Comparison of haemodynamic response to muscle reflex in heart failure with reduced vs. preserved ejection fraction

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Abstract

Aims  Isometric handgrip (IHG) training reduces the blood pressure in patients with hypertension. It is unclear how IHG exercise affects the haemodynamics and cardiovascular function through the muscle reflex in patients with heart failure (HF) with reduced (HFrEF) and preserved ejection fraction (HFpEF).

Methods and results  Twenty patients (HFrEF: n = 10, HFpEF: n = 10) underwent left ventricular (LV) pressure–volume assessments using a conductance catheter and microtip manometer to evaluate haemodynamics, LV and arterial function, and LV-arterial coupling during 3 min of IHG at 30% of maximal voluntary contraction (MVC), followed by 3 min of post-exercise circulatory arrest (PECA). Three minutes of IHG exercise produced significant and modest increases in the heart rate (HR) and LV end-systolic pressure (LVESP), respectively, in both HFpEF and HFrEF groups. In HFrEF, the increase in LVESP was caused by the variable increase in effective arterial elastance (Ea), which was counterbalanced by the increase in LV end-systolic elastance (Ees), resulting in a maintained Ees/Ea. In HFpEF, the increase in LVESP was not accompanied by changes in Ea, Ees, Ees/Ea, or LV end-diastolic pressure. LVESP during PECA was not maintained in HFpEF, suggesting smaller metabo-reflex activity in HFpEF.

Conclusions  The IHG exercise used in this study may increase the LVESP and LVEDP without detrimental effects on cardiac function or ventricular-arterial coupling, especially in HFpEF patients. The effects of IHG exercise on haemodynamics and ventricular-arterial coupling may be affected by the patient background and the type and intensity of the exercise.

Keywords  Isometric handgrip exercise; Post-exercise circulatory arrest

Received: 9 July 2021; Revised: 13 September 2021; Accepted: 5 October 2021

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Introduction

In recent years, heart failure (HF) is divided into three categories based on measurement of the left ventricular (LV) ejection fraction (LVEF): heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Among them, it is known that HFrEF and HFpEF have significantly different pathological conditions. Various studies have been conducted comparing the two categories of HF. In patients with HFrEF, drug therapy and non-drug therapy, including exercise training or cardiac rehabilitation, improve the symptoms and prognosis. However, for patients with HFpEF, who are likely to be older women with hypertension, no effective drug/non-drug therapy has been reported. Therefore, novel treatments are needed.

Isometric handgrip (IHG) training consisting of several contractions for 2 min at 30% of maximal voluntary contraction (MVC) several days per week was reported to reduce blood pressure (BP) and may improve cardiac autonomic function in patients with hypertension. However, it is unclear how
a single session of IHG exercise at 30% of MVC affects the heart rate (HR), LV pressure, and LV and arterial function in patients with HFrEF and HFpEF. Central commands, mechanical stimulation associated with muscle contraction (mechano-reflex), and metabolites produced by muscle contraction (metabo-reflex) are induced during IHG exercise, all of which are involved in the activation of the sympathetic nervous system. In patients with HF, the sympathetic nervous system is activated more than in healthy people at rest and during exercise. Post-exercise circulatory arrest (PECA), which can retain metabolites produced by exercise in muscle, have been used to distinguish the effects of muscle metabo-reflexes on haemodynamics from those by central commands and muscle mechano-reflexes.

To date, the effects of IHG exercise on the haemodynamics, LV, and arterial function during IHG exercise and PECA have not been fully evaluated in HFpEF patients. In addition, it is unclear whether haemodynamic and cardiovascular effects of IHG exercise in HFpEF are different from those in HFrEF. Therefore, the purpose of this study was to evaluate the impacts of 3 min of IHG exercise and 3 min of PECA on the haemodynamics and LV function in patients with HFpEF and HFrEF.

**Methods**

**Participants**

Twenty patients (HFrEF: \( n = 10 \), HFpEF: \( n = 10 \)) who were admitted to Mie University Hospital because of HF and whose HF symptoms were ameliorated by treatment were included. HFrEF was defined as HF with LVEF <40% by transthoracic echocardiography (TTE). HFpEF was defined according to the consensus paper of the European Society of Cardiology using specific inclusion criteria: LVEF ≥50%; New York Heart Association functional Class ≥II; and \( E/e' > 15 \) or \( E/e' < 15 \) combined with high B-type natriuretic peptide (≥35 pg/mL). Exclusion criteria were (i) unstable angina or acute myocardial infarction within 6 months before study enrolment, (ii) atrial fibrillation, (iii) severe valvular disease, (iv) resting systolic BP ≥160 mmHg or pulmonary artery wedge pressure (PAWP) ≥25 mmHg, (v) pacemaker or cardioverter-defibrillator implants, (vi) severe renal dysfunction with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m², (vii) bronchial asthma, and (viii) poor prognosis due to diseases other than HF. All patients underwent cardiac magnetic resonance imaging (MRI) to measure LV end-diastolic (LVEDV) and end-systolic volumes (LVESV). Cardiac MRI was performed before cardiac catheterization within a 4 week window. The ethics committee of Mie University Hospital approved the study protocol (No. 2904) in accordance with the Declaration of Helsinki, and all patients provided written informed consent to participate.

