Contrasting effects of isocapnic and hypocapnic hyperventilation on orthostatic circulatory control

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Thijs RD, van den Aardweg JG, Reijntjes RH, van Dijk JG, van Lieshout JJ. Contrasting effects of isocapnic and hypocapnic hyperventilation on orthostatic circulatory control. J Appl Physiol 105: 1069–1075, 2008. First published July 10, 2008; doi:10.1152/japplphysiol.00003.2008.—The effects of hyperventilation (HV) on mean arterial pressure (MAP) are variable. To identify factors affecting the MAP response to HV, we dissected the effects of hypocapnic HV (HHV) and isocapnic HV (IHV) and evaluated the effects of acute vs. prolonged HHV. In 11 healthy subjects the cardio- and cerebrovascular effects of HHV and IHV vs. normal ventilation were examined for 15 min in the supine position and also for 15 min during 60° head-up tilt. The end-tidal CO2 of the HHV condition was set at 15–20 mmHg. With HHV in the supine position, mean cerebral blood flow velocity (mCBFV) declined [95% confidence interval (CI) −43 to −34%], heart rate (HR) increased (95% CI 7 to 16 beats/min), but MAP did not change (95% CI −1 to 6 mmHg). However, an augmentation of the supine MAP was observed in the last 10 min of HHV compared with the first 5 min of HHV (95% CI 2 to 12 mmHg). During HHV in the tilted position mCBFV declined (95% CI −28 to −12%) and MAP increased (95% CI 3 to 11 mmHg) without changes in HR. With supine IHV, mCBFV decreased (95% CI −14 to −4%) and MAP increased (95% CI 1 to 13 mmHg) without changes in HR. During HV in the tilted position MAP was further augmented (95% CI 11 to 20 mmHg) without changes in CBFV or HR. Preventing hypocapnia during HV resulted in a higher MAP, suggesting two contrasting effects of HV on MAP: hypocapnia causing vasodilatation and hyperventilation without hypocapnia acting as a vasopressor.

Although hyperventilation (HV) is frequently listed as one of the causes of syncope (3, 7, 22), there is no convincing evidence that HV by itself can induce syncope (4). The role of HV in syncope is, however, unclear, in that some authors have suggested a contributory role of HV (6, 24), whereas others favored a protective role (27, 28). Whereas cerebral vasoconstriction during HV is unequivocal, there is disagreement in the literature concerning the effects of HV on mean arterial pressure (MAP) as HV was reported to increase (43) or reduce MAP (2, 15, 36) and equally to leave MAP unaffected (21, 25, 40). Since syncope results from cerebral hypoperfusion, an understanding of the MAP response to HV in the context of the cerebrovascular changes may help to elucidate the role of HV regarding the occurrence of syncope. The variety of MAP responses to HV in healthy subjects is unclear. By contrast, in case of sympathetic denervation HV invariably decreases MAP through hypocapnia-mediated vasodilatation (5, 33). Therefore, we considered that hyperventilation with and without hypocapnia could affect MAP differently. In addition, the duration of HV may affect the MAP response. In the majority of studies on the effects of HV on cardiovascular control, HV was applied for a relatively short period of time (~5 min) (15, 21, 25, 36), whereas the metabolic and ventilatory changes differ for short-lived vs. prolonged HV (32, 37). For instance, during prolonged HV end-tidal CO2 tension may become halved with only a 10% increase of ventilation, whereas during acute HV a similar decrease of CO2 tension is reached with a 160% increase of ventilation (10).

We thus hypothesized that the conflicting MAP responses to HV in healthy subjects result from contrasting effects of lowering of CO2 and the associated hyperventilation, with an effect of duration of HV. Therefore, we dissected the effects of hypocapnic HV (HHV) and isocapnic HV (IHV) and evaluated the effects of acute vs. prolonged HHV.

EXPERIMENTAL PROCEDURES

Subjects. Healthy adults [4 men and 7 women; 23 yr old (SD 9), 64 kg body weight (SD 6), and 171 cm in height (SD 6)] participated in the study. No subjects smoked, used recreational drugs, or had significant medical problems. Two subjects had once experienced a typical vasovagal syncope. The subjects were recruited by advertising in the university magazine. The experimental protocol was approved by the Leiden University Medical Centre ethics committee, and all subjects gave their oral and written informed consent.

