Prognostic Implications of Mitral Valve Inflow Pattern Overlap during Ivabradine Therapy

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Summary
The prognostic impact of mitral inflow wave overlap during ivabradine therapy in patients with heart failure with reduced ejection fraction (HFrEF) remains to be unknown. Thus, in this study, we have retrospectively examined consecutive inpatients with HFrEF admitted with decompensated heart failure who continued ivabradine following the index discharge. Ideal heart rate (HR), at which echocardiographic mitral inflow wave overlap is theoretically 0, was retrospectively calculated as follows: 96 - 0.13 × (deceleration time [msec]). HR difference was then calculated as follows: actual HR - ideal HR. The association between the HR difference at index discharge and a composite outcome of cardiovascular death and heart failure readmissions was investigated. In total, 16 patients (68 [47, 75] years old, 11 men, median left ventricular ejection fraction 28% [22%, 35%]) were included in this study for analysis. Baseline actual HR was determined to be 88 (81, 93) bpm, whereas the ideal HR was calculated as 75 (73, 76) bpm. Following the initiation of ivabradine, actual HR at index discharge was 75 (64, 84) bpm. Patients with optimal HR (actual HR - ideal HR < ± 10 bpm; n = 9) were found to have experienced a lower incidence of the composite endpoint (40% versus 100%, P = 0.013) compared with those with sub-optimal HR (n = 7) with a hazard ratio of 0.10 (95% confidence interval 0.01-0.91) adjusted for actual HR at index discharge. In conclusion, HR modulation therapy using ivabradine may improve outcomes in patients with HFrEF if individualized ideal HR was achieved.

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Key words: Hemodynamics, Heart failure, HFrEF

Heart rate (HR) modulation therapy using ivabradine, which is identified as an I, channel blocker that decreases HR without affecting sympathetic nerve activity,1 has been known to reduce morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF).2 Chronotropic rate control is often associated with increased diastolic filling and decreased myocardial oxygen demand.3 However, extreme nadirs in HR may lead to a decrease in cardiac output and upregulation in sympathetic nerve activity.4 Thus far, an optimal HR target associated with the highest odds of reverse cardiac remodeling during ivabradine therapy remains to be unknown.

Chronotropic control may improve cardiac output in patients who otherwise are tachycardic, while allowing for greater reverse remodeling and improved clinical outcomes. We hypothesized that cardiac output is maximized at HR where diastolic filling occurs without any overlap between E-wave and A-wave as measured using Doppler echocardiography.5 Given that the heart rate is largely dependent on HR and deceleration time of E-wave, we proposed a formula to calculate the ideal HR, that is, 96 - 0.13 × (deceleration time [msec]).

However, the clinical implications of an individualized HR target during ivabradine therapy have not yet been validated. Thus, in this study, we have investigated the clinical implications of optimized HR during ivabradine therapy in HFrEF patients.

Methods

Patient selection: Consecutive patients with HFrEF who initiated 5.0 mg/day of ivabradine following clinical stabilization after hospitalization for decompensated heart failure were included in this retrospective study. All patients had resting HR > 75 bpm, were in sinus rhythm as assessed through electrocardiogram at rest, and had a systolic blood pressure > 90 mmHg at baseline.6 All patients intended to initiate or up-titrate beta-blocker up to the maximum dose (20 mg/day of carvedilol equivalent). These were institutional indications of ivabradine therapy, but the final decision to initiate ivabradine was at the attending physicians’ discretion.

Those who initiated ivabradine in the outpatient clinic and those who discontinued ivabradine during the index hospitalization were excluded from analysis. The
study protocol was approved by the local institutional review board. All participants gave written informed consent before the enrollment.

**Therapeutic strategy and observational period:** All patients received guideline-directed medical therapy during the observational period.9) The dose of ivabradine was adjusted with a conventional target HR of 60 bpm, taking patients’ hemodynamics and symptomology into consideration.10 The time of index discharge was defined as day 0. All patients were observed for 1 year or until April 30, 2021.