**Testing protocol**

All patients underwent a blood test, TTE, and maximal cardiopulmonary exercise testing. Standard 2D Doppler echocardiography (Vivid 7, GE Medical Ultrasound, Horten, Norway or Artida, Toshiba Medical Systems, Tochigi, Japan) was performed for all patients by registered medical sonographers certified by the Japan Society of Ultrasoconics in Medicine who were not involved in patient care. LVEF, transmitral early (E) and late (A) diastolic inflow velocities, and early diastolic mitral annular velocity (E') were assessed in an apical four-chamber view. Maximal symptom-limited cardiopulmonary exercise was performed using a cycle ergometer (StrengthErgo240, Mitsubishi Electric Engineering Company, Ltd.) with a ramp protocol with increments of 1 W per 6 s until exhaustion. The stress system was the ML-9000 (Fukuda Denso Co. Ltd.). The expired breath-by-breath gas exchange measurements were recorded throughout the test (CPEX-1, Inter Reha Co. Ltd.) and converted into time-series data every 3 s.

**Cardiac catheterization protocol**

Prior to catheterization, MVC was measured in all patients in the upper left limb using a digital grip strength meter (T.K.K 5401, Takei Scientific Instruments Co., Ltd., Tokyo, Japan). After confirming no significant coronary artery stenosis by invasive coronary angiography, right atrial pressure (RAP), mean pulmonary artery pressure (PAP), PAWP, and cardiac output (CO) were measured by right heart catheterization. A 6-Fr conductance catheter with a microchip manometer was then introduced to the LV apex and connected to a digital stimulator microprocessor [Sigma V, Leycom (dual-field system), Zoetermeer, the Netherlands] to measure LV volumes. Real-time pressure–volume diagram generation and analog/digital conversion (333 Hz) were performed using a 16-bit microcomputer system (PC-9801VX, NEC Co, Tokyo, Japan), as previously reported. Calibration offset was corrected by matching a conductance catheter signal at end diastole with LVEDV and that at end-systole with LVESV measured by cardiac MRI.

After supine rest for at least 10 min, the resting LV pressure–volume loops were recorded. Then, IHG exercise was performed for 3 min at 30% of MVC, followed by 3 min of PECA (Figure 2). PECA was achieved through the inflation of the cuff over the exercising upper arm to 250 mmHg before cessation of IHG exercise to retain metabolites produced during exercise. The cuff was kept inflated during 3 min of PECA and then deflated. Haemodynamics and LV-arterial function, including HR, LV end-systolic (LVESP)
and diastolic pressures (LVEDP), LVEDV, LVESV, and stroke volume (SV), were measured. End-diastole was defined as the beginning of the pressure increase after the A wave. If this point was unclear, the peak of the R wave was used to indicate end-diastole. As the arm BP measurements were not available partly due to catheter from the right radial artery, arm diastolic BP was estimated as the pressure at the end QRS complex when the aortic valve opens. Mean arterial pressure (MAP) was calculated using LVESP and estimated diastolic BP. Systemic vascular resistance (SVR) was calculated from MAP, divided by CO and multiplied by 80.

We defined the metabo-reflex control of BPs to be predominant if the LVESP increase by IHG exercise was maintained during PECA. The LV end-systolic elastance (Ees), a useful measure of contractile function, was assessed by the single-beat method. The volume axis intercept of the end-systolic pressure-volume relation (V₀) was also determined. The effective arterial elastance (Ea), a measure of arterial vascular load, was calculated as LVESP divided by SV. The time constant of LV relaxation (Tau) was calculated from the LV pressure decayed to a non-zero asymptote. All measurements were performed every minute of IHG exercise and PECA.

**Statistical analysis**

All analyses were performed using SPSS 24.0 (SPSS Japan Inc., Tokyo, Japan). Continuous variables are presented as the mean ± SD in tables and mean ± SEM in figures or median with interquartile range. Data were compared by the unpaired t test or non-parametric Mann–Whitney test depending on the data distribution. Categorical data presented as percentages were compared by the χ² test. For data obtained during cardiac catheterization, two-way repeated measures analysis of variance was used to evaluate main (time; group) and interaction effects (time × group). If significant results were identified, post-hoc analysis was used for pre–post comparisons. Significance was set at a P value < 0.05.

**Results**

**Patient characteristics**

As shown in Table 1, 20 patients (HFpEF, n = 10; HFrEF, n = 10) with HF (age: 60 ± 16 years; 11 female patients) were enrolled in the present study. The average LVEF was 69 ± 9% in HFpEF and 23 ± 6% in HFrEF. HFrEF patients were older and shorter than HFpEF patients, and comprised more female patients, but the body mass index was similar between groups. The E/A ratio was slightly smaller in HFpEF than in HFrEF (0.9 ± 0.3 vs. 1.6 ± 1.2, P = 0.10), but no significant difference in E₀ was observed between the groups. Diuretics were more frequently prescribed in HFrEF than in HFpEF.

