Physiological determinants of the increase in oxygen consumption during exercise in individuals with stroke

Short title: Determinants of the increase in oxygen consumption

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Abstract

Background: Understanding the physiological limitations of the increase in oxygen consumption ($\dot{V}O_2$) during exercise is essential to improve cardiorespiratory fitness in individuals with stroke. However, the physiological determinants of the increase in $\dot{V}O_2$ during exercise have not been examined using multivariate analysis in individuals with stroke. This study aimed to identify the physiological determinants of the increase in $\dot{V}O_2$ during a graded exercise in terms of the respiratory function, cardiac function, and ability of skeletal muscles to extract oxygen.

Methods: Eighteen individuals with stroke (60.1 ± 9.4 years of age, 67.1 ± 30.8 days poststroke) underwent a graded exercise test for the assessment of cardiorespiratory response to exercise. The increase in $\dot{V}O_2$ from rest to ventilatory threshold and that from rest to peak exercise were measured as a dependent variable. The increases in respiratory rate, tidal volume, heart rate, stroke volume, and arterial-venous oxygen difference from rest to ventilatory threshold and those from rest to peak exercise were measured as independent variables.

Results: From rest to ventilatory threshold, the increases in heart rate ($\beta = 0.546$) and arterial-venous oxygen difference ($\beta = 0.398$) were significant determinants of the increase in $\dot{V}O_2$ (adjusted $R^2 = 0.703$, $p < 0.001$). From rest to peak exercise, the

increases in tidal volume ($\beta = 0.611$) and heart rate ($\beta = 0.353$) were significant determinants of the increase in $\dot{V}O_2$ (adjusted $R^2 = 0.702$, $p < 0.001$).

Conclusion: $\dot{V}O_2$ is well-known to increase nearly linearly with increasing heart rate; however, our results suggest that arterial-venous oxygen difference and tidal volume are also significant physiological determinants of the increase in $\dot{V}O_2$ from rest to ventilatory threshold and that from rest to peak exercise, respectively. Our findings could potentially contribute to the development of appropriate therapies to improve cardiorespiratory fitness in individuals with stroke.

Introduction

Individuals with stroke have reduced cardiorespiratory fitness compared with age- and sex-matched healthy individuals [1, 2]. Cardiorespiratory fitness reduction is potentially related to walking disability [3, 4], poor cognitive performance [5], and limitations in activities of daily living in individuals with stroke [6-8]. Low levels of cardiorespiratory fitness following stroke may lead to avoidance of physical activity, which causes further deconditioning [9, 10]. Therefore, understanding the physiological limitations of cardiorespiratory fitness in individuals with stroke is essential for the development of appropriate therapies to improve physical activity levels and to prevent further deconditioning.

Oxygen consumption ($\dot{V}O_2$) at ventilatory threshold and that at peak exercise measured during a graded exercise test are used to assess cardiorespiratory fitness in individuals with stroke [1, 11-13]. The physiological factors that potentially limit $\dot{V}O_2$ at peak exercise are respiratory and cardiac functions to supply oxygen and the ability of skeletal muscles to extract oxygen [12, 14, 15]. In healthy adults, $\dot{V}O_2$ at peak exercise seems to be limited primarily by cardiac function [14, 15]. Previous studies [12, 16-18] reported that tidal volume, heart rate, and arterial-venous oxygen difference at peak exercise are significantly lower in individuals with stroke than those in age- and

sex-matched healthy adults, which may lead to the deterioration of cardiorespiratory fitness after stroke. Tomczak et al. [18] reported a significant difference between individuals with stroke and healthy adults in $\dot{V}O_2$ at peak exercise, but not in $\dot{V}O_2$ at rest. Thus, identifying the determinants of the increase in $\dot{V}O_2$ during exercise contributes to understanding the physiological limitations of cardiorespiratory fitness in individuals with stroke. However, the physiological determinants of the increase in $\dot{V}O_2$ during exercise have not been examined using multivariate analysis in individuals with stroke.

Cross-sectional and longitudinal studies found the relationship between $\dot{V}O_2$ and arterial-venous oxygen difference at peak exercise in individuals with stroke [17, 19]. Therefore, we hypothesized that arterial-venous oxygen difference is a primary physiological determinant of the increase in $\dot{V}O_2$ during exercise in these individuals. In this study, we aimed to explore the physiological determinants of the increase in $\dot{V}O_2$ from rest to ventilatory threshold and that from rest to peak exercise in individuals with stroke.

Methods

Study design

This study used a cross-sectional observational design. The study protocol was approved by the appropriate ethics committees of the Tokyo Bay Rehabilitation Hospital (approval number: 172-2) and the Shinshu University (approval number: 3813). All participants provided written informed consent prior to study enrollment. The study was conducted according to the Declaration of Helsinki of 1964, as revised in 2013.

Participants

Participants were recruited from a convalescent rehabilitation hospital between November 2017 and November 2018. The inclusion criteria for the study were as follows: (1) age 40–80 years, (2) being within 180 days after first-ever stroke, (3) ability to maintain a target cadence of 50 rpm during exercise, and (4) a Mini-Mental State Examination score [20] of 24 or more. The exclusion criteria were as follows: (1) limited range of motion and/or pain that could affect the exercise test, (2) unstable medical conditions such as unstable angina, uncontrolled hypertension, and tachycardia, (3) use of beta-blocker, and (4) any comorbid neurological disorder.

Exercise testing

Participants were instructed to refrain from eating for 3 hours and to avoid caffeine and vigorous physical activity for at least 6 and 24 hours, respectively, before the exercise test [21]. All participants performed a symptom-limited graded exercise test on a recumbent cycle ergometer (Strength Ergo 240; Mitsubishi Electric Engineering Co., Ltd., Tokyo, Japan) that can be precisely load-controlled (coefficient of variation, 5%) over a wide range of pedaling resistance (0-400 W). The distance from the seat edge to pedal axis was adjusted so that the participant's knee flexion angle was 20° when extended maximally. The backrest was set at 20° reclined from the vertical position. Additional strapping was attached to secure the paretic foot to the pedal as needed. Following a 3-min of rest period (in sitting position) on the recumbent cycle ergometer to establish a steady state, a warm-up was performed at 0 W for 3 min followed by 10 W increments every minute [21, 22]. Participants were instructed to maintain a target cadence of 50 rpm throughout the exercise [21, 22]. Blood pressure was monitored every minute from the non-paretic arm using an automated system (Tango; Sun Tech Medical Inc., NC, USA). The test was terminated if the participants showed signs of angina, dyspnea, inability to maintain cycling cadence more than 40 rpm, hypertension (more than 250 mmHg systolic or more than 115 mmHg diastolic), or

drop in systolic blood pressure more than 10 mmHg despite an increase in work load [22, 23]. Participants provided their ratings of perceived exertion (6 = no exertion at all, 20 = maximal exertion) [24] for dyspnea and leg effort at the end of the test. Work rate at peak exercise was defined as the peak wattage on test termination [19]. To identify whether maximal effort was reached during the exercise test, at least 1 of the following criteria had to be met: (1) $\dot{V}O_2$ increased less than 150 mL·min^{-1} for more than 1 min despite increased work rate, (2) respiratory exchange ratio achieved greater than 1.10, (3) or heart rate achieved 85% of the age-predicted maximal heart rate (220 minus age) [23, 25].

Physiological variables were measured at rest and continuously during exercise test. $\dot{V}O_2$, respiratory rate, and tidal volume were measured on a breath-by-breath basis using an expired gas analyzer (Aerosonic AT-1100; ANIMA Corp., Tokyo, Japan). Carbon dioxide output, the ventilatory equivalents of oxygen and carbon dioxide, and the end-tidal oxygen and carbon dioxide fractions were also measured using the expired gas analyzer to determine the ventilatory threshold. Heart rate and stroke volume were measured on a beat-by-beat basis using a noninvasive impedance cardiography device (Task Force Monitor model 3040i; CN Systems Medizintechnik GmbH., Graz, Austria) [26-28]. For calculating arterial-venous oxygen difference, measurement values of

138 physiological variables were interpolated to 1-s intervals, time-aligned, and averaged
139 into 5-s bins [18]. Arterial-venous oxygen difference was calculated as the ratio between
140 $\dot{V}O_2$ and the product of heart rate and stroke volume.

