Effect of physical training on ventilatory patterns during exercise in patients with heart disease

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Original article

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Key words: Cardiac rehabilitation, respiratory pattern, rapid and shallow breathing, heart disease

Abstract

Background: Exercise training is known to improve the shortness of breath experienced by patients with heart disease when the ventilatory pattern becomes abnormal during exercise. However, the precise relationship between breathing patterns and the effect of exercise training has not not yet been elucidated. We evaluated the relationship between the effect of exercise training on exercise tolerance and the amelioration of the ventilatory response during exercise in such patients.

Methods and results: Patients with heart disease (n = 170) underwent cardiopulmonary exercise testing twice (pre- and post-exercise training for 3-6 months). They were divided into the exercise training group (Group E, n = 123) and control group (Group C, n = 47). Regression line relating tidal volume to respiratory rate (TV-RR slope) during a ramp protocol below the inflection point was regarded as an indicator of rapid ventilation. Tidal volume after the inflection point was regarded as an indicator of shallow ventilation (TV at plateau). The TV-RR slope and TV at plateau improved after exercise training from 94.8 ± 45.9 to 129.9 ± 69.5 ($p < 0.001$) and from 1473.6 ± 321.9 mL to 1673.2 ± 355.1 mL ($p < 0.001$), respectively, in group E. In contrast, no improvement was evident in Group C. In total, %anaerobic threshold (%AT)[AT improving ratio = (post AT - pre AT)/pre AT × 100] was positively correlated with both %TV-RR slope [TV-RR slope improving ratio = (post TV-RR slope – pre TV-RR slope)/pre TV-RR slope × 100] ($r = 0.60$) and %TV at plateau [TV at plateau improving ratio = (post TV at plateau – pre TV at plateau)/pre TV at plateau × 100] (r =

0.51).

Conclusion: Exercise training improved the rapidness and depth of breathing during exercise. Therefore, improvement of abnormal ventilatory patterns is correlated with exercise tolerance.

Introduction

Exertional dyspnea and working muscle fatigue are major symptoms limiting daily activities in patients with chronic heart failure (CHF); they can be assessed objectively using incremental exercise testing with metabolic gas exchange measurements [1].

Normally, below the moderate exercise intensity during incremental work, increase in minute ventilation (VE) mainly depends on increase of tidal volume (TV). However, respiratory rate (RR) also increases simulataneously in some degree. This ventilation pattern can be elucidated by plotting TV and RR during cardiopulmonary exercise testing using a ramp protocol [2]. Therefore, slope of TV-RR relation is not always vertical.

The steepness of this line is an indicator of rapidness of ventilation. After this point, subjects cannot breathe any deeper, and any increase in VE becomes RR-dependent. This breaking point is known as the inflection point. Any value of TV after the inflection point is an indicator of shallow ventilation. Accordingly, it is possible to quantify the rapidness and shallowness of ventilation using this plot.

During incremental exercise, patients with CHF adopt a breathing pattern that differs substantially from that of normal subjects at all levels of muscular work. In general, these patients breathe with a relatively smaller TV and a greater RR at any given VE, resulting in a characteristic downward shift of the TV-RR slope in comparison with that of normal subjects [2-6].

The effect of physical training on the ventilatory response to exercise in patients with heart disease has not yet been elucidated. Therefore, the aim of this study was to assess the effect of exercise training on the ventilatory pattern and the relationship between the effect of exercise training and the amelioration of the ventilatory response during exercise in these patients.

Methods

In total, 170 patients with heart disease were enrolled in this study. They were divided into two groups according to the frequency of exercise training. Group E (the exercise training group) comprised patients who participated in exercise training more than once per week, and Group C (the control group) comprised those who did not perform exercise training after enrollment in the study.

Patient characteristics and basal disease are shown in Table 1 and no differences were evident between the two groups.

Ethical approval for the study was granted by the hospital committee, and all subjects provided informed consent.

Exercise testing

Exercise tolerance was measured by a cardiopulmonary exercise test (CPX) using an upright, calibrated cycle ergometer (CPE2000, MedGraphics Co., MN, U.S.A) 2-4 h after eating a light meal. The test began with 4 min of rest and 4 min of warm-up at 20 watts, followed by a continuously increasing work rate of 1 watt every 6 s until exhaustion. The work rate increase levels were chosen

on the basis of ability of the subjects to complete an exercise program lasting between 8 and 15 min [7].

The anaerobic threshold (AT) would be determined by the V-slope method[8]. The second CPX was performed 3-6 months after the first test in the same manner.

Gas exchange measurements

Oxygen uptake ($\dot{V}O_2$), carbon- dioxide production ($\dot{V}CO_2$), and $\dot{V}E$ were measured on a breath-by-breath basis using an aeromonitor (MINATO 280E, Minato Science Co.Ltd., Osaka, Japan). The slope of the $\dot{V}E$-$\dot{V}CO_2$ relation was calculated by linear regression analysis using the values of $\dot{V}E$ and $\dot{V}CO_2$. Because the relationship of $\dot{V}E$ and $\dot{V}CO_2$ during the period of incremental exercise alters above the respiratory compensation point, the slope of $\dot{V}E$-$\dot{V}CO_2$ was calculated below the respiratory compensation point. The dead space is likely to be the same during the first and second CPX study, because the same type and size of face mask was used in both studies.

TV-RR relationship was calculated using a graph of TV as a function of RR (Fig 1). The TV-RR relationship increased linearly during exercise until moderate work intensity when the linearity broke down abruptly and was followed by a horizontal line, implying RR augmentation without an increase in TV. Usually, this inflection point occurs between AT and the respiratory compensation point. We determined the earlier portion below the inflection point to evaluate the rapidness of breathing and measured the TV-RR slope by linear regression analysis as an index of the TV-RR

relationship. The results showed the highest value of TV during exercise (TV at plateau) as an index of the depth of breathing [2]. Although no study there has shown the normal range of the TV-RR slope, our preliminary data demonstrates that class A in the Weber-Janicki classification is equal to 90 of the TV-RR slope [9,10].

Exercise training

Exercise training was performed at the intensity of the lactic acidosis threshold which was decided using the V-slope method [8]. Patients performed supervised exercise training for 30 min/day for 3-6 months.

Data analysis

All data are expressed as mean ± standard deviation. Differences between pre- and post-parameters were assessed by the paired t-test. A probability value of $p < 0.05$ was considered significant. Linear regression analysis was performed to explore the relation between variables.

Results

All patients performed CPX without any complications. The reasons for termination of exercise were shortness of breath, Borg scale≧17, and respiratory quotient≧1.1.

