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# Role of hypoxemia for the cardiovascular responses to apnea during exercise

PETER LINDHOLM, JESSICA NORDH, AND DAG LINNARSSON

*Section of Environmental Physiology, Department of Physiology and Pharmacology, Karolinska Institutet, SE-171 77 Stockholm, Sweden*

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**Lindholm, Peter, Jessica Nordh, and Dag Linnarsson.** Role of hypoxemia for the cardiovascular responses to apnea during exercise. *Am J Physiol Regul Integr Comp Physiol* 283: R1227–R1235, 2002. First published June 20, 2002; 10.1152/ajpregu.00036.2002.—We sought to define the role of hypoxemia in eliciting the cardiovascular responses to apnea during exercise. Eleven men performed repeated apneas during 100-W steady-state exercise, either with normoxic gas (air) or 95% oxygen (oxygen). Beat-by-beat arterial blood pressure, arterial oxygen saturation, and heart rate (HR) were determined, and stroke volume (SV) was estimated from impedance cardiography calibrated with soluble gas rebreathing. There were large interindividual variabilities of HR, mean arterial pressure (MAP), and total peripheral resistance (TPR) at end-apnea (ea). However, for each individual, HR<sub>ea</sub>, MAP<sub>ea</sub>, and TPR<sub>ea</sub> were highly correlated between air and oxygen ( $R = 0.94, 0.78, \text{ and } 0.93$ ). HR decreased and MAP increased faster during apnea with air than with oxygen (ANOVA,  $P < 0.05$ ), but MAP<sub>ea</sub> was not different between conditions. Cardiac output was reduced by 33% with air and by 11% with oxygen ( $P < 0.001$  for air vs. oxygen). We conclude that the hypoxemia component cannot account for the wide interindividual differences of HR and TPR responses to apnea. However, hypoxemia augments the HR and TPR responses and may limit the MAP response to apnea by preventing a bradycardia-associated increase of SV.

hypertension; bradycardia; oxygen; diving response; hypoxia

APNEA OCCURS FREQUENTLY IN humans who suffer from obstructive sleep apnea and among divers. Similar to diving animals, humans react with bradycardia and vasoconstriction during apnea (4, 18, 24). Several factors induce or modify these cardiovascular responses, such as arterial hypoxia sensed by chemoreceptors, the accompanying hypercapnia, cessation of respiratory movements, and face immersion. The present study focuses on voluntary apnea without face immersion.

The role of hypoxemia has been investigated with varying results by others: Gross et al. (8) showed in resting humans that the carotid chemoreceptors were essential for the bradycardic component of the response to apnea, so that subjects who had undergone bilateral carotid body resection instead had tachycardia during apnea. The hypertensive response to apnea,

however, appeared not to be critically dependent on the intact carotid bodies, because it was similar to control. In contrast, Chen et al. (5), studying anesthetized pigs, found very little if any difference between the heart rate (HR) responses when apnea was induced with and without oxygen, but that arterial hypoxemia was essential to elicit the marked increase of systemic vascular resistance that they found during apnea with air. These results obtained in resting humans and animals are not necessarily relevant for the understanding of the physiology of the underwater swimmer, who is physically active and therefore has increased oxygen requirement and carbon dioxide production, HR, cardiac output (CO), and systemic vascular conductance. Both the increased rate of O<sub>2</sub> consumption and the enhanced CO will tend to speed up the rate at which arterial hypoxemia develops during apnea. Thus, it is possible that hypoxemia will have a much larger relative importance for the cardiovascular responses during exercise conditions than at rest. To our knowledge, only one study has previously addressed the question of the effects of oxygen and hypoxemia on apnea in exercising humans (19) and it employed only a modest work intensity and restricted the cardiovascular measurements to that of HR.

In the present study, we investigated humans performing moderately heavy exercise at a metabolic rate that should equal that of normal swimming (9). We reasoned that to properly define the role of hypoxemia for cardiovascular responses to apnea, it would be necessary to approach the same levels of arterial desaturation as are likely to occur during actual breath-hold diving activities. We hypothesized that other factors than hypoxemia and probably the respiratory arrest per se would be the principal cause of bradycardia and hypertension during apnea. Furthermore, we wanted to take advantage of the wide interindividual variability of the strength of the cardiovascular responses to apnea that is known to exist (17, 18). Thus, we wanted to correlate the strength of the cardiovascular responses to apnea obtained with and without hypoxemia. We reasoned that if these responses were not correlated, then the individual sensitivity to hypox-

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).

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emia would be a unique and independent factor behind the cardiovascular responses to apnea. On the other hand, if there was a significant correlation between responses with and without hypoxemia, then hypoxemia could be considered merely a modifying factor superimposed on a more basic response to apnea as originally suggested by Song et al. (26) based on studies of resting humans. A second objective of this study was to investigate the effect of hypoxemia on CO. We hypothesized that hypoxemia might influence cardiac performance, so that CO might become even more reduced than HR during the apnea-induced bradycardia, or at least that stroke volume (SV) would not be increased as result of the prolonged diastolic intervals in the same period.

## MATERIALS AND METHODS

**Subjects.** Eleven healthy male volunteers were studied; another two subjects that volunteered were excluded due to their inability to hold their breath for 30 s during exercise. Age, weight, and height ranged 18–32 yr, 68–96 kg, and 176–194 cm. Subjects were nonsmokers. The protocol was approved by the Ethics Committee at Karolinska Institutet.

