Clinical Significance of a Spiral Phenomenon in the Plot of CO_2 Output versus O_2 Uptake During Exercise in Cardiac Patients

Running head: Spiral phenomenon in VCO_2-versus-VO_2 plot

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ABSTRACT

A spiral phenomenon is sometimes noted in the plots of CO_2 output (VCO_2) against O_2 uptake (VO_2) measured during cardiopulmonary exercise testing (CPX) in heart failure patients with oscillatory breathing. However, few data are available that elucidate the clinical significance of this phenomenon. Our group studied the prevalence of this phenomenon and its relation to cardiac and cardiopulmonary function. Among 2,263 cardiac patients who underwent CPX, 126 patients with a clear pattern of oscillatory breathing were identified. Cardiopulmonary indices were compared between patients who showed the spiral phenomenon (n=49) and those who did not (n=77). The amplitudes of VO_2 and VCO_2 oscillations were higher and the phase difference between VO_2 and VCO_2 oscillations was longer in the patients with the spiral phenomenon than in those without it. Patients with the spiral phenomenon also had a lower left ventricular ejection fraction (43.4±21.4 vs. 57.1±16.8 %, $p<0.001$) and a higher level of brain natriuretic peptide (637.2±698.3 vs. 228.3±351.4 pg/mL, $p=0.002$). The peak VO_2 was lower (14.5±5.6 vs. 18.1±6.3, $p=0.002$), the VE-VCO_2 slope was higher (39.8±9.5 vs. 33.6±6.8, $p<0.001$), and $PETCO_2$ both at rest and at peak exercise was lower in the patients with the spiral phenomenon than in those without it. In conclusion, the spiral phenomenon in the VCO_2-versus-VO_2 plot arising from the phase difference between VCO_2 and VO_2 oscillations reflects more advanced cardiopulmonary dysfunction in cardiac patients with oscillatory breathing.

KEY WORDS: cardiopulmonary function, oscillatory breathing, exercise testing

Oscillatory breathing in cardiac patients, a characteristic breathing pattern alternating between hyperpnea and hypopnea, can be evaluated in detail by cardiopulmonary exercise testing (CPX) [1]. Several valuable indices are obtained from CPX, including the peak O_2 uptake (VO_2), the slope of the increase in ventilation (VE) versus the increase in CO_2 output (VCO_2) (VE-VCO_2 slope), and the anaerobic threshold (AT). During incremental exercise below the AT, VCO_2 increases approximately linearly with VO_2, and its slope is theoretically 1.0 or slightly less [2]. The slope above the AT becomes greater than 1.0, because lactic acid is buffered by bicarbonate, resulting in the formation of carbonic acid, which dissociates to water and CO_2 [2]. A peculiar spiral (vortex) phenomenon progressing in a counterclockwise direction is sometimes recognized in the plot of VCO_2 against VO_2 during CPX in heart failure patients with oscillatory breathing [3]. In the present study we determined how frequently the spiral phenomenon can be observed during CPX in cardiac patients with oscillatory breathing and evaluated whether this phenomenon is related to impaired cardiopulmonary function.

METHODS

The subjects for this study were 2,263 consecutive cardiac patients who underwent CPX at the Cardiovascular Institute for the evaluation of exercise capacity and/or severity of heart failure between January 2010 and December 2013. By visual observation, we identified all of subjects who manifested at least three consecutive cycles of clear ventilatory oscillations during the period from the beginning of warm-up exercise until the end of

incremental exercise. After determining the amplitude (difference between the peak and nadir) of each VE oscillation, we calculated the percentage amplitude by dividing the amplitude by the mean VE during each oscillation and then calculated the mean value of all oscillations. Thereafter, we selected 126 subjects whose amplitudes were greater than 25 % of the mean VE, based on the report from Murphy et al. [4]. The research protocol was approved by the human subjects committee of the Cardiovascular Institute. The patients were apprised of the purposes and risks of the study, and all of them gave their informed consent.

A symptom-limited incremental 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 a 4-min rest on the ergometer followed by a 4-min warm-up at 0 W or 20 W at 60 rpm. The load was then increased incrementally by 1 W every 6 seconds (10 W/min). VO_2, VCO_2, and VE were measured throughout the test using an Aeromonitor AE-300s (Minato Medical Science, Osaka, Japan), as previously described [5]. Before the parameters from the respiratory gas analysis were calculated, 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 five-point moving average.