As shown in Figure 2, after cardiac exercise training, AT increased significantly from 11.6 ± 2.8 mL/min/kg to 13.7 ± 3.3 mL/min/kg in Group E. In contrast, it decreased significantly from 13.1 ±

2.8 mL/min/kg to 11.6 ± 2.7 mL/min/kg in Group C. The slope of the relation between VE and carbon dioxide production ($\dot{V}E$ vs. $\dot{V}CO_2$ slope) decreased significantly after exercise training (from 31.6 ± 5.8 to 30.5 ± 5.1, $p < 0.01$) in Group E, whereas it increased in Group C (from 30.9 ± 8.0 to 32.9 ± 9.4, $p < 0.01$). RR at rest and at AT significantly decreased after exercise training (from 16.4 ± 3.7 n/min to 15.1 ± 3.8 n/min, $p < 0.001$, and 22.6 ± 4.7 to 21.7 n/min ± 5.0 n/min, $p < 0.05$, respectively) in Group E. However, in Group C, no change was observed (from 16.2 ± 3.9 n/min to 16.0 ± 4.1 n/min, n.s. and from 22.9 ± 5.6 n/min to 22.0 ± 5.7 n/min, n.s., respectively).

The TV-RR slope ameliorated after exercise training from 94.8 ± 45.9 to 129.9 ± 69.5 ($p < 0.001$) in Group E, but deteriorated from 110.3 ± 61.4 to 86.7 ± 51.1 ($p < 0.001$) in Group C (Fig 3). TV at plateau improved from 1473.6 ± 321.9 mL to 1673.2 ± 355.1 mL ($p < 0.001$) in Group E, but showed no change in Group C (Fig 4).

In all patients (n = 170), AT before training positively correlated with TV at plateau before training ($r = 0.43$, $p<0.05$), as shown in Figure 5. %AT[AT improving ratio = (post AT - pre AT)/pre AT × 100] was positively correlated with both %TV-RR slope [TV-RR slope improving ratio = (post TV-RR slope – pre TV-RR slope)/pre TV-RR slope × 100] ($r = 0.60$, $p<0.01$) and %TV at plateau [TV at plateau improving ratio = (post TV at plateau – pre TV at plateau)/pre TV at plateau × 100] ($r = 0.51$, $p<0.01$), as shown in Figure 6. There were no differences in improving degree among various basal disease.

Discussion

The present study demonstrates that rapid and shallow breathing patterns were improved by 3-6 months of exercise training and that exercise tolerance and abnormal ventilation pattern was improved to the same degree. To the best of our knowledge, this is first study demonstrating the correlation between ventilation mode and exercise tolerance.

Yokoyama et al. plotted the slope relating TV and RR in patients with CHF; this slope was set as an index of the rapidness of the ventilation mode [2]. In addition, they reported a point on the TV-RR slope at which RR starts to increase in comparison with TV. The value of TV at plateau is used as an indicator of the shallowness of ventilation during exercise [9]. Based on this report, we treated the TV-RR slope as an index of the rapidness in breathing patterns and TV at plateau as an index of the shallowness in breathing patterns during exercise.

Certain mechanisms are known to induce an abnormal ventilatory pattern in patients with heart disease. First, excess ventilation during exercise in patients with heart disease, is associated with an increase in sympathetic nerve function [11,12]. Persistent sympathetic overactivity stimulates peripheral and central chemoreceptors in patients with heart disease, and the enhanced chemosensitivity of patients with heart disease correlates well with the ventilatory response to exercise. Therefore, an excessive accumulation of carbon dioxide occurs, and the increase in the

ventilation rate predominates over the increase in TV earlier than in normal subjects [3].

Diseased skeletal muscle is possibly the second factor contributing to abnormal ventilation in patients with heart disease, because it is the source of signals that disrupt normal patterns of cardiorespiratory control [13]. Depleted muscle mass is associated with ergoreflex (a peripheral reflex originating in the skeletal muscle sensitive to the products of muscle work) overactivity and impaired exercise tolerance in CHF [14]. Ergoreflex activation independently correlates with the $\dot{V}E$ vs. $\dot{V}CO_2$ slope and inversely with exercise tolerance in patients with heart disease [15].

Third, a restrictive pattern of pulmonary impairment has been well-documented in patients with heart failure and is mainly attributed to interstitial and alveolar pulmonary edema [16-20]. The incidence of restrictive lung abnormalities results in a lower rate of increase in TV, a higher RR, and a higher dead space to TV ratio (V_D/V_T) for any given work. It has been demonstrated that in patients with heart failure, pulmonary capillary wedge pressure elevates abnormally from the early phase of exercise, and this abnormality can be sensed by pulmonary juxtacapillary receptors (J-receptors) [21]. Respiratory muscle fatigue in relation to increased respiratory load and a reduced blood flow to the respiratory muscles results in a decrease in muscle tension [22].

In this study, we demonstrated that cardiac rehabilitation improved the rapidness and shallowness of the ventilation mode. It has been reported that exercise training can reduce sympathetic activity and catecholamine responses [23,24]. This may be one of the main mechanisms for improvement in

excessive ventilation and abnormal ventilation modes in this study. In addition, exercise training has been reported to improve skeletal muscle abnormalities due to muscle morphology and the metabolism in patients with heart failure [25].

Furthermore, in patients with heart failure, respiratory muscle training improves the endurance and strength of both inspiratory and expiratory muscles, with an enhancement of the submaximal and maximal exercise capacity [26]. Because exercise tolerance was improved in patients who participated in the cardiac rehabilitation program, skeletal muscle mass and function is considered to be ameliorated in our study, which may be another mechanism for improvement of abnormal ventilatory patterns.

The elevation of pulmonary wedge pressure during exercise is reduced as exercise tolerance is increased. Because exercise tolerance was improved after exercise training in Group E, the enhancement of ventilation due to any elevation of pulmonary wedge pressure would have been diminished.

In our study, we could not determine the relation between the frequency and degree of exercise training. Further investigations are required to elucidate the influence on the indices of CPX in degree and frequency of exercise training.

In conclusion, it was revealed that exercise training improved the rapidness and depth of breathing during exercise. Therefore, the results suggest that improvement of abnormal ventilatory patterns is

correlated with exercise tolerance.

Acknowledgements

We gratefully acknowledge the technical assistance provided by Ms. Iwasaki, Mr. Ueda and Mr. Kobayashi.

Disclosures

Funding Sources: None. Conflict of Interest Statement: None.

References

1) Clark AL, Poole-Wilson PA, Coats AJS. Exercise limitation in chronic heart failure: central role of the periphery. J Am Coll Cardiol 1996;28:1092-102.

2) Yokoyama H, Sato H, Hori M, Takeda H, Kanada T. A characteristic change in ventilation mode during exertional dyspnea in patients with chronic heart failure. Chest 1994;106:1007-13.

3) Weber KT, Kinasewitz GT, Janicki JS, Fisherman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation 1982;65:1213-23.

4) Nery LB, Wasserman K, French W, Oren A, Davis JA. Contrasting cardiovascular and

respiratory responses to exercise in mitral valve and chronic obstructive pulmonary disease. Chest 1983;83:446-53.

5) Gallagher CG, Younes M. Breathing pattern during and after maximal exercise in patients with chronic obstructive lung disease, interstitial lung disease, and cardiac disease, and in normal subjects. Am Rev Respir Dis 1986;133:581-6.

6) Myers J, Salleh A, Buchanan N, Smith D, Neutel J, Bowes E, Froelicher V. Ventilatory mechanisms of exercise intolerance in chronic heart failure. Am Heart J 1992;124:710-9.

