Oxygen-conserving effects of apnea in exercising men

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Lindholm, Peter, Patrik Sundblad, and Dag Linnarsson. Oxygen-conserving effects of apnea in exercising men. J. Appl. Physiol. 87(6): 2122–2127, 1999.—We sought to determine whether apnea-induced cardiovascular responses resulted in a biologically significant temporary O2 conservation during exercise. Nine healthy men performing steady-state leg exercise carried out repeated apneic (A) and rebreathing (R) maneuvers starting with residual volume +3.5 liters of air. Heart rate (HR), mean arterial pressure (MAP), and arterial O2 saturation (SaO2; pulse oximetry) were recorded continuously. Responses (ΔHR, ΔMAP) were determined as differences between HR and MAP at baseline before the maneuver and the average of values recorded between 25 and 30 s into each maneuver. The rate of O2 desaturation (ΔSaO2/Δt) was determined during the same time interval. During apnea, ΔSaO2/Δt had a significant negative correlation to the amplitudes of ΔHR and ΔMAP (r2 = 0.88, P < 0.001); i.e., individuals with the most prominent cardiovascular responses had the slowest ΔSaO2/Δt. ΔHR and ΔMAP were much larger during A (−44 ± 8 beats/min, +49 ± 4 mmHg, respectively) than during R maneuvers (−3 ± 3 beats/min, +30 ± 5 mmHg, respectively). ΔSaO2/Δt during A and R maneuvers was −1.1 ± 0.1 and −2.2 ± 0.2% units/s, respectively, and nadir SaO2 values were 58 ± 4 and 42 ± 3% units, respectively. We conclude that bradycardia and hypertension during apnea are associated with a significant temporary O2 conservation and that respiratory arrest, rather than the associated hypoxemia, is essential for these responses.

THE DIVING RESPONSE, i.e., bradycardia and peripheral vasoconstriction in response to apneic submersion, has been demonstrated to be an O2-conserving reflex in diving species (4, 9). This response is thought to maintain perfusion to the brain, to reduce blood perfusion to viscera and muscle, and to reduce cardiac work, thus reducing overall O2 consumption (VO2). In humans, apnea has been shown to elicit bradycardia. As in animals, other stimuli than the apnea per se, such as hypoxia and immersion of the face in cold water, have additive effects on the bradycardia (13, 20, 29). Previous studies showed a great variability in the human diving response, and, in addition to external stimuli, individual factors such as age and diving experience have been suggested to modify the bradycardia (20, 23).

There is also evidence of peripheral vasoconstriction during apnea in resting humans (14, 21). Lin et al. (21, 22) showed in resting men that the cardiovascular responses to apnea were temporarily attenuated when subjects breathed once every 15 s in a rebreathing bag. Where fresh gas supply is concerned, rebreathing is comparable to apnea: the available O2 stores are the same at the beginning. Their experiments suggest that it is the respiratory arrest, rather than the O2 restriction, that is the key factor behind the bradycardia. Apnea-induced bradycardia has also been found during exercise (5, 23, 29, 30). Bjertnaes et al. (3), studying two subjects during exercise and apnea, found that the bradycardia was associated with a substantial reduction in cardiac output and an increase in systemic vascular resistance.

Humans are not able to hold their breath for as long as diving mammals can. This might be due to a less developed diving response (9, 19), in which a more modest bradycardia and a less effective reduction of cardiac output in the face of peripheral vasoconstriction result in an increase in blood pressure during apnea, rather than an unchanged blood pressure, as observed in diving animals (4). The actual O2-conserving potential in humans during apnea has not been determined (9). There are studies in humans that support the existence of a functional O2-conserving effect (1, 10, 11, 32) and there are others that do not (6, 16). Wolf et al. (32), and Andersson and Schagatay (1), studying resting humans, found that apneic situations with bradycardia were associated with a slightly smaller reduction in arterial O2 saturation (SaO2) than apneic situations without bradycardia. In no case, however, did SaO2 decrease to >4% units below eupneic control. Therefore, no biologically significant O2 conservation was demonstrated.

We define O2 conservation as a temporary postponement of the uptake of O2 from the lungs and an associated slowing of the arterial desaturation, resulting in a prolongation of the period until vital functions are threatened by hypoxia.

