Editorial

Development of secondary polycythaemia in chronic airways obstruction

Much has been written about the appropriateness or otherwise of secondary polycythaemia in patients with chronic airways obstruction (CAWO), and it is common clinical experience that not all such patients have a raised haemoglobin. Some authors have argued for a predominantly subnormal red cell mass response\(^1\) to a given degree of hypoxia and others for normal\(^8\)–\(^15\) or even excessive responses.\(^1\) Indeed the justification for phlebotomy in secondary polycythaemia is sometimes based on attempted judgments as to the "appropriateness" or "excess" of red cell mass response.\(^7\) These arguments are based on certain assumptions that are open to question and therefore merit discussion.

What is the normal haemopoietic response to hypoxaemia?

An increased oxygen carrying capacity in the blood of animals acclimatised to the hypoxic conditions of high altitude was first recorded by Paul Bert.\(^1\) Early work on this phenomenon, before red cell mass (RCM) estimations by chromium 51, was extensively reviewed by Hurtado in 1945.\(^19\) Haematocrits and haemoglobins were the usual measurements of the red cell response. The subjects were generally Andean residents whose health, smoking, and nutritional status were not assessed. However, much useful information was gained and is embodied in Hurtado's classic diagram (fig 1). Note that arterial oxygen saturation (\(\text{Sao}_2\)) is taken as the measure of hypoxaemia.

Until 1968 all articles on the polycythaemia of CAWO used these results to assess appropriateness. For example, Vanier\(^5\) concluded that there was a subnormal response though she made the error of directly comparing Hurtado's results, using dyes, with \(\text{Cr}_t\) methods for RCM estimation. Dye methods (vital red and Evans blue) give values for RCM about 35% higher than the \(\text{Cr}_t\) method.\(^19\)\(^20\) In retrospect her patients probably had "normal" responses. Shaw\(^9\) and Hume\(^11\) circumvented this problem by comparing percentage of sea level values and concluded that there was a normal RCM response but diminished rises in haemoglobin and haematocrit, because of plasma expansion, in patients hypoxic from CAWO. This latter observation also appeared to explain why other authors, measuring only haemoglobin and haematocrit, had concluded that responses were subnormal.\(^1\)\(^3\)

Weil and colleagues\(^14\) in 1968 published some important reference data on haemoglobin, haematocrit, and RCM in healthy Caucasians at altitude. Their data collected at three different altitudes and therefore at varying arterial saturations were presented as a linear relationship between RCM (ml/kg) and \(\text{Sao}_2\) with 95% confidence limits for the individual results (fig 2). There are three points in their analysis which merit comment. Firstly, the three groups were dissimilar in one important respect, that of obesity. The mean Quetelet index of obesity (\(W/H^2\)) was significantly higher in the 1600 metre than in the 3100 metre residents (25.4 ± 1.73 (SD) and 23.6 ± 2.35 respectively, \(p < 0.01\)). Thus when RCMs are quoted as ml/kg the slope of the RCM/\(\text{Sao}_2\) relationship is altered falsely. Secondly, the RCM/\(\text{Sao}_2\) relationship is not a straight line. The sea level and 1600 metre residents have mean saturations of 96.4 ± 0.5% and 93.6 ± 0.6% respectively.

![Graph](http://thorax.bmj.com/)

**Fig 1** Correlation between concentration of haemoglobin in peripheral blood and percentage arterial oxygen saturation at various altitudes (from reference 19).

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(SD) and 93.9±1.4% respectively (p < 0.001), while their RCMs (% predicted normal) are 96.1±11.5% (SD) and 94.8±7.9% respectively (p < 0.05). Hence a significant fall in SaO₂ was not accompanied by a rise in RCM; the same applied to haematocrit and haemoglobin levels. Accepting these observations, it is logical that a linear relationship should only be drawn through the 3100 metre data and a horizontal line through the rest (fig 3). Residual error is significantly less with this threshold model which predicts no significant rise in RCM until saturations below 92% have been reached. Included in fig 3 are nine patients with CAWO described in the same paper. Thirdly, the altitude data only extend down to 83% saturation and should not be used for comparisons below this.

