Oxygen-conserving effects of apnea in exercising men

PETER LINDHOLM, PATRIK SUNDBLAD, AND DAG LINNARSSON
Section of Environmental Physiology, Department of Physiology and Pharmacology,
Karolinska Institutet, SE-171 77 Stockholm, Sweden

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 O_2 conservation during exercise. Nine healthy men performing steady-state leg exercise carried out repeated apnea (A) and rebreathing (R) maneuvers starting with residual volume +3.5 liters of air. Heart rate (HR), mean arterial pressure (MAP), and arterial O_2 saturation (Sa_{O_2}; 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 O_2 desaturation ($\Delta Sa_{O_2}/\Delta t$) was determined during the same time interval. During apnea, $\Delta Sa_{O_2}/\Delta t$ had a significant negative correlation to the amplitudes of ΔHR and ΔMAP ($r^2 = 0.88$, $P < 0.001$); i.e., individuals with the most prominent cardiovascular responses had the slowest $\Delta Sa_{O_2}/\Delta t$. ΔHR and ΔMAP were much larger during A (-44 ± 8 beats/min, $+49 \pm 4$ mmHg, respectively) than during R maneuver ($+3 \pm 3$ beats/min, $+30 \pm 5$ mmHg, respectively). $\Delta Sa_{O_2}/\Delta t$ during A and R maneuvers was -1.1 ± 0.1 and $-2.2 \pm 0.2\%$ units/s, respectively, and nadir Sa_{O_2} values were 58 ± 4 and $42 \pm 3\%$ units, respectively. We conclude that bradycardia and hypertension during apnea are associated with a significant temporary O_2 conservation and that respiratory arrest, rather than the associated hypoxia, is essential for these responses.

hypoxemia; bradycardia; hypertension; breath holding; diving response.

THE DIVING RESPONSE, i.e., bradycardia and peripheral vasoconstriction in response to apneic submersion, has been demonstrated to be an O_2-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 O_2 consumption ($\dot{V}o_2$). 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 O_2 stores are the same at the beginning. Their experiments suggest that it is the respiratory arrest, rather than the O_2 restric-

tion, 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 O_2-conserving potential in humans during apnea has not been determined (9). There are studies in humans that support the existence of a functional O_2-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 O_2 saturation (Sa_{O_2}) than apneic situations without bradycardia. In no case, however, did Sa_{O_2} decrease to >4% units below eupneic control. Therefore, no biologically significant O_2 conservation was demonstrated.

We define O_2 conservation as a temporary postponement of the uptake of O_2 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 O_2-conserving potential, if any, of diving responses in humans might not be demonstrable in resting humans but becomes evident only during exercise, when O_2 requirements are increased. We hypothesized that the subjects with the most marked responses to apnea also would show the highest degree of O_2 conservation, manifested as the slowest rate of Sa_{O_2} 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 B, 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 gas 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 respired gas 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 quadrupole 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 (Biotach ECG, model 20-4615-65, Gould, Valley View, OH). During arrhythmias, intervals between systolic blood pressure peaks were measured to determine beat-by-beat heart rate (HR).

For blood pressure measurement, the radial artery catheter was connected to a disposable transducer (Smith Industries Medical Systems, Ref. 1768, Kirchseeon, Germany) aligned to the horizontal level of the fourth intercostal space (heart level) and an amplifier/monitor (type SMK 154-9 Hellige Servomed, Germany). In three subjects, insertion of the arterial catheter was unsuccessful, and blood pressure was measured by the photoplethysmographic finger-cuff method (Finapres 2300, Ohmeda, Englewood, CO). The Finapres device has previously been shown to provide continuous recordings of mean arterial pressure (MAP) in close agreement with concomitant invasive recordings (17).

Earlobe Sa$_{O_2}$ was measured with a beat-by-beat pulse oximeter (Satlite trans, Datex Engstrom, Finland). The subject's earlobe was rubbed with an ointment containing capsaicin to enhance local blood flow (2).

Data acquisition and analysis. All measurements were recorded with a computer-based data-collection system (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. ΔHR and ΔMAP 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 (ΔSa$_{O_2}/\Delta t$) was determined as the slope of the Sa$_{O_2}$ 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 Sa$_{O_2}$ on one hand and ΔHR and ΔMAP on the other (Statistica, Statsoft, Tulsa, OK).

