HIGHLIGHTED TOPIC | Hypoxia

Hyperventilation, cerebral perfusion, and syncope

R. V. Immink,1,2 F. C. Pott,3 N. H. Secher,4 and J. J. van Lieshout15,6
1Laboratory for Clinical Cardiovascular Physiology, Department of Anatomy, Embryology, and Physiology, AMC Center for Heart Failure Research, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; 2Department of Anesthesiology, University Medical Center, Utrecht, the Netherlands; 3Department of Anesthesia, Bispebjerg Hospital, Copenhagen, Denmark; 4Department of Anesthesia, The Copenhagen Muscle Research Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; 5Department of Internal Medicine, AMC, University of Amsterdam, Amsterdam, The Netherlands; and 6MRC/Arthritis Research UK Centre for Musculoskeletal Ageing Research, School of Life Sciences, University of Nottingham Medical School, Queen’s Medical Centre, Nottingham, United Kingdom

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Immink RV, Pott FC, Secher NH, van Lieshout JJ. Hyperventilation, cerebral perfusion, and syncope. J Appl Physiol 116: 844–851, 2014. First published November 21, 2013; doi:10.1152/japplphysiol.00637.2013.—This review summarizes evidence in humans for an association between hyperventilation (HV)-induced hypocapnia and a reduction in cerebral perfusion leading to syncope defined as transient loss of consciousness (TLOC). The cerebral vasculature is sensitive to changes in both the arterial carbon dioxide (PaCO2) and oxygen (PaO2) partial pressures so that hypercapnia/hypoxia increases and hypocapnia/hyperoxia reduces global cerebral blood flow. Cerebral hypoperfusion and TLOC have been associated with hypocapnia related to HV. Notwithstanding pronounced cerebrovascular effects of PaCO2 the contribution of a low PaCO2 to the early postural reduction in middle cerebral artery blood velocity is transient. HV together with postural stress does not reduce cerebral perfusion to such an extent that TLOC develops. However when HV is combined with cardiovascular stressors like cold immersion or reduced cardiac output brain perfusion becomes jeopardized. Whether, in patients with cardiovascular disease and/or defect, cerebral blood flow cerebral control HV-induced hypocapnia elicits cerebral hypoperfusion, leading to TLOC, remains to be established.

cardiac output; cerebral blood flow; cerebral oxygenation; cerebral metabolism; diabetes; vascular conductance

BRAIN FUNCTION depends on continuous provision of oxygen and nutrients. Interruption of blood supply to the brain for only seconds results in loss of consciousness (LOC). Tight regulation of cerebral blood flow (CBF) is therefore critical although our understanding of the mechanisms controlling CBF in humans has not advanced much since Lassen summarized the fundamentals (54). The control mechanisms of CBF include chemoreceptors and autoregulation, endothelium-mediated signaling, and neurovascular coupling meeting local cerebral metabolic demand (21, 63). Myogenic mechanisms are represented by the brain’s capacity to autoregulate its blood flow and there is evidence for autonomic nervous control of CBF (69, 72, 75, 82, 96, 108, 110). So far the cerebral sympathetic nerve activity (SNA) response to hypotension and hypertension seems different from the muscle SNA response. This holds true as well for the responses of the cerebral vs. brachial circulations to sympathetic stimulation initiated by exercise (31). SNA recorded in the superior cervical ganglion of sheep increases prior to arterial pressure surges provoked by rapid eye movement (REM) sleep, indicating a distinct role for autonomic nervous activity in the prevention of cerebral hypoperfusion (15) until cerebral perfusion pressure increases too much and too long, breaking through the upper limit of autoregulation (103, 105).

Chemoregulation involves the cerebrovascular responsiveness to changes in the arterial carbon dioxide partial pressure (PaCO2) in direct relation to the pH and, to a lesser extent, to the arterial oxygen partial pressure (PaO2). Hypocapnia induced by hyperventilation (HV) has been associated with cerebral hypoperfusion and transient loss of consciousness (TLOC). The PaCO2 and the end-tidal PCO2 (PetCO2) decline when humans stand up (7, 109) (Fig. 1). Specifically, the positional fall in PetCO2 has been alleged the cause of the physiological reduction in CBF when humans stand up (78, 97). Postural stress increases ventilation (VE), and VE may enhance prior to a...
vasovagal faint. Nonetheless HV does not explain TLOC in humans as summarized in this short review.