We speculated that the O2-conserving potential, if any, of diving responses in humans might not be demonstrable in resting humans but becomes evident only during exercise, when O2 requirements are increased. We hypothesized that the subjects with the most marked responses to apnea also would show the highest degree of O2 conservation, manifested as the slowest rate of SaO2 decline. In addition, we wanted to confirm also, in exercising subjects, that respiratory arrest is the essential element for eliciting diving responses, rather than the associated hypoxia. To do this, we compared the cardiovascular responses to apnea with those during rebreathing.

MATERIALS AND METHODS

Subjects. Nine healthy male volunteers were studied. Age, weight, and height ranged 21–31 yr, 64–84 kg, and 177–194 cm, respectively. The subjects were nonsmokers and did not drink any caffeinated beverages on the day of the experiment. Seven of the subjects claimed to be able to swim 25 m underwater; two had no previous experience of long breath holding.
The experimental protocol was conducted in conformity with the principles of the Declaration of Helsinki and had been approved by the Ethical Committee of Karolinska Institutet. All subjects gave their informed consent after receiving a description of the procedure and an explanation of potential risks involved.

Protocol. Subjects arrived in the morning or in the afternoon, ~1 h after a meal. A 20-gauge catheter was inserted in the radial artery under local anesthesia with lidocaine hydrochloride.

Subjects performed upright dynamic leg exercise on an electrically braked cycle ergometer (type 380 R, Siemens-Elema, Stockholm, Sweden) at 120 W for ~45 min. During this steady-state exercise, subjects held their breath [apnea maneuver (A)] at a standardized lung volume or breathed in a rebreathing bag [rebreathing maneuver (R)] with an equivalent volume. In both A and R, subjects first exhaled to residual volume and then inspired 3.5 liters from a bag that had been prefilled with air. A or R maneuver was interrupted by the subject or earlier by the medical supervisor, if \( O_2 \) saturation fell below 50%. Apneas were always terminated with an expiration to estimate alveolar \( O_2 \) concentrations.

After two trials with A and one with R maneuvers, subjects exercised for 4 min and then performed each procedure four to five times, alternating between A and R. Five subjects started with R and four started with A. There were at least 3 min of eupnea between maneuvers or more if the subject did not feel that he had recovered after the previous maneuver.

Measurements. The system used for gas supply and respiratory measurements has been described previously (31). Briefly, the system allowed continuous measurements of inspired \( O_2 \) concentrations and rebreathing with preset bag volumes. The dead-space volume in the rebreathing situation was 85 ml between the bag and the mouthpiece. Gas analysis was performed by a quadrapole mass spectrometer (QMG 420, Balzer, Lichtenstein) modified for respiratory measurements (Innovision, Odense, Denmark). The gas analyzer was calibrated against mixtures of known concentrations (AGA Gas, Lidingö, Sweden).

An electrocardiogram (ECG) was acquired from chest electrodes and a combined amplifier and beat-by-beat tachometer (Biopac Systems, Goleta, CA). Calibrated analog signals were analog-to-digital converted, recorded at 100 Hz per channel, and subsequently stored and analyzed with the AcqKnowledge 3.2.6 software package (Biopac Systems). Data were stored starting 60 s before and until 30 s after each A or R maneuver. Off-line computations included the beat-by-beat computation of systolic pressure and MAP.

Baseline data for each A or R maneuver were averaged from a 15-s period immediately before subjects started to exhale to residual volume. HR and MAP were also determined as time averages during the interval 25–30 s after the initial inhalation of the 3.5 liters of air had been completed. \( \Delta HR \) and \( \Delta MAP \) were calculated as the differences between the time averages of HR and MAP, respectively, during 25–30 s and the corresponding baseline values. The rate of arterial oxygen desaturation (\( \Delta SaO_2/\Delta t \)) was determined as the slope of the \( SaO_2 \) curve measured 25–30 s into the maneuver.

Statistics. Differences between conditions were analyzed by using a paired Student’s t-test for dependent variables. Significance was accepted at the 5% level. A multiple-regression analysis was used for analyzing the correlation between the rate of decline of \( SaO_2 \) on one hand and \( \Delta HR \) and \( \Delta MAP \) on the other (Statistica, Statsoft, Tulsa, OK).

