Robin Hood for the lungs? A respiratory metaboreflex that 'steals' blood flow from locomotor muscles

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In this issue of *The Journal of Physiology*, Dempsey and colleagues (Sheel *et al.* 2001) contribute another key chapter in their ongoing series of elegant investigations on novel interactions involving the respiratory muscles, autonomic nervous system and cardiovascular regulation in humans. Earlier, they demonstrated that manipulation of the work of breathing during maximal exercise resulted in marked changes in locomotor muscle blood flow, cardiac output and both whole-body and active limb oxygen uptake (Harms *et al.* 1997, 1998). They also established the remarkable metabolic costs of supporting respiratory muscle function during maximal exercise, requiring up to 16 % of the cardiac output (Harms *et al.* 1998). Importantly, the reduced locomotor muscle blood flow and vascular conductance in the elevated work of breathing condition was associated with augmented noradrenaline (norepinephrine) spillover from the active limbs, suggesting enhanced sympathetic vasoconstriction (Harms *et al.* 1997). These physiological effects of the work of breathing have important functional consequences, as demonstrated by an ∼15 % improvement in endurance performance with respiratory muscle unloading (Harms *et al.* 2000).

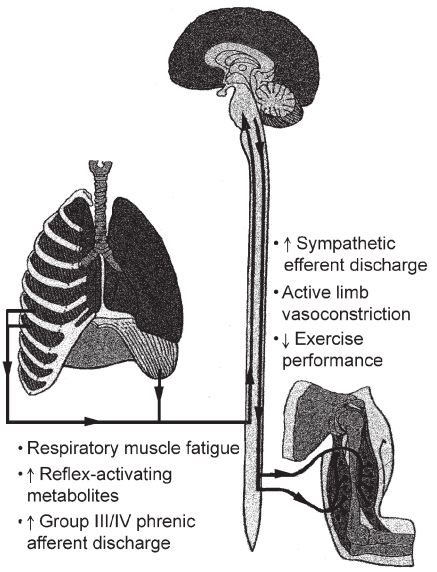

Figure 1. Respiratory muscle 'metaboreflex'

The next generation of experiments attempted to establish the mechanisms underlying these fascinating physiological connections. In a paper recently published in this journal (St Croix *et al.* 2000), high-resistance, prolonged duty cycle breathing at rest, resulting in respiratory muscle fatigue, evoked an increase in leg muscle sympathetic nerve activity (MSNA) that was independent of central respiratory motor output, indicating a reflex origin. Moreover, the temporal nature of the response (MSNA was unchanged during the initial 1–2 min of the fatiguing task but increased progressively thereafter) was characteristic of a slower-developing muscle metaboreflex (chemoreflex), rather than a mechanoreflex stimulated by force development (which would be expected to evoke sympathoexcitation at the start of contractions).

The present article by Sheel *et al.* (2001) represents a critical extension of this work by establishing that this presumed respiratory muscle–limb reflex has the ability, at least under resting conditions, to reduce significantly limb blood flow and vascular conductance. Thus, together with previous observations (St Croix *et al.* 2000), the present contribution provides compelling evidence for the existence of a metaboreflex, with its origin in the respiratory muscles, that can modulate limb perfusion via stimulation of sympathetic nervous system vasoconstrictor neurones (Fig. 1).

Teleologically, this reflex may have as its fundamental goal the protection of oxygen delivery to the respiratory muscles, thus ensuring the ability to maintain pulmonary ventilation, proper regulation of arterial blood gases and pH and overall organismic homeostasis. Presumably, as the 'vital organ' responsible for supporting pulmonary function, perfusion of the respiratory muscles, particularly during physiological states in which there is competition for cardiac output such as heavy submaximal and maximal exercise, has priority over the locomotor muscles. This subservience of active limb blood flow may be similar to that previously established for the arterial baroreflex during large-muscle dynamic exercise (Rowell, 1997). Specifically, under conditions in which widespread vasodilatation has occurred, thus threatening the maintenance of systemic vascular resistance and arterial blood pressure, arterial baroreflex deactivation (unloading) will produce a strong reflex sympathetic vasoconstriction targeted, at least in part, at the active limbs. This vasoconstrictor drive can be sufficiently strong as to produce vasoconstriction in working locomotor muscles, thus ensuring the maintenance of arterial perfusion pressure.

As with any developing drama, several unanswered questions remain. For example what is the influence, if any, of this reflex during normal *in vivo* exercise? Can the reflex explain the physiological consequences of the work of breathing in limiting maximal aerobic capacity (maximal oxygen uptake) and human performance? Is the reflex active during moderate, submaximal aerobic exercise performed for health and fitness purposes in non-athletic adults? If so, at what intensity of exercise, level of pulmonary ventilation, etc., is the reflex engaged? Perhaps the reflex is tonically active in patients with clinical disorders associated with chronic elevations in the work of breathing (e.g. congestive heart failure or chronic obstructive lung disease)? Can the conditions under which this metaboreflex is triggered be modified by training of the respiratory muscles? Finally, does the 'stealing' work both ways? That is, can active limb metaboreflexes act to redirect blood flow away from respiratory muscles to the locomotor muscles, thus potentially compromising pulmonary function during heavy submaximal and maximal exercise?

As with our favourite page-turning suspense novel, we look forward to the answers to these and other questions in the next intriguing instalment of this series.

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SHORT COMMUNICATION

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Respiratory muscle endurance training in humans increases cycling endurance without affecting blood gas concentrations

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Abstract Isolated respiratory muscle endurance training (RMT) can prolong constant-intensity cycling performance. We tested whether RMT affects O_2 supply during exercise, i.e. whether the partial pressure of oxygen in arterial blood (P_aO_2) and/or its oxygen saturation (S_aO_2) are higher during exercise after RMT than before. A group of 28 sedentary subjects were randomly assigned to either an RMT ($n=13$) or a control group ($n=15$). The RMT consisted of 40×30 min sessions of normocapnic hyperpnoea. The control group did not perform any training. Breathing and cycling endurance time as well as P_aO_2 and S_aO_2 during cycling at a constant intensity of 70% maximum power output were measured before and after the RMT or the control period. Mean breathing endurance increased significantly after RMT compared to control [RMT 5.2 (SD 2.9) vs 38.1 (SD 6.8) min, control 6.5 (SD 5.7) vs 6.4 (SD 7.6) min; $P<0.01$], as did mean cycling endurance [RMT 35.6 (SD 11.9) vs 44.0 (SD 17.2) min, control 32.8 (SD 11.6) vs 31.4 (SD 14.4) min; $P<0.05$]. The RMT did not affect P_aO_2 which ranged from 11.6 to 12.3 kPa (87–92 mmHg), and S_aO_2 which ranged from 96% to 98% throughout all tests. In conclusion, RMT substantially increased breathing and cycling endurance in sedentary subjects. These changes, however, cannot be attributed to increased O_2 supply, as neither P_aO_2 nor S_aO_2 were increased during exercise after RMT.

Keywords Arterial oxygen concentration · Arterial oxygen saturation · Endurance performance · Constant intensity exercise · Sedentary subjects

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Introduction

Isolated respiratory muscle endurance training (RMT) in the form of normocapnic hyperpnoea can prolong constant-intensity cycling performance (Spengler et al. 1999; Spengler and Boutellier 2000). The mechanisms leading to this improvement of cycling endurance after RMT still need to be determined. Among the potential mechanisms several have been excluded. Markov et al. (1996) have shown that the hypoxic ventilatory response remains unchanged after RMT. Kohl et al. (1997) found no reduction in airway resistance which would have decreased respiratory work and possibly delayed fatigue of the respiratory muscles after RMT. Spengler et al. (1999) reported reduced blood lactate concentrations after RMT, but found no shift in the balance of aerobic as opposed to anaerobic metabolism and thus could not explain the increased cycling endurance performance by reduced blood lactate concentrations. Spengler et al. (1998) found no increase in stroke volume and no decrease in heart rate (HR) after RMT. Thus, the increased cycling endurance performance after RMT was not a result of cardiovascular training induced by increased venous return while breathing very hard during RMT.

A further mechanism that could be responsible for the increased exercise performance after RMT is an increase in the arterial partial pressure of oxygen (P_aO_2) after RMT. Endurance is, for example, increased when subjects are breathing an hyperoxic gas mixture. This increase might either be directly related to an increase in O_2 supply to working muscles by an increased P_aO_2 or it might result from indirect effects of altered O_2 supply, for example changes in blood lactate, H^+ or HCO_3^- concentrations or a decrease in minute ventilation ($\dot{V}_E$). A decrease in $\dot{V}_E$ and thus a reduction of respiratory work could cause a blood redistribution towards working leg muscles and thereby leave more O_2 to these muscles (Harms et al. 1997). In addition, an increase in P_aO_2 could possibly partially prevent the increase in the

alveolar-arterial difference in the partial pressure of O_2 [$P_{(A-a)}O_2$] that can be observed during exercise at 65% of maximal O_2 consumption, for example, in trained subjects. The $P_{(A-a)}O_2$ proportionally widens with increasing O_2 consumption ($\dot{V}O_2$) due to both a decrease in P_aO_2 and an increase in the partial pressure of oxygen in the alveoli (P_AO_2) (Cerretelli and DiPrampero 1987). However, there is little data available in sedentary subjects performing constant-intensity exercise where such effects may be more pronounced with increasing exercise time.

Therefore, the aim of the present study was to investigate whether the increased endurance performance in constant-intensity cycling after RMT might be explained by a change in oxygen supply, that is a higher P_aO_2, a higher oxygen saturation of arterial blood (S_aO_2) or a smaller $P_{(A-a)}O_2$ during exercise compared to the controls.

Methods

Subjects

A group of 28 healthy, sedentary subjects were randomly assigned to one of two experimental groups: 13 subjects (5 women, 8 men), mean age 43 (SD 7) years, mean height 170 (SD 9) cm, mean body mass 67 (SD 12) kg, mean haemoglobin concentration 144 (SD 15) $g \cdot l^{-1}$, mean haematocrit 41 (SD 4)% were included in the RMT group and 15 subjects (7 women, 8 men), mean age 37 (SD 9) years, mean height 170 (SD 7) cm, mean body mass 68 (SD 13) kg, mean haemoglobin concentration 141 (SD 19) $g \cdot l^{-1}$, haematocrit 40 (SD 4)% in the control group. There were no significant differences in age, height, body mass, haemoglobin concentration or haematocrit between groups. The protocol was approved by the Ethics Commitee of the Institutes of Physiology and Pharmacology of the University of Zurich and the subjects gave their written informed consent. All the experiments complied with the current laws of Switzerland.

Equipment

Vital capacity (VC), forced expiratory volume in 1 s ($FEV_{1.0}$), peak expiratory flow (PEF), and maximum voluntary ventilation (MVV), as well as $\dot{V}_E$ and gas exchange during exercise were measured using an Oxycon Gamma ergospirometric device (Jaeger, Wuerzburg, Germany). Cycling tests were performed on an electromagnetically braked cycle (Ergometrics 900, Ergoline, Bitz, Germany). The HR was recorded using a PE4000 heart rate monitor (Polar Electro, Kempele, Finland). For RMT and for the respiratory endurance tests, a special device was developed in-house. It consisted of a rebreathing bag connected to two T-shaped tubes which were then connected to a mouthpiece. The volume of the bag was adjusted to be 50%–60% of the subjects' VC. Subjects were instructed to fill and empty the bag completely with each breath. To avoid an increase in the partial pressure of CO_2 in the arterial blood (P_aCO_2) and a fall in S_aO_2, a small hole in the tube permitted additional inspiratory and expiratory flow to and from the room. During the constant-intensity cycling tests, arterial blood samples of 1.5 ml were withdrawn anaerobically every 3 min from a catheter positioned in a radial artery. Within 30 min of sampling, P_aO_2, P_aCO_2, pH, and S_aO_2 were determined automatically at 37°C by a blood gas analyser (BGElectrolytes) connected to an IL482 Co-Oxymeter (Instrumentation Laboratory, Lexington, Mass., USA).

Tests before and after the training or control periods

Each test period consisted of three sessions separated by a minimum of 2 days. In the first session, VC, $FEV_{1.0}$, PEF, and MVV were measured first. After a break of at least 15 min, an incremental cycling test was performed to determine maximum power output ($\dot{W}_{max}$) and peak oxygen consumption ($\dot{V}O_{2,peak}$). Subjects were free to choose their own pedalling frequencies within the range of 60–100 min^{-1}. Once established, the frequency had to be maintained throughout all cycling tests. In the second session, subjects were further familiarized with the RMT device until they were capable of breathing at a $\dot{V}_E$ corresponding to 70% MVV (respiratory frequency, f_R, was paced by a metronome) for more than 2 min, or, if this time was not achieved, the target $\dot{V}_E$ was reduced to 65% MVV and another trial was performed. In the third session, a catheter was placed in a radial artery and the subjects performed a breathing endurance test to exhaustion (determined by $\dot{V}_E$ having dropped by more than 10% below target or by the subject stopping exercise) at the $\dot{V}_E$ established in the second session. There were 4 subjects who were not exhausted after 15 min, they were stopped, the target $\dot{V}_E$ was increased by 5% MVV and the test was repeated after a break of at least 15 min. Mean target $\dot{V}_E$ was similar for the RMT [69 (SD 6)% MVV] and control group [71 (SD 10)% MVV]. After the breathing endurance test, a recovery of 20 min was allowed to ensure that no carry-over effect on the subsequent cycling test would ensue (Spengler et al. 2000). Subsequently, subjects performed a 5 min warm up on the cycle ergometer at 35% of the individual $\dot{W}_{max}$ immediately followed by the cycling endurance test at 70 % $\dot{W}_{max}$ to exhaustion (determined by pedalling frequency dropping by more than 10% below target or by the subject having stopped). Subjects were not given any additional information or encouragement. The HR and $\dot{V}_E$ were measured continuously and arterial blood samples were withdrawn every 3 min.

At least 5 days after the last respiratory training session, breathing and cycling endurance tests were repeated. Procedures and exercise intensities were the same as in the tests before the training or control period except that the breathing endurance test was discontinued after 40 min whether or not the subjects were exhausted.

Training and control period

All subjects were asked to maintain their normal sedentary lifestyle. The RMT group performed 40 respiratory training sessions of 30 min duration over a period of 15 (SD 2) weeks. Compliance with the training regimen was excellent in the RMT group, as assured by HR recorded continuously during each RMT session. Mean HR during the training sessions was 104 (SD 11) min^{-1} corresponding to 57 (SD 6)% of the maximal HR in the RMT group.

Analysis and statistics

All statistical comparisons were performed between groups using factorial analysis of variance (ANOVA). This applied to the following variables:

1. Age, height, body mass, haemoglobin concentration, and haematocrit
2. Differences (Δ) in lung function variables, breathing endurance time, and cycling endurance time before compared to after training
3. $\Delta P_{(A-a)}O_2$, ΔP_aO_2, and ΔS_aO_2 in the cycling endurance tests were obtained every 3 min. Values of corresponding times were compared during two separate periods: 5–23 min after the beginning of cycling and 9–3 min before exhaustion as well as at the end of the cycling endurance tests. Due to inter-subject variation in the length of the cycling endurance tests and values missing for technical reasons, the numbers of subjects included in each analysis is not identical. Exact numbers are given in Fig. 1.

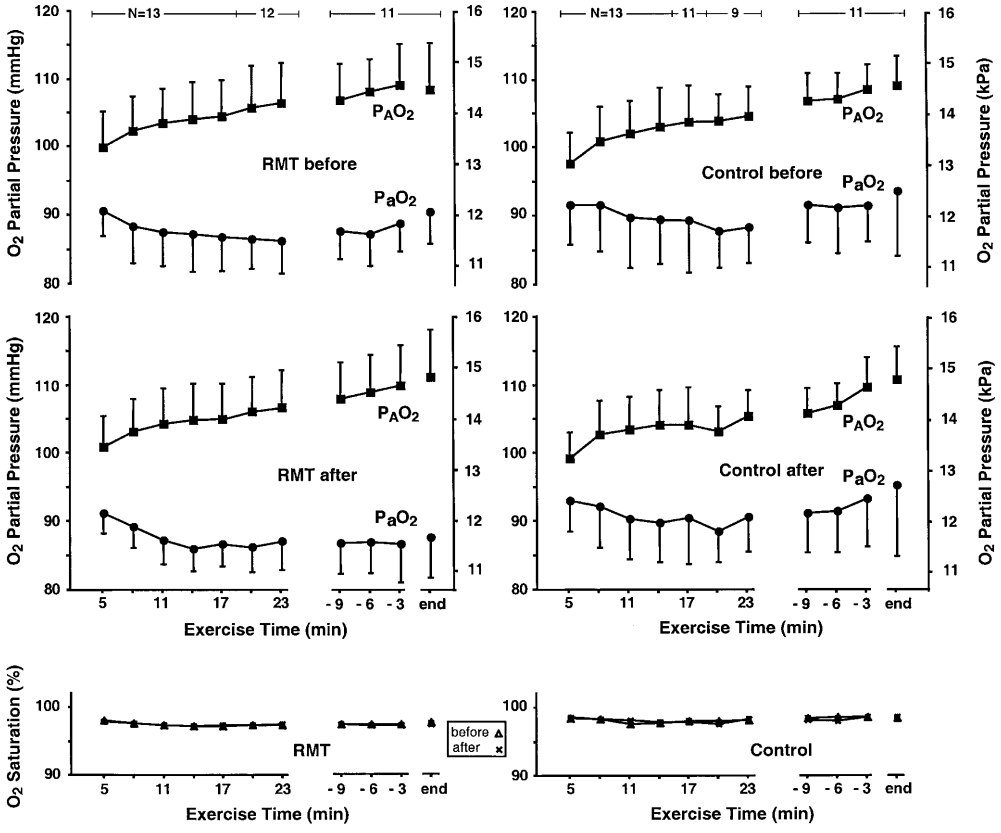

Fig. 1 Alveolar (P_AO_2) and arterial (P_aO_2) partial pressure of O_2 during constant-intensity cycling at 70% maximum power output before and after 40 sessions of respiratory muscle endurance training (*RMT*, *left*) or the control period (*right*). Arterial O_2 saturation does not differ between RMT (*bottom left*) and control group (*bottom right*). For details of calculations and comparisons see Analysis and statistics (3.) in the Methods section

4. Δ of all other variables in the cycling endurance tests were averaged during the steady state phase, i.e. from 7.5 min after the beginning of the test (2.5 min after the beginning of 70% $\dot{W}_{max}$) to 2.5 min before the end of the shorter test and during the equivalent time period of the longer test. Significance was accepted if $P < 0.05$.

Results

After RMT, significant increases of breathing endurance at 70% MVV [mean RMT, 5.2 (SD 2.9) before compared to 38.1 (SD 6.8) min after; control 6.5 (SD 5.7) before compared to 6.4 (SD 7.6) min after; $P < 0.01$], as well as of cycling endurance at 70% $\dot{W}_{max}$ [mean RMT 35.6 (SD 11.9) compared to 44.0 (SD 17.2) min; control 32.8 (SD 11.6) compared to 31.4 (SD 14.4) min; $P < 0.05$] were observed compared to control. During the cycling endurance tests, no significant changes were observed in mean steady state $\dot{V}_E$, tidal volume (V_T), f_R [RMT 29 (SD 5) compared to 29 (SD 5) min^{-1}; control 28 (SD 4) compared to 28 (SD 4) min^{-1}], the inspiratory time (t_I), the expiratory time (t_E), $\dot{V}O_2$, and HR in the RMT group compared to the control group (Table 1).

Also, no significant changes of mean VC [RMT 4.72 (SD 1.00) compared to 4.77 (SD 0.98) l; control 4.82 (SD 0.98) compared to 4.80 (SD 0.97) l], $FEV_{1.0}$ [RMT 3.71 (SD 0.86) compared to 3.78 (SD 0.84) l; control 3.81 (SD 0.73) compared to 3.76 (SD 0.64) l], PEF [RMT 8.4 (SD 1.8) compared to 9.1 (SD 2.2) $l \cdot s^{-1}$; control 8.2 (SD 1.4) compared to 8.5 (SD 1.4) $l \cdot s^{-1}$], MVV [RMT 170 (SD 49) compared to 181 (SD 40) $l \cdot min^{-1}$; control 151 (SD 37) compared to 162 (SD 37) $l \cdot min^{-1}$], $\dot{V}O_{2,peak}$ [RMT 2.39 (SD 0.76) compared to 2.38 (SD 0.77) $l \cdot min^{-1}$; control 2.35 (SD 0.60) compared to 2.23 (SD 0.55) $l \cdot min^{-1}$], and $\dot{W}_{max}$ [RMT 175 (SD 57) compared to 175 (SD 56) W; control 171 (SD 43) compared to 163 (SD 35) W] were observed after RMT in the training group compared to the control group.

After RMT, neither P_aO_2, $P_{(A-a)}O_2$, nor S_aO_2 were significantly altered during the cycling endurance tests. However, at the time of exhaustion, $\Delta P_{(A-a)}O_2$ in the RMT group tended to exceed the value in the control group ($P = 0.06$; Fig. 1). Mean pH, HCO_3^-, partial pressure of CO_2 in the alveoli and P_aCO_2 did not change significantly after RMT compared to control (Table 1); moreover, $P_{(A-a)}O_2$ was never more than 0.1 kPa (0.75 mmHg) and did not change significantly in the training group compared to the control group.

