ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 4882–4892
Published online 1 November 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13682

ORIGINAL ARTICLE

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 (HFmrEF) and heart failure with preserved ejection fraction (HFpEF).[1] 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.[2,3] 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.[4] In patients with HF, the sympathetic nervous system is activated more than in healthy people at rest and during exercise.[5] 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.[6]

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[7] using specific inclusion criteria: LVEF $\geq$50%; New York Heart Association functional Class $\geq$II; and E/e′ $>$ 15 or E/e′ 8 to 15 combined with high B-type natriuretic peptide ($\geq$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 $\geq$ 160 mmHg or pulmonary artery wedge pressure (PAWP) $\geq$25 mmHg, (v) pacemaker or cardioverter-defibrillator implants, (vi) severe renal dysfunction with an estimated glomerular filtration rate (eGFR) $<$30 mL/min/1.73 m^2, (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

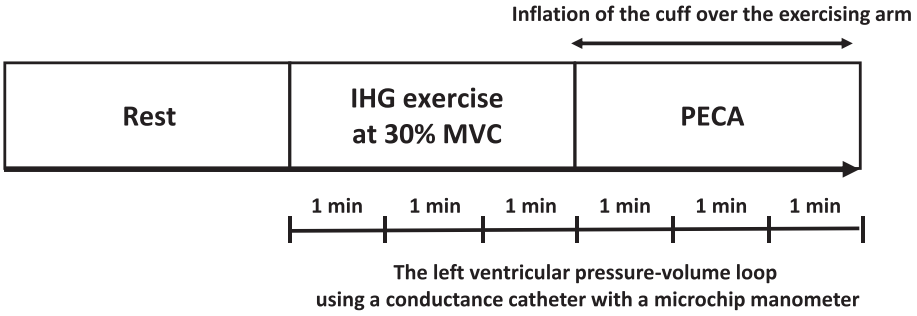
All patients underwent a blood test, TTE, and maximal cardiopulmonary exercise testing. Standard 2D Doppler echocardiography (Vivid 7, GE Medical Ultrasound, Horten, Norway or Artida, Toshiba Medical Systems, Tochigi, Japan) was performed for all patients by registered medical sonographers certified by the Japan Society of Ultrasonics 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 Denshi 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.[8] 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.[9]

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 1*). 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)

Figure 1 Examination protocol. IHG, isometric handgrip; MVC, maximal voluntary contraction; PECA, post-exercise circulatory arrest.



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.[10] The volume axis intercept of the end-systolic pressure–volume relation (V_0) was also determined.[10] The effective arterial elastance (Ea), a measure of arterial vascular load, was calculated as LVESP divided by SV.[11] The time constant of LV relaxation (Tau) was calculated from the LV pressure decayed to a non-zero asymptote.[12] 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 χ^2 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. HFpEF patients were older and shorter than HFrEF 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 E′ 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/m^2) between HFpEF and HFrEF ($P \geq 0.32$). 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

DOI: 10.1002/ehf2.13682

Table 1 Baseline clinical characteristics

	All (n = 20)	HFpEF (n = 10)	HFrEF (n = 10)	P value
Demographic parameters				
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/m^2	25 ± 5	24 ± 6	25 ± 4	0.72
Smoking, n (%)	5 (25)	3 (30)	2 (20)	0.50
Hypertension, n (%)	16 (80)	8 (80)	8 (80)	0.71
Dyslipidaemia, n (%)	6 (30)	5 (50)	1 (10)	0.07
Diabetes mellitus, n (%)	7 (35)	3 (30)	4 (40)	0.50
Maximal voluntary contraction, kg	30 ± 11	25 ± 7	35 ± 13	0.07
% MVC during IHG protocol	30 ± 6	30 ± 7	29 ± 5	0.63
Peak VO_2/kg, mL/min/kg	19 ± 6	18 ± 4	21 ± 7	0.29
Echocardiographic data				
EF, %	46 ± 25	69 ± 9	23 ± 6	<0.01
LVDd, 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$\prime$, 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 antagonist, n (%)	8 (40)	3 (30)	5 (50)	0.33
Calcium channel blocker, n (%)	7 (35)	4 (40)	3 (30)	0.5
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 m^2	70 ± 23	67 ± 29	74 ± 16	0.57

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, isometric handgrip; LAD, left atrial dimension; LVDd, left ventricular diastolic dimension; MVC, maximal voluntary contraction.
Values are the mean ± SD or n (%).