The peak VO_2 was calculated as the average values obtained during the last 15 seconds of incremental exercise. The percentage of peak VO_2 was calculated by dividing the measured peak VO_2 by the predicted peak VO_2. The predicted peak VO_2 was determined based on a normal Japanese population [6]. The gas exchange ratio, which is equal to

VCO_2/VO_2, was calculated during the last 15 seconds of incremental exercise. The VE-VCO_2 slope during incremental exercise was calculated by a method previously reported [7]. The end-tidal PCO_2 ($PETCO_2$) at rest was calculated as the average values obtained during the 4 minutes of rest. The $PETCO_2$ at peak exercise was calculated as the average of values obtained during the last 15 seconds of incremental exercise.

The amplitude of the oscillating VE was calculated as the difference between the peak and nadir of the oscillating VE for each of the cycles noted from the beginning of warm-up exercise until the end of incremental exercise, and expressed as a mean value. The percentage amplitude was calculated by dividing the amplitude by the mean VE during each oscillation, and expressed as a mean value of all oscillations. The cycle length of the oscillating VE was calculated as the interval from the peak to the following peak of the oscillating VE for each of the cycles, and expressed as a mean value. The amplitude and cycle length of the oscillating VO_2 and VCO_2 were calculated by a similar approach. The oscillatory pattern of VO_2 usually precedes VCO_2 (Figure 1). Thus, the time difference between the peak of the oscillating VO_2 and the corresponding peak of the oscillating VCO_2 (time from the peak of the oscillating VCO_2 – time of the corresponding peak of the oscillating VO_2) was calculated for each of the cycles and expressed as a mean value. A spiral phenomenon, defined as at least three consecutive counterclockwise changes in the VCO_2-versus-VO_2 plot (i.e., a movement from a left lower side to a right upper side, then slightly to a left upper side, and back to the left lower side, forming an ellipse), was visually identified (Figure 1, panel B for an example of the spiral pattern in a representative subject).

The cardiopulmonary indices were compared between patients who manifested the spiral phenomenon and those who did not.

Data are presented as the mean ± SD. Intergroup differences for variables were compared by the unpaired t-test, or by the Fisher's exact test where appropriate. Linear regression analysis was used to correlate the measured variables. All analyses were performed using SPSS version 19.0 software (SPSS Inc., Chicago, Illinois) for Windows (Microsoft Corporation, Redmond, Washington). A p value of less than 0.05 was considered statistically significant for all comparisons.

RESULTS

The peculiar spiral phenomenon was noted in the plots of VCO_2 against VO_2 during CPX in 39% of the cardiac patients with oscillatory breathing. There were no significant differences in gender, age, height, weight, body mass index, or cardiac disease etiology between the patients with and without the spiral phenomenon, though idiopathic dilated cardiomyopathy was more frequent among the former (Table 1).

Similar to the oscillating VE, clear oscillatory changes were noted in both the VO_2 and VCO_2 in the study population overall. The amplitudes and cycle lengths of the VE, VO_2, and VCO_2 oscillations were all higher in the patients with the spiral phenomenon than in those without it (Table 2). The VO_2 oscillations were found to precede the VCO_2 oscillations in 95 of the 126 subjects. The VCO_2 oscillations preceded the VO_2 oscillations in only one subject, and only by a slight degree. No phase difference between the VO_2 and VCO_2

oscillations was observed in the remaining 30 patients. The mean phase difference between the VO_2 and VCO_2 oscillations was 2.2±2.7 sec in both groups combined, and was significantly larger in the patients with the spiral phenomenon than in those without it (4.4±3.0 sec vs. 0.7±0.8 sec, $p<0.001$). The phase difference between the VCO_2 and VE oscillations was 0.8±1.0 sec in both groups combined and did not differ between the two groups.