Discussion

Cycling endurance was significantly increased in a group of 13 sedentary subjects after 40×30 min sessions of RMT, when compared with a control group which did not perform any training. This improvement occurred despite an unchanged $\dot{V}O_{2,peak}$ and $\dot{W}_{max}$. The fact that RMT does not influence maximum exercise performance has been shown repeatedly (Kohl et al. 1997; Markov

Table 1 Means of averaged steady state pH, arterial standard bicarbonate (HCO_3^-) concentration, alveolar and arterial partial pressure of CO_2 (P_ACO_2, P_aCO_2, respectively), minute ventilation ($\dot{V}_E$), tidal volume (V_T), inspiratory time (t_I), expiratory time (t_E), oxygen consumption ($\dot{V}O_2$), and heart rate (HR) during the cycling endurance tests before and after the respiratory muscle endurance training (RMT) or control period

	RMT				Control			
	before		after		before		after	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
pH	7.38	0.02	7.38	0.02	7.39	0.03	7.38	0.03
HCO_3^- ($mmol \cdot l^{-1}$)	21.0	2.2	20.6	1.7	21.1	1.8	20.8	2.3
P_aCO_2 (kPa)	4.7	0.4	4.6	0.3	4.6	0.4	4.6	0.5
(mmHg)	35.2	2.7	34.7	2.3	34.6	3.2	34.8	3.3
P_ACO_2 (kPa)	4.7	0.5	4.7	0.5	4.6	0.4	4.7	0.5
(mmHg)	35.3	3.6	35.3	3.3	34.8	3.3	35.3	3.3
$\dot{V}_E$ ($l \cdot min^{-1}$)	60.8	15.2	59.5	13.0	56.5	11.0	57.1	11.1
V_T (l)	2.13	0.55	2.08	0.47	2.03	0.33	2.07	0.42
t_I (s)	1.00	0.16	0.98	0.18	1.02	0.20	1.01	0.22
t_E (s)	1.15	0.23	1.17	0.26	1.19	0.26	1.22	0.22
$\dot{V}O_2$ ($l \cdot min^{-1}$)	1.79	0.52	1.78	0.53	1.75	0.39	1.77	0.37
HR ($beats \cdot min^{-1}$)	164	9	163	10	163	15	160	14

et al. 1996; Spengler et al. 1999). Also, breathing endurance increased significantly despite an unchanged lung function. These increases in cycling and breathing endurance are similar to those reported previously (e.g. Spengler and Boutellier 2000).

We wondered whether an increase in P_aO_2 and/or S_aO_2 during endurance exercise after RMT could possibly explain the increased cycling endurance. However, P_aO_2 and S_aO_2, as well as P_AO_2 and the resulting $P_{(A-a)}O_2$ were not affected by RMT (Fig. 1). In fact, after RMT, a tendency towards a lower P_aO_2 and a larger widening of $P_{(A-a)}O_2$ at the time of exhaustion was observed. This would tend to cause a decrease rather than an increase in cycling endurance. Moreover, the unchanged $\dot{V}O_2$ pH, blood lactate and HCO_3^- concentrations during steady-state exercise after RMT compared to control supports the notion that RMT does not shift the balance of aerobic compared to anaerobic metabolism. Also, no changes in $\dot{V}_E$, V_T, f_R, t_I and t_E were observed during steady-state exercise after RMT and thus a change in the oxygen cost of breathing (potentially causing a blood redistribution towards leg muscles; Harms et al. 1997) as a consequence of a change in breathing pattern seems unlikely. Considering the present results, the improvements in cycling endurance must be attributed to a mechanism other than an increase in P_aO_2 and/or S_aO_2. Alternative mechanisms to account for the improvement in cycling endurance could be a decrease in perceived exertion, and/or a decrease in the development of respiratory muscle fatigue that was shown to develop during exhausting exercise, even in sedentary subjects. A reduction of respiratory muscle fatigue could result from increased endurance of inspiratory or expiratory muscles per se or from a more efficient recruitment of the different respiratory muscles. Further studies will have to address these issues.

Conclusion

In sedentary subjects, RMT substantially increased breathing and cycling endurance. These changes could not be attributed to increased O_2 supply, as neither P_aO_2 nor S_aO_2 were increased during exercise after RMT.

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ORIGINAL ARTICLE

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Respiratory muscle training increases cycling endurance without affecting cardiovascular responses to exercise

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Abstract We tested whether the increased cycling endurance observed after respiratory muscle training (RMT) in healthy sedentary humans was associated with a training-induced increase in cardiac stroke volume (SV) during exercise, similar to the known effect of endurance training. Thirteen subjects underwent RMT by normocapnic hyperpnea, nine underwent aerobic endurance training (cycling and/or running) and fifteen served as non-training controls. Training comprised 40 sessions performed within 15 weeks, where each session lasted 30 min. RMT increased cycling endurance at 70% maximal aerobic power ($\dot{W}_{max}$) by 24% [mean (SD) 35.6 (11.9) min vs 44.2 (17.6) min, $P < 0.05$], but SV at 60% $\dot{W}_{max}$ was unchanged [94 (21) ml vs 93 (20) ml]. Aerobic endurance training increased both SV [89 (24) ml vs 104 (32) ml, $P < 0.01$] and cycling endurance [37.4 (12.8) min vs 52.6 (16.9) min, $P < 0.01$]. In the control group, no changes were observed in any of these variables. It is concluded that the increased cycling endurance that is observed after RMT is not due to cardiovascular adaptations, and that the results provide evidence for the role of the respiratory system as an exercise-limiting factor.

Keywords Endurance performance · Exercise-limiting factors · Respiratory muscle fatigue

Introduction

Until recently, the role of ventilation in limiting human performance was considered to be important only in highly trained athletes exercising at maximum aerobic power ($\dot{W}_{max}$, Dempsey 1986). For prolonged heavy exercise (60–85% of maximal oxygen uptake, $\dot{V}O_{2max}$) to exhaustion, it was argued that the elicited minute ventilation ($\dot{V}_E$) was not sufficient to induce exercise-limiting respiratory muscle fatigue. This argument was based mainly on the fact that even at exhaustion, both trained and sedentary subjects breathed well below their maximal voluntary ventilation (MVV) and were still capable of increasing their ventilation voluntarily.

In contrast with these views, several studies (Boutellier et al. 1992; Boutellier and Piwko 1992; Spengler et al. 1999) have shown that isolated respiratory muscle training (RMT) not only greatly increases respiratory muscle performance but also prolongs cycling endurance at constant submaximal workloads (i.e., below 85% $\dot{W}_{max}$). If it is assumed that no uncontrolled or side-effects of respiratory training (e.g., increased physical activity of the subjects during the RMT period, increased motivation of the subjects after training, or metabolic changes) were responsible for the longer cycling time, these previous findings imply that respiratory pump fatigue may indeed play a role in limiting human performance at such work intensities. For exercise above 80% $\dot{W}_{max}$, the occurrence of diaphragmatic fatigue has already been established (Johnson et al. 1993; Mador et al. 1993).

An alternative explanation that is more in line with the conventional view, is that the improved exercise times observed after RMT may be caused by concomitant cardiovascular adaptations to the specific type of RMT (i.e., normocapnic hyperpnea) used in these studies (Boutellier et al. 1992; Boutellier and Piwko 1992; Spengler et al. 1999). Acutely, hyperpnea causes large intrathoracic pressure swings that increase venous return to the heart (Willeput et al. 1984; Boutellier and Farhi 1986; Anholm et al. 1987; Coast et al. 1988) and may also increase ventricular afterload (Robotham et al. 1977). The normocapnic hyperpnea of the RMT may therefore be associated with a considerable increase in stroke work in addition to the increase in heart rate.

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From these acute effects, it may be inferred that repeated prolonged hyperpnea (30 min) at a higher level than normally occurs during exercise, performed several times per week, results in an increase in intrinsic myocardial contractility and maximal stroke volume (SV). If this were the case, the increased cycling endurance could beattributed to an increased myocardial performance, as observed after endurance training, and the respiratory system need not be considered to be implied as an exercise-limiting factor.

We therefore hypothesized that RMT by normocapnic hyperpnea leads to an increase in SV, determined at its presumed maximum. Thus, we assessed SV and cycling endurance in a group of healthy sedentary volunteers before, during and after a 15-week course of RMT. To compare SV changes with those expected from endurance training, we investigated two additional groups, one undergoing aerobic endurance training at a level that is expected to increase SV and cycling endurance, and one serving as a non-training control group with no expected changes.

If under these premises RMT neither increases SV nor lowers the heart rate during cycling, yet prolongs cycling endurance, then the prolongation can not be explained by cardiovascular effects. This would warrant the conclusion that in sedentary subjects, the exercise-limiting role of the respiratory pump during submaximal exercise is probably more important than hitherto assumed.

Methods

Subjects

The present study was approved by the Ethics Committee of the Institutes of Physiology and Pharmacology of the University of Zurich (Switzerland). Thirty-eight healthy, sedentary subjects entered the study after providing their written informed consent to participate. Two agreed to enroll first as controls and subsequently in one of the training groups. The subjects were then randomly assigned to either an RMT group ($n=15$), an endurance training group (ET, $n=10$) or a control group (C, $n=15$). Two subjects in the RMT group and one in the ET group did not complete the study. The age, height, body mass, vital capacity (VC), maximal voluntary ventilation (MVV), peak oxygen uptake ($\dot{V}O_{2peak}$) and $\dot{W}_{max}$ of the remaining subjects before training are listed in Table 1.

Table 1 Means (SD) of the subjects' characteristics, vital capacity (VC), maximal voluntary ventilation (MVV) and peak oxygen uptake ($\dot{V}O_{2peak}$) of the respiratory muscle training (RMT), the endurance training (ET) and the control (C) group before the training or control period

Characteristic	RMT	ET	C
Gender (female/male)	5/8	5/4	7/8
Age (years)	43 (7)	40 (10)	37 (9)
Height (cm)	170 (9)	172 (10)	170 (7)
Body Mass	67 (12)	73 (16)	68 (13)
VC (l)	4.7 (0.9)	4.7 (0.9)	4.8 (1.0)
MVV ($l \cdot min^{-1}$)	170 (49)	159 (46)	151 (37)
$\dot{V}O_{2peak}$ ($ml \cdot min^{-1} \cdot kg^{-1}$)	36 (11)	32 (9)	35 (9)

Equipment

VC, MVV, as well as ventilation and gas exchange during exercise were measured with an OxyconGamma unit (Jaeger, Würzburg, Germany). This system uses a turbine for ventilation measurement, a paramagnetic analyzer for oxygen measurement, an infrared absorption analyzer for carbon dioxide measurement, and a personal computer for data recording and monitoring.

All bicycle ergometer tests were carried out on an electromagnetically braked "Ergometrics 900S" bicycle ergometer (Ergoline, Bitz, Germany) that was connected to the OxyconGamma unit described above. Heart rates were recorded on PE4000 heart rate monitors (Polar Electro, Kempele, Finland) that were also connected to the OxyconGamma computer.

RMT was carried out with a self-developed device consisting of tubing (inner diameter of 19 mm) that connects a rebreathing bag with a mouthpiece at a 90° angle. In the middle of this connecting piece, a side-port (same diameter tube) is inserted. This side-port contains a 6-mm hole to allow inspiration from and expiration to ambient air; it also contains a valve. Subjects fill and empty the rebreathing bag completely while obtaining additional fresh air through the small hole during inspiration and breathing partially out through the small hole during expiration. To assure a constant tidal volume, the valve inserted in the side-portcloses when subjects have emptied the bag completely during inspiration and inspiratory air is passing purely through the side-port hole (with high flow). For the present study, the size of the bag was adjusted to 50–60% of the subject's VC, and breathing frequency was chosen such that $\dot{V}_E$ corresponded to 60% MVV (monitored while the training device was connected to the metabolic cart).

Subjects were instructed to fill and empty the bag completely while additional inspiratory and expiratory flow passed through a small hole in the tube to avoid an increase in arterial carbon dioxide partial pressure and a fall in oxygen saturation. Correct performance (i.e., the achievement of normocapnia and full arterial oxygen saturation) was checked in a preliminary session with the training device connected to the Oxycon Gamma. If necessary, the size of the hole in the tube was adjusted.

Cardiac output was assessed with the OxyconGamma unit, which uses a carbon dioxide rebreathing principle to determine mixed-venous carbon dioxide concentration and derives arterial carbon dioxide from end-tidal values. The plateau method (Collier 1956) was used to evaluate the rebreathing equilibrium. Cardiac output was estimated by using the indirect Fick equation corrected for hemoglobin concentration (Jones and Campbell 1982). Cardiac output and steady-state heart rate before rebreathing were then used to calculate SV.

Protocols

Before training was started, all subjects underwent three test sessions, which were carried out on separate days within 1–2 weeks. In the first session, lung function variables were measured according to the standard procedures of the American Thoracic Society (1995), and an incremental cycling test with simultaneous measurement of ventilation and gas exchange was performed. The initial workload was 60 W for female subjects and 80 W for male subjects; this was then increased by 20 W every 2 min until exhaustion. Pedaling frequency was kept constant at a self-chosen rate between 60 and 100 rpm. The highest workload sustained for at least 90 s was defined as $\dot{W}_{max}$, and the highest $\dot{V}O_2$ averaged over 30 s was defined as $\dot{V}O_{2peak}$. After recovery, the subjects were familiarized with the RMT device, as described above.

In the second session, cardiac output and SV were assessed while subjects cycled at 60% of their predetermined $\dot{W}_{max}$, the pedaling rate being the same as in the incremental test. Three cardiac output measurements were made within 20 min without intermittent recovery, and the median of these measurements was taken as the representative value. The median was selected to minimize the effect of potential outliers. However, final analysis revealed that the reliability of the measurements was good (average coefficient of variation 3.9%) and that outliers were virtually

nonexistent. Subsequently, the subjects were further familiarized with the RMT device until they were capable of breathing at a $\dot{V}_E$ corresponding to 70% MVV for more than 2 min. If this time was not achieved, the target $\dot{V}_E$ was reduced to 65% MVV.

In the third session, the subjects performed a breathing endurance test to exhaustion at the % MVV level established in the second session. Exhaustion was assumed when subjects stopped the test or when $\dot{V}_E$ dropped more than 10% below its target level. In those subjects who breathed for longer than 15 min, the test was interrupted because breathing load was considered to be too low. In this case, the test was repeated after a recovery period, applying a target $\dot{V}_E$ that was increased by 5% MVV. The mean $\dot{V}_E$ measured during the breathing endurance tests was similar in all three groups [mean (SD) RMT, 115 (28) l·min^{-1} or 69 (6)% MVV; ET, 104 (26) l·min^{-1} or 67 (11)% MVV; C, 105 (21) l·min^{-1} or 71 (10)% MVV]. After the breathing endurance test, a recovery time of 20 min was observed to ensure that no carry-over effect on the subsequent cycling test would ensue. This duration was based on the results of a previous study showing that exhaustive, normocapnic hyperpnea of 40 min duration that ended 15 min before an exhaustive cycling test, affected neither exercise time, metabolism nor ventilation during cycling compared to a cycling test without preceding voluntary hyperpnea (Spengler et al. 2000). In the present study, the cycling endurance test started with a 5-min warm-up at 35% $\dot{W}_{max}$, and was immediately followed by constant-load cycling at 70% $\dot{W}_{max}$. The pedaling rate was kept constant at the level chosen in the incremental test. Subjects were allowed to monitor their pedaling rate, but were not given any additional information or encouragement. Exhaustion was assumed when subjects stopped the test or when their pedaling rate dropped by more than 10% below target. Heart rate, ventilation and gas exchange were measured continuously.

The three test sessions were immediately followed by the training period, which lasted 15 (3) weeks, and comprised two times 20 training sessions, each of which was performed over 7 (2) weeks (range 4–8 weeks, depending upon subjects' availability of time), with a pause of 1–2 weeks (for testing in between, as described later). Each training session consisted of either 30 min RMT (RMT group), 30 min of endurance training (ET group), or no training (C group). The $\dot{V}_E$ for RMT was set initially at 60% MVV. For subsequent training sessions, subjects were encouraged to increase their breathing frequency or tidal volume as soon as they felt they could have continued for more than 30 min at the target $\dot{V}_E$. After an average of 30 training days, target $\dot{V}_E$ had already increased to 79% MVV. Endurance training consisted of strenuous, heart-rate-monitored running or cycling. The mean heart rate during training sessions was 104 (11) beats·min^{-1} [57 (6)% of peak heart rate] in the RMT group and 161 (8) beats·min^{-1} [88 (5)% of peak heart rate] in the ET group. The estimated training $\dot{V}_E$ of the ET group (estimated from $\dot{V}_E$ at the point where training heart rate was reached during the incremental test) resulted in an average of 34% MVV at the beginning and 46% MVV at the end of the training period. No additional RMT was included for training of the ET group. The C subjects performed no training. None of the subjects were allowed to perform any kind of additional exercise outside the training protocol and their usual activities. Most training sessions were carried out at home. To ensure full compliance and effort, subjects were obliged to save the heart-rate monitor readings of each training session and to record their training in a diary. These data were checked weekly by the investigators and showed that subjects followed their training schedule and kept their usual activities constant. Thus, compliance with the protocol was excellent. In addition, subjects in the RMT group periodically performed training sessions at the laboratory under direct supervision.

After 7 (2) weeks of training (20 training sessions), the cardiac output determination was repeated in exactly the same way as in the second session of the pre-training test series. The aim was to observe any early effects of training on SV.

When training was completed after a total of 15 (3) weeks, the initial three-session test series was repeated fully in an identical manner, with the following exceptions. Firstly, in the ET group only, the workload during the cycling endurance test was adapted proportionally to the post-training $\dot{W}_{max}$ as soon as the exhaustion time of the pre-training test was attained. The reason for this was to avoid excessively long cycling times after whole-body endurance training. Secondly, the post-training breathing endurance tests were terminated by the investigators after 40 min if no signs of exhaustion were present, again to avoid excessively long breathing times after training.

Statistical analysis

First, the test for normality of distribution by D'Agostino and Pearson (Zar 1996) was applied to all data. Normally distributed data were then analyzed statistically by one-way analysis of variance. Breathing endurance times, which were not normally distributed, were analyzed by the Kruskal-Wallis test. The Newman-Keuls test for normally distributed data and the procedure proposed by Dunn (Zar 1996) for breathing endurance data were used for post hoc multiple comparisons. All stated statistical significance refer to differences in response between the respective training groups (RMT and ET) and the C group. The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using StatView 4.5 software (Abacus Concepts, Berkeley, Calif., USA).

Results

Physical and respiratory performance

$\dot{V}O_{2peak}$ and $\dot{W}_{max}$ before and after training are shown in Table 2. No changes occurred in the RMT and C groups. In the ET group, the respective mean values increased by 19% and 22% ($P < 0.001$). Breathing endurance increased more than sixfold in the RMT group, from a median of 4.6 min (range: 2.0–10.2 min) to 40.0 min (15.4–40.0 min; $P < 0.001$), although the post-training tests were terminated after 40 min if no signs of exhaustion were present. Breathing endurance in the ET and C groups did not change significantly [mean (range) for ET: from 6.5 (1.8–15.8) min to 9.4 (1.4–40.0) min; C: from 5.2 (2.0–10.4) min to 3.9 (1.5–19.6) min)].

Table 2 Means (SD) of peak oxygen uptake ($\dot{V}O_{2peak}$), maximal aerobic power ($\dot{W}_{max}$) and cycling endurance of the respiratory muscle training (RMT), endurance training (ET) and control (C) groups before and after the training or control period

Variable	Group	Before training	After 15 weeks
$\dot{V}O_{2peak}$(l·min^{-1})	RMT	2.39 (0.76)	2.38 (0.77)
	ET	2.34 (0.66)	2.80 (0.85)***
	C	2.35 (0.60)	2.24 (0.55)
$\dot{W}_{max}$(W)	RMT	175 (57)	175 (55)
	ET	173 (42)	211 (62)***
	C	171 (43)	163 (35)
Cycling endurance (min)	RMT	35.6 (11.9)	44.2 (17.6)*
	ET	37.4 (12.8)	52.6 (16.9)[a],**
	C	32.8 (11.6)	31.4 (14.4)

[a]Workload increased when the end-time of the pre-training test was reached (see Methods)
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (compared to changes in the C group)

Cycling endurance times before and after the training period are also shown in Table 2. RMT increased mean cycling endurance time by 24% ($P < 0.05$), while there was no change in C group values. ET increased mean cycling endurance time by 41% ($P < 0.01$), but please note that the workload was partly adapted to the increased $\dot{W}_{max}$ after training, as described in the Methods section.

Cardiovascular adaptations

The responses of cardiac output, $\dot{V}O_2$ and heart rate, determined at 60% of the pre-training $\dot{W}_{max}$ after the attainment of a steady-state $\dot{V}O_2$ are shown in Table 3. These variables did not change in the RMT and C groups, whereas the ET group showed the characteristic heart rate reduction ($P < 0.001$).

