

Effects of voluntary hyperventilation on glucose, free fatty acids and several glucostatic hormones

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Summary

Background: The aim of the present study was to measure the influence of a defined period of standardised voluntary hyperventilation on the levels of glucose, free fatty acids and several glucose regulating hormones in healthy volunteers.

Study design: Eight healthy male subjects were submitted to 20 minutes of controlled hyperventilation and blood levels of glucose, free fatty acids, insulin, glucagon, cortisol, catecholamines and pCO₂ were measured before, immediately after and 20 minutes after the end of the hyperventilation period.

Results: The hyperventilation led to a significant increase in all above mentioned parameters, except for glucose, where the effect was negligible.

Conclusions: In view of the frequency of accompanying hyperventilation in a great variety of diseases and notably in some intensive care patients we postulate that pitfalls in the interpretation of plasma values of substances involved in glucose metabolism may be avoided by simultaneous determination of arterial pCO₂.

Keywords: hyperventilation; glucose; insulin; glucagons; cortisol; catecholamines

Introduction

Hyperventilation is a clinical syndrome which accompanies many somatic diseases and emergencies [1]. It is observed during exercise and in people ascending to high altitude [2], it accompanies delivery [3] and occasionally pregnancy [4], and finally, it often has a purely emotional origin [5], as a regular companion of anxiety and stress.

Hyperventilation is defined as an inappropriately increased alveolar ventilation with decreased partial pressure of CO₂. Hyperventilation itself causes a variety of symptoms such as behavioural

changes, hyper-excitability, cold sweats [6], hypovolaemia [7] and even haematological changes [8]. These symptoms often mimic those of hypoglycaemia [9]. However it is not known whether hypoglycaemia can cause hyperventilation or vice versa.

The aim of the present study was to measure the consequences of a defined period of standardised voluntary hyperventilation on glucose and its regulating hormones in healthy volunteers.

Methods

Subjects

Eight healthy male volunteers with a mean age of 25.4 (±1.6) years and a mean body mass index of 21.7 (±0.91) kg/m² took part in the study. They were non-smokers, had no bronchial asthma and had never suffered from chronic hyperventilation, epilepsy or other severe diseases. There was no positive family history of diabetes mellitus or epilepsy.

The volunteers were instructed not to drink any alcohol three days before the start of the test. They received written and verbal information about the trial and signed a consent form.

Study protocol

Subjects were randomised to two groups, each consisting of four volunteers, acting as a control group as well as a hyperventilation group in a cross-over scheme.

The study was approved of by the ethical committee of the University Hospital Berne.

Between 8.00 and 9.00 a.m., after overnight fasting, a plastic cannula (22 G) was inserted in a cubital vein and kept patent with a plastic mandrin. Following a rest period of at least 10 minutes in a supine position, venous blood samples were taken. Thereafter hyperventilation was initiated with a breathing frequency of 20/minute syn-

chronised by a metronome. The subjects were instructed to breathe as deeply as possible over a period of 20 minutes at the given frequency. The end-expiratory $p\text{CO}_2$ registered by a Capnometer (Capnocount® mini by Andos) was aimed at values <25 mm Hg (<3.3 kPa). After 20 minutes of hyperventilation, blood was sampled again and the volunteer was then asked to breathe normally. After a 20-minute rest (supine), another blood sample was taken. Following each blood sampling, the capillary blood glucose was additionally determined from the finger-tip.

Apart from hyperventilation, the control group underwent the same procedure as the study group. The lag period between the two tests was between 2 and 3 days.

Blood samples

Plasma concentrations of glucose, glucagon and catecholamines and serum concentrations of insulin, cortisol and free fatty acids were measured according to standardised techniques.

Statistics

The data was analysed with the Wilcoxon signed rank test. The results are given as mean $\pm$ SD. The respective differences (d1, d1 control) between the values after 20 minutes hyperventilation/control ("middle") and the respective starting values ("begin") were compared. The differences (d2, d2c) between the values of the last blood sample ("end") and the respective starting values ("begin") were handled as above.

