

Pulse wave transit time during exercise testing reflects the severity of heart disease in cardiac patients

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SUMMARY The pulse wave transit time (PWTT) is easily measured as the time from the R wave of an electrocardiogram to the arrival of the pulse wave measured by an oxygen saturation monitor at the earlobe. We investigated whether the change of PWTT during exercise testing reflects cardiopulmonary function. Eighty-nine cardiac patients who underwent cardiopulmonary exercise testing (CPX) were enrolled. We analyzed the change of PWTT during exercise and the relationship between the shortening of the PWTT and CPX parameters. PWTT was significantly shortened from rest to peak exercise (204.6 ± 33.6 vs. 145.6 ± 26.4 msec, $p < 0.001$) in all of the subjects. The patients with heart failure had significantly higher PWTT at peak exercise than the patients without heart failure (152.7 ± 27.1 vs. 140.4 ± 24.8 msec, $p = 0.031$). The shortening of PWTT from rest to peak exercise showed significant positive correlations with the peak O₂ uptake (VO₂) ($r = 0.56$, $p < 0.001$), anaerobic threshold ($r = 0.40$, $p = 0.016$), and % increase of systolic blood pressure during exercise ($r = 0.75$, $p < 0.001$), and a negative correlation with the slope of the increase in ventilation versus the increase in CO₂ output (VE-VCO₂ slope) ($r = -0.42$, $p = 0.010$) in the patients with heart failure. PWTT was shortened during exercise as the exercise intensity increased. In the patients with heart failure, the shortening of PWTT from rest to peak exercise was smaller in those with lower exercise capacity and those with higher VE-VCO₂ slope, an established index known to reflect the severity of heart failure.

Keywords Pulse wave transit time, exercise testing, cardiopulmonary function

1. Introduction

The pulse wave transit time (PWTT) is the time from the electrocardiogram R wave to the arrival of the pulse wave measured by an oxygen saturation monitor at the earlobe. PWTT is thought to be at least partly related to cardiovascular function, as it has been reported to shorten when the blood pressure rises (1,2). As a parameter that can be easily and continuously measured, PWTT has the potential to serve as a useful clinical tool for identifying changes in cardiovascular function, especially during exercise. Little is known, however, about the change of PWTT during exercise or the relation of that change to cardiopulmonary function.

Cardiopulmonary exercise testing (CPX) is one of the most useful clinical tools for evaluating the

severity of disease and the limitations of physical activities in cardiac patients (3). Among the parameters obtained from CPX, the peak oxygen uptake (VO₂) noninvasively reflects maximal cardiac output during exercise and is accordingly considered a strong prognostic factor and gold standard for selecting patients for cardiac transplantation (4,5). The slope of the increase in ventilation (VE) versus the increase in CO₂ output (VCO₂) during exercise (VE-VCO₂ slope) is another important parameter for evaluating the severity of heart failure (6).

In the present study we compared PWTT at rest, at anaerobic threshold (AT), and at peak exercise between patients with and without heart failure. We also evaluated the relation of the change of PWTT during exercise with the established CPX indices.

2. Methods

2.1. Study subjects

This is the retrospective study. The subjects for this study were 103 consecutive cardiac patients who underwent CPX for evaluation of exercise capacity and/or severity of cardiac disease at the University of Tsukuba Hospital between March 2017 and April 2018. Fourteen of the subjects were excluded because the PWTT at peak exercise could not be measured. In total, 89 subjects were selected (Table 1). The etiologies of heart disease in the cardiac patients were valvular heart disease in 28 patients, congenital heart disease in 25, coronary artery disease in 19, idiopathic dilated cardiomyopathy in 6, arrhythmia in 5, and other cardiac disease in 6. Thirty-eight of the patients had heart failure categorized as New York Heart Association class II or III. The protocol was approved by the Institutional Review Board of the University of Tsukuba Hospital. All of the subjects gave their informed consent to perform CPX.

2.2. Exercise testing and respiratory gas analysis

An incremental symptom limited exercise test was performed using an upright, electromagnetically braked cycle ergometer (Strength Ergo 8; Mitsubishi Electric Engineering Co., Ltd., Tokyo, Japan). The exercise test began with 4 minutes of rest on the ergometer followed by 4 minutes of warm-up at 0 or 20 W at 50 rpm. The load was then increased by 1 W every 6 seconds (10 W/min).

