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Hyperventilation-induced changes of blood cell counts depend on hypocapnia

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Abstract. Voluntary hyperventilation for 20 min causes haemoconcentration and an increase of white blood cell and thrombocyte numbers. In this study, we investigated whether these changes depend on the changes of blood gases or on the muscle work of breathing. A group of 12 healthy medical students breathed 36 $l \cdot min^{-1}$ of air, or air with 5% CO_2 for a period of 20 min. The partial pressure of CO_2 decreased by 21.4 mmHg (2.85 kPa; $P<0.001$) with air and by 4.1 mmHg (0.55 kPa; $P<0.005$) with CO_2 enriched air. This was accompanied by haemoconcentration of 8.9% with air ($P<0.01$) and of 1.6% with CO_2 enriched air ($P<0.05$), an increase in the lymphocyte count of 42% with air ($P<0.001$) and no change with CO_2 enriched air, and an increase of the platelet number of 8.4% with air ($P<0.01$) and no change with CO_2 enriched air. The number of neutrophil granulocytes did not change during the experiments, but 75 min after deep breathing of air, band-formed neutrophils had increased by 82% ($P<0.025$), whereas they were unchanged 75 min after the experiment with CO_2 enriched air. Adrenaline and noradrenaline increased by 360% and 151% during the experiment with air, but remained unchanged with CO_2 enriched air. It was concluded that the changes in the white blood cell and platelet counts and of the plasma catecholamine concentrations during and after voluntary hyperventilation for 20 min were consequences of marked hypocapnic alkalosis. It was found that minimal changes of the blood gases, the muscle work of breathing, the chest movements or mechanical influences on the spleen did not contribute to hyperventilation-induced changes of these variables.

Key words: White blood cells – Erythrocytes – Hyperventilation – Adrenaline – Noradrenaline

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Introduction

In a previous study, we found that voluntary hyperventilation for 20 min in healthy volunteers was accompanied by haemoconcentration and an increase of lymphocyte and platelet counts during, and an increase of the granulocyte count after the experiment (Stäubli et al. 1985). We have reported that hyperventilation mobilizes neutrophil granulocytes and lymphocytes from a nonsplenic pool, but that the hyperventilation-induced increase of the platelet count was entirely due to mobilization from the spleen (Stäubli et al. 1988). Another group of authors (Mooney et al 1986) have reported on a hyperventilation-associated change in the T-cell helper:suppressor ratio 45 min after a hyperventilation test of 3 min in patients with chronic symptomatic hyperventilation. Such a redistribution of peripheral blood lymphocytes was however not observed in healthy controls. The absolute number of lymphocytes remained unchanged in both groups. In the present paper, we investigated whether hyperventilation-associated changes of blood cell counts are due to the muscle work of hyperventilation or to the hyperventilation-induced changes of blood gases.

Since elevated concentrations of adrenaline and noradrenaline in active hyperventilation have been observed (Stäubli et al. 1986), the concentrations of these hormones were also measured to evaluate their possible contribution to the changes in the blood count.

Methods

Subjects. A group of healthy male medical students [age 22.5 (SD 1.0) years; body mass 72.8 (SD 4.6) kg; height 181 (SD 6) cm] were included in the study which was performed according to the declaration of Helsinki. They had normal physical characteristics, in particular normal blood pressure, resting electrocardiogram and no splenomegaly. There was no history of bronchial asthma, hyperventilation or epilepsy. None had been involved in blood donation or heavy physical exercise in the previous month and all were nonsmokers.

Study design. All the volunteers participated in two experiments with hyperventilation. One experiment was performed breathing air and the other a gas containing 5% CO_2. Of the group, 5 subjects performed the experiment with CO_2 first, while 7 subjects performed the experiment with air first. Both experiments were separated by at least 1 week. For technical reasons, the experiments took place in the afternoon. On the day of the experiments the subjects had a normal breakfast but only a light lunch, i.e. without meat and low in fat. Coffee was not allowed.

To assess the respective effects of respiratory work and hypocapnia, the experiments were performed with constant respiratory volumes in both experiments. This allowed us to exclude the possibility that the observed changes were due to differences in the muscle work of breathing.

Experimental procedure. The participants arrived in the laboratory at 1630 hours. After resting in a supine position, blood samples were taken at 1700 hours ('before hyperventilation'). Hyperventilation with air or a gas mixture with 5% CO_2, 21% O_2 and 74% N_2 was started at 1715 hours. The rate of breathing was synchronized to at a pace of 20 $\cdot$ min^{-1} using a metronome. After 20 min of hyperventilation a second blood sample was taken (during hyperventilation) and then the subject returned to normal respiration of air. A third blood sample was taken 75 min after the end of hyperventilation.