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 artery pressure, mmHg	18 ± 6	17 ± 7	0.74
Right atrial pressure, mmHg	5 ± 1	5 ± 4	0.86
Cardiac index, L/min/m^2	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^{-5}	1630 ± 732	1690 ± 747	0.87
Max positive dP/dt	1417 ± 304	955 ± 207*	<0.01
Max negative dP/dt	−1287 ± 333	−1075 ± 188	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
V_0(sb), mL	−16 ± 37	114 ± 52*	<0.01
Time constant of LV relaxation, ms	83 ± 26	88 ± 23	0.70

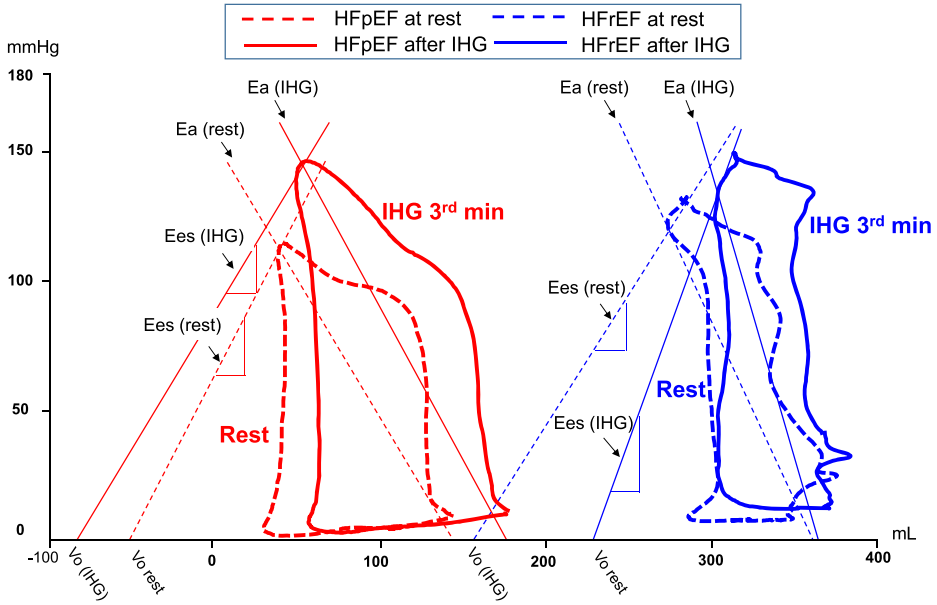
Ea, effective arterial elastance; EDV, end-diastolic volume; Ees (sb), end-systolic elastance by the single-beat method; ESV, end-systolic volume; LV, left ventricular; PAWP, pulmonary artery wedge pressure; SV, stroke volume; V_0, equilibrium volume.
Values are the mean ± SD or n (%), or median (interquartile range).
*$P < 0.05$ vs. HFpEF.