141 Physiological variables at rest were defined as the average value obtained
142 during 1 min before exercise onset, and those at peak exercise were defined as the
143 average value obtained during the last 30 s of exercise test [18, 21]. The ventilatory
144 threshold was determined using a combination of the following criteria: (1) the point
145 where the ventilatory equivalent of oxygen reaches its minimum or starts to increase,
146 without an increase in the ventilatory equivalent of carbon dioxide; (2) the point at
147 which the end-tidal oxygen fraction reaches a minimum or starts to increase, without a
148 decline in the end-tidal carbon dioxide fraction; and (3) the point of deflection of carbon
149 dioxide output versus $\dot{V}O_2$ [29]. The first two methods were prioritized in case the three
150 methods presented different results [30, 31]. The ventilatory threshold was determined
151 as an average based on the values provided by two independent raters (NI and YS),
152 when the difference in the $\dot{V}O_2$ values of the corresponding points as determined by the
153 two raters was less than 100 $mL \cdot min^{-1}$ [31, 32]. In case of any discrepancy, a third
154 experienced rater (KO) judged the point, and the ventilatory threshold was taken as the
155 average of the two closest values [30, 31].

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157 Statistical analysis

158 The G Power computer program version 3.1.9.2 (Heinrich Heine University,
159 Dusseldorf, Germany) [33] was used to calculate the sample size required for multiple
160 regression analysis. For multiple regression analyses, if up to five variables (respiratory
161 rate, tidal volume, heart rate, stroke volume, and arterial-venous oxygen difference) are
162 modeled at an effect size of 0.49 (very large) at an α level of 0.05 and power of 0.80, a
163 minimum of 12 participants are required [33, 34].

164 Normality of distribution was tested using the Shapiro-Wilk test. One-way
165 repeated-measures analysis of variance or Friedman test with exercise period as a factor
166 was used to examine whether physiological variables change during exercise. Post hoc
167 analyses were performed using the Bonferroni multiple comparison test.

168 The increase in $\dot{V}O_2$ from rest to ventilatory threshold and that from rest to
169 peak exercise were calculated as the dependent variables. Pearson's product moment
170 correlation coefficient or Spearman's rank correlation coefficient was used to test the
171 correlations between the increases from rest to ventilatory threshold in $\dot{V}O_2$ and other
172 physiological variables and between the increases from rest to peak exercise in $\dot{V}O_2$ and
173 other physiological variables. Those variables that were significantly correlated with the

increase in $\dot{V}O_2$ during exercise testing were then entered into the stepwise multiple regression analysis to determine the physiological limitations of the increase in $\dot{V}O_2$ with considering multicollinearity. Statistical analyses were performed using the Statistical Package for the Social Sciences software version 24.0 (International Business Machines Corp., NY, USA). Any p values less than 0.05 were considered statistically significant.

Results

A flow diagram of study participants is shown in Fig 1. Eighteen individuals with stroke participated in the study. Table 1 shows the characteristics of the participants.

Fig 1. Flow diagram of study participants.

Table 1. Characteristics of participants

Variable	Value
Age, years	60.1 ± 9.4
Sex, male/female	14 (78)/4 (22)
Body mass index, kg· m^{-2}	23.0 ± 3.3
Type of stroke, ischemic/hemorrhage	11 (61)/7 (39)
Side of motor paresis, right/left	8 (44)/10 (56)
Time since stroke, days	67.1 ± 30.8
Fugl-Meyer lower extremity motor scores, points	28.8 ± 7.7
Antihypertensive medications	
Angiotensin II receptor blocker	2 (11)
Calcium channel blocker	4 (22)
Comorbidities	
Hypertension	6 (33)
Diabetes mellitus	4 (22)

Hyperlipidemia	3 (17)

Values are presented as mean ± SD or number (%).

No significant adverse events occurred during or after exercise test. All participants stopped their exercise test due to inability to maintain cycling cadence more than 40 rpm. In addition, all participants met at least one of the criteria for reaching maximal effort. Median (interquartile range) values of the ratings of perceived exertion for dyspnea and leg effort at the end of the test were 13 (13–15) and 15 (13–15), respectively. Mean ± standard deviation of work rate at peak exercise was 69.4 ± 30.6 W.

Measurement values at rest, ventilatory threshold, and peak exercise are shown in Table 2. We observed a main effect of exercise period on all physiological variables ($p < 0.001$). All physiological variables at ventilatory threshold were significantly higher than those at rest ($p < 0.001$). From ventilatory threshold to peak exercise, $\dot{V}O_2$, respiratory rate, tidal volume, and heart rate significantly increased (mean difference = 198.6, 95% confidence interval [CI] = 95.4, 301.7, and $p < 0.001$; mean difference = 7.5, 95% CI = 3.2, 11.7, and $p < 0.001$; mean difference = 0.21, 95% CI = 0.08, 0.33, and $p = 0.002$; mean difference = 18.7, 95% CI = 10.2, 21.3, and $p < 0.001$, respectively),

213 whereas no significant changes in stroke volume and arterial-venous oxygen difference

214 were found (mean difference = -1.9, 95% CI = -6.9, 3.0, and p = 0.945; mean difference

215 = 0.74, 95% CI = -0.22, 1.70, and p = 0.172, respectively).

Table 2. Physiological variables at rest, ventilatory threshold, and peak exercise

Variable	Rest	Ventilatory threshold	Peak exercise	p value
$\dot{V}O_2$, mL·min^{-1}	253.1 ± 57.7	899.7 ± 224.8*	1098.3 ± 330.3$^{\dagger, \ddagger}$	< 0.001
Respiratory rate, breaths·min^{-1}	18.5 ± 2.8	25.2 ± 4.5*	32.6 ± 8.5$^{\dagger, \ddagger}$	< 0.001
Tidal volume, L	0.46 ± 0.11	1.07 ± 0.23*	1.28 ± 0.30$^{\dagger, \ddagger}$	< 0.001
Heart rate, bpm	76.0 ± 9.2	109.9 ± 13.6*	128.6 ± 17.5$^{\dagger, \ddagger}$	< 0.001
Stroke volume, mL	55.0 ± 7.6	73.0 ± 10.4*	71.0 ± 9.4†	< 0.001
Arterial-venous oxygen difference, mL·100 mL^{-1}	6.2 ± 1.6	11.2 ± 1.8*	12.0 ± 2.4†	< 0.001

Values are presented as mean ± SD.

A p value represents a significant main effect of exercise period.

*, a significant difference between ventilatory threshold and rest ($p < 0.001$).

†, a significant difference between peak exercise and rest ($p < 0.001$).

‡, a significant difference between peak exercise and ventilatory threshold ($p < 0.001$).

From rest to ventilatory threshold, correlations between the increases in $\dot{V}O_2$ and other physiological variables are shown in Fig 2. The increase in $\dot{V}O_2$ was significantly correlated with the increases in tidal volume ($r = 0.620$; 95% CI = 0.215, 0.843; and $p = 0.006$) (Fig 2b), heart rate ($r = 0.804$; 95% CI = 0.540, 0.924; and $p < 0.001$) (Fig 2c), and arterial-venous oxygen difference ($r = 0.752$; 95% CI = 0.440, 0.902; and $p < 0.001$) (Fig 2e). Stepwise multiple regression analysis revealed that the increases in heart rate ($\beta = 0.546$) and arterial-venous oxygen difference ($\beta = 0.398$) were the significant determinants for the increase in $\dot{V}O_2$ (adjusted $R^2 = 0.703$, $p < 0.001$) (Table 3).

Fig 2. Correlations between the increases in $\dot{V}O_2$ and respiratory rate (a), $\dot{V}O_2$ and tidal volume (b), $\dot{V}O_2$ and heart rate (c), $\dot{V}O_2$ and stroke volume (d), and $\dot{V}O_2$ and arterial-venous oxygen difference (e) from rest to ventilatory threshold.

241 Table 3. Stepwise multiple regression analysis for identifying the determinants of the increase in $\dot{V}O_2$ from rest to ventilatory threshold

Variable	β	Coefficient	SE	t value	p value
Increase in heart rate from rest to ventilatory threshold	0.546	8.73	2.78	3.14	0.007
Increase in arterial-venous oxygen difference from rest to ventilatory threshold	0.398	43.03	18.82	2.29	0.037
Constant		133.20	83.61	1.59	0.132
$F(2, 15) = 21.12$, $p < 0.001$, $R^2 = 0.738$, Adjusted $R^2 = 0.703$					

242 β, standard coefficient; SE, standard error.