From the British literature, Harrison16 found a group of patients with CAWO who had RCM responses which seemed truly “excessive,” being well outside the span of Weil’s data. Cocking and Darke13 also refer to Weil’s data but in their group of patients, while most had an apparently normal response, a few had very subnormal responses. Thus there do seem to be some patients who lie well beyond, in both directions, the 95% confidence limits of Weil’s corrected regression line for RCM against SaO₂ at altitude. What factors might be responsible for a wider scatter than that observed at altitude?

**Fig 2** Red cell mass SaO₂ relationship in normal men residing at sea level, 1600, and 3100 m. Broken lines represent 95% confidence limits on individual estimates.

**Fig 3** Red cell mass SaO₂ relationship using percentage predicted normal RCM. Regression of 3100 metre data analysed separately, broken lines represent 95% confidence limits on individual estimates. Also included are nine patients with CAWO (revised from reference 14).

**What is the stimulus and response to erythropoietin secretion?**

Teleologically the function of the erythropoietin control system should be to maintain oxygen delivery to the tissues in the face of diminished oxygen supply. This has to be achieved in the face of both anaemic hypoxaemia and hypoxic hypoxaemia. It is believed that a fall in oxygen tissue tension in the relevant cells in the kidney is ultimately the stimulus responsible for erythropoietin production.21,22 This parameter depends on arterial oxygen tension, haemoglobin concentration, the haemoglobin dissociation curve, and renal blood flow: the latter in turn depends on viscosity, blood pressure, and perhaps local vascular tone. Hence it would be naïve to expect erythropoietin secretion to be dependent on just one factor, SaO₂. None the less the nearest parameter to “tissue oxygen tension” easily obtainable appears empirically to be the SaO₂.22 The response expected from erythropoietin secretion is a restoration of satisfactory oxygen delivery to the tissues. In the face of arterial hypoxaemia the main ways to restore oxygen delivery to normal, thus “satisfying” the erythropoietin secreting cell, are by...
increasing either blood flow or haemoglobin concentration. The response conventionally measured is RCM: but it should be noted that a rise in RCM per se will not improve oxygen delivery unless it increases blood flow or haemoglobin concentration or both. It is unlikely to influence blood flow and if the rise in RCM is accompanied by an equal rise in plasma volume then haemoglobin concentration will stay the same, oxygen delivery would not increase and the erythropoietin cell would not be "satisfied." Conversely, patients on diuretic therapy because of a reduced plasma volume increase the haematocrit and oxygen carrying capacity of the blood without affecting RCM. Despite these reservations and because of the susceptibility of haemoglobin and the haematocrit to temporary day-to-day fluctuations in plasma volume, the RCM is generally taken to be the most consistent indication of the level of stimulation of erythropoietin. These complex inter-relationships are represented diagrammatically in fig 4.

Which arterial saturation?

Having accepted Sao₂ as the easiest guide to tissue oxygen tension under what conditions should it be measured to gauge the hypoxaemic stimulus to erythropoietin production? A single estimation of Sao₂ in a patient sitting in hospital or the clinic is unlikely to be representative of the 24-hour situation. Changes of up to 15% can occur in Sao₂ either spontaneously, or on eating, urinating, and changing posture.

Recently, nocturnal hypoxia caused by sleep apnoea has been proposed as a possible extra stimulus for producing secondary polycythaemia and cor pulmonale in patients with CAWO. Intermittent hypoxia appears to be almost as potent a stimulus for erythropoietin production as continuous hypoxia. Proving this hypothesis will be difficult for two reasons. Firstly, the weighting of the "mean Sao₂" by extra nocturnal hypoxia is unlikely to be simply arithmetic and secondly, it may be that the secondary polycythaemia itself contributes to nocturnal hypoxia. Solving this conundrum will require long-term prospective studies.