POSTURE, CBF, AND PCO2

Cerebral autoregulation (CA) indicates that CBF is adjusted in the face of changing perfusion pressure (87). However, when humans assume the upright position, global CBF (93), the transcranial Doppler determined middle cerebral artery (MCA) mean blood flow velocity ($V_{\text{mean}}$) (9, 80), and the near-infrared spectroscopy (NIRS) determined frontal cortical oxygenation ($cO2Hb$) decrease (60, 112). Such reductions in indexes of CBF take place even though the cerebral perfusion pressure remains within what is considered to be the autoregulatory range. This seems to odds with the concept of static CA implicating constancy of CBF for a range of cerebral perfusion pressures, but we may consider that constancy of CBF would require an infinite gain, which generally does not apply in biological systems (77, 88, 112).

The cerebral vasculature is sensitive to changes in PaO2 and in PaCO2, to an extent that hypercapnia/hypoxia and hypocapnia/hypoxia increase, respectively, reduce global CBF. However, when the PaCO2 is deliberately lowered the resulting reduction in MCA $V_{\text{mean}}$ is followed by a slow progressive increase (81) maybe due to an elevated pH by metabolic compensation. The reduction in global CBF in response to hypoxia/hypocapnia results from cerebral vasoconstriction (44, 45, 58) attributed exclusively to PaCO2, and related directly to changes in PH of the cerebral spinal fluid (50, 51, 55, 120). Also there is evidence for the notion that PaCO2 regulates CBF both independently and in conjunction with pH (for review, see 120). The recent finding that hypercapnia impairs neurovascular coupling (62) is pertinent to a role of PaCO2 in the regulation of CBF. Cerebral artery endothelial cells produce nitric oxide in direct proportion to PaCO2, providing a basis for the neurovascular responses to hyper- and hypocapnia (20, 122), although the reduction in MCA $V_{\text{mean}}$ for PaCO2 values below ~20 mmHg becomes smaller (119) this changed CBF-PaCO2 relationship is probably not of major importance for the development of (pre-) syncope, considering that PaCO2 in the presyncopal phase is usually relatively higher (8). Prazosin, an alpha1-adrenoreceptor blocking agent, reduces the cerebral CO2 responsiveness to hypocapnia but not to hypercapnia, alleviating evidence for an interaction between sympathetic activity and CBF CO2 responsiveness (79).

When assuming the upright position the $\text{PETCO}_2$ decreases by ~3.5 mmHg (7, 109) with a reduction of ~15% in MCA $V_{\text{mean}}$ and 7% in the $cO2Hb$ after 5 min in the upright position (30, 39, 80). Both arterial pressure and MCA $V_{\text{mean}}$ become reduced in the initial phase (first 10 s) of an active posture change and also during a vasovagal syncope but the underlying mechanisms are different (111). The initial cardio- and cerebrovascular response to orthostasis is transient and related to the instantaneous increase in vascular conductance in the activated leg muscles. This skeletal muscle vasodilation is not mediated by the autonomic nervous system, since this response is also present in patients with autonomic failure (101, 102, 116). The magnitude of the initial postural fall in blood pressure may be so large that it initiates early (near-) syncope denoted as initial orthostatic hypotension (53, 107, 117). The magnitude of the decrease in $\text{PETCO}_2$ in the initial phase of standing up is, however, limited compared with the reduction observed during vasovagal (pre) syncope (107). In patients with autonomic failure the postural reduction in $\text{PETCO}_2$ differs not much from what is observed in healthy subjects (29, 30) but the fall in MAP at brain level (108 to 31 vs. 86 to 72 mmHg in controls) and in MCA $V_{\text{mean}}$ (84 to 51 vs. 62 to 59 cm/s) is larger (30). Such observations support that in these patients the postural reduction in MAP rather than the limited reduction in $\text{PETCO}_2$ dominates the effect on CBF.