7) Buchfuhrer ML, Hartsen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ. Optimizing the exercise protocol for cardiopulmonary assessment. J Appl Physiol 1983;55:1558-64.

8) Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020-7.

9) Akaishi S, Adachi H, Oshima S, Taniguchi K, Hasegawa A, Kurabayashi M. Relationship between exercise tolerance and TV vs. RR relationship in patients with heart disease. J Cardiol. 2008;52:195-201.

10) Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic heart failure. Am J Cardiol. 1985;55:22A-31A

11) Coats AJS, Adamopoulos S, Radaelli A, McCance A, Meyer TE, Bernardi L, Solda PL, Davey P, Ormerod O, Forfar C, Conway J, Sleight P. Controlled trial of physical training in chronic heart

failure. Exercise performance, hemodynamics, ventilation, and autonomic function. Circulation 1992;85:2119-31.

12) Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJ, Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. Circulation 2001;104:2324-30.

13) Piepoli M, Clark AL, Volterrani M, Adamopoulos S, Sleight P, Coats AJ. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure. Circulation. 1996;93:940-52.

14) Piepoli MF, Kaczmarek A, Francis DP, Davies LC, Rauchhaus M, Jankowska EA, Anker SD, Capucci A, Banasiak W, Ponikowski P. Reduced peripheral skeletal muscle mass and abnormal reflex physiology in chronic heart failure. Circulation 2006;114:126-34.

15) Chua TP, Clark AL, Amadi AA, Coats AJ. Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol 1996;27:650-7.

16) Guazzi M, Agostoni P, Matturri M, Pontone G, Guazzi MG. Pulmonary function, cardiac function, and exercise capacity in a follow-up of patients with congestive heart failure treated with carvedilol. Am Heart J 1999;138:460-7.

17) Ravenscraft SA, Gross CR, Kubo SH, Olivari MT, Shumway SJ, Bolman RM. Pulmonary function after successful heart transplantation. Chest 1993;103:54-8.

18) Faggiano P, Lombardi C, Sorgato A, Ghizzoni G, Spedini C, Rusconi C. Pulmonary function tests in patients with congestive heart failure: effects of medical therapy. Cardiology 1993;83:30-5.

19) Puri S, Dutka DP, Baker BL, Hughes JMB, Cleland JGF. Acute saline infusion reduces alveolar-capillary membrane conductance and increases airflow obstruction in patients with left ventricular dysfunction. Circulation 1999;99:1190-6.

20) Hauge A, Bo G, Waaler BA. Interrelations between pulmonary liquid volumes and lung compliance. J Appl Physiol 1975;38:608-14.

21) Paintal AS. Mechanism of stimulation of type J pulmonary receptors. J Physiol 1969;203:511-32.

22) Mancini DM, Ferraro N, Nazzaro D, Chance B, Wilson JR. Respiratory muscle deoxygenation during exercise in patients with heart failure demonstrated with near-infrared spectroscopy. J Am Coll Cardiol 1991;18:492-8.

23) Roveda F, Middlekauff HR, Rondon MUPB, Reis SF, Souza M, Nastari L, Barretto ACP, Krieger EM, Negrao CE. The effects of exercise training on sympathetic neural activation in advanced heart failure. J Am Coll Cardiol 2003;42:854-60.

24) Belardinelli R, Georgiou D, Purcaro A. Low dose dobutamine echocardiography predicts improvement in functional capacity after exercise training in patients with ischaemic

cardiomyopathy: prognostic implication. J Am Coll Cardiol 1998;31:1027-34.

25) Piepoli M, Clark AL, Volterrani M, Adamopoulos S, Sleight P, Coats SJ. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. Circulation. 1996;93:940-52.

26) Mancini DM, Henson D, Manca JL, Donchez L, Levine S. Benefit of selective respiratory muscle training on exercise capacity in patients with chronic congestive heart failure. Circulation 1995;91:320-9.

Figure legends

Fig 1

Example of a TV-RR relationship. The patient (58 years old) had dilated cardiomyopathy (EF = 41%). His exercise tolerance was preserved (AT = 11.3 mL/min/kg).

Fig 2

Effect of exercise training on AT

Fig 3

Effect of exercise training on the TV-RR slope

Fig 4

Effect of exercise training on TV at plateau

Fig 5

Relationship between AT and ventilatory pattern

Fig 6

Correlation of AT improving ratio (%AT) with %TV-RR slope (left panel) and %TV at plateau (right panel).

Table 1　Patients' characteristics

	Group E	Group C	
n	123	47	n.s.
Age (years old)	63.3 ± 11.5	66.7 ± 11.7	n.s.
Height (cm)	164.3 ± 7.1	163.6 ± 7.6	n.s.
Weight (kg)	65.8 ± 11.1	63.5 ± 10.8	n.s.
Sex (M/F)	109/14	38/9	n.s.
LVEF (%)	55.7 ± 15.3	52.3 ± 17.1	n.s.
Basal disease			n.s.
IHD	92	30	
HF	31	17	
NYHA			
I	4	3	
II	13	9	
III	14	5	
Medication			
Diuretics	24	13	
BB	56	27	
ARB/ACEI	85	38	
Anaerobic threshold (mL/min/kg)	11.6 ± 2.8	13.1 ± 2.8	n.s.
$\dot{V}E$ vs. $\dot{V}CO_2$ slope	31.6 ± 5.8	30.9 ± 8.0	n.s.
Peak $\dot{V}O_2$/HR (mL/beat)	8.8 ± 2.4	9.3 ± 2.6	n.s.

IHD: ischemic heart disease (angina pectoris, myocardial infarction) who performed intervention before entry and had no ischemic change in CPX after intervention

