Erythropoietin concentrations in obstructive sleep apnoea

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Abstract

Eight patients with obstructive sleep apnoea and a normal haemoglobin concentration underwent nocturnal studies during which oxyhaemoglobin saturation was recorded continuously with an ear oximeter and serum erythropoietin concentration was measured hourly by means of a radioimmunoassay. Serum erythropoietin concentrations remained within the normal range throughout the study despite falls in oxyhaemoglobin saturation in individuals to 33–78%. There was no relation between the degree of nocturnal hypoxaemia and serum erythropoietin concentrations. The brief cyclical episodes of hypoxaemia typical of obstructive sleep apnoea may not be a sufficient stimulus for erythropoietin secretion.

Hypoxaemia in normal subjects (for example, at high altitude) stimulates renal erythropoietin production and release with subsequent increases in bone marrow red cell production and circulating red cell mass. Secondary polycythaemia in chronic obstructive lung disease is generally believed to be mediated through this mechanism. Only a proportion of patients with hypoxaemia and lung disease, however, develop polycythaemia and only about half of these have raised serum concentrations of erythropoietin. Severe nocturnal hypoxaemia has been postulated as the cause of polycythaemia in chronic obstructive lung disease and it has been suggested that intermittent hypoxia may stimulate erythropoietin production. Patients with obstructive sleep apnoea rarely develop polycythaemia despite repeated falls in arterial oxyhaemoglobin saturation (SaO₂) during six to eight hours of sleep. These patients provide a model for studying the characteristics of erythropoietin release in response to intermittent severe hypoxaemia in man.

Methods

Eight men with newly diagnosed and untreated obstructive sleep apnoea underwent all night sleep studies. Four of the patients had daytime hypoxaemia (arterial oxygen tension (PaO₂) less than 10 kPa) and two had airflow obstruction with a forced expiratory volume in one second (FEV₁) below 80% predicted; none was polycythaemic. The mean age of the patients was 52.5 (range 42–70) years and three were current smokers. The results of their haematological, biochemical, and physiological tests are summarised in the table. Daytime oxyhaemoglobin saturation was calculated from the arterial oxygen tension measured during the day. Arterial oxyhaemoglobin saturation was estimated during sleep with an ear oximeter (Ohmeda Biox IIa) accurate to within 2-5% down to an SaO₂ of 60%. A compressed summary of the all night recording of SaO₂ was constructed by joining the peak and trough values from each episode of apnoea.

Serial venous blood samples were taken from an indwelling intravenous cannula before the onset of sleep, at roughly hourly intervals during sleep (more frequently in patient 5) and the following morning after waking. The total volume of blood taken was 60 ml in all subjects except patient 5, who had 120 ml removed. Samples were allowed to clot at room temperature. Serum was separated

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**Baseline results and serum erythropoietin (sEPO) concentrations during wakefulness in eight patients with obstructive sleep apnoea**

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (y)</th>
<th>PaO₂ (kPa)</th>
<th>PaCO₂ (kPa)</th>
<th>SaO₂ (%)</th>
<th>Hb (g/dl)</th>
<th>Packed cell volume (%)</th>
<th>FEV₁ (% pred)</th>
<th>Creatinine (mmol/l)</th>
<th>Daytime sEPO (U/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>48</td>
<td>8:1</td>
<td>6:5</td>
<td>90</td>
<td>16:6</td>
<td>0:49</td>
<td>73</td>
<td>71</td>
<td>8:2</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>9:5</td>
<td>6:0</td>
<td>93</td>
<td>13:8</td>
<td>0:42</td>
<td>83</td>
<td>71</td>
<td>12:5</td>
</tr>
<tr>
<td>4*</td>
<td>47</td>
<td>10:5</td>
<td>7:9</td>
<td>92</td>
<td>13:1</td>
<td>0:42</td>
<td>83</td>
<td>90</td>
<td>22:3</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>11:6</td>
<td>6:1</td>
<td>96</td>
<td>12:9</td>
<td>0:37</td>
<td>87</td>
<td>74</td>
<td>40</td>
</tr>
<tr>
<td>6*</td>
<td>56</td>
<td>6:9</td>
<td>6:4</td>
<td>89</td>
<td>15:0</td>
<td>0:48</td>
<td>58</td>
<td>140</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>14:0</td>
<td>5:5</td>
<td>98</td>
<td>15:0</td>
<td>0:49</td>
<td>90</td>
<td>97</td>
<td>9:6</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
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<td>95</td>
<td>15:8</td>
<td>0:49</td>
<td>92</td>
<td>68</td>
<td>11:9</td>
</tr>
</tbody>
</table>

*Current smoker.
PaO₂ — arterial oxygen tension; PaCO₂ — arterial carbon dioxide tension; SaO₂ — arterial oxyhaemoglobin saturation; Hb — haemoglobin; FEV₁ — forced expiratory volume in one second.
within four hours of collection and stored at
−20°C until the time of assay. All samples
from an individual were estimated at the same
time and all the assays were completed in
three runs.

Erythropoietin levels were measured by a
modification of the radioimmunoassay
method described by Egrie et al., which uses
reagents derived from recombinant human
erythropoietin with delayed addition of the
labelled antigen. The curve derived from the
recombinant human erythropoietin was
standardised against the World Health
Organisation’s second international reference
preparation of human urinary erythropoietin.
The reference range for serum erythropoietin
in a population of 107 healthy individuals was
6–30 mU/ml (geometric mean 13.34). The
intra-assay coefficient of variation was 8% and
the interassay value 13% for serum ery-
thropoietin concentrations of 10–100 mU/ml.