**Data collection during the index hospitalization:** At the time of ivabradine initiation, demographics, laboratory, echocardiography, and hemodynamics data were assessed. Of note, a deceleration time of E-wave at trans-mitral time of ivabradine initiation, demographics, laboratory, and plasma B-type natriuretic peptide (BNP) level was measured.11 Ideal HR was calculated according to the following formula: 96 - 0.13 × (deceleration time [msec]).12 The calculation of ideal HR was done retrospectively by attending physicians who were blinded to the value during the observational period.

At the time of index discharge, laboratory, hemodynamics, and medication data were collected. Actual HR was measured in the same manner with the time of ivabradine initiation. HR difference was calculated as a value between actual HR and ideal HR. Patients with HR difference < 10 bpm were assigned to the optimal HR group, whereas those with HR difference ≥ 10 bpm were assigned to the sub-optimal HR group.

**Data collection following the index discharge:** At 3 months following index discharge, transthoracic echocardiography was performed, and plasma BNP measurements were assessed. During the 1-year observational period, cardiovascular death or heart failure readmission requiring IV-diuretics was defined the composite primary endpoint.

**Statistical analyses:** Statistical analyses were performed using SPSS Statistics 22 (SPSS Inc., Armonk, IL, USA). Two-sided P-values < 0.05 were considered statistically significant. Continuous variables were expressed as median and interquartile ranges. Categorical variables were expressed as number and percentage. Baseline characteristics and clinical outcomes were compared between the optimal HR group and the sub-optimal HR group. Continuous variables were compared using Mann-Whitney U test; meanwhile, categorical variables were compared using Fisher’s exact test.

Cumulative incidences of the primary endpoint were compared between the two groups using log-rank test. The impact of optimal HR on the primary endpoint was assessed using Cox proportional hazards ratio regression analyses. The analyses were adjusted for clinically important variables on the primary endpoint, including age, discharge BNP, and discharge HR. Heart failure readmission rates were compared between the groups using negative binomial regression analysis.

**Results**

**Baseline characteristics:** During the study period, 88 patients with HFrEF were admitted to our institute. Of them, 34 patients with atrial fibrillation or dependent on pacing did not receive ivabradine. Eight patients with short-term ivabradine therapy were also excluded. Thirty patients with sinus rhythm did not receive ivabradine due to out of hemodynamics criteria or at attending physicians’ discretion.

Finally, 16 consecutive patients with HFrEF (68 [47, 75] years old, 11 men) were included in this retrospective study (Table I). All patients were in sinus rhythm with HR > 75 bpm (88 [81, 93] bpm) and systolic blood pressure > 90 mmHg (104 [95, 111] mmHg) at baseline prior to ivabradine therapy. Median LVEF was 28% [22%, 40%], and plasma B-type natriuretic peptide (BNP) level was 281 (106, 879) pg/mL. Given the measured deceleration time was 140 (129, 154) msec, ideal HR was calculated as 75 (73, 76) bpm according to the above-described formula.

**Ivabradine therapy:** Ivabradine was initiated at 5.0 mg/day following clinical stabilization during the index hospitalization. At index discharge, plasma BNP was determined to be 170 (80, 254) pg/mL, systolic blood pressure was 99 (86, 113) mmHg, and actual HR was 75 (64, 84) bpm (Table II).

The relationship between ideal HR and actual HR is shown in Figure 1A. Nine patients had HR difference < 10 bpm; they were then assigned to the optimal HR group (red circles). Others were assigned to the sub-optimal HR group (black circles). The distribution of HR difference is shown in Figure 1B.

As per our findings, no statistically significant differences were noted as regards baseline data between the optimal and sub-optimal HR groups (Table I). Actual HR and medications at index discharge also did not significantly differ between the two groups (Table II).

**Three-month follow-up:** Absolute values and changes in echocardiographic data and plasma BNP levels are summarized in Table III. Left ventricular size decreased and LVEF increased in the optimal HR group, whereas they worsened in the sub-optimal HR group. Plasma BNP decreased in the optimal HR group and increased in the sub-optimal HR group.

**One-year follow-up:** During the observational period, no patients had medication-related adverse events such as hypotension or symptomatic bradycardia. All patients continued ivabradine during the observational follow-up period. However, one patient died due to sudden death on day 54. Seven heart failure readmissions occurred in six patients.

