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The title: Dynamics of cardiorespiratory response during and after the six-minute walk test in patients with heart failure

The names of authors:

Kae Yoshimura, Yukio Urabe, Noriaki Maeda, Satoshi Yuguchi, Toshinobu Yoshida

The position, institution and location of all authors:

Kae Yoshimura [1, 2] PT, MSc., Yukio Urabe [2] PT, Ph.D., Noriaki Maeda [2] PT, Ph.D., Satoshi Yuguchi [3] PT, Ph.D., Toshinobu Yoshida [4] M.D.

[1] Department of Rehabilitation, The Sakakibara Heart Institute of Okayama

2-5-1, Nakai-cho, Kita-ku, Okayama City, Okayama 700-0804, Japan

[2] Department of Sports Rehabilitation, Graduate School of Biomedical & Health Sciences, Hiroshima University

1-2-3, Kasumi, Minami-ku, Hiroshima City, Horoshima 734-8553, Japan

[3] Department of Physical Therapy, Japan University of Health Sciences

2-555, hirasuga, Satte City, Saitama 340-0145, Japan

[4] Department of Cardiovascular Medicine, The Sakakibara Heart Institute of Okayama

2-5-1, Nakai-cho, Kita-ku, Okayama City, Okayama 700-0804, Japan

The telephone number, fax number and e-mail address of the corresponding author

Corresponding author: Kae Yoshimura

Address: Department of Rehabilitation, The Sakakibara Heart Institute of Okayama

2-5-1, Nakai-cho, Kita-ku, Okayama City, Okayama 700-0804, Japan

The telephone number: (+81) 86-225-7111

Fax number: (+81) 86-223-5265

E-mail: yoshimukantoku_irritable@yahoo.co.jp

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Abstract

Purpose: The six-minute walk test (6MWT) is one of an useful measure to evaluate exercise capacity with simple method. The kinetics of oxygen uptake ($\dot{V}O_2$) throughout constant load exercise on cardiopulmonary exercise testing (CPX) are composed of three phases and the $\dot{V}O_2$ kinetics are delayed in patients with heart failure (HF). This study aimed to investigate the kinetics of the cardiorespiratory response during and after the 6MWT according to exercise capacity.

Methods: Forty-nine patients with HF performed CPX and the 6MWT. They were divided into two groups by 6MWT distance: 34 patients walked ≥ 300 m (HF-M), and 15 patients walked < 300 m (HF-L). $\dot{V}O_2$, minute ventilation ($\dot{V}E$), breathing frequency, tidal volume, and heart rate both during and after the 6MWT were recorded. The time courses of each parameter were compared between the two groups. CPX was used to assess functional capacity and physiological responses.

Results: In the HF-M group, $\dot{V}O_2$ and $\dot{V}E$ stabilized from 3 min during the 6MWT and recovered for 3 min, respectively, after the 6MWT ended. In the HF-L group, $\dot{V}O_2$ and $\dot{V}E$ stabilized from 4 min, respectively, during the 6MWT and did not recover within 3 min after the 6MWT ended. On CPX in the HF-M group, $\dot{V}O_2$ peak, and anaerobic threshold were significantly higher, while the relationship between minute ventilation and carbon dioxide production was lower compared with the HF-L group.

Conclusion: In lower exercise capacity patients with HF had slower $\dot{V}O_2$ and $\dot{V}E$ kinetics during and after the 6MWT.

Keywords: heart failure; six minute walk test; oxygen uptake; ventilatory response

INTRODUCTION

Heart failure (HF) is a common disease, and people living with HF have increased worldwide. In particular, the number of elderly patients with HF is predicted to gradually increase as the population ages (Inamdar, and Inamdar, 2016; Metra et al., 2007; Ponikowski et al., 2016; Writing Committee Members et al., 2013). The main symptoms of HF are dyspnea and fatigue, which may lead to low exercise capacity (Inamdar, and Inamdar, 2016; Metra et al., 2007; Ponikowski et al., 2016). Exercise capacity has commonly been evaluated by cardiopulmonary exercise testing (CPX), and one of the best indicators during CPX is oxygen uptake ($\dot{V}O_2$) (Guazzi et al., 2016; Inamdar, and Inamdar, 2016; Metra et al., 2007; Piepoli et al., 2011; Writing Committee Members et al., 2013). It has been well established that the kinetics of $\dot{V}O_2$ during constant load exercise are composed of three phases. Phase I takes place within the first breath and continues for 15-20 sec; phase II is more gradual and increases exponentially until the steady-state is reached, lasting two to three minutes; and phase III is a steady state or slow drift (Wasserman, Hansen, Sue, and Whipp, 1987; Brunner-La et al., 1999). In patients with cardiovascular disease including HF, these $\dot{V}O_2$ kinetics during and after CPX are delayed (Fleg et al., 2015; Koike et al., 1995; Sietsema et al., 1994). In the clinical field, despite several previous reports using CPX, cycle and treadmill CPX are unsuitable for some HF patients, especially elderly patients, who have co-morbidities (such as frailty and patients with arthralgia) (Fleg et al., 2015; Piepoli et al., 2011; Ponikowski et al., 2016; Vigorito et al., 2017). These prior studies have mainly involved chronic patients and outpatients with HF (Fleg et al., 2015; Koike et al., 1995; Sietsema et al., 1994). Nonetheless, health professions also have to prescribe exercise training for acute and hospitalized HF patients (Mebazaa et al., 2015; Piepoli et al., 2011). Discharge planning that includes exercise training should begin as soon as the patient's condition is stable (Papathanasiou, Tsamis, Georgiadou, and Adamopoulos, 2008; Piepoli et al., 2011; Ponikowski et al., 2016). Furthermore, exercise training guidelines for patients with HF recommend aerobic exercise (Fleg et al., 2015; Papathanasiou, Tsamis, Georgiadou, and Adamopoulos, 2008). In particular, walking can be simple and inexpensive without special equipment (Fleg et al., 2015), and it can be continued in every hospitalization phase and in the after discharge phase of HF.

Several guidelines suggest that the six-minute walk test (6MWT) is useful for measuring exercise capacity in patients with HF (Kervio et al., 2004; Lipkin, Scriven, Crake, and Poole-Wilson, 1986; Metra et al., 2007; Writing Committee Members et al., 2013). Additionally, the distance walked during 6MWT (the 6-minute walk distance: 6MWD) is an important prognostic marker, and 6MWD < 300 m is an objective definition of advanced HF (Metra et al., 2007; Writing Committee Members et al., 2013). HF has been confirmed as a disease of the elderly population (Inamdar, and Inamdar, 2016; Metra et al., 2007; Ponikowski et al., 2016; Writing Committee Members et al., 2013), and it is necessary to provide a simple measure of those that puts little load on elderly and infirm patients. Therefore, 6MWT may be a simple and easy measure without a special measuring device. One study identified that the $\dot{V}O_2$ steady state during 6MWT is delayed in HF patients compared with healthy participants (Kervio et al., 2004). However, no previous study has demonstrated the kinetics of $\dot{V}O_2$ and ventilatory response differences during the 6MWT and during the recovery time course after 6MWT according to exercise capacity in patients with HF.