Protocol. The study protocol is summarized in Fig. 1. To obtain an identical respiration pattern during HV and HHV the protocol was performed in a fixed order: a control period without intervention of normal ventilation (NV), followed by HHV, and finally by HV. NV, HHV, and IHV were preceded by 10 min of supine rest and were first studied in the supine position and subsequently in the 60° head-up tilt (HUT) position. Passive HUT was performed in 12 s (Dewert Tilt Table). The subjects were blinded for the CO2 content of the inspired air. The subjects breathed through a cushion-sealed facemask connected to a two-way nonrebreathing valve (2700, Hans Rudolph, Kansas City, MO) and a heated pneumotachograph (3830A; 3850, Hans Rudolph), delivering flow and tidal volume (VT). The subjects breathed moisturized compressed air from a 100-liter Douglas bag (Hans Rudolph), which was enriched with CO2 in the isocapnic condition. The experiments were performed in a quiet laboratory with an ambient temperature of 23 ± 1°C.

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**Measurements.** Heart rate (HR) was obtained from the electrocardiogram (ECG). A noninvasive measurement of finger arterial pressure was taken throughout the test protocol (Finometer, Finapres Medical Systems, Amsterdam, the Netherlands). The Finometer data were sampled every 10 ms. The transcranial Doppler-derived cerebral blood flow velocity (CBFV) was measured at 2 MHz in the proximal segment of the right middle cerebral artery (MCA) and insinated (TC-2-64 B, EME) through the posterior temporal "window." Once the optimal signal-to-noise ratio was obtained, the probe was secured with a headband to provide a fixed angle of insonation. Stroke volume (SV) was calculated from the blood pressure waveform using the model flow method incorporating age, sex, height, and weight (BeatScope 1.0 software; BMEye, Amsterdam, The Netherlands) (20) that tracks CO accurately during prolonged orthostatic stress (14). An infrared gas analyzer (Capnocheck sleep, BCI, Smiths Medical, Waukesha, WI) measured the end-tidal CO2 tension (PetCO2) through sampling of the expired air.

**HHV.** Custom-written software provided breath-to-breath feedback of the actual respiration pattern. Together with the actual breathing pattern, the target breathing frequency (f) as well as the target of the actual respiration pattern. Together with the actual breathing target PETCO2 was set at 15–20 mmHg. In case PETCO2 exceeded 20 mmHg together with a guided VT dependent on the actual PETCO2. The amount of inspiratory moisturized compressed air was enriched with CO2. The respiratory pattern of the subject was aimed to be identical to the HHV condition. Thus f was set at 20 breaths/min, and the sequence of VT of the previous HHV condition was stored on PC and implemented in the present experiment. The amount of inspiratory CO2 was adjusted manually with the target PetCO2 set at resting eupneic levels.

**Symptom scores.** Thirteen items reported to be associated with HV were questioned directly after HUT for both conditions (17, 47). These included fatigue, headache, anxiety/panic, rapid heart beat, cold hands or feet, muscle stiffness, bloated stomach, dizziness, unrest/tension, paresthesias, blurred vision, chest pain, and inability to think clearly. Symptoms were rated on a 5-point scale [from 0 (never) to 5 (almost always)].

**Data analysis.** All signals were recorded on hard disk (sampling rate 120 Hz, except for ventilatory measurements sampling rate of 10 Hz) for off-line analysis using custom-written software and manual editing. Beat-to-beat values for MCA mean CBFV (mCBFV) and MAP were derived as the integral over one beat divided by the corresponding beat interval. Cardiac output (CO) was the product of SV and HR, and total peripheral resistance (TPR) was expressed as MAP/CO. Cerebral and systemic hemodynamic values were expressed as the averages of 30-s manifestations of MAP, HR, SV, CO, pulse pressure, TPR, and mCBFV. To derive the effects of hyperpnea on cerebrovasculature, the supine mCBFV data are presented both unadjusted and adjusted for hypocapnia given a mCBFV-PetCO2 sensitivity of 2.5%/mmHg in the hypocapnic range (18). No such correction was made for the CBFV data in the HUT position, since there are no reliable data available for the mCBFV-PetCO2 sensitivity during HUT given the complex effects of HUT on the PetCO2-arterial PCO2 (PetCO2) (11) and mCBFV-PetCO2 relationship (19). To evaluate the effects of duration of HHV, we compared the average values of the first 5 min HHV (acute HHV) with the last 10 min of HHV (prolonged HHV).