RESULTS

All subjects completed the protocol, and maximum mean apnea time in the nine subjects was 40 s (range 30–54 s). Rebreathings were frequently interrupted by the medical supervisor as the Sa$_{O_2}$ 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 ΔHR and ΔMAP responses to apnea ranged from -10 to -93 beats/min for HR and from $+27$ to $+67$ mmHg for MAP. Corresponding values for Sa$_{O_2}/\Delta t$ 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 ΔMAP, ΔHR, or both. The following relationships were obtained

$$\Delta\text{MAP: } \Delta\text{Sa}_{O_2}/\Delta t = -2.1 + 0.021\Delta\text{MAP} \tag{1}$$

$$(P = 0.27, \text{ adjusted } r^2 = 0.05)$$

$$\Delta\text{HR (Fig. 2): } \Delta\text{Sa}_{O_2}/\Delta t = -1.98 - 0.02\Delta\text{HR} \tag{2}$$

$$(P < 0.01, \text{ adjusted } r^2 = 0.58)$$

$$\Delta\text{HR and }\Delta\text{MAP (Fig. 3): } \Delta\text{Sa}_{O_2}/\Delta t$$
$$= -3.35 - 0.022 * \Delta\text{HR} + 0.027 * \Delta\text{MAP} \tag{3}$$

$$(P < 0.001, \text{ adjusted } r^2 = 0.88)$$

where variances of ΔHR and ΔMAP explained 88% of the individual variances of ΔSa$_{O_2}/\Delta t$.

Figure 1 also shows that during R there was no bradycardia and a smaller rise in blood pressure com-
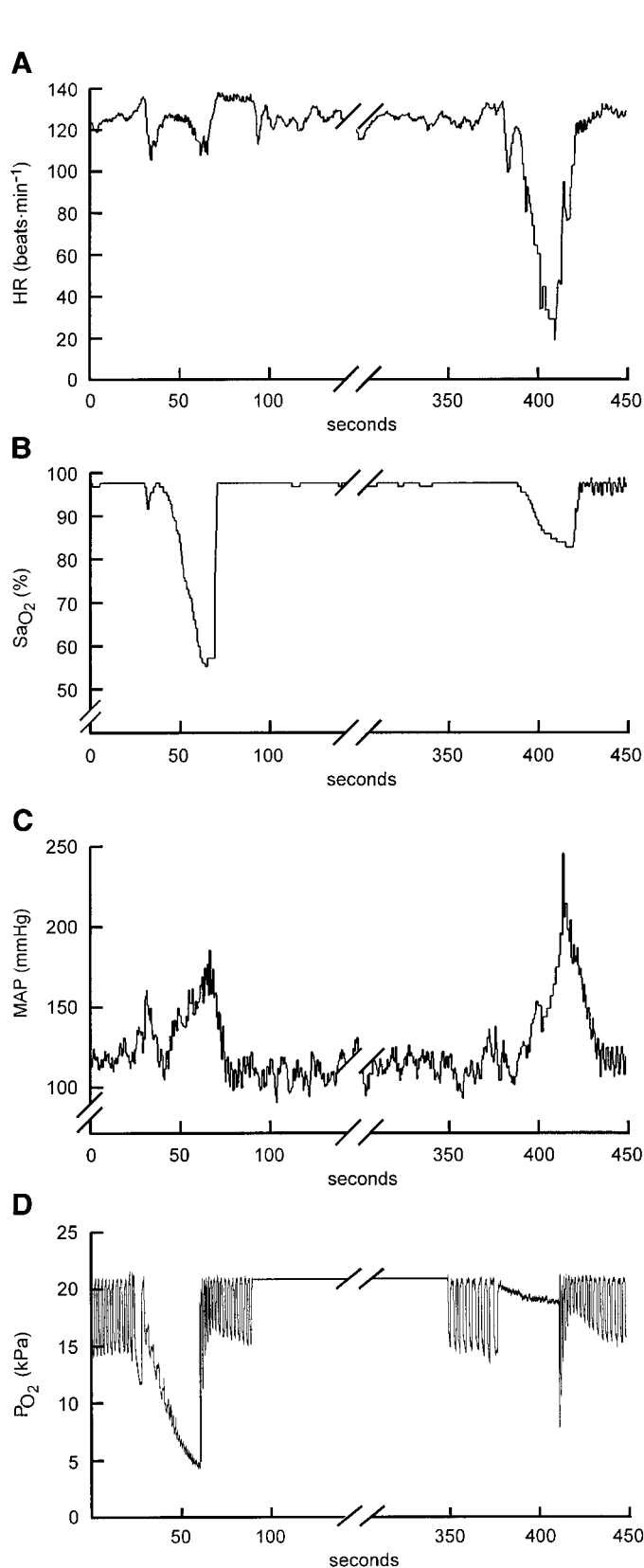
A