Therefore, in the present study, the aim was to investigate: 1) the difference in the cardiorespiratory response during and after the 6MWT between groups divided according to exercise capacity; and 2) the differences in the patterns of breathing during the 6MWT.

METHODS

Participants

Patients who were hospitalized for HF at our institution from January 2015 to April 2017 were prospectively analyzed. A flow chart of patients included in this study is shown in Figure 1. Of 638 patients with HF who participated an inpatient rehabilitation program, 86 patients underwent CPX, and 49 patients met the inclusion criteria. A symptom-limited exercise test with cycle ergometer and a 6MWT were conducted within a time interval of 24-48 h in the discharge period (Kervio et al., 2004). The patients were divided into two groups using a 6MWD of 300 m as the cut-off (Metra et al., 2007; Writing Committee Members et al., 2013); the first group walked 300 m or more (HF-M, *n* = 34, 21 women), and the second group walked less than 300 m (HF-L, *n* = 15, five women) (Table 1). Exclusion criteria were acute coronary syndrome or myocardial infarction, uncontrolled arrhythmia, severe aortic stenosis, acute phase of pulmonary embolism, and acute myocarditis. Patients were also excluded if they had significant respiratory disease and if their activity was limited by health conditions other than fatigue and exertional dyspnea (such as neurologic impairments, orthopedic impairments) for locomotor impairments. Patients who were not able to walk for six-minutes continuously without rests, and who showed significant anxiety or had difficulty in understanding this study were also excluded (Kervio et al., 2004; Lipkin, Scriven, Crake, and Poole-Wilson, 1986) (Figure 1).

All patients participated in an inpatient rehabilitation program and were clinically stable (Mebazaa et al., 2015) at the time of this study. The program was composed of several phases. The first phase aimed for prevention the deleterious effects of bed rest, to improve functionality, and prepare a safer return to daily life activities. The following phases were positioning, range of motion exercises during bed rest, sitting mild resistance, flexibility exercises, standing, and ambulation in room to a ward corridor (Papathanasiou, Tsamis, Georgiadou, and Adamopoulos, 2008). Thereafter, cycling or treadmill walking with warm-up and cool-down exercises was conducted at physical therapy department. Cycling or treadmill walking exercises was conducted for 15 to 20-min and was adjusted according to rating of perceived exertion with Borg scale 11-13, and vital signs (such as blood pressure, the heart rate) (Papathanasiou, Tsamis, Georgiadou, and Adamopoulos, 2008; Piepoli et al., 2011).

Approval by the institutional review board was obtained before the study was initiated (approval number 2014020), and all patients provided their written, informed consent to participate in the study.

Protocol

Each participant performed a cycle ergometer, symptom-limited exercise test and a 6MWT in the discharge period (Kervio et al., 2004), and each test was conducted randomly. This narrow time frame aimed to limit the potential effects of changes in patients' clinical status. Both exercise tests were conducted more than 2 hours after a meal and any oral drug ingestion. None of the participants were notified of any results prior the completion of the whole protocol. Handgrip strength (HS) was also measured by a handgrip dynamometer T.K.K.5401 GRIP-D (Takei Scientific Instruments Co., Ltd, Niigata, Japan). The highest result of three attempts each on both hands was recorded.

<u>Six-minute walk test</u>

The FitMate Pro (FIT-2200, COSMED, Rome, Italy) was used for measurement of cardiorespiratory parameters. The instrument is a portable metabolic measurement system for measuring $\dot{V}O_2$ in both clinical and athletic exercise testing. It uses a turbine flowmeter to measure ventilation and a galvanic fuel cell oxygen sensor for analyzing the fraction of expired oxygen. The metabolic system is reliable and valid for measurement of $\dot{V}O_2$ in adults (Nieman et al., 2007). Sampling data were averaged over 15-second intervals and recorded every 30 seconds. The system was carefully calibrated before each test. $\dot{V}O_2$ (ml/kg/min), minute ventilation ($\dot{V}E$, l/min), and breathing frequency (*f*, breaths/min) during the 6MWT were recorded using The FitMate Pro. Tidal volume (V_T, liter) was obtained by dividing $\dot{V}E$ by *f*. The heart rate (HR) was also recorded via electrocardiographic telemetry (DYNASCOPE; Fukuda Denshi Co., Ltd., Tokyo, Japan) and synchronized with other cardiorespiratory parameters.

The 6MWT was performed according to a standardized protocol (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002; Guyatt et al., 1985). Participants sat on a chair for 3 min before the walking test and then walked along a 30-m, flat, obstacle-free corridor at a self-selected speed. The patients were instructed to walk as far as possible, turning 180° every 30 m. After the walking test, patients again sat on a chair for 3 min. Baseline $\dot{V}O_2$ was calculated by averaging the measurements made for 2 min before the beginning of exercise (Nanas et al., 2001). Separately from the gas analysis test during the 6MWT, the total distance walked during six minutes was measured in meters (m) as the 6MWD by the same protocol as the gas analysis test.

<u>Cycle ergometer test</u>

All patients underwent a symptom-limited, graded exercise test on a cycle ergometer according to the modified Ramp protocol with a cycle ergometer (Well Bike BE-250, Fukuda Denshi Co., Ltd., Tokyo, Japan), a CPX monitoring system (STRESS TEST SYSTEM ML-9000, Fukuda

Denshi Co., Ltd.), and a gas analysis system Cpex-1 (Inter Reha, Tokyo, Japan) by a breath-by-breath method. After 3 min of unloaded pedaling, the initial workload was 10 Watts, and it was increased with a 10 Watts/min ramp until patients reached exhaustion. Patients were encouraged to cycle up to their true maximal effort during the test, defined by leg fatigue and/or dyspnea. Fatigue and dyspnea during cycle ergometer test were quantified by rating of perceived exertion with Borg scale. $\dot{V}O_{2peak}$, anaerobic threshold (AT), the relationship between minute ventilation and carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ slope), and peak O_2 pulse were recorded. $\dot{V}O_{2peak}$ was defined as the average of values obtained during the last 30 seconds of exercise. AT was determined using the V-slope method (Pereira et al., 2010), and the AT was counterchecked using the nadir of ventilatory equivalents in cases of uncertainty (Deboeck et al., 2014).

