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Secondary polycythaemia in chronic respiratory insufficiency

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Vanuxem, D., Guillot, Ch., Fornaris, E., Weiller, P. J., and Grimaud, Ch. (1977). *Thorax*, **32**, 317–321. **Secondary polycythaemia in chronic respiratory insufficiency.** The relationship between polycythaemia, P_{50} and SaCO (saturation in carboxyhaemoglobin) has been studied in 50 patients who were hypoxaemic due to chronic respiratory insufficiency. These patients were divided into two groups according to their haemoglobin concentration and haematocrit: 21 polycythaemic patients with haemoglobin $\geqslant$16 g/dl and haematocrit $\geqslant$50% and 29 patients without polycythaemia. PaO_2, $PaCO_2$, plasma and erythrocyte pH, haemoglobin, haematocrit, and carbon monoxide saturation and intraerythrocytic 2-3 diphosphoglycerate concentration were measured during steady-state ventilation.

All polycythaemic patients were smokers and their carbon monoxide level was significantly higher than that observed in patients without polycythaemia. Additionally, their P_{50} and 2-3 DPG concentration were significantly lower than in patients without polycythaemia.

The correlations between P_{50} and HbCO and between Hb and HbCO were significant ($r=-0{\cdot}672$; $r=0{\cdot}552$ respectively: $P<0{\cdot}001$).

Eleven non-polycythaemic patients who were smokers had a high level of HbCO but normal P_{50}.

A group of 29 normoxic subjects was also studied, 14 non-smokers and 15 smokers with a high HbCO level. The mean value of P_{50} was lower in smokers and their haematocrit was higher although the difference was not significant for the latter.

The HbCO increase by tobacco seems to be a factor in the occurrence of polycythaemia in patients with chronic respiratory insufficiency.

The level of increase of HbCO and/or its duration and perhaps other individual factors could explain why all patients with high HbCO level and hypoxaemia were not polycythaemic.

Polycythaemia is not observed in all patients with chronic respiratory insufficiency who have the same degree of arterial hypoxaemia, suggesting that hypoxia is not the sole factor responsible for polycythaemia in those patients.

Brewer *et al.* (1970) have suggested that smoking, by increasing haemoglobin affinity for oxygen, is a possible explanation for the excessive polycythaemia that occurs in some people living permanently at high altitude. In a previous study in patients with chronic bronchitis (Vanuxem *et al.*, 1973) we noticed that haemoglobin affinity for oxygen was higher in smokers than in non-smokers. We found a significant negative correlation between P_{50}, the partial pressure of oxygen at which haemoglobin is half saturated with oxygen (which reflects blood affinity for oxygen), and the percentage saturation of haemoglobin with carbon monoxide (SaCO%), a direct function of tobacco consumption (Russell *et al.*, 1973; Cole, 1975).

The present study was undertaken in a group of hypoxic patients with chronic respiratory insufficiency, to determine whether a relationship existed between polycythaemia and SaCO%.

Methods

SUBJECTS

Fifty hypoxaemic patients (43 with chronic bronchitis and 7 with silicosis) participated in the study (Table 1). They were divided into two groups. Group A consisted of 29 patients without polycythaemia (smokers and non-smokers). Group B consisted of 21 patients with polycythaemia (all were smokers).

In the absence of direct measurement of the red cell mass we arbitrarily defined polycythaemia as a

Table 1 *Details of 50 hypoxaemic patients: vital capacity (VC) and forced expiratory volume in one second (FEV_1) were expressed as per cent of predicted values (European Coal and Steel Organization): Values are mean ± SE*

Patients	*Age*	*Daily cigarette consumption*	*VC*	FEV_1	*PaO2 (kPa)*
Group A					
Hypoxaemia without polycythaemia (N=29)	56 ±2	7 ±1·5	66·5 ±2·6	44·6 ±3·8	8·52 ±0·18
Group B					
Hypoxaemia with polycythaemia (N=21)	48 ±2	27 ±3	68·2 ±4	51·8 ±5·5	8·40 ±0·37
	P<0·01	P<0·001	NS	NS	NS

haemoglobin concentration (Hb) equal to or greater than 16 g/dl of blood and haematocrit value (Hct) higher than 50%.