RESULTS

All subjects completed the protocol, and maximum mean \( SaO_2 \) time in the nine subjects was 40 s (range 30–54 s). Rebreathings were frequently interrupted by the medical supervisor as the \( SaO_2 \) decreased to the predetermined minimum allowed level; maximum rebreathing time in the nine subjects was 38 s (range 35–44 s). In no case, was any A or R maneuver of shorter duration than 30 s, so the period of 25–30 s was used for analysis of group responses. In accordance with instructions, subjects did not hyperventilate before A or R maneuvers.

Figure 1 presents recordings of A and R maneuvers in a subject who showed marked bradycardia and hypertension during apnea. Individual \( \Delta HR \) and \( \Delta MAP \) responses to apnea ranged from \(-10 \) to \(-93 \) beats/min for HR and from \(+27 \) to \(+67 \) mmHg for MAP. Corresponding values for \( SaO_2/\Delta t \) were \(-0.43 \) to \(-2.2 \) units/s. To analyze whether the rate of desaturation during apnea could be related to the cardiovascular responses, we performed regression analyses in which the desaturation rate during apnea in an individual was expressed as a function of corresponding \( \Delta MAP \), \( \Delta HR \), or both. The following relationships were obtained

\[
\Delta MAP: \Delta SaO_2/\Delta t = -2.1 + 0.021 \Delta MAP \\
(1)
\]

\[
\Delta HR (\text{Fig. 2}): \Delta SaO_2/\Delta t = -1.98 - 0.023 \Delta HR \\
(2)
\]

\[
\Delta HR \text{ and } \Delta MAP (\text{Fig. 3}): \Delta SaO_2/\Delta t = -3.35 - 0.022 \ast \Delta HR + 0.027 \ast \Delta MAP \\
(3)
\]

where variances of \( \Delta HR \) and \( \Delta MAP \) explained 88% of the individual variances of \( \Delta SaO_2/\Delta t \).

Figure 1 also shows that during R there was no bradycardia and a smaller rise in blood pressure com-
pared with A. In both maneuvers, there was a gradual arterial desaturation, but with a steeper slope during R. Figure 4 shows group mean values for $\Delta HR$ and $\Delta MAP$. Compared with baseline, the mean values for $\Delta HR$ were $234 \pm 67$ (SE)% during A and $126 \pm 3$% during R ($n = 9$, $P < 0.001$). The corresponding mean values for $\Delta MAP$ were $142 \pm 63$% during A and $127 \pm 64$% during R, compared with baseline ($n = 9$, $P < 0.01$).

The rate of $\Delta SaO_2$ decline between 25 and 30 s ($\Delta SaO_2/\Delta t$) was twice as large during R as during A; $\Delta SaO_2/\Delta t$ values were $2.2 \pm 0.2$ and $1.1 \pm 0.1$ units/s, respectively ($P < 0.001$).

Baseline HR was $123 \pm 3$ beats/min before R and $130 \pm 3$ beats/min before A ($P < 0.001$, $n = 9$). Baseline MAP did not differ between conditions and averaged $114 \pm 3$ mmHg ($n = 9$).

Fig. 1. Original recordings in one subject, showing rebreathing (29–61 s) and apnea (378–412 s) maneuvers. A: heart rate (HR); B: arterial $O_2$ saturation obtained with a pulse oximeter ($SaO_2$); C: invasive mean arterial pressure (MAP); and D: respired $PO_2$.

Fig. 2. Mean values ($n = 9$ subjects) of rate of arterial $O_2$ desaturation ($\Delta SaO_2/\Delta t$) as determined with earlobe pulse oximetry ($SaO_2$) and corresponding values for bradycardia as difference in HR ($\Delta HR$) between a mean value from 25 to 30 s after onset of apnea and control before apnea. Line represents a best fit relationship, see Eq. 2.

