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ORIGINAL ARTICLE

Peter Lindholm · Dag Linnarsson

Pulmonary gas exchange during apnoea in exercising men

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Abstract There is indirect evidence that cardiovascular responses to apnoea result in a temporary slowing of the O_2 uptake in the lungs in exercising humans. The present study was undertaken in an attempt to determine directly to what extent this occurs, and whether the magnitude of this slowing is such that it must be the result of concomitant cardiovascular readjustments and not merely a result of an isolated apnoea-induced fall in the arterial O_2 saturation (S_aO_2). Eight men performed 120 W leg exercise and performed repeated apnoeas of 10–40 s duration. Heart rate, S_aO_2, and breath-by-breath gas exchange were determined. Pulmonary O_2 uptake fell gradually as breath-holds proceeded by [mean (SEM)] 74 (3)% of the pre-apnoea O_2 uptake. This decrease was significantly larger than could be accounted for by the fall in S_aO_2 alone [S_aO_2 fall –30 (3)%], which it is estimated would have resulted in a fall of pulmonary O_2 uptake of –54 (5)%. We conclude that cardiovascular responses to apnoea contribute significantly to reducing pulmonary O_2 uptake during apnoea in exercising men.

Keywords Carbon dioxide exchange · Breath-hold ing · Diving response · Hypoxaemia · Oxygen uptake

Introduction

Breath-hold diving in humans and animals is accompanied by cardiovascular responses such as peripheral vasoconstriction and bradycardia (''the diving response''); these responses represent a mechanism by which diving mammals can prolong their dive time by temporarily reducing the uptake of O_2 from lung and blood stores (Butler and Jones 1997; Ferretti 2001). A number of stimuli potentially influence the breath-hold response in diving mammals including face-cooling, cessation of breathing movements and hypoxaemia, all of which have been implicated as factors eliciting the diving response (DeBurgh Daly et al. 1979; Manley 1990). However, in exercising humans, marked bradycardia producing and hypertensive responses can also be obtained during ''dry'' apnoea (Lindholm et al. 1999). These authors also showed that there was an association between cardiovascular responses and the rate of arterial oxygen desaturation. Thus, the subjects with the most marked bradycardia had the slowest rate of arterial desaturation. This was indirect evidence that the cardiovascular responses to apnoea had a quantitatively important role in reducing the rate of O_2 uptake ($\dot{V}O_2$) from blood and lung stores, thus effectively prolonging the time before critical hypoxaemia occurred in a breath-hold diver.

In the present study we determined directly $\dot{V}O_2$ from the lung, which is the largest O_2 store in the body of an exercising human (Farhi 1964). We hypothesized that there would be a progressive decline of $\dot{V}O_2$ from the lung stores, partly since the bradycardia and a postulated peripheral vasoconstriction are likely to reduce the rate of lung perfusion, and partly since the progressive arterial desaturation (Lindholm et al. 1999) is likely to reduce the arteriovenous difference in O_2 concentration ($c_{a-\bar{v}}O_2$). Furthermore, we hypothesized that the fall in $\dot{V}O_2$ from the lungs would be much larger than could be accounted for by the arterial desaturation, thereby supporting the notion that the cardiovascular responses to apnoea in humans contributes to temporarily reducing $\dot{V}O_2$ from the lungs during apnoea in exercising humans.

P. Lindholm (✉) · D. Linnarsson
Section of Environmental Physiology,
Department of Physiology and Pharmacology,
Karolinska Institutet, 171 77 Stockholm, Sweden
E-mail: peter.lindholm@fyfa.ki.se
Tel.: +46-8-7286879
Fax: +46-8-339702

Methods

Subjects

Eight healthy male volunteers were studied [one subject also had participated in a previously reported study (Lindholm et al. 1999)]. Age, body mass, and height ranged from 18 to 33 years, 71 to

85 kg, and 177 to 189 cm, respectively. Residual volumes (RV) ranged from 1.34 to 2.12 l at body temperature and pressure, saturated. All subjects claimed to be able to swim 25 m underwater. All volunteers had some experience of breath-hold diving and were engaged in physical activity two to three times a week. Two other volunteers were excluded due to their inability to hold their breaths longer than 30 s, so that they were unable to complete the predetermined protocol. All subjects were non-smokers. The experiment protocol was conducted in conformity with the principles of the Declaration of Helsinki and had been approved by the Ethics Committee of the Karolinska Institutet. All subjects gave their informed consents after receiving a description of the procedure and potential risks involved.

