J Appl Physiol 104: 205–211, 2008.
First published November 8, 2007; doi:10.1152/japplphysiol.00844.2007.

Central chemoreflex sensitivity and sympathetic neural outflow in elite breath-hold divers

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Submitted 7 August 2007; accepted in final form 5 November 2007

Dujic Z, Ivancev V, Heusser K, Dzamonja G, Palada I, Valic Z, Tank J, Obad A, Bakovic D, Diedrich A, Joyner MJ, Jordan J. Central chemoreflex sensitivity and sympathetic neural outflow in elite breath-hold divers. *J Appl Physiol* 104: 205–211, 2008. First published November 8, 2007; doi:10.1152/japplphysiol.00844.2007.—Repeated hypoxemia in obstructive sleep apnea patients increases sympathetic activity, thereby promoting arterial hypertension. Elite breath-holding divers are exposed to similar apneic episodes and hypoxemia. We hypothesized that trained divers would have increased resting sympathetic activity and blood pressure, as well as an excessive sympathetic nervous system response to hypercapnia. We recruited 11 experienced divers and 9 control subjects. During the diving season preceding the study, divers participated in 7.3 ± 1.2 diving fish-catching competitions and 76.4 ± 14.6 apnea training sessions with the last apnea 3–5 days before testing. We monitored beat-by-beat blood pressure, heart rate, femoral artery blood flow, respiration, end-tidal CO_2, and muscle sympathetic nerve activity (MSNA). After a baseline period, subjects began to rebreathe a hyperoxic gas mixture to raise end-tidal CO_2 to 60 Torr. Baseline MSNA frequency was 31 ± 11 bursts/min in divers and 33 ± 13 bursts/min in control subjects. Total MSNA activity was 1.8 ± 1.5 AU/min in divers and 1.8 ± 1.3 AU/min in control subjects. Arterial oxygen saturation did not change during rebreathing, whereas end-tidal CO_2 increased continuously. The slope of the hypercapnic ventilatory and MSNA response was similar in both groups. We conclude that repeated bouts of hypoxemia in elite, healthy breath-holding divers do not lead to sustained sympathetic activation or arterial hypertension. Repeated episodes of hypoxemia may not be sufficient to drive an increase in resting sympathetic activity in the absence of additional comorbidities.

ultrasound; muscle sympathetic nerve activity; apnea; human

CARDIOVASCULAR MORBIDITY AND MORTALITY are profoundly increased in patients with obstructive sleep apnea (26, 27). The increased risk may be explained in part by excessive sympathetic activity, endothelial dysfunction, and arterial hypertension (16, 17, 31). Sympathetic activation occurs during sleep apnea episodes as arterial oxygen saturation decreases (17). Sympathetic activation is sustained during the day when patients are breathing normally (8, 23, 24). Similarly, experimental breath holding and intermittent hypoxemia cause acute as well as sustained changes in cardiovascular autonomic regulation (3, 18, 21, 22). Sympathetic activation in clinical and in experimental apnea may be explained by resetting of the arterial baroreflex to higher blood pressure values together with changes in chemoreflex regulation (18, 21). In animals, intermittent hypoxia augments the sympathetic nervous system response to hypoxia and to hypercapnia (9). A recent study suggested that hypercapnia rather than hypoxia may increase blood pressure and cause baroreflex resetting (2). The state of affairs is disturbing since healthy people, including underwater hockey players, synchronized swimmers, and elite breath-holding divers, practice voluntary apnea on a regular basis. Divers are an extreme example of voluntary apnea. Recently, Tom Sietas set the new world record with more than 9 min of static apnea. After maximal apnea, alveolar partial pressure of oxygen can be as low as 30–40 Torr with an arterial oxygen saturation as low as 50%. Alveolar carbon dioxide partial pressure increases substantially (6). Typically, diving fish-catching competitions last for ~5 h. Cumulative apnea duration during this period is ~1 h. Thus apneic exposures in sleep apnea patients and divers may be similar in severity and duration, at least during the diving season. We hypothesized that trained divers would have increased resting sympathetic activity and blood pressure, as well as an excessive sympathetic nervous system response to hypercapnia.

METHODS

Subjects. We included 20 healthy male volunteers in our study. Of those, 11 were experienced elite breath-holding divers. Nine men did not dive regularly and served as control group. The ethical committee of the University of Split School of Medicine approved the study and written informed consent was obtained.

Protocol. We conducted our studies in October 2006 toward the end of the diving season. All experiments were carried out in a climatized room in the morning hours. Participants were instructed not to eat at least 4 h before the arrival to the laboratory.