**Haemodynamics and ventricular and vascular function at supine rest**

As shown in Table 2, at supine rest, right heart catheterization demonstrated a similar PAWP (11 ± 8 vs. 12 ± 8 mmHg) and cardiac index (2.8 ± 0.7 vs. 2.6 ± 0.4 L/min/m²) between HFpEF and HFrEF (P ≥ 0.32). HFpEF patients had a slightly higher LVESP (134 ± 21 vs. 113 ± 36 mmHg, P = 0.06) MAP (90 ± 12 vs. 75 ± 20 mmHg, P = 0.06) and lower HR than HFrEF, with a similar LVEDP (14 ± 5 vs. 14 ± 10 mmHg, P = 0.98) and SVR. Although Ees and Ea were not different between HFpEF and HFrEF, the ventricular-arterial coupling ratio (Ees/Ea) was preserved in HFpEF but not in HFrEF (1.0 ± 0.3 vs. 0.6 ± 0.3, P < 0.01). LV relaxation assessed by Tau was prolonged and similar between groups.

**Haemodynamics, and ventricular and vascular function during IHG exercise**

The MVC in HFpEF was slightly smaller than that in HFrEF (P = 0.07). All patients were able to perform IHG at 30% of
MVC for 3 min. The mean muscle activity relative to MVC was similar between HFrEF and HFrEF (30 ± 7 vs. 29 ± 5%, P = 0.63). Representative LV pressure–volume loops at rest and after 3 min of IHG exercise at 30% of MVC in HFpEF and HFrEF patients are shown in Figure 2. As shown in Table 3 and Figure 3, IHG exercise for 3 min similarly increased the HR in HFrEF (by 10 ± 8 bpm) and HFrEF (by 14 ± 6 bpm, group × time interaction P = 0.64). IHG exercise increased the LVEDP in both groups (HFrEF: 134 ± 21 vs. 158 ± 30 mmHg, HFrEF: 113 ± 25 vs. 139 ± 25 mmHg, P < 0.01). LVEDP was unaffected by IHG exercise in both HFrEF (P ≥ 0.57) and HFrEF (P > 0.85). In both groups, there were no significant changes in SV or SVR, resulting in an increased CO (HFrEF: 5.2 ± 2.5 vs. 6.2 ± 2.9 L/min, HFrEF: 4.0 ± 1.4 vs. 4.4 ± 2.1 mmHg, time effect P = 0.10) during IHG. In HFrEF, both Ees and Ea were unaffected by IHG for 3 min, resulting unchanged Ees/Ea. In HFrEF, Ees was significantly increased (1.30 ± 0.7 vs. 1.83 ± 0.8 mmHg/mL, P < 0.01). Ees/Ea was significantly increased (1.28 (1.13, 2.36) vs. 0.99 (0.63, 1.93) mmHg/mL, P < 0.01, group × time interaction P = 0.01) during IHG compared with baseline. The LVEDP after 3 min of IHG exercise was significantly higher than that at baseline in HFrEF (22 ± 11 vs. 14 ± 10 mmHg, P < 0.01), but not significantly different in HFrEF (P = 0.19). Tau was unaffected by IHG in both groups.

### Effects of PECA on haemodynamics and LV diastolic function

As shown in Table 3, the HR significantly decreased from the 1st minute into PECA compared with that at the end of IHG exercise in both groups (P < 0.01). The HR at the 1st, 2nd, and 3rd minutes during PECA was similar to that at baseline.

#### Table 1 Baseline clinical characteristics

| Demographic parameters | All (n = 20) | HFpEF (n = 10) | HFrEF (n = 10) | P value |
|------------------------|-------------|---------------|---------------|--------|
| Age, years             | 60 ± 16     | 68 ± 18       | 53 ± 11       | 0.04   |
| Female, n (%)          | 11 (55)     | 8 (80)        | 3 (30)        | 0.04   |
| Height, cm             | 162 ± 11    | 155 ± 11      | 168 ± 8       | 0.01   |
| Body weight, kg        | 66 ± 17     | 59 ± 17       | 72 ± 15       | 0.10   |
| BMI, kg/m²             | 25 ± 5      | 24 ± 6        | 25 ± 4        | 0.72   |
| Smoking, n (%)         | 6 (30)      | 5 (50)        | 1 (10)        | 0.07   |
| Hypertension, n (%)    | 18 (90)     | 16 (80)       | 2 (20)        | 0.50   |
| Dyslipidaemia, n (%)   | 6 (30)      | 5 (50)        | 1 (10)        | 0.07   |
| Diabetes               | 7 (35)      | 3 (30)        | 4 (40)        | 0.50   |
| mellitus, n (%)        | 18 (90)     | 16 (80)       | 2 (20)        | 0.50   |
| Maximal voluntary contraction, kg | 30 ± 6 | 27 ± 7 | 24 ± 6 | 0.63 |
| % MVC during IHG protocol | 30 ± 6 | 30 ± 7 | 29 ± 5 | 0.63 |
| Peak VO₂/kg, mL/min/kg | 19 ± 6 | 18 ± 4 | 21 ± 7 | 0.29 |
| Echocardiographic data |            |               |               |        |
| EF, %                  | 46 ± 25     | 69 ± 9        | 23 ± 6        | <0.01  |
| LVd, mm                | 55 ± 10     | 46 ± 5        | 63 ± 5        | <0.01  |
| LAD, mm                | 43 ± 10     | 40 ± 11       | 47 ± 9        | 0.13   |
| E/A                    | 1.3 ± 0.9   | 0.9 ± 0.3     | 1.6 ± 1.2     | 0.10   |
| E', cm/s               | 4.4 ± 1.0   | 4.7 ± 0.8     | 4.1 ± 1.1     | 0.17   |
| Medications            |             |               |               |        |
| Beta-blocker, n (%)    | 13 (65)     | 5 (50)        | 8 (80)        | 0.18   |
| ACEI/ARB, n (%)        | 15 (75)     | 6 (60)        | 9 (90)        | 0.15   |
| Diuretics, n (%)       | 14 (70)     | 4 (40)        | 10 (100)      | 0.01   |
| Aldosterone            | 8 (40)      | 3 (30)        | 5 (50)        | 0.33   |
| antagonist, n (%)       | 7 (35)      | 4 (40)        | 3 (30)        | 0.5    |
| Calcium channel blocker, n (%) | 37 (18) | 26 (30) | 11 (15) | 0.07 |
| Laboratory data        |             |               |               |        |
| BNP, pg/mL             | 181 ± 183   | 130 ± 112     | 232 ± 230     | 0.23   |
| Haemoglobin, g/dl      | 13.4 ± 2.4  | 12.5 ± 2.4    | 14.2 ± 2.2    | 0.12   |
| Albumin, g/dl          | 4.1 ± 0.4   | 4.0 ± 0.3     | 4.1 ± 0.4     | 0.46   |
| eGFR, mL/min/1.73 m²   | 70 ± 23     | 67 ± 29       | 74 ± 16       | 0.57   |