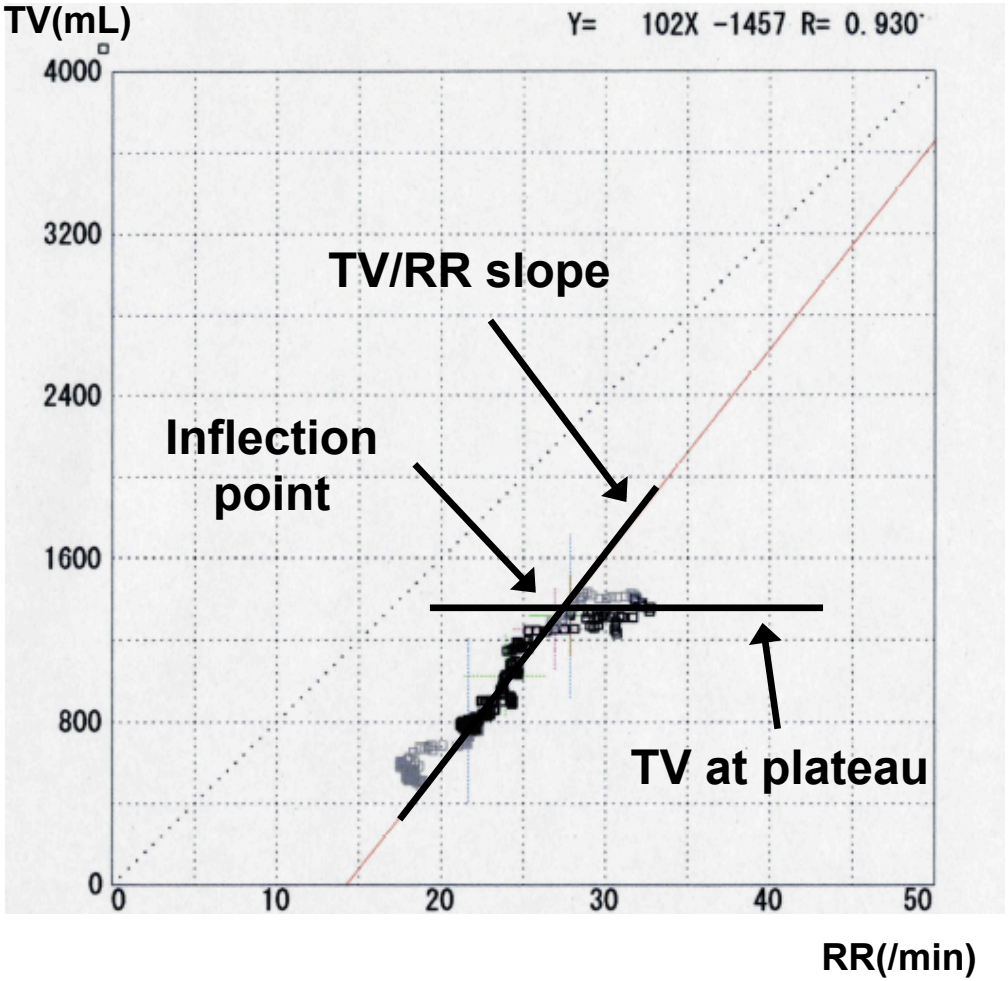
HF: heart failure due to dilated cardiomyopathy, ischemic cardiomyopathy, hypertensive heart disease or tachycardia induced cardiomyopathy