VO₂, VCO₂, and VE were measured throughout the test using an Aeromonitor AE-300s (Minato Medical Science, Osaka, Japan). The Aeromonitor AE-300s consists of a microcomputer, a hot wire flowmeter, and a gas analyzer composed of a sampling tube, filter, suction pump, infrared CO₂ analyzer, and O₂ analyzer equipped with a paramagnetic oxygen cell. The VO₂ and VCO₂ were calculated breath-by-breath based on the mathematical analysis described by Beaver *et al.* (7). The time alignment between the concentration and flow was performed based on the time delays of the O₂ and CO₂ analyzers (the flow delay from the sampling site to the analyzer plus the response time of the analyzer) (8). Before the parameters from the respiratory gas analysis were calculated, the breath-by-breath data were interpolated to give second-by-second values. These second-by-second values were then calculated as successive 3-second averages, and the averages were translated into a 5-point moving average.

The peak VO₂ was calculated as the average of the values obtained during the last 15 seconds of incremental exercise. The percentage of peak VO₂ was calculated by dividing the measured peak VO₂ by the predicted peak VO₂. The predicted peak VO₂ was determined on

the basis of a normal Japanese population (9). The VE-VCO₂ slope during incremental exercise was calculated from the start of incremental exercise to the respiratory compensation point by least-squares linear regression, as previously described (5). The AT was determined by V-slope analysis (10). The ratio of the increase in VO₂ to the increase in the work rate ($\Delta\text{VO}_2/\Delta\text{WR}$) was calculated by least-squares linear regression from the data recorded from 30 seconds after the start of incremental exercise to 30 seconds before the end of exercise (5).

2.3. Analysis of the PWTT

Figure 1 demonstrates the measurement of PWTT. PWTT was measured using an electrocardiograph (STS 2100; NIHON KOHDEN, Tokyo, Japan) and oxygen saturation monitor attached to the earlobe. PWTT was defined as the interval from the R wave of the electrocardiogram to the arrival of the pulse wave measured by an oxygen saturation monitor at the earlobe. PWTT was continuously measured from rest to the end of the exercise test as the average of the previous 64 beats, and sampled every 15 seconds. The shortening of PWTT was expressed as a percentage of the decrease in PWTT at peak exercise versus that at rest.

2.4. Statistical analysis

Data are presented as the mean \pm S.D. Intergroup differences for variables were compared by the unpaired *t* test or the Fisher's exact test where appropriate. The linear regression analysis was used to correlate the measured variables. All analyses were performed using SPSS version 22.0 software (SPSS Inc., Chicago, Illinois). A *p* value < 0.05 was considered statistically significant for all comparisons.

3. Results

The cardiopulmonary parameters of the study patients are shown in Table 2. The patients with heart failure had significantly higher brain natriuretic peptide than the patients without heart failure. In the comparison of CPX parameters between the two groups, the patients with heart failure had significantly lower values of peak VO₂ (16.5 \pm 4.3 vs. 22.7 \pm 4.3 mL/min/kg, *p* < 0.001), AT (12.5 \pm 2.6 vs. 15.4 \pm 3.1 mL/min/kg, *p* < 0.001), and $\Delta\text{VO}_2/\Delta\text{WR}$ (9.1 \pm 2.0 vs. 10.4 \pm 1.4 mL/min/W, *p* = 0.002), and a significantly higher value of VE-VCO₂ slope (34.6 \pm 5.8 vs. 29.8 \pm 4.2, *p* < 0.001).

Figure 2 shows the PWTT at rest, AT, and peak exercise in the study patients. When analyzed in the whole study population, PWTT was significantly shortened from rest to AT (204.6 \pm 33.6 vs. 169.5 \pm 31.4 msec, *p* < 0.001), and from AT to peak (169.5 \pm