| Table 2 Ventricular-vascular stiffness and LV diastolic function at supine rest |
|-----------------------------------------------|--------|--------|--------|--------|
|                  | HFpEF (n = 10) | HFrEF (n = 10) | P value |
| PAWP, mmHg       | 11 ± 8       | 12 ± 8   | 0.81   |
| Mean pulmonary   | 18 ± 6       | 17 ± 7   | 0.74   |
| pressure, mmHg   |             |          |        |
| Right atrial     | 5 ± 1        | 5 ± 4    | 0.86   |
| pressure, mmHg   |             |          |        |
| Cardiac index, L/min/m² | 2.8 ± 0.7 | 2.6 ± 0.4 | 0.32 |
| Heart rate, bpm  | 60 ± 11      | 72 ± 17  | 0.09   |
| LV end-systolic pressure, mmHg | 134 ± 21 | 113 ± 25 | 0.06 |
| LV end-diastolic pressure, mmHg | 14 ± 5 | 14 ± 10 | 0.98 |
| Mean arterial pressure, mmHg | 90 ± 12 | 75 ± 20 | 0.06 |
| SVR, dynes·s·cm⁻² | 1630 ± 732 | 1690 ± 747 | 0.87 |
| Max positive dP/dt | 1417 ± 304 | 955 ± 207* | <0.01 |
| Max negative dP/dt | −1287 ± 333 | −1075 ± 186 | 0.06 |
| LVEDV, mL        | 146 ± 51     | 268 ± 79  | <0.01  |
| LVESV, mL        | 53 (31, 99)  | 219 (132, 272)* | <0.01 |
| LVSV, mL         | 77 (58, 127) | 56 (41, 61) | 0.06  |
| Ea, mmHg/mL⁻¹    | 1.84 ± 0.86  | 2.15 ± 0.78 | 0.35  |
| Ees (sb), mmHg/mL⁻¹ | 1.28 (1.13, 2.36) | 1.13 (0.63, 1.93) | 0.22 |
| Ees/Ea            | 1.06 ± 0.26  | 0.61 ± 0.27* | <0.01 |
| V₀(sb), mL       | −16 ± 37     | 114 ± 52*  | <0.01  |
| Time constant of LV relaxation, ms           | 83 ± 26    | 88 ± 23   | 0.70   |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonists; BMI, body mass index; BNP, brain natriuretic peptide; EF, ejection fraction; eGFR, estimated glomerular filtration rate; IHG, isotonic handgrip; LAD, left atrial dimension; LVd, left ventricular diastolic dimension; MVC, maximal voluntary contraction.

Values are the mean ± SD or n (%).
in both groups ($P \geq 0.12$). The LVESP during PECA remained higher than that at baseline in both HFpEF ($P \leq 0.03$) and HFrEF ($P < 0.01$). In HFrEF, the LVESP during PECA was not different from that at the 3rd minute during IHG in HFrEF ($P \geq 0.18$). In contrast, in HFpEF, the LVESP during PECA was significantly lower than that at the 3rd min during IHG, especially during the first 2 min of PECA ($P \leq 0.04$), suggesting smaller metabo-reflex activity in HFpEF during IHG exercise at 30% MVC for 3 min. Tau was unaffected during PECA in both groups.

**Discussion**

In the present study, we demonstrated that 3 min of low-intensity IHG exercise (at 30% of MVC) produces significant and modest increases in HR and LVESP, respectively, in both HFpEF and HFrEF. IHG significantly increased the LVEDP after 3 min only in HFrEF, whereas no difference in LV relaxation was observed during the protocol in both groups. The increase in LVESP caused variable increases in Ea only in HFrEF, which counterbalanced the increases in Ees and $V_0$, resulting in a maintained Ees/Ea in HFrEF and HFpEF.