The individual values for SV at the same $\dot{V}O_2$ before and after 7 and 15 weeks of training are plotted in Fig. 1. In the RMT group, the respective mean values were 94 (21) ml, 97 (22) ml, and 93 (20) ml. The C group values were similar [90 (25) ml, 94 (25) ml and 90 (23) ml]. There were no statistical differences between any of these values. In the ET group, SV increased from an initial 89 (24) ml to 112 (35) ml after 7 weeks ($P < 0.001$), and to 104 (32) ml after 15 weeks ($P < 0.01$). The downward trend from 7 weeks to 15 weeks was not significant. The heart rate during the cycling endurance test was compared before and after training for the constant-load period that could be sustained by all subjects of each group, and the results are shown in Fig. 2. Again, no changes were noted in the RMT and C groups, whereas the reduction observed in the ET group was significant ($P < 0.01$).

Metabolic adaptations

In neither the RMT group nor the C group was $\dot{V}O_2$ (Fig. 3) or substrate utilization – as measured using the respiratory exchange ratio (Fig. 4) – changed significantly during the constant-load period of the cycling endurance test performed after 15 weeks of respiratory training or after the control period. In the ET group, however, after the 15-week physical training period $\dot{V}O_2$ was significantly decreased, as was the respiratory exchange ratio ($P < 0.05$).

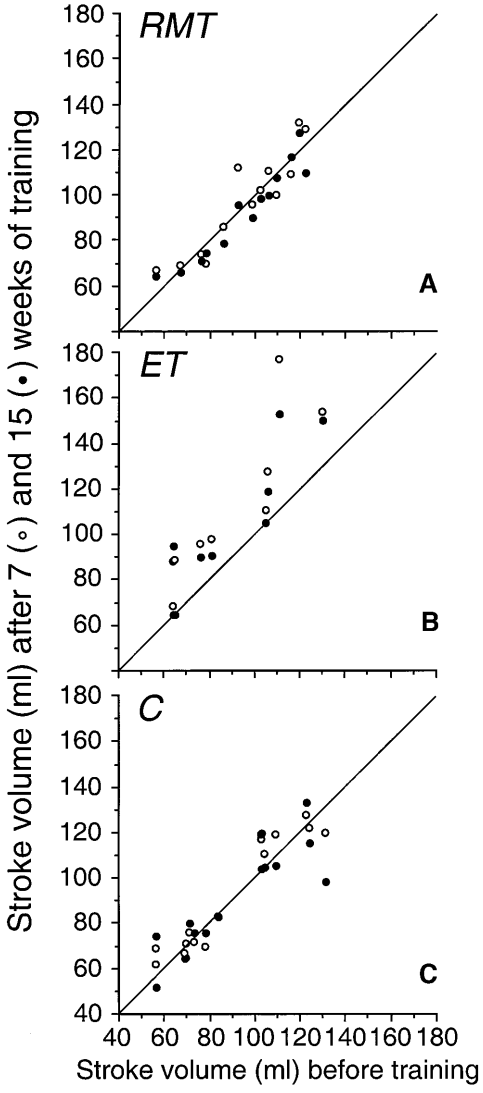

Fig. 1 Stroke volume at 60% maximal aerobic power ($\dot{W}_{max}$) of all subjects after 7 (2) weeks (○) and 15 (3) weeks (●) weeks of training, or after the control period (*ordinate*) is plotted against pre-training values (*abscissa*). The *diagonal line* represents the line of identity. Subjects were assigned to either a respiratory muscle training group (*RMT*, $n = 13$), an endurance training group (*ET*, $n = 9$), or a control group (*C*, $n = 15$). Stroke volume increased significantly in the ET group only ($P < 0.001$ compared to changes in the C group)

Table 3 Means (SD) of cardiac output, heart rate and oxygen uptake during cycling at 60% maximal aerobic power ($\dot{W}_{max}$) before, after 7 weeks and after 15 weeks of respiratory muscle training (RMT), endurance training (ET) or the control (C) period

Variable	Group	Before training	After 7 weeks	After 15 weeks
Cardiac output ($l \cdot min^{-1}$)	RMT	14.1 (3.1)	14.1 (3.5)	13.7 (3.1)
	ET	13.6 (3.2)	14.8 (3.4)	13.8 (3.1)
	C	13.7 (3.4)	14.1 (3.5)	13.8 (3.2)
Heart rate ($beats \cdot min^{-1}$)	RMT	150 (14)	146 (13)	149 (13)
	ET	155 (14)	135 (17)***	137 (17)***
	C	154 (13)	152 (11)	154 (12)
Oxygen uptake ($l \cdot min^{-1}$)	RMT	1.68 (0.48)	1.62 (0.47)	1.62 (0.45)
	ET	1.71 (0.45)	1.70 (0.41)	1.66 (0.32)
	C	1.63 (0.34)	1.63 (0.33)	1.64 (0.38)

***$P < 0.001$ (compared to changes in the C group)

Discussion

Our aim was to study the effects of RMT on SV and heart rate during submaximal heavy exercise in healthy sedentary humans in order to try to explain the increases

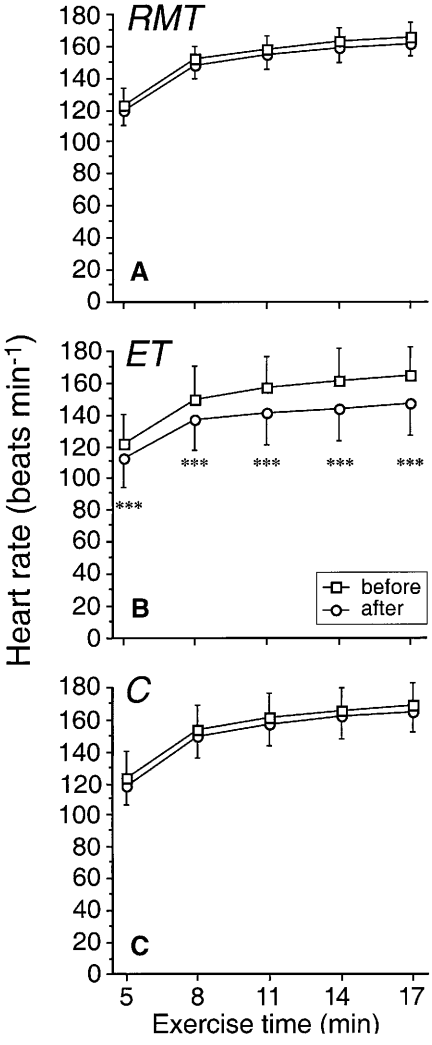

Fig. 2 Progression of heart rate during the cycling endurance test (70% $\dot{W}_{max}$) before (□) and after (○) 15 weeks of training or the control period is shown for the constant-load period that could be sustained by all subjects of each group (means ± SD). Subjects were assigned to either a respiratory muscle training group (*RMT*, $n = 13$), an endurance training group (*ET*, $n = 9$), or a control group (*C*, $n = 15$). Heart rate decreased significantly in the ET group only (***$P < 0.001$ compared to changes in the C group)

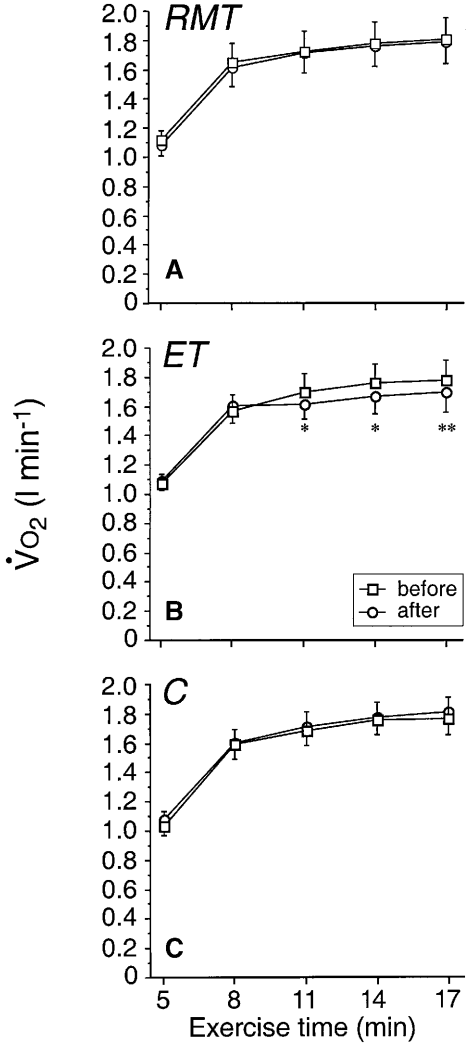

Fig. 3 Progression of oxygen consumption ($\dot{V}O_2$) during the cycling endurance test (70% $\dot{W}_{max}$) before (□) and after (○) 15 weeks of training or the control period is shown for the constant-load period that could be sustained by all subjects of each group (means ± SD). Subjects were assigned to either a respiratory muscle training group (*RMT*, $n = 13$), an endurance training group (*ET*, $n = 9$), or a control group (*C*, $n = 15$). $\dot{V}O_2$ decreased significantly in the ET group only (*$P < 0.05$, **$P < 0.01$ compared to changes in the C group)

in cycling endurance observed after RMT. We found that RMT carried out over a period of 15 weeks did not increase the SV determined at workloads that normally elicit maximal values, and that heart rate at the same absolute submaximal workloads remained unchanged.

Since our subjects were in a very low training state (mean $\dot{V}O_{2peak}$ was 30 ml·min^{-1}·kg^{-1} in the female and 38 ml·min^{-1}·kg^{-1} in the male subjects), even light exercise training was likely to induce cardiovascular adaptations. The fact that endurance training increased SV by 17% and reduced heart rate by 12% in the present study indicates that SV changes in the RMT group would not have been missed with the method used. Moreover, the absolute values obtained for cardiac output and SV were similar to those reported in the literature (Hartley et al. 1969; Hossack et al. 1981; Higginbotham et al. 1984). The results thus reliably indicate the absence of any cardiovascular training effects of RMT comparable to those of endurance training (Ehsani et al. 1978; Wolfe et al. 1979; Mier et al. 1997). The significant increase in cycling endurance after RMT can not therefore be attributed to the hypothesized cardiovascular adaptations. Thus, the possible acute effects of RMT, such as increases in venous return (Willeput et al. 1984; Boutellier and Farhi 1986; Anholm et al. 1987; Coast et al. 1988) and/or afterload (Robotham et al. 1977), appear to be insufficient to induce cardiovascular training effects.

Since our data reject the hypothesis of any cardiovascular effects of RMT, the increased cycling endur-

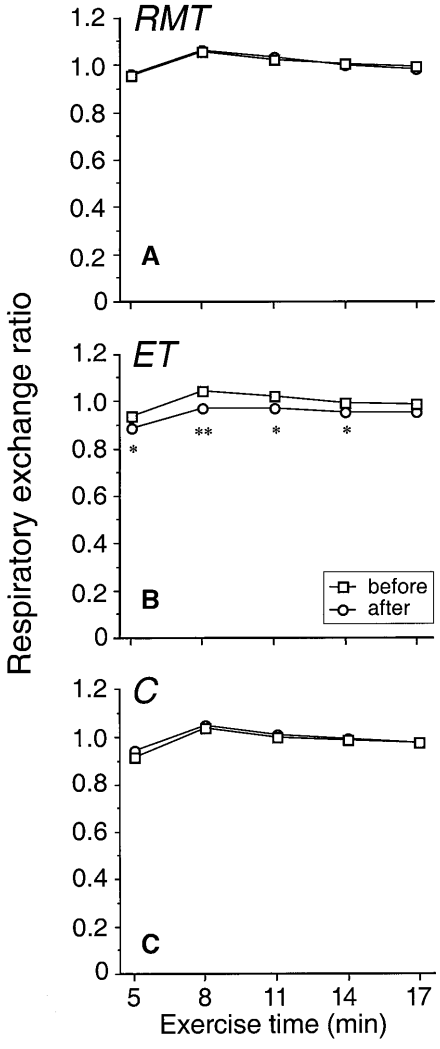

Fig. 4 Progression of the respiratory exchange ratio during the cycling endurance test (70% $\dot{W}_{max}$) before (□) and after (○) 15 weeks of training or the control period is shown for the constant-load period that could be sustained by all subjects of each group (means ± SD). Subjects were assigned to either a respiratory muscle training group (*RMT*, $n = 13$), an endurance training group (*ET*, $n = 9$), or a control group (*C*, $n = 15$). The respiratory exchange ratio decreased significantly in the ET group only (*$P < 0.05$, **$P < 0.01$ compared to changes in the C group)

ance after RMT may indeed originate from direct training effects on the respiratory system. Among such effects, delay of respiratory muscle fatigue may play a role (Dempsey 1986; Johnson et al. 1996; Boutellier 1998). Diaphragmatic fatigue has been demonstrated to occur during exhaustive exercise at workloads above 70% $\dot{W}_{max}$ (Johnson et al. 1993; Mador et al. 1993; Mador and Dahuja 1996), and expiratory muscle fatigue can also occur after exhaustive exercise (Fuller et al. 1996). These findings and the consistent effects of RMT on both breathing and cycling endurance (present study; Boutellier et al. 1992; Boutellier and Piwko 1992; Spengler et al. 1999) indicate that respiratory muscle fatigue may contribute to the limitation of cycling endurance at workloads that can be sustained for 15 min or more. In the light of these studies, our findings suggest that fatigue of the respiratory muscles might be reduced by RMT, allowing subjects to cycle for longer.

However, since respiratory function in the cycling-exhausted state was not assessed in the present study, it cannot be excluded that factors other than respiratory muscle fatigue may have been affected by the training and thus have caused the improvement of cycling endurance. For example, it may be surmised that RMT brings about a reduction of the blood flow required by the respiratory muscles due to increased respiratory muscle efficiency. This would tend to favor blood flow to the legs and help explain the increase in cycling endurance. For example, when Harms et al. (1998) reduced the work of breathing during maximal exercise by mechanical unloading, they showed that such a reduction resulted in a greater proportion of the total $\dot{V}O_2$ and cardiac output being utilized by the legs. This effect was accompanied by a reduction in total $\dot{V}O_2$ and cardiac output. In addition, Wetter et al. (1999) found a reduction in total $\dot{V}O_2$ with assisted breathing at submaximal workloads, but they did not find a concomitant change in leg blood flow or leg $\dot{V}O_2$. In the present study, which also tested submaximal exercise performance, neither $\dot{V}O_2$, cardiac output nor substrate utilization (respiratory exchange ratio) were reduced after RMT. Therefore, it appears unlikely that RMT decreased the blood flow or oxygen demand of the respiratory muscles during the submaximal exercise test, and the increased cycling times after RMT are not likely to be attributable to an increased blood supply to the leg muscles.

Another way by which RMT may influence cycling endurance is a reduction in the sensation of breathlessness at similar workloads. Since RMT does not alter chemoreceptor sensitivity (Markov et al. 1996), such an effect may be related either to a sensation of lower demand relative to the increased performance capacity of the respiratory muscles, or to a central nervous conditioning mechanism. Of course respiratory muscle fatigue and the sensation of breathlessness are not mutually exclusive factors, but they may interact and/or combine to limit exercise endurance. Further studies may help to determine whether delayed respiratory muscle fatigue or other factors related to the respiratory system (i.e., the sensation of breathlessness,or mechanical load) are responsible for the improvement of cycling endurance after RMT.

Conclusions

Fifteen weeks of RMT increased respiratory and cycling endurance but did not affect cardiac SV, $\dot{V}O_2$ or substrate utilization during exercise in healthy sedentary subjects. This indicates that the increased cycling endurance observed after RMT is not due to cardiac adaptations or changes in substrate utilization similar to those observed after endurance training, but that factors associated with the respiratory system are likely to limit

exercise endurance at submaximal intensities in healthy humans.

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Influence of endurance exercise on respiratory muscle performance

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ABSTRACT

PERRET, C., C. M. SPENGLER, G. EGGER, and U. BOUTELLIER. Influence of endurance exercise on respiratory muscle performance. *Med. Sci. Sports Exerc.*, Vol. 32, No. 12, 2000, pp. 2052–2058. **Purpose:** During high-intensity, exhaustive, constant-load exercise above 85% of maximal oxygen consumption, the diaphragm of healthy subjects can fatigue. Although a decrease in trans-diaphragmatic pressure is the most objective measure of diaphragmatic fatigue, possible extra-diaphragmatic muscle fatigue would not be detected by this method. The aim of the present study was to investigate the impact of exhaustive, constant-load cycling exercise at different intensities on global respiratory performance determined by the time to exhaustion while breathing against a constant resistance. **Methods:** Ten healthy, male subjects performed an exhaustive cycling endurance test at 65, 75, 85, and 95% of peak oxygen consumption ($\dot{V}O_{2peak}$). Before cycling (t_0) as well as at 10 min (t_{10}) and 45 min (t_{45}) after cycling, respiratory performance was determined. **Results:** Breathing endurance was equivalently reduced after exhaustive cycling at either 65% (8.4 ± 4.1 min [t_0] vs 3.9 ± 2.8 min [t_{10}]), 75% (9.9 ± 6.1 vs 4.4 ± 2.8 min), 85% (9.3 ± 6.0 vs 3.8 ± 2.9 min), or 95% $\dot{V}O_{2peak}$ (8.5 ± 5.1 vs 4.0 ± 2.5 min) and, therefore, was independent of exercise intensity. **Conclusion:** This result contradicts previous findings, possibly due to the fact that extra-diaphragmatic muscles are tested in addition to the diaphragm during resistive breathing. **Key Words:** RESISTIVE BREATHING, RESPIRATORY MUSCLE FATIGUE

During high-intensity, exhaustive, constant-load running or cycling exercise above 85% $\dot{V}O_{2max}$ (1-3,12) or 80% W_{max} (18), the diaphragm of healthy subjects can fatigue—as shown by a reduction of transdiaphragmatic twitch pressure ($P_{di,tw}$) during electrical or magnetic stimulation of the phrenic nerves. At intensities of 70–75% W_{max}, $P_{di,tw}$ was reduced in 9 of 14 subjects only (17). In general, the higher the intensity of exercise, the larger the diaphragmatic fatigue (12)—even in the face of shorter exercise durations at higher intensities.

Although the measurement of $P_{di,tw}$ is certainly the most objective measure of diaphragmatic fatigue, there are some limitations to this technique. On the one hand, it is an exclusive measure of diaphragmatic fatigue neglecting possible extra-diaphragmatic inspiratory muscle fatigue and on the other hand, this technique is laboratory-bound and somewhat "invasive."

In contrast, breathing against a constant resistance until exhaustion, an easy to use and "noninvasive" technique involving most of the inspiratory muscles, has been used in the past to measure global inspiratory muscle fatigue: Ker and Schultz (13) had their subjects breathe to exhaustion against a constant resistive load before and after completion of an ultramarathon. The maximal breathing endurance time remained reduced even 3 d after the ultramarathon. In a recent study, we showed that respiratory performance was reduced by 43% after exhaustive cycling at 85% $\dot{V}O_{2max}$ (21), a workload at which diaphragmatic fatigue had previously been demonstrated (12). The 43% reduction in breathing endurance time was larger than the reduction in $P_{di,tw}$ (8–32%) reported by Johnson et al. (12) after exercise at similar workloads. This difference might result from extra-diaphragmatic fatigue which is measured during resistive breathing.

The aim of the present study was to investigate the impact of exhaustive, constant-load cycling exercise at 65, 75, 85, and 95% $\dot{V}O_{2peak}$ on respiratory muscle performance as determined by the maximal breathing endurance time in a constant-load resistive breathing test. Additionally, we measured blood lactate concentration, pH, serum potassium concentration, and core body temperature, factors known to affect skeletal muscle contractility (6,9,11) and performance (14). We hypothesized that the decrease in respiratory performance after exercise would correlate with exercise intensity as does the decrease in $P_{di,tw}$ (12) but that this correlation would possibly have a different slope due to the measurement of both extra-diaphragmatic muscle performance and diaphragmatic muscle performance.

METHODS

Subjects. Ten healthy, nonsmoking, male subjects (study group) participated in the main study. Their average

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TABLE 1. Spirometric characteristics (mean ± SD) of study ($N = 10$) and control subjects ($N = 10$).

Group	VC (L)	FEV_1 (L)	PEF ($L \cdot s^{-1}$)	MVV_{20} ($L \cdot min^{-1}$)	P_{Imax} (cm H_2O)
Study	6.4 ± 0.6	4.8 ± 0.4	11.0 ± 1.0	194 ± 21	−165 ± 27
Control	5.9 ± 1.2	4.7 ± 0.8	11.3 ± 1.7	199 ± 36	−185 ± 28

VC, vital capacity; FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; MVV_{20}, maximal voluntary ventilation in 20 s; P_{Imax}, maximal inspiratory mouth pressure.

age was 29 ± 4 yr, their height was 181 ± 5 cm, and their weight was 72 ± 7 kg. They were physically fit ($\dot{V}O_{2peak}$ 60 ± 4 $mL \cdot kg^{-1} \cdot min^{-1}$) and had normal lung function (Table 1). An additional group of 10 subjects (control group) performed two series of control experiments. Their average age was 26 ± 4 yr, their height was 183 ± 6 cm, and their weight was 71 ± 7 kg. They were physically fit and had normal lung function (Table 1). The two groups had similar physical and lung function characteristics. Informed written consent was obtained from each subject and the study protocol was approved by the Ethics Committee of Physiology and Pharmacology Departments at the University of Zurich.