Protocol

Subjects arrived in the morning or in the afternoon approximately 1 h after a light meal. They performed upright dynamic leg exercise on an electrically braked cycle ergometer (type 380 B, Siemens-Elema AB, Stockholm, Sweden) at 120 W for 60–70 min. During this steady-state exercise, the subjects held their breaths (apnoea) at a standardized lung volume; they first exhaled to RV and then inspired 3.5 l from a bag that had been pre-filled with a gas mixture containing 21% O_2, 5% He and 74% nitrogen. The apnoea was interrupted by the supervisor at the predetermined times of 10, 20, 30, or 40 s, and there was always a possibility for the subject to start breathing if he aborted a trial. Also, a trial was interrupted by the supervisor if oxygen saturation (SO_2) fell below 50%. Apnoeas were always terminated with a maximal expiration for estimation of alveolar gas concentrations and expiratory reserve volume.

After two test trials with short (10 s) apnoeas, subjects exercised for 4 min and then performed two 20 s, two 30 s and two 40 s apnoeas. Subjects also performed two 30 s rebreathing manoeuvres for determination of RV using a He dilution method, one after the first 20 s apnoea and the other after the first 30 s apnoea. There was at least 5 min of eupnoea between all manoeuvres, or more if the subject did not feel that he had recovered from the previous manoeuvre.

Measurements

The system used for gas supply and respiratory measurements has been described previously (Verbanck et al. 1996). Briefly, the system allowed continuous measurements of respired gas flow and concentrations, and rebreathing using preset bag volumes. Gas analysis was performed using a quadrupole mass spectrometer (QMG 420, Balzer, Lichtenstein) modified for respiratory measurements (Innovision AS, Odense, Denmark). The gas analyser was calibrated against mixtures of known concentrations (AGA Gas AB, Lidingö, Sweden).

An electrocardiogram (ECG) was acquired from chest electrodes and a combined amplifier and beat-by-beat tachometer (Biotach ECG, model 20-4615-65, Gould Inc., Valley View, Ohio). Ear-lobe arterial oxygen saturation (S_aO_2) was measured using a beat-by-beat pulse oximeter (Satlite trans, Datex Engstrom, Finland). The subject's earlobe was prepared by rubbing with an ointment containing capsaicin to enhance local blood flow (Benoit et al. 1997). In a comparison with invasive measurements, and using a technique which was identical to that of the present study, Benoit et al. (1997) found an agreement within 2% units.

Data acquisition and analysis

All measurements were recorded using a computer-based data collection system (Biopac Systems Inc., Goleta, Calif.). Calibrated analogue signals were A-D converted and recorded at 100 Hz per channel, and subsequently stored and analysed with an Acq-Knowledge 3.2.6 software package (Biopac Systems Inc., Goleta, Calif.). Data were stored starting 60 s before each apnoea manoeuvre. Baseline data were obtained as time averages for 20 s periods 30–10 s before apnoeas started. Heart rate (HR) and S_aO_2 were also determined as time averages in 10 s intervals of the 40 s apnoeas. Steady-state $\dot{V}O_2$) and carbon dioxide production before apnoea were determined from the product of respired flow and O_2 and CO_2 fractions to obtain inspired and expired volumes of O_2 and CO_2. Net inspired O_2 volume and expired CO_2 volume were determined from a series of complete breaths for approximately 50 s ending 10 s before apnoeas (Linnarsson 1974). In addition, the pulmonary O_2 and CO_2 exchanges during apnoea were computed as: $[RV\times F_i + V_b\times F_b]$–$[(RV + V_E)\times F_f]$, (Liner et al. 1993), where F_i and F_f are the end-tidal fractional gas concentrations during expirations to RV before (i, initial) and after (f, final) apnoea, V_b and F_b are the volume and gas fraction of the gas inspired from the bag before apnoea, and V_E is the volume expired to RV immediately after apnoea. End-tidal readings obtained at RV were considered sufficiently representative of the overall gas remaining in the lungs at RV. This assumption is supported by the generally accepted method for determining lung diffusing capacity from end-tidal samples during expiration to RV (American Thoracic Society 1987).

