Increased pulmonary vascular resistance and reduced stroke volume in association with CO₂ retention and inferior vena cava dilatation

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Baković, Darija, Davor Eterović, Zoran Valić, Žana Saratlija-Novaković, Ivan Palada, Ante Obad, and Željko Dujić. Increased pulmonary vascular resistance and reduced stroke volume in association with CO₂ retention and inferior vena cava dilatation. J Appl Physiol 101: 866–872, 2006. First published May 25, 2006; doi:10.1152/japplphysiol.00759.2005.—Changes in cardiovascular parameters elicited during a maximal breath hold are well described. However, the impact of consecutive maximal breath holds on central hemodynamics in the postapneic period is unknown. Eight trained apnea divers and eight control subjects performed five successive maximal apneas, separated by a 2-min resting interval, with face immersion in cold water. Ultrasound examinations of inferior vena cava (IVC) and the heart were carried out at times 0, 10, 20, 40, and 60 min after the last apnea. The arterial oxygen saturation level and blood pressure, heart rate, and transcutaneous partial pressures of CO₂ and O₂ were monitored continuously. At 20 min after breath holds, IVC diameter increased (27.6 and 16.8% for apnea divers and controls, respectively). Subsequently, pulmonary vascular resistance increased and cardiac output decreased both in apnea divers (62.8 and 21.4%, respectively) and the control group (74.6 and 17.8%, respectively). Pulmonary vascular resistance increased (27.6 and 16.8% for apnea divers and controls, respectively). Subsequently, pulmonary vascular resistance increased and cardiac output decreased both in apnea divers (62.8 and 21.4%, respectively) and the control group (74.6 and 17.8%, respectively). Cardiac output decrements were due to reductions in stroke volumes in the presence of reduced end-diastolic ventricular volumes. Transcutaneous partial pressure of CO₂ increased in all participants during breath holding, returned to baseline between apneas, but remained slightly elevated during the postive observation period (~4.5%). Thus increased right ventricular afterload and decreased cardiac output were associated with CO₂ retention and signs of peripheralization of blood volume. These results indicate that repeated apneas may cause prolonged hemodynamic changes after resumption of normal breathing, which may suggest what happens in sleep apnea syndrome.

Breath-hold diving response; ultrasound scanning; Doppler; arterial pressure; human

Breath-hold diving in humans is associated with a diving reflex characterized by bradycardia, peripheral vasoconstriction, increased arterial blood pressure, and decreased cardiac output (CO) (16). These physiological responses are caused by simultaneous activation of the sympathetic and parasympathetic nervous systems (9, 11), achieving temporary reduction of O₂ uptake from air trapped in the lungs, which increases dive duration (8). Although these intra-apneic effects are well documented, the impact of consecutive breath holds on central hemodynamics in the postapneic period is unknown. Yet, these effects may be substantial and last over an hour after the last apnea, as indicated by our laboratory’s earlier studies on peripheral hemodynamics, spleen size (1), and plasma volume (2), using the model of cold water-face immersion apneas. The sustained effects of repetitive episodes of hypoxia and hypercapnia on central hemodynamics may partly be due to substantial slowing of tissue O₂ and CO₂ store dynamics after breath-hold diving (17, 20). On the other hand, consecutive breath holds may serve as a human model of sleep apnea caused by either intermittent obstruction of upper airways (OSA) or reduced drive to breathe. Although intermittent hypoxia training improves exercise performance in athletes, the chronic cyclic episodes of hypoxia and hypercapnia in OSA are associated with the number of adverse changes, including increased systemic and pulmonary vascular resistance (PVR), right ventricular hypertrophy, and cardiac arrhythmias (19). In animal models, hypercapnia has been shown to produce negative inotropic and chronotropic effects and to dilate peripheral arterioles (5, 21), whereas in humans Kiely et al. (15) provided echocardiographic evidences that hypercapnia increases the PVR and pulmonary pressure without affecting the heart contractility. The use of animal models or nonphysiological levels of respiratory gases and the absence of breath hold limit the extrapolation of these results to what happens in patients with sleep apnea. Therefore, the purpose of this study was to investigate the influences of five maximal breath holds on peripheral and central hemodynamics in the postive period, up to 60 min. This would augment our knowledge on breath-hold diving and suggest what may be happening in sleep apnea syndrome. The use of both trained apnea divers and subjects without diving experience would account for potentially different response to intermittent breath holds of persons with chronic episodes of hypoxia and hypercapnia compared with persons without sleep apnea. We hypothesized that the series of apneas will be followed by CO₂ retention, an increase in PVR, reduction of venous return and decrease in CO for relatively long period after the cessation of apneas.