Subjects were asked to abstain from caffeine intake for at least 2 h before each test, as caffeine increases breathing endurance during loaded breathing tests (22) and attenuates the exercise-induced increase in plasma potassium levels (16). Subjects were also instructed to keep their personal training schedule constant throughout the study protocol and to perform no strenuous workouts the day before a test.

Equipment. Vital capacity (VC), forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF), maximal voluntary ventilation in 20 s (MVV_{20}), as well as ventilation and gas exchange variables during cycling were determined with an ergo-spirometric device, Oxycon Beta (Jaeger, Würzburg, Germany) using a turbine for volume measurements, a paramagnetic analyzer for O_2, and an infrared absorption analyzer for CO_2 measurements.

Maximal inspiratory mouth pressure (P_{Imax}) was determined with a special device (Tecuria, Chur, Switzerland). This apparatus was also used for resistive breathing. It consists of a mouthpiece connected to a tube system including a flow sensor (163PC01D75, Honeywell, Phoenix, AZ) and a pressure sensor (143C05PCB, Sensym, Milpitas, CA). The tube system extends to two electronically controlled valves (inspiratory and expiratory). Breathing resistance increases proportionally to the voltage applied to the valves. Feedback on the generated mouth pressure is displayed on an oscilloscope. Cycling tests were performed on an electronically breaked cycle ergometer (Ergometrics 800 S, Ergoline, Bitz, Germany).

Core body temperature was measured by a rectal temperature probe (YSI Reusable Temperature Probe, Yellow Springs Instruments, Yellow Springs, OH) and monitored on a Duotemp TM101 (Fisher & Paykel, Auckland, New Zealand). Blood samples were drawn by a catheter inserted into a forearm vein. Blood lactate concentrations were determined enzymatically (Ebio 6666, Eppendorf, Hamburg, Germany), pH was measured with a blood gas analyzer (IL1304, Instrumentation Laboratory, Milano, Italy), and serum potassium concentrations were analyzed with a flame photometer (IL 943, Instrumentation Laboratory).

Preliminary testing. First, all subjects were familiarized with the different testing devices, in particular with the resistive breathing device as it is well known that subjects need to learn such a breathing technique (7). Spirometric measurements (VC, FEV_1, PEF, MVV_{20}) as well as P_{Imax}-maneuvers were performed until values were reproducible. P_{Imax} was measured from residual volume (RV), whereas the subject performed a maximal inspiration against an occluded airway. An 18-gauge needle was inserted into the mouthpiece to ensure that the glottis stayed open (4,20). An incremental breathing test was then performed: subjects began by breathing against an inspiratory resistive load at a pressure corresponding to 60% P_{Imax} with the exception of one subject who started at 55% P_{Imax}, because he was not able to sustain a load of 60% P_{Imax} for at least 3 min (see below). Expiration was unloaded and breathing frequency (f_R) was set at 18 $breaths \cdot min^{-1}$ and paced by a metronome. Every 3 min, the resistive load was increased by five percents of P_{Imax}. The test continued until the subjects were no longer able to overcome the load. The P_I of the last step that the subjects were able to sustain for 3 min was selected as the target pressure for the constant-load test.

At least 2 d later, all subjects performed two consecutive resistive breathing tests at the predetermined, constant load (see above). The two tests were separated by a 15-min rest period. During each test, the subjects matched the mouth pressure to a pressure waveform (previously determined to be comfortable) displayed on the oscilloscope. All subjects breathed at an f_R of 18 $breaths \cdot min^{-1}$. The maximal breathing endurance time was defined as the time when subjects were no longer able to overcome the load and/or to achieve the target pressure. During this test series, subjects were asked every minute to rate their respiratory exertion and air hunger on a modified Borg scale (24). This test series served as control to assure that the breathing tests that were performed after exercise in the main study (see below) would not be influenced by the baseline breathing test performed before exercise.

Study subjects performed an incremental cycling test to exhaustion to determine W_{max} as well as $\dot{V}O_{2peak}$. Starting at 100 W, the load was increased by 30 W every 2 min. The subjects chose their preferred pedaling frequency at the beginning of the test, and it was held constant thereafter. The highest load a subject could tolerate for at least 90 s was considered to be W_{max}, the highest $\dot{V}O_2$ measured over 15 s was determined to be $\dot{V}O_{2peak}$.

Main study. The main tests were performed in random order on four different days separated by at least 48 h. Before each test, a catheter was inserted into the subjects' forearm vein for blood sampling, and a rectal temperature probe was inserted and fixed with adhesive tape to prevent

displacement. Before cycling (t_0), the subjects performed a constant-load breathing test to exhaustion to determine the maximal breathing endurance time. After a break of 15 min, subjects started cycling to exhaustion at either 65, 75, 85, or 95% $\dot{V}O_{2peak}$. These cycling endurance tests were started at 100 W and, in order to reach the predetermined workload within 3 min, the workload was increased in three equal increments of 1 min duration. Ten (t_{10}) and 45 min (t_{45}) after the subjects stopped cycling, the breathing test to task failure was repeated. During each constant-load breathing test, subjects were asked to rate their respiratory exertion as well as their perception of air hunger on a modified Borg scale (24) every minute. Blood samples were drawn before and after each breathing test.

Control series. The subjects of the control group performed three constant load breathing tests separated by the same interval as the resistive breathing tests of the study group's longest lasting test series (series with cycling at 65% $\dot{V}O_{2peak}$). Also, subjects were asked to rate their respiratory exertion as well as their perception of air hunger on a modified Borg scale (24) every minute. This test series was performed to further assure that no decrease in respiratory endurance times measured after cycling in the main test series could possibly be a result of the preexercise resistive breathing test.

Statistics. An analysis of variance (ANOVA) with repeated measures was applied to compare variables of the constant-load breathing tests at t_{10} and t_{45} with variables at t_0 of the same test series, to compare the four constant-load breathing tests at the same time point (t_0, t_{10} or t_{45}), and to compare cycling endurance times and ventilatory variables of the four different cycling endurance tests. If significance was found, Fisher's PLSD *post hoc* test was used to locate the significant differences. Average values of blood lactate concentrations, pH, serum potassium concentrations, and core body temperature measured before and after the constant-load breathing tests were calculated for the above statistical comparisons. Variables of the two preliminary consecutive resistive breathing tests as well as baseline characteristics of the two groups were also compared by ANOVA. Results are given as mean ± SD. Values were considered to be significantly different if $P < 0.05$.

RESULTS

Breathing endurance was similarly reduced in constant-load breathing tests 10 min (t_{10}) after exhaustive cycling at 65, 75, 85, and 95% $\dot{V}O_{2peak}$ as well as 45 min (t_{45}) after cycling at 65, 75, and 85% $\dot{V}O_{2peak}$ (Fig. 1). The paced f_R during the constant-load breathing tests at t_0, t_{10} and t_{45} were not significantly different between tests (average 18.4 ± 0.1 min^{-1}). Tidal volume (V_T) showed small but significant differences (Table 2). No significant differences were found in the ratings of perceived respiratory exertion or air hunger of the last minute of the constant-load breathing tests (Table 2).

The three breathing endurance tests of the control group were of similar length (first: 7.7 ± 4.4 min; second: 8.2 ± 4.1 min; third: 7.0 ± 3.3 min). The paced f_R was the same in all three tests (18.2 ± 0.1 min^{-1}). Tidal volume did not differ significantly either (first: 1.11 ± 0.11 L; second: 1.06 ± 0.14 L; third: 1.06 ± 0.12 L). No significant differences were found in the ratings of perceived respiratory exertion (first: 8.3 ± 1.3; second: 9.0 ± 1.2; third: 9.2 ± 1.3) or air hunger (first: 7.8 ± 1.9; second: 9.0 ± 0.9; third: 8.5 ± 1.6) in the last minute of the constant-load breathing tests.

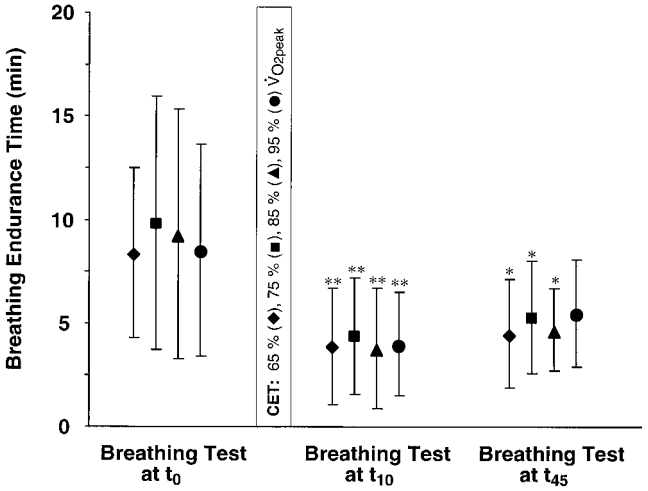

FIGURE 1—Breathing endurance times of the constant-load breathing tests (average of 10 subjects) before (t_0) as well as 10 (t_{10}) and 45 min (t_{45}) after cessation of an exhaustive cycling endurance test (CET) at 65, 75, 85, or 95% of peak oxygen uptake ($\dot{V}O_{2peak}$). Significant differences in variables at t_{10} and t_{45} compared with t_0 are marked with asterisks (* $P < 0.05$; ** $P < 0.01$). Note that there was no significant difference among tests at t_0, t_{10}, or t_{45}.

The exercise duration differed significantly among the cycling endurance tests (Table 3). Average power outputs during cycling at 65, 75, 85, and 95% $\dot{V}O_{2peak}$ were 206 ± 24 W (67 ± 3% W_{max}), 238 ± 28 W (78 ± 2% W_{max}), 267 ± 32 W (87 ± 2% W_{max}), and 295 ± 37 W (96 ± 2% W_{max}). Steady-state ventilation (averaged ventilation during the constant load period of the cycling test excluding the last 2 min), total ventilation (sum of the ventilation over the entire cycling time), as well as ventilation during the last 2 min of each test (average ventilation of the last 2 min) were significantly different between tests (Table 3). Values for blood lactate concentrations (Fig. 2), pH (Fig. 3), serum potassium concentrations (Fig. 4), and core body temperature (Fig. 5) were not significantly different before the cycling endurance tests, but they differed significantly at t_{10} after the cycling endurance tests.

Breathing endurance times of the two consecutive constant-load breathing tests were similar in the study group (6.6 ± 2.6 vs 6.9 ± 2.5 min) and in the control group (6.2 ± 2.2 vs 6.1 ± 2.3 min). Also, f_R (study group: 18.4 ± 0.4 min^{-1} vs 18.4 ± 0.4 min^{-1}; control group: 18.2 ± 0.1 min^{-1} vs 18.2 ± 0.1 min^{-1}) was the same in both tests of both groups. Tidal volume was the same in both tests of the study group (0.82 ± 0.13 L vs 0.83 ± 0.15 L) while it was slightly smaller in the control group's second test (1.14 ± 0.16 L vs 1.08 ± 0.18 L).

TABLE 2. Tidal volume ($N = 10$) as well as rating of perceived respiratory exertion and air hunger ($N = 7$) during the last minute of each constant-load breathing test before (t_0) and after (t_{10} and t_{45}) exhaustive cycling at 65, 75, 85, or 95% of peak oxygen uptake ($\dot{V}O_{2peak}$).

	65% $\dot{V}O_{2peak}$	75% $\dot{V}O_{2peak}$	85% $\dot{V}O_{2peak}$	95% $\dot{V}O_{2peak}$
Tidal volume				
at t_0	0.88 ± 0.12	0.85 ± 0.11	0.85 ± 0.17	0.84 ± 0.11
at t_{10}	0.80 ± 0.16	0.81 ± 0.19	0.87 ± 0.21	0.89 ± 0.16
at t_{45}	0.78 ± 0.15*	0.76 ± 0.16*	0.80 ± 0.21	0.76 ± 0.17
Perceived exertion				
at t_0	9.4 ± 0.5	9.3 ± 0.8	9.7 ± 0.5	9.1 ± 1.1
at t_{10}	8.9 ± 1.5	9.4 ± 1.0	9.4 ± 0.5	9.1 ± 1.1
at t_{45}	9.4 ± 0.8	9.1 ± 0.9	8.7 ± 1.7	9.6 ± 0.5
Air hunger				
at t_0	8.9 ± 1.1	8.7 ± 1.1	8.9 ± 1.5	8.9 ± 1.3
at t_{10}	8.8 ± 2.1	8.1 ± 2.2	8.1 ± 1.1	8.6 ± 1.0
at t_{45}	8.9 ± 1.9	8.0 ± 1.3	7.4 ± 2.2	8.9 ± 1.1

* Significant differences of variables at t_{10} and t_{45} compared with t_0 ($P < 0.05$).

DISCUSSION

The main finding of the present study is that the time to exhaustion during constant-load resistive breathing was significantly reduced after exhaustive cycling at either 65, 75, 85, or 95% $\dot{V}O_{2peak}$ and that this reduction was independent of exercise intensity. This result contrasts with findings of Johnson et al. (12), who showed that the extent of diaphragmatic fatigue—decrease in $P_{di,tw}$—after exhaustive cycling correlated with the intensity of the endurance exercise test.

This difference between the two studies could possibly result from different methods used to detect the decrease in respiratory muscle performance. While $P_{di,tw}$ exclusively measures fatigue of the diaphragm, constant-load resistive breathing also involves extra-diaphragmatic inspiratory muscles. This can be inferred from a study which showed that breathing against a threshold load preferentially fatigues rib cage muscles rather than the diaphragm (10). In fact, McKenzie et al. (19) were unable to detect diaphragmatic fatigue in their subjects at the point of task failure after breathing against resistive loads. It is possible that, during cycling, rib cage muscles fatigue to a similar or even larger extent than the diaphragm. This assumption is supported by the data of Johnson et al. (12), who have shown that the relative contribution of the diaphragm to total respiratory motor output was progressively reduced as exercise proceeded, indicating that the work of breathing was increasingly performed by extra-diaphragmatic muscles. Thus, one could speculate that extra-diaphragmatic muscles fatigued to a similar extent during the four different cycling tests in the present study.

On the other hand, factors other than muscle fatigue may have led to the reduced respiratory muscle performance during constant-load resistive breathing after exhaustive cycling. In a subject-limited endurance test such as breathing to exhaustion against a resistance, subjects' motivation is crucial. To prevent lack of motivation influencing the outcome of the study, only highly motivated subjects were chosen to participate. In fact, ratings of perceived respiratory exertion and air hunger (Table 2) were similar at the end of all constant-load resistive breathing tests, suggesting that the subjects performed maximally.

Alternatively, a change in minute ventilation and/or breathing pattern during resistive breathing, as shown by Clanton et al. (5), could have been responsible for a reduced respiratory performance during tests at t_{10} and t_{45} compared with t_0. In the present study, we did not observe any significant differences in f_R between any of the breathing tests. However, mean V_T during breathing tests at t_{45} after the 65%- and the 75%-cycling runs was slightly but significantly lower than precycling V_T. Thus, we assume that breathing endurance times would have been slightly smaller at t_{45} after the 65%- and 75%-cycling runs had V_T been slightly higher, i.e., had V_T been the same at t_{45} and at t_0. A larger reduction in breathing endurance after 65%- and 75%-cycling runs than after 85%- and 95%-cycling runs would be even more surprising as we predicted less or no reduction in respiratory performance to occur after exhaustive cycling exercise at 65 and 75% $\dot{V}O_{2peak}$ as the diaphragm hardly fatigues at these intensities (12,18).

Further, one could argue that a reduction of respiratory performance at t_{10} might be a consequence of preexisting fatigue of the respiratory muscles from breathing against the resistance at t_0 as Laghi et al. (15) and Travaline et al. (23) have shown that diaphragmatic fatigue can last for at least 24 h when subjects breathe against inspiratory resistive loads of 60% of maximal P_{di} ($P_{di,max}$) for 33 min or 80% $P_{di,max}$ for 25 min. However, those loaded breathing tasks were substantially longer than the resistive breathing tests of

TABLE 3. Minute ventilation during ($\dot{V}_E$ steady state and $\dot{V}_E$ total) and at the end ($\dot{V}_E$ end) of cycling exercise as well as duration of the exhaustive cycling endurance tests at 65, 75, 85, and 95% of peak oxygen uptake ($\dot{V}O_{2peak}$) in 10 subjects.

	65% $\dot{V}O_{2peak}$	75% $\dot{V}O_{2peak}$	85% $\dot{V}O_{2peak}$	95% $\dot{V}O_{2peak}$
$\dot{V}_E$ steady state ($L \cdot min^{-1}$)	77.3 ± 9.3	93.1 ± 12.2∞	98.6 ± 14.0∞∞	101.2 ± 12.2∞∞
$\dot{V}_E$ total (L)	3049 ± 1004	2011 ± 775∞	1189 ± 609∞∞,§	783 ± 277∞∞,§§
$\dot{V}_E$ end ($L \cdot min^{-1}$)	87.5 ± 14.7	110.2 ± 17.3∞	121.6 ± 17.2∞∞	124.4 ± 16.0∞∞,§§
Time (min)	41.5 ± 14.5	23.7 ± 10.5∞∞	13.4 ± 6.1∞∞,§	8.6 ± 2.4∞∞,§§§,††

$\dot{V}_E$ steady state, averaged minute ventilation during the constant load period (excluding the last 2 min); $\dot{V}_E$ total, sum of ventilation during the entire exercise period; $\dot{V}_E$ end, averaged minute ventilation during the last 2 min of exercise. Significant differences compared to values at 65% (∞ $P < 0.01$; ∞∞ $P < 0.001$), 75% (§ $P < 0.05$; §§ $P < 0.01$; §§§ $P < 0.001$) and 85% $\dot{V}O_{2peak}$ (†† $P < 0.01$) are shown.

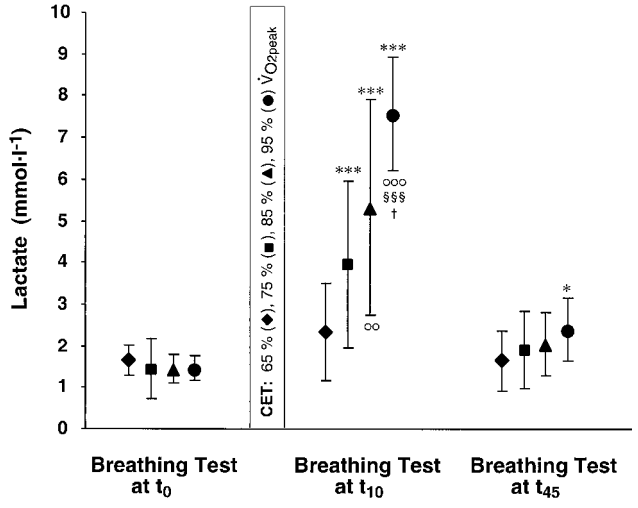

FIGURE 2—Mean blood lactate concentrations of the constant-load breathing tests (average of 10 subjects) before (t_0) as well as 10 (t_{10}) and 45 min (t_{45}) after cessation of an exhaustive cycling endurance test (CET) at 65, 75, 85, or 95% of peak oxygen uptake ($\dot{V}O_{2peak}$). Significant differences of variables at t_{10} and t_{45} compared with t_0 are marked with asterisks (* $P < 0.05$; *** $P < 0.001$). Significant differences to values of the 65% series (°° $P < 0.01$; °°° $P < 0.001$), the 75% series (§§§ $P < 0.001$), and the 85% series († $P < 0.05$) compared at the same time point (t_0, t_{10} or t_{45}) are also shown.