**Protocol.** During a separate session, subjects were familiarized with the experiment, and their maximal O<sub>2</sub> uptake was determined with an incremental cycle ergometer test.

During the subsequent session with apneas, subjects performed sitting upright dynamic leg exercise on an electrically braked cycle ergometer (Type 380 B, Siemens-Elema AB, Stockholm, Sweden) at 100 W for ~60 min. During this steady-state exercise period, subjects held their breath repeatedly at a standardized lung volume with their glottis closed; before apneas, subjects exhaled to residual volume (RV) and then inspired 60% of their vital capacity (VC) from a bag that had been prefilled with either a normoxic gas with 1.6% CHClF<sub>2</sub> (Freon 22, R22) and 5% helium in nitrogen or 95% oxygen with 5% helium. For simplicity, these two gas mixtures will be referred to below as air and oxygen, respectively. Apneas were interrupted by the medical supervisor if oxygen saturation fell below 50% or at the will of the subject. Shortly after the onset of exercise, subjects performed two test trials with short (10 s) apneas and then performed alternating apneas with air and oxygen, three of each. In a pilot study, we determined that subjects could always detect whether air or oxygen was used, so randomization would not be meaningful. Subjects also performed two 15-s rebreathing maneuvers for determination of CO from R22 uptake (3), one after the second apnea and the other after the fourth apnea using the air mixture. There was at least 5 min of eupnea between all apnea 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 (32). Briefly, the system allowed continuous measurements of respired gas flow and concentrations and rebreathing with preset bag volumes. Gas analysis was performed with a quadrupole mass spectrometer (QMG 420, Balzer, Lichtenstein) modified for respiratory measurements (Innovision AS, Odense, Denmark). The gas analyzer was calibrated against mixtures of known concentrations (AGA Gas AB, Lidingö, Sweden). VC was determined for each subject when sitting on the cycle ergometer. The largest value of three trials was adopted.

An 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). Earlobe arterial oxygen saturation (SaO<sub>2</sub>) 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 (1).

Blood pressure was measured with a photoplethysmographic finger-cuff method (Finapres 2300, Ohmeda, Englewood, CO).

Transthoracic impedance was recorded from two pairs of tape electrodes around the neck and lower thorax (29).

**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 and recorded at 200 Hz per channel and subsequently stored and analyzed with an Acq-Knowledge 3.2.6 software package (Biopac Systems).

During resting apnea, HR values were obtained as an average during the 10 s with the lowest HR. During exercise, baseline data were obtained as time averages for 30-s periods 15–45 s before apneas started. HR and mean arterial pressure (MAP) during apneas were determined from beat-by-beat curves as time averages during 5-s intervals. SV was calculated from 10 beats during baseline before apnea and during the last 10 beats of each apnea. SV was determined with a modification of the impedance method originally described by Kubicek et al. (11). Thus, SV estimates were obtained from the maximal first derivative of the impedance signal together with ejection time, which was assessed from the contour of the second derivative of the blood pressure curve (25). The impedance estimates of SV were calibrated during steady-state exercise using simultaneous rebreathing measurements of CO and impedance cardiography. The calibration factor obtained in this way for each individual was then used to calculate SV during apnea. CO was obtained as SV × HR and total peripheral resistance (TPR) as MAP/CO. Below, variables from the 10 last heart beats of apnea during exercise will be indexed with <sub>ea</sub> for end-apnea, e.g., HR<sub>ea</sub>. Also, the terms apnea and end-apnea will refer to exercise conditions when not stated otherwise.

**Statistics.** Differences between conditions were analyzed using a paired Student's *t*-test for dependent variables. Also, multiple regression analysis and ANOVA were used (Statistica, Statsoft, Tulsa, OK). Significance was accepted at the 5% level.

## RESULTS

Mean apnea time was 40 s (range 27–67 s) for apneas with air and 69 s (range 35–136 s) for oxygen. Subjects did three apneas with air and three with oxygen in an alternating order starting with air. All subjects completed at least two apneas with air of 30 s or more. During apneas with air, subjects became hypoxemic; SaO<sub>2</sub> fell by 20–50%, and after the apneas were terminated, SaO<sub>2</sub> continued to fall for ~5 s before returning within a few seconds to 98–100%. During all apneas with oxygen, SaO<sub>2</sub> remained at 98–100%. VCs ranged from 5.7 to 8.8 l BTPS.

Figure 1 shows original recordings from two subjects, who started their apneas with comparable lung volumes but had markedly different HR responses. Note the similarity of MAP responses between subjects and differences in HR and SaO<sub>2</sub>. *Subject A* held his breath for 51 s with air and *subject B* for 44 s. Apneas