Statistics

Paired Student's *t*-tests for dependent samples were used to correlate the studied parameters. Significance was accepted at the 5% level (Statistica, Statsoft, Tulsa, Okla.). If not stated otherwise, data are given as means (SEM).

Results

Apnoeas of 10, 20, 30 and 40 s duration were completed by seven subjects and the values for apnoea duration, end-tidal gas concentrations, and cumulative alveolo-capillary O_2 and CO_2 transfer, and respiratory exchange ratio are shown in Table 1. Apnoeas of longer duration than 20 s showed significantly lower volumes of cumulative alveolo-capillary CO_2 transfer compared to the 20 s apnoea ($P < 0.05$, $n = 7$). During 40 s apnoeas end

Table 1 Pulmonary gas exchange as a function of apnoea time during apnoeas during submaximal exercise. $P_{ET}O_2$ End-tidal partial pressure of oxygen, $P_{ET}CO_2$ end-tidal partial pressure of carbon dioxide, VO_2, VCO_2 cumulative volumes of alveolo-capillary oxygen and carbon dioxide gas transfer respectively, R cumulative respiratory exchange ratio. Values are means (SEM; $n = 7$)

Apnoea time (s)	0 (pre)	15 (0.4)	24 (0.6)	34 (0.3)	44 (0.5)
$P_{ET}O_2$ (kPa)	13.3 (2)	10.2 (2)	7.6 (0.7)	6.2 (3)	5.0 (3)
$P_{ET}CO_2$ (kPa)	6.0 (2)	7.8 (2)	8.5 (2)	8.7 (2)	8.7 (3)
V O_2 (ml)	0	343.0 (22)	535.0 (17)	637.0 (22)	702.0 (15)
VCO_2 (ml)	0	–275.0 (10)*	–302.0 (8)	–288.0 (6)*	−274.0 (8)*
R	0.98 (0.06)	0.82 (0.06)	0.57 (0.02)	0.46 (0.02)	0.39 (0.01)

*Significant difference compared to corresponding value at 24 s

tidal partial pressure of O_2 ($P_{ET}O_2$) fell to 5 kPa (38 mmHg) and partial pressure of CO_2 (PCO_2) increased to approximately 9 kPa (65 mmHg).

Apnoeas of 20, 30 and 40 s duration with successful measurements were completed in eight subjects and enabled calculation of pulmonary $\dot{V}O_2$ during the periods 0–20, 20–30, 30–40 s, as shown in Fig. 1. The apnoea duration used to calculate $\dot{V}O_2$ during an apnoea included inspiration and expiration, thus a typical 20 s apnoea could be 24 s; each 20 s apnoea $\dot{V}O_2$ was therefore divided by the total time and then multiplied by 20. Apnoeas of longer nominal duration were treated correspondingly, thus allowing the pooling of data from these eight subjects. That pulmonary $\dot{V}O_2$ was reduced during apnoea and decreased further as the apnoea proceeded is shown in Fig. 1. Corresponding numbers in percentage of pre-apnoea $\dot{V}O_2$ were 0–20 s 76%, 20–30 s 47%, 30–40 s 24%. Mean S_aO_2 values were 90%, 77%, and 70%, respectively, for the corresponding intervals. These S_aO_2 values were used to calculate the hypothetical curve shown in Fig. 1 representing the $\dot{V}O_2$ that would be expected if venous cardiac output and SO_2 were to remain constant, the latter at an assumed pre-apnoea value of 35% (Astrand et al. 1964), so that the $\dot{V}O_2$ reduction would be caused exclusively by the fall in S_aO_2. After 20 s of apnoea, the observed $\dot{V}O_2$ values were significantly less than those that would result from the change in S_aO_2 alone (20–30 s, $P=0.007$; 30–40 s, $P=0.001$, $n=8$, Student's t-test).