Results

The degree of hyperventilation is documented by a drop in $p\text{CO}_2$ from 35.5 ± 2 mm Hg (4.75 ± 0.27 kPa) to 17.4 ± 1.7 mm Hg (2.32 ± 0.23 kPa) and by the following physical symptoms and signs: numbness and paraesthesia mostly of the hands in 87.5%, carpopedal spasm in 75%, epigastric distress in 62.5%, giddiness in 50%, disturbance of both consciousness and blurring of vision in 37.5%, both fatigue and precordial pressure in 25% and occasionally nervousness, "heaviness," tremor and euphoria. The symptoms were rapidly reversible except in one subject with tremor lasting 40 minutes after cessation of voluntary hyperventilation.

Plasma glucose did not change significantly at the end of hyperventilation but was significantly higher 20 minutes after the end of hyperventilation than in the control group.

Free fatty acids showed a highly significant transient rise at the end of hyperventilation.

Plasma insulin was more than double the initial value at the end of hyperventilation and remained somewhat elevated even 20 minutes after ending hyperventilation.

Plasma cortisol showed a transient rise at the end of hyperventilation, which was significantly different from the change in the control group.

Plasma glucagon also showed a transient significant rise.

Plasma adrenaline showed a rise of more than three times the initial value and remained significantly elevated even 20 minutes after ending the experiment. Noradrenaline rose up to a third of the initial value.

The heart rate rose during hyperventilation and dropped below the initial rate after 20 minutes of normal breathing.

Discussion

The previously unknown and surprisingly drastic changes in substrate and hormone parameters induced by voluntary hyperventilation in healthy young volunteers include a significant rise in free fatty acids, a significant doubling of plasma insulin and a significant increase of plasma glucagon and plasma cortisol. The dramatic increase in plasma catecholamines has been documented in previous work [7]. Despite these marked changes the effect of hyperventilation on plasma glucose was negligible.

Interpretation of the findings is difficult. It seems possible that the simultaneous increase of insulin and of hormones which up-regulate glucose, including catecholamines, maintained glucose-homeostasis, at least till the end of the 20 minute hyperventilation period.

The increase in the various hormones and in free fatty acids may be due both to increased res-

piratory work and contraction of skeletal musculature. It is well known that exercise leads to a comparable increase in catecholamines [10]. In exercise the rise in insulin may be a consequence of increased glycogenolysis and the increase in free fatty acids a consequence of activation of the hormone-sensitive lipase. It is also known that catecholamines have a direct β -adrenergic stimulatory effect on the secretion of glucagon by islet cells. However, their effect on insulin secretion is inhibitory, mediated by α -adrenergic mechanisms, with a weaker stimulatory effect being mediated by β -adrenergic mechanisms [11]. Glucagon itself may stimulate insulin secretion and repeated measurements during the 20 minute hyperventilation period may give better insight into the sequence of events.

Although interpretation of the drastic metabolic changes induced by a simple 20 minute vol-

Table 1

Data table.

		Control		Hyperventilation		
		Mean ± SD	Diff. 1; 2	Mean ± SD	Diff. 1; 2	p
Glucose (mmol/l)	B	4.9 ± 0.3		4.9 ± 0.3		
	M	4.9 ± 0.3	0.0	4.8 ± 0.4	– 0.1	p = 0.32
	E	4.9 ± 0.3	0.0	5.1 ± 0.2	+ 0.2	p = 0.03
Free Fatty Acids (mmol/l)	B	0.42 ± 0.18		0.41 ± 0.20		
	M	0.33 ± 0.15	– 0.09	0.67 ± 0.35	+ 0.26	p = 0.01
	E	0.35 ± 0.18	– 0.07	0.45 ± 0.18	+ 0.04	p = 0.2
Insulin (mU/l)	B	5.3 ± 0.6		5.8 ± 1.9		
	M	5.2 ± 1.3	– 0.1	11.7 ± 7.4	+ 5.9	p = 0.03
	E	5.5 ± 2.4	+ 0.2	8.7 ± 2.7	+ 2.9	p = 0.09
Cortisol (nmol/l)	B	501.4 ± 136.7		520.5 ± 82.5		
	M	385.9 ± 62.3	– 115.5	529.5 ± 89.9	+ 9	p = 0.01
	E	350.6 ± 65.4	– 150.8	429.5 ± 109.7	– 91	p = 0.48
Glucagon (pg/ml)	B	101.2 ± 27.3		102.4 ± 30.9		
	M	91.6 ± 36.9	– 9.6	122.2 ± 39.7	+ 19.8	p = 0.02
	E	91.0 ± 33.3	– 10.2	100.9 ± 28.8	– 1.5	p = 0.16
Adrenaline (pmol/l)	B	184.9 ± 150.3		153.6 ± 85.1		
	M	164.0 ± 114.3	– 20.9	560.7 ± 469.2	+ 407.1	p = 0.03
	E	123.0 ± 63.6	– 61.9	194.0 ± 88.9	+ 40.4	p = 0.01
Noradrenaline (pmol/l)	B	736.5 ± 664.7		614.2 ± 156.1		
	M	560.6 ± 212.4	– 175.9	922.5 ± 552.8	+ 308.3	p = 0.06
	E	557.2 ± 256.9	– 179.3	480.6 ± 201.1	– 133.6	p = 0.32
Pulse (/min)	B	63 ± 11		71 ± 8		
	M	59 ± 8	– 4	91 ± 12	+ 20	p = 0.01
	E	58 ± 6	– 5	60 ± 6	– 11	p = 0.16