B

C

D

Fig. 1. Original recordings in one subject, showing rebreathing (29–61 s) and apnea (378–412 s) maneuvers. *A:* heart rate (HR); *B:* arterial O₂ saturation obtained with a pulse oximeter (Sa$_{O_2}$); *C:* invasive mean arterial pressure (MAP); and *D:* respired P$_{O_2}$.
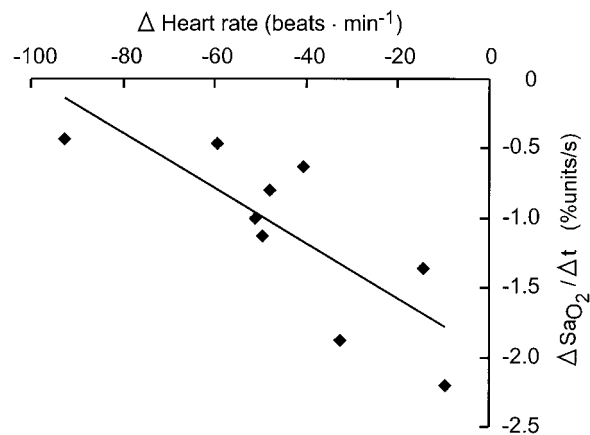

Fig. 2. Mean values ($n = 9$ subjects) of rate of arterial O₂ desaturation (ΔSa$_{O_2}$/Δt) as determined with earlobe pulse oximetry (Sa$_{O2}$) and corresponding values for bradycardia as difference in HR (ΔHR) between a mean value from 25 to 30 s after onset of apnea and control before apnea. Line represents a best fit relationship, see *Eq. 2.*

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 ΔHR and ΔMAP. Compared with baseline, the mean values for ΔHR were -34 ± 7 (SE)% during A and $+2 \pm 3$% during R ($n = 9$, $P < 0.001$). The corresponding mean values for ΔMAP were $+42 \pm 3$% during A and $+27 \pm 4$% during R, compared with baseline ($n = 9$, $P < 0.01$). The rate of Sa$_{O_2}$ decline between 25 and 30 s (ΔSa$_{O_2}$/Δt) was twice as large during R as during A; ΔSa$_{O_2}$/Δt values were 2.2 ± 0.2 and 1.1 ± 0.1% units/s, respectively ($P < 0.001$).

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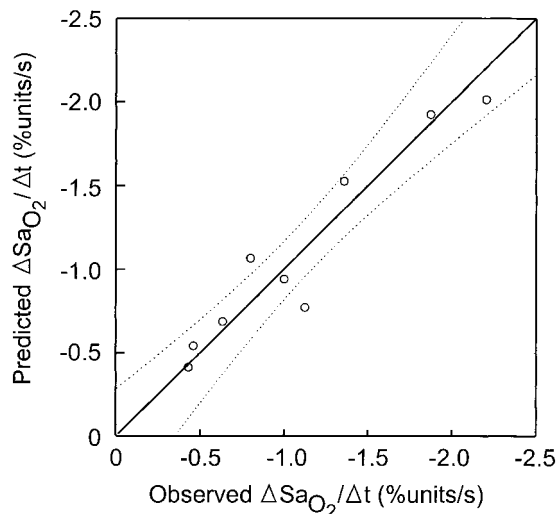