From rest to peak exercise, correlations between the increases in $\dot{V}O_2$ and other physiological variables are shown in Fig 3. The increase in $\dot{V}O_2$ was significantly correlated with the increases in tidal volume ($r = 0.806$; 95% CI = 0.544, 0.925; and $p < 0.001$) (Fig 3b), heart rate ($r = 0.691$; 95% CI = 0.330, 0.875; and $p = 0.002$) (Fig 3c), and arterial-venous oxygen difference ($r = 0.729$; 95% CI = 0.398, 0.892; and $p < 0.001$) (Fig 3e). Stepwise multiple regression analysis revealed that the increases in tidal volume ($\beta = 0.611$) and heart rate ($\beta = 0.353$) were significant determinants for the increase in $\dot{V}O_2$ (adjusted $R^2 = 0.702$, $p < 0.001$) (Table 4).

Fig 3. Correlations between the increases in $\dot{V}O_2$ and respiratory rate (a), $\dot{V}O_2$ and tidal volume (b), $\dot{V}O_2$ and heart rate (c), $\dot{V}O_2$ and stroke volume (d), and $\dot{V}O_2$ and arterial-venous oxygen difference (e) from rest to peak exercise.

Table 4. Stepwise multiple regression analysis for identifying the determinants of the increase in $\dot{V}O_2$ from rest to peak exercise

Variable	β	Coefficient	SE	t value	p value
Increase in tidal volume from rest to peak exercise	0.611	749.82	194.88	3.85	0.002
Increase in heart rate from rest to peak exercise	0.353	6.72	3.02	2.23	0.041
Constant		-117.65	155.12	0.76	0.460
$F(2, 15) = 20.99$, $p < 0.001$, $R^2 = 0.737$, Adjusted $R^2 = 0.702$					

β, standard coefficient: SE, standard error.

Discussion

This study is the first to explore the physiological determinants of the increase in $\dot{V}O_2$ during graded exercise in individuals with stroke. From rest to ventilatory threshold, the increases in heart rate and arterial-venous oxygen difference were the significant determinants of the increase in $\dot{V}O_2$. From rest to peak exercise, the increases in tidal volume and heart rate were the significant determinants of the increase in $\dot{V}O_2$. Physiological impairments in these variables may negatively affect cardiorespiratory fitness in individuals with stroke.

The results of correlation analyses may support previous studies suggesting that impaired tidal volume, heart rate, and arterial-venous oxygen difference at peak exercise limit cardiorespiratory fitness in individuals with stroke [12, 16-18, 31]. Contrary to our hypothesis, only the increase in heart rate was identified as one of the significant determinants of both the increases in $\dot{V}O_2$ from rest to ventilatory threshold and that from rest to peak exercise, which can be explained by the fact that $\dot{V}O_2$ increases nearly linearly with increasing heart rate during exercise [35]. Tomczak et al. [18] indicated that the impaired increase in $\dot{V}O_2$ during exercise in individuals with stroke may be attributed to the impaired increase in heart rate. Our results suggest that cardiac function to supply oxygen rather than the ability of skeletal muscles to extract oxygen affects cardiorespiratory fitness in individuals with stroke. Conversely, Jakovljevic et al. [17] and Moore et al. [19] reported that oxygen extraction

283 rather than oxygen supply is related with cardiorespiratory fitness in individuals with chronic
284 stroke. The discrepancy in results between the present and previous studies [17, 19] may be
285 caused by the characteristics of participants such as time since stroke.

286 Skeletal muscle changes after stroke, such as muscle atrophy and shift of muscle
287 fiber type (from type I slow-twitch muscle fibers to type II fast-twitch muscle fibers)
288 particularly in the paretic lower extremity, are observed in individuals with stroke [36]. In
289 addition, impaired vasodilatory function and reduction in blood flow in the paretic lower
290 extremity have also been reported [37, 38]. These changes after stroke may reduce the ability
291 of skeletal muscles to extract oxygen. Reduction in the ability of skeletal muscles to extract
292 oxygen during exercise may increase the dependence of anaerobic glycolysis for energy
293 output, thus increasing the output of lactic acid [39, 40]. Minute ventilation begins to increase
294 exponentially relative to the increase in $\dot{V}O_2$ to eliminate the excess carbon dioxide produced
295 from bicarbonate buffering of lactic acid, which is defined as ventilatory threshold [41].
296 These findings support our results that arterial-venous oxygen difference was identified as
297 one of the physiological determinants of the increase in $\dot{V}O_2$ from rest to ventilatory
298 threshold.

299 Although arterial-venous oxygen difference increases with incremental exercise, that
300 is assumed to be relatively constant at a submaximal work rate [35]. We observed a
301 significant increase in $\dot{V}O_2$ but not in arterial-venous oxygen difference from ventilatory

threshold to peak exercise. This may explain the reason why the increase in arterial-venous oxygen difference was not selected as the significant physiological determinant of the increase in $\dot{V}O_2$ from rest to peak exercise. Our stepwise regression analysis indicated that the increase in tidal volume was a major physiological determinant of the increase in $\dot{V}O_2$ from rest to peak exercise. Sisante et al. [16] and Tomczak et al. [18] reported that tidal volume and $\dot{V}O_2$ at peak exercise are significantly lower in individuals with stroke than in healthy controls. Their findings suggest that decreased tidal volume limits the increase in $\dot{V}O_2$ during exercise. The paralysis of the expiratory muscles on the affected side, decreased motion of the diaphragm, and reduced chest wall excursion may limit the increase in tidal volume during exercise [12, 42].

This study had several limitations. First, all participants were in the subacute stages of recovery from stroke. Therefore, generalization of the findings to individuals with chronic stroke should be made with caution. Second, we used a recumbent cycle ergometer. A treadmill [6], a total-body recumbent steppe [43], a robotics-assisted tilt table [30], and an arm crank ergometer [31] are also used to assess cardiorespiratory fitness in individuals with stroke. Further studies are warranted to examine whether the major physiological determinant of the increase in $\dot{V}O_2$ during exercise differs with the exercise devices. Finally, as this study used the cross-sectional observational design, the physiological determinants of the temporal changes in $\dot{V}O_2$ at ventilatory threshold and at peak exercise could not be examined. Further

longitudinal studies are needed to examine whether physiological impairments in tidal volume, heart rate, and arterial-venous oxygen difference affect the temporal changes in $\dot{V}O_2$ for the development of appropriate therapies to improve cardiorespiratory fitness in individuals with stroke.

Conclusions

$\dot{V}O_2$ is well-known to increase nearly linearly with increasing heart rate [35, 41]; however our results suggest that arterial-venous oxygen difference and tidal volume are also significant physiological determinants of increase in $\dot{V}O_2$ from rest to ventilatory threshold and that from rest to peak exercise, respectively. Our findings could potentially contribute to the development of appropriate therapies to improve cardiorespiratory fitness in individuals with stroke.