<u>Statistical analysis</u>

The data are presented as means ± SD. Data analyses were conducted using JMP® 13 (SAS Institute Inc., Cary, NC, USA). Between-group comparisons were made with the unpaired *t*-test, Mann-Whitney *U* test, and χ^2 test as appropriate for baseline characteristics. Effect sizes were calculated using G*Power 3.1 (Faul, Erdfelder, Lang, and Buchner, 2007). The time course of cardiorespiratory values including $\dot{V}O_2$, $\dot{V}E$, and HR during the 6MWT was analyzed in each group using one-way repeated measures ANOVA, followed, when significant, by Tukey's method. Before the ANOVA, each variable of the physiologic profile throughout the 6MWT was confirmed to follow a normal distribution by the Shapiro-Wilk test and Mauchly's sphericity test. The definition of steady state was the first point in time after which there was no further statistical significant difference during the 6MWT in each value of $\dot{V}O_2$, $\dot{V}E$, and HR (Kervio et al., 2004). The beginning of recovery corresponded to be the point at which no further changes compared to the resting baseline before the 6MWT occurred (Witte et al., 2005). The resting baseline was adopted the mean value of 3 min before 6MWT started in each value of $\dot{V}O_2$, $\dot{V}E$, and HR. Pearson's correlation coefficient was used to assess the relationships between 6MWD and values that were recorded by CPX, and to determine the correlation between V_T and f during the 6MWT in both groups. Statistical significance was accepted at $P < 0.05$.

RESULTS

The baseline characteristics are shown in Table 1. There were no differences between the groups in terms of age, proportions of males and females, BMI, LVEF, and beta-blocker use. Patients in the HF-L group walked shorter 6MWD and had lower HS than the HF-M group. On CPX, compared with the HF-L group, $\dot{V}O_{2peak}$ (15.79 ± 3.90 vs. 12.08 ± 3.37 ml/kg/min ; $P < 0.01$), AT (12.06 ± 2.59 vs. 9.50 ± 2.88 ml/kg/min ; $P < 0.01$), and peak O_2 pulse (8.68 ± 2.24 vs. 7.06 ± 1.58 ml/beat ; $P < 0.01$) were significantly higher, while $\dot{V}E/\dot{V}CO_2$ slope (27.44 ± 5.71 vs. 34.53 ± 6.51 ; $P < 0.001$) was significantly lower in the HF-M group (Table 1).

Significant positive correlations were observed between the 6MWD and $\dot{V}O_{2peak}$ ($r = 0.62$, $P < 0.001$), AT ($r = 0.55$, $P < 0.001$), and peak O_2 pulse ($r = 0.41$, $P < 0.01$). The 6MWD and $\dot{V}E/\dot{V}CO_2$ slope showed a significant negative correlation ($r = -0.57$, $P < 0.001$) (Figure 2).

Figure 3 shows the cardiorespiratory kinetics before, during, and after the 6MWT in both groups. In the HF-M group, $\dot{V}O_2$ was stabilized from 3 min during the 6MWT and recovered for 3 min after the 6MWT ended. $\dot{V}E$ was stabilized from 3 min and recovered for 3 min after the 6MWT ended. HR stabilized from 3 min and recovered for 1 min 30 s. In the HF-L group, $\dot{V}O_2$ was stabilized from 4 min during the 6MWT and did not recover within 3 min after the 6MWT ended. $\dot{V}E$ was stabilized from 4 min and did not recover within 3 min after the 6MWT ended. HR stabilized from 3 min and recovered for 1 min 30 s (Figure 3).

With regard to the breathing pattern of each group, in the HF-M group, VE rose from 8.26 ± 2.01 l/min at rest to 17.95 ± 5.00 ml/min at the sixth minute of the 6MWT. The increase in VE was due to both an increase in V_T (rest V_T 0.48 ± 0.12 l vs. the sixth minute V_T of the 6MWT 0.79 ± 0.22 l, $P < 0.001$) and an increase in f (rest f 17.68 ± 4.07 vs. the sixth minute f of the 6MWT 23.10 ± 4.28, $P < 0.001$). In the HF-L group, VE rose from 7.44 ± 1.81 l/min at rest to 17.62 ± 4.46 ml/min at the sixth minute of the 6MWT. The increase in VE was also due to increases in V_T (rest V_T 0.43 ± 0.17 l vs. the sixth minute V_T of the 6MWT 0.68 ± 0.18 l, $P < 0.001$) and f (rest f 18.25 ± 5.35 vs. the sixth minute f of the 6MWT 26.79 ± 6.41, $P < 0.001$). Additionally, as shown in Figure 4, comparing the

V_T and *f* relationship during the 6MWT between the two groups, the relationship in the HF-L group shifted gradually to the upper left due to increasing *f* throughout the 6MWT compared to the HF-M group.

DISCUSSION

The results of the present study suggested that the kinetics of cardiorespiratory parameters during and after the 6MWD in patients with HF have several differences according to the 6MWD. Furthermore, varying breathing patterns were seen during the 6MWT.

In this study, steady state of $\dot{V}O_2$ during the 6MWT was from 3 min in the HF-M group and 4 min in the HF-L group. Additionally, the HF-L group had lower $\dot{V}O_{2peak}$, AT, and HS compared to the HF-M group. Kervio et al. (2004) reported that the time to steady state $\dot{V}O_2$ during the 6MWT was longer in patients with HF (3-5 min) than in healthy participants (2 min 30 s). The delayed O_2 kinetics in patients with HF were linked to a decrease in O_2 availability to poorly perfused segments of exercising muscles as a result of an insufficient increase in cardiac output (Guazzi et al., 2016; Witte et al., 2005) and slower adaptation of cardiac function (Deboeck, Van Muylem, Vachiéry, and Naeije, 2014). This slower $\dot{V}O_2$ response may not only include abnormalities in cardiac function, but also in peripheral mechanisms. The abnormalities related to limitations in O_2 delivery in patients with HF (Fleg et al., 2015; Okita et al., 1998; Papathanasiou, Tsamis, Georgiadou, and Adamopoulos, 2008; Witte et al., 2005) include reduced nutritive blood flow to the active skeletal muscles, decreased capillary density, diminished oxidative capacity, abnormal peripheral circulation affected by neurohumoral mechanisms (Fleg et al., 2015; Francis, 1985; Papathanasiou, Tsamis, Georgiadou, and Adamopoulos, 2008; Solal, Chabernaud, and Gourgon, 1990), and the worsening local acidosis (Witte et al., 2005). The decreased O_2 availability in the exercising muscles leads to slower $\dot{V}O_2$ kinetics, because pulmonary $\dot{V}O_2$ kinetics reflect muscular $\dot{V}O_2$ during the onset of constant load exercise (Koike et al., 1995). Moreover, impaired muscle metabolism associated with early metabolic limitation in patients with HF, and they are dependent on the degree of exertion performed, which is related to peak functional capacity that reflects time of onset for O_2 (Okita et al., 1998; Witte et al., 2005). Additionally, reduced ventilatory efficiency may also contribute to delayed oxygen kinetics

(Brunner-La Rocca et al., 1999). Therefore, our results may be related with differences of exercise capacity including skeletal muscle functions.