Subjects underwent dynamic spirometry (Quark PFT, Cosmed, Rome, Italy) while standing. Then, they were asked to lie down and were instrumented for the rebreathing test. Respiration was measured breath by breath. End-tidal CO_2 ($P_{ET}CO_2$) was determined using an infrared analyzer (Poet II, Criticare Systems, Waukesha, WI) connected to a mouthpiece. We applied an infrared probe on the middle finger to monitor arterial oxygen saturation (Poet II). Beat-by-beat blood pressure and heart rate were measured using a finger cuff (Finometer, Finapress Medical Systems, Arnhem, The Netherlands) and electrocardiography, respectively. Femoral artery mean blood velocity was determined using pulsed-wave Doppler sonography. The

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Table 1. *Anthropometric characteristics and pulmonary function*

	Breath-Hold Divers (n = 11)	Nondivers (n = 9)
Age, yr	27±4.0	28±7.1
Height, cm	187±7.0	181±7.5
Weight, kg	89±12.0	87±9.8
Body mass index, kg/m^2	25±3.2	27±2.3
Body fat index, %	17±6.5	19±5.3
FEV_1, % predicted	109±15	105±14
FVC, % predicted	115±16	110±12

Values are means ± SD. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 2. *Baseline measurements*

	Breath-Hold Divers (n = 11)	Nondivers (n = 9)
Heart rate, beats/min	61±9.6	62±8.8
Mean arterial pressure, mmHg	89±7.7	92±10
Sa_{O_2}, %	99±0.8	98±0.6
FAMBV, cm/s	11±5.7	10±4.8
End-tidal CO_2, Torr	36±4.9	43±1.6
MSNA, bursts/min	31±11	33±13
MSNAi, AU	1.8±1.5	1.8±1.3

Values are means± SD. Sa_{O_2}, arterial oxygen saturation; FAMBV, femoral artery blood flow; MSNA, muscle sympathetic nerve activity; MSNAi, muscle sympathetic nerve activity integral.

4-MHz ultrasound probe (Transcranial Doppler, Neurovision System, Multigon, Yonkers, NY) was placed over the left femoral artery and held in place with adhesive tape. Muscle sympathetic nerve activity (MSNA) was recorded from the right peroneal nerve with a unipolar tungsten electrode as described previously (12).

After instrumentation, subjects performed two rebreathing tests with a recovery period of 15 min between tests. The hypercapnic ventilatory response was assessed using a slightly modified rebreathing method (28). Subjects were breathing through a mouthpiece with a pneumatic one-way valve. The valve was connected to breath-by-breath respiratory analyzer (Quark b^2, Cosmed, Rome, Italy) and spirometer (Harvard Apparatus, Student model, Holliston, MA). The spirometer was filled with 6 liters of a 5% CO_2-95% O_2 gas mixture. Subjects were breathing room air normally and quietly at rest for 2 min through the mouthpiece. Then, they were switched to the spirometer gas mixture and continued with normal breathing. The rebreathing protocol lasted until $P_{ET}CO_2$ values reached 60 Torr.

Data acquisition and analysis. Data were analog-to-digital converted at 500 Hz using the Windaq pro+ software (Dataq Instruments). R-R intervals, diastolic and systolic blood pressure values, and respiration were defined offline for the complete records using a program written by one of the authors (A. Diedrich) that is based on PV-wave software (Visual Numerics, Houston, TX). MSNA bursts were identified after filtering the integrated signal and defining the baseline according to following criteria: *1*) signal-to-noise ratio of >2; *2*) latency limit; *3*) burst width limit (short duration = artifact, long duration = skin sympathetic nerve activity or afferent activity); *4*) no preceding premature beats (33). To assess chemoreflex regulation of ventilation and sympathetic activity, we plotted minute ventilation or MSNA over $P_{ET}CO_2$ during the rebreathing test. The data was analyzed using linear regression analysis. Changes in left ventricular stroke volume were estimated by pulse wave analysis using an improved method of Wesseling (Modelflow program) (14). Femoral artery vascular resistance was calculated as mean arterial pressure divided by femoral artery mean blood velocity. Because the duration of the rebreathing test differed between subjects, data were matched for the relative duration of rebreathing.

Statistical analysis. All data are expressed as means + SD. The effects of hypercapnia on all measured variables were assessed using a repeated-measures two-way ANOVA procedure and, if significant, a Bonferroni test was used as post hoc test. To compare ventilatory responses to hypercapnia, an unpaired t-test was applied. The relationships between different variables were examined by using the Pearson correlation test. The level of probability for statistical significance was $P < 0.05$.

RESULTS

Anthropometric data and pulmonary function data are given in Table 1. Age, body mass index, and body fat content determined by skinfold thickness (Harpenden skinfold caliper) measurements were similar in divers and in control subjects. During the diving season that immediately preceded the study, divers participated in 7.3 ± 1.2 diving fish-catching competitions and 76.4 ± 14.6 training sessions. Divers performed four to five training sessions per week in the period of 16–20 wk in row before the study. Personal best apnea time and maximal diving depth were 281.6 ± 34.1 s and 31.6 ± 5.2 m, respectively. All divers went apnea diving 3–5 days before start of the study.