The left ventricular ejection fraction (LVEF) measured by echocardiography was significantly lower in the patients with the spiral phenomenon than in the patients without the spiral phenomenon (Table 2). The level of brain natriuretic peptide (BNP), a parameter measured in 87 out of the 126 patients, was significantly higher in the patients with the spiral phenomenon than in those without it. Meanwhile, the patients with the spiral phenomenon had a significantly lower peak VO_2. The VE-VCO_2 slope was significantly higher in the patients with the spiral phenomenon than in those without it. $PETCO_2$ both at rest and at peak exercise was significantly lower in the patients with the spiral phenomenon than in those without it.

Figure 2 shows the relation between cardiopulmonary indices and the cycle length of the VO_2 oscillations. The cycle length of the VO_2 oscillations showed significant positive correlations with the BNP and VE-VCO_2 slope, and significant negative correlations with the LVEF and peak VO_2. Figure 3 shows the relation between cardiopulmonary indices and phase difference between the VO_2 and VCO_2 oscillations. The phase difference showed significant positive correlations with the BNP and VE-VCO_2 slope, and significant negative

correlations with the LVEF and peak VO_2.

DISCUSSION

In the present study we investigated the clinical significance of the spiral phenomenon in the VCO_2-versus-VO_2 plot recorded during CPX in patients with oscillatory breathing. According to our experiments, 39% of the cardiac patients with oscillatory breathing manifested the spiral phenomenon during exercise. The amplitudes of VO_2 and VCO_2 oscillations were higher and the phase difference between VO_2 and VCO_2 oscillations was longer and in the patients with the spiral phenomenon than in those without it. The patients with the spiral phenomenon exhibited a lower LVEF, higher BNP, lower peak VO_2, higher VE-VCO_2 slope, and lower $PETCO_2$ than the patients without the spiral phenomenon. The patients with the spiral phenomenon also exhibited the lower heart rate and lower systolic blood pressure at peak exercise, suggesting lower cardiac output during exercise in these patients. Judging from these findings, we concluded that the spiral phenomenon was related to cardiopulmonary dysfunction and could be directly attributed both to the phase difference between the VO_2 and VCO_2 and to the higher amplitudes of the VO_2 and VCO_2 oscillations.

The VE-VCO_2 slope relates mainly to a ventilation/perfusion (V/Q) mismatch, and progressively steepens in patients with heart failure of worsening severity resulting from either systolic or diastolic dysfunction [8,9]. In patients with left ventricular dysfunction, as the hypo-perfusion to the lung caused by reduced pulmonary blood flow exacerbates the V/Q mismatch (high V/Q), leading to progressively lower $PETCO_2$ as the cardiac disease worsens

[1,10,11]. The lower peak VO_2, higher VE-VCO_2 slope, and lower $PETCO_2$ observed in patients with the spiral phenomenon suggest that the cardiopulmonary dysfunction is more advanced in these patients than in the patients without the spiral phenomenon.

Instability of the respiratory control system is believed to be a major cause of not only central sleep apnea, but also oscillatory breathing during exercise. In 1994, Yajima et al. [12] reported that cardiac patients with oscillatory breathing present oscillatory changes in LVEF with a similar cyclical nature. Since then, fluctuation of the pulmonary blood flow has been proposed as another possible mechanism underlying oscillatory breathing [5,12,13]. VO_2 oscillation, a phenomenon reflective of a change of pulmonary blood flow, preceded the VCO_2 and VE oscillations in most of the subjects in our study. If the VE changes primarily due to a stimulus from the central nervous system to the respiratory muscles, the change of VE must precede the change of VO_2. Our findings may therefore further support the central hypothesis, namely, that fluctuations in the pulmonary blood flow produce oscillatory breathing.

The spiral phenomenon in the VCO_2-versus-VO_2 plot probably derives from both the high amplitudes of the VO_2 and VCO_2 oscillations and the longer phase difference between the oscillations. The VCO_2 kinetics is reported to be slower than the VO_2 kinetics during the onset of exercise [14,15], although the mechanisms responsible for the phase difference between the VO_2 and VCO_2 kinetics are complicated and still undetermined. During mild to moderate exercise, ventilation normally increases at the rate required to remove the additional CO_2 generated in order to keep the arterial PCO_2 and pH close to their

resting values [2,15]. Thus, the VE kinetics is usually closely related to the VCO_2 kinetics during exercise [15]. And this, in turn, suggests that the phase difference between the VO_2 and VCO_2 oscillations probably stems not only from the prolonged physiological delay of the VCO_2 kinetics, but also from the delay of the ventilatory response to the fluctuations of the pulmonary CO_2 flow. The latter, in particular, may relate to prolonged circulation time which is known to increase with the severity of heart failure.