Our primary outcome measures included MAP and mCBFV. Secondary outcome measures were HR, SV, CO, and TPR. Four types of comparisons were made for the supine and the tilted position: 1) HHV vs. NV, 2) HV vs. NV, 3) acute vs. prolonged HHV, and 4) for MAP only, an additional comparison was made between HHV and HV.

**Statistics.** ANOVA for repeated measures was used with two factors: condition (NV, HHV, and IHV) and position (supine or HUT). If a significant interaction between position and condition was detected, a within-subjects ANOVA per position was performed. When a significant difference was found between the three conditions, paired Student t-tests were used for post hoc comparisons. The Wilcoxon signed rank test was used to compare symptom scores during HHV vs. NV and IHV vs. NV. Data analysis was performed with SPSS software, version 12.0, with two-sided testing. Significance threshold was set at 5%. In case of multiple comparisons the false discovery rate procedure was used to correct the critical significance level (8).

**RESULTS.**

The ventilatory variables (f and breathing minute volume) did not differ significantly between HV and HHV (Table 1). In the supine position PetCO2 was lower during IHV compared with NV (P = 0.001), while PetCO2 during HHV and NV in the tilted position (HHVHUT and NVIHUT) was comparable. No differences were found in baseline circulatory variables before HHV and IHV. The coefficient of variation of the mCBFV measurements of the MCA during NV in the supine position was 4.6%. Excerpts from original tracings in a typical subject are shown in Fig. 2. The effects of HHV and IHV on MAP are given in Fig. 3. Figure 4 demonstrates the temporal profile of HR, MAP, SV, TPR, CO, mCBFV, and PetCO2. In Fig. 5 the changes of MAP during HHV and IHV are plotted in relation to CBFV changes. In Fig. 6 the effects of IHV and HHV on SV, TPR, and CO are plotted.

**HHV vs. NV.** In the supine position with HHV, HR increased [95% confidence interval (CI) 7 to 16 beats/min] and mCBFV declined (95% CI -43 to -34%). In addition, there was a tendency toward an increase of MAP (95% CI -1 to 6 mmHg) and CO (95% CI -2 to 29%), whereas SV and TPR did not change substantially. During HHV in the tilted position (HHVHUT), MAP was higher (95% CI 3 to 11 mmHg) related to a rise of SV (95% CI 1 to 12%) without significant changes of orthostatic HR, TPR, or CO. In addition, HHVHUT caused a reduction of mCBFV (95% CI -28 to -12%).

**IHV vs. NV.** With supine IHV, MAP increased (95% CI 1 to 13 mmHg) together with a reduction of mCBFV (95% CI -19 to -8%) (unadjusted); -14 to -4% (adjusted for changes in

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**Fig. 1. Study protocol.**
No substantial changes of supine HR, SV, CO, or TPR were found. During IHV in the tilted position, both MAP (95% CI 11 to 20%) and TPR (95% CI 10 to 60%) were elevated without significant changes of HR, SV, CO, or mCBFV.

**Acute vs. prolonged HHV.** Supine MAP (95% CI 2 to 12 mmHg) increased in the last 10 min vs. the first 5 min of HHV. This augmentation of MAP was accompanied by an increase of TPR (95% CI 0 to 30%) without significant changes of HR, SV, CO, or mCBFV.

**IHV vs. HHV.** In the supine position with IHV, a small rise of MAP was observed compared with HHV supine (95% CI −1 to 11 mmHg). In the tilted position, IHV significantly augmented MAP compared with HHV (95% CI 4 to 13 mmHg).

**Symptoms.** HHV led to an increased median symptom score: 12 during HHV (25th–75th percentile 6–17) vs. 2 (1–7) for NV ($P = 0.002$). Significant items included paresthesias, muscle stiffness, cold hands or feet, headache, fatigue, and inability to think clearly. The symptom scores during IHV and NV did not differ significantly. None of the subjects experienced a syncope during the experiment.

**DISCUSSION**

Our study provides novel information on the cerebro- and cardiovascular effects of prolonged hyperventilation, yielding four principal findings: 1) prolonged HHV differs from acute HHV in that prolonged HHV gradually increases MAP over time; 2) IHV has a stronger pressor effect on MAP compared...
with HHV; 3) cerebral vasoconstriction is most pronounced during HHV but also present during IHV; and 4) orthostatic stress augments the pressor effect of both HHV and IHV and causes a relative increase of CBFV.