Before the rebreathing test, heart rate, mean arterial pressure, femoral artery blood flow velocity, arterial oxygen saturation, and muscle oxygenation were similar in divers and in control subjects (Table 2). Spontaneous $P_{ET}CO_2$ tended to be

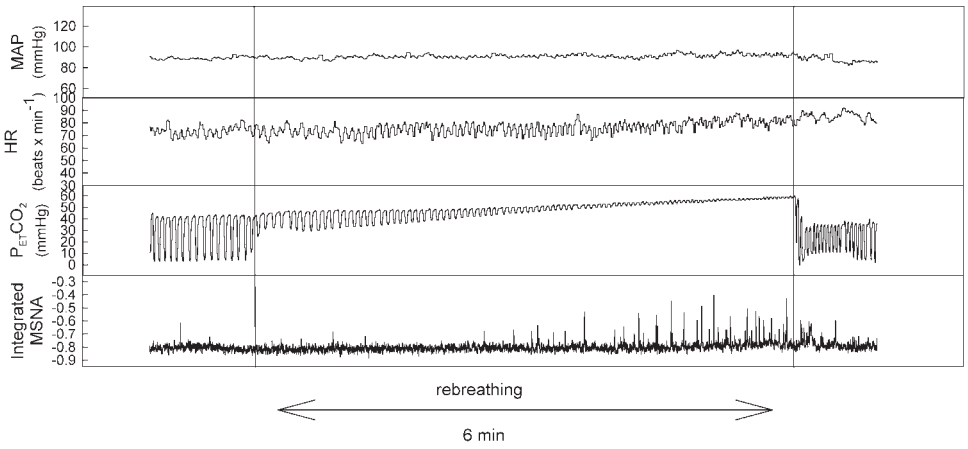


Fig. 1. Representative recording of mean arterial blood pressure (MAP), heart rate (HR), end-tidal CO_2 ($P_{ET}CO_2$), and integrated muscle sympathetic nerve activity (MSNA) signal for one rebreathing attempt in a breath-hold diver.

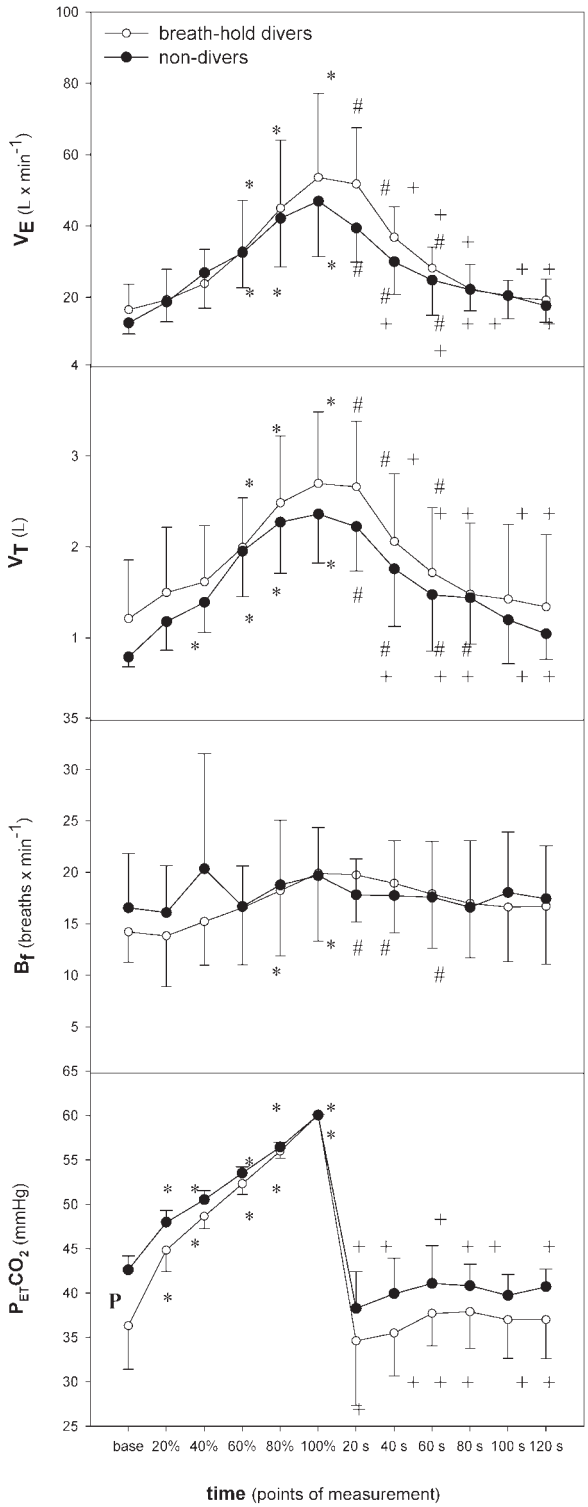


Fig. 2. Minute ventilation ($\dot{V}_E$), tidal volume (V_T), respiratory frequency (Rf), and $P_{ET}CO_2$ at baseline, during rebreathing, and during recovery. Significant within-group difference ($P < 0.05$): *when baseline value is compared with rebreathing data points; #when baseline is compared with recovery data points; +when end of rebreathing is compared with recovery data points; and ^{P}when between-groups values by repeated-measures ANOVA are compared with Bonferroni post hoc test.