The HR values were 151 (6) (baseline) and 159 (6), 118 (5), 68 (13), 56 (5) beats·min^{-1}, respectively, for successive 10 s intervals in 40 s apnoeas ($n=6$).

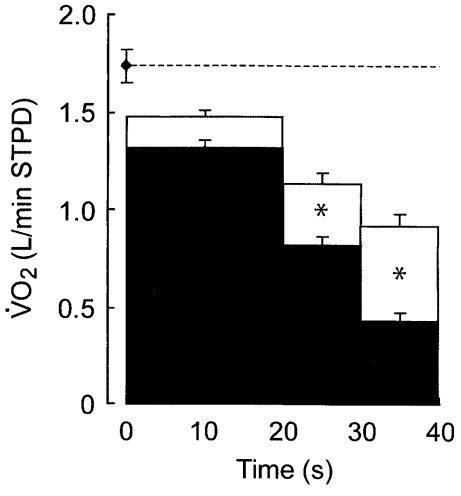

Fig. 1 Pulmonary oxygen uptake ($\dot{V}O_2$ during successive intervals of 40 s apnoeas (*filled areas*, $n=8$). *Unfilled areas* show how much higher $\dot{V}O_2$ would be in a hypothetical case if cardiac output and venous O_2 saturation were to remain constant during the period of apnoea, and thus the $\dot{V}O_2$ reduction would be caused only by the observed fall in the arterial O_2 saturation. *Significant difference between observed and theoretical $\dot{V}O_2$. *Broken line* represents pre-apnoea $\dot{V}O_2$. *STPD* Standard temperature and pressure, dry

Discussion

Reduced pulmonary $\dot{V}O_2$ during apnoea

If during *apnoea*, the rate of $\dot{V}O_2$ from the lungs were to be reduced, the rate of arterial desaturation would be slowed and there would be a prolongation of the effective apnoea period before there would be a risk of loss of consciousness. Possible mechanisms of temporary postponement of $\dot{V}O_2$ from the lungs in an exercising human are O_2 extraction from blood and tissue stores, and energy yield from tissue stores of energy-rich phosphates and anaerobic glycolysis. The depletion of O_2 stores and of local energy stores are in turn dictated by a reduced O_2 delivery to the working muscles as a consequence of falling arterial O_2 content and postulated reductions of cardiac output and muscle perfusion. Necessarily, the reduction in pulmonary $\dot{V}O_2$ can only be temporary; O_2 and energy stores must be replenished once the apnoea period has ended.

A rough quantitative assessment of available O_2 stores at the onset and end of an apnoea can be made from the present $P_{ET}O_2$ and S_aO_2 data and data from the literature on the mixed venous O_2 content during upright steady-state exercise (Astrand et al. 1964) and on the arterial fraction of the total blood volume (Holtz 1996). Assuming a 35% saturation in the mixed venous blood before apnoea and that arterialised blood constitutes 25% of the total blood volume, a maximum of 0.25 of the O_2 that is extracted from the O_2 stores during apnoea can be extracted from the blood, the remainder being supplied by the lung, which therefore is the principal O_2 store during apnoea in exercising humans.