Table 1. Clinical characteristics of the study patients

Characteristics	All Patients (n = 89)	Patients with HF (n = 38)	Patients without HF (n = 51)	p value
Male/Female	45/44	18/20	27/24	0.380
Age (years)	53.3 ± 21.9	59.8 ± 21.1	48.4 ± 21.4	0.014
Height (cm)	160.2 ± 8.3	159.1 ± 7.9	161.1 ± 8.6	0.460
Weight (kg)	59.9 ± 11.6	59.8 ± 11.8	60.0 ± 11.7	0.909
BMI (kg/m ²)	23.2 ± 3.6	23.6 ± 4.1	23.0 ± 3.2	0.774
Etiology				
Valvular disease	28 (31.5)	8 (21.1)	20 (39.2)	0.105
Congenital heart disease	25 (28.1)	7 (18.4)	18 (35.3)	0.098
Coronary artery disease	19 (21.3)	12 (31.6)	7 (13.7)	0.066
Idiopathic dilated cardiomyopathy	6 (6.7)	6 (15.8)	0	0.005
Arrhythmia	5 (5.6)	0	5 (9.8)	0.069
Other cardiac disease	6 (6.7)	5 (13.2)	1 (2.0)	0.080
Complication				
Hypertension	44 (49.4)	23 (60.5)	21 (41.2)	0.088
Hyperlipidemia	30 (33.7)	16 (42.1)	14 (27.5)	0.177
Diabetes	25 (28.1)	16 (42.1)	9 (17.6)	0.017
Smokers	22 (24.7)	13 (34.2)	9 (17.6)	0.087
Chronic kidney disease	9 (10.1)	8 (21.1)	1 (2.0)	0.004
Creatinine	0.81 ± 0.25	0.90 ± 0.31	0.73 ± 0.15	0.006
Non-HDL cholesterol	130.3 ± 36.2	130.5 ± 36.1	130.0 ± 37.1	0.412
Rhythm				
Sinus	84 (94.4)	34 (89.5)	50 (98.0)	0.159
Atrial fibrillation	2 (2.2)	2 (5.3)	0	0.180
Pacing	3 (3.4)	2 (5.3)	1 (2.0)	0.573
Medication				
β-blockers	36 (40.4)	26 (68.4)	10 (19.6)	< 0.001
ACEI/ARB	41 (46.1)	25 (65.8)	16 (31.4)	0.001
Diuretics	30 (33.7)	22 (57.9)	8 (15.7)	< 0.001
Ca-channel blockers	23 (25.8)	16 (42.1)	7 (13.7)	0.003

Data are presented as the mean ± S.D. or No. (%) of patients unless otherwise indicated. HF, Heart failure; ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker.

Table 2. Cardiopulmonary parameters of the study patients

Characteristics	All Patients (n = 89)	Patients with HF (n = 38)	Patients without HF (n = 51)	p value
At rest				
BNP (pg/mL)	96.0 ± 132.8	145.0 ± 178.2	57.4 ± 59.1	0.006
LVEF (%)	62.3 ± 10.5	59.9 ± 10.6	64.1 ± 10.2	0.074
LVDd (mm)	46.6 ± 7.0	47.8 ± 6.4	45.8 ± 7.3	0.176
LVDs (mm)	31.0 ± 7.1	32.6 ± 7.3	30.0 ± 6.8	0.103
Heart rate (beats/min)	75.5 ± 13.0	74.9 ± 15.1	75.9 ± 11.4	0.723
Systolic blood pressure (mmHg)	133.9 ± 24.7	138.8 ± 30.0	130.3 ± 19.4	0.107
Diastolic blood pressure (mmHg)	76.0 ± 12.9	73.8 ± 12.7	77.7 ± 12.9	0.150
At Peak Exercise				
Work rate (W)	86.0 ± 32.2	69.8 ± 26.4	98.0 ± 31.0	< 0.001
Heart rate (beats/min)	135.6 ± 27.0	123.4 ± 27.1	144.6 ± 23.2	< 0.001
Systolic blood pressure (mmHg)	181.2 ± 33.8	170.2 ± 34.4	189.3 ± 31.3	0.008
Diastolic blood pressure (mmHg)	88.8 ± 16.4	83.7 ± 16.2	92.6 ± 15.7	0.011
R	1.14 ± 0.13	1.11 ± 0.14	1.15 ± 0.12	0.126
Peak VO ₂ (mL/min/kg)	20.0 ± 5.3	16.5 ± 4.3	22.7 ± 4.3	< 0.001
Peak VO ₂ (%)	78.2 ± 19.3	64.7 ± 14.6	88.3 ± 15.9	< 0.001
VE-VCO ₂ slope	31.8 ± 5.4	34.6 ± 5.8	29.8 ± 4.2	< 0.001
AT (mL/min/kg)	14.2 ± 3.2	12.5 ± 2.6	15.4 ± 3.1	< 0.001
ΔVO ₂ /ΔWR (mL/min/W)	9.8 ± 1.8	9.1 ± 2.0	10.4 ± 1.4	0.002
PWTT				
Rest (ms)	204.6 ± 33.6	202.9 ± 37.4	205.8 ± 30.8	0.687
AT (ms)	169.5 ± 31.4	171.7 ± 34.4	167.7 ± 29.0	0.570
Peak (ms)	145.6 ± 26.4	152.7 ± 27.1	140.4 ± 24.8	0.031
Shortening of PWTT (%)	28.3 ± 10.1	23.8 ± 11.2	31.6 ± 7.8	< 0.001