Methods

Participants. All experimental procedures were conducted in accordance with the American Physiological Society’s Guiding Principles for Research Involving Animals and Human Beings and were approved by Research Ethics Committee of the University of Split School of Medicine. Each method and potential risks were explained to the participants in detail, and they gave written, informed consent before the experiment. Sixteen men participated in the study. There were eight trained breathhold divers (BHD) and eight untrained (UT) subjects. There were only two smokers in the study, and they both belonged to untrained group. The groups were anthropometrically matched (Table 1).

Experimental protocols. All experiments were carried out in an acclimatized environment during afternoon hours. One participant...
Table 1. Anthropometric data

<table>
<thead>
<tr>
<th></th>
<th>Trained Apnea Divers</th>
<th>Untrained Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 8)</td>
<td>(n = 8)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>29.9±0.9</td>
<td>30.4±1.4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>183.6±1.4</td>
<td>181.9±1.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>89.2±2.7</td>
<td>77.3±3.0</td>
</tr>
<tr>
<td>Years diving</td>
<td>9.5±2.2</td>
<td></td>
</tr>
<tr>
<td>FVC, % of normal predicted</td>
<td>111.3±4.1</td>
<td>103.8±3.3</td>
</tr>
<tr>
<td>FEV₁, % of normal predicted</td>
<td>109.2±5.6</td>
<td>99.5±3.8</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s.

was tested each day. Participants were instructed not to eat for at least 4 h and to abstain from smoking for at least 12 h before the arrival to the laboratory. They were directed to arrive at the laboratory 30 min before the start of the testing for acclimatization and detailed explanation of the experimental procedures. Each participant had body mass and height measured, from which we calculated body mass index. We carried out dynamic spirometry (Quark b², Cosmed, Rome, Italy) in all subjects, who then resumed a prone position for the rest of the experiment. The participants were instructed to rest for 15 min in a prone position on a bed with the head placed on the cover of a container filled with cold water (12°C). The participants were instructed not to hyperventilate before diving. They wore nose clips and were not allowed to exhale into the water during simulated diving. Apnea times were recorded by the use of a stopwatch. After collection of baseline parameters, each participant performed five maximal breath hold with the face immersed in cold water. The subjects were instructed to expire to residual volume and take a deep but not maximal breath before the apneas and to expire completely after the apneas. Successive apneas were separated by 2-min intervals, allowing for data collection. This was the same diving protocol used previously (1, 2, 22).

Initially, Doppler and two-dimensional echocardiographic evaluation of the left and right sides of the heart were performed, followed by inferior vena cava (IVC) diameter and flow velocity measurements. This lasted −2 min. Simultaneously, arterial blood pressure and oxygen saturation (SaO₂), heart rate [HR, respiratory movement, and transcendentu- 
aneous partial pressures of oxygen (PtcO₂) and carbon dioxide (PtcCO₂) were continuously measured and stored on a personal computer. After collection of baseline parameters, each participant performed five maximal breath holds with the face immersed in cold water. The subjects were instructed to expire to residual volume and take a deep but not maximal breath before the apneas and to expire completely after the apneas. Successive apneas were separated by 2-min intervals, allowing for data collection. This was the same diving protocol used previously (1, 2, 22).