Fig. 3. Correlation between individual ΔHR and ΔMAP on one hand and rate of Sa$_{O_2}$ decline during apnea. *y*-Axis represents ΔSa$_{O_2}$/Δt predicted from ΔHR and difference in MAP (ΔMAP) according to a best fit linear relationship, ΔSa$_{O_2}$/$\Delta t = -3.35 - 0.022 * \Delta$HR $+ 0.027 * \Delta$MAP ($P < 0.001$, adjusted $r^2 = 0.88$). The larger the cardiovascular responses, the slower ΔSa$_{O_2}$/Δt.
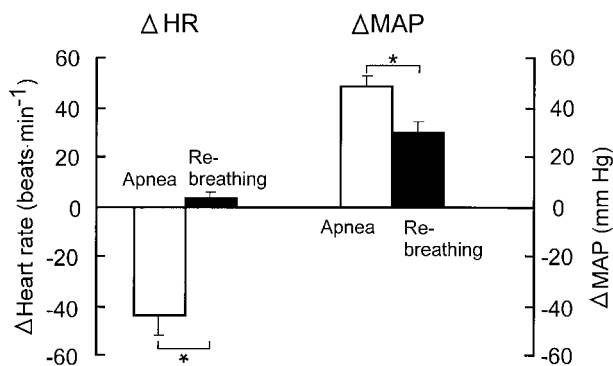
Fig. 4. HR and MAP responses (ΔHR, ΔMAP) to apnea and rebreathing. Values calculated as difference between time averages of HR and MAP from 25 to 30 s of apnea or rebreathing and corresponding premaneuver baseline values; $n = 6$ subjects for invasive MAP; $n = 9$ for all subjects. Values are means $\pm$ SE. *Significant difference between conditions, $P < 0.05$.

The HR $\times$ 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 Sa$_{O_2}$ are presented in Fig. 5. There was no significant difference between conditions at 25 s, whereas at 30 s Sa$_{O_2}$ was lower during rebreathing ($P < 0.01$). Minimum Sa$_{O_2}$ 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 Sa$_{O_2}$ were recorded a few seconds after breathing was resumed (cf. Fig. 1). The mean nadir of the Sa$_{O_2}$ 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
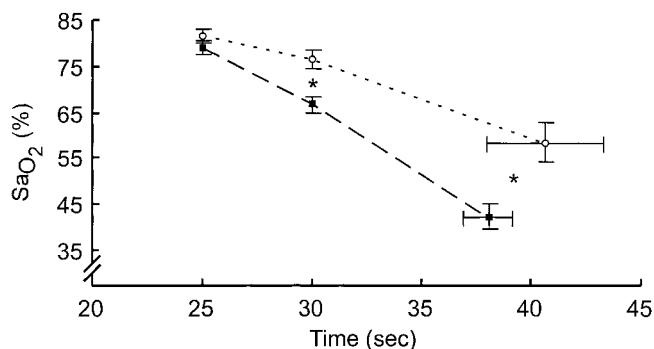

Fig. 5. Mean values ($n = 9$ subjects) of Sa$_{O_2}$ as determined with earlobe pulse oximetry 25 and 30 s after onset and at the interruption of apnea ($\bigcirc$) and rebreathing ($\blacksquare$). Bars indicate SE. Rebreathings were often interrupted by medical supervisor due to low Sa$_{O_2}$. *Significant difference in Sa$_{O_2}$ between conditions, $P < 0.05$.
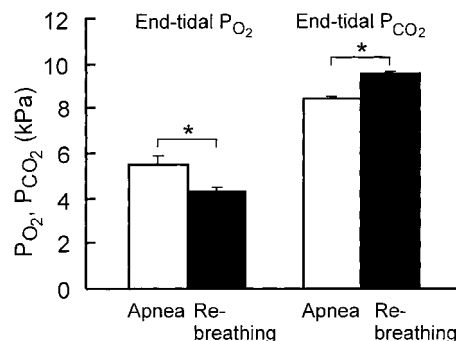

Fig. 6. End-tidal values of P$_{O_2}$ and P$_{CO_2}$ at end of apnea and after an identical time of rebreathing. Values are means $\pm$ SE; $n = 9$ subjects. *Significant difference between conditions, $P < 0.05$.

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 Sa$_{O_2}$ decreased at a slower rate in subjects with pronounced bradycardia and hypertension; i.e. the stronger the diving response, the slower the ΔSa$_{O_2}$/Δt.