Data are presented as the mean ± S.D. or No. (%) of patients unless otherwise indicated. BNP, brain natriuretic peptide; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; R, gas exchange ratio; VO₂, O₂ uptake; VE, minute ventilation; VCO₂, CO₂ output; AT, anaerobic threshold.

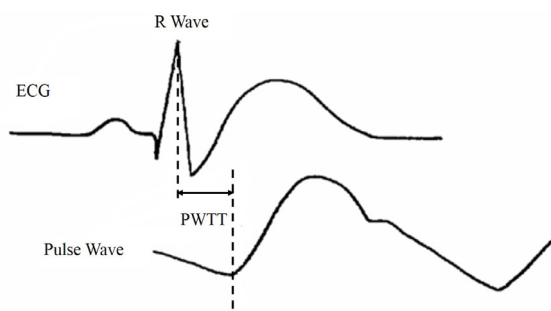


Figure 1. The pulse wave transit time (PWTT) was calculated as the interval from the R wave of the electrocardiogram (ECG) to the arrival of the pulse wave measured by an oxygen saturation monitor at the earlobe.

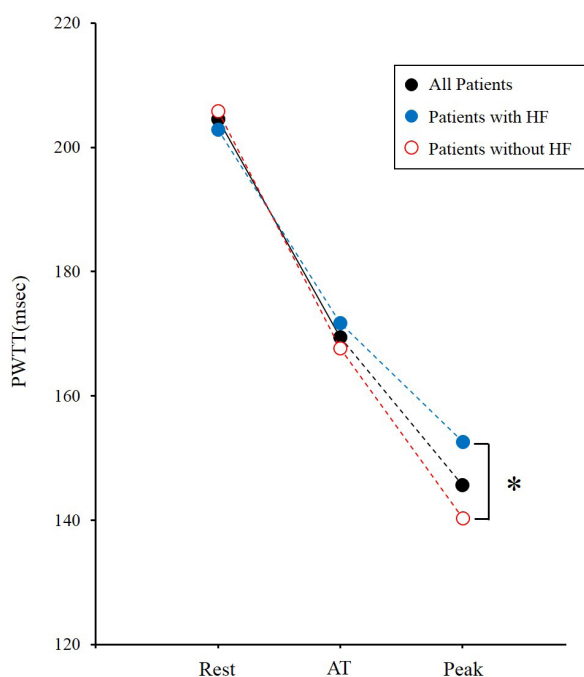


Figure 2. Comparisons of the pulse wave transit time (PWTT) at rest, anaerobic threshold (AT), and peak exercise among the study patients. * $p < 0.05$ compared between the patients with heart failure (HF) and patients without HF.

31.4 vs. 145.6 ± 26.4 msec, $p < 0.001$). There were no significant differences in PWTT at rest or in AT between the patients with and without heart failure. The patients with heart failure, however, had significantly higher PWTT at peak exercise (152.7 ± 27.1 vs. 140.4 ± 24.8 msec, $p = 0.031$). The degree to which PWTT was shortened from rest to peak exercise was significantly lower in the patients with heart failure than in the patients without heart failure (23.8 ± 11.2 vs. $31.6 \pm 7.8\%$, $p < 0.001$).

Figure 3 shows the correlations between the CPX indices and the shortening of the PWTT from rest to peak exercise in the patients with heart failure. The shortening of the PWTT showed significant positive correlations with the peak VO_2 ($r = 0.56$, $p < 0.001$) and AT ($r = 0.40$, $p = 0.016$), and a negative correlation

with the VE- VCO_2 slope ($r = -0.42$, $p < 0.010$). The shortening of PWTT showed a significant positive correlation with the % increase in systolic blood pressure ($r = 0.75$, $p < 0.001$).