Table 3. *Hypercapnic ventilatory response*

	Breath-Hold Divers	Nondivers
SHCVR, liter·min^{-1}·mmHg^{-1}	1.7±1.0	2.1±0.76
IHCVR, mmHg	30±6.7	37±2.9*

Values are means ± SD. SHVCR, slope of the hypercapnic ventilatory response; IHCVR, intercept of the hypercapnic ventilatory response. *$P < 0.05$.

decreased in apnea divers. Baseline MSNA frequency and total MSNA activity were similar in both groups (Table 2).

Original tracings of blood pressure, heart rate, respiration, $P_{ET}CO_2$, and sympathetic activity before and during rebreathing in a diver are illustrated in Fig. 1.

Arterial oxygen saturation did not change during rebreathing, whereas $P_{ET}CO_2$ increased continuously. Increased minute ventilation during rebreathing was primarily explained by an increase in tidal volume (Fig. 2). Breathing frequency increased in divers only.

Rebreathing duration until subjects reached a $P_{ET}CO_2$ of 60 Torr was on average 76 s longer in divers than in control subjects. The slope of the hypercapnic ventilatory response was similar in both groups (Table 3). All subjects remained normoxic throughout the rebreathing test.

With hypercapnia, blood pressure increased from 89 ± 7.7 to 97 ± 7.5 mmHg in divers and from 92 ± 10 to 98 ± 13 mmHg in control subjects ($P < 0.001$ for both; Fig. 3).

Total peripheral resistance and femoral vascular resistance did not increase during rebreathing. During the recovery period, blood pressure rapidly returned to the baseline value. After rebreathing, total peripheral resistance and femoral vascular resistance decreased below the baseline value. Increased cardiac output maintained blood pressure during this period. During rebreathing, MSNA frequency increased in divers only. However, total MSNA activity increased similarly in both groups (Fig. 4).

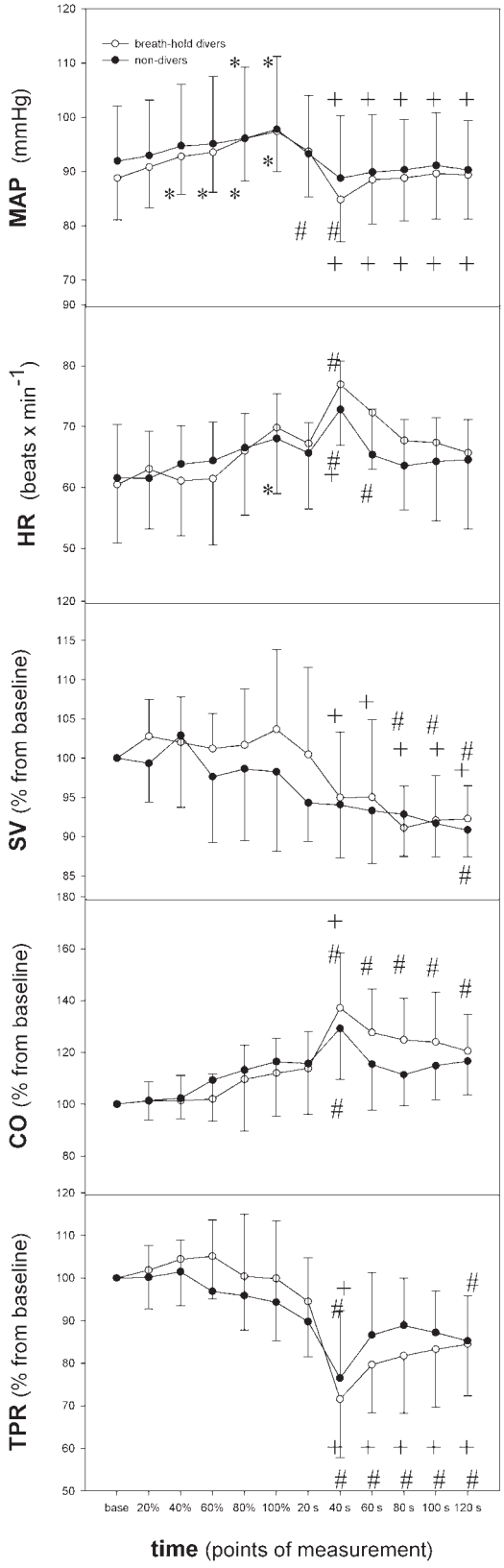
We plotted individual sympathetic chemoreflex curves in divers and in control subjects as illustrated in Fig. 5. The slope at the linear portion of these curves was identical in both groups (Fig. 6).

DISCUSSION

Elite divers regularly explore the limits of human physiology in terms of hypoxia and hypercapnia. Therefore, we reasoned that breath-hold diving could serve as a human model of intermittent asphyxia, similar to the situation that occurs in sleep apnea. The model is appealing because confounding co-morbid conditions are absent in divers. In the present study, we explored cardiovascular sympathetic mechanisms in divers using microneurography. Resting sympathetic activity and blood pressure were similar in breath-hold divers and in control subjects. This observation suggests that the set point of the sympathetic baroreflex was within the normal range in divers. In contrast, intermittent asphyxia during obstructive sleep apnea episodes results in chronically increased MSNA during wakefulness, thus promoting systemic arterial hypertension (8, 23, 24). The observation suggests that intermittent asphyxia in the absence of additional risk factors is not sufficient to drive a sustained increase in sympathetic vasomotor tone and blood pressure. We cannot exclude the possibility that the slope of

the baroreflex curve was altered as it is in patients with obstructive sleep apnea (23).