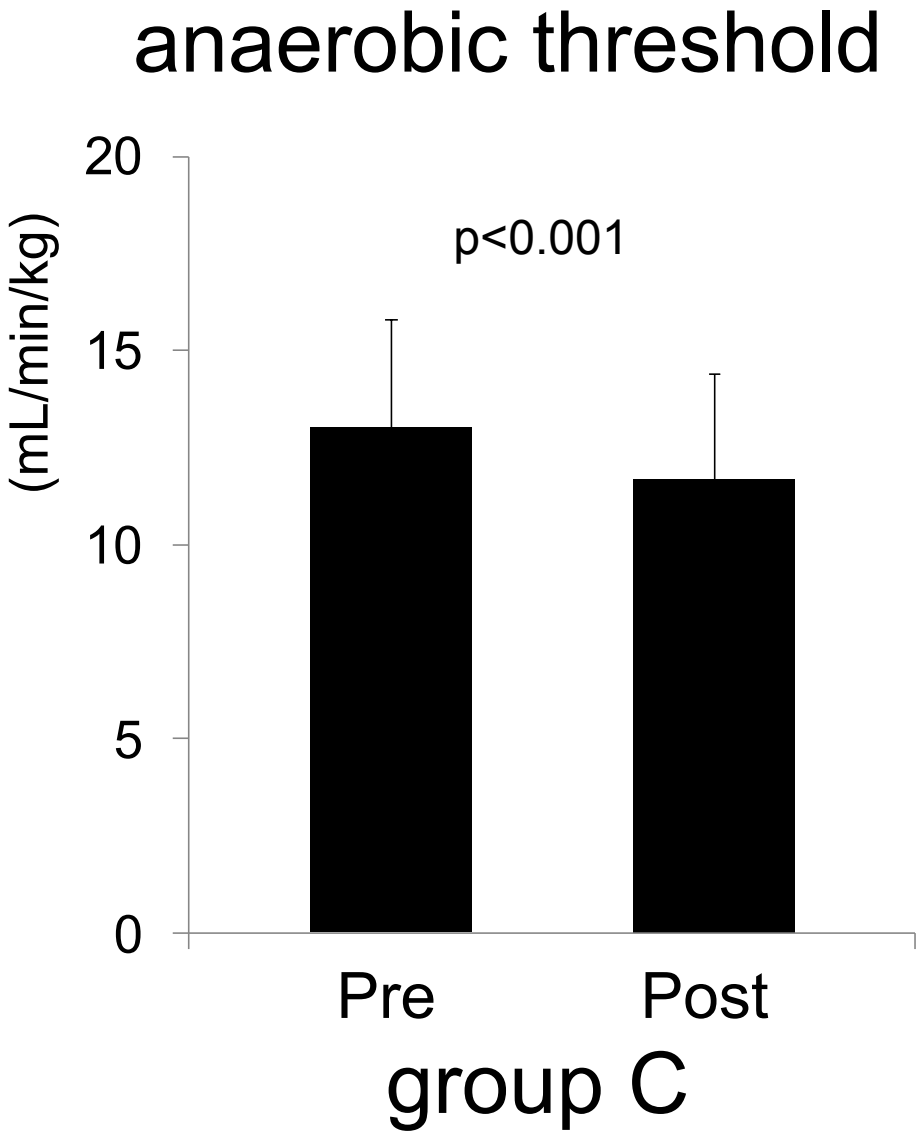
BB: beta blockers

ARB: angiotensin receptor blockers

ACEI: angiotensin converting enzyme inhibitors

TV vs. RR relationship

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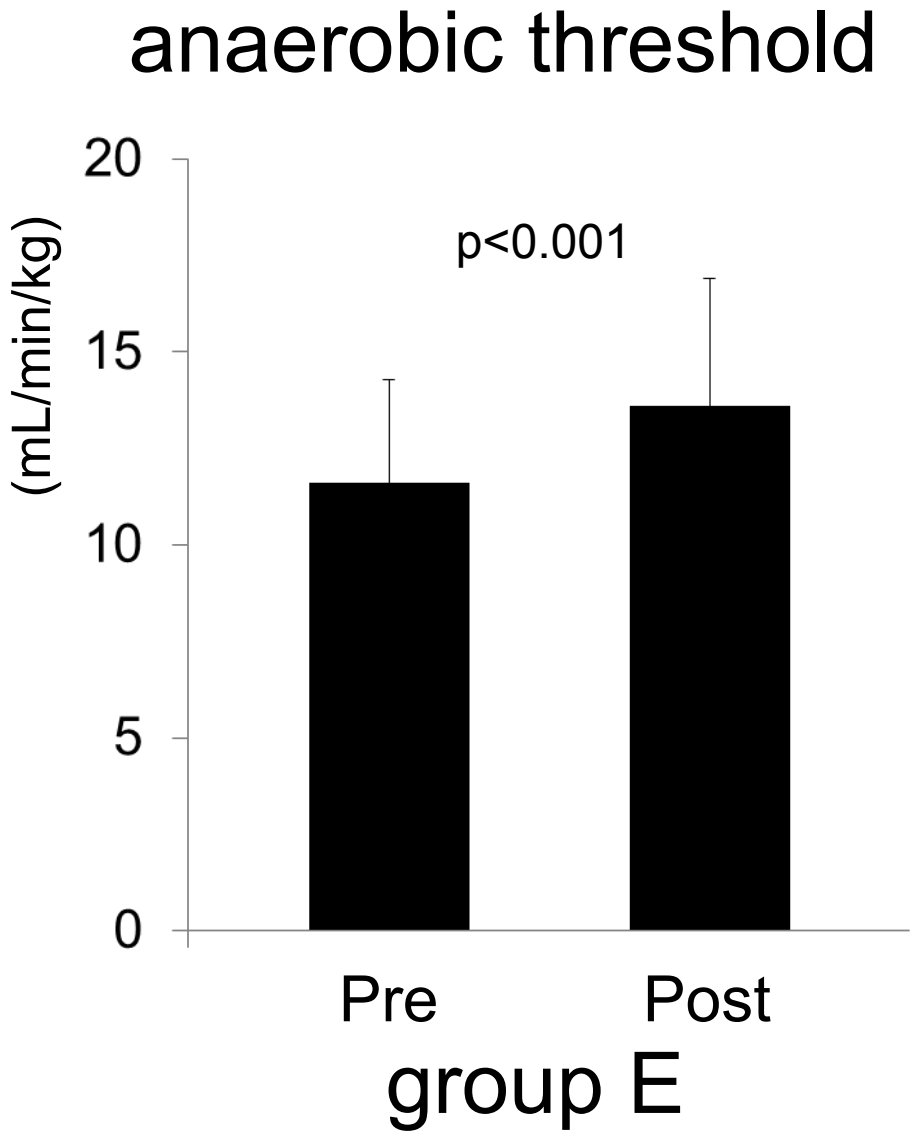
(mL/min/kg)
20
15
10
5
0
p<0.001
Pre
Post
group C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(mL/min/kg)
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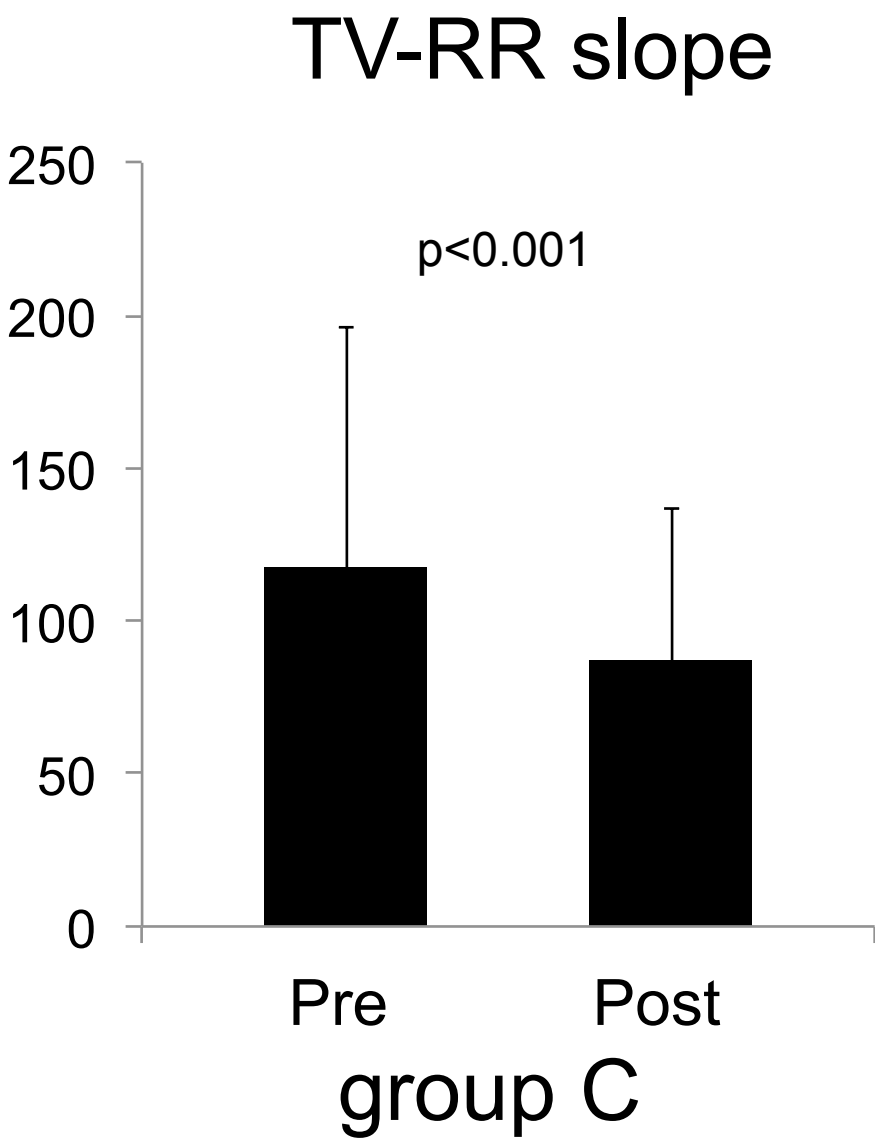
Pre
Post
group E