4. Discussion

The PWTT was significantly shortened as the exercise intensity increased in the cardiac patients enrolled in this study. The patients with heart failure had significantly higher PWTT at peak exercise than the patients without heart failure. The shortening of PWTT from rest to peak exercise showed positive correlations with the peak VO_2 , AT, and % increase in systolic blood pressure, and a negative correlation with the VE- VCO_2 slope, indicating a lesser degree of shortening of PWTT in patients with lower exercise capacity and/or lower cardiopulmonary function during exercise.

4.1. Parameters obtained from CPX

The peak VO_2 generally reflects the maximal cardiac output during exercise. The peak VO_2 has been used as the main parameter of exercise capacity. The AT represents the highest level of VO_2 that a subject can perform without developing sustained lactic acidosis. The lower AT in cardiac patients signifies that the exercise-induced lactic acidosis occurs at a lower intensity of exercise (11,12). The $\Delta VO_2/\Delta WR$ is mainly determined by the rate of the increase in cardiac output during incremental exercise. In normal subjects, the $\Delta VO_2/\Delta WR$ is approximately 10 mL/min/W, and a lower $\Delta VO_2/\Delta WR$ implies impaired response of cardiac output during exercise (13). The VE- VCO_2 slope ranges approximately from 24 to 34 in normal subjects. The steeper VE- VCO_2 slope in heart failure patients mainly reflects high V/Q mismatch caused by reduced pulmonary blood flow (14). In the present study we found that the shortening of PWTT during exercise was lower in subjects with more advanced cardiopulmonary dysfunction, as reflected in a lower peak VO_2 , lower AT, lower $\Delta VO_2/\Delta WR$, and higher VE- VCO_2 slope.

4.2. Mechanisms of the shortening of PWTT during exercise

The oxygen demand in skeletal muscle during exercise becomes higher with increasing exercise intensity. In response, the blood pressure, heart rate, and cardiac output rise to meet the increased oxygen demand in skeletal muscle. PWTT, the time of the pulse wave from the heart to the periphery, can therefore be expected to shorten in step with the increasing cardiac output as the exercise intensity increases.

There was no significant difference in PWTT at rest between patients with and without heart failure in the present study. However, PWTT at peak exercise