For comparison, 29 normoxic subjects were also examined: 14 were non-smokers (group C: mean age 31±1) and 15 were smokers (group D: mean age 41, 5±3, daily cigarette consumption 22±3).

TECHNIQUES

All subjects gave informed consent to the study.

In all hypoxaemic patients (groups A and B) and in 12 normoxic subjects from group D, blood samples were collected from the brachial artery through a catheter during steady-state ventilation ($\dot{V}E$ <10 l min^{-1}). The blood samples were obtained from a forearm vein in 17 normal subjects. In seven of them a sample of arterialised capillary blood was also collected from the ear.

Arterial pH, PO_2, and PCO_2 (pHa—PaO_2—$PaCO_2$) were measured by means of Radiometer electrodes.

Intraerythrocytic pH (pHi) was measured with the same apparatus after cold haemolysis.

Per cent saturations of haemoglobin were calculated from blood oxygen and capacities measured by a colorimetric procedure (Lex O_2 Con; Lexington Instrument Corporation). This technique enables the calculation of the 'functional haemoglobin', ie, the only haemoglobin able to 'fix' oxygen. Saco% was measured with a CO—Oxymeter IL—182. The cyanmethaemoglobin method was used to determine the haemoglobin concentration. The haematocrit ratio (Hct) was determined using the microtechnique. The haemoglobin affinity for oxygen was assessed by measuring P_{50} according to the technique of Bartels and Harms (1959).

Hill's equation was used to calculate P_{50} (at pH 7·4) as follows:

$$\log \frac{HbO_2}{100-HbO_2} = n \log PO_2 + \log K$$

at P_{50}, $HbO_2 = 50\%$

$$\text{hence } \log \frac{HbO_2}{100-HbO_2} = 0$$

$$\text{and } \log P_{50} = \frac{-\log K}{n}$$

where n represents haem-haem interaction.

The following gas mixtures were used for tonometric equilibrations: O_2=2·97%; CO_2=5·56%; N_2=91·47%, and O_2=4·36%; CO_2=5·52%; N_2=90·12%.

An enzymatic method (Krimsky, 1961; Chambon, 1971) which uses phosphoenol pyruvate (PEP) as substrate was used to measure the intracellular concentration of 2-3 diphosphoglycerate (2-3 DPG) in the following manner:

$$PEP \xrightarrow{\text{Enolase}} 2\,PGA$$

$$2\,PGA \xrightarrow{PGM} 3\,PGA$$

$$\xrightarrow{\text{2-3 DPG}}$$

in which 2 PGA=2 phosphoglycerate, 3 PGA=3 phosphoglycerate, and PGM=phosphoglycerate mutase.

Optical density readings were done at 240 nm with an ultraviolet spectrophotometer (Jean et Constant).

Results

The mean values and standard errors of the measured haematological data are shown in Table 2.

In the hypoxaemic patients, statistical comparison (Student's *t* test) between the two groups A and B showed no difference regarding the degree of ventilatory impairment and the mean value of PaO_2. There was a significant difference in age and smoking habits (Table 1). There were, however, significant differences in the haematological measurements between the two groups: the Hbco level was higher (P<0·001), the P_{50} value and the 2-3 DPG concentration lower in group B (P<0·001 and P<0·02) (Table 2).

In group A, we separated 11 subjects whose Saco was equal to or higher than 4% and who were smokers (Table 3). In these 11 patients, the Hbco level was lower (P<0·01) and the P_{50} higher (P<0·001) than in the polycythaemic patients; PaO_2, pHi, pHa, and 2-3 DPG were not different.

