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Syncope : an integrative physiological approach

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Part III

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Effects of Hyperventilation

Can hyperventilation cause syncope?

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Submitted

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Chapter 6

Abstract

Aims: Hyperventilation (HV) is frequently listed as a cause of syncope, but evidence is lacking. We therefore questioned the concept of HV induced syncope.

Methods and results: In 11 healthy subjects the cardiovascular effects of HV versus normal ventilation were examined for 15 min in the supine and 15 min in the head-up tilted position. The target end-tidal CO₂ tension of the HV condition was set at 2.0-2.5%. In both positions HV significantly decreased mean cerebral blood flow velocity (supine: 95% CI -43 to -34%; head-up tilt: 95% CI -28 to -12%). HV caused mild changes of the supine mean arterial pressure (MAP) (95% CI -1 to 6 mmHg). However, a significant increase of the supine MAP was observed during prolonged HV (≥ 5 min) compared with acute HV (< 5 min) (95% CI 2 to 12 mmHg). In the tilted position with HV MAP increased significantly (95% CI 3 to 11 mmHg). Prolonged HV did not provoke syncope in any of the subjects.

Conclusions: HV does not act as a significant trigger for syncope in healthy subjects, as prolonged HV did neither induce syncope nor hypotension. These findings do not support the inclusion of HV in the differential diagnosis of syncope.



Introduction

Hyperventilation (HV) is frequently listed as one of the causes of syncope.^{15,34,48,129} However, according to the ESC guidelines on syncope there is in fact no clear evidence that HV by itself can induce syncope.²⁹ HV can indeed be involved in the chain of events preceding syncope,^{42,154,167} but its role is disputed: some authors have suggested that HV contributes to syncope,^{42,142} whereas others favoured a protective role.^{154,167} How blood pressure (BP) reacts to HV must be understood in order to interpret the pathophysiological significance of HV in syncope. Studies addressing the effects of prolonged HV on orthostatic BP regulation are scarce, as in the majority of studies HV was applied for a relatively short period of time.^{147,201} Prolonged HV differs from short lived HV in metabolic and ventilatory changes.²⁰⁸ For example, during prolonged HV end-tidal CO₂ tension may halve with 10% increase of ventilation only, whereas during acute HV a similar decrease of CO₂ tension is to be reached with 160% increase of ventilation.⁸³ The characteristic deep and rapid breathing is therefore not always clinically evident during prolonged HV obscuring identification of HV-induced syncope. The purpose of this study was thus to question the concept of HV induced syncope by quantifying the cardio- and cerebrovascular effects of short lived versus prolonged HV in healthy subjects in the supine and upright position.

Methods

Subjects

We studied 11 healthy, non-smoking adults (mean (SD): 23 (9) years) without a history of cardiopulmonary disease, who did not currently used any medication except for oral contraceptives. Two subjects had experienced one typical vasovagal syncope in their lives. The subjects were recruited by advertising in the university magazine. The experimental protocol was approved by the Leiden University Medical Centre ethics committee. Informed consent was obtained.

Study Protocol

Each subject was studied during two subsequent conditions in a fixed order: a control condition without intervention of ventilation (normal ventilation; NV) and hyperventilation (HV). Both conditions were applied for 15 minutes in the supine position and for 15 minutes

Chapter 6

during 60 degrees head-up tilt (HUT). Each condition was preceded by 10 minutes of supine rest.

Measurements

Heart rate (HR) was obtained from the electrocardiogram (ECG). Systolic, mean and diastolic blood pressures (BP) were obtained from a continuous recording of finger arterial pressure (Finometer, Finapres Medical Systems, Amsterdam, the Netherlands) maintained at heart level. Changes in finger pressure accurately track changes in intra-arterial pressure both during normotension and hypertension.¹¹⁹ The effects of HV on stroke volume, cardiac output and total peripheral resistance as well as the effects of isocapnic HV on BP control will be discussed elsewhere.

Cerebral blood flow velocity (CBFV) was obtained from transcranial determined pulsed Doppler ultrasound (TC-2-64 B, EME) in the proximal segment of the right middle cerebral artery with the probe secured to provide a fixed angle of insonation. Mean CBFV (mCBFV) was calculated by dividing the sum of systolic CBFV and twice diastolic CBFV, divided by three.

The subjects breathed through a cushion-sealed facemask connected to a heated pneumotachograph (3830A; 3850, Hans Rudolph, Kansas City, MO, USA), by a two-way non-rebreathing valve (2700, Hans Rudolph, Kansas City, MO USA) delivering flow and tidal volumes (TV). An infrared gas analyser (Capnostream, BCI, Smiths Medical, Waukesha, WI, USA) measured the end-tidal CO₂ tension (PETCO₂) through sampling of the expired air.