**Haemodynamic response to IHG exercise at 30% of MVC**

Haemodynamic responses during HG exercise have been reported in HFrEF$^{13-15}$ and HFpEF patients.$^{16-18}$ For example, Barrett-O’Keefe et al. assessed the haemodynamic responses to IHG at different intensities (15%, 30%, and 45% of MVC) in HFrEF patients and healthy controls.$^{15}$ They found that as workload increased, the CO and MAP significantly increased with no change in SVR in healthy subjects. However, in HFrEF patients, MAP increased with no change in CO, resulting in an increase in SVR. Crisafulli et al. also reported that IHG exercise induced vasoconstriction to compensate for the limited cardiac contractility and pre-load reserves in HFrEF patients.$^{19}$ Similar to the previous studies, we observed no increase in SV and a small increase in CO during IHG exercise in our HFrEF patients. The vasoconstriction in order to compensate for the inability to increase LV pump function were observed not only during IHG exercise using small muscles, but also during dynamic exercise using large muscles in HFrEF patients.$^{16}$

In HFpEF patients, Borlaug et al. reported a significant increase in CO during dynamic exercise.$^{16}$ On the other hand, Westermann et al. reported no increase in CO during IHG exercise.$^{17}$ Consistent with the previous study, we also observed no changes in CO and SV in HFpEF patients during IHG exercise, although HR increased by 10 beats per minute.
Table 3  Haemodynamics and ventricular-vascular function during IHG and PECA

|                          | HFpEF (n = 10) | HFrEF (n = 10) | Group effect | Time effect | Group × time effect |
|--------------------------|---------------|----------------|--------------|-------------|---------------------|
| Heart rate, bpm           |               |                |              |             |                     |
| Rest                     | 60 ± 11       | 72 ± 17        |              |             |                     |
| HG 1 min                 | 64 ± 14       | 76 ± 117       |              |             |                     |
| HG 2 min                 | 67 ± 12*      | 81 ± 18†       | 0.040        | <0.01       | 0.64                |
| HG 3 min                 | 71 ± 13*      | 86 ± 17†       |              |             |                     |
| PECA 1 min               | 61 ± 11†      | 77 ± 17†       |              |             |                     |
| PECA 2 min               | 62 ± 11†      | 75 ± 15†       |              |             |                     |
| PECA 3 min               | 61 ± 10†      | 75 ± 15†       |              |             |                     |
| LV end-systolic pressure, mmHg |             |                |              |             |                     |
| Rest                     | 134 ± 21      | 113 ± 25       |              |             |                     |
| HG 1 min                 | 147 ± 27*     | 120 ± 21†      |              |             |                     |
| HG 2 min                 | 152 ± 25*     | 129 ± 24†      |              |             |                     |
| HG 3 min                 | 158 ± 30*     | 139 ± 25*      | 0.08         | <0.01       | 0.25                |
| PECA 1 min               | 146 ± 23†     | 131 ± 26*      |              |             |                     |
| PECA 2 min               | 146 ± 23†     | 131 ± 28*      |              |             |                     |
| PECA 3 min               | 149 ± 18*     | 130 ± 28*      |              |             |                     |
| LV end-diastolic pressure, mmHg |             |                |              |             |                     |
| Rest                     | 14 ± 5        | 14 ± 10        |              |             |                     |
| HG 1 min                 | 17 ± 9        | 16 ± 10        |              |             |                     |
| HG 2 min                 | 18 ± 9        | 18 ± 10        |              |             |                     |
| HG 3 min                 | 19 ± 10       | 22 ± 11*       | 0.97         | >0.01       | 0.36                |
| PECA 1 min               | 21 ± 15*      | 17 ± 9         |              |             |                     |
| PECA 2 min               | 16 ± 7        | 17 ± 11        |              |             |                     |
| PECA 3 min               | 17 ± 7        | 16 ± 10        |              |             |                     |
| Mean arterial pressure, mmHg |             |                |              |             |                     |
| Rest                     | 90 ± 12       | 75 ± 20        |              |             |                     |
| HG 1 min                 | 96 ± 11       | 81 ± 19        |              |             |                     |
| HG 2 min                 | 98 ± 10*      | 87 ± 19*       |              |             |                     |
| HG 3 min                 | 101 ± 14*     | 93 ± 20†       | 0.11         | <0.01       | 0.35                |
| PECA 1 min               | 98 ± 14*      | 85 ± 24†       |              |             |                     |
| PECA 2 min               | 94 ± 11       | 85 ± 24†       |              |             |                     |
| PECA 3 min               | 99 ± 10*      | 84 ± 24†       |              |             |                     |
| SVR, dynes·s·cm⁻⁵         |               |                |              |             |                     |
| Rest                     | 1630 ± 732    | 1690 ± 747     |              |             |                     |
| HG 1 min                 | 1713 ± 787    | 2035 ± 1409    |              |             |                     |
| HG 2 min                 | 1600 ± 839    | 2408 ± 2406    |              |             |                     |
| HG 3 min                 | 1619 ± 785    | 2534 ± 2434    | 0.45         | 0.38        | 0.49                |
| PECA 1 min               | 1757 ± 784    | 2513 ± 3102    |              |             |                     |
| PECA 2 min               | 1739 ± 747    | 2747 ± 3761    |              |             |                     |
| PECA 3 min               | 1729 ± 799    | 2160 ± 2100    |              |             |                     |
| Max negative dP/dt       |               |                |              |             |                     |
| Rest                     | –1319 ± 338   | –1075 ± 188    |              |             |                     |
| HG 1 min                 | –1423 ± 312   | –1116 ± 218    |              |             |                     |
| HG 2 min                 | –1508 ± 347†  | –1111 ± 149†   |              |             |                     |
| HG 3 min                 | –1577 ± 378†  | –1130 ± 157†   | 0.01         | <0.01       | 0.02                |
| PECA 1 min               | –1443 ± 332†  | –1137 ± 192†   |              |             |                     |
| PECA 2 min               | –1428 ± 368†  | –1128 ± 195†   |              |             |                     |
| PECA 3 min               | –1457 ± 285‡  | –1151 ± 212‡   |              |             |                     |
| LVEDV, mL                |               |                |              |             |                     |
| Rest                     | 150 ± 53      | 268 ± 79†      |              |             |                     |
| HG 1 min                 | 156 ± 64      | 276 ± 79†      |              |             |                     |
| HG 2 min                 | 161 ± 62      | 273 ± 79†      |              |             |                     |
| HG 3 min                 | 161 ± 60      | 276 ± 74†      | <0.01        | 0.16        | 0.96                |
| PECA 1 min               | 158 ± 55      | 270 ± 77†      |              |             |                     |
| PECA 2 min               | 150 ± 56      | 268 ± 79†      |              |             |                     |
| PECA 3 min               | 154 ± 57      | 266 ± 80†      |              |             |                     |
| LVESV, mL                |               |                |              |             |                     |
| Rest                     | 62 ± 35       | 211 ± 75†      |              |             |                     |
| HG 1 min                 | 69 ± 42       | 224 ± 74†      |              |             |                     |
| HG 2 min                 | 69 ± 44       | 220 ± 69‡      |              |             |                     |
| HG 3 min                 | 72 ± 45       | 227 ± 64‡      | <0.01        | <0.01       | 0.66                |
| PECA 1 min               | 68 ± 36       | 214 ± 73†      |              |             |                     |
| PECA 2 min               | 67 ± 33       | 211 ± 69‡      |              |             |                     |
| PECA 3 min               | 66 ± 37       | 207 ± 71†      |              |             |                     |
| LSV, mL                  |               |                |              |             |                     |

