Effect of a cardiac rehabilitation program on exercise oscillatory ventilation in Japanese patients with heart failure

Fumitake Yamauchi • Hitoshi Adachi, • Jun-ichi Tomono • Shigeru Toyoda • Koichi Iwamatsu • Masashi Sakuma • Toshiaki Nakajima • Shigeru Oshima • Teruo Inoue

Yamauchi F • Adachi H • Tomono J • Iwamatsu K • Oshima S

Department of Cardiovascular Medicine, Gunma Prefectural Cardiovascular Center, Maebashi, Gunma, Japan

Yamauchi F • Toyoda S (✉) • Sakuma M • Nakajima T • Inoue T

Department of Cardiovascular Medicine, Dokkyo Medical University, Mibu, Tochigi, Japan

Nakajima T

Heart Center, Dokkyo Medical University Hospital, Mibu, Tochigi, Japan

For correspondence: Shigeru Toyoda, MD, PhD

Department of Cardiovascular Medicine, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Tochigi 321-0293, Japan

TEL: +81-282-87-2146

FAX: +81-282-86-5633

E-mail: s-toyoda@dokkyomed.ac.jp

Abstract

Although exercise oscillatory ventilation has emerged as a potent independent risk factor for adverse prognosis in heart failure, it is not well-known whether cardiac rehabilitation can improve oscillatory ventilation. In this study, we investigated the magnitude of oscillations in ventilation before and after cardiac rehabilitation in chronic heart failure patients with exercise oscillatory ventilation. Cardiac rehabilitation (5-month program) was performed in 26 patients with chronic heart failure who showed an oscillatory ventilation pattern during cardiopulmonary exercise testing (CPX). After the 5-month rehabilitation program was completed, the patients again underwent CPX. To determine the magnitude of oscillations in ventilation, the amplitude and cycle length of the oscillations were calculated and compared with several other parameters, including biomarkers that have established prognostic value in heart failure. At baseline before cardiac rehabilitation, both oscillation amplitude ($R=0.625$, $P<0.01$) and cycle length ($R=0.469$, $P<0.05$) were positively correlated with the slope of minute ventilation vs. carbon dioxide production. Plasma BNP levels were positively correlated with amplitude ($R=0.615$, $P<0.01$) but not cycle length ($R=0.371$). Cardiac rehabilitation decreased oscillation amplitude ($P<0.01$) but failed to change cycle length. The change in amplitude was positively correlated with the change in BNP levels ($R=0.760$, $P<0.01$). Multiple regression analysis showed that only the change in amplitude was an independent predictor of the change in BNP levels ($R=0.717$, $P<0.01$). A 5-month cardiac rehabilitation program improves exercise oscillatory ventilation in chronic heart failure patients by reducing the oscillation amplitude. This effect is associated with a reduction of plasma BNP levels, potentially contributing to an improvement of heart failure.

Key words: exercise oscillatory ventilation, oscillation amplitude, chronic heart failure, cardiopulmonary exercise testing, brain natriuretic peptide

Introduction

Exercise oscillatory ventilation is characterized by the regular alternation of hyperpnea and hypopnea during exercise without interposed apnea [1], which distinguished it from other forms of periodic breathing observed in heart failure patients including Cheyne-Stokes respiration or central sleep apnea [2-4]. Exercise oscillatory ventilation has been observed in 19-58% of heart failure patients [5-10] and has emerged as a potent independent risk factor for adverse prognosis in heart failure that is additive to traditional echocardiographic and metabolic indices of clinical risk [5, 7, 9-12]. Treatment with sildenafil has been reported to decrease the amplitude and cycle length of oscillatory ventilation [13]. However, there are no established therapeutic approaches to improve oscillatory ventilation during exercise. In addition, it has not been elucidated whether interventions that reduce exercise oscillatory ventilation lead to an improvement of prognosis in heart failure.

Exercise-based cardiac rehabilitation is well-known for its safety and effectiveness to improve exercise capacity and quality of life in patients with heart failure [14-16]. In addition, there is evidence that exercise training improves the long-term prognosis of heart failure in terms of all-cause mortality, cardiovascular mortality and hospitalization [15]. Zurek et al. [17] reported that exercise training leads to a significant decrease of oscillatory ventilation and improves ventilatory efficiency in heart failure patients. However, it still remains uncertain whether cardiac rehabilitation can ameliorate the oscillatory ventilation in heart failure patients.

In this study, we hypothesized that cardiac rehabilitation can improve exercise oscillatory ventilation, leading in part to an improvement of prognosis in heart failure patients. To test our hypothesis, we selected chronic heart failure patients with exercise oscillatory

ventilation from patients who underwent cardiopulmonary exercise testing (CPX), and enrolled these patients in a 5-month cardiac rehabilitation program. We investigated changes in parameters for the magnitude of exercise oscillatory ventilation after cardiac rehabilitation and compared them with several other parameters, including biomarkers that have established prognostic value in heart failure.

Methods

Patient selection and study design

We selected patients with chronic heart failure who showed an oscillatory ventilation pattern during exercise from consecutive outpatients who underwent CPX between January 2008 and December 2013 at Gunma Prefectural Cardiovascular Center. The patients with exercise oscillatory ventilation were entered into a 5-month cardiac rehabilitation program. After the rehabilitation program was completed, the patients again underwent CPX. Echocardiography and blood testing were also performed at baseline before starting rehabilitation and at follow-up after the rehabilitation program was completed. This study was approved by the ethics committee of Gunma Prefectural Cardiovascular Center. Written informed consent was obtained from all patients.

Cardiopulmonary exercise testing

CPX was performed using an upright, calibrated cycle ergometer (CPE2000, MedGraphics Co., St. Paul, MN, USA) 2-4 h after eating a light meal. The test began with 3 min of rest and 3 min of warm-up at 0 W, followed by a continuously increasing work rate of 1 W every 6 sec until exhaustion. The levels of work-rate increase were chosen on the basis

of ability of the subjects to complete an exercise program lasting between 8 and 15 min [18]. The anaerobic threshold (AT) was determined by the V-slope method [19]. Oxygen uptake ($\dot{V}O2$), carbon dioxide production ($\dot{V}CO2$) and minute ventilation ($\dot{V}E$) were measured on a breath-by-breath basis using an aeromonitor (MINATO 300S, Minato Science Co. Ltd., Osaka, Japan). The slope of the $\dot{V}E$ vs. $\dot{V}CO2$ relationship was calculated by linear regression analysis using the values of $\dot{V}E$ and $\dot{V}CO2$. Because the relationship between $\dot{V}E$ and $\dot{V}CO2$ during the period of incremental exercise exceeded the respiratory compensation point, the slope of $\dot{V}E$ vs. $\dot{V}CO2$ was calculated below the respiratory compensation point. The dead space was likely to be the same during the first and second CPX study, because the same type and size of face mask were used in both studies.