Hypercapnia elicits ventilatory, cardiovascular, and autonomic responses mainly through central chemoreceptors located at the ventral surface of the medulla (7). We applied a rebreathing protocol to increase $P_{ET}CO_2$ by ~20 Torr. We added oxygen to achieve selective central chemoreceptor stimulation. With this method, inspired CO_2 is a function of previously expired P_{CO_2}, leading to equilibration of the venous, arterial, and tissue CO_2 (20). Central chemoreflex regulation elicits a profound increase in ventilation. The slope of the hypercapnic ventilatory response was similar in breath-holding divers and in control subjects. However, basal $P_{ET}CO_2$ was slightly reduced in divers. Previously, the ventilatory response to hypercapnia was shown to be blunted in persons engaging in various underwater sports in some (4, 5, 19) but not in all studies (1). Similarly, studies in obstructive sleep apnea patients showed variable hypercapnic ventilatory responses (24, 30, 34).



We observed a similar increase in mean arterial blood pressure in divers and in control subjects during rebreathing. The pressor response was not mediated through systemic vasoconstriction. Hyperoxic hypercapnia increased mean arterial blood pressure and cardiac output in a previous study (29). The hemodynamic response after discontinuation of the rebreathing test differed between divers and control subjects. In both groups, mean arterial blood pressure rapidly returned to the baseline values while heart rate increased. Divers exhibited a marked increase in cardiac output and reduction in systemic vascular resistance after discontinuation. The response was less pronounced or absent in control subjects. The cardiovascular response after discontinuation is somewhat unexpected because $P_{ET}CO_2$ rapidly returned to baseline.

The overall cardiovascular response to hypercapnia may result from direct influences on vascular tone and cardiac contractility together with reflex-mediated changes in sympathetic activity. The microneurography data are useful in dissecting central nervous and peripheral mechanisms. We observed a marked increase in sympathetic nerve traffic during rebreathing with a rapid return to the baseline value after discontinuation. Previous studies showed a similar response (29, 32). Total sympathetic activity increased more markedly than burst frequency. This observation suggests increased recruitment of efferent sympathetic neurons during hypercapnia. Individual relationships between $P_{ET}CO_2$ and sympathetic nerve traffic and sympathetic activity at 60-Torr $P_{ET}CO_2$ were similar in divers and in control subjects.

With an increase in sympathetic vasomotor tone during rebreathing, one would expect to observe systemic vasoconstriction. Instead, vascular resistance remained unchanged. Apparently, hypercapnia interfered with coupling between sympathetic nerve traffic and vascular contraction. Our finding that vascular resistance was decreased in the recovery period supports the idea. We propose that influences of hypercapnia on peripheral vascular regulation were unmasked after discontinuation of the rebreathing protocol. Previous studies assessed peripheral hemodynamic responses to hypercapnia in patients with severe autonomic failure (25) or in healthy subjects

Fig. 3. Changes in MAP, HR, stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) are presented as relative values between baseline, five rebreathing data points (%), and six points during recovery (each 20 s). Significant within-group difference ($P < 0.05$) by repeated-measures ANOVA with Bonferroni post hoc test: *when baseline value is compared with rebreathing data points; #when baseline is compared with recovery data points; and +when end of rebreathing is compared with recovery data points.