(Continues)
|                      | HFrEF (n = 10) | HFrEF (n = 10) | Group effect | Time effect | Group × time effect |
|----------------------|----------------|----------------|--------------|-------------|---------------------|
| Rest                 | 87 ± 38        | 56 ± 16        |              |             |                     |
| HG 1 min             | 87 ± 42        | 52 ± 19        |              |             |                     |
| HG 2 min             | 92 ± 41        | 53 ± 19        |              |             |                     |
| HG 3 min             | 89 ± 40        | 50 ± 20        | 0.03         | 0.79        | 0.30                |
| PECA 1 min           | 89 ± 39        | 56 ± 18        |              |             |                     |
| PECA 2 min           | 83 ± 37        | 58 ± 22        |              |             |                     |
| PECA 3 min           | 89 ± 34        | 59 ± 21        |              |             |                     |
| CO, L/min            |                |                |              |             |                     |
| Rest                 | 5.2 ± 2.5      | 4.0 ± 1.4      |              |             |                     |
| HG 1 min             | 5.5 ± 2.9      | 4.0 ± 1.8      |              |             |                     |
| HG 2 min             | 6.0 ± 2.8      | 4.4 ± 2.1      |              |             |                     |
| HG 3 min             | 6.2 ± 2.9      | 4.4 ± 2.1      |              |             |                     |
| PECA 1 min           | 5.4 ± 2.6      | 4.4 ± 1.8      |              |             |                     |
| PECA 2 min           | 5.1 ± 2.3      | 4.4 ± 2.0      |              |             |                     |
| PECA 3 min           | 5.5 ± 2.4      | 4.5 ± 1.9      |              |             |                     |
| Ea, mmHg·mL⁻¹       |                |                |              |             |                     |
| Rest                 | 1.9 ± 0.9      | 2.2 ± 0.8      |              |             |                     |
| HG 1 min             | 2.1 ± 1.1      | 2.7 ± 1.2      |              |             |                     |
| HG 2 min             | 2.0 ± 1.1      | 3.3 ± 2.6      |              |             |                     |
| HG 3 min             | 2.2 ± 1.3      | 3.9 ± 3.1      | 0.20         | 0.10        | 0.33                |
| PECA 1 min           | 2.0 ± 0.9      | 3.4 ± 3.3      |              |             |                     |
| PECA 2 min           | 2.0 ± 0.8      | 3.7 ± 4.3      |              |             |                     |
| PECA 3 min           | 1.9 ± 0.8      | 3.0 ± 2.4      |              |             |                     |
| Ees (sb), mmHg·mL⁻¹  |                |                |              |             |                     |
| Rest                 | 1.8 ± 0.9      | 1.3 ± 0.7      |              |             |                     |
| HG 1 min             | 1.9 ± 1.0      | 1.9 ± 0.9      |              |             |                     |
| HG 2 min             | 2.0 ± 0.8      | 2.4 ± 1.7*     |              |             |                     |
| HG 3 min             | 2.3 ± 1.0      | 3.1 ± 2.1*     |              |             |                     |
| PECA 1 min           | 2.0 ± 0.9      | 2.3 ± 1.7*     |              |             |                     |
| PECA 2 min           | 2.1 ± 1.1      | 2.5 ± 2.2*     |              |             |                     |
| PECA 3 min           | 2.0 ± 0.8      | 1.9 ± 1.4†     |              |             |                     |
| Ees/Ea               |                |                |              |             |                     |
| Rest                 | 1.0 ± 0.3      | 0.6 ± 0.3†     |              |             |                     |
| HG 1 min             | 1.0 ± 0.3      | 0.7 ± 0.2      |              |             |                     |
| HG 2 min             | 1.0 ± 0.3      | 0.8 ± 0.2      |              |             |                     |
| HG 3 min             | 1.1 ± 0.4      | 0.8 ± 0.4      | 0.03         | 0.27        | 0.95                |
| PECA 1 min           | 1.1 ± 0.5      | 0.8 ± 0.4      |              |             |                     |
| PECA 2 min           | 1.1 ± 0.7      | 0.8 ± 0.3      |              |             |                     |
| PECA 3 min           | 1.2 ± 0.5      | 0.7 ± 0.3†     |              |             |                     |
| V₀(sb), mL           |                |                |              |             |                     |
| Rest                 | −16 ± 37       | 114 ± 52‡      |              |             |                     |
| HG 1 min             | −9 ± 44        | 161 ± 65‡      |              |             |                     |
| HG 2 min             | −3 ± 48        | 166 ± 56‡      |              |             |                     |
| HG 3 min             | 6 ± 54         | 175 ± 57‡      | <0.01        | <0.01       | 0.15                |
| PECA 1 min           | −11 ± 54       | 155 ± 77‡      |              |             |                     |
| PECA 2 min           | −4 ± 43        | 150 ± 64‡      |              |             |                     |
| PECA 3 min           | −3 ± 35        | 135 ± 73‡      |              |             |                     |
| Tau (best-fit), ms   |                |                |              |             |                     |
| Rest                 | 83 ± 26        | 88 ± 23        |              |             |                     |
| HG 1 min             | 78 ± 23        | 86 ± 17        |              |             |                     |
| HG 2 min             | 80 ± 30        | 91 ± 15        | 0.40         | 0.28        | 0.32                |
| HG 3 min             | 76 ± 23        | 91 ± 16        |              |             |                     |
| PECA 1 min           | 77 ± 24        | 92 ± 20        |              |             |                     |
| PECA 2 min           | 88 ± 46        | 91 ± 16        |              |             |                     |
| PECA 3 min           | 81 ± 30        | 88 ± 18        |              |             |                     |