Exercise oscillatory ventilation: definition and magnitude assessment

For the definition of exercise oscillatory ventilation, we chose the criteria described by Leite et al. [20] as follows: 1) at least three oscillatory fluctuations in $\dot{V}E$ during warm-up and exercise; 2) regular oscillations, as defined by a standard deviation of three consecutive cycle length durations (time between two consecutive nadirs) within 20% of the average; and 3) a minimal average ventilation amplitude of $\geq$5 L, defined as peak $\dot{V}E$ of one oscillation minus the average of two adjacent nadirs. To determine the magnitude of oscillatory ventilation, the amplitude of oscillating $\dot{V}E$ was calculated as the difference between the peak and nadir of oscillating $\dot{V}E$ for each of the cycles noted, and then expressed as the mean value. The cycle length of oscillating $\dot{V}E$ was also calculated as the interval from the peak to the following peak of oscillating $\dot{V}E$ for each of the cycles noted, and then expressed as the mean value (Fig. 1).

Echocardiography and blood testing

Transthoracic echocardiography was performed with the patients in the left lateral decubitus position using a Vivid 7 (GE Vingmed Ultrasound AS, Horten, Norway) system. Left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes were calculated using the modified Simpson method. Left ventricular ejection fraction (LVEF) was calculated as (LVEDV-LVESV) × 100/LVEDV (%). Tricuspid regurgitation velocity was measured from the highest peak velocity obtained with continuous pulsed-wave Doppler through the tricuspid valve using multiple views. Right ventricular systolic pressure (RVSP) was calculated from the tricuspid regurgitation velocity and right atrial pressure (estimated by inspection of the inferior vena cava) using the modified Bernoulli equation. Left ventricular diastolic transmitral flow was recorded at the mitral valve leaflet in the pulsed-Doppler apical view. The peak early diastolic flow velocity (E) and early diastolic mitral annular velocity (E') were determined, and the E to E' ratio (E/E') was calculated.

Blood testing included the levels of hemoglobin, creatinine, sodium and potassium, which were automatically measured. Plasma BNP levels were also measured using a specific immunoradiometric assay kit (Shionoria BNP kit, Shionogi, Osaka, Japan). BNP levels were obtained in 18 of the 26 patients before and after cardiac rehabilitation. The assay uses 2 monoclonal antibodies, which recognize the carboxyterminal sequence and ring structure of human BNP. The minimal detectable quantity of BNP is 2 pg/mL. The intra- and inter-assay coefficients of variation were 5.3% and 5.9%, respectively.

Cardiac rehabilitation program

Exercise training was performed at the intensity of the AT level [19]. Patients underwent supervised exercise including both aerobic and resistance training of 30

min/session, which was performed 3 times a week for 5 months, namely, total of 60 sessions. Our rehabilitation program is a wide and comprehensive program of exercise training that also includes psychological and nutritional consultation, blood pressure control, blood lipid control, blood sugar control, smoking cessation and other risk factor modifications.

Statistical analysis

All data are expressed as the mean±standard deviation. The change in parameters was calculated as the follow-up value as a percent of the baseline value. The significance of changes in parameters from baseline to follow-up was assessed by the paired t-test. Linear regression analysis was performed to explore the relationship between two parameters. Multiple regression analysis was performed for predicting the change in plasma BNP levels using changes in CPX parameters. A P value < 0.05 was considered significant.

Results

For 6 years, between January 2008 and December 2013, a total of 3933 consecutive patients underwent CPX. Among them, 26 patients (0.66%) showed an oscillatory ventilation pattern during exercise testing. Baseline characteristics of these 26 patients are shown in Table 1. During the 5-month cardiac rehabilitation program, medications were not changed in any of the 26 patients. Of total 60 sessions rehabilitation program, the frequency of participation was 23±12 sessions in overall 26 patients.

Table 2 shows the blood test results, echocardiographic findings and CPX parameters at baseline and after 5 months of cardiac rehabilitation. After the cardiac rehabilitation

program was completed, there was a significant decrease in both plasma BNP levels ($P<0.05$) and RVSP ($P<0.05$). The value of AT significantly increased ($P<0.05$), the peak $\dot{V}O_2$ tended to increase ($P=0.05$) and the $\dot{V}E$ vs. $\dot{V}CO_2$ slope tended to decrease ($P=0.08$). After the cardiac rehabilitation program was completed, the oscillatory ventilation pattern during exercise testing was still remained in all of the 26 patients. For the magnitude of oscillatory ventilation, however, the oscillation amplitude decreased significantly ($P<0.01$), while there was no significant change in the oscillation cycle length. Figure 2 is the representative images of the changes in $\dot{V}E$ in a case (66 yr-old male), in whom oscillatory ventilation was improved. After the cardiac rehabilitation, the oscillation amplitude decreased (17.4 to 10.3 L/min) but the oscillation cycle length did not change (62 to 64 sec).

At baseline, the oscillation amplitude and oscillation cycle length were correlated each other ($R=0.483$, $P<0.05$). Each of the amplitude ($R=0.625$, $P<0.01$, Fig. 3A) and cycle length ($R=0.469$, $P<0.05$, Fig. 3B) was positively correlated with the $\dot{V}E$ vs. $\dot{V}CO_2$ slope. Plasma BNP levels were positively correlated with the amplitude ($n=18$, $R=0.615$, $P<0.01$, Fig. 3C) but not the cycle length ($R=0.371$, Fig. 3D). After the rehabilitation program was completed, changes in amplitude and cycle length tended to be correlated each other ($R=0.402$, $P=0.05$). Neither the change in amplitude ($n=24$, $R=0.028$, Fig 4A) nor the change in cycle length ($n=24$, $R=0.250$, Fig 4B) was correlated with change in $\dot{V}E$ vs. $\dot{V}CO_2$ slope. The change in amplitude was positively correlated with the change in BNP levels ($n=14$, $R=0.760$, $P<0.01$, Fig. 4C). However, the change in cycle length ($n=14$, $R=0.231$, Fig 4D) was not correlated with the change in BNP levels. Multiple regression analysis showed that only the change in amplitude was an independent predictor of the change in BNP levels ($R=0.717$, $P<0.01$, Table 3).

Although the oscillation amplitude decreased significantly in overall assessment of 24

patients, in whom the data for the amplitude before and after cardiac rehabilitation were collected, the amplitude decreased in 15 patients but did not in 9 patients in the individual assessment. When clinical characteristics and parameters were compared between patients with and without decrease in oscillation amplitude, age, gender, body mass index, basal diseases, baseline blood test parameters, and baseline echocardiographic parameters were comparative between both patient groups. However, the change in BNP levels after cardiac rehabilitation was greater ($P<0.05$) and the frequency of participation of cardiac rehabilitation program was higher ($P<0.05$) in patients with decrease in oscillation amplitude (Table 4).