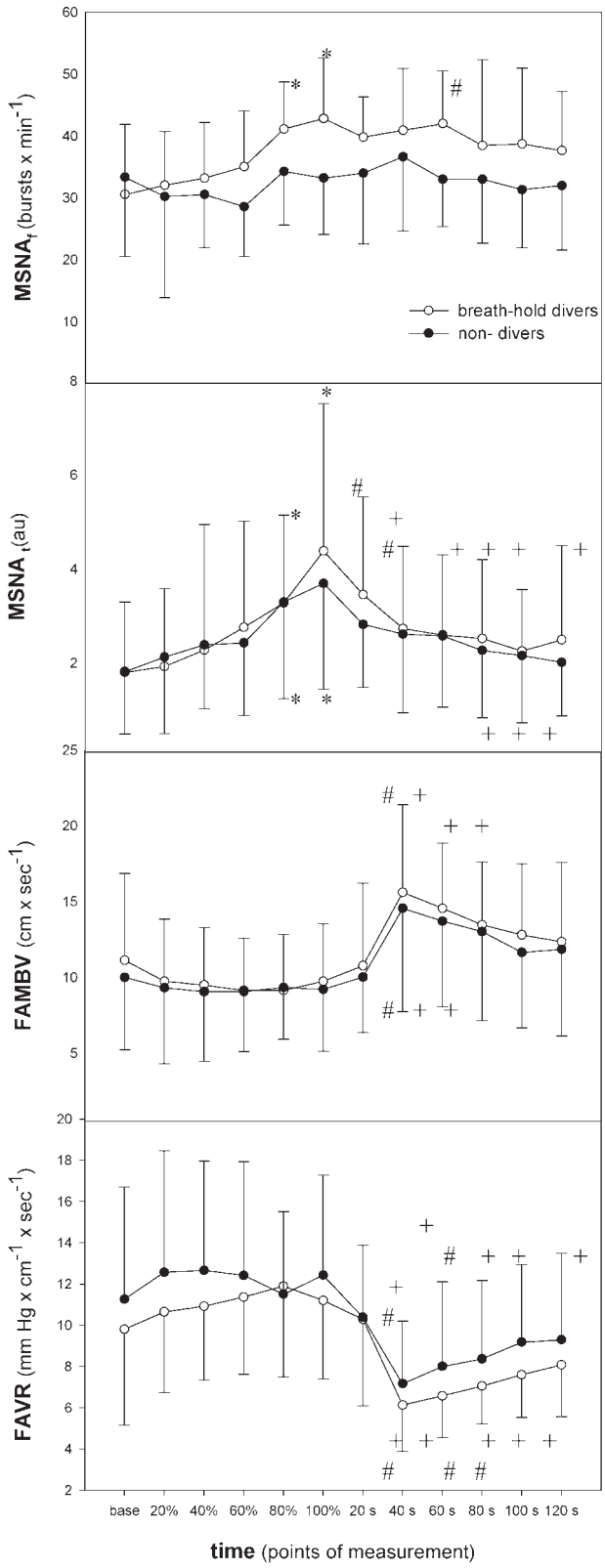


Fig. 4. Changes in MSNA (as bursts per minute and area under curve), femoral artery mean blood velocity (FAMBV), and femoral artery vascular resistance (FAVR) between baseline, five rebreathing data points (%), and six points during recovery (each 20 s). Significant within-group difference ($P < 0.05$) by repeated-measures ANOVA with Bonferroni post hoc test: *when baseline value is compared with rebreathing data points; #when baseline is compared with recovery data points; and +when end of rebreathing is compared with recovery data points.

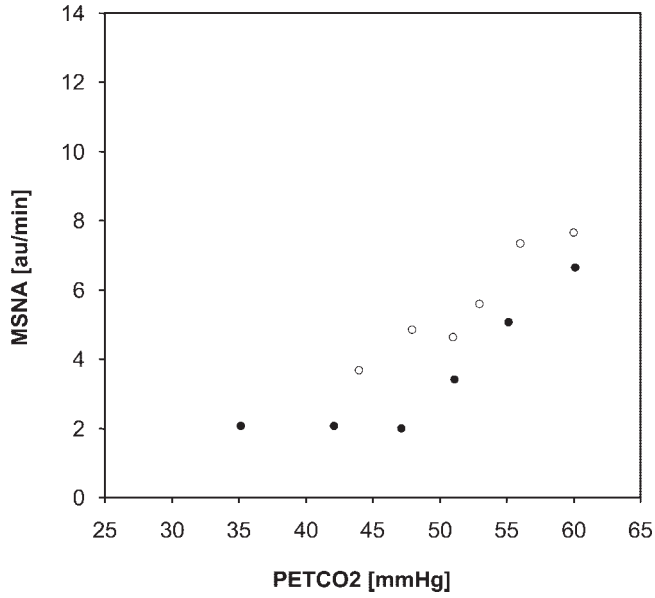


Fig. 5. Representative plots of sympathetic activity over $P_{ET_{CO_2}}$ in one control subject (○) and in one breath-hold diver (●) during the rebreathing test.

during near complete pharmacological ganglionic blockade (15). In the absence of sympathetic nervous system input, hypercapnia elicited a pressor response. Thus a direct influence of CO_2 on vascular tone may not explain our findings. Possibly, hypercapnia altered norepinephrine and/or epinephrine release through presynaptic mechanisms. Acidosis has been shown to attenuate electrically evoked norepinephrine release (11).

The main limitation of our study is that the divers did not undergo standardized diving protocols before the study. Even when all precautions are taken into account, breath-hold diving is not without risk. Deadly accidents can and do occur. We therefore did not assign our subjects additional dives for the

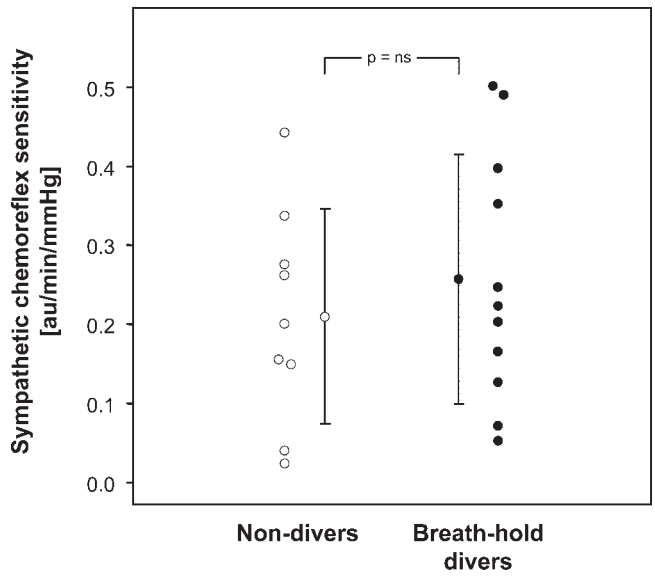


Fig. 6. Sympathetic chemoreflex sensitivity determined as the slope of the regression between sympathetic activity and $P_{ET_{CO_2}}$ during the rebreathing test (P = not significant, unpaired t-test).