In the present study, the recoveries of both $\dot{V}O_2$ and $\dot{V}E$ after the 6MWT ended were slower in the HF-L group. It is well known that O_2 deficit and O_2 debt have relationships with constant load exercise in healthy participants (Whipp, Seard, and Wasserman, 1970), and patients with HF have a slow increase of $\dot{V}O_2$ following the onset of exercise, which is associated with prolonged recovery time in prior study using CPX (Fleg et al., 2005; Sietsema et al., 1994). O_2 debt, namely, oxygen consumption during recovery above the control level, equaled O_2 deficit when exercise lasted 4 min and longer (Whipp, Seard, and Wasserman, 1970). Time of recovery O_2 kinetics depends on the workload and the proportion of functional capacity of the individual (Koike et al., 1995; Nanas et al., 2001; Witte et al., 2005). It is common knowledge that exercise training can improve exercise capacity and skeletal O_2 delivery due to multiple mechanisms (Fleg et al., 2015; Inamdar, and Inamdar, 2016; Papathanasiou, Tsamis, Georgiadou, and Adamopoulos, 2008; Piña et al., 2003; Roditis et al., 2007; Writing Committee Members et al., 2013).

As shown in Figure 3, HR recovered earlier than $\dot{V}O_2$ and $\dot{V}E$ in both groups. Moreover, in the present study, 45 patients (91.8%) were receiving β-blockers, and there was no difference between the groups in terms of their usage. β-blockers have been recommended for several years in international guidelines as a standard therapy in HF (McMurray et al., 2012). β-blockers are the primary pharmacological option available to lower HR. There is a linear correlation between $\dot{V}O_2$ and HR. On the other hand, in patients with HF, this correlation is only certain for those who use a full dose of β-blockers and have a resting HR of 50 to 60 beats per minute (Carvalho, Guimaraes, and Bocchi, 2008). Monitoring exercise intensity based on the HR alone should be avoided, especially in patients who are taking β-blockers, since patients with HF have a poor chronotropic response to exercise (Brubaker, and Kitzman, 2013; Piña et al., 2003). For these reasons, the HR might not adequately reflect the intensity of exercise, which includes the 6MWT, compared with other cardiopulmonary parameters.

Comparing the HF-L group to the HF-M group, the kinetics of $\dot{V}E$ during the 6MWT showed slower increases and patients in the HF-L group have lower $\dot{V}E$ (Figure3) Furthermore, their breathing pattern seemed to be composed of lower V_T and higher f throughout the 6MWT comparing the HF-M. Patients with HF have lower functional capacity and $\dot{V}E$ compared with age-matched healthy controls assessed using CPX (Clark, Chua, and Coats, 1995; Deboeck, Van Muylem, Vachiéry, and Naeije, 2014; Zavin et al., 2013). The $\dot{V}E$ values increased throughout the 6MWT in patients with HF, and this drift could be due to their higher intensity maintained during the test (Kervio et al., 2004). Patients with HF have an altered ventilatory response to exercise, primarily rapid shallow respiration (Dimopoulou, Tsintzas, Alivizatos, and Tzelepis, 2001; McConnell, 2004). Specific breathing patterns in patients with HF are associated with greater impairment in functional capacity, and are less efficient because it contributes to relatively lower V_T, higher f, and increased dead space ventilation (Dimopoulou, Tsintzas, Alivizatos, and Tzelepis, 2001; McConnell, 2004). Pulmonary dysfunction in patients with HF is composed of ventilation-perfusion mismatching, decreased lung compliance, restriction, airway obstruction, and decreased respiratory and skeletal muscle strength (Dall'Ago et al., 2006; McConnell, 2004). In addition to these factors, which contribute to the ventilatory response to exercise in patients with HF, increased afferent neural activity from the large locomotor muscles is related to metabolites generated during exercise (Olson, Joyner, and Johnson, 2010). Consequently, this results in an inefficient breathing pattern and increased work of breathing (McConnell, 2004). Typically, the most efficient pattern is adopted due to adaptation to the disease by the cardiorespiratory control systems (Davies et al., 1992). Possible mechanisms in current study may include a significantly higher $\dot{V}E/\dot{V}CO_2$ slope in the HF-L group (Table 1). $\dot{V}E/\dot{V}CO_2$ slope is a variable reflecting ventilatory efficiency in patients with HF and is related to an excessive ventilatory response during exercise with skeletal muscle metabolic production (Arena et al., 2004; Guazzi et al., 2016; Olson, Joyner, and Johnson, 2010). A high $\dot{V}E/\dot{V}CO_2$ slope is an important prognostic marker in patients with HF, and the degree of slope elevation increases with disease severity (Arena et al., 2004; Guazzi et al., 2016; Metra et al., 2007), which is associated with increasing dead space (Clark , Chua, and Coats, 1995).

The 6MWT is an useful measure of functional capacity and is a powerful indicator for HF patients due to correlations with $\dot{V}O_{2peak}$ and $\dot{V}O_{2max}$ of CPX (Guyatt et al., 1985; Metra et al., 2007; Opasich et al., 2001; Papathanasiou, Tsamis, Georgiadou, and Adamopoulos, 2008; Piepoli et al., 2011; Writing Committee Members et al., 2013), whereas the 6MWT does not accurately predict functional capacity in older HF patients (Maldonado-Martín et al., 2006). Age, sex, and body mass index must be considered when the 6MWT is used for the assessment of HF patients because these factors have an important influence on 6MWT performance (Metra et al., 2007). On the other hand, previous studies have shown that $\dot{V}O_2$ peak and AT are still the best indicators of functional capacity also in HF patients (Guazzi et al., 2016; Metra et al., 2007; Pereira et al., 2010). The current study showed that the 6MWD was correlated with $\dot{V}O_{2peak}$ and AT measured by CPX. Therefore, it is conceivable that 6MWD in the present study is a parameter of functional capacity.