TV-RR slope
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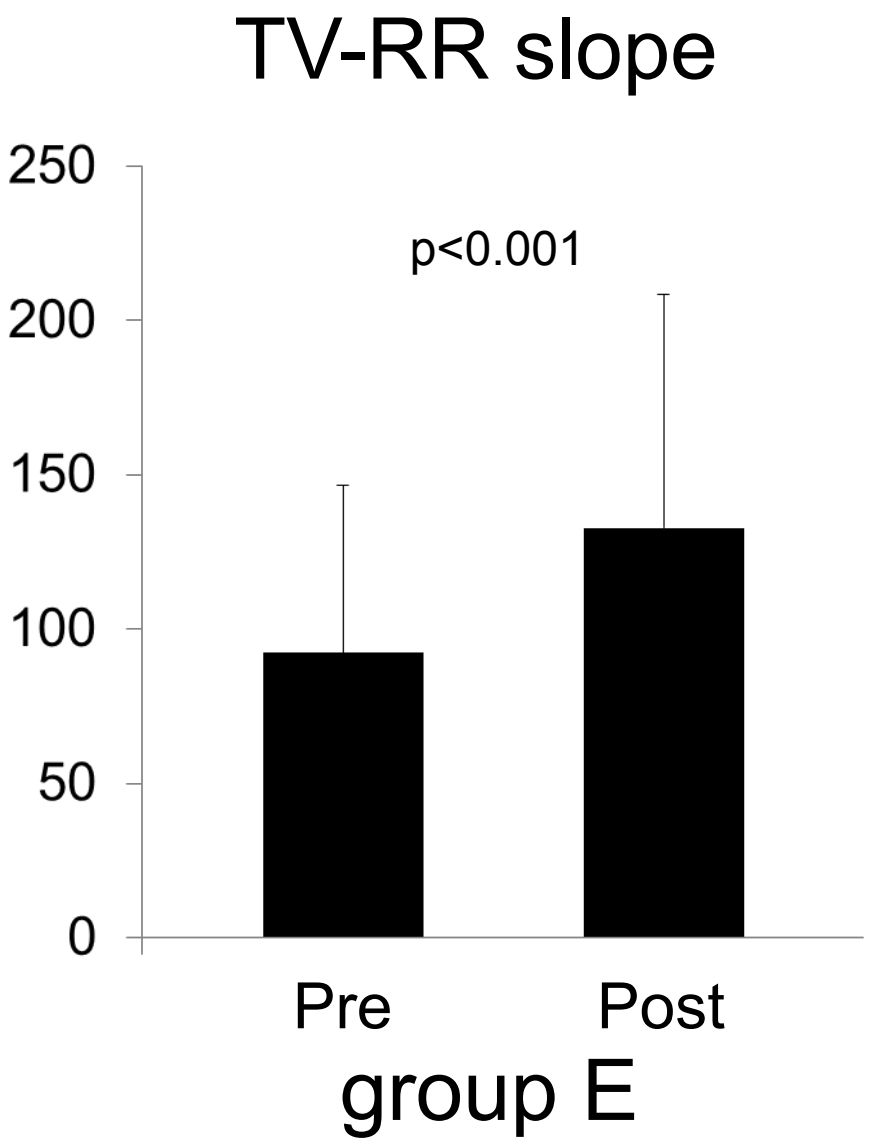
200
150
100
50
0
p<0.001
Pre
Post
group C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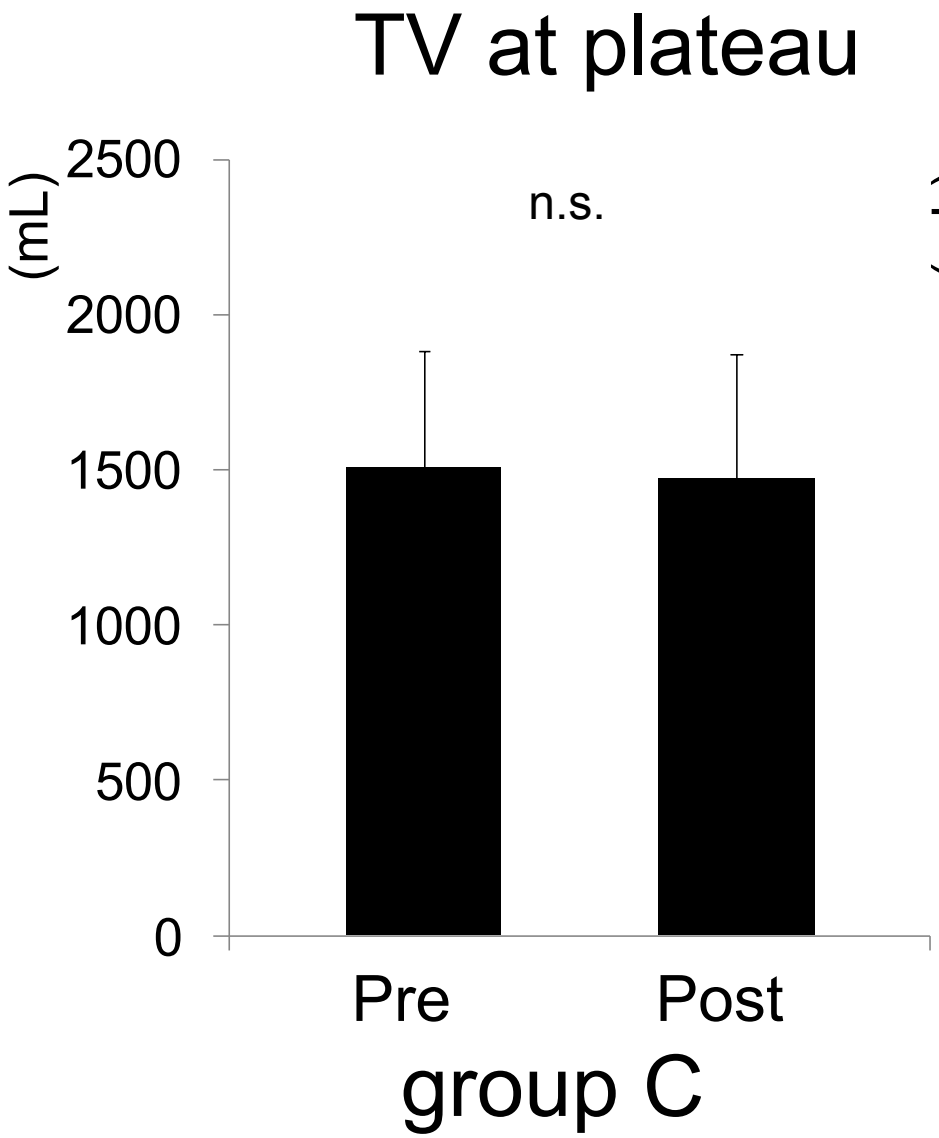
200
150
100
50
0
p<0.001
Pre
Post
group E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(mL)
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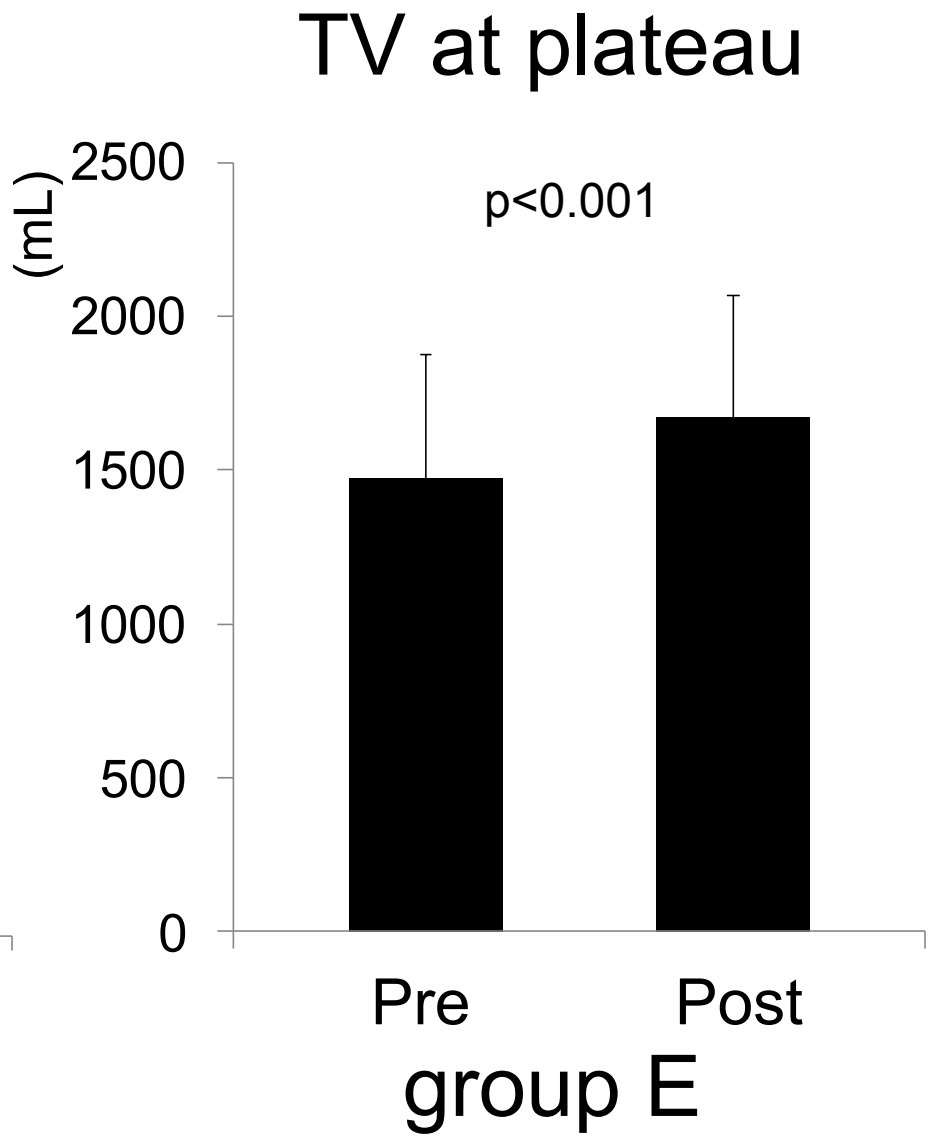
2000
1500
1000
500
0
n.s.
Pre
Post
group C