There are several limitations in this study. The BNP was obtained only in 87 out of 126 patients in the present study. Our criterion for enrolling subjects with oscillatory breathing was at least three consecutive cycles with an amplitude of greater than 25%. The frequency of the spiral phenomenon in cardiac patients depends on the specific definition used for determining the oscillatory breathing, as well as the severity and/or etiology of cardiac disease in the study population. While β-blockers, diuretics, and digitalis were prescribed more frequently in the patients with spiral phenomenon, we could not clearly determine whether one or more of these medications diminished or enhanced the spiral phenomenon. We could not perform a subgroup analysis stratified by heart failure in patients with preserved versus reduced LVEF. We also do not know the relation between the spiral phenomenon and diastolic LV function. A larger study population would be necessary to clarify these issues. Among 2,263 patients who were screened for oscillatory breathing, the exercise tests of 102 patients (4.5%) were prematurely stopped due to adverse signs or symptoms, potentially precluding them from attaining maximum effort.

To our knowledge, this is the first report linking the mechanisms and clinical

significance of the spiral phenomenon in the VCO_2-versus-VO_2 plot in cardiac patients. Our findings indicate that the spiral phenomenon is a novel marker of cardiopulmonary dysfunction during exercise. We believe that the spiral phenomenon can be used to stratify patients with heart failure, although long term follow-up and additional prognostic studies are needed to establish the clinical role of this phenomenon.

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FIGURE LEGENDS

Figure 1. Panel A: Changes in the O_2 uptake (VO_2), CO_2 output (VCO_2), and gas exchange ratio (R) during cardiopulmonary exercise testing in a patient with the spiral phenomenon. Panel B: VCO_2-versus-VO_2 plot produced from the data of panel A. Panel C: Changes in VO_2, VCO_2, and R during cardiopulmonary exercise testing in a patient without the spiral phenomenon. Panel D: VCO_2-versus-VO_2 plot produced from the data of panel C.

Figure 2. Brain natriuretic peptide (BNP) (panel A), left ventricular ejection fraction (LVEF) (panel B), peak O_2 uptake (VO_2) (panel C), and slope of the increase in ventilation versus the increase in CO_2 output (VE-VCO_2 slope) (panel D) plotted against the cycle length of VO_2 oscillations.

Figure 3. Brain natriuretic peptide (BNP) (panel A), left ventricular ejection fraction (LVEF) (panel B), peak O_2 uptake (VO_2) (panel C), and slope of the increase in ventilation versus the increase in CO_2 output (VE-VCO_2 slope) (panel D) plotted against the phase difference between VO_2 and VCO_2 oscillations.

Table 1. Patient characteristics in patients with and without a spiral phenomenon

Characteristics	All patients (n = 126)	A Spiral Phenomenon YES (n = 49)	NO (n = 77)	p value
Male/female	103 / 23	42 / 7	61 / 16	NS
Age (years)	63 ± 12	65 ± 11	61 ± 13	NS
Height (cm)	166 ± 8	165 ± 8	167 ± 9	NS
Weight (kg)	65 ± 13	65 ± 13	65 ± 12	NS
Body mass index (kg/m^2)	24 ± 4	24 ± 4	23 ± 4	NS
Etiology				
Valvular disease	35 (28%)	14 (29%)	21 (27%)	NS
Coronary artery disease	35 (28%)	12 (24%)	23 (30%)	NS
Idiopathic dilated cardiomyopathy	20 (16%)	12 (24%)	8 (10%)	0.035
Hypertrophic cardiomyopathy	10 (8%)	2 (4%)	8 (10%)	NS
Other cardiac disease	26 (21%)	9 (18%)	17 (22%)	NS
Medication				
β-blockers	82 (65%)	40 (82%)	42 (55%)	0.002
ACEI/ARB	67 (53%)	26 (53%)	41 (53%)	NS
Diuretics	62 (49%)	32 (65%)	30 (39%)	0.004
Ca-channel blockers	33 (26%)	10 (20%)	23 (30%)	NS
Nitrates	20 (16%)	9 (18%)	11 (14%)	NS
Digitalis	7 (6%)	7 (14%)	0	0.001

Data are presented as the mean ± SD.

ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker;

NS, not significant.

Table 2. Patient characteristics in patients with and without a spiral phenomenon

Characteristics	All patients	A Spiral Phenomenon		p value
		YES	NO	
	(n = 126)	(n = 49)	(n = 77)	
At rest				
Creatinine (mg/dL)	1.1 ± 0.8	1.3 ± 1.2	0.9 ± 0.3	0.039
Brain natriuretic peptide (pg/mL)	398 ± 558	637 ± 698	228 ± 351	0.002
Left ventricular ejection fraction (%)	52 ± 20	43 ± 21	57 ± 17	<0.001
Left ventricular diastolic dimension (mm)	54 ± 12	59 ± 14	51 ± 9	0.001
Left ventricular systolic dimension (mm)	40 ± 15	47 ± 17	36 ± 12	<0.001
Heart rate (beats/min)	75 ± 16	76 ± 16	75 ± 15	NS
Systolic blood pressure (mmHg)	115 ± 24	109 ± 26	119 ± 22	0.018
Diastolic blood pressure (mmHg)	73 ± 15	71 ± 16	75 ± 14	NS
End-tidal PCO_2 (mmHg)	32 ± 4	31 ± 4	33 ± 4	0.007
At peak exercise				
Heart rate (beats/min)	125 ± 33	117 ± 29	130 ± 35	0.026
Systolic blood pressure (mmHg)	163 ± 38	149 ± 42	172 ± 33	0.001
Diastolic blood pressure (mmHg)	81 ± 20	80 ± 21	82 ± 19	NS
End-tidal PCO_2 (mmHg)	35 ± 5	33 ± 5	36 ± 5	0.001
Gas exchange ratio	1.10 ± 0.10	1.09 ± 0.11	1.11 ± 0.09	NS
Peak VO_2 (mL/min/kg)	16.7 ± 6.3	14.5 ± 5.6	18.1 ± 6.3	0.002
Peak VO_2 (%)	67 ± 23	60 ± 23	72 ± 21	0.006
VE-VCO_2 slope	36 ± 9	40 ± 10	34 ± 7	<0.001
Amplitude of VE (L/min)	6.3 ± 2.2	7.5 ± 2.5	5.6 ± 1.7	<0.001
Amplitude of VE (%)	38 ± 13	45 ± 15	34 ± 10	<0.001
Cycle length of VE (sec)	57 ± 16	65 ± 19	51 ± 12	<0.001
Amplitude of VO_2 (mL/min)	186 ± 64	203 ± 70	176 ± 58	0.023
Amplitude of VO_2 (%)	46 ± 16	52 ± 19	42 ± 13	0.002
Cycle length of VO_2 (sec)	56 ± 16	65 ± 17	51 ± 11	<0.001
Amplitude of VCO_2 (mL/min)	168 ± 56	187 ± 57	155 ± 52	0.002
Amplitude of VCO_2 (%)	46 ± 16	53 ± 18	41 ± 14	<0.001
Cycle length of VCO_2 (sec)	56 ± 17	65 ± 19	51 ± 11	<0.001
Phase difference between VO_2 and VCO_2 (sec)	2.2 ± 2.7	4.4 ± 3.0	0.7 ± 0.8	<0.001

The brain natriuretic peptide was obtained in 87 patients (36 patients with a spiral phenomenon and 51 patients without it).
Data are presented as the mean ± SD.