ARTERIAL-TO-END-TIDAL PCO2 RELATIONSHIP AND CEREBROVASCULAR TONE

The sensitivity of CBF to CO2 is expressed as the percentage change in CBF per mmHg PaCO2, (the CO2 reactivity of the brain) (58, 84) and is quantified by relating changes in MCA $V_{\text{mean}}$ to those in $\text{PETCO}_2$. In the normocapnic range, MCA $V_{\text{mean}}$ changes ~3.5% per mmHg $\text{PETCO}_2$ (37, 43). In the MCA territory subserving the largest part of the hemispheres the postural reduction in $\text{PETCO}_2$, of ~5% of the resting value (39) suggests a contribution of hypocapnia to the reduction in cerebral perfusion. However, $\text{PETCO}_2$ tracks changes in the PaCO2 in a fixed body position only. When assuming the upright body position, cardiac output (Q) decreases whereas $V_{E}$ increases resulting in a ~50% increase in the $V_{E}/Q$ ratio (26, 39, 86). Accordingly, the PaCO2-to-$\text{PETCO}_2$ gradient is enhanced and the postural decrease in $\text{PETCO}_2$ overestimates the reduction in PaCO2 ($\Delta \text{PETCO}_2 = -2.75 + 0.84 \Delta \text{PaCO}_2$) (39). Also, when during passive head-up tilt $\text{PETCO}_2$ is clamped to the level in the supine position, MCA $V_{\text{mean}}$ declines in the first minute of tilt only. Afterward the postural reduction in MCA $V_{\text{mean}}$ has become independent of the ~4 mmHg reduction in $\text{PETCO}_2$ (Fig. 2). The postural circulatory response to a reduced central blood volume does not interfere with CA, also when arterial hypotension develops (28). In the presyncopal phase
indexes of cerebrovascular resistance (CVR) decline whereas critical closing pressure (CrCP) increases to a level that approaches MCA diastolic pressure to be followed by a precipitous fall at onset of syncope (14, 122). Presyncopal changes in patients with recurrent syncope and in healthy controls who occasionally faint are in essence similar. It has been suggested that an increase in CrCP related to hypocapnia may offset a fall in CVR, with a reduction in CBF in the presyncopal phase (14). The hypothesis has been advanced that a reduction in $P_{\text{a}}CO_2$ increases cerebrovascular tone prior to a drop in arterial pressure, leading to syncope (106). Prior to and following 5 days head-down bed rest leading to central blood volume depletion, healthy humans were subjected to, respectively, HUT and lower body negative pressure until presyncope. The postural change in $P_{\text{a}}CO_2$ appeared related to an increase in cerebrovascular tone indexed by CVR, CrCP, and resistance area product with a reduction in MCA $V_{\text{mean}}$ when progressing toward syncope, whereas the orthostatic response was dominated by changes in arterial pressure if preceded by head-down bed rest (122).

**HETEROGENEITY OF BRAIN VASCULAR $P_{\text{a}}CO_2$ RESPONSIVENESS**

Recent evidence has been alleged for considerable heterogeneity in the cerebrovascular $P_{\text{a}}CO_2$ responsiveness with regional differences in the CBF response to hypoxia, orthostatic stress, and exercise (90, 92, 119). Orthostatic stress evokes a reduction in blood flow in the internal carotid artery (ICA) but not in the vertebral artery (VA) (90). This heterogeneity has been proposed as being advantageous for the protection of brain stem regions with homeostatic cardiovascular function (90). Under hypoxic conditions, blood flow in the VA but not in the ICA increases in response to lowering of $P_{\text{a}}CO_2$. The $CO_2$ responsiveness of the VA compared with that of the ICA is lower, with the lowest $CO_2$ responsiveness for the external carotid artery (74). This explains much of the hitherto unresolved finding that during graded exercise ICA blood flow initially increased, followed by a decline to the resting level in the later stages of strenuous exercise together with the $P_{\text{a}}CO_2$. In contrast, blood flow in the external and common carotid arteries and in the VA increased proportionally with workload (91). Collectively, these findings indicate that the heterogeneity in $CO_2$ responsiveness among the intra- and extracranial arteries affects the distribution of global CBF flow in response to daily life physiological stress (92). This opens new avenues in the research of cerebrovascular chemoregulation, of relevance for both healthy subjects with orthostatic intolerance and patients with cerebrovascular disease (94).