TV at plateau
(mL)
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2000
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500
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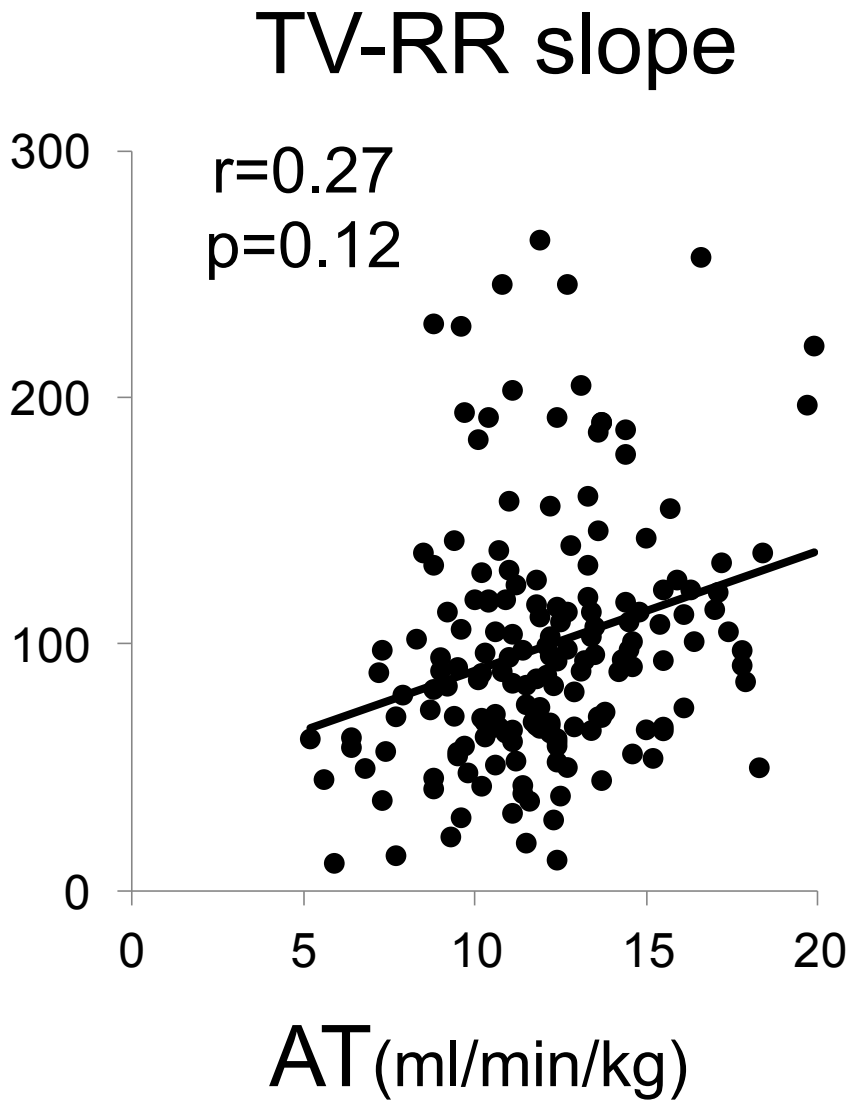
p<0.001
Pre
Post
group E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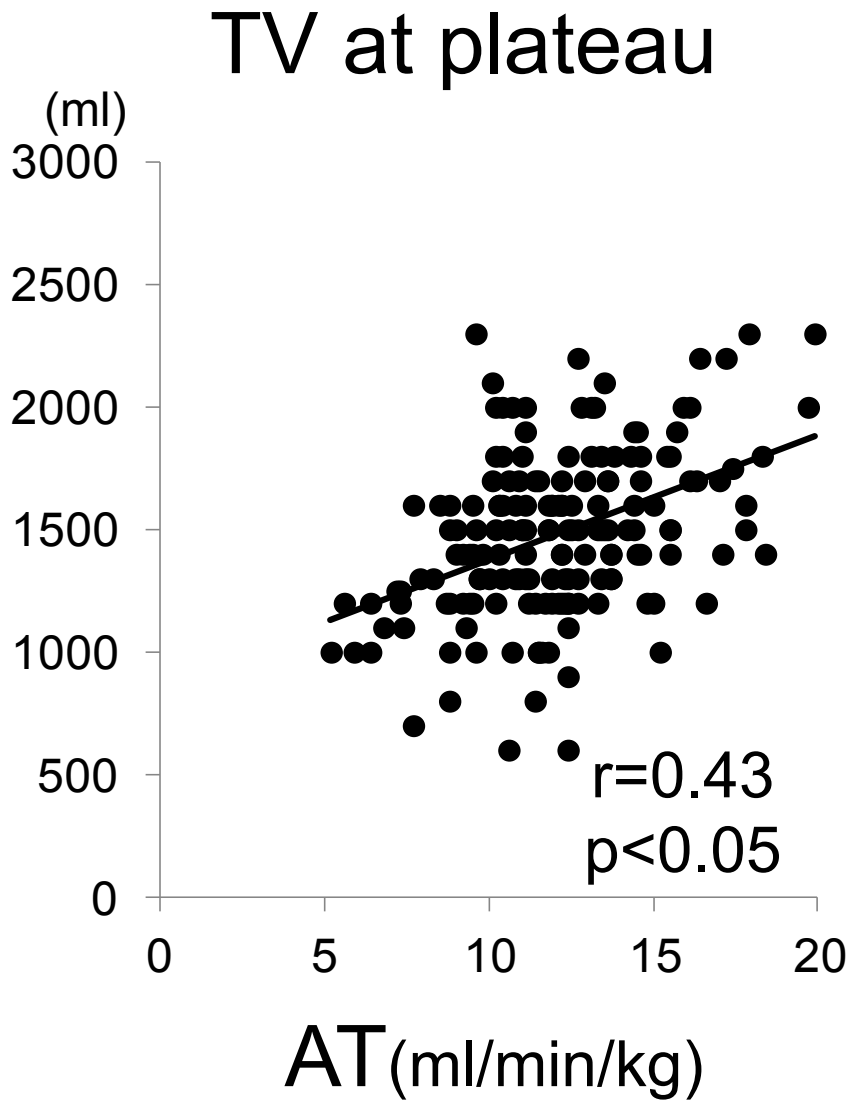
5
10
15
20
AT(ml/min/kg)