**Limitations.** Before reviewing the major findings, several potential limitations deserve mention. First, despite our efforts to avoid hypocapnia during IHV, PETCO₂ during IHV supine was lower compared with NV supine. This may have underestimated the pressor effect of IHV in the supine position, leading to an underestimation of the pressor effect of IHV in the supine position, given a mCBFV-PETCO₂ sensitivity of 2.5%/mmHg in the hypocapnic range (18).
given the higher MAP with isocapnic vs. hypocapnic HV. In addition, the effects of IHV supine on CBFV should be interpreted cautiously, as even slight decreases of PETCO2, cause cerebral vasoconstriction and thus lower CBFV (46). Second, we assessed changes in PETCO2 rather than PaCO2. PETCO2 closely matches PaCO2 in the supine position, whereas the relation between PETCO2 and PaCO2 is affected by a change of posture (19). The larger alveolar-arterial CO2 difference during orthostasis is probably due to changes in the pulmonary ventilation-perfusion matching (11). With tilting the initial reduction in PETCO2 vs. PaCO2 was larger (1.5–3 mmHg) and from then on remains stable (1, 38). Therefore, the degree of hypocapnia may have been overestimated by ~2 mmHg during HHVHUT, as PETCO2 was used to set the degree of hypocapnia. However, a smaller difference could be expected, as PETCO2 was ~1 mmHg lower during HHVHUT compared with HHV supine. Also when taking into account the differences in PETCO2, PaCO2, and jugular venous PCO2-MCA mean velocity relationship (34), we consider that a similar PETCO2 for IHVHUT and NVHUT makes it unlikely that the alveolar-arterial CO2 difference affected the results of IHVHUT. Third, we did not control or assess changes in end-tidal O2 tension (PETO2). Nevertheless, the amount of hyperpnea was comparable between HHV and IHV, thus probably resulting in similar amounts of hyperoxia. Furthermore, the influence of PETCO2 on blood pressure control in the hypoxic range through modulation of the peripheral chemoreceptor is relatively small (16, 41). Fourth, to create an identical respiration pattern we used a fixed order of the breathing conditions. No significant differences were found in the circulatory variables at the start of each condition. However, we cannot fully exclude crossover effects in the present data. Finally, SV was derived from the blood pressure waveform using the model flow method. Although this method has not been validated for hypocapnia alone, it has been shown that this technique accurately tracks SV changes during moderate hypocapnia (PETCO2 ~30 mmHg) induced by orthostatic stress (14).

Effects of HV on MAP regulation. We compared acute and prolonged HHV and HV with and without hypocapnia and hereby identified two factors affecting the MAP response to HV. First, prolonged HHV gradually augmented MAP over time. Previous studies on the time course of MAP changes during acute HHV demonstrated a MAP fall in the first minute of HHV with a subsequent return to control values within 4 min (2, 36). The MAP increase during prolonged HHV in our study was accompanied by an augmentation of TPR. It is unclear why the MAP response to HHV increases over time. The latency of the response (~5 min) suggests involvement of neurohumoral control mechanisms (13). Poulin et al. (35) indicated that even after 20 min of HHV no steady state in the CBFV response to hypocapnia is reached. The time-dependent effects of HHV in our study may thus be augmented if the period of HHV is extended. Second, preventing hypocapnia during HV (IHV) resulted in a higher MAP, thus suggesting that hypocapnia has a vasodepressive effect and hyperpnea without hypocapnia acts as a vasopressor. The increase of MAP during HV was related to an increase of TPR. IHV reduced baroreflex sensitivity to MAP changes as HHV augmented MAP but did not elicit a reduction of HR or muscle sympathetic nerve activity (44, 45). The “respiratory pump” predominantly modulates venous return within each breath (29). Increase of respiration hereby causes large oscillations of venous return and thus MAP. The baroreflex response to large respiratory MAP oscillations may be relatively blunted as these MAP changes occur at the less steep and less sensitive portion of the sigmoidal baroreflex response curve (44). Additionally, lung stretch afferents suppress the input of baroreceptor afferents centrally at the nucleus of the solitary tract, hereby reducing baroreflex sensitivity (12).