In the interpretation of the present study results, some limitations should be considered. The sample size was small, and there was no healthy control group. Additionally, there is a difference of the sample sizes between two groups, and the timing of the protocol from onset of HF was not stipulated. The assessor of the 6MWT with portable metabolic measurement system was the same physical therapist and it could be potential of assessor's bias. In our current study, we investigated the relationship between 6MWD and values that were recorded by CPX. However, the 6MWT is not able to supersede CPX as the same role of measurement. Moreover, the relationship between V_T and f during the 6MWT in both groups were investigated with correlations and it might not clarify causal relationship. Other limitations of this study are the effects of type of HF (HFrEF, HFmrEF, and HFpEF) (Ponikowski et al., 2016) and the etiology of HF (Antunes-Correa et al., 2017). Further research that takes into account the pathophysiological characteristics is needed.

CONCLUSION

The cardiorespiratory responses during and after the 6MWT differ according to the 6MWD. In lower exercise capacity patients with HF have slower $\dot{V}O_2$ and VE kinetics, and their breathing pattern during the 6MWT seems to consist of a higher breathing frequency and a lower V_T.

Declaration of interest

The authors declare that there is no conflict of interest.

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Footnotes

1. New York Heart Association Functional Classification (The Criteria Committee of the New York Heart Association, 1994)

Class I. No limitation of physical activity.

Class II. Slight limitation of physical activity. Ordinary physical activity results in symptoms including fatigue, palpitation, dyspnea, or anginal pain.

Class III. Marked limitation of physical activity. Less than ordinary activity causes symptoms.

Class IV. Symptoms even at rest.

Table 1. Baseline characteristics and exercise data of each group

Variables	HF-M	HF-L	95% CI of difference	*P*-value	Effect size
n	34	15			
Age * (years)	68.86 ± 11.24	72.27 ± 12.42	- 3.78 to 10.60	0.17	0.29
Sex † (male/female)	13/21	10/5	- 0.53 to 0.01	0.06	0.44
BMI * (kg/m^2)	22.28 ± 3.93	22.80 ± 4.12	- 2.02 to 3.06	0.28	0.15
LVEF ‡ (%)	37 (22.7-57.5)	34 (30-53)	- 10.97 to 12.83	0.76	0.20
NYHA class[1] †					
II/ III (n)	32/ 2	8/ 7		< 0.01	0.49
Etiology of HF † (n)				0.50	0.22
Ischemic Cardiomyopathy	1	1			
Cardiomyopathy	19	10			
Valvular disease	10	4			
Arrhythmia	4	0			
Current prescription † (n)					
Beata blockers	31	14		0.27	0.06
ACE inhibitor	17	7		0.68	0.05
ARB	23	8		0.33	0.14
Diuretics	31	14		0.79	0.04
Aldosterone antagonists	22	9		0.75	0.05
Hospitalization days*(days)	25.02 ± 12.44	28.60 ± 10.17	- 6.37 to 13.51	0.85	0.31
Duration of the inpatient rehabilitation program* (days)	18.94 ± 10.06	22.80 ± 10.36	- 4.46 to 12.18	0.54	0.38
6MWD (m) *	412.20 ± 10.03	228.33 ± 15.10	-220.35 to – 147.39	< 0.001	14.43

Handgrip strength* (kg)	27.15 ± 6.44	16.80 ± 4.40	6.65 to 14.04	< 0.001	1.87
CPX					
$\dot{V}O_2$ peak* (ml/kg/min)	15.79 ± 3.90	12.08 ± 3.37	1.36 to 6.04	< 0.01	0.92
AT* (ml/kg/min)	12.06 ± 2.59	9.50 ± 2.88	0.88 to 4.23	< 0.01	0.93
$\dot{V}E/\dot{V}CO_2$ slope*	27.44 ± 5.71	34.53 ± 6.51	3.37 to 10.80	< 0.001	1.16
peak O_2 pulse* (ml/beat)	8.68 ± 2.24	7.06 ± 1.58	0.32 to 2.90	< 0.01	0.70

*Data presented as mean ± standard deviation and the unpaired t-test was used. †Data presented as number and chi-square test was used. ‡Data presented as median (interquartile range) and Mann-Whitney U test was used.

n, number; BMI, body mass index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; HF, heart failure; ACE, angiotensin-converting enzyme; ARB, Angiotensin II Receptor Blocker; 6MWD, the 6-minute walk distance; CPX, cardiopulmonary exercise testing; $\dot{V}O_{2peak}$, peak oxygen uptake; AT, anaerobic threshold; $\dot{V}E/\dot{V}CO_2$ slope, the minute ventilation - carbon dioxide production relationship; peak O2 pulse, peak oxygen pulse.

Figure captions

Figure 1: A flow chart of patients included in this study

Figure 2: Correlations of the 6-minute walk distance (6MWD) with peak oxygen uptake ($\dot{V}O_{2\ peak}$), anaerobic threshold (AT), the relationship between minute ventilation and carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ slope), and peak O_2 pulse in a cardiopulmonary exercise test

Figure 3: Kinetics of the cardiorespiratory parameters before, during, and after the 6MWT in patients with heart failure who walked 300 m or more (HF-M), and patients with heart failure who walked less than 300 m (HF-L)

Figure 4: The correlation between tidal volume (V_T) and breathing frequency (f) during the 6MWT in patients with heart failure who walked 300 m or more (HF-M), and patients with heart failure who walked less than 300 m (HF-L)