The 1-year cumulative incidence of the primary endpoint was lower in the optimal HR group (40% versus 100%; P = 0.013; Figure 2A). Optimal HR was significantly associated with the primary endpoint in the univariate analysis (hazard ratio 0.10, P = 0.040) and multivariate analyses adjusted for age, discharge BNP, and discharge HR, respectively (P < 0.05 for all; Table IV). Actual HR at index discharge was determined to be not associated with the primary endpoint (hazard ratio 0.95, 95% confidence interval 0.87-1.05, P = 0.35).

Heart failure readmission rate was observed to be 0.36 events/year in the optimal HR group versus 1.39 events/year in the sub-optimal HR group (incidence rate ratio 0.26, 95% confidence interval 0.05-1.35, P = 0.11; Figure 2B).
Table I. Baseline Characteristics Prior to Initiation of Ivabradine

| Demographics | Total (n = 16) | Optimal HR (n = 9) | Sub-optimal HR (n = 7) | P-value |
|--------------|---------------|--------------------|------------------------|---------|
| Age, years   | 68 (47, 75)   | 63 (45, 73)        | 72 (58, 75)            | 0.47    |
| Men          | 11 (69%)      | 7 (78%)            | 4 (57%)                | 0.37    |
| Body surface area, m² | 1.67 (1.50, 1.75) | 1.66 (1.51, 1.76) | 1.67 (1.51, 1.72) | 0.76    |
| Comorbidity  |               |                    |                        |         |
| Atrial fibrillation | 0              | 0                  | 0                      | -       |
| Diabetes mellitus | 8 (50%)        | 3 (33%)            | 5 (71%)                | 0.16    |
| Dyslipidemia  | 9 (56%)       | 5 (56%)            | 4 (57%)                | 0.67    |
| Ischemic heart disease | 7 (44%)   | 3 (33%)            | 4 (57%)                | 0.33    |

| Laboratory   | Total (n = 16) | Optimal HR (n = 9) | Sub-optimal HR (n = 7) | P-value |
|--------------|---------------|--------------------|------------------------|---------|
| Hemoglobin, g/dL | 13.5 (12.0, 15.9) | 14.9 (12.1, 16.2) | 13.0 (11.8, 14.1) | 0.41    |
| Serum albumin, g/dL | 3.5 (3.3, 3.9)  | 3.4 (3.3, 3.9)     | 3.6 (3.4, 3.7)        | 0.92    |
| Serum total bilirubin, mg/dL | 0.7 (0.5, 1.5) | 0.7 (0.5, 0.8) | 1.0 (0.5, 1.9) | 0.68    |
| eGFR, mL/minute/1.73 m² | 64.2 (36.4, 73.3) | 32.8 (31.9, 73.9) | 67.6 (53.5, 70.8) | 0.41    |
| Plasma B-type natriuretic peptide, pg/mL | 281 (106, 879) | 142 (92, 272) | 331 (211, 537) | 0.25    |

| Echocardiography | Total (n = 16) | Optimal HR (n = 9) | Sub-optimal HR (n = 7) | P-value |
|------------------|---------------|--------------------|------------------------|---------|
| Left ventricular end-diastolic diameter, mm | 58 (50, 71) | 55 (49, 72) | 58 (54, 66) | 0.92    |
| Left ventricular ejection fraction, % | 28 (22, 40) | 28 (22, 35) | 27 (24, 37) | 0.84    |
| Mild or greater mitral regurgitation | 5 (31%) | 2 (22%) | 3 (43%) | 0.37    |
| Mild or greater tricuspid regurgitation | 3 (19%) | 2 (22%) | 1 (14%) | 0.60    |
| Deceleration time, msec | 140 (129, 154) | 144 (132, 149) | 136 (106, 151) | 0.47    |
| Ideal heart rate, bpm | 75 (73, 76) | 74 (74, 76) | 75 (74, 79) | 0.47    |

| Hemodynamics   | Total (n = 16) | Optimal HR (n = 9) | Sub-optimal HR (n = 7) | P-value |
|----------------|---------------|--------------------|------------------------|---------|
| Systolic blood pressure, mmHg | 104 (95, 111) | 102 (98, 114) | 106 (94, 108) | 0.54    |
| Actual heart rate, bpm | 88 (81, 93) | 86 (84, 93) | 89 (80, 96) | 1.0     |