HHV affects vessels both directly and by influencing the vasomotor centers and neurohumoral systems. A direct peripheral vasodilator effect of HV is illustrated by HHV-induced hypotension in patients with sympathetic denervation and in healthy controls after ganglionic blockade (21, 33, 42). It is likely that HHV in patients with sympathetic denervation lowers MAP through hypocapnia, as effects could not be reproduced through other features associated with hyperventilation, such as an increase of pH or arterial Po2, or by an increase of respiratory movements without hypocapnia (33). The MAP responses to HHV in healthy subjects thus contrast to those in patients with autonomic failure, underscoring the importance of integrity of the sympathetic nervous system in the maintenance of normotension during HHV. In accordance, HHV increases muscle sympathetic nerve activity in healthy subjects (40), related to complex interactions between CO2 chemoreflexes and arterial baroreflexes (15, 40). In addition, the sympathetic response to HHV is further modulated by the opioid and the histaminergic system (9, 36). The variable results of HHV on MAP in healthy subjects thus likely result from contrasting effects of HHV on the peripheral vasculature, chemoreflex-baroreflex interactions, neurohumoral system, and...
the respiratory pump. The time dependent effect of HV provides an additional explanation for the variety of results.

The present study confirms data from Shoemaker et al. (40) that HUT increases the pressor effect of both HHV and HV. The augmentation of the HV pressor effect by HUT may be explained by a reduction of baroreflex sensitivity during gravitational stress (11, 48). The reduced baroreflex sensitivity induced by HUT may add to the blunted baroreflex gain seen during IHV (44).

Cerebrovascular responses to HV. The arterial CO2 tension has a pronounced influence on cerebral blood flow (CBF) and hypocapnia induces a reduction in CBF by vasoconstriction (26). As the diameter of the MCA remains stable under hypocapnia, the CBFV is a valid index of changes in CBF (39). The postural reduction of mCBFV as seen in NV is not explained by PaCO2, (19). When assuming the upright position, PETCO2 decreases while overestimating the decline in Paco2, as the primary dominator of the cerebral CO2 responsiveness. The mCBFV-PETCO2 relationship is nonlinear with a lower sensitivity of mCBFV to changes in CO2 in hypocapnia supporting that the postural decrease in mCBFV cannot be accounted for by the cerebral CO2 reactivity (18). As expected, HHV decreased mCBFV both in supine and tilted position. However, the finding of an orthostatic increase of mCBFV with HHV is contrasted with the difference on mCBFV was remarkable and contrasts with the postural reduction of mCBFV as seen in NV is not explained by PaCO2 (19). When assuming the upright position, PETCO2 decreases while overestimating the decline in Paco2, as the primary dominator of the cerebral CO2 responsiveness. The mCBFV-PETCO2 relationship is nonlinear with a lower sensitivity of mCBFV to changes in CO2 in hypocapnia supporting that the postural decrease in mCBFV cannot be accounted for by the cerebral CO2 reactivity (18). As expected, HHV decreased mCBFV both in supine and tilted position. However, the finding of an orthostatic increase of mCBFV with HHV even after correction for the effects of the alveolar-arterial CO2 difference on mCBFV was remarkable and contrasts with the orthostatic decrease seen with NV (18). Possible explanations include the concomitant increased MAP and the lower sensitivity of mCBFV to changes in CO2 during tilt or lower body negative pressure (30, 38).

IHV decreased mCBFV in the supine position, even after adjustment for slight hypocapnia during IHV (18). IHV may decrease CBFV through sympathetic activation (21, 39). However, our study was not designed to elucidate the complex interactions between HV, sympathetic activity, and cerebral perfusion.

Clinical implications. Despite prolonged severe hypocapnia, HHV induced neither syncope nor vasodepression, whereas upright blood pressure increased. This has also been reported earlier: in 1958 Wayne (47) studied 165 healthy subjects who vigorously hyperventilated for several minutes until they could no longer write legibly. In 1963 Saltzman (37) observed 13 healthy subjects during sustained HV for 1 h in the supine position. In neither study was syncope provoked by HV. In addition, the CBFV reduction caused by prolonged HV did not surpass 50% of the resting value, which is considered to be the critical lower limit of cerebral perfusion at loss of consciousness (46). In addition, although HHV led to an increased total symptom score, symptoms that may precede syncope such as dizziness and blurred vision were not increased during HHV. Collectively, these findings underscore that HV by itself is not capable of inducing syncope in healthy subjects. Nevertheless, HV may lower the threshold to loss of consciousness in patients with frequent neurally mediated syncope or autonomic failure (23, 31, 42).

In summary, we found that HHV has a time-dependent effect on MAP. Prolonged HHV gradually augments MAP over time. Preventing hypocapnia during HV (IHV) resulted in a higher MAP. These findings suggest that HHV has two contrasting effects on MAP control: hypocapnia causing vaso-depression and hyperpnea without hypocapnia acting as a vasopressor, through a still undetermined mechanism.

REFERENCES