Figure 1

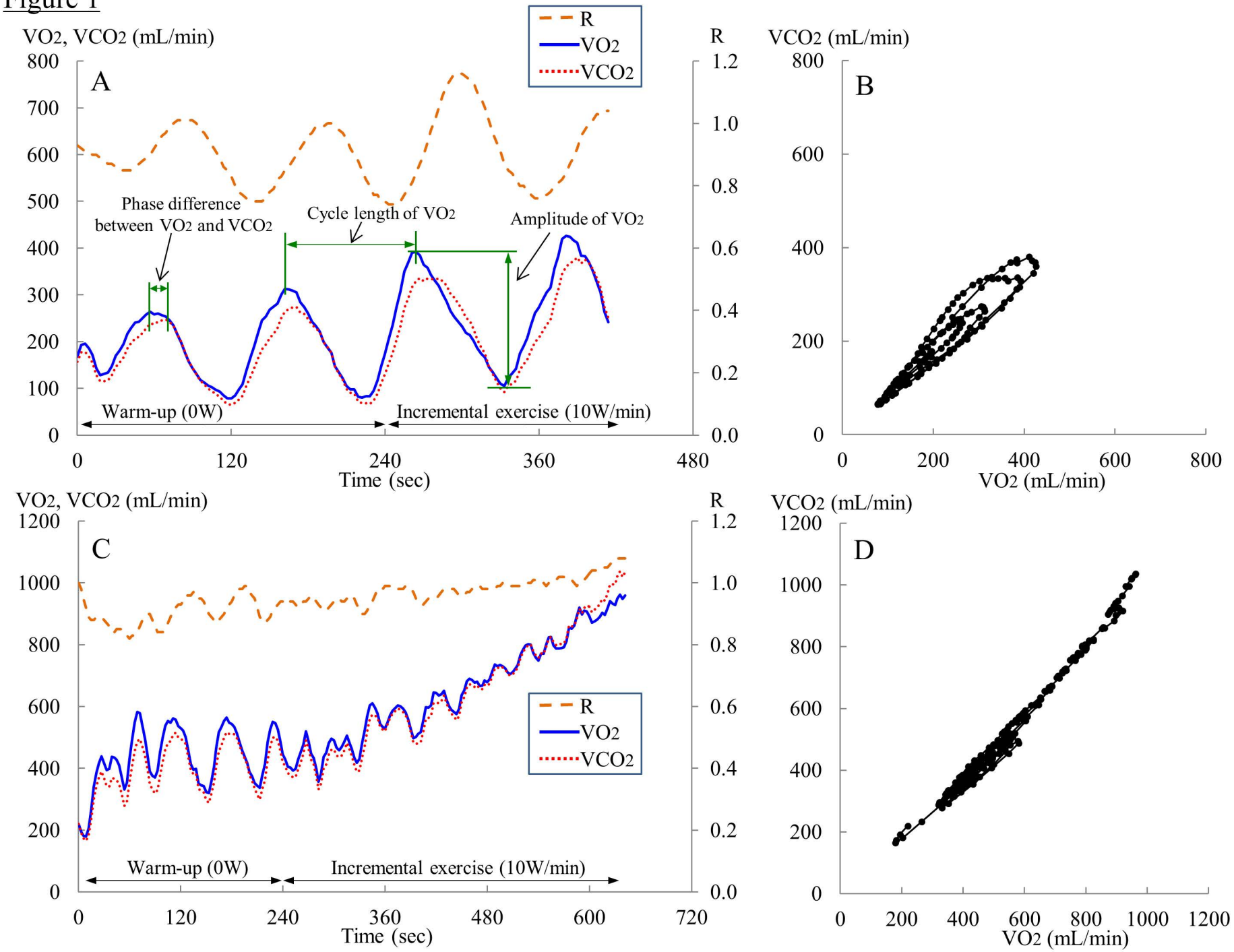

A
VO2, VCO2 (mL/min)
R
R
VO2
VCO2
Phase difference between VO2 and VCO2
Cycle length of VO2
Amplitude of VO2
Warm-up (0W)
Incremental exercise (10W/min)
Time (sec)
B
VCO2 (mL/min)
VO2 (mL/min)
C
VO2, VCO2 (mL/min)
R
R
VO2
VCO2
Warm-up (0W)
Incremental exercise (10W/min)
Time (sec)
D
VCO2 (mL/min)
VO2 (mL/min)