Values are the mean ± SD or n (%). MVC indicates maximal voluntary contraction; PECA, post-exercise circulatory arrest; LV, left ventricular; HG, handgrip; SVR, systemic vascular resistance; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; Ea, effective arterial elastance; Ees (sb), end-systolic elastance by the single-beat method; V₀, equilibrium volume.

*P < 0.05 vs. rest,
†P < 0.05 for PECA vs. HG 3 min in each group.
‡P < 0.05 for HFrEF vs. HFrEF at the same time point.
This suggests that small muscle mass exercise proposed as a training protocol to reduce the daily BP by IHG exercise at a low intensity had little effect on CO, although LV systolic function was maintained in HFpEF patients.

**Ventricular and arterial function during IHG exercise**

In HFrEF patients, both Ees and $V_O$ slightly increased along with the increase in $E_a$, resulting in a maintained $Ees/Ea$ during IHG exercise. The ventricular-arterial coupling may be maintained by altering Ees in response to the increased $E_a$, suggesting that the LV function can be well compensated for during IHG exercise at 30% of MVC. A previous study examining the haemodynamic response to a symptom-limited treadmill exercise revealed that $Ees/Ea$ significantly decreased during exercise in HFrEF patients. The discrepancy between these two studies may be due to the difference in the type of exercise performed (IHG vs. dynamic exercise). Inconsistent with these two studies, neither the increase in $LVEDP$, nor the prolongation of LV relaxation was observed in our HFpEF patients. $Ees$, $E_a$, and $Ees/Ea$ were unaffected by IHG exercise. We only enrolled HF patients after their HF symptoms resolved and excluded patients with a high baseline BP. Thus, the $LVESP$ was $134 \pm 21 \text{mmHg}$ and $LVEDP$ was $14 \pm 5 \text{mmHg}$ before IHG exercise. Furthermore, the increase in $LVESP$ was modest after IHG exercise, probably because the intensity of IHG exercise was low and the exercise time was only 3 min. LV relaxation is prolonged with the increase in $LVESP$, which may result in an increased $LVEDP$. The differences in the baseline haemodynamics, and the type and intensity of the exercise may be related to the inconsistent findings.