Table II. Clinical Variables at Index Discharge following Initiation of Ivabradine

| Laboratory at index discharge | Total (n = 16) | Optimal HR (n = 9) | Sub-optimal HR (n = 7) | P-value |
|-------------------------------|---------------|--------------------|------------------------|---------|
| Hemoglobin, g/dL              | 11.6 (10.8, 14.9) | 11.9 (11.1, 15.4) | 11.2 (10.9, 12.2) | 0.54    |
| Serum albumin, g/dL           | 3.5 (3.3, 3.9)  | 3.4 (3.3, 3.9)     | 3.6 (3.4, 3.7)        | 0.92    |
| Serum total bilirubin, mg/dL  | 0.5 (0.4, 0.8) | 0.5 (0.4, 0.8) | 0.5 (0.5, 0.6) | 0.84    |
| eGFR, mL/minute/1.73 m²       | 59.3 (37.8, 78.0) | 51.7 (32.1, 63.9) | 61.5 (57.0, 74.7) | 0.14    |
| Plasma B-type natriuretic peptide, pg/mL | 170 (80, 254) | 201 (96, 340) | 143 (101, 206) |         |

| Hemodynamics at index discharge | Total (n = 16) | Optimal HR (n = 9) | Sub-optimal HR (n = 7) | P-value |
|--------------------------------|---------------|--------------------|------------------------|---------|
| Systolic blood pressure, mmHg | 99 (86, 113) | 92 (86, 105) | 99 (92, 111) | 0.76    |
| Actual heart rate, bpm | 75 (64, 84) | 76 (72, 78) | 71 (61, 88) | 0.84    |
| Heart rate difference between actual and ideal ones, bpm | 1 (-9, 8) | 2 (-1, 3) | -11 (-14, 13) | 0.68    |

| Medications at index discharge | Total (n = 16) | Optimal HR (n = 9) | Sub-optimal HR (n = 7) | P-value |
|-------------------------------|---------------|--------------------|------------------------|---------|
| Beta-blocker, mg/day | 10 (5, 12.5) | 7.5 (2.5, 10) | 10 (7.5, 15) | 0.30    |
| Renin-angiotensin system inhibitor, mg/day | 2.5 (1.25, 2.5) | 2.5 (1.25, 2.5) | 2.5 (2.5, 3.75) | 0.35    |
| Mineralocorticoid receptor antagonist, mg/day | 25 (0, 25) | 12.5 (0, 25) | 25 (12.5, 25) | 0.47    |

Discussion

In this retrospective study, we investigated the impact of HR difference between actual and ideal HR on cardiovascular mortality and risk of heart failure events in patients with HFrEF who were initiated on ivabradine therapy. Major findings are as follows: (1) ivabradine therapy decreased the median actual HR from 88 bpm to 75 bpm; (2) half of the patients achieved optimal HR, defined as HR difference < 10 bpm, during the ivabradine therapy; (3) the optimal HF group showed evidence of improved reverse remodeling and decreased plasma BNP levels at 3-month follow-up; (4) the optimal HR group had a lower incidence of cardiovascular death or heart failure recurrence at 1-year follow-up.

Implication of ideal HR defined by the diastolic filling flow overlap: Inappropriate tachycardia in patients with HFrEF is associated with a high adverse event rate from...
Association between ideal heart rate and actual heart rate (A) and distribution of heart rate difference between ideal and actual heart rate (B). Optimal heart rate was defined as heart rate difference within 10 bpm and indicated as a red circle. Others were assigned to the sub-optimal groups.