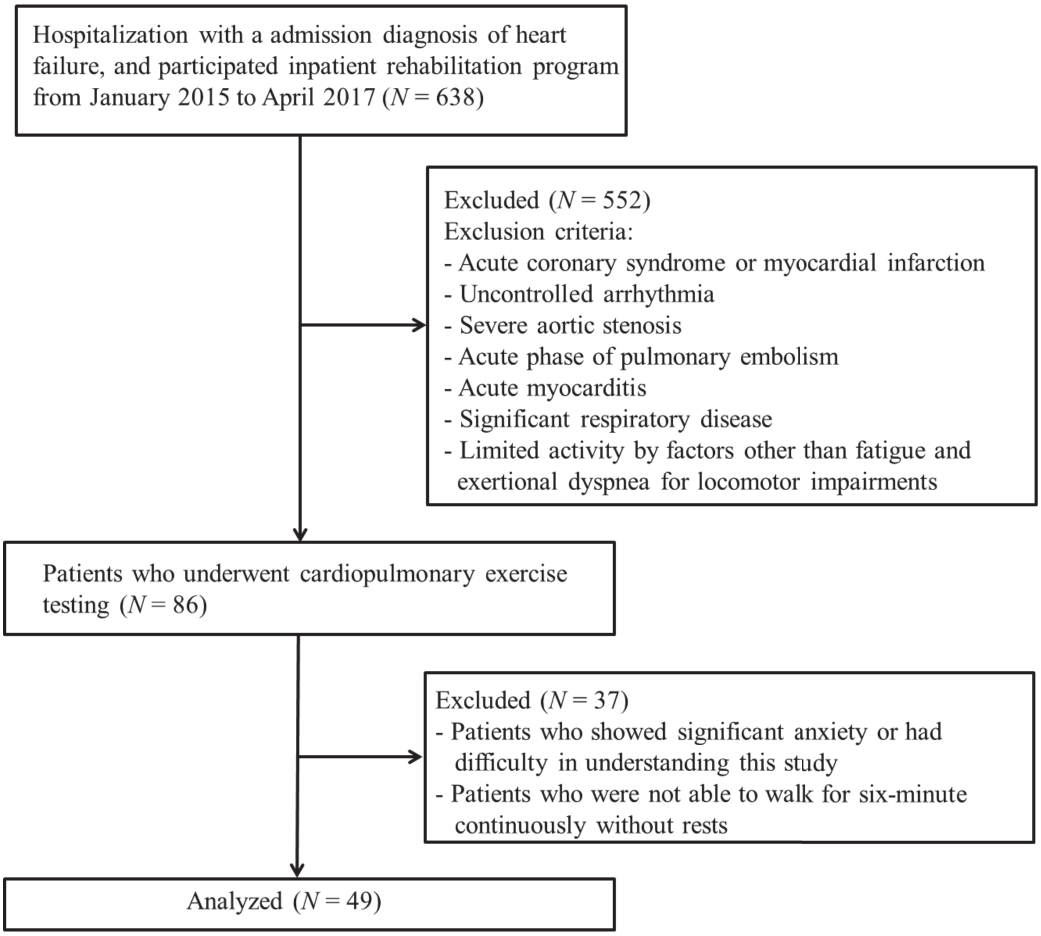


Figure 1. A flow chart of patients included in this study.

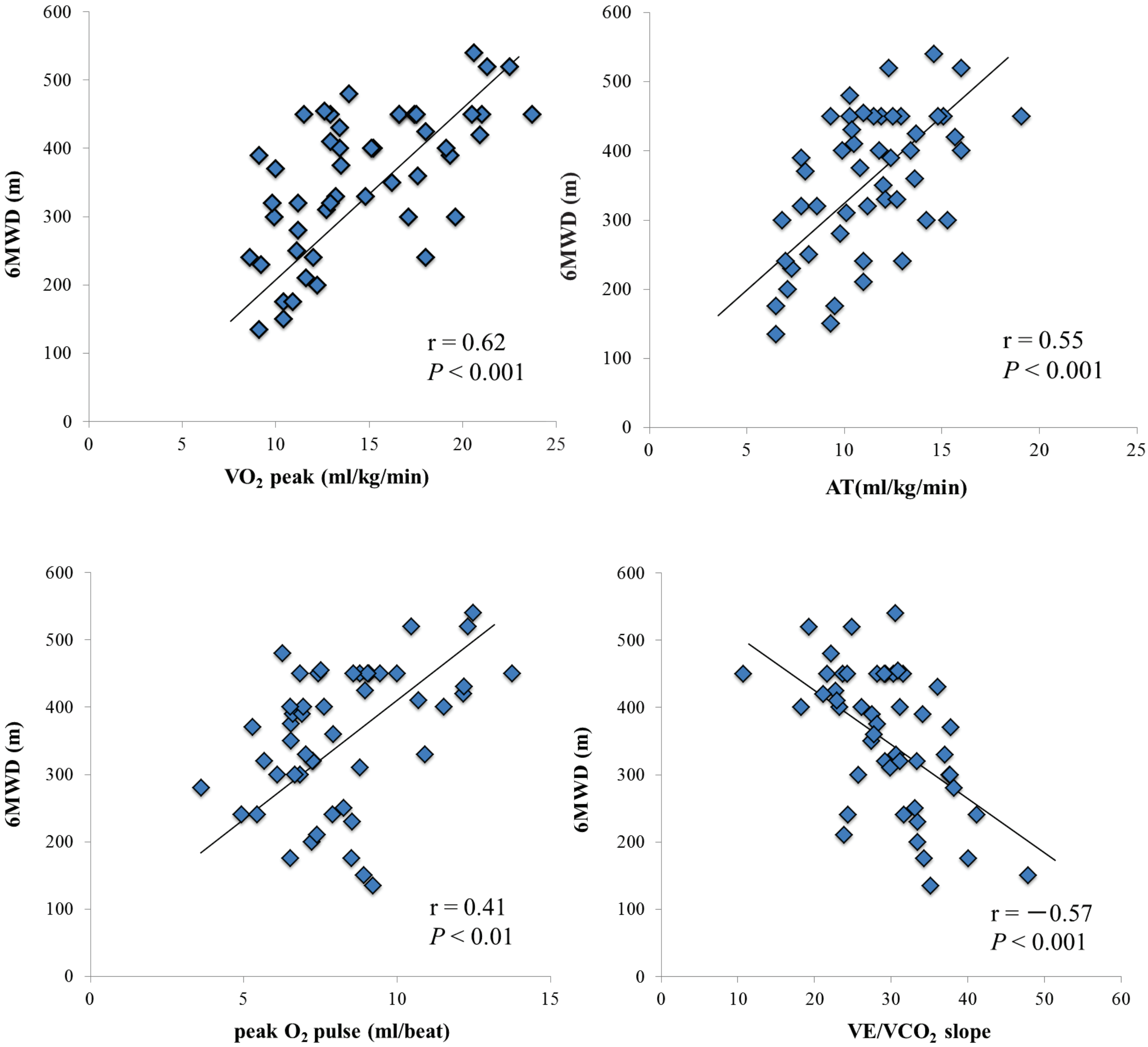


Figure 2. Correlations of the 6-minute walk distance (6MWD) with peak oxygen uptake ($\dot{V}O_{2\ peak}$), anaerobic threshold (AT), the relationship between minute ventilation and carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ slope), and peak O_2 pulse in a cardiopulmonary exercise test. Pearson's correlation coefficient was used to determine the correlation among the variables.