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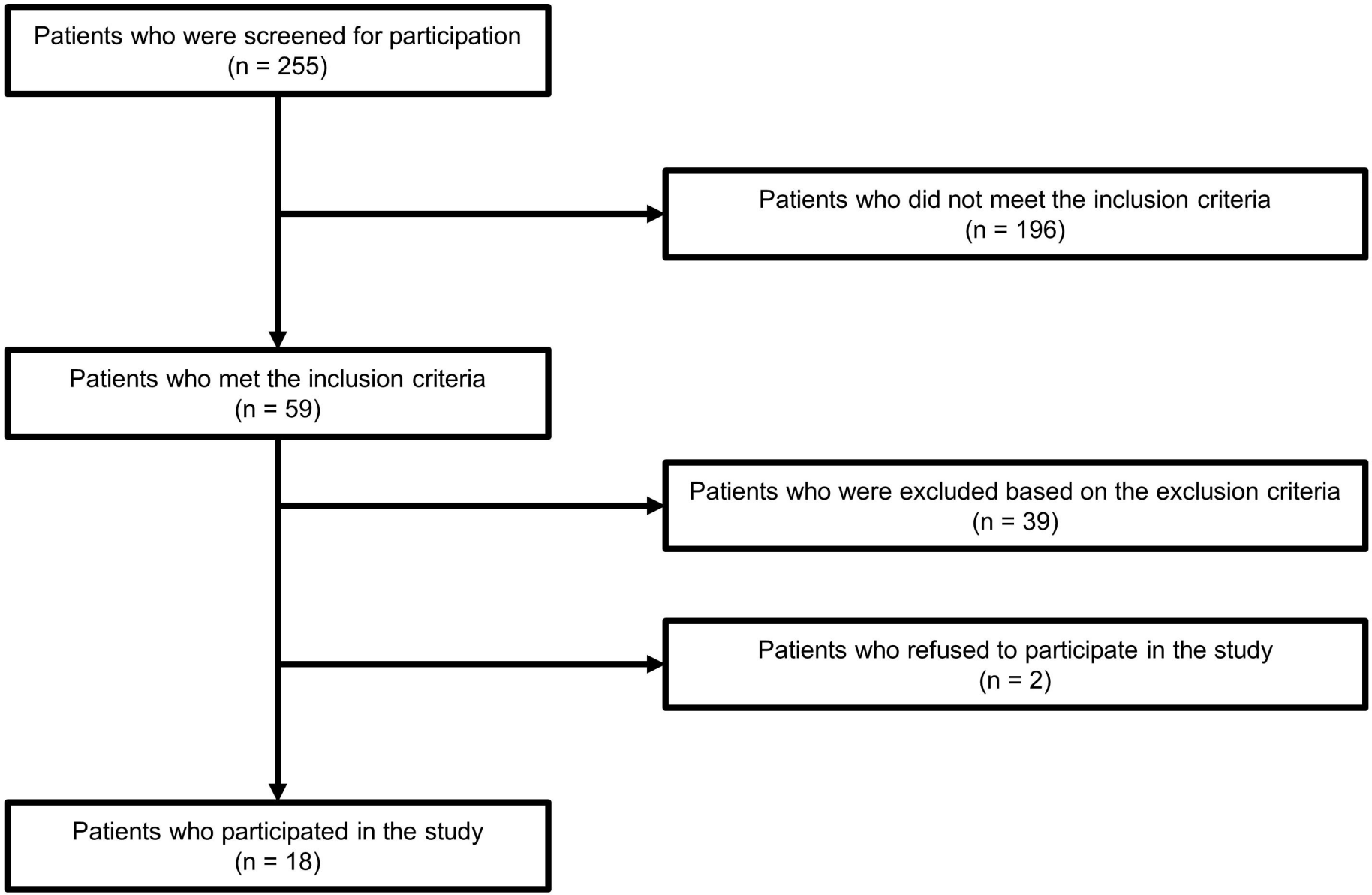
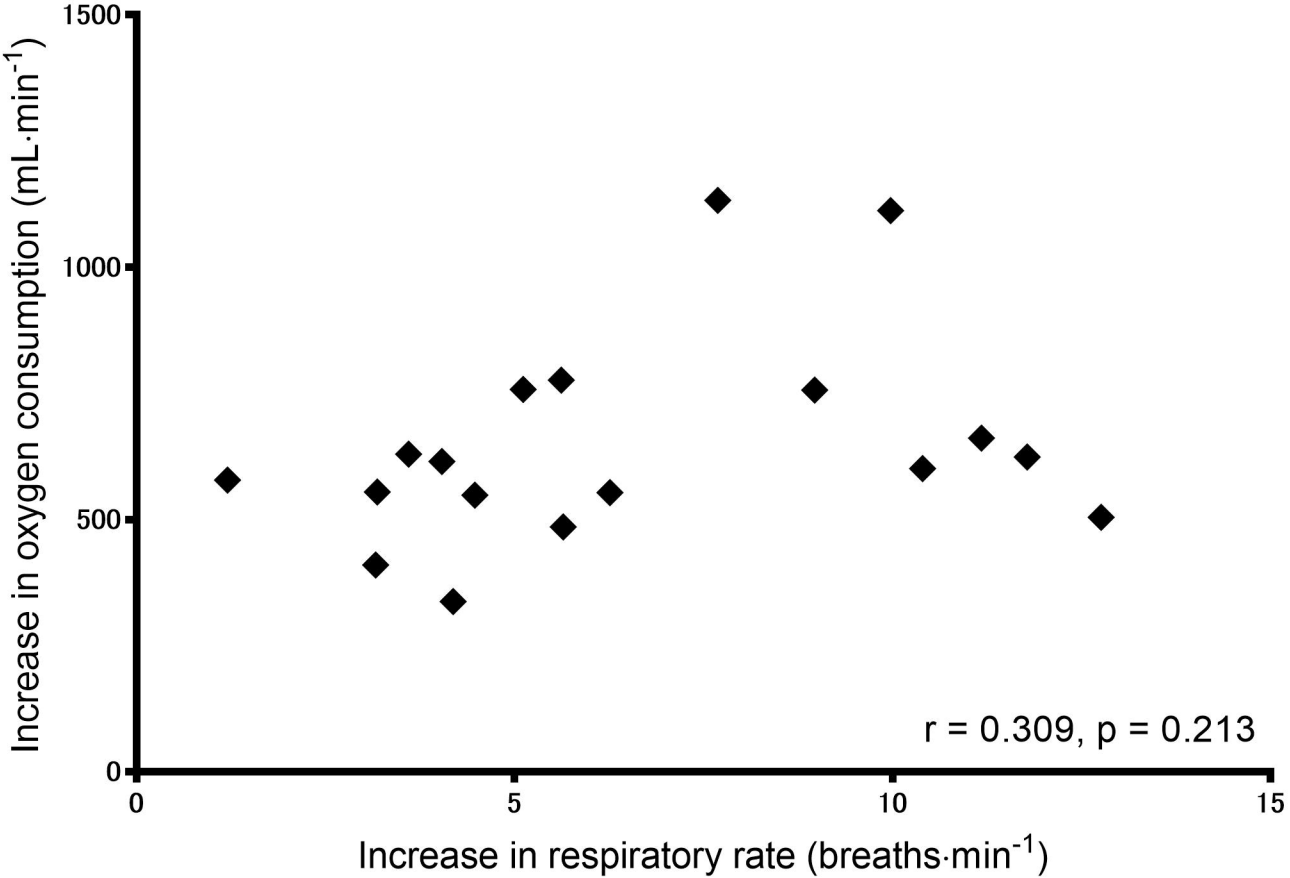
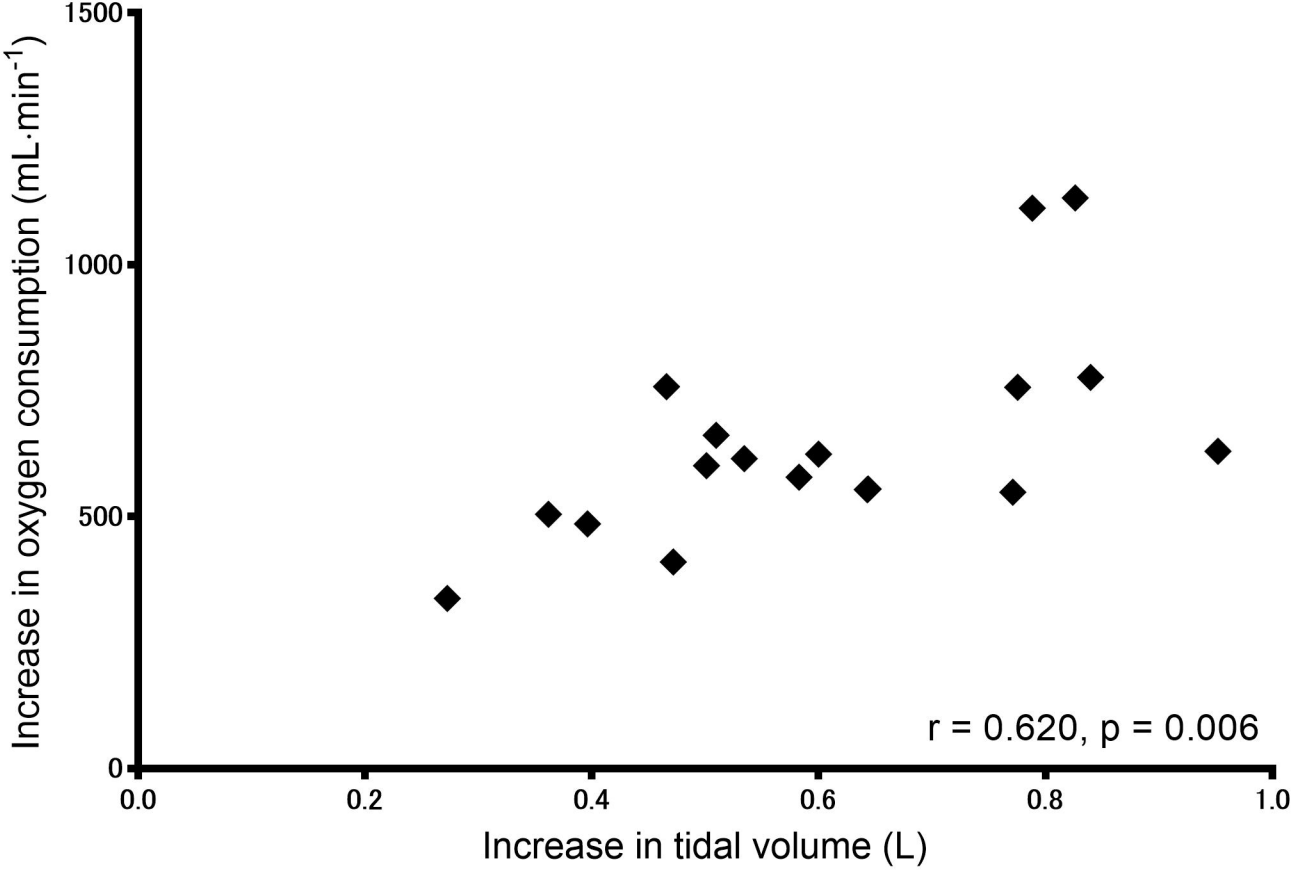