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 Sa$_{O_2}$ 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 Sa$_{O_2}$. The absolute magnitude of the O$_2$ conservation in terms of a temporarily reduced $\dot{V}_{O_2}$, 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 in cardiac output amounting to 83% of that of HR. If we adopt these relationships between HR and cardiac output changes to the present data from apnea maneuvers, we can estimate a reduction in 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 apnea, 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, Strømme 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 Sa_{O_2} 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 Sa_{O_2} indicate a slower rate of pulmonary gas exchange in A, and this conclusion is supported by the differences in end-tidal P_{O_2} and P_{CO_2} (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 Sa_{O_2} 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 $\dot{V}_{O_2}$ 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 $\dot{V}_{O_2}$. 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 $\dot{V}_{O_2}$ during 120-W steady-state leg exercise could be estimated to be 1.5–2 l/min. This $\dot{V}_{O_2}$ 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 $\dot{V}_{O_2}$ 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 Sa_{O_2} 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 Sa_{O_2} decline than the subject with the least marked cardiovascular response.

Address for reprint requests and other correspondence: P. Lindholm, Section of Environmental Physiology, Dept. of Physiology and Pharmacology, Karolinska Institutet, SE-171 77 Stockholm, Sweden (E-mail: peter.lindholm@fyfa.ki.se).