Fig. 3. Correlation between individual $\Delta HR$ and $\Delta MAP$ on one hand and rate of $\Delta SaO_2$ decline during apnea. y-Axis represents $\Delta SaO_2/\Delta t$ predicted from $\Delta HR$ and difference in MAP ($\Delta MAP$) according to a best fit linear relationship, $\Delta SaO_2/\Delta t = -3.35 - 0.022 \cdot \Delta HR + 0.027 \cdot \Delta MAP$ ($P < 0.001$, adjusted $r^2 = 0.88$). The larger the cardiovascular responses, the slower $\Delta SaO_2/\Delta t$. 
The HR x systolic arterial pressure product was reduced in A and increased in R. Mean changes for the six subjects on whom intra-arterial measurements were performed were $-3,319 \pm 3,165$ and $+5,742 \pm 967$ beats min$^{-1}$ mmHg$^{-1}$ ($P < 0.05$) for A and R, respectively.

Group mean data for SaO$_2$ are presented in Fig. 5. There was no significant difference between conditions at 25 s, whereas at 30 s SaO$_2$ was lower during rebreathing ($P < 0.01$). Minimum SaO$_2$ and maximum A/R times have been obtained from the A and R maneuver of the longest duration for each subject. Because there is a circulatory delay from the lungs to the earlobe, nadirs of SaO$_2$ were recorded a few seconds after breathing was resumed (cf. Fig. 1). The mean nadir of the SaO$_2$ decline was 16% units lower ($P < 0.01$) during R than during A, despite the fact that R maneuvers on the average were of shorter duration.

End-tidal P$_O_2$ and P$_CO_2$ from the end of A were compared with corresponding data obtained at an equivalent time during a subsequent R (Fig. 6). For each subject, an A maneuver was selected that was slightly shorter than the longest R maneuver, and a paired comparison was made. There was a higher P$_O_2$ ($P < 0.001$) and lower P$_CO_2$ ($P < 0.0001$) during apnea compared with rebreathing; group mean differences were on the order of 1 kPa for both gases.

**DISCUSSION**

The distinctive feature of the present study is that cardiovascular responses (bradycardia, hypertension) were related to arterial O$_2$ desaturation during apnea in exercising men. The principal finding is that the SaO$_2$ decreased at a slower rate in subjects with pronounced bradycardia and hypertension; i.e. the stronger the diving response, the slower the $\Delta$SaO$_2$/At.

The most commonly used measurement of the human diving response in most studies is bradycardia (23). Figure 2 and Eq. 2 show that the degree of bradycardia correlates with the rate of SaO$_2$ decrease. However, when the hypertensive response also is introduced as a term in the correlation between cardiovascular responses and desaturation rate, the desaturation rate can be predicted much more accurately (Fig. 3, Eq. 3). This correlation indicates that there is a causal relationship between intensity of the cardiovascular responses to apnea and O$_2$ conservation, as reflected by a less steep decline of SaO$_2$. The absolute magnitude of the O$_2$ conservation in terms of a temporarily reduced V˙O$_2$, however, remains to be established.

**Vascular conductance.** Although we did not directly determine cardiac output, stroke volume, and total peripheral conductance (TPC) in the present study, limited data from Bjertnaes et al. (3) could be used to roughly assess these variables. Using thermodilution to measure cardiac output in two exercising subjects during apnea, they found a 49% decrease by the end of a 30-s apnea combined with face immersion. These authors calculated that a concomitant fall in TPC reached 53–74%. An estimation based on five measurements in these two subjects suggests that a given relative reduction in HR results in a relative reduction of TPC by 33–70% in our nine subjects after 25–30 s of apnea. The corresponding reduction during R would be 3–39%, assuming constant stroke volume. These estimates suggest that there was a marked peripheral vasoconstriction in the...
present A experiments. Because most of the cardiac output in exercise is directed to the working muscles (25), this must be where most of the reduction in TPC took place.

Cardiac function. During A, the bradycardia and hypertension developed gradually (Fig. 1). During resting A, the final level of bradycardia has usually been reached within 30 s (26). Butler and Woaks (5) showed that the bradycardia during swimming developed faster and reached the same minimum values in 30 s as during resting submersion, even though the initial HR was much higher in the swimming condition.