In the normoxic subjects (Table 2) there was a highly significant difference between smokers (group D) and non-smokers (group C): subjects who smoked

Table 2 *Haematological data in hypoxic patients and normoxic subjects: Values are mean ±SE*

Subjects	PaO_2 (*kPa*)	$PaCO_2$ (*kPa*)	*pHa*	*Hb* (*g/dl*)	*Hct* %	*HbCO* %	*pHi*	*DPG* (*mmol l* RBC^{-1})	P_{50} (7·40) (*kPa*)
Group A	8·52	5·60	7·400	14·4	45	3·52	7·189	4·31	3·61
Hypoxaemic without polycythaemia (N=29)	0·18	0·16	0·007	0·2	0·6	0·32	0·007	0·13	0·02
Group B	8·40	5·97	7·388	17·2	55	9·55	7·189	3·79	3·20
Hypoxaemic with polycythaemia (N=21)	0·37	0·25	0·008	0·2	0·7	0·91	0·007	0·16	0·04
Group C	12·2	5·24	7·412	14·5	45·2	2·16		4·12	3·60
Normoxic non-smokers (N=14)	0·26	0·10	0·005	0·1	0·4	0·1		0·06	0·02
Group D	12	4·78	7·400	14·8	47·2	7·66	7·192	4·25	3·44
Normoxic smokers (N=15)	0·32	0·10	0·008	0·6	2·2	0·66	0·005	0·12	0·04

Table 3 *Haematological data in 11 hypoxic patients (non polycythaemics) of group A, with HbCO level ⩾4%; (mean cigarette consumption, 5 daily)*

PaO_2 (*kPa*)	$PaCO_2$ (*kPa*)	*pHa*	*Hb* (*g/dl*)	*Hct* %	*HbCO* %	*pHi*	*DPG* (*mmol l* RBC^{-1})	P_{50} (7·40) (*kPa*)
8·05	5·70	7·386	14·2	44·3	5·34	7·193	4·12	3·55
0·29	0·29	0·009	0·35	0·9	0·39	0·009	0·10	0·04

were found to have a higher CO level ($P < 0·001$) and a lower P_{50} ($P < 0·005$) than the subjects who did not.

Discussion

Our results show that in two groups of patients with the same degree of hypoxia only one group presented with polycythaemia. All subjects of this group were smokers with a high level of Hbco. Other studies in apparently healthy smokers living at altitude have demonstrated a similar correlation between polycythaemia and smoking with increased Hbco (Brewer *et al.*, 1970). In the present work normal subjects who are smokers (group D) had a higher haematocrit than non-smoking subjects (group C) although the difference was not significant. Similar observations in apparently healthy smokers have been reported by other authors (Eisen and Hammond, 1956; Russell and Conley, 1964; Sagone *et al.*, 1973; Sagone and Balcerzak, 1975).

In the two groups of hypoxic patients, the haemoglobin level was correlated with the Hbco level ($P < 0·001$) (Fig. 1).

All these findings strongly suggest that increased Hbco may play an important role in determining polycythaemia when associated with hypoxaemia.

Polycythaemia in patients with hypoxia is thought to be due to excess erythropoietin release by an indirect mechanism relating to the influence of tissue hypoxia (Fried *et al.*, 1957; Adamson and Finch, 1975).

Furthermore, it is known that the fixation of CO on haemoglobin leads to a decrease of the quantity

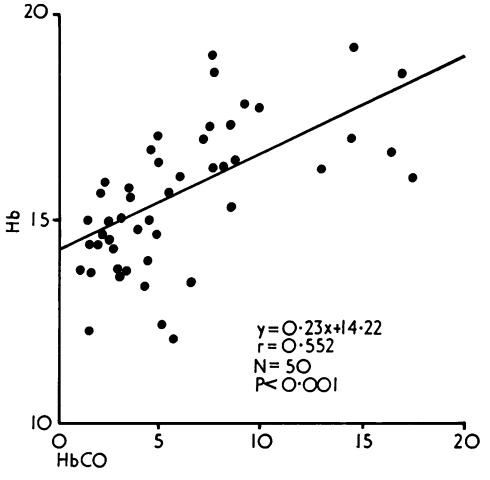

Fig. 1 *Relationship between haemoglobin concentration (g/dl) and HbCO level (%).*

of functional haemoglobin and a shift to the left of the haemoglobin dissociation curve (ie, an increased affinity of haemoglobin for O_2) (Roughton, 1964; Astrup *et al.*, 1966; Goldsmith and Landaw, 1968).