Figure 2

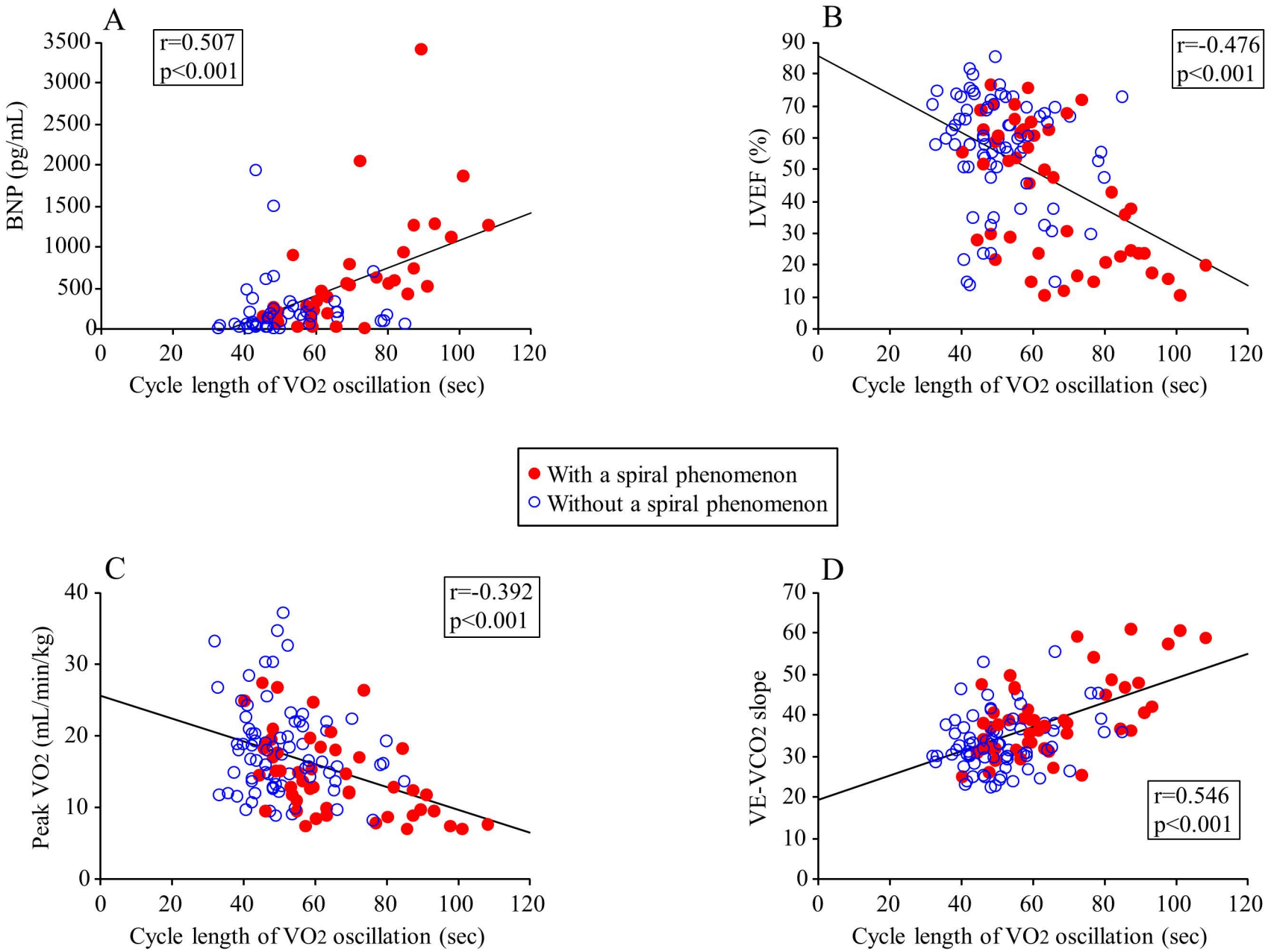
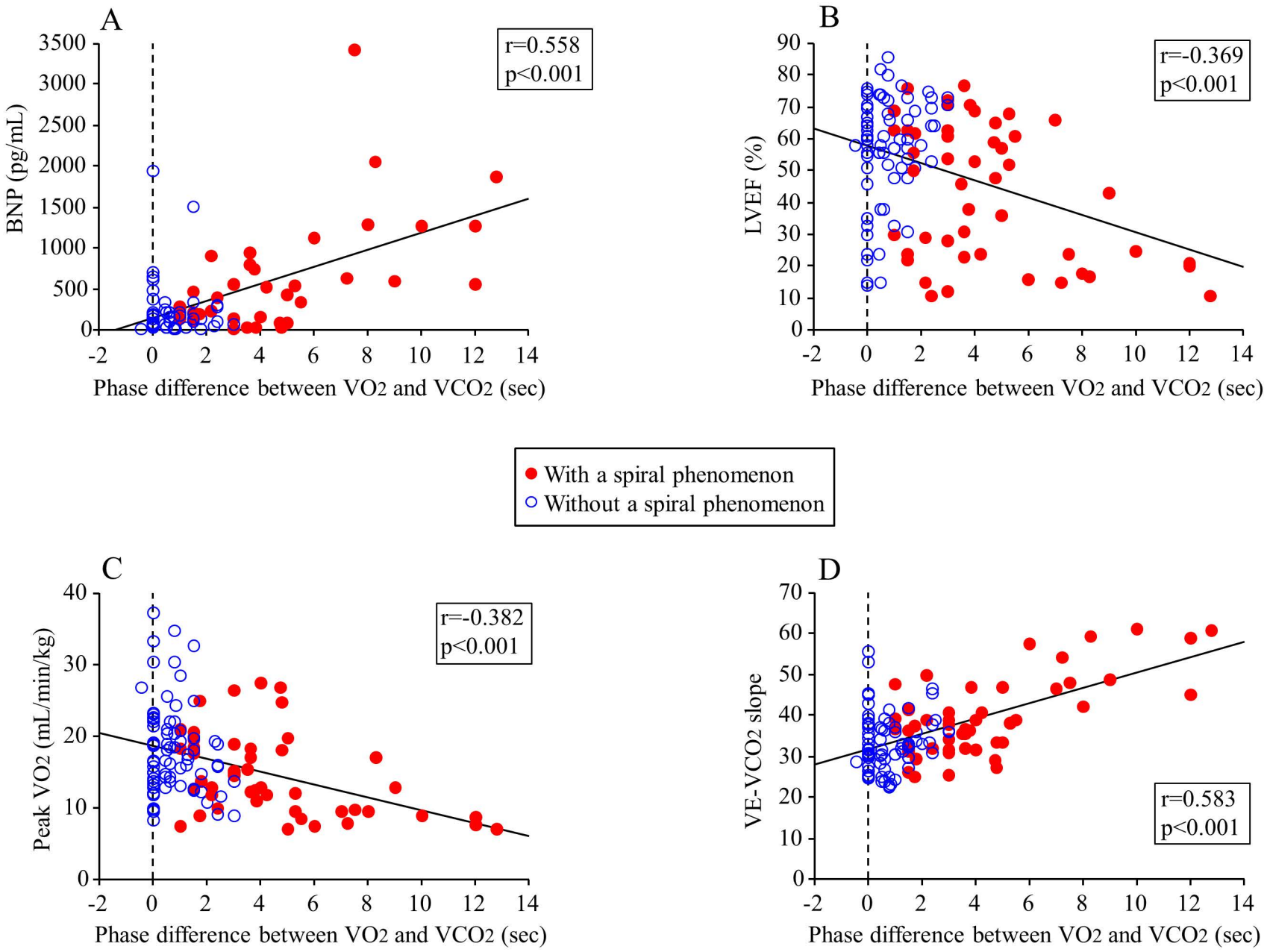

A
r=0.507
p<0.001
BNP (pg/mL)
Cycle length of VO2 oscillation (sec)
B
r=-0.476
p<0.001
LVEF (%)
Cycle length of VO2 oscillation (sec)
With a spiral phenomenon
Without a spiral phenomenon
C
r=-0.392
p<0.001
Peak VO2 (mL/min/kg)
Cycle length of VO2 oscillation (sec)
D
r=0.546
p<0.001
VE-VCO2 slope
Cycle length of VO2 oscillation (sec)

Figure 3


A
BNP (pg/mL)
r=0.558
p<0.001
Phase difference between VO2 and VCO2 (sec)
B
LVEF (%)
r=-0.369
p<0.001
Phase difference between VO2 and VCO2 (sec)
With a spiral phenomenon
Without a spiral phenomenon
C
Peak VO2 (mL/min/kg)
r=-0.382
p<0.001
Phase difference between VO2 and VCO2 (sec)
D
VE-VCO2 slope
r=0.583
p<0.001
Phase difference between VO2 and VCO2 (sec)