Discussion

In the present study, we determined relationships between parameters for magnitude of oscillatory ventilation and other CPX parameters as well as echocardiographic and blood testing parameters in 26 chronic heart failure patients who showed an oscillatory ventilation pattern during CPX. These parameters were also compared between the baseline before cardiac rehabilitation was started and follow-up after it was completed. The major findings of our results are that baseline oscillation amplitude was positively correlated with $\dot{V}E$ vs. $\dot{V}CO2$ slope and plasma BNP levels. After a 5-month rehabilitation program was completed, there was a significant decrease in oscillation amplitude but not cycle length, and the plasma BNP levels also decreased significantly. The change in amplitude was positively correlated with the change in BNP levels, although it was not correlated with the change in $\dot{V}E$ vs. $\dot{V}CO2$ slope. Interestingly, multiple regression analysis indicated that only the change in amplitude was an independent predictor of the change in BNP levels. In addition, the

frequency of participation of cardiac rehabilitation was associated with decrease in amplitude, namely, improved oscillatory ventilation. These findings suggest that our cardiac rehabilitation program improves exercise oscillatory ventilation in patients with chronic heart failure, and that this is associated with an improvement of cardiac function. The improvement in oscillatory ventilation possibly contributes to an improvement in prognosis.

In our study, we enrolled 26 heart failure patients (0.66%) with exercise oscillatory ventilation in 3933 consecutive patients undergoing CPX, during long time span such as 6 years. This seems like a lower prevalence rate of exercise oscillatory ventilation, compared with rates reported in previous studies, in which exercise oscillatory ventilation has been observed in 19-58% of heart failure patients [5-10]. However, subjects in our study who underwent CPX were not only heart failure patients but also included patients with coronary artery disease or peripheral artery disease and post-operative patients. Similarly, Kato et al. [21] identified 17 patients (0.30%) with this condition among 5634 cardiac patients who underwent CPX for 5 years.

The mechanisms underlying oscillatory ventilation while patients are awake are assumed to overlap, at least in part, with those of central sleep apnea. However, reports on the mechanisms of exercise oscillatory ventilation are limited. Murphy et al. [13] showed that exercise oscillatory ventilation indicates an inadequate hemodynamic response to exercise in terms of an impaired increase of cardiac index, increased cardiac filling pressure and augmented reliance on oxygen extraction. Javaheli et al. [22] also reported that increased cardiac filling pressures and pulmonary congestion might be implicated as a primary factor in the pathogenesis of oscillatory ventilation. Pulmonary congestion reduces lung compliance, which limits the increase in tidal volume with exercise, requiring an increased breathing frequency to maintain $\dot{V}E$ [23]. In addition, the stretching of type J pulmonary receptors by

vascular congestion and interstitial edema stimulates medullary respiratory centers, which promotes rapid, shallow breathing and heightens chemosensitivity with consequent hyperventilation and then hypocapnia [24, 25]. Oscillatory ventilation then ensues as the partial pressure of arterial carbon dioxide (PaCO2) is driven to values near or below the apnea threshold [26]. As PaCO2 falls, hypoventilation occurs, and subsequently PaCO2 rises. Then, hyperventilation resumes, thereby completing an oscillatory cycle during exercise. In our results, oscillation amplitude and oscillation cycle length were correlated each other at baseline before cardiac rehabilitation was started, and each of the amplitude and cycle length was positively correlated with $\dot{V}E$ vs. $\dot{V}CO2$ slope, an established index reflecting cardiopulmonary dysfunction during exercise. On the other hand, Kato et al. [21] reported a close relationship between the oscillatory cycle length and $\dot{V}E$ vs. $\dot{V}CO2$ slope, but there was no significant relationship between the amplitude and the $\dot{V}E$ vs. $\dot{V}CO2$ slope. The reason for these discrepancies is unclear, but it may be due to the severity of heart disease. The mean peak $\dot{V}O2$ (13.6 vs 10.3 mL/kg/min) and $\dot{V}E$ vs. $\dot{V}CO2$ slope (38.5 vs 45.6) in our present study and the study by Kato et al. [21] suggests that heart failure severity seems to be a little lower in our study population. In addition, the amplitude and cycle length during oscillatory ventilation may be different in their pathophysiological significance. The oscillation cycle length is strongly related to circulation time. However, the oscillation amplitude might be determined not only by the circulation time, but also by other factors, including degree of chemosensitivity and intensity of baroreflex of each subject [21]. Further studies are needed to clarify the cause of discrepancy. However, it may be certain that exercise oscillatory ventilation might represent an abnormal ventilatory response to exercise. We also demonstrated that amplitude but not cycle length during oscillatory ventilation was significantly correlated with plasma BNP levels at baseline. Since the $\dot{V}E$ vs. $\dot{V}CO2$ slope is

closely related to cardiac function [27] and the BNP levels can predict prognosis in heart failure [28, 29], the oscillatory amplitude might be an important parameter in chronic heart failure patients with exercise oscillatory ventilation.

The most noteworthy finding in our study is that our cardiac rehabilitation program improved exercise oscillatory ventilation. However, its mechanism cannot be completely explained. Exercise-based cardiac rehabilitation is safe and cost-effective and has been established to improve cardiac function, quality of life and long-term prognosis in patients with chronic heart failure. For chronic heart failure patients, moderate intensity exercise training for 2-6 months produces a 15-30% increase in peak $\dot{V}O2$ and AT [30]. These effects are considered mainly to result from metabolic and functional improvement of skeletal muscles including respiratory muscles such as the diaphragm and intercostal muscles, possibly leading to an improvement of exercise oscillatory ventilation via the improvement of respiratory control mechanisms on the level of ergo- [31] and peripheral chemoreceptors [32]. Contrary to normal subjects, in whom ventilation is triggered via central chemoreceptors, in chronic heart failure patients, lactate may affect intramuscular ergo-receptors before entering the circulation in chronic heart failure patients [33]. Lactic acid accumulates locally with exercise in both the diaphragm [34] and skeletal muscles [33]. This suggests an important role for local muscular acidosis as a stimulus of ergo-receptors and peripheral chemoreceptor reflex activation and hyperventilation. By reducing this abnormal metabolic response, exercise training can suppress the overactive metabolic reflex [31]. On the other hand, in chronic heart failure patients with pulmonary congestion, there is a redistribution of pulmonary blood flow from the basal lung region to apical lung region at rest, and this prevents an increase in upper-zone perfusion during exercise [35]. Exercise training improves pulmonary blood flow distribution and reduces ventilation/perfusion mismatch, and this

might be associated with the improvement of exercise oscillatory ventilation. Zurek et al. [17] first reported that exercise training reversed exercise oscillatory ventilation in heart failure patients. They found that the change in oscillation amplitude was correlated with the change in $\dot{V}E$ vs. $\dot{V}CO2$ slope after exercise training 3 times a week for a period of 3 months. In contrast, in our study, there was no correlation between the changes in amplitude and $\dot{V}E$ vs. $\dot{V}CO2$ slope after cardiac rehabilitation therapy, although baseline values of both parameters were correlated. The reason of discrepancy between the results of Zurek et al.[17] and ours remains unclear, but it is likely that the amplitude of the oscillatory ventilation is an independent marker of the benefits of cardiac rehabilitation. We also compared the changes in oscillatory parameters with those in several other parameters including biomarkers that have prognostic value in heart failure. We found that the change in oscillation amplitude but not that in oscillation cycle length was significantly correlated with the change in plasma BNP levels, suggesting that the amplitude might be more sensitive for improvement of heart failure, compared with the cycle length. In addition, multiple regression analysis showed that the only independent predictor of the change in the BNP levels was the change in amplitude, but not the changes in AT, peak $\dot{V}O2$ or $\dot{V}E$ vs. $\dot{V}CO2$ slope. To our knowledge, this is a novel finding that provides additional insight into the effect of cardiac rehabilitation on the improvement of exercise oscillatory ventilation.