Table III. Echocardiographic and BNP Data at 3-Month Follow-Up

| Data at 3-month follow-up | Total (n = 12) | Optimal HR (n = 7) | Sub-optimal HR (n = 5) | P-value |
|----------------------------|---------------|-------------------|----------------------|--------|
| Left ventricular end-diastolic diameter, mm | 63 (48, 71) | 53 (46, 68) | 66 (60, 70) | 0.34 |
| Left ventricular ejection fraction, % | 26 (22, 44) | 32 (26, 49) | 21 (16, 24) | 0.048* |
| Mild or greater mitral regurgitation | 4 (33%) | 0 | 4 (80%) | 0.004* |
| Mild or greater tricuspid regurgitation | 4 (33%) | 0 | 4 (80%) | 0.004* |
| Plasma BNP, pg/mL | 264 (69, 302) | 93 (38, 211) | 265 (264, 347) | 0.035* |
| Change at 3-month follow-up | | | | |
| Left ventricular end-diastolic diameter, mm | -2 (-4, 2) | -3 (-4, -3) | 2 (2, 2) | 0.003* |
| Left ventricular ejection fraction, % | 6 (-3, 9) | 8 (7, 12) | -3 (-4, -2) | 0.003* |
| Worsening in mitral regurgitation | 4 (33%) | 1 (14%) | 3 (60%) | 0.098 |
| Worsening in tricuspid regurgitation | 4 (33%) | 0 | 4 (80%) | 0.004* |
| Plasma BNP, pg/mL | -57 (-96, 124) | -72 (-183, -67) | 126 (122, 240) | 0.001* |

BNP, B-type natriuretic peptide. Continuous variables were presented as median and interquartile and compared between the groups using Mann-Whitney U test. Categorical variables were presented as number and percentage and compared between the groups using Fisher’s exact test. *P < 0.05.

Figure 2. Cumulative incidence of the primary endpoint (A) and heart failure readmission rates (B) between the optimal heart rate group and the sub-optimal heart rate group. *P < 0.05 by log-rank test.

compromised stroke volume, increased myocardial oxygen demand, and neurohormonal activation. This subsequently leads to decreased reverse remodeling and higher long-term risk of cardiovascular death and worsening heart failure. This motivates the rationale to modulate HR in heart failure patients.

However, the ideal HR target yielding a broad benefit across the spectrum of HFrEF phenotypes remains uncertain. Inappropriate bradycardia decreases cardiac output despite an increase in stroke volume and may stimulate
that deceleration time is constant, but it should fluctuate during the observational period. We assumed our hypothesis. We did not consider the trends of HR and fluctuation, but further studies are warranted to validate needed to validate this hypothesis. We defined optimal HR investigations; thus, larger-scale multi-center studies are small sample of patients. This is a novel proof-of-concept. Of note, four out of seven patients in the sub-optimal pations; for one, this is a retrospective study comprised of a bradycardia might be explained by inappropriately low HR, heart rate; BNP, B-type natriuretic peptide. The primary endpoint is composites of all-cause death and heart failure readmissions. The impact of optimal heart rate was adjusted for clinically important variables, respectively. *P < 0.05 by Cox proportional hazard ratio regression analyses. sympathetic nerve activity.4) We thus hypothesize that HR is ideal when E-wave and A-wave at mitral inflow stand adjacent without any overlap.5) Given that the overlap length is predominantly determined by the actual HR and the deceleration time of E-wave, we proposed a formula to calculate the ideal HR: 96 - 0.13 × (deceleration time [msec]). Prior data has suggested that cardiac output is maximized when the overlap between both waves approached 0 during the 3-day ivabradine therapy.10) In this study, we expanded these findings and investigated the clinical outcomes in patients with optimized HR modulated by ivabradine. Uniquely, ideal HR was distributed widely depending on a variety of deceleration times. As a result, optimal HR (i.e., actual HR within 10 bpm of ideal HR) was achieved in patients with various degrees of actual HR ranging between 62 bpm and 85 bpm. Morphologic and prognostic change during ivabradine therapy: The theoretical hemodynamic improvement, owing to the optimization of HR by ivabradine, resulted in structural echocardiographic changes including a reduction in left ventricular size, improved ejection fraction, and lower B-type natriuretic peptide levels. Sub-analysis from the SHIFT trial confirmed this physiologic benefit with an observed improvement in reverse remodeling following initiation of ivabradine.10) As expected, improvements in cardiac structure and function were determined to be associated with an improvement in prognosis. Interestingly, the prognostic impact of HR optimization was independent of actual HR itself. Of note, four out of seven patients in the sub-optimal HR group had HR that was lower than the ideal. Adverse outcomes in this subgroup of patients with exaggerated bradycardia might be explained by inappropriately low cardiac output.5) Given these findings, we propose to calculate ideal HR using each patient’s deceleration time and use it as a target HR, instead of conventional targets which may not be broadly applicable. Limitations and future directions: This study has limitations; for one, this is a retrospective study comprised of a small sample of patients. This is a novel proof-of-concept investigation; thus, larger-scale multi-center studies are needed to validate this hypothesis. We defined optimal HR as HR difference within 10 bpm given the real-world HR fluctuation, but further studies are warranted to validate our hypothesis. We did not consider the trends of HR and medication during the observational period. We assumed that deceleration time is constant, but it should fluctuate as heart failure progresses. We have also investigated the association between HR at index discharge and clinical outcomes. During the ideal long-term ivabradine therapy, ideal HR is recommended to be re-calculated, and HR should be re-optimized repeatedly. We did not prospectively calculate the ideal HR, and the dose adjustment of ivabradine was performed targeting absolute HR of 60 bpm. Prospective studies are under way at our institution to determine the prognostic implications of deceleration time-guided HR modulation targeting calculated ideal HR (CRB4180003). The prospective randomized control trial to investigate the impact of ivabradine for those with acute heart failure is currently ongoing (SHIFT-AHF trial).12) Our concept might be applicable also to this study because a HR range to provide clinical benefit is currently unknown.13) Conclusion HR modulation therapy using ivabradine to target uniquely individualized HR may be associated with improved clinical outcomes in patients with HFrEF.