TV at plateau
(ml)
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r=0.43
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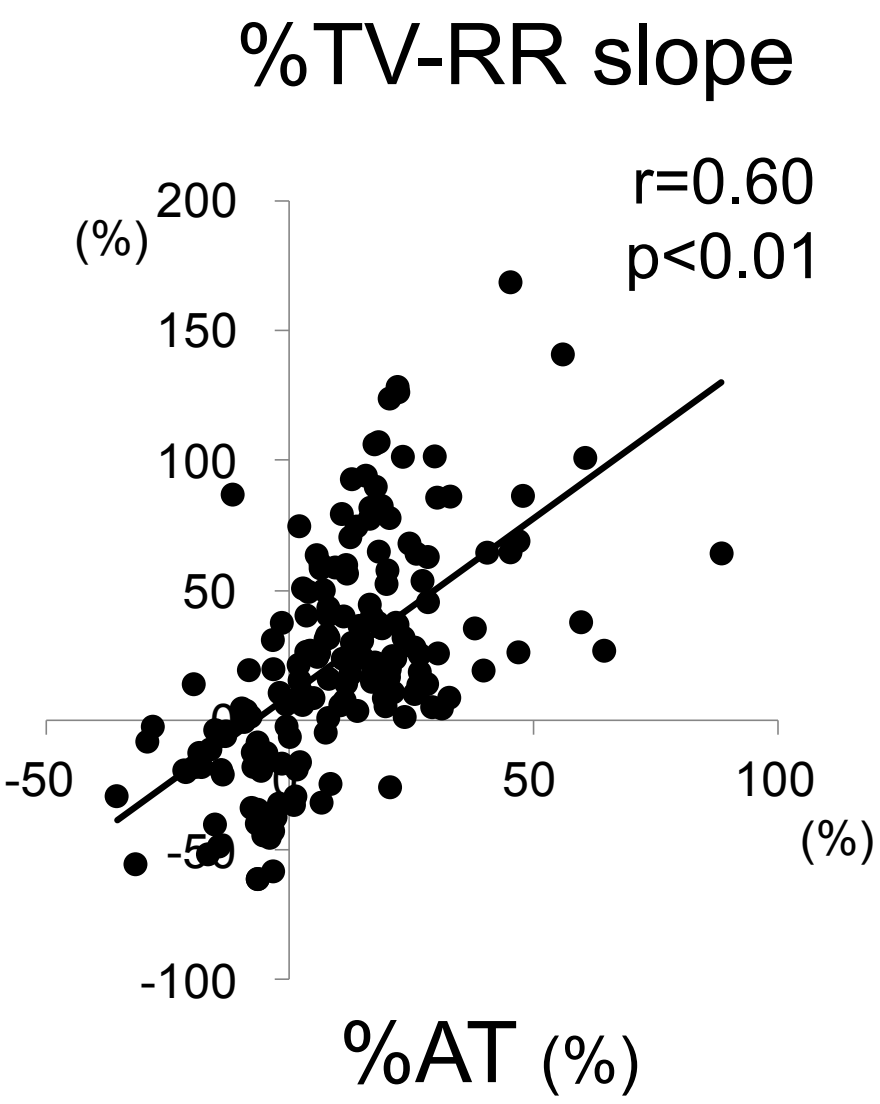
0
5
10
15
20
AT(ml/min/kg)


%TV-RR slope
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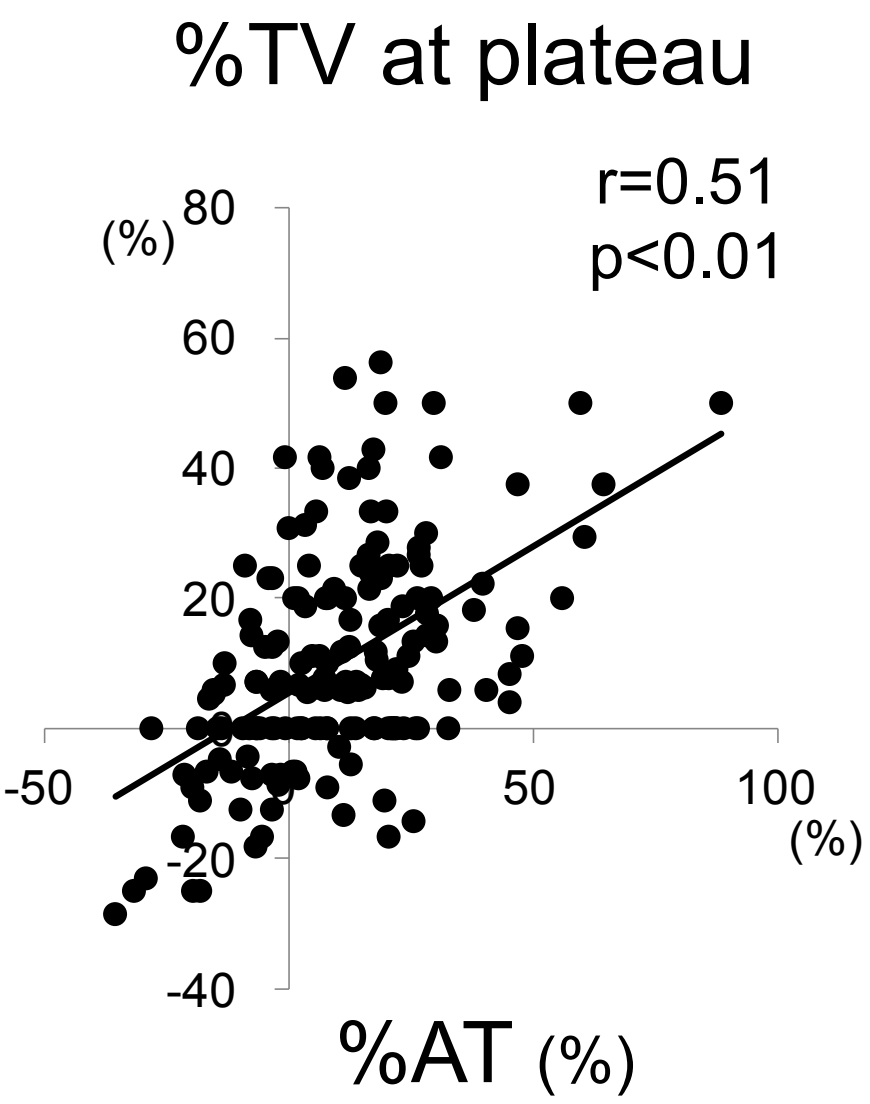
p<0.01
(%)
200
150
100
50
-50
50
100
(%)
-100
%AT (%)


%TV at plateau
r=0.51
p<0.01
(%)
80
60
40
20
-50
50
100
(%)
-20
-40
%AT (%)