Because of the presence of these periods of nocturnal hypoxia we believe it is incorrect to try and estimate whether or not the extra oxygen carriage afforded by a high haematocrit is more than offset by the increased viscosity. This exercise is sometimes done in order to justify phlebotomy. A certain rise in the haematocrit might well seem excessive for the degree of daytime arterial desaturation on the grounds that the increased viscosity would actually lead to a diminished oxygen supply to the tissues. However, when the very much lower nocturnal saturations are considered, one could argue that this rise in the oxygen carrying capacity of the blood was vital for adequate tissue oxygenation at night.

Direct experimentation and computer modelling of the lung suggest that the arterial hypoxaemia of subjects with normal lungs resident at high altitude is only minimally affected by the extra stress of a fall in mixed venous Po₂ from exercise or reduced cardiac output. However similar stress inflicted on patients with hypoxaemia from abnormal lungs at sea level will cause a more marked deterioration in Sao₂. Add to this the fluctuating behaviour of lung function in patients with CAWO and it becomes clear why the hypoxia of altitude is an inadequate
model for predicting Sao2/RCM relationships in these patients.

A further important factor which actually lowers the true Sao2 is a raised carboxyhaemoglobin level caused by smoking.36-38 This not only reduces oxygen delivery to the tissues by titrating away available haemoglobin but also alters the P5037 thus changing the Sao2 and renal Po2 relationship. There is also evidence that smoking can cause supine hypoxaemia.39 Smocking appeared to be the only cause of a raised RCM in five smokers studied by Sagone and Balcerzak.36 In a larger survey of 22 smokers with mean blood carboxyhaemoglobin levels of 11.6% Smith and Landaw37 found the RCM raised in 14 out of 18. Unfortunately no assessment was made of postural or nocturnal hypoxaemia but the RCM did decrease in all five patients who were able to considerably reduce or stop smoking. Similarly Calverley et al38 found RCM estimations higher at any given level of Pao2 in 30 smokers than in 17 non-smokers all with cor pulmonale. Furthermore, in 12 of these patients given long-term oxygen therapy, smoking appeared to prevent the expected fall in RCM as had also been observed by Foster et al.40

Despite this very real effect from smoking it is not yet possible to state by how much it affects the overall Sao2/RCM relationship either at altitude or in hypoxic patients.

What might block the RCM response?

Some early explanations for the presumed deficient RCM response to hypoxaemia in patients with CAWO included chronic infection, CO2 retention, and incipient iron deficiency. Iron deficiency was certainly sometimes present, possibly because of recurrent phlebotomy. Failure of the bone marrow to respond, rather than low erythropoietin levels, has been demonstrated,4 6-8 but although iron and total iron binding capacities were measured in these studies, the patients' B12, folate, urea, ESR, liver function tests, and alcohol intake were not recorded. Thus recognised reasons for diminished erythropoiesis were not excluded. It is of interest here that iron deficiency renders the red cells hypochromic but may not prevent the red cell mass and haemato-
crit from increasing15; hence the induction of iron deficiency as a way to control secondary polycythaemia is not advised.

Finally, the association between hypoxia in CAWO and testosterone levels may be an important factor. It has been shown that the serum testosterone level correlates to an extent with the severity of the hypoxia.41 Testosterone withdrawal reduces the bone marrow response to hypoxia47 48 and thus would alter the Sao2/RCM relationship. Whether testosterone levels are similarly depressed at altitude is unknown.

Conclusion

Given the number of factors involved in the relationship between single measured values of reduced Sao2 and red cell mass it is interesting that the relationship recorded for subjects at altitude is as good as it is.

In CAWO the additional factors causing variability of the Sao2 make it easy to understand that this relationship, particularly at low arterial saturations, is unlikely to match closely that obtained at altitude. Statements about the appropriateness or otherwise of rises in RCM, in the face of hypoxaemia from CAWO, which are based on predictions from altitude data are not justified.

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References


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