Disclosure
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References
1. Ide T, Ohtani K, Higo T, Tanaka M, Kawasaki Y, Tsutsui H. Ivabradine for the treatment of cardiovascular diseases. Circ J 2019; 83: 252-60.
2. 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.
3. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Tavazzi L. Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: the Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial (SHIFT). Eur J Heart Fail 2010; 12: 75-81.
4. Alboni P, Brignole M, Menozzi C, Scarfo S. Is sinus bradycardia a factor facilitating overt heart failure? Eur Heart J 1999; 20: 252-5.
5. 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: 321-4.
6. Tsutsui H, Momomura S, Yamashina A, et al. Efficacy and safety of ivabradine in Japanese patients with chronic heart
failure-J-SHIFT study. Circ J 2019; 83: 2049-60.
7. Tsutsui H, Isobe M, Ito H, et al. JCS 2017/JHFS 2017 Guide-
line on Diagnosis and Treatment of Acute and Chronic Heart
Failure- Digest Version. Circ J 2019; 83: 2084-184.
8. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations
for the evaluation of left ventricular diastolic function by echo-
cardiography: an update from the American Society of Echocar-
diography and the European Association of Cardiovascular Im-
ing. J Am Soc Echocardiogr 2016; 29: 277-314.
9. Huizar JF, Ellenbogen KA, Tan AV, Kaszala K. Arrhythmia-
induced cardiomyopathy: JACC state-of-the-art review. J Am
Coll Cardiol 2019; 73: 2328-44.
10. Tardif JC, O’Meara E, Komajda M, et al. Effects of selective
heart rate reduction with ivabradine on left ventricular remodel-
ing and function: results from the SHIFT echocardiography
substudy. Eur Heart J 2011; 32: 2507-15.
11. Hori M, Imamura T, Narang N, Kinugawa K. Implications of
doppler echocardiography-guided heart rate modulation using
ivabradine. Intern Med 2021; (in press).
12. Su Y, Ma T, Wang Z, et al. Efficacy of early initiation of iv-
abradine treatment in patients with acute heart failure: rationale
and design of SHIFT-AHF trial. ESC Heart Fail 2020; 7: 4465-71.
13. Imamura T, Narang N. Comment on: Efficacy of early initiation
of ivabradine treatment in patients with acute heart failure: ration-
ale and design of SHIFT-AHF trial. ESC Heart Fail 2021; 8:
1725-6.