purpose of standardization. In previous studies, combined hypoxia with or without hypercapnia evoked sympathetic activation in human subjects that was sustained for more than an hour when subjects returned to room air breathing (3, 22, 35). Because we did not study our subjects immediately after diving, we cannot exclude a short-lived increase in sympathetic activity and blood pressure. Indeed, in obstructive sleep apnea patients, treatment with a continuous positive airway pressure apparatus appears to attenuate sympathetic activity within 2 wk (13). In another study, exposure to hypobaric hypoxia resulted in sympathetic activation in healthy subjects. Sympathetic activity was still increased 3 days after return to sea level (10). Our subjects performed their last dives 3–5 days before start of the study. The observation that hypobaric hypoxia but not apnea diving elicits sustained sympathetic activation over several days is surprising. One possible explanation is a difference in the physiological stimulus elicited by high altitude and repeated breath holding. For example, in high altitude, hypoxia occurs together with hyperventilation-induced hypocapnia. Breath holding causes hypercapnia and hypoxia.

Perspective

Repeated bouts of hypoxemia in elite divers do not lead to sustained sympathetic activation or arterial hypertension. Moreover, central chemoreflex control of respiration and sympathetic activity is maintained in these unique individuals. Preserved central chemoreflex control of sympathetic activity may serve as a protective mechanism by stabilizing blood pressure during hypercapnia. Sympathetic responses differ markedly between apnea divers and patients with obstructive sleep apnea. Our findings suggest that repeated episodes of hypoxemia alone are not sufficient to drive an increase in resting sympathetic activity in the absence of additional comorbidities.

ACKNOWLEDGMENTS

We thank the support staff of the University of Split School of Medicine for facilitating this study and the subjects for enthusiastic participation.

GRANTS

This study was supported by the Croatian Ministry of Science, Education and Sports, Grants No. 216-2160133-0330 and 216-2160133-0130. M. J. Joyner was supported by the Mayo Foundation, and K. Heusser, J. Tank, and J. Jordan were supported by Deutsche Forschungsgemeinschaft grants.