Hyperventilation

Hyperventilation was induced by implementation of a paced breathing frequency of 20 breaths per minute together with a guided TV dependent on the actual PETCO₂. The target PETCO₂ was set at 2.0-2.5 kPa. Custom written software provided breath-to-breath feedback of the actual respiration pattern. Together with the actual breathing pattern, the target breathing frequency as well as the target inspiratory TV were visualised on a flat screen monitor fixated above the tilt table. In case PETCO₂ exceeded 2.5 kPa the implemented TV increased and, conversely, if the PETCO₂ was lower than 2.0 kPa the target TV was decreased.

Symptom scores

13 items reported to be associated with HV were questioned directly after HUT for both conditions.^{113,263} 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, inability to think clearly. Symptoms were rated on a 5 point scale (from 0 (never) to 5 (almost always)).

Data analysis

All signals recorded on a computer hard disc (sampling rate 120 Hz, except for ventilatory measurements sampling rate 10 Hz) for off-line analysis using custom-written software and manual editing. Mean values were calculated for consecutive epochs of 30 sec and averaged for each condition. Our primary outcome measure was the MAP. Secondary outcome measures included HR and mCBFV.

Statistics

The paired student's *t*-test was used to compare the effects of HV and NV for the supine and the tilted position and the effects of acute (<5 minutes) and prolonged HV (≥5 min) in the supine position. The Wilcoxon signed rank test was used to compare symptom scores during NV and HV. All tests were performed two-sided. Significance threshold was set at 5%.

Results

All subjects were able to maintain PETCO₂ very close to targeted levels throughout the experiment (Table 1). HV led to an increased median symptom score: 12 during HV (25th-75th percentile 6-17) vs. 2 (1-7) for the control condition (*p*<0.01). Significant items included paresthesias, muscle stiffness, fatigue and inability to think clearly.

No subject experienced a syncopal episode during the experiment. Figure 1 depicts the effects of HV on the supine and orthostatic MAP. In the supine position with HV, HR increased and mCBFV decreased significantly but MAP did not change. However, a significant increase of the supine MAP was observed during prolonged HV (≥5 min) compared to acute HV (<5 min) (95% CI 2 mmHg – 12 mmHg). HR and mCBFV did not change over time during supine HV. In the tilted position with HV, MAP increased significantly with a significant reduction of mCBFV. No changes of orthostatic HR were seen.

Table 1 Cardiovascular and respiratory parameters during normal ventilation (NV), hyperventilation (HV) and the change during HV from NV (Δ HV) in the supine and the tilted position.

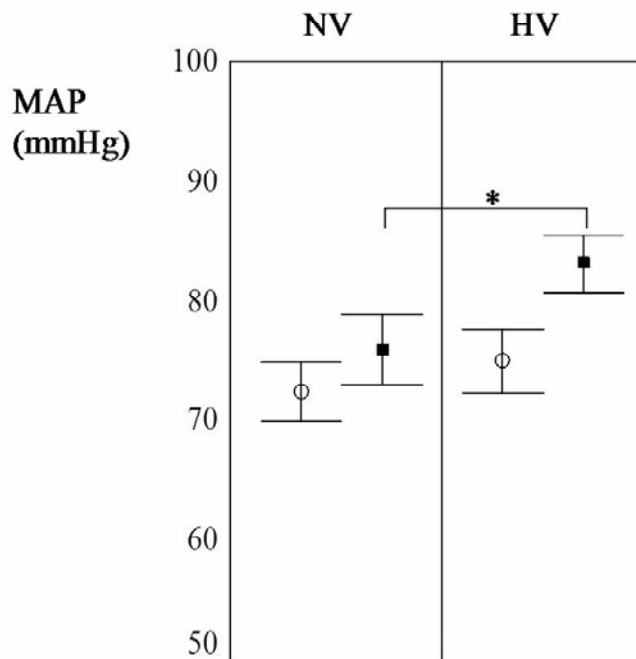
	Supine			60° Head-up tilt		
	NV	HV	Δ HV (95% CI)	NV	HV	Δ HV (95% CI)
Heart Rate (bpm)	63 \pm 3	74 \pm 10	7 to 16‡	79 \pm 8	78 \pm 11	-7 to 4
Systolic BP (mmHg)	116 \pm 9	116 \pm 10	-6 to 6	112 \pm 10	119 \pm 10	1 to 13†
Diastolic BP (mmHg)	51 \pm 10	55 \pm 10	0 to 7	58 \pm 10	65 \pm 8	4 to 10†
MAP (mmHg)	72 \pm 8	75 \pm 9	-1 to 6	76 \pm 10	83 \pm 8	3 to 11†
Δ Systolic CBFV (%)	100	67 \pm 7	-37 to -28‡	88 \pm 8	72 \pm 6	-22 to -9‡
Δ Diastolic CBFV (%)	100	59 \pm 7	-46 to -36‡	89 \pm 6	67 \pm 9	-31 to -13‡
Δ Mean CBFV (%)	100	62 \pm 7	-43 to -34‡	88 \pm 6	69 \pm 8	-28 to -12‡
P _{ET} CO ₂ (kPa)	4.0 \pm 0.2	2.5 \pm 0.2	-1.7 to -1.3‡	3.7 \pm 0.3	2.4 \pm 0.1	-1.6 to -1.1‡
f (bpm)	14 \pm 4	23 \pm 5	6 to 12‡	13 \pm 4	20 \pm 2	4 to 10‡
Δ Ventilation (%)	100	295 \pm 43	160 to 226‡	120 \pm 81	243 \pm 112	87 to 160‡