A volume of 36 l $\cdot$ min^{-1} of air or CO_2-enriched air was supplied from bottles (Carba AG, Bern, Switzerland) and the volume of the gas was checked by a flow meter. The gases were humidified by passing through water and then supplied to a rubber balloon with a capacity of about 15 l. From the balloon the gas flowed to a mouth-piece with a unidirectional valve. measured immediately before entry to the mouth-piece, gas temperature was 24° C and humidity 50%. The rubber balloon was visible to the subjects. Each participant adjusted his tidal volume to the state of filling of the balloon so that on average its volume remained constant.

Blood samples. Under a venous stasis of 40 mmHg (5.3 kPa) blood samples were taken by the puncturing of a cubital or antebrachial vein at each stage. A quantity of 4 ml of blood, anticoagulated with potassium ethylendiaminetetra-acetate was used for determination of erythrocyte, leucocyte and platelet counts in a Coulter Counter S+ automatic particle counter and for blood smears. An amount of 200 leucocytes were differentiated by an independent technician. A sample of 2-ml heparinized blood (125 USP U $\cdot$ ml^{-1} Liquemin Roche, Hofmann-La Roche, Basel, Switzerland) was put on ice and analysed for pH and partial pressure of CO_2 (PCO_2) using a blood gas analyser (model 1303, Instrumentation Laboratories, Lexington, Mass., USA) . A sample of 5 ml heparinized blood (7.5 USP U ammonium heparinate $\cdot$ ml^{-1}) was put on ice and centrifuged at 4° C and the plasma was stored at −20° C for determination of adrenaline and noradrenaline (Da Prada and Zürcher 1976).

Calculations. The total leucocyte as well as granulocyte, lymphocyte, and thrombocyte counts during and after the experiments were compared with the respective expected counts (Stäubli et al. 1985). Expected counts were derived from the counts before deep breathing by correcting them for the individual change in erythrocyte count, e.g. the expected platelet count during hyperventilation (HV) = platelet count before

$$HV \times \frac{\text{erythrocyte count during } HV}{\text{erythrocyte count before } HV}$$

Expected values for white cells were calculated accordingly. Percentage increases were calculated from expected values.

Statistics. The data were analysed using Student's t-test for paired samples. Differences were considered statistically significant at values of $P<0.05$ (two-tailed).

Results

Clinical observations

During the experiments without CO_2, all the subjects experienced tetanic muscle contractions and showed mydriasis. During the experiment with CO_2, no tetanic symptoms or signs of adrenergic stimulation were observed. The baseline heart rates of 72 (SD 12) beats $\cdot$ min^{-1} before the experiment without CO_2 and of 69 (SD 12) beats $\cdot$ min^{-1} before the experiment with CO_2 were identical ($P>0.1$), but the heart rates of 105 (SD 17) beats $\cdot$ min^{-1} during the experiment without CO_2 and of 81 (SD 11) beats $\cdot$ min^{-1} during the experiment with CO_2 were different ($P<0.001$). Compared to baseline, there was a small but significant decrease of PCO_2 of −4.1 (SD 4.0) mmHg [−0.55 (SD 0.53) kPa] in the experiment with CO_2. This change was accompanied by a small but significant increase of the pH and a 1.6% increase of the red cell count, which was also significant (Table 1). There was no correlation between this change in the red cell count and the change in the PCO_2 ($P>0.5$) or the pH ($P>0.5$). The decrease of the PCO_2 of 21.4 (SD 7.0) mmHg [2.85 (SD 0.93) kPa] in the experiment with air was associated with an increase of the pH and an increase of

Table 1. Partial pressure of CO_2 (PCO_2), pH, red cell count before, during and after hyperventilation with air and with air supplemented with 5% CO_2

	Experiment	n	Before hyperventilation		During hyperventilation		P	75 min After hyperventilation		P
			mean	SD	mean	SD		mean	SD	
PCO_2	+5% CO_2	12	48.6	3.2	44.5	3.8	<0.005	48.8	4.2	>0.1
(mmHg)	air	12	46.8	3.6	25.4	5.0	<0.001	47.1	2.8	>0.1
pH	+5% CO_2	12	7.38	0.02	7.41	0.03	<0.005	7.38	0.02	>0.1
	air	12	7.39	0.02	7.55	0.06	<0.001	7.39	0.01	>0.1
Red cell count	+5% CO_2	12	5.15	0.28	5.23	0.23	<0.05	5.19	0.24	>0.1
($\cdot 10^{12} \cdot l^{-1}$)	air	12	5.07	0.29	5.52	0.20	<0.01	5.11	0.23	>0.2

