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.1,2 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.3 Severe nocturnal hypoxaemia has been postulated as the cause of polycythaemia in chronic obstructive lung disease3 and it has been suggested that intermittent hypoxia may stimulate erythropoietin production.4 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 11a) 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

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>42</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>2</td>
<td>62</td>
<td>13.6</td>
<td>5.6</td>
<td>97</td>
<td>14.4</td>
<td>0.44</td>
<td>94</td>
<td>111</td>
<td>11.9</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>8.5</td>
<td>7.9</td>
<td>92</td>
<td>15.1</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>4.0</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>4.9</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>0.48</td>
<td>90</td>
<td>97</td>
<td>9.6</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>10.1</td>
<td>5.5</td>
<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.
Sao,
apnoea.
concentrations
the
range
Changes
of
41
each
represented
section.
during
an
(Sao.)
traces
four
within
an
time
described
with
erthropoietin
reagents
the
recombinant
labelled
antigen.
The
preparation
against
in
measurements
the
and
was
intra-assay
thropoietin
concentrations
compare
concentration
poietin
compare
Analysis
against
in
Sao2
-20°C
during
Results
eight
All
as
a
level
duration
subjects ranged
were
at
patients
seconds and
fall of
night study
(Sao.)
changes
at
patients
6
2
33%
from
33%
Apr
the
cumulative
effect
secondary
to
night
fatigue,
but
with
hypoxaemia,
we
have
not
missed
the
secretion
initiated
each
apnoeic
episode:
the
plasma
life
of
endogenous
erythropoietin
is
at
least
three
hours,1
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
hypoxaemia,
but
neither
morning
nor
evening
erthropoietin
concentrations
were
significantly
raised,
which
supports
previous
findings
in
patients
with
chronic
obstructive
lung
disease.4
There
was
no
significant
difference
between
pre-study
and
post-study
concentrations
of
erthropoietin
(evening
and
morning),
suggesting
an
absence
of
diurnal
variation
in
our
subjects.
Early
evidence
was
against
the
presence
of
diurnal
variation
in
erthropoietin
concentrations,4
apart
from
one
report
on
a
single
subject.7
Recent
work
using
the
more
sensitive
radio-
imunoassay
showed
clear
evidence
of
diurnal
variation
in
serum
erthropoietin
in
27
patients
in
hospital9
and
these
results
have
subsequently
been
repeated
(P J Gomes, personal
communication).
The
lack
of
diurnal
variation
in
our
patients
with
obstructive
sleep
apnoea
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
Erythropoietin
levels
were
measured
by
a
modification
of
the
radioimmunoassay
method
described
by
Egrie
et
al,1
which
uses
reagents
derived
from
recombinant
human
erthropoietin
with
delayed
addition
of
the
labelled
antigen.
The
curve
derived
from
the
recombinant
human
erthropoietin
was
standardised
against
the
World
Health
Organisation's
second
international
reference
preparation
of
human
urinary
erythropoietin.
The
reference
range
for
serum
erthropoietin
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
erthropoietin
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
erthropoietin
concentrations.
Analysis
of
variability
was
used
to
compare
areas
under
the
curve
erthropoietin
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
33% 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
erthropoietin
measurements
were
within
the
defined
normal
range
in
all
the
patients
at
times.
There
was
no
relation
between
the
serum
erthropoietin
concentration,
haemoglobin,
or
"awake" Sao2 and Pao2
(table). Serum
erthropoietin
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
overnight
with
time.
There
was
also
no
significant
correlation
between
the
areas
under
the
curves
for
Sao2
time
or
for
serum
erthropoietin
concentrations
against
time
(analysis
of
variability:
$R^2 = 0.138$; $F = 0.962$, $P < 0.25$).

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
erthropoietin
secretion.
Our
results
showed
no
relation
between
serum
erthropoietin
concentration
and
oxyhaemoglobin
saturation.

We
measured
serum
erthropoietin
using
a
modification
of
a
well
established
radioimunoassay
method9
that
was
both
sensitive
and
reliable.
Samples
were
taken
at
appropriate
times
to
detect
a
rise
in
erthropoietin,
as
this
has
been
reported
to
begin
after
as
little
as
one
hour
of
hypoxaemia
in
animal
models.1
We
do
not
believe
that
we
missed
bursts
of
secretion
initiated
by
each
individual
apnoeic
episode:
the
plasma
half
life
of
endogenous
erthropoietin
is
at
least
three
hours,1
and
we
took
samples
as
frequently
as
every
five
minutes
in
patient
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(for
two
hours)
and
hourly
in
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rest.
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postulated
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might
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a
cumulative
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secondary
to
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hypoxaemia,
but
neither
morning
nor
evening
erthropoietin
concentrations
were
significantly
raised,
which
supports
previous
findings
in
patients
with
chronic
obstructive
lung
disease.4
There
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and
post-study
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of
erthropoietin
(evening
and
morning),
suggesting
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absence
of
diurnal
variation
in
our
subjects.
Early
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against
the
presence
of
diurnal
variation
in
erthropoietin
concentrations,4
apart
from
one
report
on
a
single
subject.7
Recent
work
using
the
more
sensitive
radio-
imunoassay
showed
clear
evidence
of
diurnal
variation
in
serum
erthropoietin
in
27
patients
in
hospital9
and
these
results
have
subsequently
been
repeated
(P J Gomes,
personal
communication).
The
lack
of
diurnal
variation
in
our
patients
with
obstructive
sleep
apnoea

Changes
in
oxyhaemoglobin
saturation
(Sao2)
and
serum
erthropoietin
(sEPO) concentrations
with
time
during
an
all
night
study
of
eight
patients
with
obstructive
sleep
apnoea.
Sao2
is
represented
by
the
traces
at
the
top
and
serum
erythropoietin
by
the
bars
at
the
bottom
of
each
section.
The
light
horizontal
line
indicates
the
upper
limit
of
the
reference
range
of
serum
erthropoietin.
Erythropoietin concentrations in obstructive sleep apnoea

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 SaO₂ 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.

It is, however, puzzling that only half of patients with chronic obstructive lung disease and polycythaemia have raised erythropoietin concentrations. 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.