**HYPERVENTILATION AND SYNCOPE**

The $CO_2$ chemoreflexes and arterial baroreflexes are intertwined at a variety of levels (32, 76), leaving an understanding of the manifold cardiorespiratory interactions extremely complex. The primary stimuli that underlie the HV response during orthostatic stress probably find their origin in both the brain and the periphery. When in the cat the hindlimb is passively moved, both cervical sympathetic and carotid body chemoreceptor activity become enhanced. The sympathetic response likely finds its origin from afferents from the periphery since it was abolished by cutting the leg nerves (4) whereas cervical sympatheticotomy attenuated the latency of the ventilatory response to leg movement. In humans, limb venous distension evokes a strong sympathoexcitatory reflex with ventilatory activation that is no longer present following blockade of limb afferents (4, 18). We speculate that in the upright position the larger BP variability and less stable blood flow enhance fluctuation of $P_{\text{a}}CO_2$ as an input signal to the carotid body chemoreceptors. The interaction of enhanced baroreceptor activity and carotid body chemoreceptor stimulation may modify the respiratory drive (5, 6). Recent data in humans suggest that a postural reduction in CBF as simulated by LBNP modifies the central respiratory chemoreflex by moving its operating point (73). Still, a single stimulus or combination of stimuli that...
convincingly explain the HV response has not been identified (24).

In susceptible subjects spontaneous HV is assumed to play a significant role in the pathophysiology of TLOC in vasovagal syncope (66, 89, 113). Hypocapnia produced a greater reduction in CBF velocity and in forearm vascular resistance in patients with neurally mediated syncope compared with control subjects (70). Accordingly, HV is considered to be contributory to the cerebral hypoperfusion that precedes TLOC (16, 19, 42). Arterial hypocapnia has been associated with orthostatic intolerance and lowering of PaCO2 may reduce the prevailing peripheral vasomotor tone (100). This is manifested in patients suffering from autonomic failure where hypocapnia reduces blood pressure (76). It remains difficult to identify HV as the isolated primary mover toward syncope, considering that enhanced Ve may promote orthostatic tolerance. Enhanced Ve (“the respiratory pump”) (34, 59) along with skeletal muscle activity (“the muscle pump”) combats the postural reduction of the central blood volume. The increase in Ve is assumed to reinforce the cardiovascular adjustments to central hypervolaemia by facilitating venous return (33, 57, 104, 121). Application of an artificial inspiratory resistor was demonstrated to enhance this beneficial circulatory effect (17, 68, 85). In a similar vein, slow breathing may improve symptoms in orthostatic intolerance (59).

Available evidence thus far suggests a contribution of a low PaO2 in developing TLOC but does not settle whether HV is capable in provoking syncope. Also there is uncertainty on the effects of hypocapnia on arterial pressure ranging from no influence to an increase as well as a reduction. In an attempt to dissect the effects of HV, PaCO2 and postural stress, the cardiovascular effects of hypocapnic and isocapnic acute vs. chronic HV were evaluated in both the supine and in the 60° HUT position with the PETCO2 of hypocapnic HV set at 15–20 mmHg, i.e., half of the normal resting value (106). Contrasting effects of HV on arterial pressure with hypocapnia causing vasodepression were found with a vasopressor effect of isocapnic hyperpnea. In the supine position the reduction in MCA mean was larger with hypocapnic HV compared with isocapnic HV (38% vs. 13%). Imposing postural stress reduced MCA mean by 12%, and when combined with isocapnic HV by 15%, whereas hypocapnic HV reduced MCA mean by 36%. In consequence in healthy subjects the contribution of PaCO2 to the physiological postural reduction in MCA mean, if anything, is transient. CBFV and CrCP may become related to PaCO2 prior to HUT-induced syncope (122), but adding hypo-
capnic HV to postural stress does not elicit TLOC in healthy humans (106).

Combining HV-induced hypocapnia with known challengers of cerebral perfusion changes the picture. HV added to acute arterial hypotension by gravity and raised intrathoracic pressure as a prominent example results without exception in TLOC (the “fainting lark”; Fig. 3) (36, 118). Humans exposed to acceleration (+Gz) stress may develop G-force induced LOC (G-LOC) (12, 115). For high-performance fighter aircraft pilots trained to counteract high G forces and equipped with an elaborate anti-G pressure suit, no data are available on actual V˙E and PaCO₂ under combat conditions. It is, however, not unlikely that these pilots hyperventilate which, in combination with a reduction of CBF at high G levels, may occasionally precipitate LOC (114).