Study limitations

Our study has several potential limitations. First, this study included a small number of patients in the cohort, possibly leading to type 2 errors. The discrepant results on the relationship between oscillatory amplitude and $\dot{V}E$ vs. $\dot{V}CO2$ slope between the study by Zurek et al. [17] and ours may be due to such an error. Next, this study was a retrospective,

single-center study. In addition, the data analysis was not blinded. However, the impact of our cardiac rehabilitation program on the decreased oscillatory amplitude was so pronounced that these limitations should have little influence on the main findings of the study. In our results, the value of AT significantly increased after the cardiac rehabilitation. However, it seems hard, in general, to determine accurate AT levels in cases showing exercise oscillatory ventilation. So this result may be uncertain. Cardiac rehabilitation program is a comprehensive program including not only exercise training but also psychological and nutritional consultation, blood pressure control, blood lipid control, blood sugar control, smoking cessation and other risk factor modifications. In addition to effects of exercise training, these comprehensive interventions might lead to ameliorating exercise oscillatory ventilation. However, we cannot show any data supporting this hypothesis because it is impossible to strictly dissect the effects of these interventions from those produced by exercise training alone. In this study, rennin angiotensin system inhibitors such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers were given in only 65% of the patients, so our study patients might be undertreated for heart failure in overall. Finally, in this study, we used a criteria described by Leite et al. [20] for the definition of exercise oscillatory ventilation, which might result in the exclusion of patients with low-grade oscillations. The optimal cut-off points for the definition of exercise oscillatory ventilation have yet to be established. However, our findings indicating the clinical significance of oscillation amplitude in the study population selected using such a criteria suggest that low-grade oscillations in ventilation may be less clinically relevant.

Conclusion

A 5-month cardiac rehabilitation program in chronic heart failure patients improved exercise oscillatory ventilation by reducing the oscillation amplitude. This effect was associated with a reduction of plasma BNP levels, potentially contributing to an improvement of heart failure. In addition, higher frequency participation of cardiac rehabilitation program might improve exercise oscillatory ventilation and cardiac function.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgments

We thank Ms. Mayumi Kofuji and Ms. Noriko Ogawara for their secretarial assistance.

References

1 Olson LJ, Arruda-Olson AM, Somers VK, Scott CG, Johnson BD (2008). Exercise oscillatory ventilation Chest 133: 474-481

2 Cheyne J (1818) A case of apoplexy in which the fleshy part of the heart was converted to fat. Dublin Hosp Rep 2: 216-219

3 Stokes W (1854) The Disease of the Heart and the Aorta. Hodges and Smith Dublin, Ireland, pp323-324

4 Spießhöfer J, Fox H, Lehmann R, Efken C, Heinrich J, Bitter T, Köber B, Horstkotte D, Oldenberg O (2015) Heterogenous haemodynamic effects of adaptive servoventilation therapy in sleeping patients with heart failure and Chyne-Stokes respitration compared to healthy volunteers. Heart Vessels doi: 10.1007/s00380-015-0717-6

5 Corra U, Pistono M, Mezzani A, Braghiroli A, Giordano A, Lanfranchi P, Bosimini E, Gnemmi M, Giannuzzi P (2006) Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. Circulation 113: 44-50

6 Kremser CB, O'Toole MF, Leff AR (1987) Oscillatory hyperventilation in severe congestive heart failure secondary to idiopathic dilated cardiomyopathy or to ischemic cardiomyopathy. Am J Cardiol 59: 900-905

7 Sun XG, Hansen JE, Beshai JF, Wasserman K (2010) Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. J Am Coll Cardiol 55: 1814-1823

8 Guazzi M, Raimondo R, Vicenzi M, Arena R, Proserpio C, Sarzi Braga S, Pedretti R (2007) Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. J Am Coll Cardiol 50: 299-308

9 Arena R, Myers J, Abella J, Peberdy MA, Pinkstaff S, Bensimhon D, Chase P, Guazzi M (2008) Prognostic value of timing and duration characteristics of exercise oscillatory ventilation in patients with heart failure. J Heart Lung Transplant 27: 341-347

10 Leite JJ, Mansur AJ, de Freitas HF, Chizola PR, Bocchi EA, Terra-Filho M, Neder JA, Lorenzi-Filho G. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation (2003) J Am Coll Cardiol 41: 2175-2181

11 Corra U, Mezzani A, Giordano A, Bosimini E, Giannuzzi P (2009) Exercise haemodynamic variables rather than ventilatory efficiency indexes contribute to risk assessment in chronic heart failure patients treated with carvedilol. Eur Heart J 30: 3000-3006

12 Guazzi M, Dickstein K, Vicenzi M, Arena R (2009) Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. Circ Heart Fail 2: 549-555

13 Murphy RM, Shah RV, Malhotra R, Pappagianopoulos PP, Hough SS, Systrom DM, Semigran MJ, Lewis GD (2011) Exercise oscillatory ventilation in systolic heart failure: An indicator of impaired hemodynamic response to exercise. Circulation 124: 1442-1451

14 Stolen KQ, Kemppainen J, Ukkonen H, Kalliokoski KK, Luotolahti M, Lehikoinen P, Hämäläinen H, Salo T, Airaksinen KE, Nuutila P, Knuuti J (2003) Exercise training improves biventricular oxidative metabolism and left ventricular efficiency in patients with dilated cardiomyopathy. J Am Coll Cardiol 41: 460-467

15 Belardinelli R, Georgiou D, Cianci G, Purcaro A (1999) Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional

capacity, quality of life, and clinical outcome. Circulation 99: 1173-1182

16 O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL; HF-ACTION Investigators (2009) Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 301: 1439-1150

17 Zurek M, Corra U, Piepoli M, Binder RK, Saner H, Schmid JP (2012) Exercise training reverses exertional oscillatory ventilation in heart failure patients. Eur Respir J 40: 1238-1244

18 Buchfuhrer ML, Hartsen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ (1983) Optimizing the exercise protocol for cardiopulmonary assessment. J Appl Physiol 55: 1558-1564

19 Beaver WL, Wasserman K, Whipp BJ (1986) A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 60: 2020-2027

20 Leite JJ, Mansur AJ, de Freitas HF, Chizola PR, Bocchi EA, Terra-Filho M, Neder JA, Lorenzi-Filho G (2003) Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. J Am Coll Cardiol 41: 2175-2181