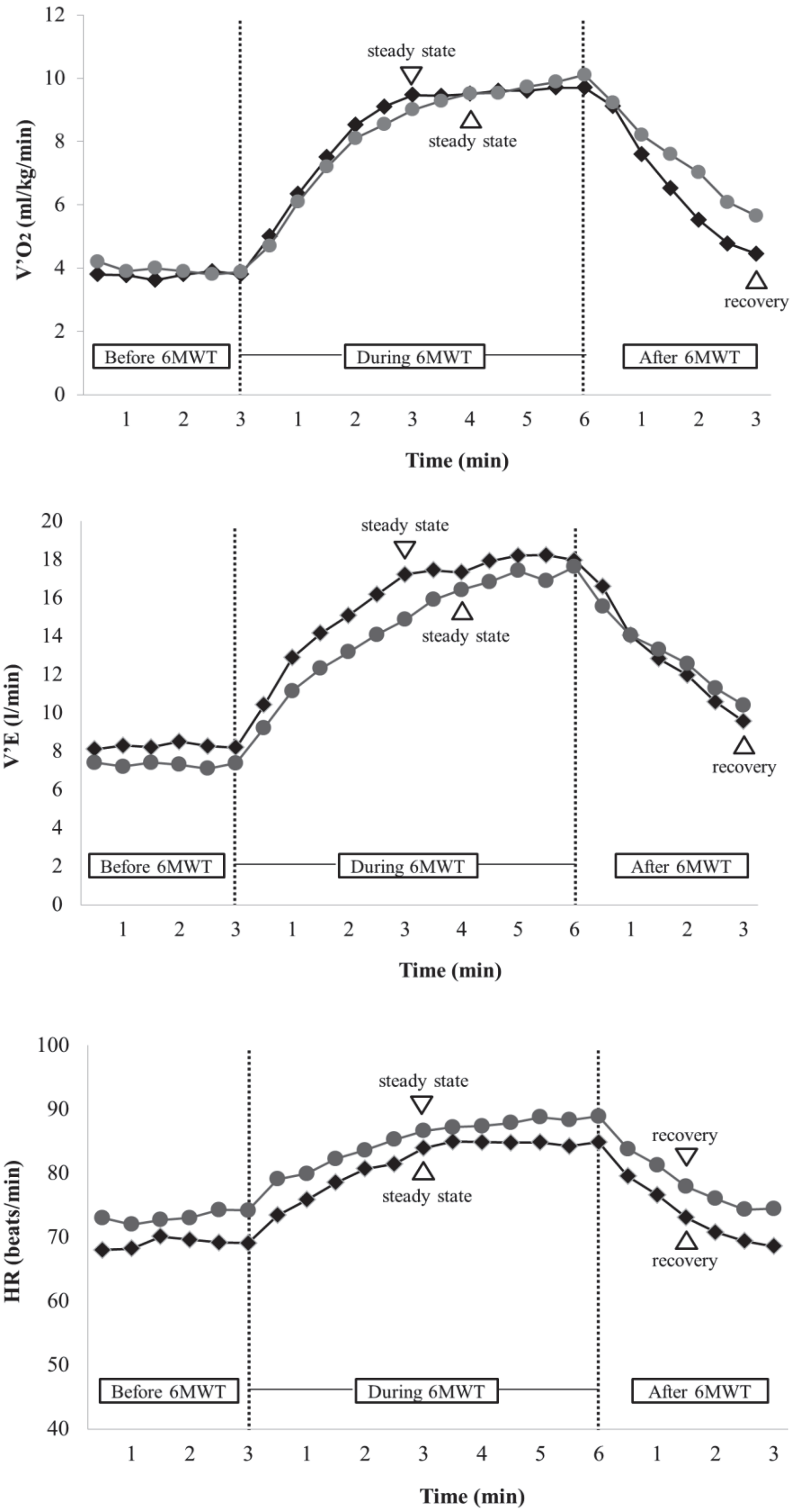
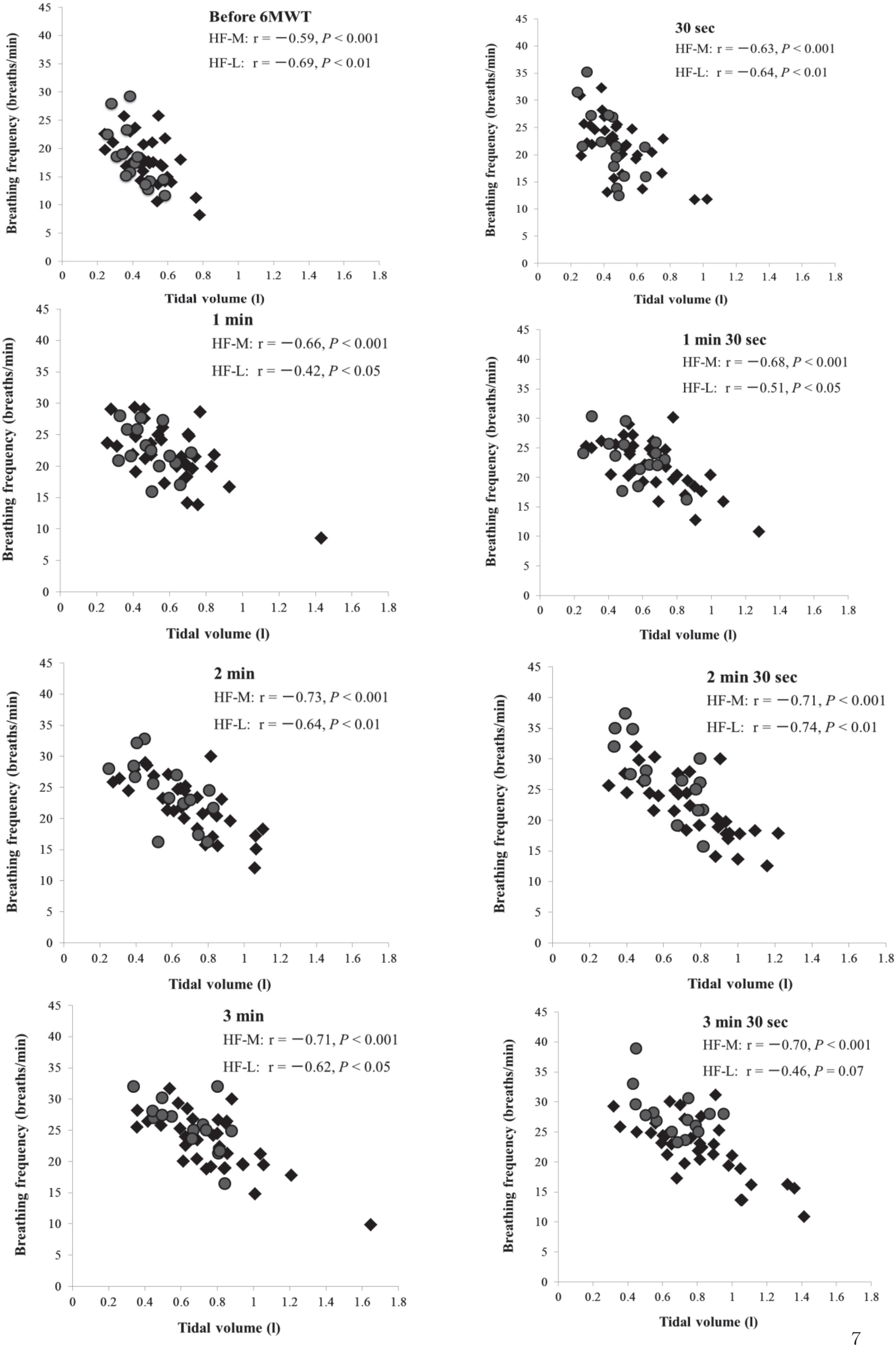