P Values refer to significance of comparison with before hyperventilation

Table 2. White blood cells and platelets before, during and after hyperventilation with air and air supplemented with 5% CO_2

	Experiment	n	Before hyperventilation 1700 hours		During hyperventilation 1735 hours				P	75 min After hyperventilation 1850 hours				P
					Expected		Observed			Expected		Observed		
			mean	SD	mean	SD	mean	SD		mean	SD	mean	SD	
Total leucocyte count	+5% CO_2	12	5.20	0.18	5.28	0.83	5.58	0.93	<0.05	5.24	0.82	5.88	0.85	<0.025
($\cdot 10^9 \cdot l^{-1}$)	air	12	5.87	1.24	6.37	1.18	7.18	1.38	<0.001	5.90	1.15	7.33	1.72	<0.025
Lymphocytes	+5% CO_2	12	1.83	0.37	1.86	0.36	1.96	0.36	NS	1.85	0.35	1.83	0.49	NS
($\cdot 10^9 \cdot l^{-1}$)	air	12	1.85	0.40	2.01	0.42	2.85	0.59[a]	<0.001	1.87	0.41	1.66	0.49	NS
Band-formed neutrophils	+5% CO_2	12	0.29	0.22	0.30	0.23	0.32	0.21	NS	0.30	0.22	0.37	0.26	NS
($\cdot 10^9 \cdot l^{-1}$)	air	12	0.42	0.33	0.45	0.34	0.41	0.33[a]	NS	0.42	0.32	0.76	0.45	<0.025
Segmented neutrophils	+5% CO_2	12	2.45	0.90	2.58	0.91	2.68	0.94	NS	2.56	0.90	3.09	0.92	<0.05
($\cdot 10^9 \cdot l^{-1}$)	air	12	3.12	1.01	3.37	1.01	3.17	0.83[a]	NS	3.13	0.96	4.21	1.63	<0.05
Total neutrophils	+5% CO_2	12	2.83	0.92	2.87	0.93	3.00	1.01	NS	2.85	0.92	3.46	0.99	<0.05
($\cdot 10^9 \cdot l^{-1}$)	air	12	3.53	1.24	3.82	1.24	3.57	0.98	NS	3.55	1.17	4.97	1.82	<0.05
Platelets	+5% CO_2	12	209	29	213	30	210	31	NS	211	30	207	29	NS
($\cdot 10^9 \cdot l^{-1}$)	air	12	208	28	227	33	246	38	<0.01	210	30	203	24	NS

[a] $n=11$; P, significance of difference between expected and observed values; NS, not significant

Table 3. Catecholamine concentrations before, during and after hyperventilation with air and air supplemented with 5% CO_2

	Experiment	n	Before hyperventilation		During hyperventilation		P	75 min After hyperventilation		P
			mean	SD	mean	SD		mean	SD	
Adrenaline	+5% CO_2	12	76.4	30.1	69.3	35.0	>0.20	78.8	35.7	>0.50
($pg \cdot ml^{-1}$)	air	12	89.9	39.4	419.8	168.7	<0.0001	77.6	23.8	>0.05
Noradrenaline	+5% CO_2	12	284	69	298	82	>0.20	277	60	>0.20
($pg \cdot ml^{-1}$)	air	12	304	39	762	203	<0.0001	274	38	<0.01

P values refer to significance of comparisons with before hyperventilation

the red cell count by 8.9% (Table 1). There was no correlation between this change of the red cell count and the change of the PCO_2 ($P>0.5$) or the pH ($P>0.2$).

Table 2 shows the results of the white blood cell differentiation and the platelet counts. During hyperventilation with air, lymphocyte and platelet numbers increased by 42% and 8.4% as compared to expected values. In contrast, neutrophil numbers did not change. During hyperventilation with CO_2 enriched air there were no changes of lymphocyte, platelet and neutrophil counts. At 75 min after hyperventilation with air however, the total neutrophil count had increased by 40%. This was due to an increase of band-formed and segmented neutrophils. At this stage, after hyperventilation with CO_2 enriched air, the total neutrophil count had also increased by 21%, which was entirely due to an increase of segmented forms. At the same time lymphocyte and platelet counts had returned to the values before hyperventilation.

Table 3 shows an increase in adrenaline concentration of 360% and in noradrenaline concentration of 151% during the experiment with air, but shows no change during the experiment with CO_2.