MVC for 3 min. The mean muscle activity relative to MVC was similar between HFpEF 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 HFpEF (by 10 ± 8 bpm) and HFrEF (by 14 ± 6 bpm, group × time interaction P = 0.64). IHG exercise increased the LVESP in both groups (HFpEF: 134 ± 21 vs. 158 ± 30 mmHg, HFrEF: 113 ± 25 vs. 139 ± 25 mmHg, $P < 0.01$). LVEDV was unaffected by IHG exercise in both HFpEF ($P \geq 0.57$) and HFrEF ($P \geq 0.85$). In both groups, there were no significant changes in SV or SVR, resulting in an increased CO (HFpEF: 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 HFpEF, 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. 3.1 ± 2.1 mmHg/mL, $P < 0.01$, group × time interaction effect P = 0.10) and Ea was slightly increased (2.2 ± 0.8 vs. 3.9 ± 3.1 mmHg/mL, P = 0.1) by IHG for 3 min. Ees/Ea was maintained due to the increased V_0 (114 ± 52 vs. 175 ± 56 mL, $P < 0.01$, group × time effect P = 0.15) 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 HFpEF (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

Figure 2 Representative left ventricular (LV) pressure–volume loops at rest and after isometric handgrip (IHG) exercise at 30% of maximal voluntary contraction (MVC) for 3 min in HFpEF and HFrEF. The slopes of the LV end-systolic pressure–volume relation and Ea after 3 min of IHG exercise were similar to those at rest in heart failure with preserved ejection fraction (HFpEF). In heart failure with reduced ejection fraction (HFrEF), the slopes of the LV end-systolic pressure–volume relation and Ea were greater after IHG exercise than those at rest. Ees indicates LV end-systolic elastance; Ea, effective arterial elastance; V_0, the volume axis intercept of the end-systolic pressure–volume relation.



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 for 3 min 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*‡			
HG 3 min	71 ± 13*	86 ± 17*‡	0.040	<0.01	0.64
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†‡			
LVSV, mL					

(*Continues*)

DOI: 10.1002/ehf2.13682

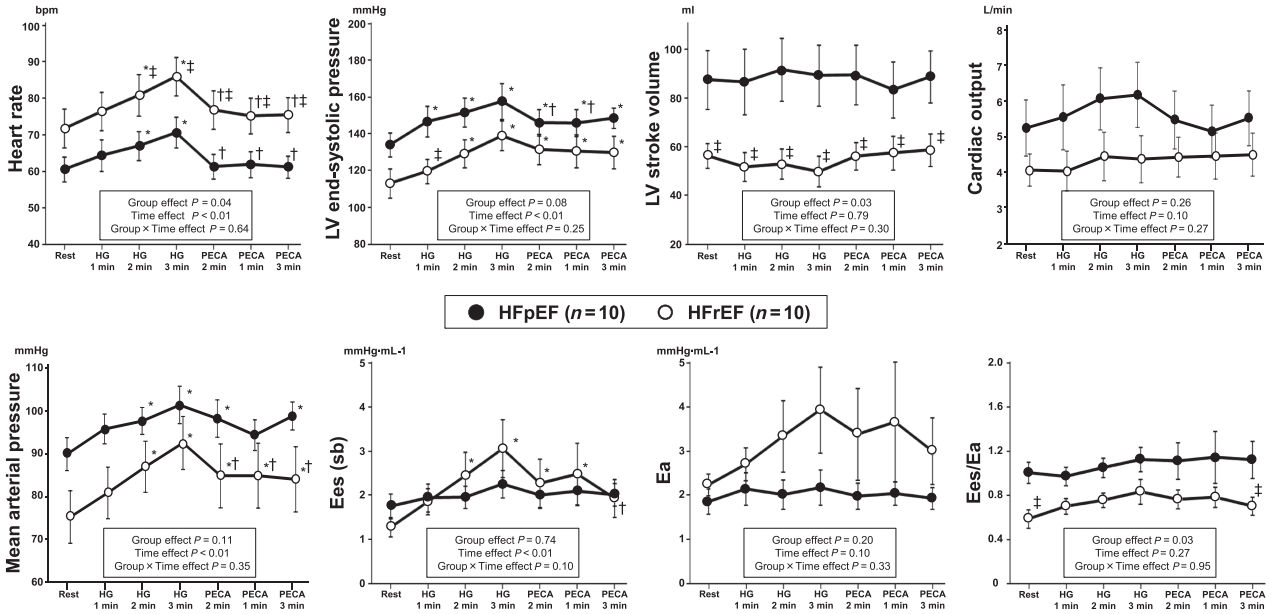
Table 3 (continued)

	HFpEF (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	0.26	0.10	0.27
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*	0.74	<0.01	0.10
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‡			
V_0(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			
HG 3 min	76 ± 23	91 ± 16	0.40	0.28	0.32
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; V_0, 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. HFpEF at the same time point.