21 Kato J, Koike A, Hoshimoto-Iwamoto M, Nagayama O, Sakurada K, Sato A, Yamashita T, Wasserman K, Aonuma K (2013) Relation between oscillatory breathing and cardiopulmonary function during exercise in cardiac patients. Circ J 77: 661-666

22 Javaheri S (1999) A mechanism of central sleep apnea in patients with heart failure. N Engl J Med 341: 949-954

23 Agostoni P, Pellegrino R, Conca C, Rodarte JR, Brusasco V (2002) Exercise hyperpnea

in chronic heart failure: relationships to lung stiffness and expiratory flow limitation. J Appl Physiol 92: 1409-1416

24 Hatridge J, Haji A, Perez-Padilla JR, Remmers JE (1989) Rapid shallow breathing caused by pulmonary vascular congestion in cats. J Appl Physiol 67: 2257-2264

25 Roberts AM, Bhattacharya J, Schultz HD, Coleridge HM, Coleridge JC (1986) Stimulation of pulmonary vagal afferent C-fibers by lung edema in dogs. Circ Res 58: 512-522

26 Ponikowski P, Anker SD, Chua TP, Francis D, Banasiak W, Poole-Wilson PA, Coats AJ, Piepoli M (1999) Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity.Circulation 100: 2418-2424

27 Arena R, Myers J, Aslam SS, Varughese EB, MD, Peberdy MA (2004) Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. Am Heart J 147: 354-360

28 Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D, Ohnishi M, Sugimoto Y, Kinoshita M (1997) Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 96: 509-516

29 Karavidas A, Lazaros G, Matsakas E, Farmakis D, Parissis J, Paraskevaidis IA, Michailidis C, Avramidis D, Zacharoulis A, Arapi S, Kaoukis A, Zacharoulis A (2008) Clinical value of B-type natriuretic peptide for the assessment of left ventricular filling pressures in patients with systolic heart failure and inconclusive tissue Doppler indexes. Heart Vessels 23: 181-186

30 Pina IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, Fletcher BJ, Fleg JL, Myers JN, Sullivan MJ; American Heart Association Committee on exercise, rehabilitation, and prevention (2003) Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation 107: 1210-1225

31 Piepoli M, Clark AL, Volterrani M, Adamopoulous S, Sleight P, Coats AJ (1996) Contribution of muscle afferents to the hemodynamic, autonomic, and ventilator responses to exercise in patients with chronic heart failure: effects of physical training. Circulation 93: 940-952

32 Tomita T, Takaki H, Hara Y, Sakamaki F, Sato T, Takagi S, Yasumura Y, Aihara N, Goto Y, Sunagawa K (2003) Attenuation of hypercapnic carbon dioxide chemosensitivity after postinfarction exercise training: possible contribution to the improvement in exercise hyperventilation. Heart 89: 404-410

33 Wensel R, Francis DP, Georgiadou P, Scott A, Genth-Zots S, Anker SD, Coats AJ, Piepoli MF (2005) Exercise hyperventilation in chronic heart failure is not caused by systemic lactic acidosis. Eur J Heart Fail 7: 1105-1111

34 Chiappa GR, Roseguini BT, Vieira PJ, Alves CN, Tavares A, Winkelmann ER, Ferlin EL, Stein R, Ribeiro JP (2008) Inspiratory muscle training improves blood flow to resting and exercising limbs in patients with chronic heart failure. J Am Coll Cardiol 51: 1663-1671

35 Wada O, Asanoi H, Miyagi K, Ishizaka S, Kameyama T, Seto H, Sasayama S (1993) Importance of abnormal lung perfusion in excessive exercise ventilation in chronic heart failure. Am Heart J 125: 790-798

Figure legends

Figure 1. Representative data obtained from a patient with chronic heart failure with oscillatory ventilation. Exercise oscillatory ventilation was defined as follows: 1) at least three oscillatory fluctuations in $\dot{V}E$ during warm-up and exercise; 2) regular oscillations, as defined by a standard deviation of three consecutive cycle length durations within 20% of the average; and 3) a minimal average ventilation amplitude of ≥5 L, defined as peak $\dot{V}E$ of one oscillation minus the average of two adjacent nadirs. To determine the magnitude of oscillatory ventilation, the amplitude of oscillating $\dot{V}E$ was calculated as the difference between the peak and nadir of oscillating $\dot{V}E$ for each of the cycles noted, and then expressed as the mean value. The cycle length of oscillating $\dot{V}E$ was also calculated as the interval from the peak to the following peak of oscillating $\dot{V}E$ for each of the cycles noted, and then expressed as the mean value. $\dot{V}E$=minute ventilation, VT=tidal ventilation

Figure 2. Representative images of the changes in $\dot{V}E$ in a case (66 yr-old male), in whom oscillatory ventilation was improved after the cardiac rehabilitation program was completed. At baseline before the program was started, the $\dot{V}E$ curve showed oscillatory ventilation pattern. The oscillation amplitude was 17.4 L/min and the oscillation cycle length was 62 sec. After the program was completed, the oscillation pattern still remained. The amplitude decreased (to 10.3 L/min) but the cycle length did not change (to 64 sec).

Figure 3. Relationships between oscillatory parameters (the oscillation amplitude and oscillation cycle length) and $\dot{V}E$-$\dot{V}CO2$ slope or BNP before cardiac rehabilitation. A & B: Relationships between the oscillation amplitude (A) / oscillation cycle length (B) and $\dot{V}E$-$\dot{V}CO2$ slope. C & D: Relationships between the oscillation amplitude (C) / oscillation cycle length (D) and BNP levels.

$\dot{V}E$-$\dot{V}CO2$ slope = minute ventilation-carbon dioxide production slope, BNP=brain natriuretic peptide

Figure 4. Relationships between the change in the oscillation parameters (the oscillation amplitude and oscillation cycle length) and $\dot{V}E$-$\dot{V}CO2$ slope or BNP levels after a 5-month cardiac rehabilitation program. A & B: Relationships between the change in the oscillation parameters (the oscillation amplitude (A) and oscillation cycle length (B)) and the change in $\dot{V}E$-$\dot{V}CO2$ slope. C & D: Relationships between the change in the oscillation parameters (the oscillation amplitude (C) and oscillation cycle length (D)) and the change in BNP levels. Note that the change in the amplitude, but not oscillation cycle length, was positively correlated with the change in BNP levels.