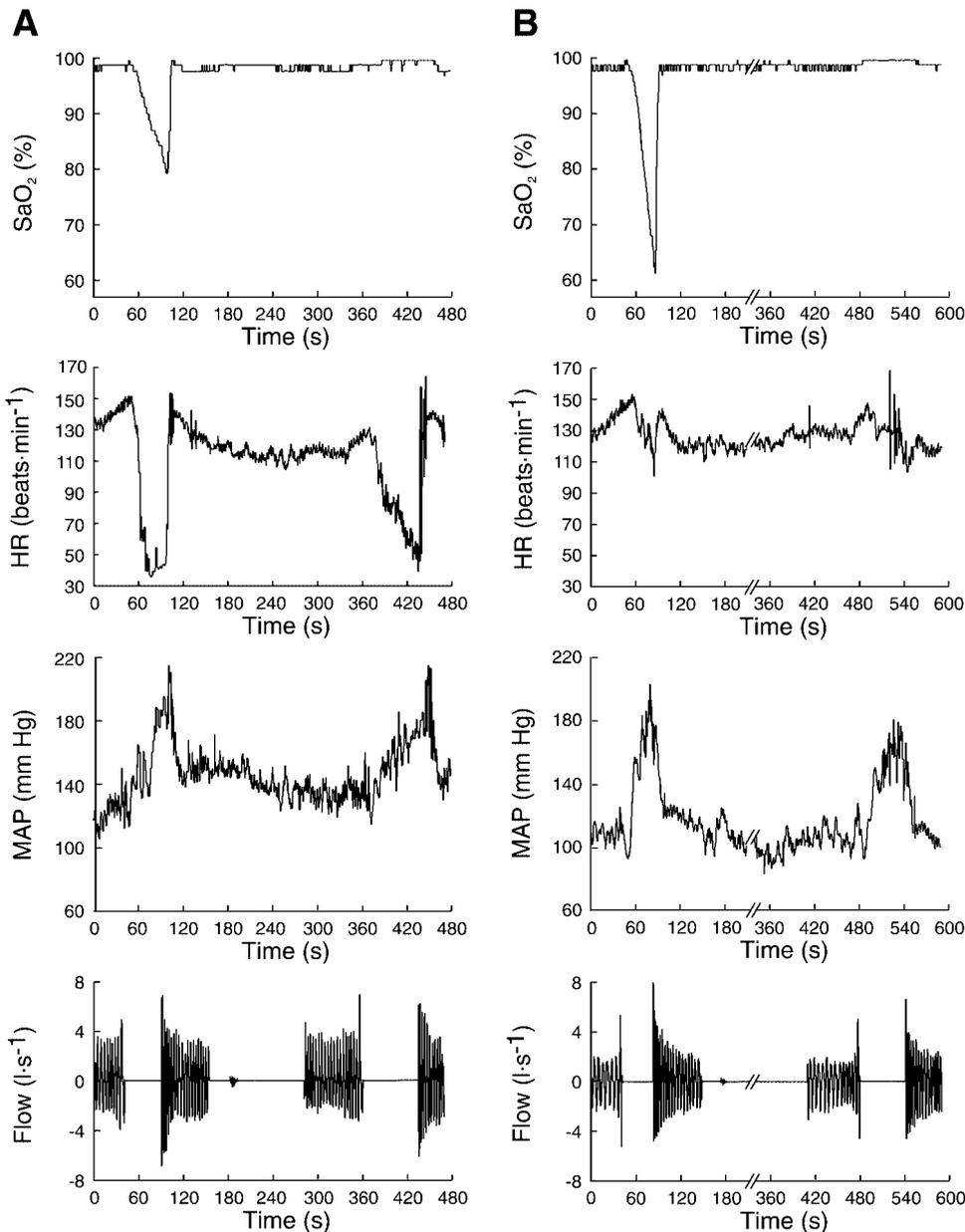


Fig. 1. Original recordings from 2 subjects, showing earlobe arterial oxygen saturation ( $\text{SaO}_2$ ), heart rate (HR), mean arterial pressure (MAP), and respiratory flow rate as functions of time. Recordings show apneas with air (first apnea) and oxygen (second apnea) in both subjects. Inspired lung volumes before apnea in these subjects were 3.5 liters for A and 3.4 liters for B. Note the difference between HR responses of the 2 individuals. Respiratory flow data are missing between maneuvers because subjects temporarily remove the mouthpiece.

with oxygen were 76 s (Fig. 1A) and 63 s (Fig. 1B), respectively.

Figure 2 shows group mean time courses of HR and MAP vs. time during apnea with air and oxygen (mean  $\pm$  SD). The figure demonstrates that cardiovascular responses to apnea develop faster during hypoxia (air) (ANOVA,  $P < 0.05$ ,  $n = 11$ , 0–30 s). Also, note the large SD, reflecting large individual differences of HR and MAP responses.

Group mean responses at end-apnea are shown in Fig. 3.  $\text{MAP}_{\text{ea}}$  was not different between the two conditions, whereas  $\text{SV}_{\text{ea}}$  remained at preapnea control level with air but increased significantly by  $14 \pm 14\%$  during apnea with oxygen.  $\text{HR}_{\text{ea}}$  and  $\text{CO}_{\text{ea}}$  were also higher during apneas with oxygen than with air. HR and TPR responses to apnea during exercise varied widely among the subjects: the coefficient of variations

for the differences from preapnea was 64% for  $\text{TPR}_{\text{ea}}$ , 74% for  $\text{HR}_{\text{ea}}$ , and 15% for  $\text{MAP}_{\text{ea}}$  during apnea with air. The corresponding values with oxygen were 56, 81, and 24%.

Maximum  $\text{O}_2$  uptake ( $\dot{V}\text{O}_{2\text{max}}$ ) ranged from 3.34 to 6.10 l/min STPD, and relative work intensity at 100 W ranged from 45 to 25% of  $\dot{V}\text{O}_{2\text{max}}$ .