Submersion and the release of breath holding activate two powerful antagonistic responses: the “cold shock response” and the “diving response” (98). The cold shock response encompasses inspiratory gasps, hyperventilation, tachycardia, and hypertension in the first 2–3 min of immersion. Healthy volunteers being immersed in ice water started hyperventilating with an increase in both respiratory rate (from 16 to 38 breaths/min) and tidal volume (from 0.9 up to 2.3 liters) with development of hypocapnia (PaCO₂, 38 to 26 Torr) and a 43% reduction in MCA Vmean (Fig. 4) (64). Two participating subjects with a large reduction in MCA Vmean (62% and 68%, respectively) became symptomatic with development of drowsiness, blurred vision, and loss of responsiveness. Voluntary control of the ventilatory response to submersion minimizes the degree of hypocapnia and the fall in MCA Vmean (65).

CBF, OXYGEN DELIVERY, AND AGEING

Physiological ageing is associated with a decline in resting CBF (67, 99). Nonetheless the initial postural decrease in CBF and cerebral oxygenation is more prominent in the young compared with older individuals (47). In contrast, CBF increases by ~25% (95) when the brain is activated, e.g., by exercise (23, 25, 38, 41). In response to exercise the associated increase in CBF enhances cerebral oxygenation whereas, in contrast, muscle oxygenation declines with increasing work rate (83). The increase in CBF from rest to submaximal exercise secures indexes of brain capillary O₂ saturation and O₂ partial pressure until cerebral perfusion and oxygenation decrease at maximal exercise notwithstanding an enhanced fractional O₂ extraction (by ~14%). At maximal exercise MCA Vmean may fall by ~15% accompanied by a further increase in brain O₂ extraction by ~45% (27). Even though in older vs. younger individuals CBF is lower during exercise, brain uptake of O₂ is similar (23). In the later stages of exercise the reduction of the increased CBF to baseline is attributed to the effects of hypocapnia on cerebrovascular conductance (1, 71). Brain function deteriorates when its oxygenation is reduced by more than 10% from the resting level (27, 61, 112) in contrast to skeletal muscles tolerating ~90% O₂ desaturation (3). When brain O₂ demand increases, brain oxygenation is secured only as long as O₂ supply is maintained by enhancing CBF and/or O₂ extraction. Postural reduction of the central blood volume and HV may each aggravate the decline in CBF. Progressing to vasovagal syncope puts brain perfusion in jeopardy due to the competition for O₂ supply with the large and progressively dilating skeletal muscle vascular bed (56). Skeletal muscle blood flow may raise 50-fold (2, 13), but the brain’s potential for vascular recruitment is limited. Failure to augment O₂ extraction is followed by TLOC. The level of CBF associated with TLOC has been studied in a heterogeneous group of subjects including healthy young and older subjects, and subjects with hypertension as well as postural hypotension.

Fig. 4. Heart rate (HR), minute ventilation (V˙E), end-tidal CO₂ tension (PetCO₂), and percentage change in blood flow velocity in the middle cerebral artery (Vmean) before, during, and after ice-water immersion. Variables presented as means ± SD. Modified from (64).
AGEING AND VASCULAR DISEASE

The aforementioned considerations do not necessarily apply to elderly humans or subjects with vascular disease. First, in physiological aging global CBF declines (99) with an ~15% reduction in gray matter flow between the third and fifth decade (67). Second, the anatomic variation of brain arteries is substantial as established by MR angiography revealing incompleteness of the anterior and posterior parts of the circle of Willis in, respectively, 26% and in 58%. An entirely complete completeness of the anterior and posterior parts of the circle of Willis was established in a minority, with a smaller vessel diameter in the elderly (52). Third, the brain vascular response to PaCO2 is not homogeneous throughout the brain, and heterogeneity may apply for myogenic mechanisms as well. Recent data indicate that also CA efficiency is heterogeneous with slower recovery of gray vs. white matter in response to a hypotensive stimulus (35). Finally, orthostatic stress evokes regional differences in CBF related to a transient whereas HV together with postural stress in itself improves cerebral perfusion (48).

In summary, in healthy subjects the contribution of PaCO2 to the physiological postural reduction in CBF, if anything, is transient whereas HV together with postural stress in itself does not lower cerebral perfusion up to TLOC. HV together with cardiovascular stressors, however, may jeopardize brain perfusion. Whether hypocapnia induced by HV may add sufficiently to explain TLOC in patients with cardiovascular disease and impaired in cerebrovascular control is uncertain. Specifically for this rapidly growing category we modestly agree with Seymour Kety and Carl Schmidt: “The possible effects of hyperventilation on cerebral functions are so numerous and so poorly understood that it is impossible at present to evaluate the part played by any single factor with even approximate accuracy” (44).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