Table 1 Baseline characteristics of 26 selected patients

Age; yrs	62±16
Male gender; n (%)	24 (92)
Body mass index; kg/m^2	22±5
Basal diseases; n (%)	
Ischemic heart disease	7 (27)
Cardiomyopathy	11 (42)
Valvular heart disease	4 (15)
Hypertensive heart disease	3 (12)
Other	1 (4)
Complications; n (%)	
Hypertention	16 (62)
Diabetes	7 (27)
Dyslipidemia	16 (62)
Chronic kidney disease	16 (62)
Atrial fibrillation	6 (23)
Medications; n (%)	
ACE inhibitor/ARB	17 (65)
β blocker	20 (77)
Spironolactone	11 (42)
Loop diuretics	14 (54)

ACE=angiotensin converting enzyme, ARB=angiotensin receptor blocker

Table 2 Blood test results, echocardiographic findings and CPX parameters before and after cardiac rehabilitation

	Baseline	Follow-up	P value
Blood test			
Hb; mg/dL	14.2±2.1	14.1±2.0	0.604
Cr; mg/dL	1.1±0.3	1.1±0.3	0.925
Na; mEq/L	141±3	140±4	0.733
K; mEq/L	4.3±0.4	4.5±0.4	0.271
BNP; pg/mL	967±796	477±336	0.017
Echocardiography			
EF; %	31.2±13.5	33.9±16.4	0.285
E/E'	11.3±5.6	11.6±6.4	0.456
RVSP; mmHg	38.0±14.0	28.0±8.9	0.026
CPX			
AT; mL/kg/min	9.6±2.4	11.1±2.6	0.026
Peak$\dot{V}$O2; mL/kg/min	13.6±3.4	15.5±4.6	0.053
$\dot{V}$E vs. $\dot{V}$CO2 slope	38.5±9.4	35.3±6.3	0.081
Amplitude; L/min	18.6±11.9	12.1±5.2	0.009
Cycle length; sec	69.8±14.5	77.1±32.1	0.158

CPX=cardiopulmonary exercise testing, Hb=hemoglobin, Cr=creatinine, BNP= brain natriuretic peptide, EF=ejection fraction, $\dot{V}$O2=oxygen uptake, $\dot{V}$E= minute ventilation, $\dot{V}$CO2= carbon dioxide production

Table 3 Multiple regression analysis for predicting the change in BNP levels using changes in CPX parameters

CPX parameters	Standard regression coeffeicient	P value
AT; mL/kg/min	0.760	0.151
Peak$\dot{V}$O2; mL/kg/min	-0.433	0.268
$\dot{V}$E vs. $\dot{V}$CO2 slope	0.032	0.9164
Amplitude; L/min	0.717	0.006

Table 4 Comparison of clinical characteristics between patients with and without decrease in oscillatory amplitude

	Decrease (n=15)	No decrease (n=9)	P value
Age; yrs	62±16	66±10	0.577
Male gender; n (%)	14 (93)	8 (89)	0.702
Body mass index; kg/m^2	22±5	24±3	0.314
Basal diseases; n (%)			0.261
Ischemic heart disease	3 (20)	3 (33)	
Cardiomyopathy	5 (33)	4 (44)	
Valvular heart disease	5 (33)	0 (0)	
Hypertensive heart disease	1 (7)	2 (23)	
Other	1 (7)	0 (0)	
Blood test			
Hb; mg/dL	14.4±1.7	13.4±2.9	0.318
Cr; mg/dL	1.1±0.3	1.1±0.2	0.985
Na; mEq/L	140±3	141±3	0.562
K; mEq/L	4.4±0.3	4.2±0.4	0.081
BNP; pg/mL	1202±919	597±355	0.118
BNP change; %	47.6±33.4	91.2±38.5	0.047
Echocardiography			
EF; %	29.9±13.9	33.4±13.3	0.543
E/E';	10.6±3.7	12.5±8.0	0.492
RVSP; mmHg	39.1±16.5	36.1±9.2	0.672
Participation of cardiac rehabilitation program; /60 sessions	26.4±12.8	16.2±9.0	0.048

Fig. 1

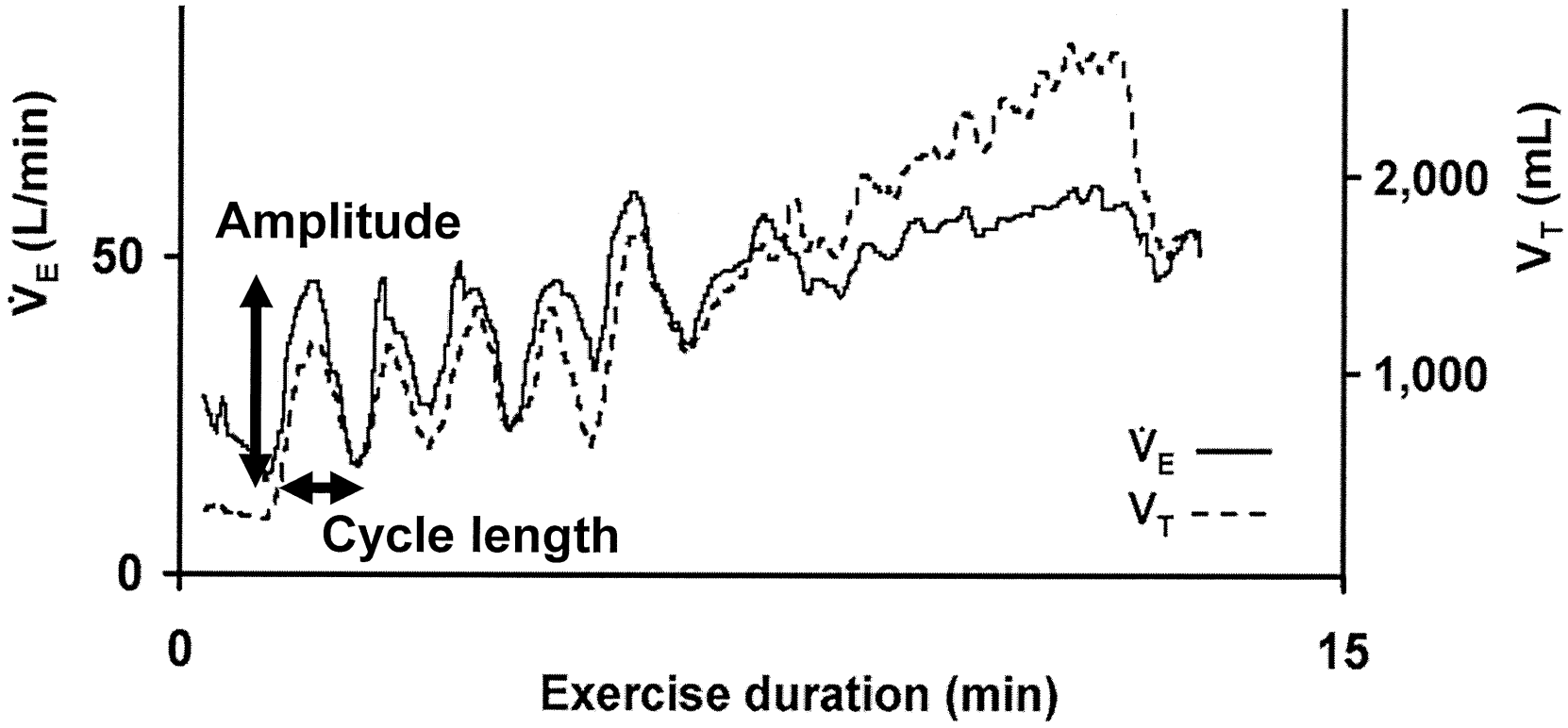

$\dot{V}_E$ (L/min)
50
0
Amplitude
Cycle length
0
15
Exercise duration (min)
2,000
1,000
V_T (mL)
$\dot{V}_E$
V_T