To further analyze individual differences in responses to apnea, we performed multiple correlations (Figs. 4 and 5 and Table 1). Subjects that reacted to apnea with a marked bradycardia did so under both conditions. Thus,  $\text{HR}_{\text{ea}}$  values with oxygen were well correlated with corresponding values with air. Also, for  $\text{MAP}_{\text{ea}}$  and  $\text{TPR}_{\text{ea}}$ , there were significant correlations between values obtained with air and oxygen. Subjects with the lowest HR during apnea with air had the highest value of  $\text{TPR}_{\text{ea}}$  (Fig. 5). The correlation be-

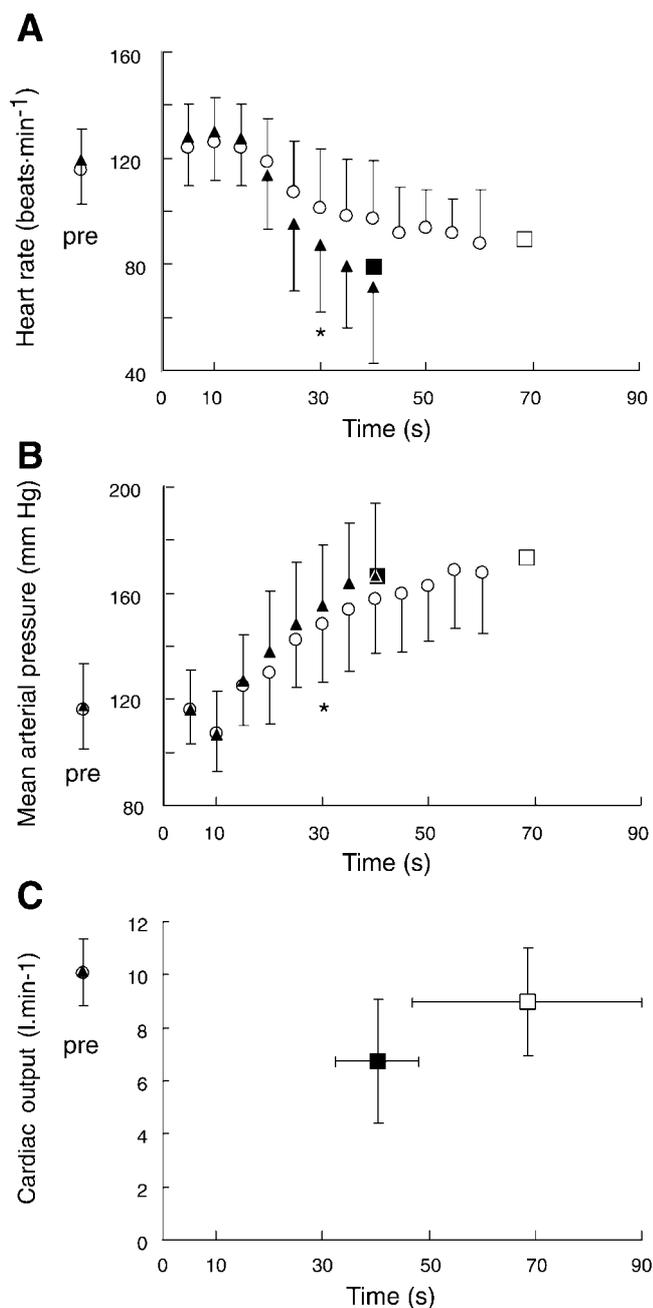


Fig. 2. Group mean time courses of HR (A) and MAP (B) in exercising men during apnea with air (▲) or oxygen (○); vertical bars are  $\pm 1$  SD. The points to the left of the ordinate (pre) show baseline average 15–45 s before apneas;  $n = 11$  until and including 30 s for both conditions, thereafter  $n$  gradually decreases to 6 with air at 40 s and 9 with oxygen at 60 s. Both HR (A) and MAP (B) changed faster with air than with oxygen (ANOVA,  $*P < 0.05$ ,  $n = 11$  at 30 s). Also shown are group means ( $n = 11$ ) for end-apnea. C: cardiac output at end-apnea for all subjects. Corresponding group mean values for HR and MAP are also shown with large square symbols. For clarity, the SEs of group means at end-apnea are only shown in C; see Fig 3 for SEs of HR and MAP at end-apnea.

tween  $\text{TPR}_{\text{ea}}$  and  $\text{HR}_{\text{ea}}$  was not significant during apnea with oxygen. The hypertensive response during apnea as determined by  $\text{MAP}_{\text{ea}}$  was not statistically correlated to  $\text{HR}_{\text{ea}}$  (Table 1), nor were changes in MAP significantly correlated to changes in HR during apnea.

There were no significant correlations between  $\dot{V}\text{O}_{2\text{max}}$  or relative work intensity on one hand and any of the cardiovascular response parameters during apnea on the other.

Group mean  $\text{PCO}_2$  at the end of the longest apnea for each subject was 7.8 kPa (range 6.7–8.8 kPa) for apneas with air and 9.4 kPa (range 7.5–11.9 kPa) for oxygen ( $P = 0.0004$ ). In the air experiments, there was no correlation between  $\Delta\text{PCO}_2$  (end-tidal  $\text{PCO}_2$  after apnea – end-tidal  $\text{PCO}_2$  before apnea) and apnea duration, but with oxygen, end-apneic  $\Delta\text{PCO}_2$  was significantly correlated to apnea duration (Fig. 6). For both air and oxygen, we found no correlations between end-tidal  $\text{PCO}_2$  after apnea and  $\text{HR}_{\text{ea}}$  and no correlation between apnea time and  $\text{HR}_{\text{ea}}$ .