Ultrasound evaluations. The same experienced cardiologist took all ultrasonographic measurements with a 1.5- to 3.3-MHz phase array probe (Vivid 3, GE, Milwaukee, WI). The subjects rested supine for 15 min before baseline measurements. In between apneas, the participants switched from the prone to the lateral decubitus and supine positions for ultrasound evaluation. First, the subjects switched to the lateral decubitus position where heart images were obtained in three views: parasternal long and short axis, and apical. The parasternal long-axis view was obtained by placing the transducer at the left parasternal area in the second or third intercostal space, whereas the parasternal short-axis view was obtained by rotating the transducer 90° clockwise from the longitudinal position. The parasternal short-axis view at the aortic valve level was used for visualization and Doppler measurement of volume flow in the pulmonary artery. The apical four-chamber view was identified initially by palpation of the left ventricular apex with the patient in the left lateral decubitus position. Transducer position was then adjusted as needed to obtain optimal images. The four-chamber view displays all four cardiac chambers, as well as the ventricular and atrial septa. This view was used for left ventricular end-systolic (ESV) and end-diastolic volume (EDV) calculations using Simpson’s method. Because both end-diastolic and end-systolic measurements are needed for volume calculations, the electrocardiogram was continuously recorded. By an- gulating the transducer in a clockwise rotation, the five-chamber apical view allowed us to see the aortic valve and the measure aortic diameter and aortic flow velocity curve. After collection of data for cardiac evaluation, subjects switched to the supine posture for IVC recording on the abdominal echograms. Evaluation of the diameter and volume flow of the IVC was done from a subcostal window. Measurement of an IVC diameter was performed with the IVC in its retrohepatic position and always cranial to the crossing of portal vein to record the same site. The site of the sampling was guided by color-flow mapping to position the sample volume at the center of the color flow signal and to create the smallest angle of insonation between the direction of blood flow and the Doppler beam. The images were stored on a personal computer. At a later date, by using scanner software, all images were analyzed by the same author (Ante Obad). The accuracy, reliability, and validity of measuring IVC diameter by abdominal echograms were reported in an earlier study (14).

Cardiopulmonary measurements. Arterial pressure was measured continuously using photoplethysmometer [mean arterial pressure (MAP); Finometer, Finapres Medical Systems, Arnhem, The Netherlands] with the cuff on the middle finger of the nondominant hand. SaO₂ was monitored continuously by pulse oximetry (Dash 2000, GE, Marquette, WI) with the probe placed on the middle finger of the dominant hand. HR was continuously recorded on a personal computer by the use of Polar belts positioned around the subject’s chest. PeₐCO₂ and PeₐCO₂ were measured continuously by placing the sensor electrode of the analyzer (model TC3, Radiometer, Copenhagen, Denmark) over the subscapular muscle. Piezo respiratory belt transducer (AD Instruments, Castle Hill, Australia) was located around the chest of 10 subjects (5 apnea divers and 5 controls) for analysis of the voluntary phase in total breath-hold time. Analog signals of arterial pressure, HR, SaO₂, and respiratory movement were continuously recorded and stored on a personal computer (Apple eMac PC) using a PowerLab 165 data-acquisition system (ADInstruments) at a sampling rate of 100 Hz.

Data analysis. MAP was calculated offline from recorded arterial pressure analog signal. Average values for HR, MAP, SaO₂, PeₐCO₂, and PeₐCO₂ were calculated as control values during the period 30–90 s before each apnea. For HR and MAP, an average value was calculated during each 5 s period during the apnea and also for the last 10 s. For SaO₂, the average value was calculated for each 5-s period from the beginning of apnea until 30 s after apnea and also for the 10 s period ending with the nadir SaO₂.