There was a significant decrease in P_{50} in patients with polycythaemia and the P_{50} value of the group of normal smokers with an increased Hbco level was also found to be lower than the P_{50} observed in normal non-smokers.

However, factors other than Hbco could shift the Hbo_2 dissociation curve to the left and must be

considered. There was no significant difference between the two groups of patients in plasma and intraerythrocytic pH and $PaCO_2$, so that these factors can be excluded (Astrup, 1970; Bellingham, *et al.*, 1971; Vanuxem *et al.*, 1975). The concentration of 2-3 DPG was found to be significantly lower in patients with polycythaemia, probably due to the inhibitory influence of CO on 2-3 DPG synthesis (Asakura *et al.*, 1966; Morena *et al.*, 1974). However, as the mean difference is only about 0·56 mmol l RBC^{-1} it cannot account for the observed decrease in P_{50} of 0·4 kPa, since a decrease in 2-3 DPG of 1 mmol l RBC^{-1} results in a decrease of only 0·21 kPa (Vanuxem *et al.*, 1975). Furthermore, no correlation was found in the polycythaemic group between P_{50} and 2-3 DPG. This lack of correlation contrasts with the results obtained by Edwards *et al.* (1972) and with our own observations in normal subjects and in patients without polycythaemia ($P < 0{\cdot}001$).

In patients with respiratory insufficiency, the strong correlation between P_{50} and Saco (Fig. 2) shows the determinant role of CO in the increased affinity of haemoglobin for oxygen. We calculate that a 1% increase in Hbco level causes a decrease in P_{50} of 0·04 kPa which agrees with other findings (Robert, 1975).

It is interesting to notice that 11 patients of group A were smokers and had raised Hbco levels, but not polycythaemia. It is possible that polycythaemia was undetected in our study because we measured only haematocrit and haemoglobin concentration since Shaw and Simpson (1961) and Murray (1965) have found that, in some cases, there is a parallel increase in erythrocytic mass and plasma volume. There are nevertheless several other explanations; first, it is possible that their Hbco level was not high enough to lead to polycythaemia since it was lower than that observed in group B; secondly, the duration of hypoxia and/or increased Hbco could also be important; thirdly, these differences could be related to variable individual susceptibility by a still unknown mechanism.

Our results show that each time polycythaemia is observed in patients with chronic respiratory insufficiency the Hbco level is greatly increased, but, on the other hand, a high Hbco level can be found without polycythaemia. This latter condition has harmful haemodynamic consequences (Cotes, 1975) and so it is an additional reason why patients with respiratory impairment should avoid smoking.

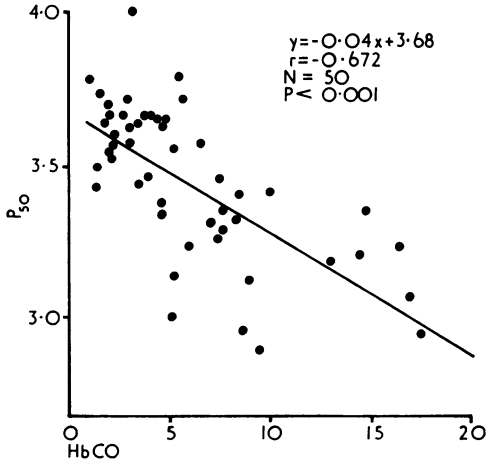

Fig. 2 *Relationship between P_{50} (7·40) (kPa) and Hbco level (%).*

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