Figure 3. Kinetics of the cardiorespiratory parameters before, during, and after the 6MWT ($\dot{V}O_2$, oxygen uptake; $\dot{V}E$, minute ventilation; HR, heart rate) in patients with heart failure who walked 300

m or more (HF-M, ◆), and patients with heart failure who walked less than 300 m (HF-L, ●). The time between the broken lines indicates the 6MWT. The open triangle symbols indicate the cardiorespiratory parameters steady state during the 6MWT and recovery point after the 6MWT. The time course of cardiorespiratory values including $\dot{V}O_2$, $\dot{V}E$, and HR during the 6MWT was analyzed in each group using one-way repeated measures ANOVA, followed, when significant, by Tukey's method. The definition of steady state was the first point in time after which there was no further statistical significant difference during the 6MWT in each value of $\dot{V}O_2$, $\dot{V}E$, and HR. The beginning of recovery corresponded to be the point at which no further changes compared to the resting baseline before the 6MWT occurred (Witte et al, 2005). The resting baseline was adopted the mean value of 3 min before 6MWT started in each value of $\dot{V}O_2$, $\dot{V}E$, and HR.


Before 6MWT
HF-M: r = −0.59, P < 0.001
HF-L: r = −0.69, P < 0.01
30 sec
HF-M: r = −0.63, P < 0.001
HF-L: r = −0.64, P < 0.01
1 min
HF-M: r = −0.66, P < 0.001
HF-L: r = −0.42, P < 0.05
1 min 30 sec
HF-M: r = −0.68, P < 0.001
HF-L: r = −0.51, P < 0.05
2 min
HF-M: r = −0.73, P < 0.001
HF-L: r = −0.64, P < 0.01
2 min 30 sec
HF-M: r = −0.71, P < 0.001
HF-L: r = −0.74, P < 0.01
3 min
HF-M: r = −0.71, P < 0.001
HF-L: r = −0.62, P < 0.05
3 min 30 sec
HF-M: r = −0.70, P < 0.001
HF-L: r = −0.46, P = 0.07
Breathing frequency (breaths/min)
Tidal volume (l)

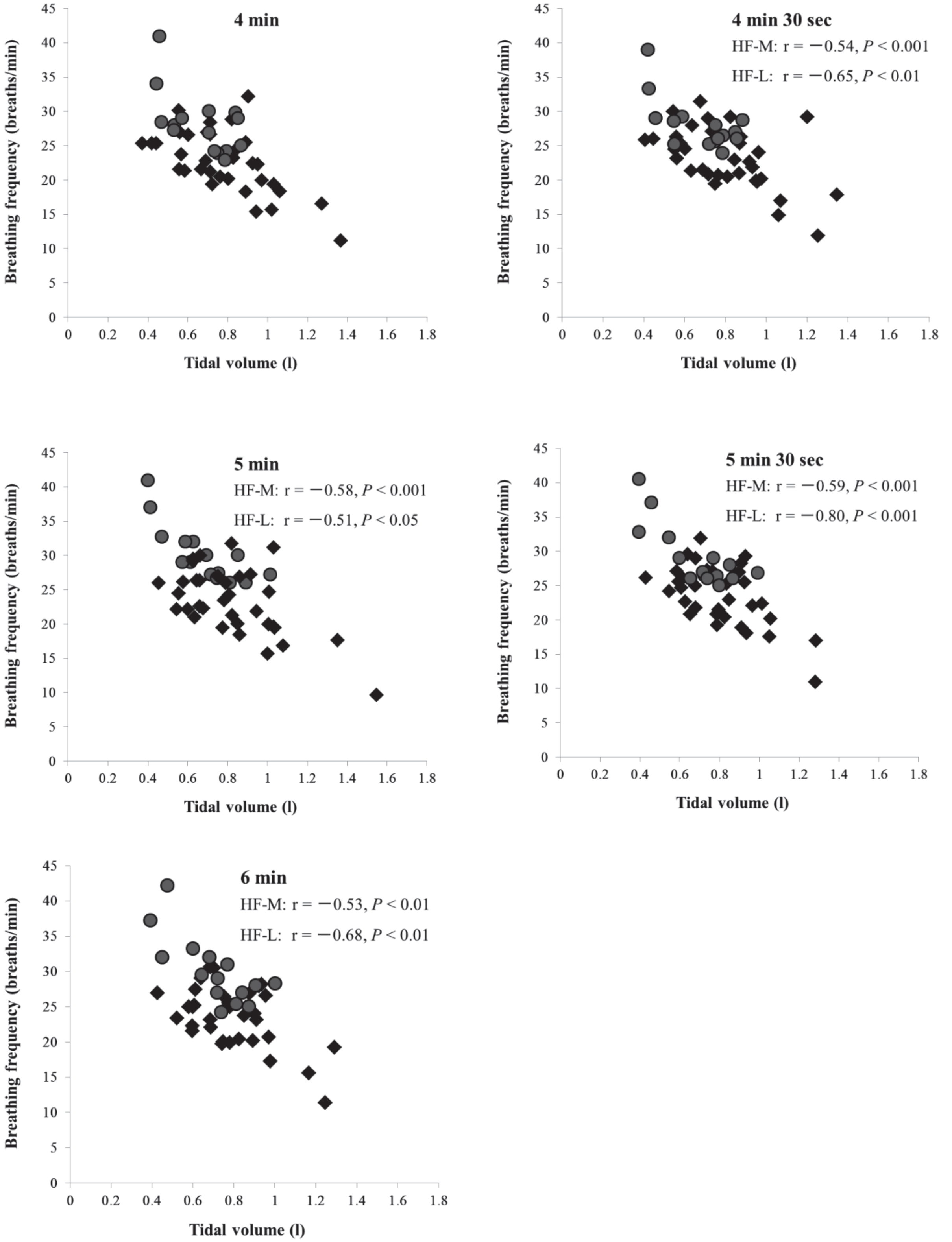


Figure 4. The correlation between tidal volume (V_T) and breathing frequency (f) during the 6MWT in patients with heart failure who walked 300 m or more (HF-M, ◆) and patients with heart failure who walked less than 300 m (HF-L, ●). Pearson's correlation coefficient was used to determine the

correlation between V_T and f every 30 seconds during the 6MWT.