## DISCUSSION

*Hypoxemia and cardiovascular responses to apnea.* Figure 2 clearly demonstrates that both with and without a progressive hypoxemia there was a gradual fall of HR and a gradual rise of MAP during apnea in exercising men. Furthermore, cardiovascular responses to apnea developed faster during hypoxic apnea than during hyperoxic apnea, and as apnea was continued for a longer period with hyperoxia, blood pressure continued to rise and HR continued to drop. Overall, therefore, our data obtained in exercising men demonstrate that there are at least two components of both the bradycardic and hypertensive responses to apnea. In the case of MAP, there is one major nonhypoxic component and one quantitatively smaller component that is associated with gradually developing hypoxemia. For HR, the two components appear to be of similar magnitudes. These findings could be interpreted against the background of a previous study comparing responses for similar degrees of hypoxemia in both apnea and rebreathing in exercising men (17): they found a marked bradycardia with apnea but not when the same progressive hypoxemia was induced by rebreathing and concluded that respiratory arrest rather than the accompanying hypoxemia was essential for the bradycardic responses to apnea. Taken together, the present data and those of Lindholm et al. (17) support the notion that there are specific bradycardic and hypertensive responses to hypoxemia, but these will only be apparent if associated with respiratory arrest.

These conclusions contrast somewhat to the results of Van den Aardweg and Karemaker (31), who showed that during resting apnea, there was no hypertension without hypoxemia. One tentative explanation for the difference between the present findings and those of Van den Aardweg and Karemaker (31) could be that they studied apneas of 20-s duration, and because the hypertensive and bradycardic responses develop gradually, their observation time may have been too brief to reveal responses in the absence of hypoxemia, when these responses develop at a slower rate.

There is much evidence that hypoxic components of the cardiovascular responses to apnea are mediated