Patients who were screened for participation
(n = 255)
Patients who did not meet the inclusion criteria
(n = 196)
Patients who met the inclusion criteria
(n = 59)
Patients who were excluded based on the exclusion criteria
(n = 39)
Patients who refused to participate in the study
(n = 2)
Patients who participated in the study
(n = 18)

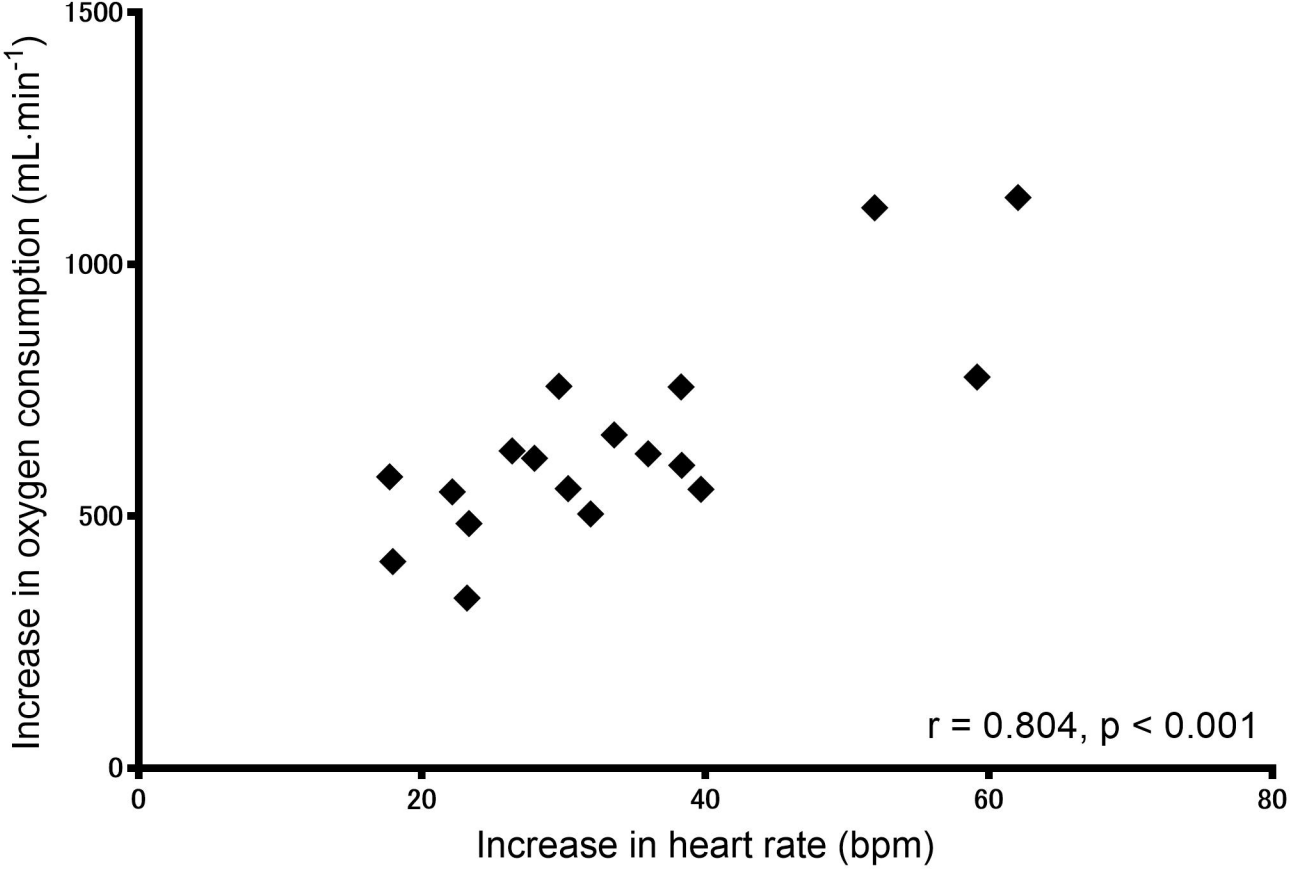
a


1500
1000
500
0
Increase in oxygen consumption (mL·min-1)
r = 0.309, p = 0.213
0
5
10
15
Increase in respiratory rate (breaths·min-1)