REFERENCES

1. **Andersson J., and E. Schagatay.** Arterial oxygen desaturation during apnea in humans. *Undersea Hyper. Med.* 25: 21–25, 1998.
2. **Benoit, H., F. Costes, L. Feasson, J. R., Lacour, F. Roche, C. Denis, A. Geyssant, and J. C. Barthélémy.** Accuracy of pulse oximetry during intense exercise under severe hypoxic conditions. *Eur. J. Appl. Physiol.* 76: 260–263, 1997.
3. **Bjertnaes, L., A. Hauge, J. Kjekshus, and E. Soyland.** Cardiovascular responses to face immersion and apnea during steady-state muscle exercise. A heart catheterization study on humans. *Acta Physiol. Scand.* 120: 605–612, 1984.
4. **Butler, P. J., and D. R. Jones.** Physiology of diving of birds and mammals. *Physiol. Rev.* 77: 837–899, 1997.
5. **Butler, P. J., and A. J. Woakes.** Heart rate in humans during underwater swimming with and without breath-hold. *Respir. Physiol.* 69: 387–399, 1987.
6. **Craig, A. B., Jr., and W. L. Medd.** Man's responses to breath-hold exercise in air and in water. *J. Appl. Physiol.* 24: 773–777, 1968.
7. **Daly, M. DeB., J. E. Angell-James, and R. Elsner.** Role of carotid-body chemoreceptors and their reflex interactions in bradycardia and cardiac arrest. *Lancet* 7: 764–767, 1979.
8. **Dempsey, J. A., L. Adams, D. M. Ainsworth, R. F. Fregosi, C. G. Gallagher, A. Guz, B. D. Johnson, and S. K. Powers.** Airway, lung, and respiratory muscle function during exercise. In: *Handbook of Physiology, Exercise: Regulation and Integration of Multiple Systems.* Bethesda, MD: Am. Physiol. Soc., 1996, sect. 12, chapt. 11, p. 448–514.
9. **Elsner, R., and B. Gooden.** Metabolic conservation by cardiovascular adjustments. In: *Diving and Asphyxia. A Comparative Study of Animals and Man.* New York: Cambridge Univ. Press, 1983, p. 14–29.
10. **Elsner, R., B. Gooden, and S. M. Robinson.** Arterial blood gas changes and the diving response in man. *Aust. J. Exp. Biol. Med. Sci.* 49: 435–444, 1971.
11. **Ferretti, G., M. Costa, M. Ferrigno, B. Grassi, C. Marconi, C. E. G. Lundgren, and P. Cerretelli.** Alveolar gas composition and exchange during deep breath-hold diving and dry breath holds in elite divers. *J. Appl. Physiol.* 70: 794–802, 1991.
12. **Ferrigno, M., G. Ferretti, A. Ellis, D. Warkander, M. Costa, P. Cerretelli, and C. E. G. Lundgren.** Cardiovascular changes during deep breath-hold dives in a pressure chamber. *J. Appl. Physiol.* 83: 1282–1290, 1997.
13. **Gross, P. M., B. J. Whipp, J. T. Davidson, S. N. Koyal, and K. Wasserman.** Role of the carotid bodies in the heart rate response to breath-holding in man. *J. Appl. Physiol.* 41: 336–340, 1976.
14. **Heistad, D. D., F. M. Abboud, and J. W. Eckstein.** Vasoconstrictor response to simulated diving in man. *J. Appl. Physiol.* 25: 542–549, 1968.
15. **Holmer, I.** Oxygen uptake during swimming in man. *J. Appl. Physiol.* 33: 502–509, 1972.
16. **Hong, S. K., Y. C. Lin, D. A. Lally, B. J. B. Yim, N. Kominani, P. W. Hong, and T. O. Moore.** Alveolar gas exchanges and cardiovascular function during breath-holding with air. *J. Appl. Physiol.* 30: 540–547, 1971.
17. **Idema, R. N., A. H. van der Meiracker, B. P. M. Imholz, A. J. Man in't Veld, J. J. Settels, H. J. Ritsema van Eck, and A. D. H. Schalekamp.** Comparison of Finapres non-invasive beat-to-beat finger blood pressure with intrabrachial artery pressure during and after bicycle ergometry. *J. Hypertens.* 7: S58–S59, 1989.
18. **Kurenkov, H. I.** Human work performance in hyperbaric environment. *Försvarsmedicin* (*Swed. J. Defence Med.*) 9: 332–336, 1973.
19. **Lin, Y. C.** Breath-holding in terrestrial mammals. In: *Exercise and Sport Sciences Reviews,* edited by R. L. Terljung. Philadelphia, PA: Franklin, 1982, vol. 10, p. 270–307.
20. **Lin, Y. C., and S. K. Hong.** Hyperbaria: breath-hold diving. In: *Handbook of Physiology, Environmental Physiology.* Bethesda, MD: Am. Physiol. Soc., 1996, sect. 4, vol. II, chapt. 42, p. 979–995.
21. **Lin, Y. C., K. K. Shida, and S. K. Hong.** Effects of hypercapnia, hypoxia, and rebreathing on heart rate response during apnea. *J. Appl. Physiol.* 54: 166–171, 1983.
22. **Lin, Y. C., K. K. Shida, and S. K. Hong.** Effects of hypercapnia, hypoxia, and rebreathing on circulatory response to apnea. *J. Appl. Physiol.* 54: 172–177, 1983.
23. **Manley, L.** Apnoeic heart rate responses in humans. A review. *Sports Med.* 9: 286–310, 1990.
24. **Otis, A. B.** The work of breathing. In: *Handbook of Physiology. Respiration.* Washington, DC: Am. Physiol. Soc., 1964, sect. 3, vol. I, chapt. 17, p. 463–476.
25. **Rowell, L. B., D. S. O'Leary, and D. L. Kellogg, Jr.** Integration of cardiovascular control systems in dynamic exercise. In: *Handbook of Physiology. Exercise: Regulation and Integration of Multiple Systems.* Bethesda, MD: Am. Physiol. Soc., 1996, sect. 12, chapt. 17, p. 770–838.
26. **Schagatay, E., and J. Andersson.** Diving response and apneic time in humans. *Undersea Hyper. Med.* 25: 13–19, 1998.
27. **Scholander, P. F., H. T. Hammel, H. LeMessurier, E. Hemmingsen, and W. Garey.** Circulatory adjustments in pearl divers. *J. Appl. Physiol.* 17: 184–190, 1962.
28. **Somers, V. K., and F. M. Abboud.** Chemoreflex control of cardiac vagal activity. In: *Vagal Control of the Heart: Experimental Basis and Clinical Implications.* edited by M. N. Levy and P. J. Schwartz. New York: Futura, 1994, chapt. 25, p. 403–416.
29. **Strømme, S. B., D. Kerem, and R. Elsner.** Diving bradycardia during rest and exercise and its relation to physical fitness. *J. Appl. Physiol.* 28: 614–621, 1970.
30. **Sundblad, P., and D. Linnarsson.** Influence of apnea on cardiovascular responses to neck suction during exercise. *Am. J. Physiol.* 271 (*Heart Circ. Physiol.* 40): H1370–H1374, 1996.
31. **Verbanck, S., D. Linnarsson, G. K. Prisk, and M. Paiva.** Specific ventilation distribution in microgravity. *J. Appl. Physiol.* 76: 445–454, 1994.
32. **Wolf, S., R. A. Schneider, and M. E. Groover.** Further studies on the circulatory and metabolic alterations of the oxygen-conserving (diving) reflex in man. *Trans. Assoc. Am. Physicians* 78: 242–254, 1965.