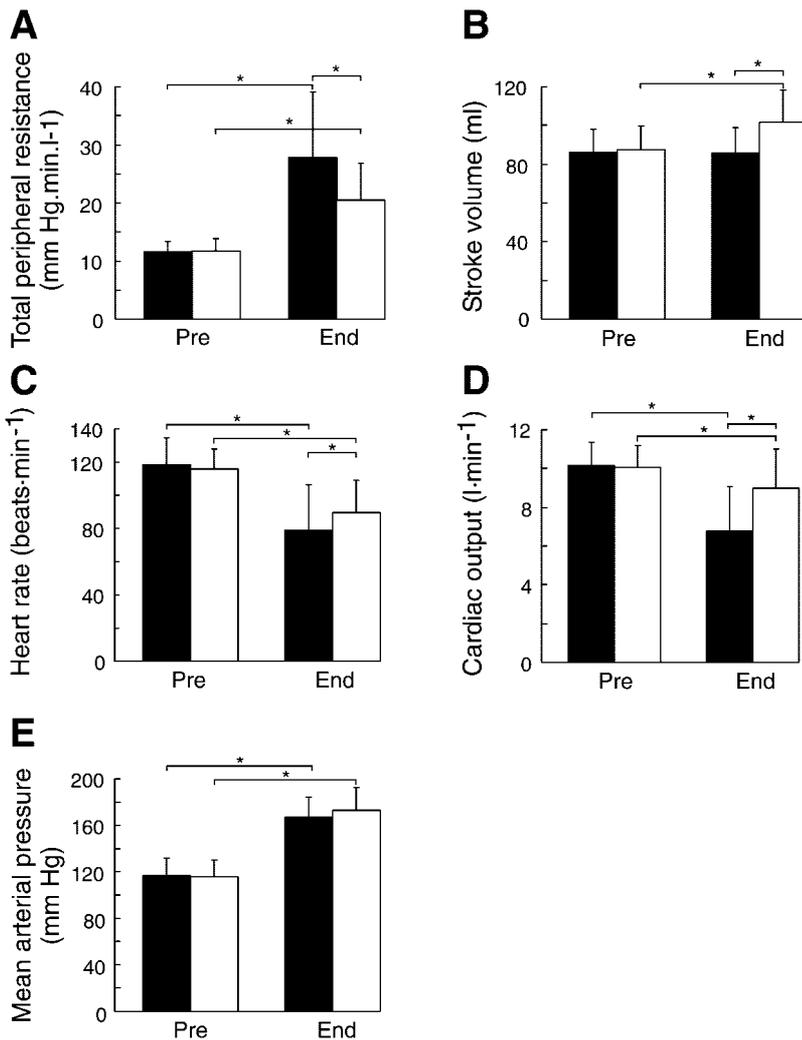


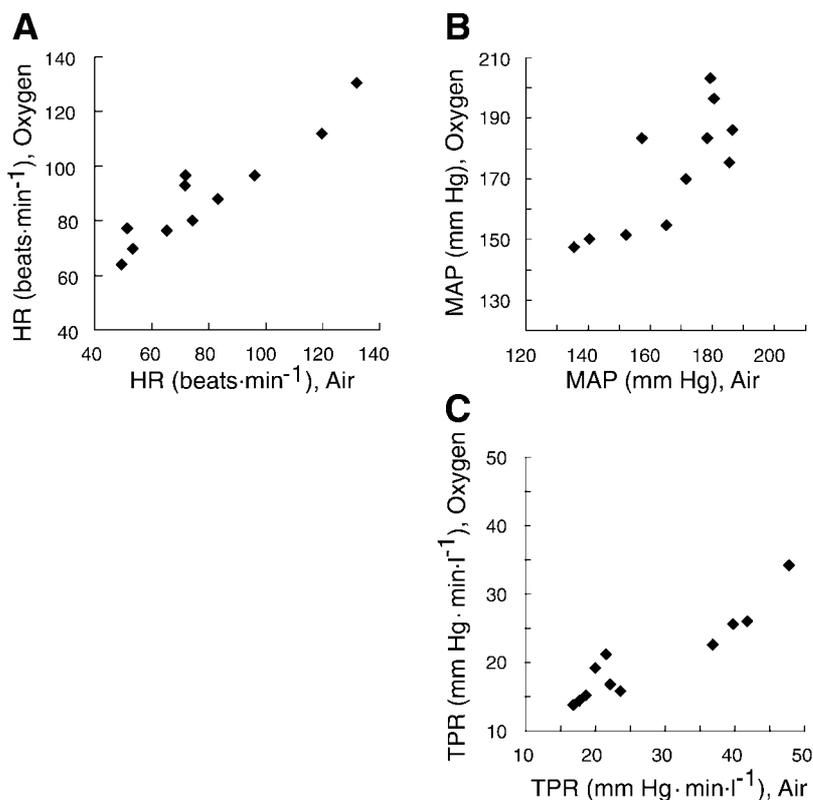
Fig. 3. Group mean hemodynamic data 15–45 s before apnea and during the last 10 heart beats of apnea in 11 exercising subjects. Filled bars represent apnea with air, and open bars represent apnea with oxygen. Horizontal bars with \* indicate significant differences between conditions ( $P < 0.05$ ).

by arterial chemoreceptors (8, 22). However, indirect cardiovascular effects of oxygenation must also be considered. Thus, hypercapnia has been shown to attenuate the bradycardic response to apnea (15), and if the degree of hypercapnia was more severe with hyperoxic apnea, that might have contributed to the higher HR values for a given apnea duration. At a given  $\text{CO}_2$  content, oxygenated blood will have a higher  $\text{PCO}_2$  than deoxygenated blood due to the Haldane effect (10). Consequently, the higher end-apneic  $\text{PCO}_2$  with oxygen may not only be a product of the 70% longer apnea duration, but arterial  $\text{PCO}_2$  might also have been higher with oxygen for a given apnea duration. In the present study, it was not possible to determine end-tidal  $\text{PCO}_2$  as a function of apnea duration within one subject. However, on a group basis, this relationship could be studied as shown in Fig. 6. These data suggest that there is no time-dependent increase of  $\text{PCO}_2$  during apnea with air but that there was such an increase during apnea with oxygen. However, the range of apnea times differs greatly between the two conditions with a much smaller range with air, so the lack of time-dependent trend with air cannot be considered as conclusive. More conclusive evidence for a lack of time-

dependent increase of  $\text{PCO}_2$  during apnea with air can be found in a recent study by Lindholm and Linnarsson (16). These authors studied apneas with air of 15-, 24-, 34-, and 44-s durations in exercising men, and from 24 s and onwards, there was no increase in postapneic end-tidal  $\text{PCO}_2$ . Taken together, data from the present study and those of Lindholm and Linnarsson (16) indicate that there is a time-dependent gradual increase of  $\text{PCO}_2$  during apnea when arterial oxygen saturation is maintained because the subject inhaled oxygen before the apnea but not when there is a gradually developing hypoxemia during apnea after inhaling air. We cannot therefore exclude that part of the presently observed attenuation of apnea-induced bradycardia and hypertension with oxygen was an indirect effect of oxygen mediated through interaction with  $\text{CO}_2$  transport in the blood and a resulting elevation of arterial  $\text{PCO}_2$ .

In an attempt to further analyze the role of hypoxemia for the cardiovascular responses to apnea, we studied the interindividual variation of responses and how these correlated between experimental conditions. The interindividual variation of the bradycardic responses was fairly large with coefficients of variation of

Fig. 4. Correlations of HR, MAP, and total peripheral resistance (TPR) at end-apnea with oxygen vs. corresponding data obtained with air. Data from 11 subjects; each data point represents the average of 2–3 repetitions in each subject and condition. There were significant correlations between data obtained with air and oxygen for all 3 variables, see Table 1. See also Fig. 1 for explanation of symbols.



74 and 81% for air and oxygen. At the same time, there was a significant correlation between individual responses in the two conditions (Table 1, Fig. 4). Similar variabilities and correlations were found for TPR and MAP (Table 1, Fig. 4). Thus, subjects with the largest bradycardic, vasoconstrictive, and hypertensive responses with air also had the largest responses with oxygen. There was also a significant negative correlation between  $HR_{ea}$  and  $TPR_{ea}$  during apnea with air, showing that individuals with the largest chronotropic response also had the largest vasoconstrictive response. There was a similar nonsignificant trend at the end of apnea after oxygen inhalation. These findings

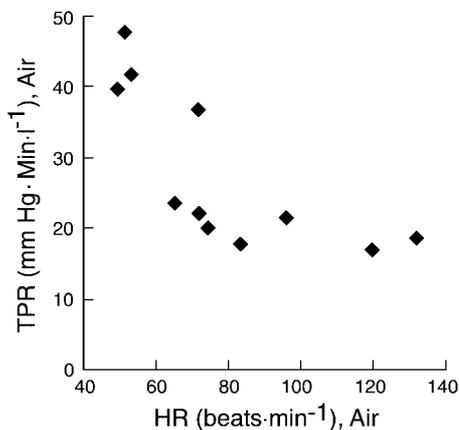


Fig. 5. Correlation of TPR (ordinate) vs. HR (abscissa) at end-apnea with air. There was a significant correlation between TPR and HR, see Table 1. See also Fig. 4 for explanations.

support the notion that the strength of the cardiovascular response to apnea in a given individual is determined primarily by other mechanisms than the individual sensitivity to hypoxemia. Furthermore, the individual response pattern appears to be determined at the level of central cardiovascular control rather than at effector organ level, because it includes both cardiac-chronotropic and vasoconstrictive responses.