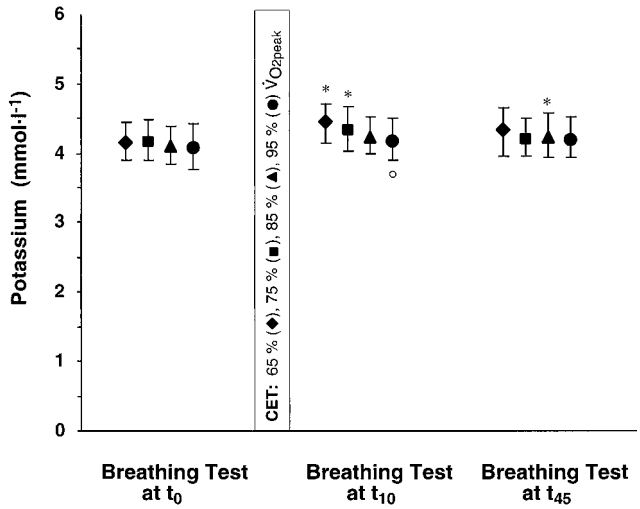

FIGURE 4—Mean serum potassium concentrations of the constant-load breathing tests (average of 10 subjects) before (t_0) as well as 10 (t_{10}) and 45 min (t_{45}) after cessation of an exhaustive cycling endurance test (CET) at 65, 75, 85, or 95% of peak oxygen uptake ($\dot{V}O_{2peak}$). Significant differences of variables at t_{10} and t_{45} compared with t_0 are marked with asterisks (* $P < 0.05$). Significant differences to values of the 65% series (° $P < 0.05$) compared at the same time point (t_0, t_{10} or t_{45}) are also shown.

the present study (average 9.0 ± 5.2 min). To assure that the recovery period between the preexercise breathing test and the start of cycling exercise would be long enough for the following breathing tests not to be affected by the first breathing test, all subjects performed a preliminary control test series. In this test series, respiratory muscle performance of the subjects was assessed in two subsequent constant-load resistive breathing tests to exhaustion with a 15-min pause in-between that previously proved to be long enough for a following breathing or cycling test not to be affected (21). Under these conditions, both breathing tests were of similar duration, suggesting that reduced breathing endurance times after cycling would not be caused by the precycling breathing test. To also assure that resistive breathing tests dispersed over a period of almost 2 h (similar to the longest lasting series) would be of similar lengths without intervening cycling, an additional group of subjects was recruited. These subjects performed two test series: first they also completed the above described preliminary test series with two consecutive breathing tests with a 15-min-

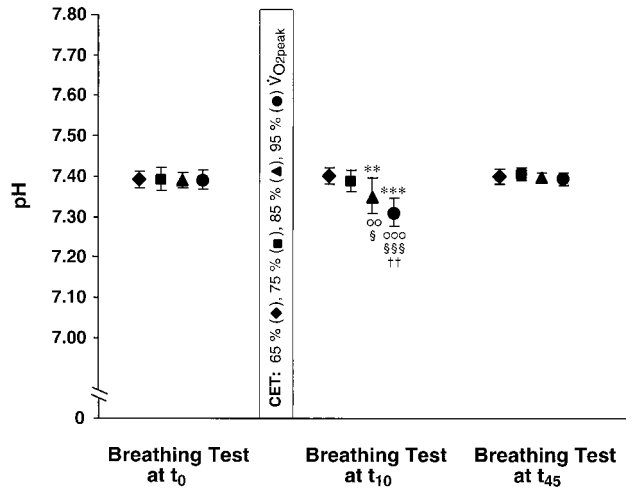

FIGURE 3—Mean blood pH of the constant-load breathing tests (average of 10 subjects) before (t_0) as well as 10 (t_{10}) and 45 min (t_{45}) after cessation of an exhaustive cycling endurance test (CET) at 65, 75, 85, or 95% of peak oxygen uptake ($\dot{V}O_{2peak}$). Significant differences of variables at t_{10} and t_{45} compared with t_0 are marked with asterisks ($P < 0.01$; *** $P < 0.001$). Significant differences to values of the 65% series (°° $P < 0.01$; °°° $P < 0.001$), the 75% series (§ $P < 0.05$; §§§ $P < 0.001$), and the 85% series (†† $P < 0.01$) compared at the same time point (t_0, t_{10} or t_{45}) are also shown.**

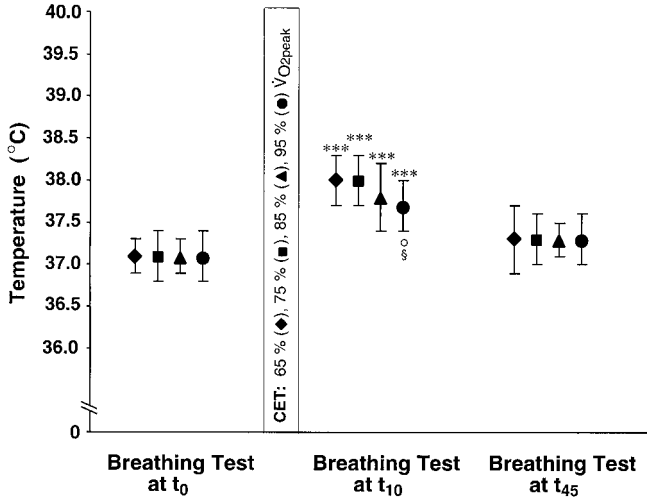

FIGURE 5—Mean core body temperature of the constant-load breathing tests (average of 10 subjects) before (t_0) as well as 10 (t_{10}) and 45 min (t_{45}) after cessation of an exhaustive cycling endurance test (CET) at 65, 75, 85, or 95% of peak oxygen uptake ($\dot{V}O_{2peak}$). Significant differences of variables at t_{10} and t_{45} compared with t_0 are marked with asterisks (* $P < 0.001$). Significant differences to values of the 65% series (° $P < 0.05$) and the 75% series (§ $P < 0.05$) compared at the same time point (t_0, t_{10} or t_{45}) are also shown.**

pause, and then they performed three subsequent constant-load breathing tests to exhaustion without cycling in-between, the resting period between tests being similar to the time spans between breathing tests in the 65%-test series of the study group. As breathing endurance times of the three constant-load resistive breathing tests did not differ significantly in length in this control test series either, we suggest that the reduced breathing endurance times after cycling, at t_{10}, were a result of decreased respiratory performance due to the ventilatory work performed during exercise rather than being a result of fatigue from the precycling resistive breathing tests at t_0.

Finally, changes in blood lactate concentration, pH, serum potassium concentration, or core body temperature—factors known to influence muscle contractility (6,9,11) and performance (14)—might possibly account for the changes in respiratory performance after exhaustive cycling. Directly after cycling (t_{10}) at 85 and 95% $\dot{V}O_{2peak}$, blood lactate concentrations were significantly higher and pH was significantly lower than after cycling at 65 and 75% $\dot{V}O_{2peak}$. These changes would predict—if large enough to affect muscle contractility—a larger reduction in breathing endurance time after exercise at higher workloads. In contrast, serum potassium concentration and core body temperature were significantly higher at 65 than at 95% $\dot{V}O_{2peak}$, which in turn would predict—if these changes were large enough to affect muscle contractility—a larger reduction in breathing endurance time after cycling at lower intensities. These different effects on muscle contractility do not need to be mutually exclusive and may in fact be additive. We could only speculate to which extent they possibly contributed to the decrease in respiratory muscle performance after exhaustive cycling but we believe that the changes were too small to have a major effect. Also, we believe that these small changes did not affect breathing endurance time, because most of these variables had reached baseline levels at t_{45}, but three of four breathing endurance times were still significantly reduced at this time.

To possibly explain why respiratory performance was reduced by similar degrees after exhaustive cycling at different intensities (65, 75, 85, and 95% $\dot{V}O_{2peak}$), we compared the level of ventilation during the constant-load part of the cycling test as well as total ventilation summed over the entire exercise period as an index of total ventilatory work performed during the cycling test. As the level of steady-state ventilation was significantly lower during the 65% test, gradually increasing up to the test with the highest cycling workload, we can rule out the level of steady state ventilation as a possible reason for the similarly reduced respiratory performance after exercise. As the test performed at 65% $\dot{V}O_{2peak}$ lasted about 5 times longer than the 95%-test, one could argue that a lower ventilation held for a longer time might add up to the same ventilatory work as a larger ventilation performed over a shorter time and thus affecting respiratory muscles to a similar degree. We therefore summed ventilation over the entire exercise time: this total ventilation was significantly larger during the 65% test than during the 95% test, indicating that total ventilation *per se* cannot be responsible for the similarly decreased respiratory performance during all four breathing tests at t_{10}. Therefore, we additionally compared the ventilatory output during the last 2 min of exercise as it is known that only 2 min of maximal voluntary ventilation can cause respiratory muscle fatigue (8). Minute ventilation at the very end of the test may therefore be crucial for inducing respiratory muscle fatigue. As is evident from Table 3, there were significant differences of minute ventilation during these last minutes of exercise, ventilation being significantly smaller during the 65%-test than during the cycling tests at higher workloads, again indicating that the final ventilation *per se* cannot be responsible for the similar reduction in respiratory performance after different intensities of exercise. Possibly a mixture of a long exercise time with a smaller ventilation and a smaller increase in ventilation at the end of exercise may result in the same impact on respiratory muscles as a short exercise time with a higher ventilation and a very high final output of the ventilatory system. To fully answer the seemingly contradicting results of previous studies and the present findings, further studies, possibly including ventilatory interventions and focusing on extra-diaphragmatic respiratory muscles during exercise, are needed.

CONCLUSIONS

The reduction of respiratory performance after exhaustive constant-load cycling tests at 65, 75, 85, and 95% $\dot{V}O_{2peak}$ was of similar degree when measured by exhaustive breathing against a constant resistive inspiratory load. These results contrast with measurements of diaphragmatic fatigue (reduced $P_{di,tw}$), which is more pronounced after exercise of higher intensity. This difference possibly results from the involvement of extra-diaphragmatic muscles in addition to the diaphragm during resistive breathing.

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ORIGINAL ARTICLE

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Decreased exercise blood lactate concentrations after respiratory endurance training in humans

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Abstract For many years, it was believed that ventilation does not limit performance in healthy humans. Recently, however, it has been shown that inspiratory muscles can become fatigued during intense endurance exercise and decrease their exercise performance. Therefore, it is not surprising that respiratory endurance training can prolong intense constant-intensity cycling exercise. To investigate the effects of respiratory endurance training on blood lactate concentration and oxygen consumption ($\dot{V}O_2$) during exercise and their relationship to performance, 20 healthy, active subjects underwent 30 min of voluntary, isocapnic hyperpnoea 5 days a week, for 4 weeks. Respiratory endurance tests, as well as incremental and constant-intensity exercise tests on a cycle ergometer, were performed before and after the 4-week period. Respiratory endurance increased from 4.6 (SD 2.5) to 29.1 (SD 4.0) min ($P < 0.001$) and cycling endurance time was prolonged from 20.9 (SD 5.5) to 26.6 (SD 11.8) min ($P < 0.01$) after respiratory training. The $\dot{V}O_2$ did not change at any exercise intensity whereas blood lactate concentration was lower at the end of the incremental [10.4 (SD 2.1) vs 8.8 (SD 1.9) mmol · l^{-1}, $P < 0.001$] as well as at the end of the endurance exercise [10.4 (SD 3.6) vs 9.6 (SD 2.7) mmol · l^{-1}, $P < 0.01$] test after respiratory training. We speculate that the reduction in blood lactate concentration was most likely caused by an improved lactate uptake by the trained respiratory muscles. However, reduced exercise blood lactate concentrations per se are unlikely to explain the improved cycling performance after respiratory endurance training.

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Key words Inspiratory and expiratory muscle training · Lactate metabolism · Incremental exercise · Constant-intensity exercise · Respiratory muscle fatigue

Introduction

It has generally been accepted that ventilation does not limit exercise performance in healthy humans (Leith and Bradley 1976; Dempsey 1986). More recently, Johnson et al. (1993) and Mador et al. (1993) have shown that the diaphragm fatigues during exercise at a constant intensity of at least 80% of maximal oxygen consumption. After an endurance competition, overall inspiratory muscle fatigue (reduced inspiratory function) has been found (Loke et al. 1982; Hill et al. 1991; Chevrolet et al. 1993) and many hours are needed for complete recovery. Fatigued respiratory muscles in turn have been shown to decrease exercise performance (Martin et al. 1982; Mador and Acevedo 1991b). In addition, it has been found that endurance training of respiratory muscles can increase constant-intensity cycling time in sedentary subjects by 50% (Boutellier and Piwko 1992) and in endurance trained (athletic) subjects by 38% (Boutellier et al. 1992).

At present, we do not know the mechanism by which endurance training of the respiratory muscles prolongs the duration of constant-intensity exercise. One possibility is the occurrence of a reduction in blood lactate accumulation during exercise after respiratory training. This hypothesis has been inferred from observations that whole-body endurance training substantially reduces blood lactate concentrations at a given exercise intensity (Casaburi et al. 1987; MacRae et al. 1992). However, in previous studies, we have been unable to demonstrate that respiratory endurance training consistently alters blood lactate concentrations measured at the end of exercise. Although a significant reduction in the increase of blood lactate concentration above the resting level has been seen in sedentary subjects [5.4 (SD 0.3) vs 2.9 (SD 1.0) mmol · l^{-1}; Boutellier and Piwko 1992], in athletic

subjects, the changes were not significant [2.2 (SD 1.4) vs 2.7 (SD 1.4) mmol · l^{-1}; Boutellier et al. 1992].

With this in mind we decided to examine the accumulation of blood lactate during incremental and constant-intensity exercise before and after endurance training of the respiratory muscles in 20 endurance trained subjects.

Methods

Subjects

A group of 20 healthy, athletic, male subjects [mean age: 26.3 (SD 5.5) years; height: 179.1 (SD 5.9) cm; body mass: 70.3 (SD 7.8) kg] participated in the study. Their weekly endurance training lasted at least 3 h. The subjects were informed in detail about the tests and training involved before they gave their written informed consent (in accordance with the Helsinki Declaration). They kept their habitual physical training constant for 2 weeks prior to the start of the study as well as throughout the entire testing and training period. For the record the subjects kept a diary in which they entered all details of training, including the respiratory training (see below).

Equipment

Respiratory training was performed by voluntary hyperpnoea. To avoid dizziness, the subjects used a portable device which allowed normocapnic rebreathing. The training device consisted of a latex balloon connected to a tube equiped with inlet and outlet valves. The valves permitted the addition of fresh air to the air inspired from the rebreathing balloon to add O_2 and to keep the end-tidal CO_2 fraction at a constant level. Tidal volume (V_T) was therefore slightly greater than the volume of the balloon. Breathing frequency (f_b) was paced by a digital metronome, DM-30 (Seiko, Tokyo, Japan).

Respiratory endurance tests (RET) were also performed with the training device. During the endurance run, minute ventilation ($\dot{V}_E$), V_T, and f_b were monitored with an ergo-spirometric apparatus, OxyconBeta (Mijnhardt, Bunnik, Netherlands), a breath-by-breath system which uses fast responding gas analysers (paramagnetic for O_2 and infrared for CO_2) and a turbine for volume measurements and which can be connected to a mouthpiece. Vital capacity (VC), forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF), and maximal voluntary ventilation (MVV) were also measured with the OxyconBeta.

Incremental and constant-intensity exercise tests were performed on an electronically-braked cycle ergometer, Ergo-metrics 800S (Ergoline, Bitz, Germany). During these tests, $\dot{V}_E$, V_T, f_b, oxygen uptake ($\dot{V}O_2$) and carbon dioxide production were measured. Heart rate (f_c) was recorded in parallel with the respiratory variables using a PE4000 heart rate monitor (Polar Electro, Kempele, Finland).

Blood lactate concentrations were measured with an ESAT 6661 analyser (Eppendorf, Hamburg, Germany) using 20 µl of blood taken from an earlobe. To calibrate the analyser and to check the calibration after the measurements, tubes with a standard solution (10 mmol · l^{-1} lactate concentration) were added before and after a set of blood samples.

Protocol

Firstly, spirometric variables (VC, FEV_1, PEF, and MVV) were measured at least three times. The largest of three similar values was used for analysis. While the subjects familiarized themselves with the respiratory training device, they were asked to breathe with a V_T of 60% of their VC and with a f_b of 40–50 breaths · min^{-1}. These preliminary tests allowed us to choose a $\dot{V}_E$ which the subjects could maintain for only 10 min at most during the first respiratory endurance test (RET_1).

Peak oxygen consumption ($\dot{V}O_{2peak}$) and maximal work capacity (W_{max}) were measured on the cycle ergometer during an incremental exercise test 1 day later. The subjects started pedalling at 100 W and thereafter, the intensity was increased by 30 W every 2 min. The subjects were allowed to choose their own cycling frequency within a range of 70–90 rpm. After that, they kept the number of revolutions per minute constant to assure a constant muscle efficiency (Heinrich et al. 1968). The cycling frequency was presented to the subjects visually and was supervised by an investigator who told the subjects to adjust the speed if necessary. At the end of each intensity, a blood sample was taken. Ventilatory variables and f_c were recorded continuously. The intensity for the cycling endurance test (W_{CET}) was determined for each subject by averaging the anaerobic threshold values calculated by the following three methods: the modified heart rate deflection method (Conconi et al. 1982), the ventilatory threshold method (Wasserman and McIlroy 1964), and the lactate deflection method (Heck et al. 1985).

At least 3 days later, the first cycling endurance test (CET_1) was performed. After 3 min of cycling at 120 W, the intensity was increased to the individual level [W_{CET} = 294 (SD 37) W, representing 85 (SD 3) % W_{max} and 87 (SD 3) % $\dot{V}O_{2peak}$]. Ventilatory variables and f_c were measured continuously. Blood was taken every 5 min to measure lactate concentrations. The subjects were asked to cycle until they were exhausted. When they could no longer hold constant the number of revolutions per minute – even with the encouragement of the investigator – the test was stopped and the duration of the test noted. After 10 min RET_1 was performed. Mean $\dot{V}_E$ was 138.5 (SD 18.6) l · min^{-1} corresponding to 71 (SD 10) % of the initial MVV. When the subjects could no longer maintain target V_T or f_b for five consecutive breaths, the test was stopped and the duration of the test recorded.

After these control measurements, respiratory training was started. The subjects trained for 30 min continuously each day, 5 days a week, for 4 weeks. They performed the daily training at home and recorded all training in their diaries. To make sure that the training was being performed as prescribed, the subjects came to the laboratory every week, where the training device was attached to the OxyconBeta system and, under the supervision of an investigator, they performed their respiratory training. This allowed us to judge the progress of training and to determine the increase in $\dot{V}_E$ (5–10 l) either by raising target V_T (up to maximal 60% of VC) or f_b. The choice of breathing pattern during respiratory training has been shown to have no effect on the outcome of a cycling endurance test (Spengler et al. 1996). The subjects began with a $\dot{V}_E$ of 123 (SD 17) l · min^{-1} [corresponding to 63 (SD 11) % of initial MVV] in the 1st week, which increased to 162 (SD 21) l · min^{-1} [83 (SD 15) % of initial or 70 (SD 16) % of trained MVV] by the end of the 4th training week.

After the end of the respiratory training period, at least 5 days passed without respiratory training before the second cycling endurance test (CET_2) was performed followed by the second respiratory endurance test (RET_2) after a 10-min break. The RET_2 was discontinued after 30 min whether or not the subjects were tired. The exercise intensities for CET_1 and CET_2 were identical [W_{CET} = 294 (SD 37) W] as were V_T and f_b of RET_1 and RET_2. After a further 3 to 4 days, spirometric variables were measured and the post-training incremental cycling test was performed.

Statistics

For comparison of cycling endurance tests, values are presented at two different times:

1. The steady-state values of the cycling endurance tests were calculated by averaging, for each subject, the data from the 10th to 14th min (Table 2). As one subject stopped cycling after 11 min before respiratory training, we used the data of the

7th–11th min instead of the 10th–14th min for this subject. Steady-state blood lactate concentrations were measured in the 13th min (8th min for 1 subject).
2. To compare results at the end of exercise (Tables 1, 2), breath-by-breath values of the last completed minute were averaged.

Of the many tests performed during the study, four tests failed due to technical problems. Therefore, the number of subjects was not always 20.

To detect significant differences between tests before and after respiratory training, paired Student's *t*-tests were performed. For comparison of blood lactate concentrations during exercise before and after respiratory training, an analysis of variance was performed with a Student-Newman-Keuls post-hoc analysis. The level of significance was set to $P < 0.05$. Fisher's *r* to *z* *P*-values were used to test the correlation coefficients for significance.

Results

Spirometry and respiratory endurance

The subjects ($n = 19$) had normal lung functions which did not change with respiratory training: mean VC 5.7 (SD 0.7) compared to 6.0 (SD 0.8) l, mean FEV_1 90.1 (SD 8.1) compared to 88.1 (SD 8.4)% of VC, and mean PEF 10.9 (SD 1.8) compared to 11.2 (SD 1.2) $l \cdot s^{-1}$. The mean MVV increased significantly from 195.5 (SD 24.8) to 232.7 (SD 28.4) $l \cdot min^{-1}$ after respiratory training ($P < 0.001$).

Respiratory endurance time increased significantly from an average of 4.6 (SD 2.5) before to 29.1 (SD 4.0) min after training ($P < 0.001$). It should be noted that after training 19 out of 20 subjects reached 30 min without showing any signs of fatigue.