Stoke volume (SV) is equal to the product of the cross-sectional area (CSA) of the aorta and aortic flow velocity integral: SV = CSA × VTI. Because flow velocity varies during a flow ejection period, individual velocities of Doppler spectrum are summed (i.e., integrated) to measure total flow during a given ejection period. The sum of velocities is called time velocity integral (VTI). CSA is calculated from measured aortic diameter as CSA = πD²/4, where D is aortic diameter. CO was calculated from a product of SV and HR. The total peripheral resistance (TPR) was calculated as MAP/CO (mmHg × min × 1−³). Ascending aortic diameter and the flow velocity curve are recorded from an apical window. The diameter and velocity measurements are made at the same anatomic site. By using pulsed Doppler, the pulmonary artery flow was recorded from the parasternal short axis. Next, the sample volume was placed in the region of the pulmonary valve annulus. Pulmonary artery acceleration time (PAT) in milliseconds was determined as the time interval between beginning of flow and its peak velocity. The mean of three consistent waveforms at each time point was used for the purpose of analysis. Mean pulmonary artery pressure (MPAP) in mmHg was calculated as MPAP = 73 − (0.42 × PAT) (6). Total PVR was calculated as PVR = MPAP/CO × 80 dyn·s·cm⁻⁵. The left ventricular global ejection fraction (EF) was calculated as EF = [(EDV − ESV)/EDV] × 100%. The IVC diameter was measured from the B images at the same location as the Doppler interrogation (1–2 cm
distal to the junction with the hepatic vein) for VTI. Measurements were done in B mode because of deep localization of the IVC. By using technical skills of the ultrasound (cine loop), we managed the similar effect as we were using M mode for measuring excursions of the IVC diameter. Direct timing was not done, but by using always the same method (cine loop) enabled us to measure IVC diameter in the same moment of maximal dilatation.

Statistical analysis. Data are expressed as means ± SE. The effect of apnea diving on studied variables in different postdive times was evaluated by Friedman analysis of variance, whereas post hoc comparisons were done by Wilcoxon signed-rank test. Nonparametric tests were used because of the small sample size (n = 8). To minimize the effect of intersubject variability, the postdive changes from baseline values were used in these analyses, instead of the raw data. Associations between metric variables were evaluated by Pearson’s coefficient of correlation. A P value < 0.05 was considered significant. All analyses were done using Statistica 6.0 software (Statsoft, Tulsa, OK).

RESULTS

Descriptive data. Anthropometric data for all subjects, BHD (n = 8) and UT (n = 8), are shown in Table 1. The two groups were anthropometrically comparable, except that BHD were heavier than the UT persons. Spirometry in the two body postures did not differ significantly between groups.

MAP, HR, SaO₂, TPR, and transcutaneous blood gases. Durations of the five maximal apneas and the responses of MAP, SaO₂, HR, and PtcCO₂ are summarized in Fig. 1A. Apneic time increased over the series of five apneas significantly by 49.8 s (48%; P = 0.0005) in BHD, whereas UT subjects did not show significant increases (9 s). Overall, BHD performed longer apneas than UT persons (P = 0.0001). MAP increases were approximately equal after all five apneas and quickly normalized after the cessation of apneas. Significantly greater bradycardia was found in the BHD group (P = 0.03). Anticipatory HR increased before the onset of the first apnea and subsequently decreased below baseline values equally after all apneas. HR was quickly restored to baseline values in the 2-min periods between apneas in all participants (data not shown). There was no distinction in baseline SaO₂ between BHD and UT subjects (98.0 ± 0.3 and 98 ± 0.3%, respectively). SaO₂ decreased significantly below baseline values after

