommend performing Doppler echocardiography to determine the optimal heart rate for each individual, instead of generalizing heart rate targets which might not prove universally beneficial.

### Limitations

Given the small sample size, applying these clinical data to routine patient care should be done with caution. This is a proof of concept study. We did not directly study if maximizing the cardiac output during ivabradine therapy is associated with cardiac reverse remodeling. Given the observational nature of this study, we did not adjust clinical man-

agement considering the data of overlap length. Based on the hypothesis that the cardiac output, instead of the stroke volume, is more closely associated with reverse remodeling, we preferred the cardiac output to stroke volume as an outcome variable.

Given our findings, the heart rate should be modulated targeting “zero” overlap. Prospective randomized control trials are needed to compare the clinical outcomes between the Doppler echocardiography-guided ivabradine therapy targeting “zero” overlap versus standard ivabradine therapy targeting conventional heart rates.

## Conclusion

The overlap length between E-wave and A-wave in the Doppler echocardiography was associated with changes in the cardiac output during ivabradine therapy. The implications of Doppler echocardiography-guided heart rate modulation therapy therefore require further prospective investigation.

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

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Masakazu Hori and Teruhiko Imamura contributed equally to this work.

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