Incremental exercise

Respiratory training did not affect $\dot{V}O_{2peak}$, W_{max}, maximal f_c (Table 1), or the intensity averaged from the calculations of the three anaerobic threshold [294 (SD 37) compared to 291 (SD 38) W]. From 220 W onward, blood lactate concentrations were significantly reduced after respiratory training (Fig. 1). Blood lactate concentrations at the end of exercise decreased by

Table 1 Respiratory variables, heart rate (f_c), and exercise intensity of 20 subjects during the last minute of incremental exercise (peak) before and after respiratory training. $\dot{V}_E$ Minute ventilation; V_T tidal volume, f_b breathing frequency, $P_{ET}CO_2$ end-tidal CO_2 partial pressure, $\dot{V}O_2$ oxygen consumption, $\dot{V}CO_2$ carbon dioxide production

	Before mean	SD	After mean	SD
$\dot{V}_E$ ($l \cdot min^{-1}$)	141.7	26.1	147.3	21.1
V_T ($ml \cdot breath^{-1}$)	3074	418	3259	514 **
f_b ($breaths \cdot min^{-1}$)	46.6	8.2	46.3	9.0
$P_{ET}CO_2$ (mmHg)	36.0	4.4	35.2	4.2
$\dot{V}O_2$ ($ml \cdot min^{-1}$)	4310	591	4452	522
$\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	61.5	6.7	63.8	8.0
$\dot{V}CO_2$ ($ml \cdot min^{-1}$)	4624	786	4926	710 ***
f_c ($beats \cdot min^{-1}$)	181	8	179	6
Exercise intensity (W)	343	41	345	40

** $P < 0.01$, *** $P < 0.001$

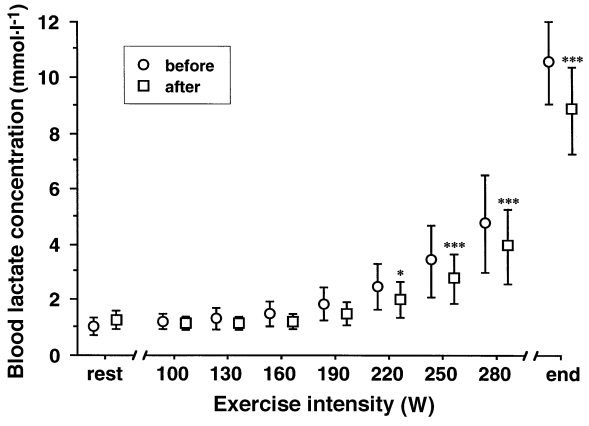

Fig. 1 Blood lactate concentration (mean and SD) plotted at rest and as a function of the intensity of incremental exercise before and after respiratory training. $n = 19$; *$P < 0.05$, ***$P < 0.001$

Table 2 Respiratory variables (18 subjects) and heart rate (f_c; 20 subjects) during the 10th to 14th min (steady state) and during the last minute (end) of cycling endurance exercise test before (CET_1) and after respiratory training (CET_2). $\dot{V}_E$ Minute ventilation, V_T tidal volume, f_b breathing frequency, $P_{ET}CO_2$ end-tidal CO_2 partial pressure, $\dot{V}O_2$ oxygen consumption, $\dot{V}CO_2$ carbon dioxide production

	Steady state				End			
	CET_1		CET_2		CET_1		CET_2	
	mean	SD	mean	SD	mean	SD	mean	SD
$\dot{V}_E$ ($l \cdot min^{-1}$)	109.7	17.1	113.9	15.4	130.1	19.7	141.6	24.1***
V_T ($ml \cdot breath^{-1}$)	3088	552	3161	611	2830	402	2829	410
f_b ($breaths \cdot min^{-1}$)	36.5	6.3	36.8	6.7	46.4	7.2	50.6	9.0**
$P_{ET}CO_2$ (mmHg)	39.7	4.7	38.8	3.4	32.9	3.5	30.8	3.4***
$\dot{V}O_2$ ($ml \cdot min^{-1}$)	3941	631	3986	605	3956	691	4035	660
$\dot{V}CO_2$ ($ml \cdot min^{-1}$)	3926	625	4049	742	3922	614	4071	727*
f_c ($beats \cdot min^{-1}$)	171	9	169	8	182	9	181	8

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

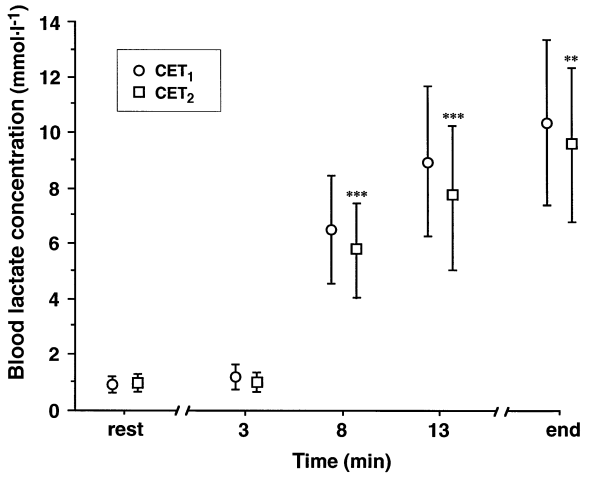

Fig. 2 Blood lactate concentration (mean and SD) measured at rest and during cycling endurance exercise test before (CET_1) and after (CET_2) respiratory training. $n = 20$; $^{**}P < 0.01$, $^{***}P < 0.001$

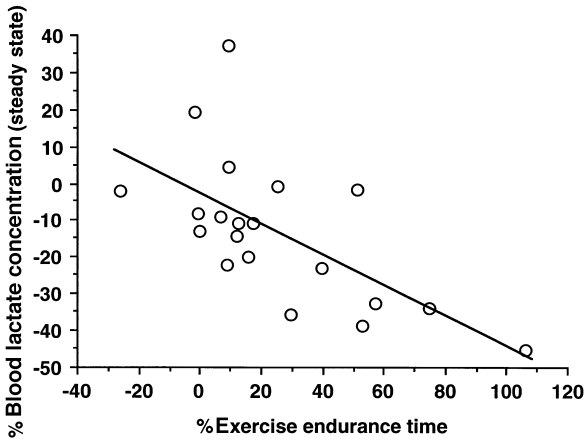

Fig. 3 Decrease in blood lactate concentration during steady-state exercise (13th min) plotted as a function of the increase in exercise time. Values are calculated as the percentage change in both parameters measured from before to after respiratory endurance training. $n = 20$; $y = -0.42\ x - 2.49$

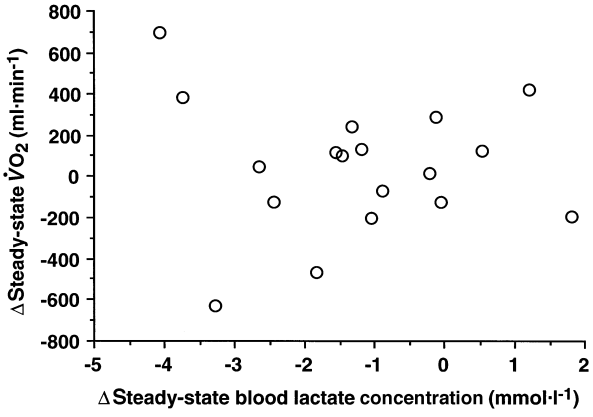

Fig. 4 Change of oxygen uptake ($\dot{V}O_2$ mean of 10th to 14th min) plotted as a function of the change in blood lactate concentration during steady-state exercise (13th min). Values are calculated as the difference in both parameters measured from before to after respiratory endurance training. $n = 18$

1.53 mmol · l^{-1} on average (Fig. 1, $P < 0.001$) after respiratory training.

Endurance exercise

Mean cycling time during endurance exercise significantly increased from 20.9 (SD 5.5) min before, to 26.6 (SD 11.8) min after respiratory training ($P < 0.01$). This represents an average 27% elevation above CET_1. After respiratory training, $\dot{V}O_2$ and f_c, whether measured during the 10th to 14th min or at the end of CET_2 were unchanged (Table 2). Blood lactate concentrations were significantly reduced from 5 min of exercise onward (Fig. 2). Steady-state $\dot{V}_E$ of CET_2 was not influenced by respiratory training (Table 2). Also, V_T and f_b as well as end tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) did not change significantly. During the last minute of CET_2, $\dot{V}_E$ was higher compared to CET_1 (Table 2). This increase was caused by a higher f_b whereas V_T remained constant. The higher $\dot{V}_E$ caused a significant reduction of $P_{ET}CO_2$.

A possible influence of blood lactate concentration on cycling endurance could be inferred from the significant correlation between the percentage decrease in blood lactate concentration, measured either at steady-state ($r = 0.64$, $P < 0.01$; Fig. 3) or end exercise ($r = 0.54$, $P < 0.05$), with the percentage increase of endurance time.

To detect a shift in the balance of aerobic versus anaerobic metabolism, we compared blood lactate concentrations with $\dot{V}O_2$. Not only was $\dot{V}O_2$ unchanged after respiratory training (Table 2) but also there was no correlation between the change in blood lactate concentration and the change in $\dot{V}O_2$ before and after respiratory training whether measured during steady state ($r = 0.06$, $P = 0.80$; Fig. 4) or at the end of exercise ($r = 0.27$, $P = 0.29$).

Discussion

The main findings of the present study were prolonged cycling endurance times but unchanged incremental cycling performance after respiratory training. During both tests after respiratory training, blood lactate concentrations were reduced and $\dot{V}O_2$ remained unchanged. We will discuss first the effectiveness of the respiratory training and then focus on the main findings.

The effectiveness of the respiratory training was evident from the significant increases of MVV and respiratory endurance time. Our observation of increased MVV and respiratory endurance time was in agreement with other studies where healthy subjects have received vigorous respiratory endurance training (Leith and Bradley 1976; Morgan et al. 1987; Fairbarn et al. 1991; Boutellier et al. 1992). The results of the incremental

exercise test and the information in the training diaries indicated that the subjects did not change their level of activity during the study period: $\dot{V}O_{2peak}$, W_{max}, and the intensity at the anaerobic threshold were similar before and after respiratory training. As has been observed in earlier studies (Morgan et al. 1987; Fairbarn et al. 1991; Boutellier et al. 1992), respiratory endurance training did not affect maximal performance in the incremental exercise test. Since the physical status of the subjects did not change with respiratory training but MVV and respiratory endurance time increased, we concluded that respiratory training was effective and that it was the most likely reason for the changes observed during the study.

As a consequence of respiratory training, in the incremental exercise test, blood lactate concentrations were significantly reduced at intensities higher than 220 W. The reduced blood lactate concentration had no influence on either the subjects' maximal performance or on $\dot{V}_E$. During constant-intensity exercise after respiratory training, blood lactate concentrations were also reduced whereas steady-state ventilation (10th–14th min) remained the same. As the decrease of blood lactate concentration was not accompanied by a decrease of $\dot{V}_E$ during incremental and endurance exercise, the two variables are not necessarily linked. This observation confirms earlier studies (Hagberg et al. 1990; Busse et al. 1991) which have also indicated that the link between $\dot{V}_E$ and blood lactate concentration is not as tight as has been shown by Casaburi et al. (1987) after whole-body endurance training. They, however, have concluded that the endurance training resulted in substantially reduced $\dot{V}_E$, an effect probably linked to the reduction in blood lactate concentration. This link does not exist after respiratory training.

To explain the reduced blood lactate concentrations after respiratory training, we would suggest two possible mechanisms:

1. Working muscles produced less lactate because of a reduced overall energy demand due to less respiratory work or
2. Trained respiratory muscles used more lactate as fuel for their own activity.

Previously (Boutellier and Piwko 1992), we have favoured the first explanation because $\dot{V}_E$ was drastically reduced during endurance cycling after respiratory training in sedentary subjects. The present findings clearly disagree with our earlier hypothesis because $\dot{V}_E$ was not reduced during the steady-state phase after respiratory training. Therefore, a reduced lactate production after respiratory training was unlikely in the present study. In addition, increased aerobic relative to anaerobic energy production would have been associated with an increased $\dot{V}O_2$ (Boutellier et al. 1990). We did not observe a higher $\dot{V}O_2$ during CET_2 compared to CET_1 (Table 2) nor did the changes in blood lactate concentration correlate with changes in $\dot{V}O_2$ (Fig. 4). This suggests that the reduced blood lactate accumulation after respiratory training was not due to a decreased lactate production.

Therefore we speculate that in the present study the subject's respiratory muscles increased their ability to metabolize lactate and, as a result, increased lactate removal from circulating blood. This is in accordance with investigations in animals where respiratory muscles have been shown to consume rather than produce lactate even during intense exercise (Fregosi and Dempsey 1986; Manohar and Hassan 1991). Rochester and Briscoe (1979) have shown that approximately one half of the energy required by the diaphragm is derived from carbohydrate metabolism, primarily in the form of lactate utilisation. Furthermore, after whole-body endurance training in humans, blood lactate concentrations have been found to be reduced due to an increased rate of lactate metabolic clearance during intense exercise (MacRae et al. 1992).

As a possible mechanism for an improved lactate clearance after respiratory training, we would suggest that trained respiratory muscles increase their ability to metabolize lactate. A study performed by Bigard et al. (1992) has supported this suggestion. They have found that 12 weeks of endurance training enhanced the ratio of the heart-specific lactate dehydrogenase isozyme (LDH_1) to total LDH activity in the rat diaphragm by 92%. Since the heart is known to metabolize a significant amount of lactate, an increased lactate metabolization by the diaphragm as the result of a shift of isozyme activity might be the cause for the decrease in blood lactate concentration found during exercise in our subjects. If respiratory muscles use more lactate as fuel, they can spare glycogen. A significant relationship between contractile fatigue of the diaphragm and glycogen depletion has been shown in rabbits (Ferguson et al. 1990) and suggested in humans (Martin et al. 1982; Chevrolet et al. 1993). So, the subjects of the present study might have postponed glycogen depletion and thereby postponed respiratory muscle fatigue.

As well as the mechanism of glycogen sparing, we also should consider a direct effect of reduced blood lactate concentrations on performance. It is well known that increased blood lactate concentrations impair performance. Therefore, one can speculate that reduced blood lactate concentrations might improve performance. The significant correlation between the percentage decrease in blood lactate concentration, measured either at steady-state or end exercise, with the percentage increase of endurance time, points in this direction. But incremental exercise was not improved despite lower blood lactate concentrations after respiratory training. Also, to our knowledge, a direct, beneficial effect of reduced blood lactate concentrations on performance has never been shown. Thus, we do not believe that the reduced blood lactate concentration per se had a beneficial effect on performance.

Therefore we would suggest that delayed respiratory muscle fatigue could possibly explain improved cycling performance after respiratory training. During CET, $\dot{V}_E$

of active subjects (Boutellier et al. 1992; this study) reached a plateau with a small incline with time during exercise. Before exhaustion, a further ventilatory increase occurred caused by an augmented f_b. This final respiratory increase has often been observed before subjects finally stop intense constant-intensity exercise (Kearon et al. 1991; Boutellier et al. 1992; Johnson et al. 1993). The increase in f_b suggests that fatigue of respiratory muscles might be a possible explanation for the final increase of $\dot{V}_E$. It has been shown that rapid shallow breathing occurs when respiratory muscles are fatigued (Gallagher et al. 1985; Mador 1991; Mador and Acevedo 1991a). However, in these studies the increase in f_b was accompanied by a reduced V_T which we have not observed (Boutellier and Piwko 1992; Boutellier et al. 1992; present study). Sliwinski et al. (1996) have just recently confirmed our results by showing that overall inspiratory muscle fatigue increased f_b and $\dot{V}_E$ with minor changes in V_T during subsequent intense exercise whereas mild or moderate exercise did not affect ventilatory variables. As, in the present study, constant-intensity performance was prolonged despite an unchanged steady-state $\dot{V}_E$, one can assume that steady-state $\dot{V}_E$ is less important for the duration of exercise than the start of final hyperventilation.

Conclusions

Endurance training of respiratory muscles significantly prolonged intense constant-intensity exercise and reduced blood lactate concentrations during exercise. The reduced lactate concentrations were most likely caused by an improved lactate uptake by trained respiratory muscles. However, reduced exercise blood lactate concentrations per se were probably not the reason for better cycling performance after respiratory endurance training.

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Respiratory Muscle Endurance Training in Chronic Obstructive Pulmonary Disease

Impact on Exercise Capacity, Dyspnea, and Quality of Life

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Inspiratory muscle training may have beneficial effects in certain patients with chronic obstructive pulmonary disease (COPD). Because of the lack of a home training device, normocapnic hyperpnea has rarely been used as a training mode for patients with COPD, and is generally considered unsuitable to large-scale application. To study the effects of hyperpnea training, we randomized 30 patients with COPD and ventilatory limitation to respiratory muscle training (RMT; n = 15) with a new portable device or to breathing exercises with an incentive spirometer (controls; n = 15). Both groups trained twice daily for 15 min for 5 d per week for 8 wk. Training-induced changes were significantly greater in the RMT than in the control group for the following variables: respiratory muscle endurance measured through sustained ventilation (+825 ± 170 s [mean ± SEM] versus −27 ± 61 s, p < 0.001), inspiratory muscle endurance measured through incremental inspiratory threshold loading (+58 ± 10 g versus +21.7 ± 9.5 g, p = 0.016), maximal expiratory pressure (+20 ± 7 cm H_2O versus −6 ± 6 cm H_2O, p = 0.009), 6-min walking distance (+58 ± 11 m versus +11 ± 11 m, p = 0.002), $\dot{V}o_{2peak}$ (+2.5 ± 0.6 ml/kg/min versus −0.3 ± 0.9 ml/kg/min, p = 0.015), and the SF-12 physical component score (+9.9 ± 2.7 versus +1.8 ± 2.4, p = 0.03). Changes in dyspnea, maximal inspiratory pressure, treadmill endurance, and the SF-12 mental component score did not differ significantly between the RMT and control groups. In conclusion, home-based respiratory muscle endurance training with the new device used in this study is feasible and has beneficial effects in subjects with COPD and ventilatory limitation.

Many patients with chronic obstructive pulmonary disease (COPD) are limited in their physical activity by dyspnea. Lung hyperinflation, increased deadspace ventilation, and increased energy consumption during hyperpnea lead to decreased ventilatory reserve and dyspnea on exertion (1, 2). Some subjects with COPD show decreased maximal respiratory pressures (3, 4), which are indicative of respiratory muscle weakness and which may contribute to the perception of dyspnea.

Some studies have shown that the respiratory muscles can be trained if an adequate training stimulus is applied, and that exercise performance (5, 6) and dyspnea (6, 7) may improve as a result of such training. In most studies inspiratory muscle training has been done with resistive breathing or threshold loading (TL) (6–11). Few patients have been trained with normocapnic hyperpnea (5, 12, 13) because the complicated equipment needed to prevent hypocapnia has usually required a hospital facility or research laboratory, and has not been available for home training. Therefore, this training mode, which imitates most closely the load on the respiratory muscles during exercise, was considered difficult to apply on a large scale (14). In only one study was home-based training applied in conjunction with a comprehensive rehabilitation program (15).

As compared with resistive breathing through a fixed orifice (0.5 cm) at a breathing rate of 15 breaths/min, or TL with a threshold pressure of 30% of maximum inspiratory pressure ($P_{I_{max}}$) at a breathing rate of 15 breaths/min, normocapnic hyperpnea at a target minute ventilation (V_E) of 75% of maximal voluntary ventilation (MVV) generates the greatest work of breathing (16). Prior work in subjects with COPD showed that training with normocapnic hyperpnea improves respiratory muscle endurance and exercise performance (5, 15). The effects of such training on dyspnea and quality of life, important outcome variables for patient compliance and well-being, have not been yet studied.

A recently developed training device allows respiratory muscle training (RMT) with normocapnic hyperpnea at home. Studies with healthy subjects using this device resulted in increased cycling endurance (17) and decreased perceived respiratory exertion during exercise (18). On the basis of these results, we wanted to test the feasibility and effectiveness of home training with this device in a randomized, controlled study of subjects with COPD. The aim was not only to assess the effects on respiratory muscle and exercise performance, but also to include the important variables of dyspnea and health-related quality of life.

METHODS

The study protocol was approved by the ethics committee of the Triemli Hospital, Zurich.

Subjects

Subjects were recruited from the outpatient clinic of the Pulmonary Division of the Triemli Hospital. Consecutive patients were screened by reviewing their charts and by interview. Those who met the inclusion criteria, agreed to participate, and had signed the informed consent form were randomly assigned to an RMT group or a control group, according to a computer-generated randomization table. Inclusion criteria were chronic airflow obstruction (FEV_1 < 70% predicted, FEV_1/FVC < 70% predicted, < 15% improvement in FEV_1 after bronchodilatation with 200 μg of albuterol inhaled from a pressurized metered-dose inhaler with a spacer), an age of 20 to 80 yr, and a stable clinical condition for at least 1 mo. The patients' physical activity had to be limited by pulmonary dyspnea only. In case of any possibility that cardiac disease limited physical performance, patients underwent cardiopulmonary exercise testing and echocardiography before inclusion in the study. Patients with dyspnea at rest, cardiac disease, poor compliance, drug or alcohol abuse, pregnancy or lactation, a requirement for supplemental oxygen, CO_2 retention, or use of any mechanical ventilatory support were excluded.

Forty-nine patients were initially screened for the study. Ten patients refused to participate and five met one or more exclusion criteria. Thirty-four subjects were initially included. One patient assigned

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to RMT withdrew during the initial testing and one control subject withdrew during Week 2 of the study. One patient in the RMT and one in the control group had to be excluded after traumatic hip and rib fractures. Thirty subjects completed the study.