SD: standard deviation
 Diff.: differences; diff. 1 = M–B; diff. 2 = E–B
 B: Begin: starting values
 M: Middle: values after 20 minutes
 E: End: last blood sample
 p: p values of the respective differences

untary hyperventilation remains speculative, our findings are definitely of clinical relevance since a comparable degree of hyperventilation is a frequent finding in many diseases and even more commonly encountered in the intensive care setting. Extrapolation of our findings in acute hyperventilation to patients hyperventilating chronically, e.g., under some intensive care circumstances is difficult. To assess glucose homeostasis under controlled chronic hyperventilation would necessitate respirator assisted mechanical hyperventilation, which seems an impossibility in volunteers and would be extremely difficult in intensive care patients due to the innumerable confounding factors. As long as such studies are not available it seems reasonable to state that values for plasma hormones of glucose metabolism and free fatty acid blood levels cannot be interpreted without simultaneously determining arterial pCO₂ as a measure of actual hyperventilation.

The findings associated with acute hyperventilation are also relevant for the work-up of patients with hypoglycaemia, hyperinsulinaemia and suspected insulinoma. For example, we have found extreme hyperventilation and no evidence of insulinoma in a 20-year-old girl referred because of recurrent marginal hypoglycaemia and occasional hyperinsulinaemia of up to 34–57 mU/l. Again, the simultaneous measurement of arterial pCO₂ appears to be mandatory to avoid pitfalls in the interpretation of abnormal hormone values.

Finally, our study has shown that acute hyperventilation does not induce hypo- or hyperglycaemia in healthy volunteers. However, the number of volunteers was too small to exclude an imbalance of the homeostatic mechanisms in some individuals leading to a hyperventilation-induced rise or fall of plasma glucose.

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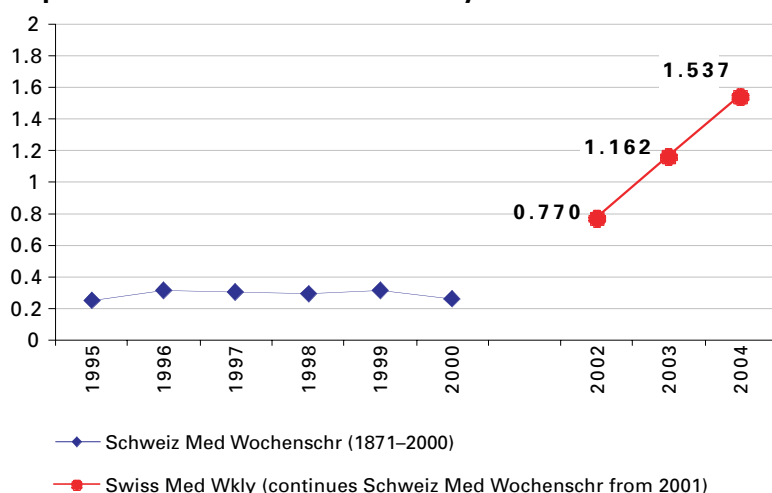
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