The more marked and faster developing bradycardia during exercise [see Butler and Woaks (5) and present study compared with Schagatay and Andersson (26)] is compatible with the assumption that there is primarily a vagal mechanism behind the bradycardic response; the more complete the vagal withdrawal before apnea, the larger the potential for vagally induced bradycardia. The notion that there is at the same time a substantial sympathetic outflow to the heart is supported by our present observation and those of others (9, 12, 20, 27) of arrhythmias during the bradycardic response; vagal inhibition of atrioventricular conduction combined with sympathetically induced enhancement of automaticity in other latent pacemakers would promote ectopic beats (28).

Respiratory arrest as a trigger for cardiovascular and metabolic responses. The marked differences between the cardiovascular responses to gradually increased hypoxia-hypercapnia with and without breathing movements support and extend the previously established notion that the respiratory arrest per se is required to elicit the cardiovascular responses to apnea (7, 21, 22) in resting humans. Thus also during exercise, when additional inputs such as central command and proprioceptive afferents contribute to HR control (25), the presence or absence of regular respiratory movements appear to be critical for the maintenance of HR during a hypoxic period.

We suggest that the slightly higher HR before A compared with R was an anticipation effect, since all subjects were aware of the starting time for maneuvers and generally felt that apneas were harder to perform than rebreathings. In support of this assumption, Stromme et al. (29) found an anticipatory rise in HR before apneas.

At first sight, there appears also to be a strong association between respiratory arrest and O2 conservation when A and R experiments are compared (Figs. 1 and 5). The SaO2 declined at a faster rate during R than during A, with the subjects starting from the same initial amount of O2 stores and exercising at the same intensity. These differences between A and R in SaO2 indicate a slower rate of pulmonary gas exchange in A, and this conclusion is supported by the differences in end-tidal PO2 and PCO2 (Fig. 6). However, with the present experimental design, a causal relationship cannot be established from such a comparison. This is so because the work of breathing during rebreathing will maintain and probably even increase O2 demand, thereby contributing to a difference in O2 uptake between A and R, as reflected by the rates of SaO2 decline. Estimates of the O2 cost of breathing during exercise range from 0.5 to 2 ml/l ventilated volume (8, 24). Depending on which estimate is adopted, all or only a small part of a possible O2 uptake reduction during A compared with R can be accounted for by the absence of breathing movements. Thus the principal conclusion that can be drawn from a comparison between the present A and R experiments is that respiratory arrest is essential for the cardiovascular responses, not only, as has previously been shown, in resting humans and animals (7, 21, 22) but also in exercising humans.

Biological significance of O2 conservation. A temporary reduction in peripheral consumption of O2, resulting in a slower O2 uptake from the alveolar space to the blood, would temporarily conserve O2 for the benefit of the central nervous system and the heart, which cannot sustain their metabolism without O2. To reduce VO2 during exercise, one possible mechanism would be to reduce the blood flow to the working skeletal muscles, which temporarily can provide the energy needed for continued exercise by anaerobic metabolism. Although similar mechanisms may be active at rest, the fairly modest blood flow and O2 delivery to, for example, resting muscles may make it difficult to detect a further temporary reduction of blood flow as a temporary drop in VO2. From a teleological standpoint, it could be argued that the physiological need for conserving O2 during apnea would arise during physical activity rather than during rest; in both animals and humans, apnea occurs normally during underwater swimming. The present preapneic VO2 during 120-W steady-state leg exercise could be estimated to be 1.5–2 l/min. This VO2 corresponds to swimming at a speed of 0.4–0.5 m/s without fins (breast stroke, untrained subjects) (15), a speed that would be expected to be normally occurring in breath-hold diving activities. For a diver with fins, the same VO2 corresponds to a swimming speed of 0.9–1.0 m/s (18).

Conclusions. Despite evidence that the cardiovascular responses to apnea in humans are similar to those in animals, no study so far has convincingly shown any quantitatively significant benefits in terms of O2 conservation in humans.

In the present study, however, we have been able to demonstrate a significant benefit of apnea-induced cardiovascular responses in terms of a much slower rate of SaO2 decline. Thus, after 30 s of apnea during medium-intensity dynamic leg exercise, the subject with the most marked cardiovascular responses had a four to five times slower rate of SaO2 decline than the subject with the least marked cardiovascular response.

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