Fig. 1. Duration of 5 maximal apneas and response in mean arterial pressure (MAP), arterial oxygen saturation (SaO₂), heart rate (HR), total peripheral resistance (TPR) (A), and transcutaneous partial pressure of carbon dioxide (PtcCO₂) (B). Values are means ± SE. Graphs represent values obtained after 5 successive maximal apneas (A1–A5) separated by 2-min recovery period, and the values during the 1-h postapnea period (10–60), in all subjects. Values are statistically significant (P < 0.05) compared with baseline (B) values: * for breath-hold divers (BHD); † for untrained subjects (UT).
all apneas in both groups ($P = 0.00000$). Oxygen desaturation was less apparent in UT persons ($P = 0.005$, compared with BHD). $S\alpha_2$ was restored in the period between apneas in both groups and in all apnea attempts (data not shown). TPR increased significantly after the last apnea in both groups ($P = 0.02$) and remained at elevated levels even $1 \text{ h}$ after cessation of breath holds. Preapneic $Pt\text{CO}_2$ in tissue remained unchanged over all five apneas in all groups, indicating constant baseline conditions in blood gases for each apnea attempt (Fig. 1B). After the series of apneas, $Pt\text{CO}_2$ remained significantly elevated in trained and untrained persons ($P = 0.01$).

Central hemodynamic variables. CO decreased significantly after the cessation of apneas in both groups ($P = 0.01$) predominantly due to SV reduction (Fig. 2), because HR was unchanged. EDV decreased by $13.5\%$ in BHD and by $7.95\%$ in UT persons $10 \text{ min}$ after cessation of apneas and was followed by a gradual return to baseline values in the $60\text{-min}$ postapnea period (Fig. 3). EF decreased nonsignificantly after apneas (Fig. 4). MPAP and PVR increased significantly after the cessation of breath holds ($P < 0.05$; Fig. 5, A and B). There was no difference in increase between groups.

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**IVC hemodynamics.** Figure 5 shows the IVC diameter changes during the period after the series of apnea in BHD and UT persons. The greatest increase in IVC diameter occurred 10 min after the cessation of apneas (16.2% in BHD and 10.4% in UT persons). It was still elevated after at the 1-h period following cessation of diving in both groups ($P = 0.01$; Fig. 6A). Maximal IVC dilatation occurred 40 min after the last apnea, most notably in BHD subjects. VTI through IVC decreased significantly in the BHD group ($P = 0.01$) in the 10-min postdiving period, and was followed by a gradual return to baseline values in the 60-min postapnea period. In the UT persons, nonsignificant decreases were found (Fig. 6B). Figure 7 shows the IVC diameter changes in subject 5 before and after a series of five maximal apneas.

**DISCUSSION**

This study shows that substantial hemodynamic effects of a series of maximal apneas, interrupted by short interapneic intervals, last at least 1 h after the last apnea. During that postapneic time, the CO$_2$ retention occurred in association with dilatation of IVC. This fact, substantiated with reduction of ventricular volume and EDV, suggests that hypercapnia-related venodilation decreased venous return, causing the observed decrease in SV and CO. Elevated levels of CO$_2$ or prolonged effects of previous hypoxic/hypercapnic episodes may also explain rather large, persistent elevations in PAP and PVR after the apnea series. These data suggest that hemodynamic effects of a series of hypoxic/hypercapnic episodes may be well extended after resumption of normal breathing. Although the signs of blood volume peripheralization were more pronounced in trained apnea divers, overall the effects were not found to depend significantly on chronic exposure to hypoxic/hypercapnic episodes.

PtcCO$_2$ increased in all participants during breath holding, returned to baseline in between apneas, but remained slightly elevated during the postdiving observation (4.5%).
accordance with previous findings of large tissue CO₂ retention and prolonged recovery of CO₂ elimination after repetitive breath holds with short interapneic resting intervals (20). Muscle tissue is the largest CO₂ reservoir, holding 10 liters of CO₂, or 60% of the total labile CO₂ store. Muscle’s time constant for CO₂ mobilization is 30 min, whereas other soft tissues have both smaller CO₂ stores and faster CO₂ mobilization, with time constants between 1.6 and 2.5 min (10). If apnea duration is long enough with a short interapneic period, as in the present study, a substantial CO₂ retention in slow-equilibrating tissues can occur. A CO₂ retention after apneas in BHD may be potentiated by chronically blunted ventilatory response to hypercapnia. This effect was found in assisted-diving Ama (18) and in Royal Navy divers (12) as an effect of training. An acute resetting of chemoreceptors by a series of maximal breath holds should also be considered as a cause. Unfortunately, in this study the ventilation was not measured. However, a significant CO₂ retention occurred even 1 h after a series of maximal breath holds, which could have contributed to changes in peripheral and central hemodynamics.