The aim of the present study was to perform a quantitative analysis of $\dot{V}O_2$ from the lungs during apnoea in exercising humans, and to assess whether or not the magnitude of the apnoea-induced reductions in $\dot{V}O_2$ from the lungs was such that reductions in cardiac output and/or muscle blood flow must have contributed to its reduction, in addition to the obvious effect of arterial desaturation.

A compilation of pulmonary $\dot{V}O_2$ data from apnoeas of different durations (Fig. 1) demonstrated that pulmonary $\dot{V}O_2$ was gradually reduced as the apnoea proceeded; $\dot{V}O_2$ was only 24% of pre-apnoea values during the last 10 s of 40 s apnoeas. Since $\dot{V}O_2$ in the lungs equals the cardiac output times the $c_{a-\bar{v}}O_2$, this finding indicates substantial reductions of cardiac output, or $c_{a-v}O_2$ or a combination of the two. At the present work intensity, $c_{a-\bar{v}}O_2$can be estimated to have been 130 ml·l^{-1} [change in SO_2 (ΔSO_2) = 65%] during steady-state pre-apnoea conditions (Astrand et al. 1964). The maximal possible degree of O_2 extraction as reflected by the O_2 content of venous blood during maximal exercise is 170–180 ml·l^{-1} ($\Delta SO_2=90\%$) (Astrand et al. 1964), so a further fall of SO_2 by 25% from 35% to 10% is theoretically possible and also likely in view of the acidosis and hypercapnia which promote peripheral O_2 extrac-

tion. If so, arterial and venous saturations will change in the same direction, and the fall in $c_{a-v}O_2$would be smaller than the observed fall in S_aO_2, and a significant portion of the fall in pulmonary $\dot{V}O_2$ must be accounted for by a change in cardiac output.

An hypothetical reduction in pulmonary $\dot{V}O_2$ was calculated from the observed reduction in S_aO_2 and the theoretical case that cardiac output and venous SO_2 would remain at pre-apnoea levels (Fig. 1). Such a theoretical case could occur if there were to be no reflex alterations of HR and peripheral vascular conductance as a result of the apnoea. Clearly, the presently found reductions of pulmonary $\dot{V}O_2$ during apnoea were much larger than could be accounted for by the fall in S_aO_2 alone. The difference between actual and theoretical fall in pulmonary $\dot{V}O_2$ would be even larger, had the model included a fall in venous SO_2 , which would tend to preserve $c_{a-v}O_2$.

The time course of $\dot{V}O_2$ from the lungs during successive 10 s intervals of 40 s of apnoea in the six subjects, where data from all intervals were available, is shown in Fig. 2. Three different theoretical cases are depicted together with actual data. Case 1 is the same as shown in Fig. 1, namely maintained cardiac output and maintained 35% mixed venous SO_2. This is a theoretical case in which there are no cardiovascular responses with influences on cardiac output, peripheral blood flow distribution and peripheral O_2 extraction. In case 2 it is assumed that cardiac output is reduced in proportion to the reduction in HR and that mixed-venous SO_2 is maintained at 35% throughout the apnoea, so here the cardiovascular response is limited to a change in cardiac output. In case 3, finally, there is both a HR-proportional fall of cardiac output and a gradual fall of mixed-venous SO_2 from 35% to 10% during the apnoea. As in Fig. 1, data from the theoretical case 1 differs from actual data and case 3 strongly resembles actual data after the first 10 s. With such a comparison of theoretical models, exact mechanisms cannot be identified. However, models which do agree with observed data can be distinguished from those that do not.