Fig. 2

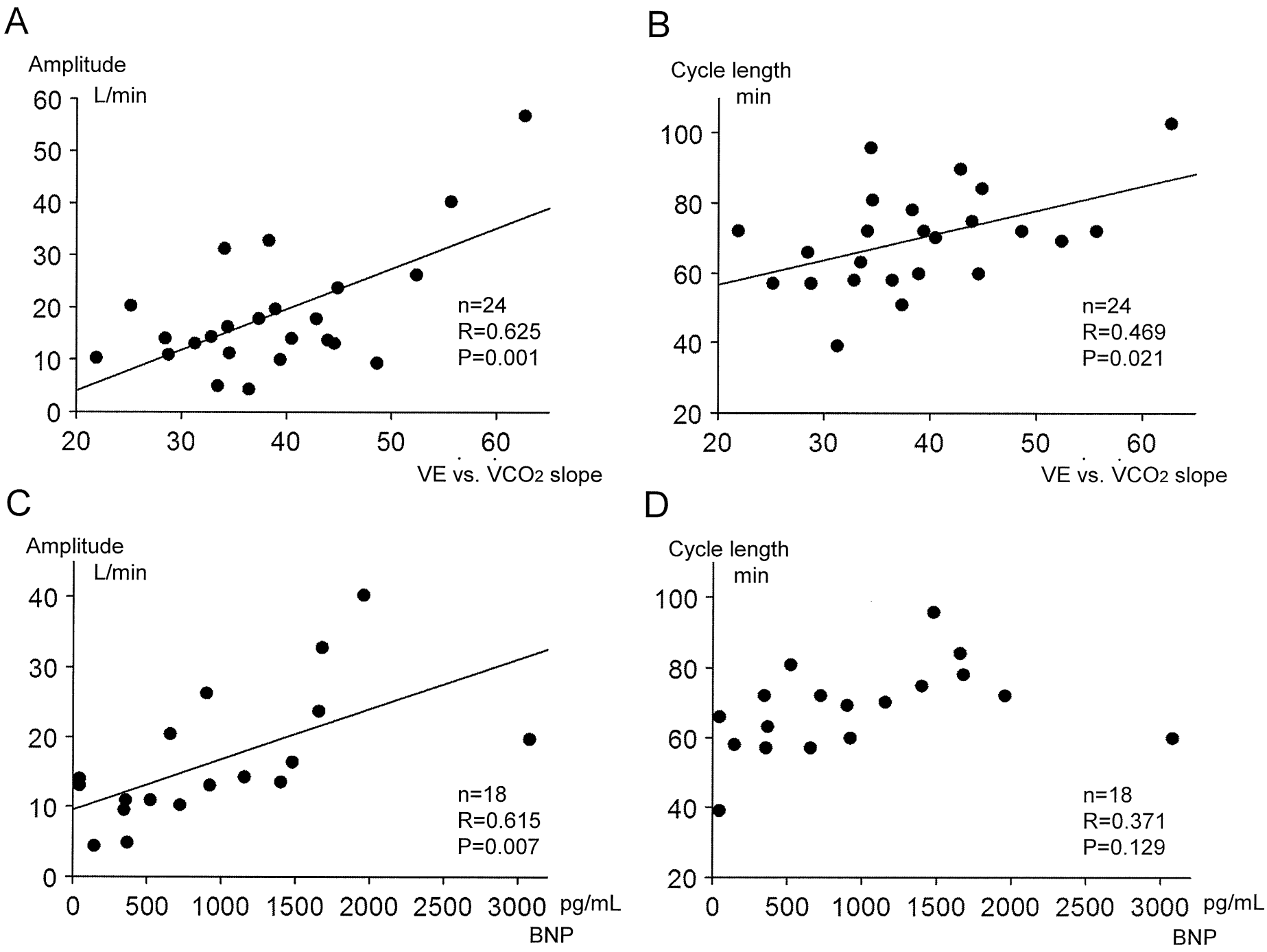
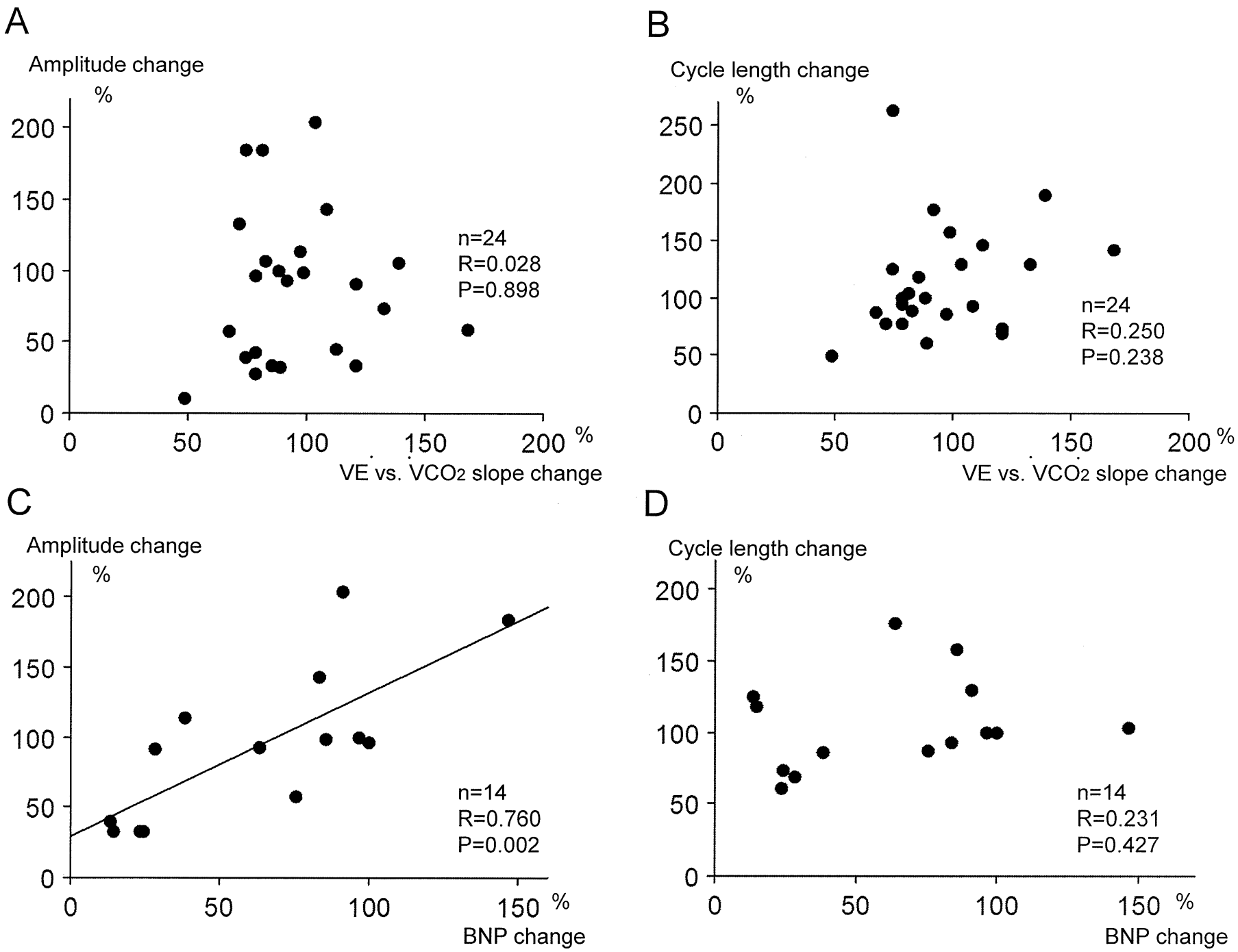
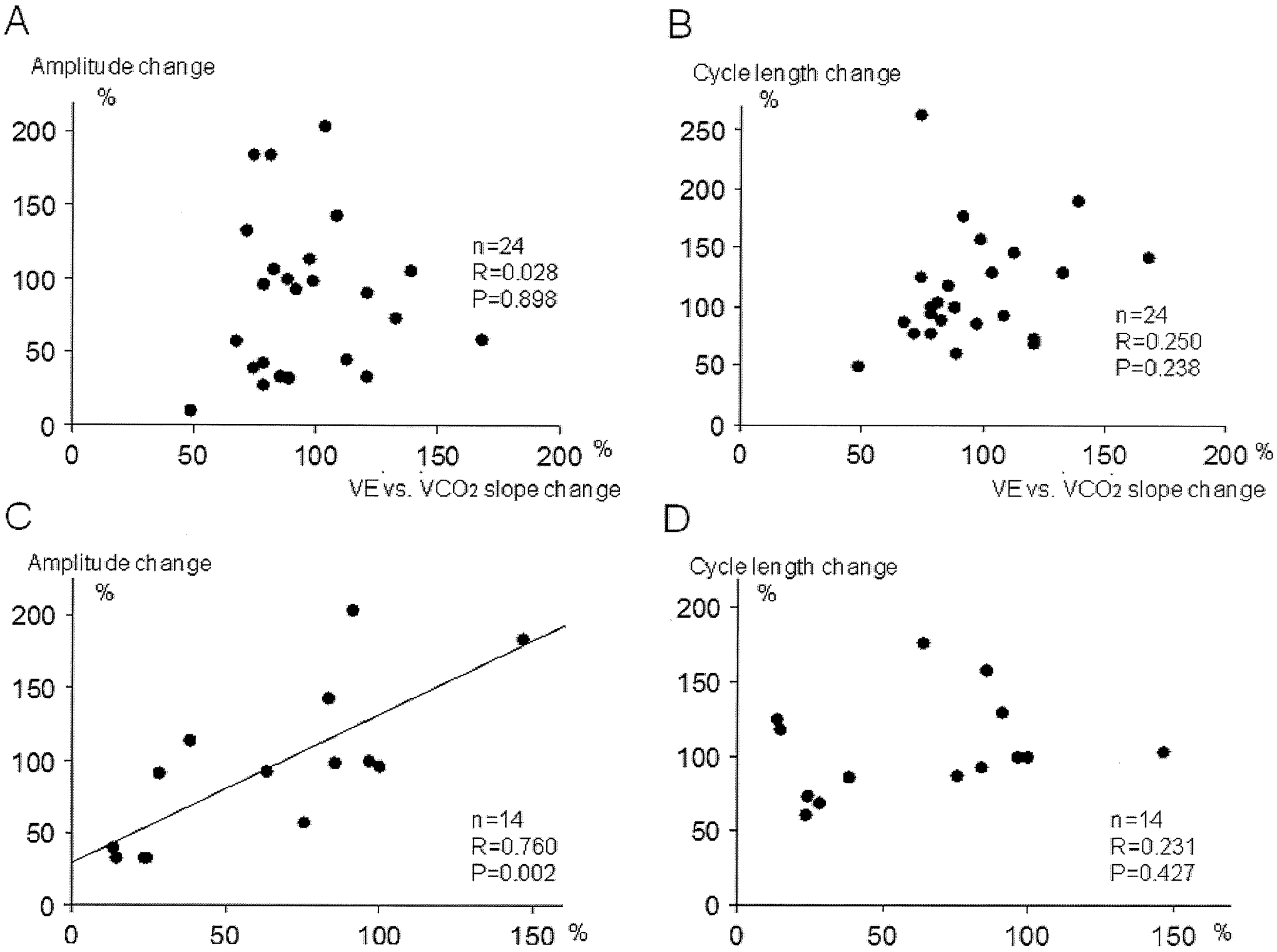