It should be considered to what extent arterial baroreflexes play a role in the combined bradycardia and hypertension during apnea. If so, one would expect a significant negative correlation between MAP and HR so that subjects with the largest hypertensive response would also have the largest degree of bradycardia. This was, however, not the case (Table 1). The lack of correlation between MAP and HR responses is also illustrated in Fig. 1, showing two individuals with similar hypertensive responses but with markedly different bradycardic responses. Further evidence against a baroreflex origin of the bradycardic response to apnea is to be found in the study of Lindholm et al. (17) where apnea was compared with rebreathing. Despite a significant hypertensive response to rebreathing, albeit less than during apnea, there was no bradycardic response. In addition, Sundblad and Linnarsson (28) studied combined effects of apnea and baroreceptor stimulation by means of neck suction in exercising subjects and concluded that there was an apnea-specific bradycardia far in excess of what could be accounted for by the hypertensive baroreceptor stimulus.

A study performed by Finley et al. (6) lends further support to the notion that the bradycardic response to

Table 1. Linear correlation matrix for cardiovascular variables determined at end-apnea in 11 exercising subjects who inhaled either air or oxygen before apnea

	MAP Air	TPR Air	HR Oxygen	MAP Oxygen	TPR Oxygen
HR Air	NS	$R = 0.74$ $P = 0.009$	$R = 0.94$ $P = 0.00002$	NS	$R = 0.67$ $P = 0.02$
MAP Air	—	—	NS	$R = 0.78$ $P = 0.004$	—
TPR Air	—	—	$R = 0.62$ $P = 0.04$	—	$R = 0.93$ $P = 0.00003$
HR Oxygen	—	—	—	NS	NS ( $P = 0.06$ )

HR, heart rate; MAP, mean arterial pressure; TPR, total peripheral resistance; NS, not significant; —, variables not independent.

apnea is “preprogrammed” rather than baroreflex induced. These authors studied subjects performing short-lasting apnea and face immersion during exercise at an intensity similar to that in the present study and with various types of autonomic blockade. During parasympathetic blockade with atropine, the bradycardic response was abolished, confirming the previously established notion that an increase of vagal outflow is the final common pathway for the bradycardia during apnea. This does not in itself distinguish between a primary or a secondary baroreflex origin of the bradycardia, but Finley et al. (6) also studied the effects of  $\beta$ -blockade in these subjects. During  $\beta$ -blockade, the hypertensive response was abolished but the bradycardia was the same as during control. With reservations for the limited subject population of their study, and for the differing apnea procedure compared with the present study, their results suggest that hypertension is not a necessary prerequisite for the apnea-associated bradycardia, which is therefore primarily not of baroreflex origin.

**CO.** CO is determined by a number of influences during apnea. Clearly, the hypertensive response during apnea leads to an increased afterload that will tend to reduce CO. The increase of TPR during apnea will also decrease the rate at which the dependent deep

muscle veins fill between muscle contractions (21). Thus, the apnea-associated increase of TPR will tend to decrease the efficiency of the muscle pump, and the associated reduction of venous return will also act to reduce CO. At the same time, the associated bradycardia will prolong the time for diastolic filling and thereby promote increased SVs. The net effect on CO and SV of combined increases of sympathetic and vagal outflow to the heart (6) is difficult to predict, because of the multiple levels of sympathovagal interaction (13).

Subjects held their breath against a closed glottis, and the diaphragmatic contractions during the late phase of the apnea were likely to have caused large intrathoracic pressure swings with a mean pressure below zero as shown by Lin et al. (14). The possibility should be considered whether these repeated waves of negative intrathoracic pressure contributed to the hypertensive response by augmenting venous return to the right heart and thereby SV. A closer inspection of the time course of the hypertensive response (Fig. 1), however, reveals that it peaks after the apnea period and when normal breathing is resumed, speaking against involuntary diaphragmatic movements during end-apnea as a factor behind the hypertension. Further evidence against this possibility has been shown in resting humans by Leuenberger et al. (12), who showed that the leg peripheral resistance reached its peak and leg blood flow its nadir during the first 5 s of resumed breathing after apnea.

In the present experiments with oxygen,  $CO_{ea}$  was reduced by 11% and  $SV_{ea}$  was increased by 14% compared with preapnea. This shows that the positive effects of prolonged diastolic filling and possibly also sympathetically induced increase of contractility (6) outbalance the effects of the increased TPR when there is no hypoxemia. With air, however, the associated hypoxemia appears to result in an unchanged  $SV_{ea}$  compared with preapnea control. The mechanism behind this difference between SV responses to apnea with and without hypoxemia is not evident. It cannot be the time for diastolic filling because that would work in the opposite direction. A more likely explanation may be temporary myocardial hypoxemia toward the end of apnea with air. A second and possibly coexisting mechanism might be pulmonary hypoxic vasoconstriction, which can have a fairly rapid onset (2, 23) and which might have prevented potential apnea-induced