Trained BHD had an augmented diving reflex (bradycardia and apparently increased MAP), as was previously shown by Lin (16). Postdiving ultrasound measurements showed IVC dilatation with subsequent decreases in CO in both groups, due to decreased SV, in the presence of decreased ventricular EDV and increased right ventricular afterload. HR was unchanged, whereas TPR increased in both groups. Possible factors affecting SV are preload, afterload and myocardial contractility. Reduced EDV suggests decreased preload to the right ventricle, which, in conjunction with its significantly increased afterload, explains the diminution of the right ventricular SV. Given unchanged/slightly decreased left ventricular afterload (assessed by peripheral systolic pressure), the left ventricular performance was likely only the reflection of the conditions on the right side. However, a small contribution from the reduction in left ventricular contractility, suggested by apparent decrease in its ejection fraction, cannot be excluded.

Reduced ventricular EDV and increased IVC diameter suggest the redistribution of blood volume from central blood pools to peripheral veins, after the reduction in venous return. The venous return is expected to decrease if either the peripheral blood volume or vessels capacitance decreases (as the determinants of the mean circulation filling pressure). The blood volume was not measured in this study, but in our laboratory’s previous study, using the same apnea diving protocol, the plasma volume increased after apneas, likely due to CO₂ retention (2). This, in conjunction with signs of peripheralization of blood, suggests an increase rather than decrease in peripheral blood pools after apnea series, reducing the possible causes of reduced venous return to decreased capacitance of peripheral blood vessels. If real, decreased peripheral vessels capacitance can also be explained by hypercapnia, which directly relaxes the vascular smooth muscle (3, 13).

The series of voluntary apneas is a unique human model of sleep apnea, with presence and realistic intensities of all three factors: cyclic hypoxemia, hypercapnia, and absent ventilation. This study shows that the aggravating hemodynamic effects of consecutive apneas are long lasting and primarily affect the right heart. If these results can be extrapolated to sleep apnea, the prolonged increase in the PVR after apneic episodes may contribute to the observed association of obstructive sleep apnea and pulmonary hypertension (19).

There are several study limitations. Although we did measure both IVC diameter and its VTI, IVC irregular shape precluded calculating IVC flow by combining these data. Therefore, we were not able to measure directly this significant portion (~2/3) of the venous return. As for the ultrasound cardiopulmonary assessments, the reliability of the methods vary from accepted standards (aortic CO) to less well-evaluated methods (assessment of MPAP). Also the transcutaneous estimates of arterial respiratory gases depend on stable cutaneous blood flow; the methods work best in neonates (25) and worst in hemodynamically unstable patients (24). In healthy individuals, the methods reliably monitor trends due to respiratory changes (4, 7, 23, 26); the O₂ absolute readings are systematically below the corresponding arterial values, whereas temperature-corrected CO₂ readings deviate much less (26). Theoretically, in this study, the observed decrease in cardiac output could have influenced the cutaneous blood flow and thus the transcutaneous estimates of blood gases. However, this effect would be more pronounced in case of O₂, contrary to what was observed: only PtcCO₂ remained elevated in the postapneic period.

In conclusion, we have found that hemodynamic effects of a series of maximal face-immersion apneas with short interapneic intervals last over an hour after, both in trained apnea divers and in controls. These effects include the reduced filling and increased afterload to the right heart, reduced SV and cardiac output in the presence of CO₂ retention, and signs of blood volume peripheralization.

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GRANTS

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REFERENCES