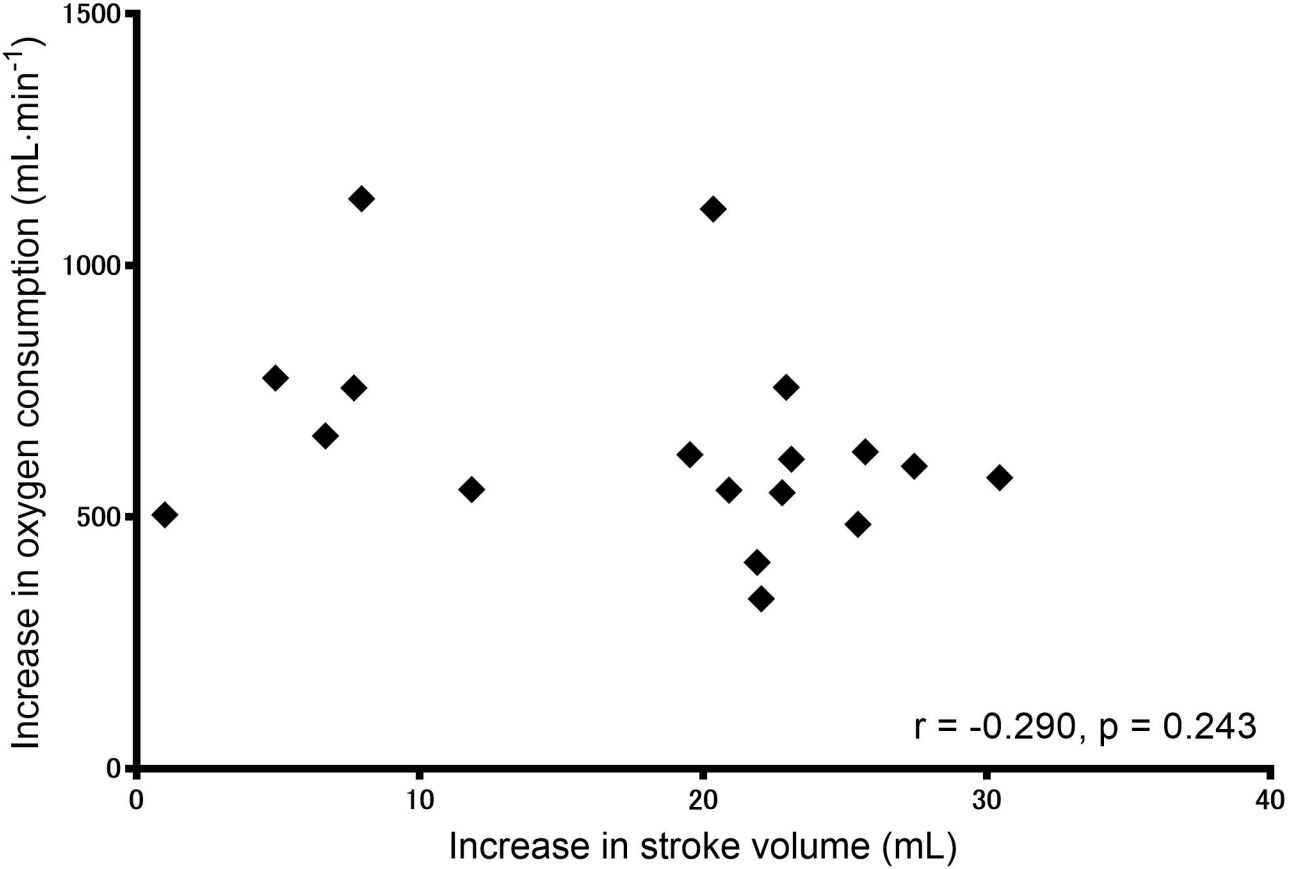
b

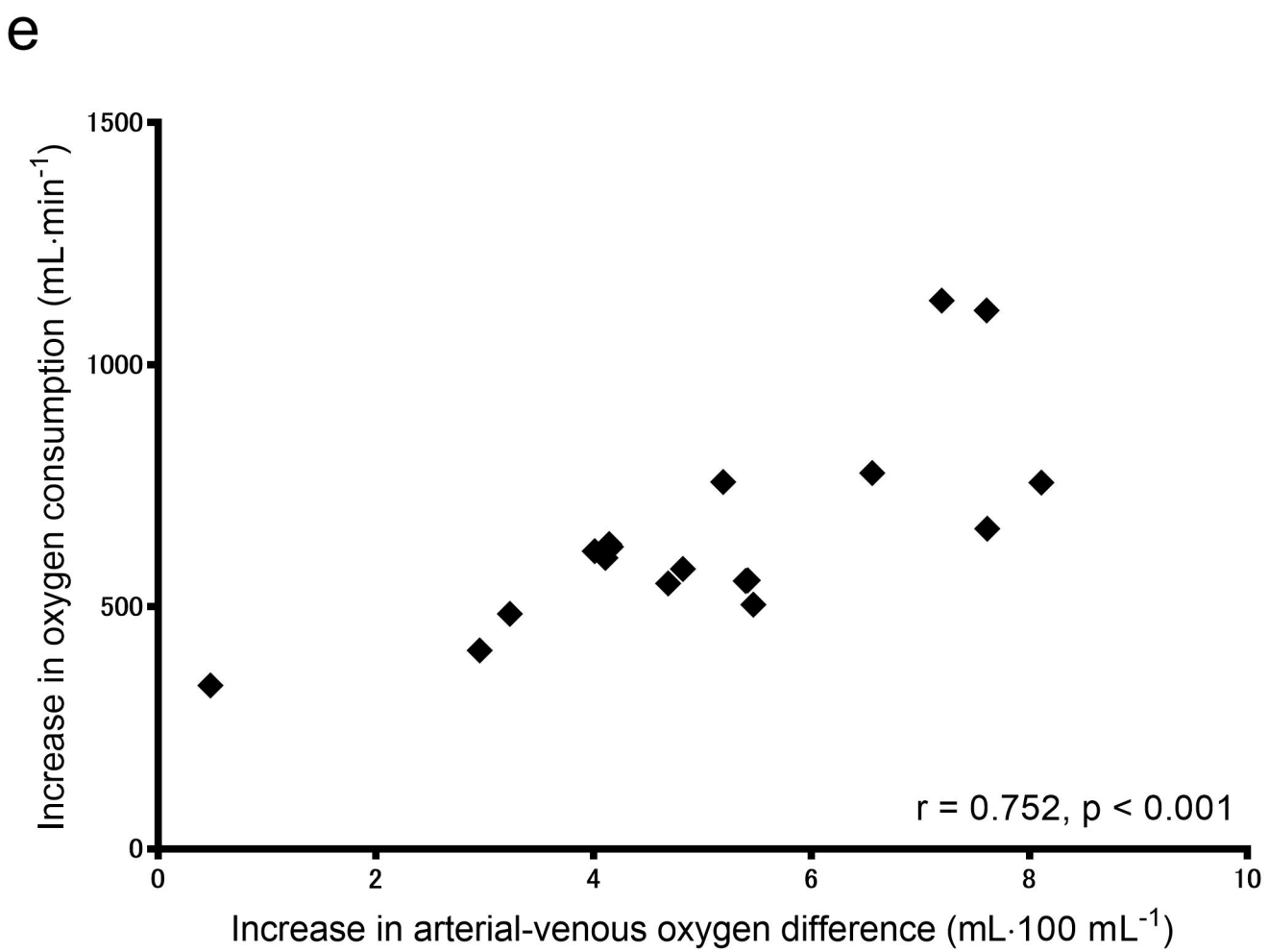

1500
1000
500
0
Increase in oxygen consumption (mL·min-1)
0.0
0.2
0.4
0.6
0.8
1.0
Increase in tidal volume (L)
r = 0.620, p = 0.006

C

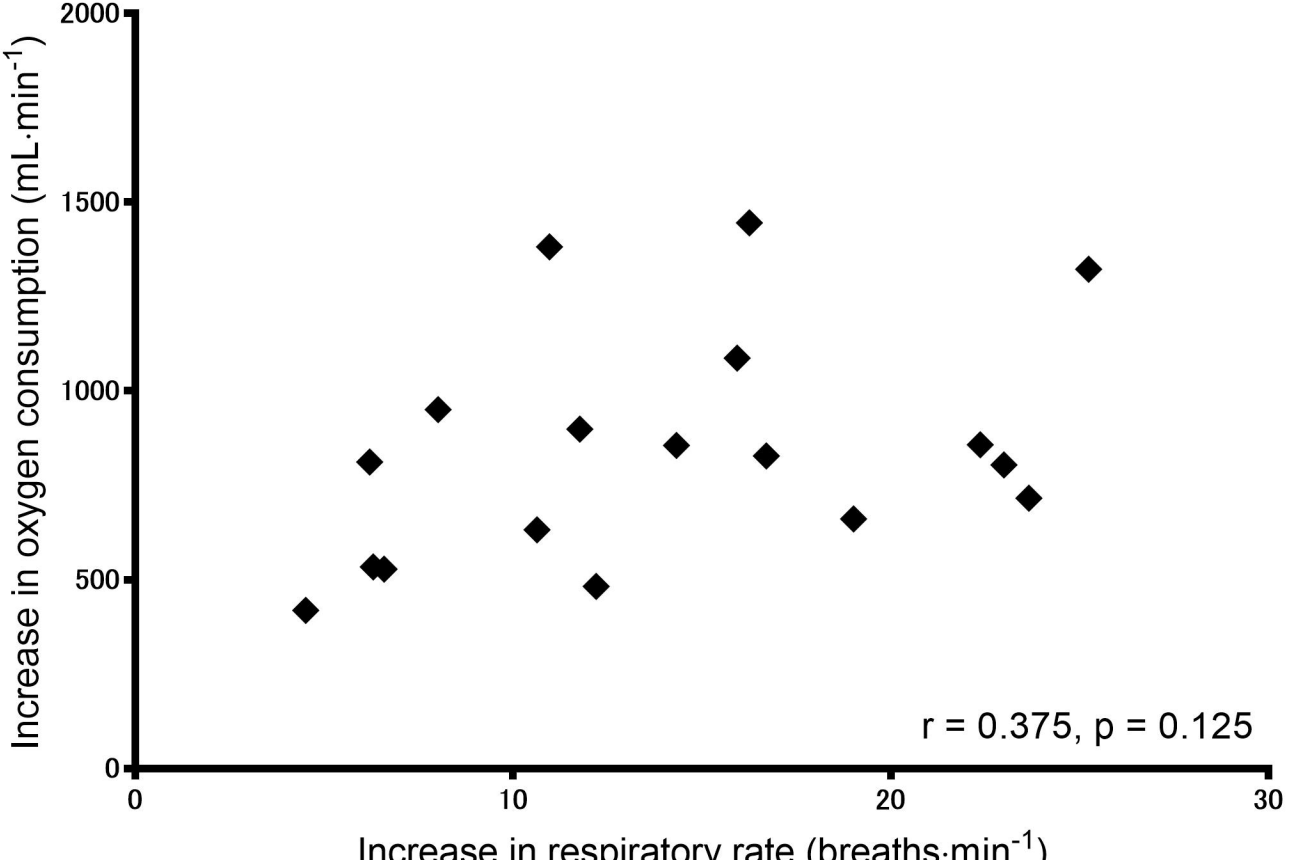

1500
1000
500
0
Increase in oxygen consumption (mL·min-1)
0
20
40
60
80
Increase in heart rate (bpm)
r = 0.804, p < 0.001