A
Amplitude
L/min
60
50
40
30
20
10
0
20
30
40
50
60
VE vs. VCO2 slope
n=24
R=0.625
P=0.001
B
Cycle length
min
100
80
60
40
20
20
30
40
50
60
VE vs. VCO2 slope
n=24
R=0.469
P=0.021
C
Amplitude
L/min
40
30
20
10
0
0
500
1000
1500
2000
2500
3000
pg/mL
BNP
n=18
R=0.615
P=0.007
D
Cycle length
min
100
80
60
40
20
0
500
1000
1500
2000
2500
3000
pg/mL
BNP
n=18
R=0.371
P=0.129

Fig. 3


A
Amplitude change
%
200
150
100
50
0
0
50
100
150
200 %
VE vs. VCO2 slope change
n=24
R=0.028
P=0.898
B
Cycle length change
%
250
200
150
100
50
0
0
50
100
150
200 %
VE vs. VCO2 slope change
n=24
R=0.250
P=0.238
C
Amplitude change
%
200
150
100
50
0
0
50
100
150 %
BNP change
n=14
R=0.760
P=0.002
D
Cycle length change
%
200
150
100
50
0
0
50
100
150 %
BNP change
n=14
R=0.231
P=0.427


A
Amplitude change
%
200
150
100
50
0
0
50
100
150
200
%
VE vs. VCO2 slope change
n=24
R=0.028
P=0.898
B
Cycle length change
%
250
200
150
100
50
0
0
50
100
150
200
%
VE vs. VCO2 slope change
n=24
R=0.250
P=0.238
C
Amplitude change
%
200
150
100
50
0
0
50
100
150
%
n=14
R=0.760
P=0.002
D
Cycle length change
%
200
150
100
50
0
0
50
100
150
%
n=14
R=0.231
P=0.427