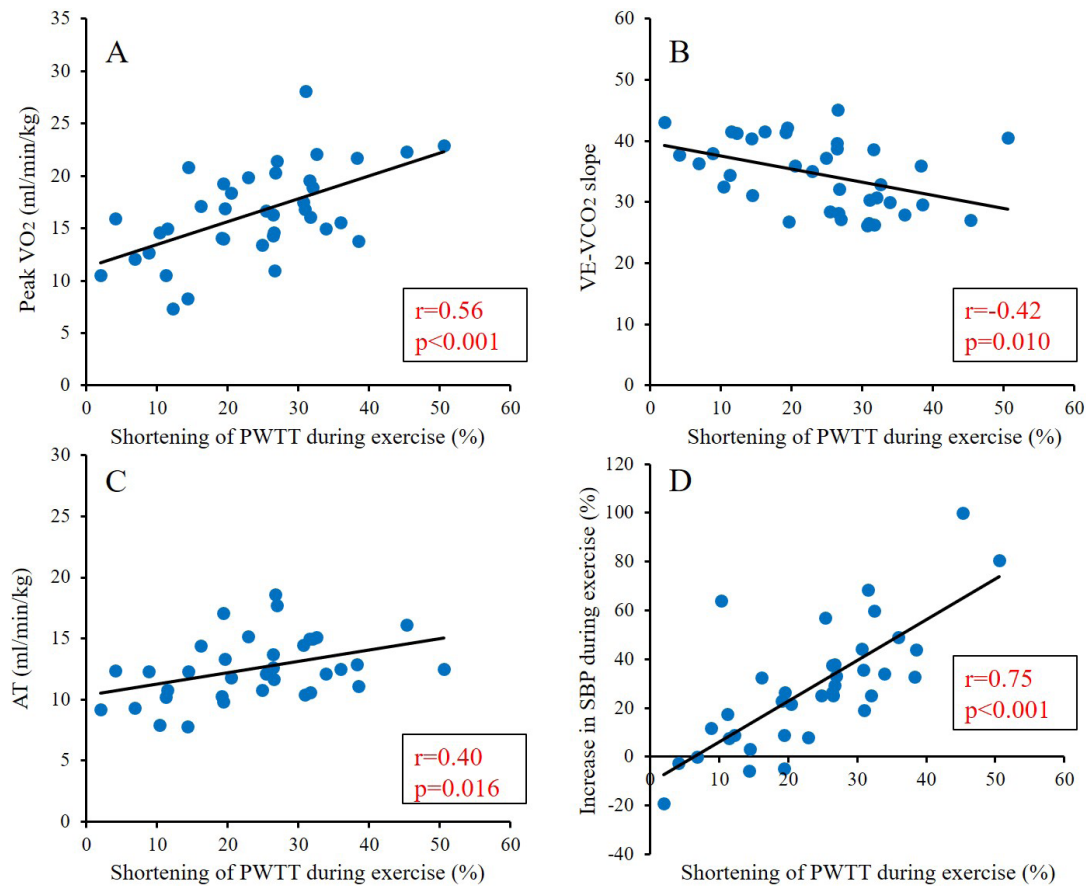


Figure 3. Peak O_2 uptake (VO_2) (panel A), slope of the increase in ventilation versus the increase in CO_2 output (VE-VCO₂ slope) (panel B), anaerobic threshold (AT) (panel C), and % increase in systolic blood pressure (SBP) during exercise (panel D) plotted against the shortening of the pulse wave transit time (PWTT) in the patients with heart failure.

was significantly higher, and the degree of shortening of PWTT during exercise was significantly lower, in the heart failure patients. The shortening of PWTT during exercise was positively correlated with the increase in systolic blood pressure during exercise. Therefore, we assume that the lesser degree of PWTT shortening in the heart failure patients was caused by the limited increase in cardiac output during exercise, as systolic blood pressure partly reflects cardiac output. An impaired increase in cardiac output during exercise can be attributed to factors such as the appearance of myocardial ischemia or a worsening of valvular disease. Increased afterload resulting from excessive activity of the sympathetic nervous system or impaired production of the nitric oxide due to the vascular endothelial dysfunction in cardiac patients must also impair cardiac contractility, thereby influencing cardiac output during exercise.

To our knowledge, the present study is the first report which evaluated the change of PWTT during exercise and its relation with the parameters reflecting cardiopulmonary function during exercise. Standard noninvasive technologies estimating cardiac output have major limitations with regard to the applicability during routine clinical care (15). Very recently, Sano *et al.* (16) found that the change in PWTT predicts

fluid responsiveness in mechanically ventilated anesthetized dogs given a fluid challenge. Suzuki *et al.* (17) also reported the usefulness of estimating cardiac output by PWTT at resting condition in patients after cardiovascular surgeries. Based on the findings of the recent reports and our study, monitoring of PWTT during exercise testing would provide noninvasive, and continuous estimate of cardiac output during exercise.

4.3. Limitations

PWTT during the whole period from rest to peak exercise could not be obtained in 13.6 % of the patients investigated in this study. The PWTT values were missing most often near the point of peak exercise, probably as consequence of noise in the electrocardiogram caused by body movement or failure of the adhesive used to attach the oxygen saturation monitor to the earlobe. In the present study, 2 patients with atrial fibrillation and 3 patients with a pacemaker were included. Although the PWTT could be clearly recorded in these subjects, there is the possibility that the PWTT measurement might be influenced by the presence of atrial fibrillation or pacemakers. The small number of patients in the study precluded any subgroup analysis to consider parameters such as heart

failure with reduced or preserved EF or the cardiac disease etiology. The patients with heart failure were more frequently prescribed medications that may have influenced the circulatory response, such as antihypertensive drugs and beta-blockers. The effects of these medications might be the reason for the higher exercise PWTT in the heart failure group compared to the non-heart failure group. Therefore, the consideration to choose a research design that can exclude the effects of these medications would have been desirable.

4.4. Future directions

Monitoring of PWTT during exercise testing might be useful as a noninvasive estimate of cardiac output during exercise. Further study in a larger population of cardiac patients will be needed to establish the clinical significance of PWTT during exercise.

4.5. Conclusions

PWTT was shortened during exercise as the exercise intensity increased. In the patients with heart failure, the shortening of PWTT from rest to peak exercise was smaller in those with lower exercise capacity and those with higher VE-VCO₂ slope, an established index known to reflect the severity of heart failure.

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