Discussion

This study demonstrated that the addition of 5% CO_2 to the inspired air prevented the increases of lymphocyte and platelet counts and of plasma concentrations of catecholamines during acute hyperventilation. Since ventilation was equal in both experiments, we concluded that changes in these blood cells and hormones during hyperventilation with normal air depended on hypocapnia and not on the work of breathing. However, the addition of 5% CO_2 did not maintain isocapnia in all the subjects during hyperventilation. This minor respiratory alkalosis in addition to the work of breathing, may have contributed to the increases of 1.6% in the red cell count during and of 21% in the neutrophil count after hyperventilation with CO_2 enriched air. It is more likely, however, that the increased neutrophil count with CO_2 enriched air was due to rest in a supine position, as has been demonstrated in earlier control experiments (Stäubli et al. 1985). Furthermore, the changes in the red cell count within this small range (Table 1) in hyperventilation with CO_2 enriched air were not correlated with the changes of PCO_2 and pH

and changes in the red cell count did not affect the analysis of our data, since we compared the cell counts with expected values corrected for the changes in the erythrocyte count.

Breathing of air resulted in a similar degree of haemoconcentration as has been observed in earlier studies (Stäubli et al. 1985, 1986; Straub and Bühlmann 1970). The increase of the erythrocyte concentration of 8.9% in the experiment with air compared to only 1.6% in the experiment with CO_2 enriched air shows that more than four fifths of the increase of the erythrocyte concentration in the experiment with air was not due to muscle work or chest movements, but to the associated changes of the blood gases.

The percentage increase in the lymphocyte count in marked respiratory alkalosis was smaller than in hyperventilation without a tube system although the decrease of 19.4 mmHg (2.6 kPa) of the PCO_2 (Stäubli et al. 1985) was virtually identical to the change in the present study. From the lymphocyte data (Table 2) we concluded that neither the muscle work of breathing nor the movements of the lungs contributed to the hyperventilation-induced increase of the lymphocyte count. It could also be concluded that mechanical factors acting on the spleen during deep breathing did not play a causal role in the hyperventilation-induced increase of the lymphocyte count. This is in line with the observation that the same number of lymphocytes is mobilized during hyperventilation in splenectomized and nonsplenectomized subjects (Stäubli et al. 1988). Intramuscular injection of 1 mg of adrenaline (Steel et al. 1971) has been shown to be associated with an increase of the blood lymphocyte count by 100% within a few minutes. The increase of plasma adrenaline concentration in the experiment with air may therefore have played a role in the increase of the lymphocyte count.

The granulocyte count did not change during deep breathing of CO_2 or air and it would seem that this clearly demonstrated that neither the respiratory work and chest movements nor the hypocapnic alkalosis had immediate effects on neutrophil mobilization. The numbers of band-formed and segmented neutrophils increased 75 min after deep breathing of air, whereas with 5% CO_2 only the number of segmented neutrophils rose significantly. The changes in the neutrophil counts during the experiment with air were similar but less pronounced, compared to those using room air without a tube system (Stäubli et al. 1985, 1988).

The increase in the thrombocyte count of 8.4% during deep breathing of air confirmed our earlier experience, although, as for the lymphocytes, the increase was smaller than in the earlier study (Stäubli et al. 1985). It has been shown that the increase in the thrombocyte count very clearly depends on the presence of the spleen (Stäubli et al. 1988) and this study showed that it also depends on the changes of the blood gases. Mechanical influence on the spleen by ventilatory movements does not therefore contribute to the increase of the thrombocyte count. It can be concluded that hyperventilation-associated metabolic changes mobilized platelets from the spleen. It has been demonstrated that adrenaline injection in the splenic artery increases the thrombocyte count in the splenic vein in patients with hypersplenic syndromes (Wright et al. 1951) and that the spleen contracts. By ultrasound investigation, Schaffner et al. (1985) have observed that enlarged spleens contracted when adrenaline was injected subcutaneously and that this contraction was associated with an increase of the thrombocyte count in the peripheral blood, which was proportional to the change in the splenic dimensions. These observations would seem to suggest that the catecholamine release in this study could have played a role in the hyperventilation-induced mobilization of platelets from the spleen. This is supported by the observation that propranolol decreased the mobilization of platelets by about 50% (Stäubli et al. 1988).

Bierman et al. (1952) have demonstrated that a pulmonary platelet pool can be mobilized by intravenous injection of adrenaline and Freedman et al. (1977) have found that a nonsplenic platelet pool can be mobilized by vigorous exercise in man. As an extension to the earlier findings that platelets cannot be mobilized by hyperventilation in splenectomized subjects (Stäubli et al. 1988), this study provided no indication that pulmonary or other nonsplenic platelet pools were mobilized by the muscle work of deep breathing for 20 min.