For statistical analysis simple regression
was used to assess correlation between
measurements and Student’s paired t test to
compare morning and evening erythropoietin
concentrations. Analysis of variance was used
to compare areas under the curve of erythro-
poietin concentration against time and Sao2
against time.

Results
All eight patients had repeated episodes of
hypoxaemia during sleep (figure). The lowest
Sao2 recorded during sleep in individual
subjects ranged from 35% to 78%. The mean
duration of an episode of desaturation (defined
as a fall of 4% or more in Sao2 from the baseline
level while they were lying supine) was 50
seconds and the longest lasted three minutes.

The serum erythropoietin measurements
were within the defined normal range in all the
patients at all times. There was no relation
between the serum erythropoietin concen-
tration, haemoglobin, or “awake” Sao2 and PaO2
(table). Serum erythropoietin concentrations
in blood samples taken between 10.00 and
12.00 hours the morning after the study did not
correlate with the degree or duration of
nocturnal hypoxaemia. Four patients (2, 3, 4, 8)
had samples taken for measurement of serum
erthropoietin concentrations while they were
awake before (21.00–22.00 hours) and after the
sleep study (10.00–12.00 hours). There was no
significant difference in the values (mean (SD)
15.2 (7.3) and 14.6 (5.1) mU/ml).

There was no significant correlation between
mean overnight erythropoietin concentration
or any of the following measures of Sao2: mean
Sao2 (r = 0.17), mean Sao2 at arousal
(r = 0.30), mean Sao2 between episodes of
apnoea (r = 0.21), total hypoxic dose
(r = 0.12), lowest Sao2 (r = 0.18). There was
no significant increase in erythropoietin over-
night with time. There was also no significant
correlation between the areas under the curves
for Sao2 against time or for serum erythro-
poietin concentrations against time (analysis of
variance: R2 = 0.138; F = 0.962, p < 0.25).

Discussion
Erythropoietin production in response to
induced hypoxia has been investigated in
animals but cannot readily be studied in man.
Patients with obstructive sleep apnoea have
recurrent spontaneous episodes of severe
hypoxaemia and offer a human model for the
study of erythropoietin secretion. Our results
showed no relation between serum erythro-
poietin concentration and oxyhaemoglobin
saturation.

We measured serum erythropoietin using a
modification of a well established radio-
immunoassay method that was both sensitive
and reliable. Samples were taken at appropriate
times to detect a rise in erythropoietin, as this
has been reported to begin after as little as one
hour of hypoxaemia in animal models. We do
not believe that we missed bursts of secretion
initiated by each individual apnoeic episode:
the plasma half life of endogenous eryth-
ropoietin is at least three hours, and we took
samples as frequently as every five minutes in
patient 5 (for two hours) and hourly in the rest.
We postulated that there might be a cumulative
effect secondary to night time hypoxaemia, but
neither morning nor evening erythropoietin
concentrations were significantly raised, which
supports previous findings in patients with
chronic obstructive lung disease. There was no
significant difference between pre-study and
post-study concentrations of erythropoietin
(evening and morning), suggesting an absence
of diurnal variation in our subjects. Early
evidence was against the presence of diurnal
variation in erythropoietin concentrations, apart
from one report on a single subject. Recent
work using the more sensitive radio-
immunoassay showed clear evidence of diurnal
variation in serum erythropoietin in 27 patients
in hospital and these results have subsequently
been repeated (P J Gomes, personal com-
munication). The lack of diurnal variation in
our patients with obstructive sleep apnoea
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contrasts with these findings and may be explained by the disruption of sleep by cyclical hypoxaemia and consequent arousal. An alternative explanation would be that our subjects remained awake during their studies. As we did not perform electroencephalography to stage sleep we do not have documentary evidence to refute this suggestion; but the observations of our experienced sleep laboratory staff and the pattern of the oximetry recordings are against it.

A direct relation between the degree of hypoxaemia and erythropoietin concentrations has been described, but despite falls in \( \text{Sao}_2 \), to below 50% in four patients we could detect no such change. Possibly our patients had adapted to their nocturnal hypoxaemia, as normal individuals do at altitude. In these circumstances there is an initial rise in erythropoietin but secretion then falls to within the normal range, though polycythaemia is maintained. The patients in our study were not polycythaemic, which would seem to argue against this "adaptive" explanation. Longer episodes of constant rather than episodic hypoxaemia may be required to initiate erythropoietin secretion and increase red cell mass, such as occur in the "overlap" syndrome of obstructive sleep apnoea and chronic obstructive lung disease. Perhaps, as in normal individuals exposed to hypoxia, this is due to down regulation of erythropoietin secretion after an initial rise. None of our patients was polycythaemic, though four had some degree of daytime hypoxaemia. It therefore seems probable that sustained nocturnal hypoxaemia is needed to stimulate erythropoietin release and initiate an increase in red cell mass.

Other factors may also be important in the generation of polycythaemia. In patients with chronic obstructive lung disease carboxyhaemoglobin is the only variable that has been shown to correlate with erythropoietin concentration, and there is a clear association between cigarette smoking and polycythaemia in this condition. Patients with sleep hypoxaemia often have low testosterone concentrations, and as androgens stimulate erythropoiesis by an unknown mechanism androgen deficiency associated with obstructive sleep apnoea is possibly responsible for a reduction in erythropoietin production.

In conclusion, we did not find raised erythropoietin concentrations in patients with obstructive sleep apnoea and recurrent short episodes of severe nocturnal hypoxaemia. We suggest that prolonged episodes of nocturnal hypoxaemia may be necessary to stimulate erythropoietin production. These findings may explain why polycythaemia is uncommon in patients with obstructive sleep apnoea.

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