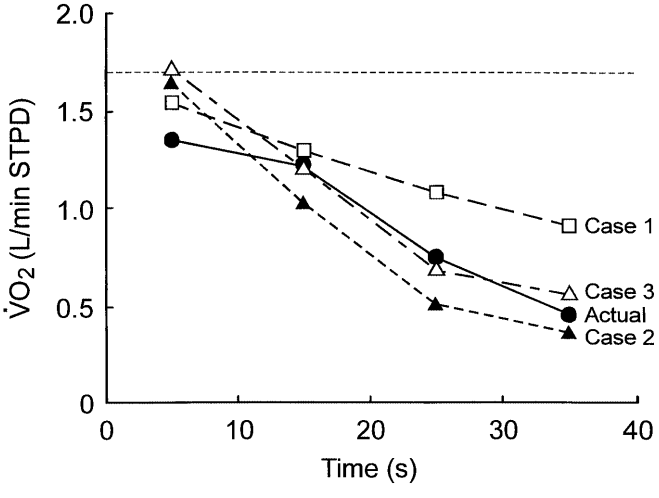

Fig. 2 Oxygen uptake ($\dot{V}O_2$) from the lung gas to the blood during successive 10 s periods of 40 s apnoeas in exercising men ($n=6$). *Continuous line* is actual experiment data shown together with three hypothetical cases. Case 1, no change in cardiac output or mixed-venous O_2 content. Case 2, cardiac output is reduced in proportion to the apnoea-induced bradycardia, but mixed-venous O_2 content is as in case 1. Case 3, cardiac output as in case 2 and with a gradual reduction of mixed-venous O_2 saturation from 35% to 10%. Note agreement between case 3 and actual data after the first 10 s. *Horizontal broken line*, pre-apnoea $\dot{V}O_2$

In summary, therefore, peripheral and/or central-circulatory changes must have been present in parallel to the presently observed fall in S_aO_2 to explain the full extent of the observed fall in pulmonary $\dot{V}O_2$ during apnoea. The most likely circulatory change is a fall in cardiac output roughly in proportion to the bradycardia (Bjertnaes et al. 1984); exercise stroke volume has been shown to reach its highest level during exercise at the present intensity (Astrand et al. 1964)and it is therefore unlikely that the bradycardia would be accompanied by compensatory increases of stroke volume. The concomitant arterial hypertension (Lindholm et al. 1999) indicates a marked reduction of total systemic conductance, which must have induced active vasoconstriction in working muscles, which in the present pre-apnoea condition received most of the cardiac output (Astrand et al. 1964).

Reversal of pulmonary CO_2 flux during apnoea

As shown in Table 1, the amount of pulmonary CO_2 after 30 and 40 s of apnoea was lower than after 20 s, thus showing that CO_2 exchange between lung and blood became reversed during the apnoeas of longer duration (Table 1). A similar reversal of CO_2 *flux* has been observed during apnoea in resting humans and animals (Lanphier and Rahn 1963; Hesser et al. 1968; Hong et al. 1971; Ferretti et al. 1991) and in breath-hold divers (Ferretti 2001).

The mechanism behind the reversal of the direction of CO_2 flux between the blood and the lungs is well established: as $\dot{V}O_2$ to the blood reduces the lung gas volume, its contents become enriched with respect to *all* other gas components *including* CO_2. At the same time, blood and peripheral tissues have a much larger capacity for CO_2 storage than the lungs, and over-all PCO_2 does not rise as fast as the partial pressure of O_2 falls during apnoea. As a consequence, alveolar PCO_2 tends to increase faster than mixed-venous PCO_2, which in turn results in reversal of CO_2 flux from the lungs to the pulmonary-capillary blood. Had the $\dot{V}O_2$ in the lungs not been slowed by a reduction in cardiac output *this* reversal of CO_2 *flux* would occur earlier during the apnoea and be more evident. A reversal of the CO_2 flux in the lungs by the end of apnoea does not necessarily mean that there is a corresponding and simultaneous reversal of the CO_2 flux between the blood and the peripheral tissues. This is so because the progressive fall in SO_2 during apnoea increases the CO_2 carrying capacity

of the blood, and because of circulatory transport delays between the lung and the peripheral tissues.

Conclusions

The $\dot{V}O_2$ from the lungs to the blood is markedly slowed during apnoea in exercising men. The magnitude of this slowing is such that it must, to a significant extent, be due to cardiovascular responses to apnoea such as a bradycardia-dependent fall of cardiac output.

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