DOI: 10.1002/ehf2.13682

Figure 3 Changes in cardiovascular function and haemodynamics during isometric handgrip (IHG) and post-exercise circulatory arrest (PECA) in heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) patients. LV, left ventricular; Ees (sb), LV end-systolic elastance by the single-beat method; Ea, effective arterial elastance; Ees/Ea, the ratio of Ees to Ea. *$P < 0.05$ vs. rest, †$P < 0.05$ vs. HG 3 min in each group, and ‡$P < 0.05$ for HFrEF vs. HFpEF at the same time point.



*p<0.05 vs. rest, †p<0.05 for PECA vs. HG 3 min in each group, and ‡p<0.05 for HFrEF vs. HFpEF 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[1] 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_0 slightly increased along with the increase in Ea, resulting in a maintained Ees/Ea during IHG exercise. The ventricular-arterial coupling may be maintained by altering Ees in response to the increased Ea, 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.[20] Thus, whether ventricular function can be compensated for at higher workloads may depend on the individual baseline cardiac capacity and the afterload during exercise in HFrEF patients.

In HFpEF patients, Kawaguchi *et al*. reported that IHG exercise significantly increased Ea and LVESP to 200 mmHg with no changes in Ees, resulting in a decreased Ees/Ea ratio.[18] They also reported that IHG exercise prolonged LV relaxation and increased the LVEDP. On the other hand, Borlaug *et al*. examined LV diastolic function during dynamic exercise to the level of patient exhaustion and demonstrated increased LV chamber stiffness with no further prolongation of LV relaxation.[16] The discrepancy between these two studies may be due to the difference in the type of exercise performed (IHG vs. dynamic exercise).[21] Inconsistent with these two studies, neither the increase in LVEDP, nor the prolongation of LV relaxation was observed in our HFpEF patients. Ees, Ea, 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 ± 21 mmHg and LVEDP was 14 ± 5 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.[22] 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 predominately sensitive to stretch during contraction (mechano-receptors), and the Group IV afferent fibres, which are principally sensitive to ischaemic metabolites produced during exercise.[4] Several studies in humans suggested that muscle mechano-reflex activity increases in HFrEF patients.[23–25] 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.[19] 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.[14] 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 HFpEF 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.[26] 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 HFpEF patients.[27] In our HFpEF 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 HFpEF 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 HFpEF 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.[28] Similar to the epidemiological data[29], the proportion of women was higher in HFpEF than in HFrEF in the present study. The sex difference in HF might partly explain the reduced metabo-reflex response in HFpEF 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.[2] Furthermore, in HFrEF patients, a recent study demonstrated that low-intensity exercise training can attenuate muscle sympathetic nerve activity[30] and that forearm training reduced metabo-reflex, resulting in the reduced diastolic pressures and leg vascular resistance.[31] 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 HFpEF 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 HFpEF 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,[13–18] 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 HFpEF 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 HFpEF (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 HFpEF. 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 HFpEF patients. Second, patients in the HFpEF group were older than those in the HFrEF group. As the proportion of the elderly was high in HFpEF, 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 HFpEF 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 HFpEF 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, Nippon Boehringer Ingelheim Co., Ltd., Novartis Japan, and Takeda Pharmaceutical Company Limited. Kaoru Dohi received departmental research grant support from Daiichi Sankyo Company Limited, Shionogi Co., Ltd., Takeda Pharmaceutical Company Limited, Abbott Japan LLC, Otsuka Pharmaceutical Co., Ltd., Novartis Japan, Kowa Company, Ltd., Dainippon 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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