d

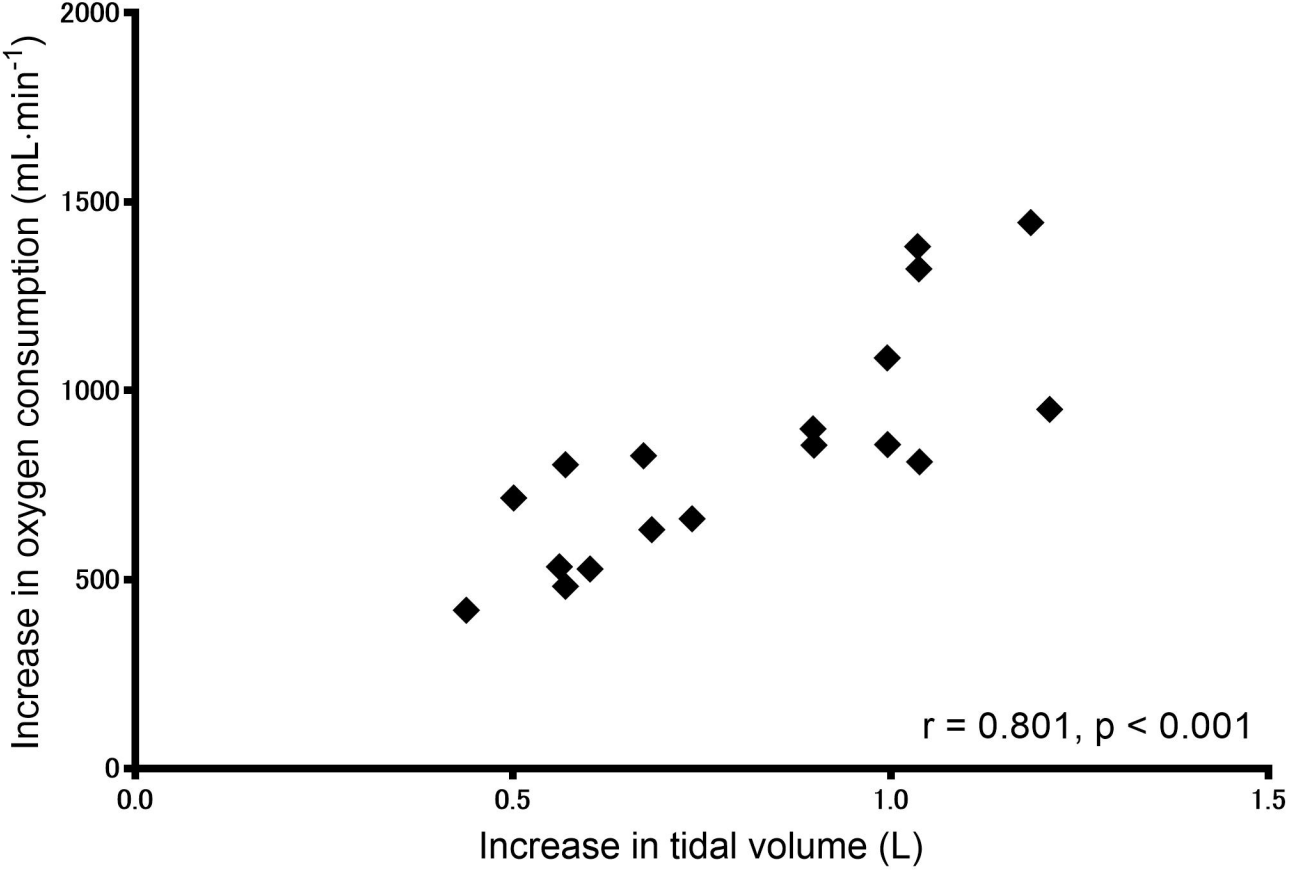

1500
1000
500
0
Increase in oxygen consumption (mL·min-1)
0
10
20
30
40
Increase in stroke volume (mL)
r = -0.290, p = 0.243


e
1500
1000
500
0
Increase in oxygen consumption (mL·min-1)
r = 0.752, p < 0.001
0
2
4
6
8
10
Increase in arterial-venous oxygen difference (mL·100 mL-1)

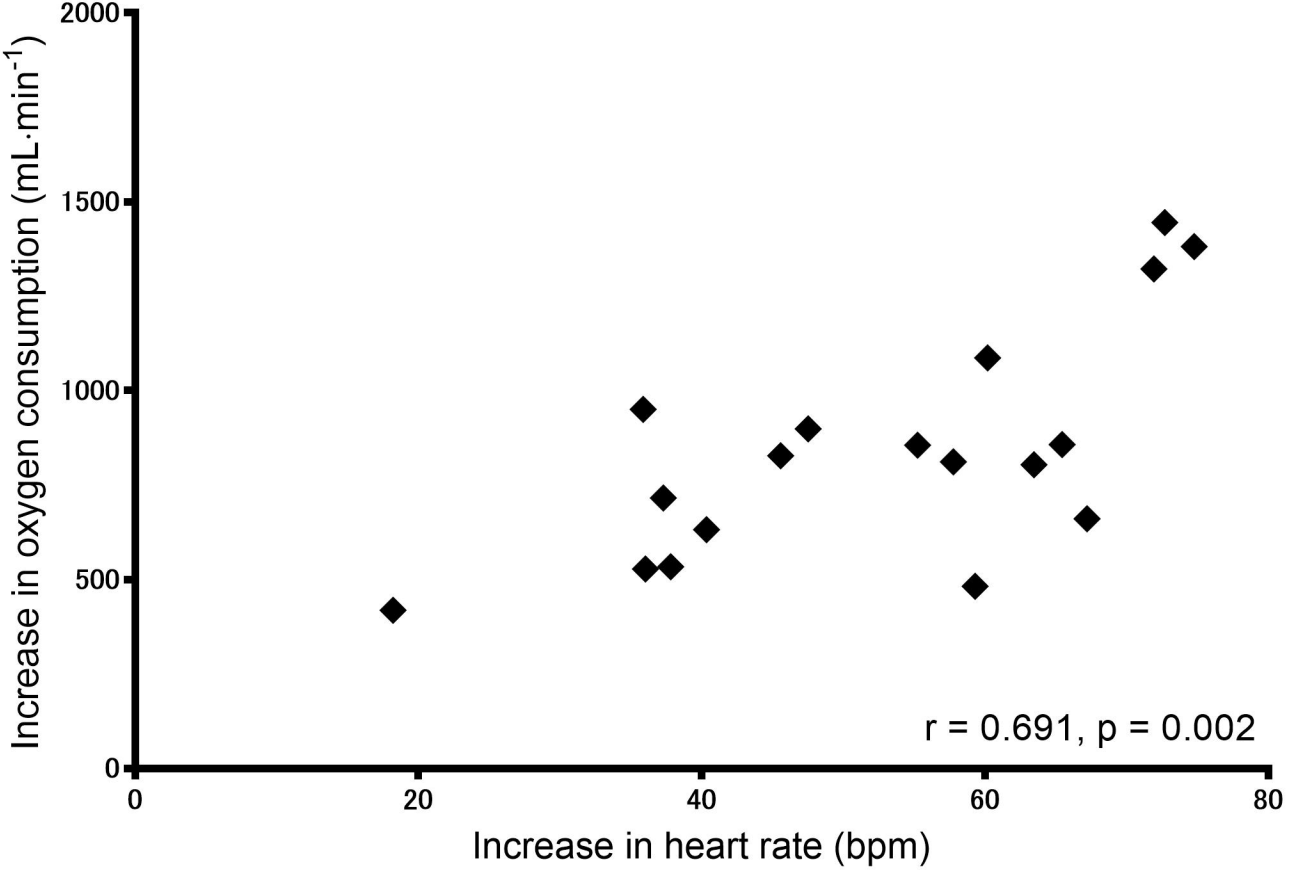
a


2000
1500
1000
500
0
Increase in oxygen consumption (mL·min-1)
0
10
20
30
Increase in respiratory rate (breaths·min-1)
r = 0.375, p = 0.125