**Haemodynamic responses to PECA in HFpEF and HFrEF**

The exercise pressor reflex is a feedback system controlled by two distinct sensory afferent nerve fibres located in the...
skeletal muscle: the Group III afferent fibres, which are predominantly sensitive to stretch during contraction (mechano-receptors), and the Group IV afferent fibres, which are principally sensitive to ischaemic metabolites produced during exercise. Several studies in humans suggested that muscle mechano-reflex activity increases in HFrEF patients. However, Crisafulli et al. reported that the muscle metabo-reflex increases in HFrEF patients based on the maintained MAP during rhythmic HG exercise at 30% of MVC and PECA. Barrett-O’Keefe et al. examined the effects of muscle metabo-reflex on haemodynamics during three levels of IHG exercise and PECA in HFrEF, and also reported that a preserved role of the metabo-reflex induced the pressor response, which increased depending on exercise intensity. Consistent with previous studies, the LVESP was maintained through preserved Ea during 3 min of PECA, suggesting a role of metabo-reflex activation in HFrEF patients.

Few studies have examined the effects of muscle metabo-reflex and mechano-reflex on the haemodynamics in HFP EF patients. Sarma et al. noninvasively reported using PECA after 40% of MVC to fatigue that metabo-receptor activity may be similar to that in healthy controls. Roberto et al. observed maintained MAP via an increase in SVR during PECA after dynamic handgrip at 30% of MVC, suggesting the muscle metabo-reflex control of the haemodynamics in HFP EF patients. In our HFP EF patients, the high LVESP, which was significantly increased by IHG exercise at 30% of MVC, was not maintained during PECA, suggesting lower metabo-reflex activity in HFP EF patients than in HFrEF patients. To our knowledge, the current study is the first to suggest that the effects of the metabo-reflex are blunted in HFP EF patients compared with HFrEF patients. Jarvis et al. observed attenuated BP and muscle sympathetic nerve activity responses during IHG and PECA in healthy women more than in men. They hypothesized that the metabo-reflex was blunted in women due to differences in muscle mass, fibre type, and metabolic stimulation of group IV afferents. Similar to the epidemiological data, the proportion of women was higher in HFP EF than in HFrEF in the present study. The sex difference in HF might partly explain the reduced metabo-reflex response in HFP EF in our study. As few studies have evaluated the metabo-reflex response in women with HF, further studies are warranted.

Clinical implications

IHG exercise training at 30–40% MVC performed several times/week for months may reduce the BP in medicated hypertensive patients. Furthermore, in HFrEF patients, a recent study demonstrated that low-intensity exercise training can attenuate muscle sympathetic nerve activity and that forearm training reduced metabo-reflex, resulting in the reduced diastolic pressures and leg vascular resistance. These beneficial effects of IHG training may have the potential to improve LV function, exercise capacity, and survival if similar BP-reducing effects exist in hypertensive HF patients. In the present study, response to IHG exercise and PECA in haemodynamics and cardiovascular function were different between patients with HFP EF and HFrEF. IHG exercise protocol used in the present study elevates the LVESP and LVEDP without detrimental effects on cardiac function or ventricular-arterial coupling, especially in HFP EF patients. As the response to exercise in haemodynamics and cardiovascular function varies depending on the patient background and the type and intensity of the exercise, more intense IHG exercise might have detrimental effects on cardiac function or ventricular-arterial coupling. Therefore, it is important to evaluate individual characteristics including the phenotype of HF for safer and more effective exercise training.

Limitations

Several study limitations must be acknowledged. First, the present study was performed in a small population in a single centre. The changes in LVESP and LVEDP were of our interest. During the 3 min of handgrip exercise, LVESP and LVEDP similarly elevated in both HFP EF and HFrEF groups. Power analysis showed that the power of our study to detect the difference between LVESP at rest and that after 3 min of IHG was 0.950 in HFP EF (n = 10, difference 23.68; SD, 18.29) and 0.992 in HFrEF (n = 10, difference 25.98; SD, 15.72) with Type I error of 0.05. On the other hand, the power to detect the difference between LVEDP at rest and that after 3 min of IHG was 0.473 in HFP EF. As our study population was highly selected (no pacer, defibrillator, and completely normalized PAWP) under strict inclusion criteria and the study protocol was very invasive, it was not easy to increase the number of HFP EF patients. Second, patients in the HFP EF group were older than those in the HFrEF group. As the proportion of the elderly was high in HFP EF, our data are considered to be closer to those in clinical practice. Third, the effects of chronic medication on haemodynamics cannot be fully excluded. However, no difference was found in medications between HFP EF and HFrEF patients except for diuretics. Diuretics may have affected baseline data by reducing the preload, but had little effect on exercise response.

Conclusions

IHG exercise used in the present study may increase the LVESP and LVEDP without detrimental effects on cardiac function or ventricular-arterial coupling, especially in HFP EF patients. As the effects of IHG exercise on haemodynamics and ventricular-arterial coupling may be affected by the
phenotype of HF, the patient background, and the type and intensity of the exercise, further studies are needed.

Conflict of interest

Kaoru Dohi received lecture fees from Otsuka Pharmaceutical Co., Ltd., Daiichi Sankyo Company Limited, Sumitomo Pharma Co., Ltd., ONO PHARMACEUTICAL CO., LTD. Other authors have no financial conflicts of interest to disclose.

Funding

This study was supported by the Japan Society for the Promotion of Science JSPS KAKENHI Grant Number JP16K09430.

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