Baseline characteristics of the study population are outlined in Table 1. The age range of the study population was 46 to 80 yr. No significant differences existed between the two study groups. During the study, subjects in the RMT group experienced 1.1 ± 0.2 (mean ± SEM) intercurrent illnesses, had 1.1 ± 0.2 medication changes, and had 1.3 ± 0.5 missed training days per patient, versus 1.0 ± 0.2 intercurrent illnesses, 1.1 ± 0.2 medication changes, and 0.7 ± 0.3 missed training days per patient, respectively, in the control group (no significant differences existed between the RMT and control groups in these variables).

Study Protocol

All tests were performed in a standardized manner and sequence before starting the training and 1 wk after its completion. Care was given that subjects were familiarized with the different tests and devices used. Throughout the study period, subjects documented their training, their pulmonary and other physical symptoms, physical activity, and any medication change in a diary, which, in addition to interviews of the subjects and evaluation of their training progress, served as a control for compliance with the training program. The study was conducted in a single-blind manner (i.e., subjects of both groups were told that they were undergoing respiratory muscle training, and that two different devices for this were being compared). The subjects in one group were not informed about the device or training of the other group.

Testing

The sequence of testing was as follows:

Day 1. On Day 1 of the study, subjects were given pulmonary function tests (PFTs), had their 12-s MVV, maximal inspiratory and expiratory pressures ($P_{I_{max}}$ and $P_{E_{max}}$) measured at the mouth, and were given a dyspnea questionnaire (baseline or transition dyspnea index), 6-min walking test, 20-min rest period, respiratory muscle endurance test (sustained ventilation), and health questionnaire, and underwent measurement of peak oxygen consumption ($\dot{V}O_{2max}$), had a 20-min rest period, testing of inspiratory muscle endurance (TL), a third 20-min rest period, and an endurance test on a treadmill.

Day 2. On Day 2 of the study the subjects had a 6-min walking test, 20-min rest period, inspiratory muscle endurance test (TL), 20-min rest period, 6-min walking test, 20-min rest period, and second inspiratory muscle endurance test (TL).

Pulmonary function tests were done according to American Thoracic Society criteria (19, 20), with measurement of slow VC, tidal volume (V_T), FVC, FEV_1, peak expiratory flow (PEF), and 12-s MVV, with the Medical Graphics CPX/D System (Medical Graphics Corporation, St. Paul, MN). Reference normal values were taken from the European Community for Steel and Coal (21).

$P_{I_{max}}$ and $P_{E_{max}}$ were measured from RV and TLC, respectively, with a handheld device (Micro M.P.M.; Micro Medical Ltd., Rochester, UK) that has a built-in small air leak to prevent pressure generation by glottis closure. The highest pressure from among 10 measurements was recorded. Reference normal values were taken from Black and Hyatt (22).

Endurance of the respiratory muscles was measured in two ways, as follows:

1. With the respiratory muscle endurance test to assess performance of the inspiratory and expiratory muscles. This test was based on the 12-s MVV, which was performed three times. The highest MVV was recorded. Respiratory muscle endurance was measured as sustained ventilation at 66% of each subject's highest MVV. The time during which subjects were able to sustain this target ventilation was recorded. If a subject surpassed 15 min of breathing at this level, the test was repeated on the following day at 75% of MVV. Subjects were not coached and breathing was not paced. To assure normocapnia, the training device (described subsequently), connected to the metabolic cart (CPX/D system; Medical Graphics), was used. Patients had visual feedback of their $\dot{V}E$. $\dot{V}E$, end-tidal carbon dioxide pressure ($P_{ET_{CO_2}}$), and Sa_{O_2} (Minolta Pulsox 5; Minolta Switzerland, Dietikon, Switzerland) were measured continuously.
2. With the inspiratory muscle endurance test to assess performance of the inspiratory muscles. This test was done with an inspiratory TL device built according to the specifications of Nickerson and Keens (23). The inspiratory threshold pressure was varied with weights that were attached to a plunger, which closed the inspiratory valve. The initial threshold pressure was set to about 20% of $P_{I_{max}}$. The weight was increased every 2 min by 50% of the initial weight until the subject was unable to continue breathing. The greatest weight the subject was able to sustain for at least 1 min was taken as the measure for inspiratory muscle endurance. The test was performed three times, and the greatest weight the subject endured was recorded. Results were compared with normal reference values established by Johnson and coworkers (24).

Exercise performance was tested with a 6-min walking test and a treadmill endurance test. The 6-min walking test was performed in a corridor of 90 m length. The subjects were instructed to cover as much distance as possible during 6 min. They were not verbally coached, but a person was walking about 1 m behind them. The test was repeated three times, and the longest distance walked was recorded. Results were compared with normal reference values established by Troosters and coworkers in healthy elderly subjects (25).

The endurance test on the treadmill was performed at a submaximal workload (*see* the subsequent discussion), and subjects were not encouraged during this test. To determine the level of the submaximal workload used in the test, peak power output and $\dot{V}O_{2peak}$ were measured with an incremental treadmill test by first gradually adjusting the treadmill speed until the subject walked comfortably. The inclination of the treadmill was then increased by 2.5% in 2-min intervals until the subject was exhausted. Normal reference values for $\dot{V}O_{2peak}$ were taken from Hansen and coworkers (26). To determine treadmill endurance, the treadmill was set to 80% of the inclination and to 100% of the speed reached at $\dot{V}O_{2peak}$. For subjects unable to walk

TABLE 1

BASELINE CHARACTERISTICS OF THE GROUP ASSIGNED TO RESPIRATORY MUSCLE TRAINING AND CONTROL GROUPS

	RMT Group	Control Group	p Value
n	15	15	
Age, yr	66.9 ± 2.4	71.0 ± 1.2	0.18
Sex, M/F	9 / 6	10 / 5	0.77
BMI	23.8 ± 0.8	25.9 ± 0.9	0.19
FEV_1, %pred	50.2 ± 4.4	52.3 ± 3.5	0.46
FVC, %pred	86.8 ± 3.9	89.0 ± 4.7	0.97
$P_{I_{max}}$, cm H_2O	66.5 ± 9.2	70.3 ± 6.5	0.51
$P_{I_{max}}$, %pred	70.0 ± 12.1	67.4 ± 6.2	0.59
$P_{E_{max}}$, cm H_2O	94.2 ± 8.1	109.7 ± 11.2	0.37
$P_{E_{max}}$, %pred	90.1 ± 6.9	106.9 ± 14.6	0.59
MVV, L/min	50.3 ± 4.7	47.9 ± 4.3	0.81
MVV, %pred	49.7 ± 4.2	46.0 ± 4.1	0.51
RET, s	320.3 ± 48.6	400.2 ± 68.0	0.37
TL, g	106.3 ± 26.6	117.8 ± 22.7	0.59
TL, %pred	59.1 ± 4.8	61.0 ± 4.6	0.68
6-min WD, m	615.7 ± 36.0	664.3 ± 37.4	0.16
6-min WD, %pred	95.7 ± 6.1	105.1 ± 6.1	0.25
$\dot{V}O_{2peak}$, ml/kg/min	14.0 ± 1.3	16.6 ± 1.2	0.14
$\dot{V}O_{2peak}$, %pred	63.8 ± 7.7	74.2 ± 5.6	0.13
$\dot{V}E$ /MVV	82.3 ± 3.6	88.4 ± 3.8	0.17
TM, s	460.8 ± 65.7	596.3 ± 79.1	0.25
BDI	5.7 ± 0.4	6.3 ± 0.5	0.41
SF-12 P score	34.3 ± 2.2	39.4 ± 2.3	0.14
SF-12 M score	53.0 ± 3.6	53.9 ± 1.8	0.46

Definition of abbreviations: BDI = Baseline Dyspnea Index; BMI = body mass index; MVV = 12-s maximal voluntary ventilation; $P_{E_{max}}$ = maximal expiratory pressure $P_{I_{max}}$ = maximal inspiratory pressure; PEF = peak expiratory flow; RET = respiratory muscle endurance measured as sustained ventilation; RMT = respiratory muscle training; SF-12 P = score on physical component of the SF-12 health questionnaire; SF-12 M = score on mental component of the SF-12 questionnaire; TL = inspiratory muscle endurance measuring with threshold loading device; TM = endurance on treadmill; $\dot{V}E/MVV$ = minute ventilation at $\dot{V}O_{2peak}$ as a percentage of MVV; $\dot{V}O_{2peak}$ = maximal oxygen consumption; WD = walking distance.

with an inclination, the $\dot{V}O_{2peak}$ speed was reduced by 20%. The test was terminated when subjects indicated that they were exhausted and unable to keep up with the speed of the treadmill. The time during which a subject was able to walk at the preset load was recorded as treadmill endurance.

Before training, dyspnea in daily activities was assessed with Mahler's Baseline Dyspnea Index, and the change after training was assessed with Mahler's Transition Dyspnea Index (TDI) (27, 28). Health-related quality of life was tested with the SF-12 health questionnaire (acute form), issued by the Medical Outcomes Trust (Boston, MA), which consists of a physical (SF-12 P) and a mental component (SF-12 M) score. Because both questionnaires were originally written in English, three persons fluent in English translated the questionnaires independently into German, and one bilingual person translated the German versions back into English. All translations were compared, discussed, and adjusted to the most correct version.

RMT

Respiratory muscle endurance training was done with a device that we developed, consisting of tubing (I.D. = 19 mm) that connects a rebreathing bag with a mouthpiece in a 90-degree angle. A sideport (of the same diameter as the tube) is inserted in the middle of this connecting piece. This sideport contains a 6-mm hole that allows inspiration from and expiration to fresh air, and also contains a valve. Subjects fill and empty the rebreathing bag completely during inspiration and expiration, while also inhaling additional fresh air through the sideport during inspiration and breathing partly out through the sideport during expiration. To assure a constant V_T, the valve inserted in the sideport closes when subjects have emptied the bag during inspiration. In our study the size of the bag was adjusted to 50 to 60% of the subject's VC, and the breathing frequency chosen was such that $\dot{V}_E$ corresponded to 60% of MVV (monitored while the training device was connected to the metabolic cart). Correct performance was checked by analyzing $P_{ET_{CO_2}}$ with the metabolic cart and Sa_{O_2} with the pulse oximeter. If $P_{ET_{CO_2}}$ deviated from normal baseline values during the 10- to 15-min trial run, V_T was adjusted by changing the size of the rebreathing bag and breathing frequency was changed accordingly to keep $\dot{V}_E$ at 60% of MVV. Values of training $P_{ET_{CO_2}}$ ranged from 33.1 ± 1.1 mm Hg to 38.5 ± 1.3 mm Hg. Hypocapnia during training was corrected by increasing the size of the rebreathing bag, and hypercapnia was corrected by decreasing the size of the bag. Hypoxemia was never observed.

While performing the breathing exercises, subjects wore a nose clip to ensure breathing exclusively through the training device. The exercises were performed twice daily for 15 min on 5 d per week for 8 wk. Splitting the exercise into 5-min sessions was allowed if the subject was unable to train for 15 min without interruption. Inspiration and expiration were paced by an electronic metronome (Seiko Digital Metronome; Seiko Corp., Tokyo, Japan).

Before the 8-wk training period and once every week during the training, Sa_{O_2}, $P_{ET_{CO_2}}$, breathing rate, and V_T were monitored in the pulmonary laboratory while subjects performed the breathing exercises. This was done by connecting the training device to the metabolic cart and attaching a pulse oximeter to the subject's finger. During these weekly control sessions, breathing frequency was increased whenever possible in order to increase $\dot{V}_E$ during training, so as to reach a maximal training stimulus. Three subjects complained of dyspnea or dizziness during training. They were immediately called to the laboratory to monitor training instrument settings, Sa_{O_2}, and $P_{ET_{CO_2}}$. In the cases of two patients, settings had to be adjusted to correct for hyper- and hypoventilation.

The mean respiratory rate (RR) increased by 29% during the training period ($p < 0.001$; Week 1: 26.3 ± 1.0 breaths/min; Week 2: 28.6 ± 1.5 breaths/min; Week 3: 29.1 ± 1.2 breaths/min; Week 4: 30.9 ± 1.5 breaths/min; Week 6: 32.6 ± 1.8 breaths/min; Week 7: 33.5 ± 2.1 breaths/min; and Week 8: 33.9 ± 2.0 breaths/min). V_T did not change significantly during training (1.07 ± 0.06 L at start of the training versus 1.12 ± 0.05 L at the end; $p = 0.50$).

Breathing Exercises in the Control Group

Subjects in the control group were told that they were engaging in respiratory muscle training with an incentive spirometer (COACH 2 Volumetric Incentive Spirometer; DHD Healthcare, Canastota, NY). This device was chosen for the sham training to give the subjects the impression that they were undergoing training. Because airflow resistance through this device is minimal, and the RR during breathing exercises was kept at about 6 to 8 breaths/min, we assumed that no training effect would result. The target inspiratory V_T was set to 70% of each subject's VC. Subjects were instructed to breathe in slowly after a deep exhalation at a rate of 6 to 8 breaths/min, but their breathing was not paced. The exercises were performed twice daily for 15 min on 5 d per week for 8 wk. Splitting the exercises into 5-min sessions was allowed if the subject was unable to train for 15 min without interruption. The subjects also had weekly control sessions of their breathing exercises without a change in V_T or breathing rate.

Subjects in both the RMT and control groups who experienced acute breathing problems (e.g., due to an exacerbation of their COPD) were allowed to stop training for a maximum of 14 d. These subjects resumed their training from the same point at which they had stopped, in order to complete 40 training days.

Statistics

The results of the study are presented as mean ± SEM. Because the values were not normally distributed (normality of distribution was tested with the Shapiro–Wille's test), the nonparametric Mann–Whitney U test was used to compare baseline characteristics and training-related changes in the RMT and control groups, Wilcoxon's matched pairs test was used to assess training-induced changes within a particular group, and Friedman's analysis of variance with Kendall's concordance was used to assess weekly changes over the course of the training. A value of $p < 0.05$ was considered significant. The Statistica for Windows software program (Statsoft Inc., Tulsa, OK) was used for all calculations. To achieve a difference in change in respiratory muscle endurance of 20% with an SD of 50 s and a statistical power of 80%, it was calculated that 12 to 15 patients had to be included in each study group. The primary endpoint of the study was respiratory muscle endurance; secondary endpoints were respiratory muscle strength, exercise performance, dyspnea, and health-related quality of life.

RESULTS

Training-related changes in the RMT as compared with the control group are shown in Table 2 and Figures 1 through 6.

TABLE 2

TRAINING RELATED CHANGES IN THE GROUP ASSIGNED TO RESPIRATORY MUSCLE TRAINING AND IN THE CONTROL GROUP

	RMT Group	Control Group	p Value
n	15	15	
ΔFEV_1, %	+0.6 ± 5.3	+3.7 ± 3.9	0.84
ΔPEF, %	−3.1 ± 5.1	+10.9 ± 8.0	0.15
ΔFVC, %	+0.3 ± 3.9	+6.6 ± 3.9	0.32
$\Delta P_{I_{max}}$, cm H_2O	+19.7 ± 4.3	+12.3 ± 3.7	0.30
$\Delta P_{E_{max}}$, cm H_2O	+20.3 ± 7.0	−5.6 ± 6.2	0.009
$\Delta \dot{V}O_{2peak}$, ml/kg/min	+2.5 ± 0.6	−0.3 ± 0.9	0.015
ΔSF-12 M score	+1.0 ± 3.6	+1.7 ± 2.5	0.71

Definition of abbreviations: ΔFEV_1 = change in forced expiratory volume in 1 s; ΔFVC = change in FVC; $\Delta P_{E_{max}}$ = change in maximal expiratory pressure; $\Delta P_{I_{max}}$ = change in maximal inspiratory pressure; ΔPEF = change in peak expiratory flow; RMT = respiratory muscle training; ΔSF-12 M = change in score on mental component of the SF-12 questionnaire; $\Delta \dot{V}O_{2peak}$ = change in maximal oxygen consumption.

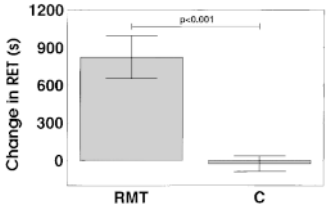

Figure 1. Change in respiratory muscle endurance (RET), measured as time of sustained ventilation. RMT = respiratory muscle endurance training group; C = control group.

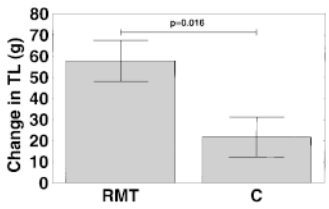

Figure 2. Change in inspiratory muscle endurance, measured with incremental threshold loading (TL). Results are presented as weight added to the plunger closing the inspiratory valve. RMT = respiratory muscle endurance training group; C = control group.

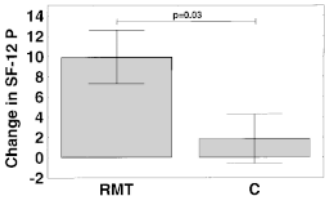

Figure 4. Change in score of the physical component of the SF-12 health questionnaire (SF-12 P). RMT = respiratory muscle endurance training group; C = control group.

Improvement in respiratory muscle endurance measured as sustained ventilation (RMT group at 69 ± 7% of MVV; control group at 70 ± 5% of MVV) (Figure 1), and assessed with incremental TL (Figure 2), was significantly greater in the RMT group. Likewise, change in $P_{E_{max}}$ (but not in $P_{I_{max}}$), increase in 6-min walking distance (Figure 3), $\dot{V}O_{2peak}$, and the physical (Figure 4) (but not the mental) component of the SF-12 health survey were significantly greater in the RMT than in the control group. Both groups showed a decrease in dyspnea in daily activities, but the difference was not significant (Figure 5). Likewise, the change in treadmill endurance did not differ significantly between the two groups (Figure 6).

DISCUSSION

Our results in subjects with COPD and ventilatory limitation show that home-based RMT with normocapnic hyperpnea improved respiratory muscle endurance, exercise performance, health-related quality of life, and dyspnea in daily activities, whereas pulmonary function did not change significantly. Baseline characteristics, incidences of intercurrent illnesses, and medication changes were comparable in the RMT and control groups in the study.

The inclusion criteria for the study were directed to chronic airflow limitation and limitation in physical activity by pulmonary dyspnea. Respiratory muscle weakness and/or ventilatory limitation of physical activity were not prerequisites to study inclusion. Analysis of our data show, however, that ventilatory limitation, reflected by high ventilation at $\dot{V}O_{2peak}$ ($\dot{V}E$/MVV of 85%), was clearly present. As compared with a healthy control population, our study subjects also had some weakness of their respiratory muscles, as expressed by their low $P_{I_{max}}$, MVV, and TL. These findings probably had an effect on our results, and support the view that subjects with COPD, respiratory muscle weakness, and ventilatory limitation may benefit from RMT.

The hyperpnea training in our study was usually well tolerated. Only three patients called because they experienced adverse effects, and their problems were readily solved.

In RMT, the increase in respiratory muscle endurance, measured as sustained ventilation, was large (258%). Previous studies, using normocapnic hyperpnea as a training mode in subjects with COPD, had already demonstrated the beneficial effects of this training mode on respiratory muscle endurance. Using maximal sustained ventilatory capacity (MSVC) as a measure of respiratory muscle endurance, Belman and Mittman (5) reported an increase from 32 to 42 L/min (+31%), Keens and coworkers (12) found an increase from 74 to 109 L/min (+47%), and Levine and coworkers (13) found an increase from 56 to 79 L/min (+41%) in MSVC. We are aware of only one study that evaluated home-based training (15). The investigators in this study achieved an increase from 34 to 44 L/min (+29%) in MSVC.

Subjects in the present study also increased their exercise performance as a result of RMT. Their 6-min walking distance increased by 10% and $\dot{V}O_{2peak}$ increased by 19%. These changes were significantly larger in the RMT than in the control group. The 58-m increase in 6-min walking distance in the RMT group was large enough to be considered clinically relevant (29). Belman and Mittman (5) reported comparable results. A 6-wk period of training increased the 12-min walking distance from 1,058 m to 1,188 m (+12%). Ries and Moser (15), who applied home-based respiratory muscle endurance training in conjunction with pulmonary rehabilitation, observed significant improvements in $\dot{V}O_{2max}$, from 15.1 ml/kg/min to 16.4 ml/kg/min (+9%), and in 12-min walking distance, from 943 m to 1,020 m (+8%), which are also in the range of our training-induced changes. Although the training-related increase in treadmill endurance was considerably greater in the RMT group in our study, the changes did not differ significantly between the two study groups. One reason for this insignificant difference may be that the individual improvements varied widely. The sample size was too small to reliably exclude a difference in treadmill endurance, and a type II error therefore cannot be excluded.

The increased exercise performance with RMT is important for patients with COPD, since it may help in their daily activities. It is unclear, however, how this translates into an improvement in dyspnea and quality of life, which are important parameters (30, 31). Without subjective benefits, patients will hardly be willing to engage in daily training of their respiratory muscles. We therefore included the SF-12 Health Survey and Mahler's dyspnea indices in our study. The SF-12 Health Survey is a 12-item questionnaire that closely mirrors the scores of the SF-36 short-form Health Survey (32), and which had proved to reflect health status in patients with chronic lung disease (33). The significant impact of RMT on the physical component of the SF-12 health questionnaire is an important finding, because the effect of hyperpnea training on quality of life has not yet been tested. It is already known that pulmonary rehabilitation with and without additional inspiratory muscle training can improve quality of life in patients with COPD (34–36); however, the effect of RMT without additional intervention is unknown.