Values are expressed as mean \pm SD. HR= heart rate; BP= Finger blood pressure; MAP= Mean arterial pressure; Δ CBFV= percentage change of cerebral blood flow velocity from supine NV; P_{ET}CO₂ = end-tidal CO₂ tension; f = breathing rate; Δ Ventilation= percentage change of respiratory flow from supine NV. † Significance p <0.01. ‡ Significance p <0.001.

Discussion

This is the first study to systematically address the concept of HV induced syncope. There are several arguments against HV as a cause of syncope in healthy subjects. Firstly, despite prolonged severe hypocapnia, HV did not induce syncope in our study. This has also been reported earlier: in 1958 Wayne studied 165 healthy subjects after they vigorously hyperventilated for several minutes until they could no longer write legibly.²⁶³ In 1963 Saltzman observed 13 healthy subjects during sustained HV for one hour in the supine position.²⁰⁸ In neither study syncope was provoked by HV. Although both studies lacked continuous BP and CO₂ recordings, these observations underscore that HV does not act as an important trigger for syncope in healthy subjects. Secondly, prolonged HV did not lead to hypotension as seen in syncope,^{29,257} but instead increased orthostatic BP. Finally, the degree of 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.²⁵⁷ Also the CBFV changes during HV differed from vasovagal syncope: HV equally reduced systolic and diastolic CBFV, whereas vasovagal syncope is characterized by a strong reduction of diastolic

Figure 1 Mean arterial pressure (MAP) during normal ventilation (NV) (left box), and hyperventilation (HV) (right box) while supine (open circles) and during head-up tilt (black squares). Values are expressed as mean \pm SEM.
* Significant difference ($p < 0.001$).



CBFV and a nearly unchanged systolic CBFV.²⁵⁷ Collectively, these findings suggest that HV in itself is not capable of inducing syncope in healthy subjects. We cannot however fully discount the theoretical possibility that HV might cause syncope through cerebral vasoconstriction in the absence of any systemic hypotension. Grubb coined the term “cerebral syncope” for this supposed condition.⁹² Since continuous BP recordings were not available in all five reported cases and simultaneous EEG monitoring was performed in one patient only, its existence is still disputable and the differential diagnosis includes vasovagal (pre)syncope and psychogenic pseudosyncope.

We conclude that HV is not a significant trigger for syncope in healthy subjects, and there is therefore no need to include HV in lists of causes of syncope; in fact, its inclusion may harm understanding of the nature of syncope. While we stress that HV by itself does not cause syncope, we acknowledge that it may have more subtle effects as an additional influence in the

presence of syncope. The effects of HV on BP regulation may alter when the cardiovascular regulation has been disturbed as seen prior to vasovagal syncope or in autonomic failure. The episode prior to vasovagal syncope is characterised by a sudden reduction of muscle sympathetic outflow and sympathoadrenal imbalance.⁸⁸ Given these structural changes in cardiovascular control, we cannot extrapolate the effects of HV in the complex chains of events preceding syncope from our results. The effects of HV on the occurrence of syncope are markedly different in patients with autonomic failure. In case of severe sympathetic denervation, HV is capable of inducing hypotension and syncope,^{192,245} which is attributed to a direct peripheral vasodilatory effect of hypocapnia unopposed by baroreflex vasomotor control.¹⁹² The BP responses to HV 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 HV.