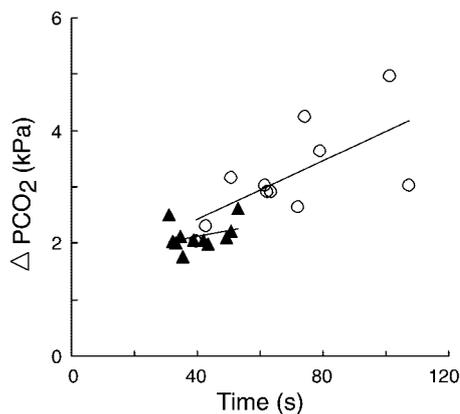


Fig. 6. Change in end-tidal  $PCO_2$  between preapnea and the first expiration to residual volume after apnea ( $\Delta PCO_2$ ), as a function of apnea duration in 11 exercising men.  $\blacktriangle$  Symbols are air, and  $\circ$  symbols are oxygen. Each data point represents the average of 2–3 repetitions in each condition. Only with oxygen was there a positive correlation between  $\Delta PCO_2$  and apnea duration in the oxygen condition ( $R = 0.67$ ,  $P = 0.02$ ).

increase of SV by increasing right ventricular afterload and reducing left ventricular preload. A third possibility is that the increased end-apneic  $\text{PCO}_2$  with oxygen might have given rise to an increased sympathetic outflow to the heart and an associated augmented contractility (6). Chen et al. (5) performed invasive determinations of CO and SV in resting pigs during apneas of 30-s duration with and without hypoxemia but with similar degrees of hypercapnia. With air, both CO and SV at end-apnea were decreased by ~25% compared with apnea with oxygen. The data of Chen et al. (5) support the notion that the higher SV during apnea with oxygen in the present study was also caused by normalization of hypoxemia, with the caveat that, as described above, both species and important aspects of the experimental conditions were different.

As a consequence of the unchanged SV during apnea with air, compared with preapnea control, the apnea-induced changes of CO during exercise and air breathing can be estimated fairly well from concomitant changes of HR.

*Limitations of the study.* An important limitation of this and all other human studies of non-steady-state hemodynamics is the absence of a direct method for beat-by-beat determination of SV and the associated values for CO and TPR. When right heart catheterization is feasible, thermodilution would come closest to the ideal in terms of time resolution, and among the noninvasive methods, soluble gas rebreathing is the most well-documented alternative (30) but requires steady state for the duration of a circulation time through the systemic circulation. For the purpose of the present study, right heart catheterization was not feasible, and rebreathing could not be employed because it has been shown to eliminate the bradycardic response to apnea (17). The present compromise was to employ impedance cardiography as an index of SV but with preceding individual calibration during eupnea. Fuller (7) in a meta-analysis of impedance cardiography concluded that there was a moderately good correlation with other techniques in healthy subjects, with  $r$  values ranging from 0.80 to 0.83 when thermodilution, dye dilution, and direct Fick techniques were used as references. Important factors causing variability of impedance cardiography estimates when using standard algorithms are interindividual differences in thoracic shape and interexperiment variability of electrode placement (20). We attempted to circumvent these problems by comparing data from air and oxygen within one specific experimental session and by calibrating the impedance estimates with rebreathing within the same session, thereby avoiding standard algorithms and the associated assumptions of, for example, a standard thoracic geometry and a standard blood conductivity. Our findings during apnea with air are similar to those obtained by Bjertnaes et al. (2) in two subjects using thermodilution. Moreover, the air-oxygen CO differences obtained at end-apnea in the present study agree well with corresponding animal data obtained by Chen et al. (5). In conclusion, we feel confident that our noninvasive estimates of SV are at

least sufficiently accurate to detect relative differences between the various conditions in the present study.

The relative work intensity during the apneas differed between subjects, which potentially may have increased the interindividual variability of responses. However, Strömme et al. (27) and the present study found no correlation between cardiovascular response parameters to apnea and relative work intensity. Instead, by choosing constant submaximal work load and breath-hold volume above RV, we standardized the ratios between  $\text{O}_2$  need and pulmonary  $\text{O}_2$  stores and thereby the rate of development of hypoxemia as far as possible.

This and earlier studies of apnea during dynamic leg exercise (16, 17) showed that it takes ~20 s of apnea before significant cardiovascular responses can be observed. By definition, then, such responses can only be observed in volunteers that can tolerate apnea during exercise for longer than that, in our case 30 s. We cannot be sure, therefore, that the presently observed cardiovascular responses are typical of a larger population. However, the great variability of responses, e.g., bradycardic responses ranging from almost none to profound, speak against the notion that our subject selection criteria biased the outcome of the study.

### Perspectives

When the data of the present study are put together with previous studies of apnea in exercising men (2, 16, 17), the following overall picture emerges. First, the cardiovascular responses to apnea in exercising humans clearly delay the development of hypoxemia (17) by reducing the rate of uptake from the main oxygen store, i.e., the lungs (16). Second, the respiratory arrest per se is instrumental in eliciting the cardiovascular responses; neither the associated hypercapnia nor hypoxemia elicits bradycardia when occurring without respiratory arrest (17). Third, hypoxemia when occurring with respiratory arrest appears to provide an additional stimulus for bradycardia and to some extent hypertension. Fourth, the hypoxemia influences the heart directly or indirectly so that there is no increase in SV despite a marked bradycardia-related increase of diastolic filling time. Finally, the cardiovascular responses to apnea and the associated protective effect against hypoxemia are highly variable among individuals, rendering some individuals more fit for breath-hold diving than others.

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