Possible causal relationships between hypocapnia, catecholamines, haemoconcentration and white cell counts

Since there have been no previous investigations concerning the mechanisms which connect red and white blood cell concentrations and hypocapnic alkalosis, possible causal relationships will be discussed briefly. It is likely that the changes of these blood cell concentrations, which occur within 20 min of hyperventilation, are the result of cell redistribution in the blood and the lymphatic vessels. Therefore, changes of flow conditions in blood and lymphatic vessels during hyperventilation are probably causally involved in cell redistribution. Changes in the flow conditions as induced by changes of vascular tone and, therefore, resistance have been found to depend on the hyperventilation time and on the region of the body (Richardson et al. 1961). During the 1st min of hyperventilation it has been shown that a net systemic vasodilatation takes place, which is probably mediated by histamine (Kontos et al. 1972). During the subsequent minutes of hyperventilation a net systemic vasoconstriction is observed, which could be due to a direct action of hypocapnic alkalosis on the vascular tone (Kontos et al. 1972). In addition, it has been thought that the sympatho-adrenergic system might also compensate for vasodilatation (Burnum et al. 1954). Our observation of increased catecholamine concentration supports this view and indicates that adrenaline and noradrenaline

may play a part in the stabilisation of the cardiovascular system in voluntary hyperventilation.

By changes in the vascular tone, catecholamine-induced changes in the blood cell counts are thought to be possible in the following ways: adrenaline-induced vasoconstriction in the skin, in the splanchnic vessels and the veins, together with the additional cardiac stimulation by adrenaline, induces a loss of protein-deficient salt solution from the intravascular space and consequently the haematocrit rises (Kaltreider et al. 1942). The noradrenaline-induced decrease of the vascular volume (Rose and Freis 1957) and the direct vasoconstrictive effect of hypocapnic alkalosis (Kontos et al. 1972) have been shown to enhance this mechanism of haemoconcentration.

It has been demonstrated that the normal spleen does not play a role as a donor organ for erythrocytes if this function is tested by adrenaline injection (Kaltreider et al. 1942), and we have shown that in hyperventilation the normal spleen does not add erythrocytes to the circulating blood (Stäubli et al. 1988).

The rapid increase of the lymphocyte number must be due to a redistribution of these cells within the blood vessels and/or between blood vessels and lymphatic vessels, and the following mechanisms could contribute to this:

1. It is possible that lymph flow increased due to tetanic muscle contraction, which has been observed in experiments without CO_2, and that the number of lymphocytes added to the venous blood by the lymphatic ducts therefore increased (Engeset et al. 1977).
2. Another mechanism probably contributing to the increase in the lymphocyte count might be an adrenaline- and noradrenaline-induced increase of the hepatic portal vascular resistance as has been suggested by animal experiments (Clark 1928; McLaughlin 1928; Richardson et al. 1977). This could contribute to the well-established finding of an adrenaline-induced increase of lymph flow in the thoracic duct (Bainbrige et al. 1917), and, therefore, to the addition of lymphocytes to the blood.
3. Theoretically, changes of blood flow conditions as induced by catecholamines and by hypocapnic alkalosis (Kontos et al.1972) could mobilize lymphocytes if these were unevenly distributed within the blood vessels. There are, however, only vague indications from animal experiments that lymphocytes may hold positions in the marginal blood stream under very particular experimental conditions, but there is no evidence that lymphocyte margination occurs in man (Vejlens 1938).
4. It has been found that lymphocytes adhere to specialized endothelium of postcapillary veins (high endothelial vessels) within lymph nodes and Peyer's patches in the gut, from where they emigrate to extravascular tissue. This is part of the permanent immunological tissue surveillance by recirculating lymphocytes which reenter the bloodstream by the lymphatics (Harlan 1985).

Theoretically it is conceivable that hypocapnic alkalosis with its associated changes of catecholamine concentration interrupts or reverses the process of lymphocyte adherence, resulting in increased blood lymphocyte concentration. Such a mechanism is, however, entirely hypothetical.

An explanation for the change in the granulocyte number is even more difficult. It is possible that we missed the peak neutrophil count because the intervals between blood samples were relatively long and interpretation is, therefore, limited. Demargination of neutrophils in response to an increase of blood flow due to vasoconstrictive effects of catecholamines and hypocapnic alkalosis is a possible explanation for the increase of the granulocyte count (Vejlens 1938; Athens et al. 1961), but since only the count of the band-formed neutrophils was increased 75 min after hyperventilation with air, granulocyte release from the bone marrow may also have played a role.

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