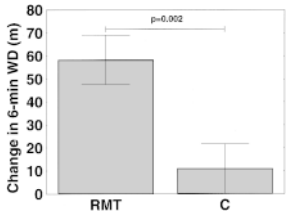

Figure 3. Change in 6-min walking distance (6-min WD). RMT = respiratory muscle endurance training group; C = control group.

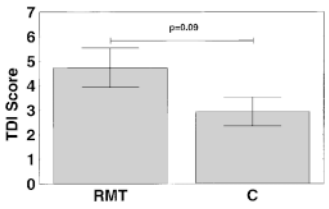

Figure 5. Change in Transition Dyspnea Index (TDI) score. RMT = respiratory muscle endurance training group; C = control group.

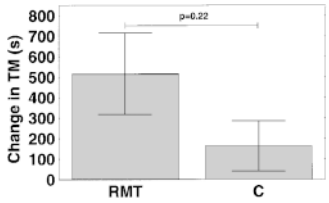

Figure 6. Change in treadmill endurance (TM). RMT = respiratory muscle endurance training group; C = control group.

The TDI of 4.7 in our RMT group represents a distinct improvement in dyspnea. Lisboa and coworkers (6) reported comparable results after TL training at 30% of $P_{I_{max}}$. Their subjects achieved significant increases in $P_{I_{max}}$ (+23 cm H_2O; +34%) and 6-min walking distance (+114 m; +38%), and these improvements were associated with a TDI of 3.8. In the study by Harver and coworkers (7), subjects with COPD increased their $P_{I_{max}}$ by 11 cm H_2O (+13%) after targeted inspiratory muscle training, which was associated with a TDI of 3.5. Lisboa and coworkers (6) reported that their subjects, who trained with an inspiratory threshold load of 10% of their $P_{I_{max}}$, were able to increase their $P_{I_{max}}$ by 12 cm H_2O (+19%), and this improvement was associated with a TDI of 1.7. Direct comparison of these studies done with different training modes is not possible. The optimal training mode in subjects with COPD remains to be investigated.

The breathing exercises in our control group probably affected $P_{I_{max}}$ (+12 cm H_2O; +18%) and dyspnea (TDI = 2.9). Although we originally designed our study to have a control group undergoing sham training, subjects assigned to the control group experienced an improvement in their inspiratory muscle performance. In some subjects who were eager to undergo training, this training effect was generated by the subjects' intention to continuously increase their training V_T above the preset volume. Additionally, subjects who started inspiration at a level well above their FRC generated some load on their inspiratory muscles at the end of inspiration. We assume that the improvement in these subjects' dyspnea resulted from their increased inspiratory muscle performance, as reflected by the increase in their $P_{I_{max}}$ and inspiratory muscle endurance. Although it can be argued that these changes were a placebo effect or based purely on motivation, the fact that $P_{I_{max}}$ and TL, but not $P_{E_{max}}$ or respiratory muscle endurance (involving unaffected expiratory muscles) improved suggests that a mild training effect occurred. The increase in $P_{I_{max}}$ in the control group may have been at least partly responsible for the lack of difference in the training-induced change in $P_{I_{max}}$ between the two groups.

The training-induced increase in $P_{E_{max}}$ was significantly greater in the RMT than in the control group. This was probably caused by the load on the expiratory muscles induced by the hyperpnea training. Suzuki and coworkers (37) reported that expiratory muscle training in healthy subjects could improve expiratory muscle strength and decrease V_E and the sensation of respiratory effort during exercise. It is conceivable that the increase in expiratory muscle strength in our RMT group contributed to the decrease in their dyspnea. Further studies are needed to clarify this issue.

RMT with normocapnic hyperpnea requires personal effort and good motivation. Of the 49 persons screened for our study, 10 refused to participate, mainly because of lack of motivation. This shows that not every patient is a good candidate for this kind of treatment. Furthermore, it remains to be clarified whether the addition of RMT to a pulmonary rehabilitation program is worthwhile, and which patients in particular will benefit from it. Results of published trials are equivocal (38–40). Currently, it is recommended that ventilatory muscle training be considered within a pulmonary rehabilitation program only for selected patients with decreased ventilatory muscle strength (41).

In summary, the results of the present study show that respiratory muscle endurance training with normocapnic hyperpnea improves respiratory muscle and exercise performance, health-related quality of life, and dyspnea. The new portable training device used in the study makes home-based endurance training with normocapnic hyperpnea feasible, and allows its widespread application.

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Breathless Legs? Consider Training Your Respiration

Christina M. Spengler and Urs Boutellier

The condition of the respiratory system is more important for endurance exercise performance of healthy subjects than hitherto assumed. Not only do respiratory muscles fatigue during intensive endurance exercise, but prefatigued respiratory muscles can also impair performance. In turn, respiratory endurance training can improve endurance exercise performance.

It is well accepted that the respiratory system may limit exercise performance in disease, e.g., pulmonary or cardiovascular disease, but to what extent the respiratory system may play a significant role in limiting exercise performance of healthy subjects is still controversial. Different studies indicate that exercise does induce respiratory muscle fatigue (6, 9), that respiratory muscle fatigue can limit exercise performance (8, 10), that endurance of respiratory muscles can be trained (1–3, 11–13), and that respiratory endurance training can enhance endurance (but not peak) exercise performance (1, 2, 12, 13), even in healthy subjects. Changes in breathing pattern that occur with increasing exercise duration, possibly as a consequence of respiratory muscle fatigue, i.e., increased respiratory frequency, hyperventilation, and/or increased sense of respiratory effort, are reversed after respiratory endurance training, i.e., these changes are delayed or absent.

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Exercise induces respiratory muscle fatigue

Several studies have brought forward evidence that respiratory muscles may fatigue during exercise; i.e., after long distance races such as a marathon, ultramarathon, or triathlon, respiratory muscle function is impaired. This impairment can last for more than three days after exercise. Also, respiratory muscle fatigue can develop during shorter but more intensive tasks. Diaphragmatic fatigue was shown to occur in subjects who were cycling to exhaustion at a constant workload of ~80% of their maximal workload (W_{max}). At the point of exhaustion, maximal transdiaphragmatic pressure (P_{di}, the difference between esophageal and gastric pressure), a measure of maximal diaphragmatic force, was reduced during a maximal inspiratory maneuver and electromyographic recordings of the diaphragm indicated diaphragmatic fatigue. Possible mechanisms accounting for these findings are peripheral fatigue (i.e., muscular fatigue) or central fatigue. As recent as 1993, Johnson et al. (6) and Mador et al. (9) were able to show that the force-generating capacity of the diaphragm is reduced after short (10–30 min) intensive [80–95% of maximal oxygen consumption ($\dot{V}O_{2max}$)] exercise. Both groups used bilateral supramaximal electrical phrenic nerve stimulation to elicit twitches of the diaphragm, and they measured the transdiaphragmatic pressure achieved during the twitch ($P_{di,tw}$). $P_{di,tw}$ is considered an objective measure of diaphragm contractility independent of the subject's effort. These findings (25% decrements in $P_{di,tw}$) have been confirmed several times since then.

Although all of these studies concentrate on fatigue of the diaphragm, the main inspiratory muscle, we also need to consider potential fatigue of extradiaphragmatic inspiratory muscles (i.e., sternocleidomastoids, parasternals, and scalenes) as well as expiratory muscles, since these muscle groups also come into play during heavy exercise. For instance, Johnson et al. (6) demonstrated that the relative contribution of the diaphragm to total respiratory motor output is progressively reduced with exercise duration, indicating an increasing activity of extradiaphragmatic muscles. Regarding expiratory muscle fatigue, Fuller et al. (4) recently demonstrated that the ability to voluntarily maximally activate abdominal expiratory muscles and to generate maximum expiratory pressures is impaired after exhaustive exercise. Moreover, after only 2 min of maximal isocapnic ventilation, the force-generating capacity of abdominal muscles—tested by magnetic stimulation—is reduced for >90 min (7), which indicates that the reduced ability to maximally activate expiratory muscles after exhaustive exercise is likely to be caused, at least in part, by muscular fatigue. Since respiratory muscles other than the diaphragm become increasingly active during exercise, it is also likely that fatigue of those muscles can contribute to exercise limitation.

Fatigued respiratory muscles impair endurance exercise performance

A few authors have demonstrated impairment of exercise performance after subjects have voluntarily fatigued their respiratory muscles. Martin et al. (10), for example, had their subjects breathe at 60% of maximal voluntary ventilation for 150 min. After this enormous ventilatory work, the subjects' running time at high speed was significantly reduced, from 7.6 to 6.5 min. Also, respiratory muscle fatigue induced by breathing with a threshold inspiratory load of ~80% of the maximal inspiratory pressure (P_{imax}) compromised endurance time of a subsequent cycling test, i.e., exercise time was reduced from 5.2 to 4 min (8). At the same time, minute ventilation and breathing frequency were increased during exercise. It is indeed astonishing that the output of a fatigued system is larger than normal, a fact that is not yet fully explained. A similar type of hyperventilation, i.e., increased breathing frequency with or without a reduction in tidal volume, frequently occurs toward the end of an endurance exercise test. It is thus possible that this hyperventilation is a result of developing respiratory muscle fatigue. Since in the two studies mentioned above respiratory muscles were likely fatigued to a much larger extent than occurs during exercise, it is still unresolved whether the diaphragmatic fatigue measured after exhaustive cycling tests (6, 9) is large enough to impair endurance performance.

Unloading respiratory muscles may improve endurance exercise performance

Several authors have used unloading of respiratory muscles during exercise to investigate whether a reduction of respiratory work, and thus less development of fatigue, would allow subjects to improve endurance performance (Table 1). Two different approaches were used to unload respiratory muscles: subjects either breathed a helium/oxygen mixture or their breathing was assisted by a ventilator. The authors found either no effect or a small and insignificant increase of exercise time if subjects were studied at workloads of <80% W_{max} and significant increases in exercise time at intensities >90% $\dot{V}O_{2max}$, independent of the method used. These results suggest that respiratory muscle fatigue and/or the respiratory load plays a significant role in limiting human performance at intensities exceeding 90% $\dot{V}O_{2max}$. This improvement was likely the result of the concomitant increase in blood flow to working leg muscles (5). The results also seem consistent with the fact that diaphragmatic fatigue was detected most commonly during exercise at loads >85% $\dot{V}O_{2max}$ (6). On the other hand, we need to be aware that helium breathing, as well as assisted ventilation, may have effects other than simply unloading the respiratory muscles, e.g., they may alter respiratory sensations and normal breathing mechanics, affect ventilation distribution (helium), change distribution of blood flow (ventilator), and so forth. Thus other, more "natural" approaches to testing for respiratory limitation may give further insight into the question of respiratory limitation, e.g., respiratory endurance training. If respiratory muscle training can increase cycling endurance time, then it is more than likely that exercise was limited by the respiratory system before the specific training.

Respiratory muscle training may improve endurance exercise performance

It is known that respiratory muscles of healthy humans can be trained, as is true for any other skeletal muscles, to specifically

TABLE 1. Overview of reported changes in endurance performance after respiratory enudrance training and with respiratory muscle unloading

Intervention	Exercise Load	Endurance Change with Intervention	Subjects' Fitness	References
Respiratory endurance training				
85% MVV : 15 x (2+5+9+12) min in 3 wks	95% $\dot{V}O_{2max}$	⊣ −6% n.s.	trained	Morgan et al., *Int. J. Sports Med.* 8: 88-93, 1987
≥ MSVC : 16 x (8+8+8) min in 4 wks	90% W_{max}	⊢ + 14% n.s.	trained	Fairbarn et al., *Int. J. Sports Med.* 12: 66-70, 1991
65–85% MVV : 20 x 30 min in 4 wks	86% W_{max}	⊢—— + 28%	trained	Spengler et al., *Eur. J. Appl. Physiol.* 79: 299-305, 1999
55–68% MVV : 20 x 30 min in 4 wks	77% $\dot{V}O_{2max}$	⊢——— + 38%	trained	Boutellier et al., *Eur. J. Appl. Physiol.* 65: 347-353, 1992
60–80% MVV : 40 x 30 min in 13–17 wks	70% W_{max}	⊢—— + 26%	sedentary	Spengler et al., *Am. J. Resp. Crit. Care Med.* 157: A782, 1998
58–63% MVV : 20 x 30 min in 4 wks	64% $\dot{V}O_{2max}$	⊢———— + 50%	sedentary	Boutellier and Piwko, *Eur. J. Appl. Physiol.* 64:145-152, 1992
Respiratory muscle unloading				
He/O_2	>95% $\dot{V}O_{2max}$	⊢—— + 21%	highly trained	Aaron et al., *Med. Sci. Sports Exerc.* 17: 290, 1985
Ventilator	>90% $\dot{V}O_{2max}$	⊢ ••• sig.	trained	Dempsey et al., F*ASEB J.* 12: A41, 1998
He/O_2	80–85% $\dot{V}O_{2max}$	⊢ + 13%	highly trained	Aaron et al., *Med. Sci. Sports Exerc.* 17: 290, 1985
He/O_2	80% W_{max}	⊢ + 11% n.s.	trained	Krishnan et al., *J. Physiol. (Lond.)* 490: 537-550, 1996
Ventilator	72–82% W_{max}	⊢ + 0.7% n.s.	unknown	Marciniuk et al., *J. Appl. Physiol.* 76: 236-241, 1994

MVV, maximal voluntary ventilation; MSVC, maximal sustainable ventilatory capacity; W_{max}, maximal power output; and $\dot{V}O_{2max}$ and $\dot{V}O_{2peak}$, maximal and peak oxygen consumption; n.s., not significant.

improve either strength or endurance. Although some authors used hyperpnea training and showed increases in either maximal voluntary ventilation or maximal sustainable ventilatory capacity, others had their subjects breathe with an inspiratory resistance or threshold load, and those subjects improved respiratory muscle strength. Because ventilation during exercise is high-flow, low-resistance respiratory work, hyperpnea training is likely to improve not only respiratory capacity but also exercise performance.

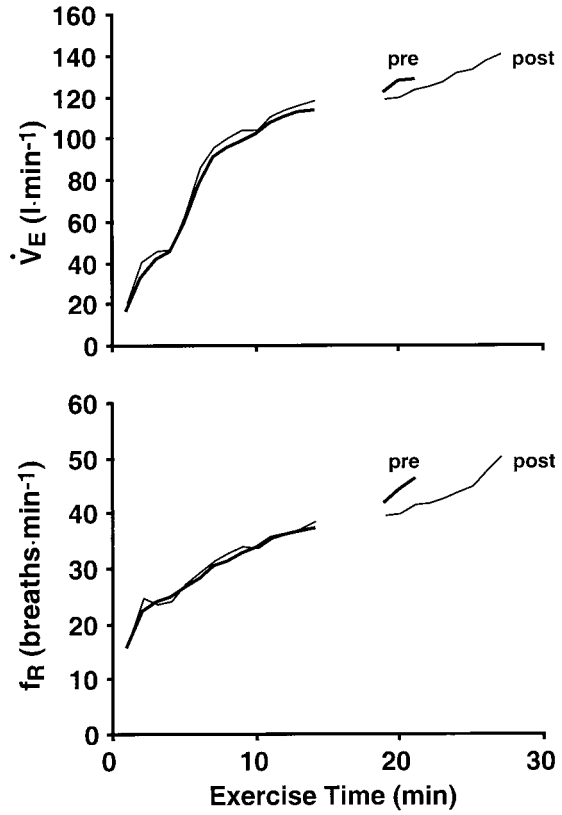

FIGURE 1. Minute ventilation (V_E) and respiratory frequency (f_R) before (pre) and after (post) 20 respiratory endurance training sessions of 30-min duration. Group average data (n = 20) before gap are aligned to beginning of exercise. Data after gap are aligned to end of exercise. Curves end at mean time of exhaustion. After respiratory endurance training, increase of V_E and f_R shortly before exhaustion is delayed compared with before training.

Several studies investigated the effect of hyperpnea training on exercise performance, most of them interested in improving patients' symptoms. Twelve-minute walking distance, a common measure in hospital settings, was improved after hyperpnea training or target flow training in patients with chronic obstructive pulmonary disease. However, the benefits of increased physical performance at submaximal exercise intensities are not limited to patients (Table 1). Increased cycling endurance times were shown after hyperpnea training in sedentary subjects cycling at 64% $\dot{V}O_{2peak}$ [+50%, from 26.8 to 40.2 min (2)], as well as in trained subjects exercising at 75–85% $\dot{V}O_{2peak}$ [+38%, from 22.8 to 31.5 min (1) and +28%, from 17.9 to 23.6 min (13)]. These benefits in endurance may be limited to submaximal exercise levels in the range of 65–85% $\dot{V}O_{2peak}$ (depending on the subject's physical fitness), since improvements were less evident or even absent when endurance was tested at higher exercise intensities by other investigators. Highly trained cyclists showed an insignificant increase in cycling time (from 5.6 to 6.4 min) at 90% W_{max} after 16 sessions of hyperpnea training (3), whereas moderately trained cyclists did not increase cycling endurance time at 95% $\dot{V}O_{2max}$ after 3 weeks of very intense hyperpnea training (11).

Why does respiratory endurance training seem to be mostly effective at and below 85% $\dot{V}O_{2max}$, whereas diaphragmatic fatigue occurs mainly above this exercise intensity? Different factors, which do not need to be mutually exclusive, could be contributing to this difference. Respiratory endurance training might mainly train those extradiaphragmatic respiratory muscles (inspiratory and expiratory) that are used less than the diaphragm during daily living and that are increasingly recruited as exercise proceeds (6). Thus, at submaximal workloads at which subjects cycle for a longer time (>10 min), the subjects could benefit more from respiratory training. Fatigue of extradiaphragmatic muscles is not tested by measurement of $P_{di,tw}$. Also, because hyperpnea training intensity and the regimes used are different among research groups (1–3, 11, 13) and the training status of subjects differs as well, results from different studies cannot be readily compared. More studies are needed, including measurement of diaphragmatic and extradiaphragmatic muscle fatigue before and after respiratory endurance training, to shed light on these seemingly conflicting results.

Interestingly, in those subjects who showed a clear improvement in exercise endurance after hyperpnea training, the increase in breathing frequency was delayed during exhaustive exercise after respiratory training (Fig. 1) and the relative decrease in ventilation (compared at the time of pretraining exhaustion) correlated significantly with the relative increase in exercise time (1). If this change in breathing pattern toward the end of exercise is indeed, in part, a result of increasing respiratory muscle fatigue, this might be indirect evidence for a delayed onset of respiratory muscle fatigue after respiratory training. Further investigations are needed to determine which muscle groups are trained the most with hyperpnea training, i.e., inspiratory vs. expiratory muscles, and whether the onset of respiratory muscle fatigue during exercise is indeed postponed.

Respiratory muscle training may decrease perception of respiratory exertion and breathlessness during exercise

In addition to muscular changes after respiratory endurance training, changes in perception of breathing, such as decreased sense of respiratory exertion or breathlessness, may also contribute to increased endurance times. Some subjects, in fact, need to stop exercise because of an extreme sensation of breathlessness, whereas others experience some breathlessness, but leg fatigue ("breathless legs"?) makes them stop the test. Indeed, Harms et al. (5) have shown an interaction between ventilatory and leg muscle work. They showed that locomotor muscle perfusion and $\dot{V}O_2$ are compromised to some extent by the work of breathing.

Preliminary results from our laboratory indicate that perceived respiratory exertion is diminished after hyperpnea training (1, 12). It is possible that breathlessness is reduced as well; at least some subjects spontaneously report that they experience less breathlessness during their sports activities or when climbing stairs after the respiratory training. Mechanisms responsible for the perception of respiratory exertion and breathlessness during exercise are still debated. Although some authors suggest that the degree of reflex ventilatory

activation is the important determinant of the intensity of the sensation of breathlessness irrespective of the exact nature of the ventilatory stimulus, others find a disproportionate increase in the perceived intensity of breathlessness above some threshold level of ventilation. This may suggest an increase in breathlessness with developing respiratory muscle fatigue despite minimal change in ventilation. Because Johnson et al. (6) showed a time-dependent decrease in the relative contribution of the diaphragm to total ventilation during constant-load exercise, i.e., extradiaphragmatic muscles are taking over a larger part of the respiratory work, increasing breathlessness with little change in ventilation might mainly be caused by increased perception of extradiaphragmatic muscle activity and/or development of rib cage and expiratory muscle fatigue. Further studies will show whether this hypothesis holds true.

Perspectives

Respiratory muscle fatigue seems more important than previously assumed in limiting submaximal exercise performance in healthy subjects. Hyperpnea training, shown to improve endurance performance of healthy sedentary as well as trained subjects, may not only be an advantage in the improvement of endurance athletes' performance but also for people who need to compete or work under extreme environmental conditions, such as at high altitude or under water. Also, patients with respiratory disease may benefit from this type of respiratory training, getting additional degrees of freedom in daily living or profiting from a decrease in adverse respiratory sensations during daily exertions.

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