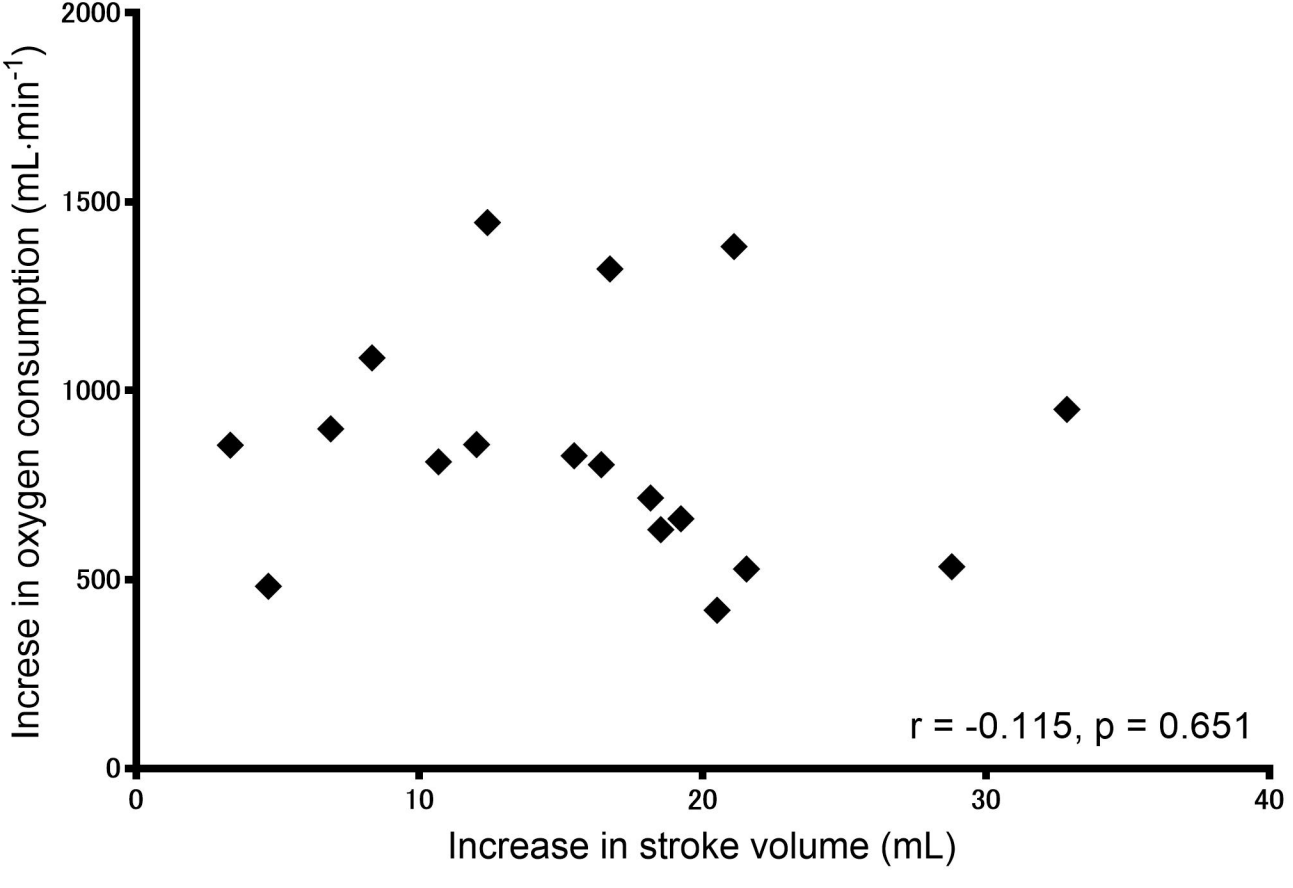
b

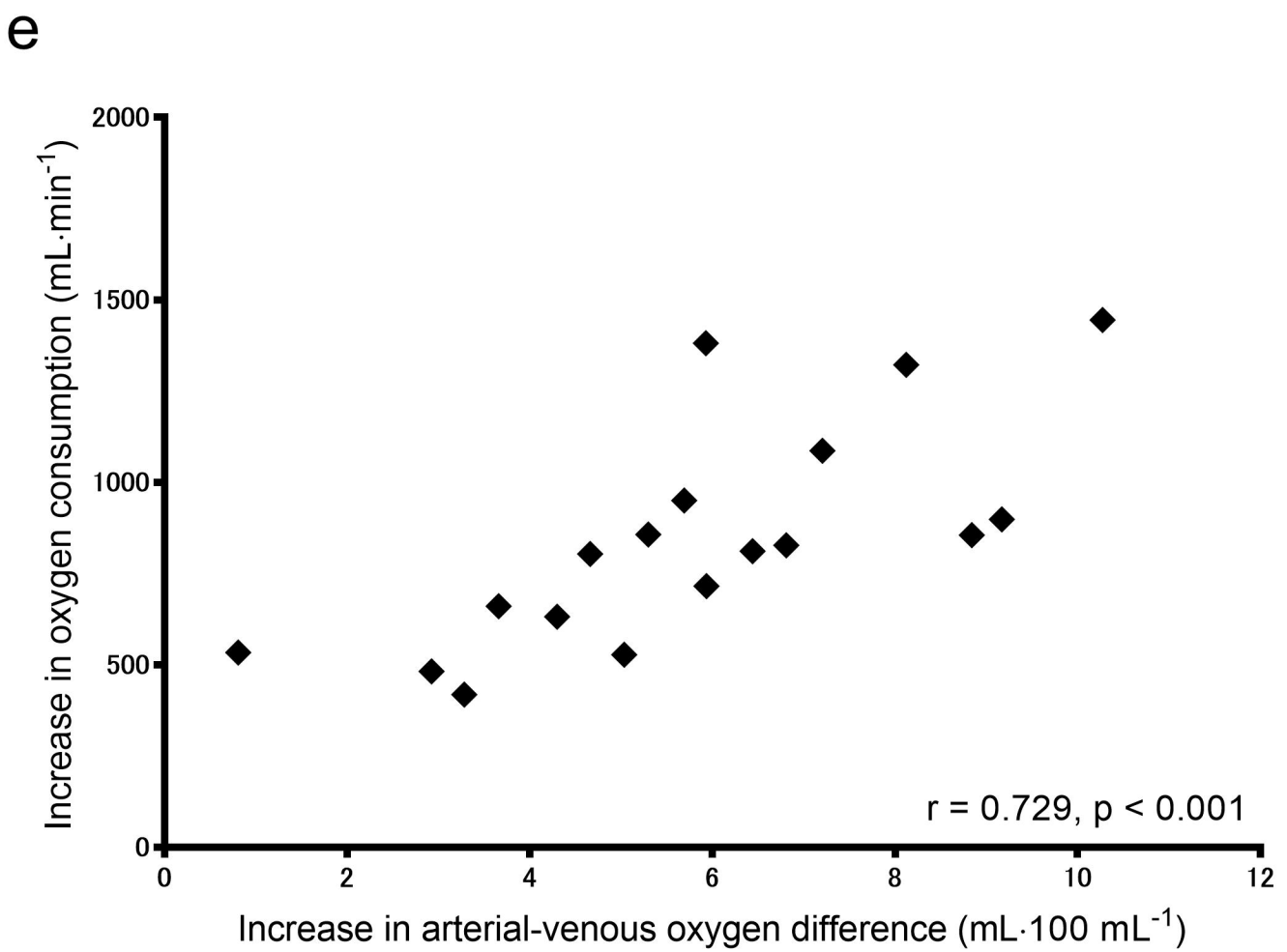

2000
1500
1000
500
0
Increase in oxygen consumption (mL·min-1)
r = 0.801, p < 0.001
0.0
0.5
1.0
1.5
Increase in tidal volume (L)

C


Increase in oxygen consumption (mL·min-1)
2000
1500
1000
500
0
0
20
40
60
80
Increase in heart rate (bpm)
r = 0.691, p = 0.002

d


2000
1500
1000
500
0
Increse in oxygen consumption (mL·min-1)
0
10
20
30
40
Increase in stroke volume (mL)
r = -0.115, p = 0.651


e
2000
1500
1000
500
0
Increase in oxygen consumption (mL·min-1)
r = 0.729, p < 0.001
0
2
4
6
8
10
12
Increase in arterial-venous oxygen difference (mL·100 mL-1)