REFERENCES

1. **Bjurstrom RL, Schoene RB.** Control of ventilation in elite synchronized swimmers. *J Appl Physiol* 63: 1019–1024, 1987.
2. **Cooper VL, Pearson SB, Bowker CM, Elliott MW, Hainsworth R.** Interaction of chemoreceptor and baroreceptor reflexes by hypoxia and hypercapnia - a mechanism for promoting hypertension in obstructive sleep apnoea. *J Physiol* 568: 677–687, 2005.
3. **Cutler MJ, Swift NM, Keller DM, Wasmund WL, Smith ML.** Hypoxia-mediated prolonged elevation of sympathetic nerve activity after periods of intermittent hypoxic apnea. *J Appl Physiol* 96: 754–761, 2004.
4. **Davis FM, Graves MP, Guy HJ, Prisk GK, Tanner TE.** Carbon dioxide response and breath-hold times in underwater hockey players. *Undersea Biomed Res* 14: 527–534, 1987.
5. **Delapille P, Verin E, Tourny-Chollet C, Pasquis P.** Ventilatory responses to hypercapnia in divers and non-divers: effects of posture and immersion. *Eur J Appl Physiol* 86: 97–103, 2001.
6. **Ferretti G.** Extreme human breath-hold diving. *Eur J Appl Physiol* 84: 254–271, 2001.
7. **Gelfand R, Lambertsen CJ.** Dynamic respiratory response to abrupt change of inspired CO_2 at normal and high P_{O_2}. *J Appl Physiol* 35: 903–913, 1973.
8. **Grassi G, Facchini A, Trevano FQ, Dell'Oro R, Arenare F, Tana F, Bolla G, Monzani A, Robuschi M, Mancia G.** Obstructive sleep apnea-dependent and -independent adrenergic activation in obesity. *Hypertension* 46: 321–325, 2005.
9. **Greenberg HE, Sica A, Batson D, Scharf SM.** Chronic intermittent hypoxia increases sympathetic responsiveness to hypoxia and hypercapnia. *J Appl Physiol* 86: 298–305, 1999.
10. **Hansen J, Sander M.** Sympathetic neural overactivity in healthy humans after prolonged exposure to hypobaric hypoxia. *J Physiol* 546: 921–929, 2003.
11. **Haunstetter A, Schulze IB, Backs J, Kruger C, Haass M.** Differential effects of acidosis, high potassium concentrations, and metabolic inhibition on noradrenaline release and its presynaptic muscarinic regulation. *Pharmacol Res* 45: 221–228, 2002.
12. **Heusser K, Tank J, Diedrich A, Engeli S, Klaua S, Kruger N, Strauss A, Stoffels G, Luft FC, Jordan J.** Influence of sibutramine treatment on sympathetic vasomotor tone in obese subjects. *Clin Pharmacol Ther* 79: 500–508, 2006.
13. **Imadojemu VA, Gleeson K, Quraishi SA, Kunselman AR, Sinoway LI, Leuenberger UA.** Impaired vasodilator responses in obstructive sleep apnea are improved with continuous positive airway pressure therapy. *Am J Respir Crit Care Med* 165: 950–953, 2002.
14. **Jellema WT, Imholz BP, Oosting H, Wesseling KH, Van Lieshout JJ.** Estimation of beat-to-beat changes in stroke volume from arterial pressure: a comparison of two pressure wave analysis techniques during head-up tilt testing in young, healthy men. *Clin Auton Res* 9: 185–192, 1999.
15. **Jordan J, Shannon JR, Diedrich A, Black BK, Costa F, Robertson D, Biaggioni I.** Interaction of carbon dioxide and sympathetic nervous system activity in the regulation of cerebral perfusion in humans. *Hypertension* 36: 383–388, 2000.
16. **Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V, Somers VK.** Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation* 102: 2607–2610, 2000.
17. **Leuenberger U, Jacob E, Sweer L, Waravdekar N, Zwillich C, Sinoway L.** Surges of muscle sympathetic nerve activity during obstructive apnea are linked to hypoxemia. *J Appl Physiol* 79: 581–588, 1995.
18. **Leuenberger UA, Brubaker D, Quraishi S, Hogeman CS, Imadojemu VA, Gray KS.** Effects of intermittent hypoxia on sympathetic activity and blood pressure in humans. *Auton Neurosci* 121: 87–93, 2005.
19. **Masuda Y, Yoshida A, Hayashi F, Sasaki K, Honda Y.** Attenuated ventilatory responses to hypercapnia and hypoxia in assisted breath-hold drivers (Funado). *Jpn J Physiol* 32: 327–336, 1982.
20. **Mohan RM, Amara CE, Cunningham DA, Duffin J.** Measuring central-chemoreflex sensitivity in man: rebreathing and steady-state methods compared. *Respir Physiol* 115: 23–33, 1999.
21. **Monahan KD, Leuenberger UA, Ray CA.** Effect of repetitive hypoxic apnoeas on baroreflex function in humans. *J Physiol* 574: 605–613, 2006.
22. **Morgan BJ, Crabtree DC, Palta M, Skatrud JB.** Combined hypoxia and hypercapnia evokes long-lasting sympathetic activation in humans. *J Appl Physiol* 79: 205–213, 1995.
23. **Narkiewicz K, Pesek CA, Kato M, Phillips BG, Davison DE, Somers VK.** Baroreflex control of sympathetic nerve activity and heart rate in obstructive sleep apnea. *Hypertension* 32: 1039–1043, 1998.
24. **Narkiewicz K, van de Borne PJ, Pesek CA, Dyken ME, Montano N, Somers VK.** Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. *Circulation* 99: 1183–1189, 1999.
25. **Onrot J, Bernard GR, Biaggioni I, Hollister AS, Robertson D.** Direct vasodilator effect of hyperventilation-induced hypocarbia in autonomic failure patients. *Am J Med Sci* 301: 305–309, 1991.
26. **Peker Y, Hedner J, Kraiczi H, Loth S.** Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. *Am J Respir Crit Care Med* 162: 81–86, 2000.
27. **Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J.** Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. *Am J Respir Crit Care Med* 166: 159–165, 2002.
28. **Read DJ.** A clinical method for assessing the ventilatory response to carbon dioxide. *Australas Ann Med* 16: 20–32, 1967.
29. **Shoemaker JK, Vovk A, Cunningham DA.** Peripheral chemoreceptor contributions to sympathetic and cardiovascular responses during hypercapnia. *Can J Physiol Pharmacol* 80: 1136–1144, 2002.

30. **Sin DD, Jones RL, Man GC.** Hypercapnic ventilatory response in patients with and without obstructive sleep apnea: do age, gender, obesity, and daytime Pa_{CO_2} matter? *Chest* 117: 454–459, 2000.
31. **Somers VK, Dyken ME, Clary MP, Abboud FM.** Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 96: 1897–1904, 1995.
32. **Somers VK, Mark AL, Zavala DC, Abboud FM.** Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. *J Appl Physiol* 67: 2101–2106, 1989.
33. **Tank J, Diedrich A, Schroeder C, Stoffels M, Franke G, Sharma AM, Luft FC, Jordan J.** Limited effect of systemic beta-blockade on sympathetic outflow. *Hypertension* 38: 1377–1381, 2001.
34. **Verbraecken J, De BW, Willemen M, De CW, Wittesaele W, Van dH.** Chronic CO_2 drive in patients with obstructive sleep apnea and effect of CPAP. *Respir Physiol* 101: 279–287, 1995.
35. **Xie A, Skatrud JB, Crabtree DC, Puleo DS, Goodman BM, Morgan BJ.** Neurocirculatory consequences of intermittent asphyxia in humans. *J Appl Physiol* 89: 1333–1339, 2000.