S-erythropoietin levels decrease in patients with chronic hypoxia starting domiciliary oxygen therapy


ABSTRACT: Consecutive determinations of erythropoietin in serum (s-Epo) were made in ten patients with chronic hypoxia starting domiciliary long-term oxygen therapy (LTO). After 24 h of supplementary oxygen treatment there was a fall in the median s-Epo level from 11.3 to 4.4 IU/l (p<0.01). The initial decrease in s-Epo in conjunction with oxygen treatment was not sustained after one and three months of LTO. S-Epo levels above the reference range (3.3–13.5 IU/l) were found in three patients before and during LTO and in another two patients during LTO. Markedly elevated s-Epo levels were found in two patients with hypoxia and hypercapnia at the time of blood sampling. A significant negative relationship was found between the arterial oxygen tension and the log value for the s-Epo level (r=0.40, p<0.005). The s-Epo levels were found to be normal in half of the measurements in patients using oxygen less than 15 h daily, a fact that indicates that s-Epo measurements are probably not suitable as indicators of compliance with LTO.


Erythrocytosis is sometimes found in chronic hypoxia and diminishes or disappears when long-term domiciliary oxygen therapy is given [1]. Erythrocytosis is caused by the stimulation of erythropoietin by the hormone erythropoietin, which is released from the kidney cells in response to tissue hypoxia. In chronic hypoxic lung disease the s-erythropoietin (s-Epo) levels are elevated in some patients [2, 3]. We measured the s-Epo levels in ten patients with chronic hypoxia selected for long-term domiciliary oxygen therapy (LTO) before and during the first three months of treatment to elucidate the effect of elimination of the chronic hypoxia on s-Epo levels. We also investigated whether the s-Epo levels during LTO might be used as indicators of compliance with the prescribed oxygen therapy.

Material and methods

Patients

Ten patients (6 males) with a mean age of 67 yrs (range 55–84 yrs) took part in a study of s-Epo levels before and during LTO in four county hospitals in the southern part of Sweden. The diagnoses leading to chronic hypoxia were chronic obstructive airways disease (COAD) in eight patients, pulmonary fibrosis and COAD in one patient and late sequelae of pulmonary tuberculosis in one patient. All of the patients were selected for LTO because of stable chronic hypoxia and had not received oxygen therapy before. No patient was a current smoker. During the start and adjustment of oxygen therapy the patients were in-patients in chest wards.

All patients used bronchodilators. Nine patients were on oral theophylline medication during the whole observation period. The bronchodilator therapy was kept constant during the observation period. During exacerbations of the airways disease antibiotics and in one case steroids were used.

Blood specimens for s-Epo analysis were obtained before LTO and 24 hrs, 3, 30 and 90 days after the start of LTO. The blood specimens were taken between 08.00 and 15.00 h. Specimens for haemoglobin and arterial oxygen and carbon dioxide tensions were taken simultaneously. The study was approved by the regional Ethics Committee.

Oxygen therapy

Oxygen was prescribed for 16–24 h·day⁻¹ (mean 19 h) with oxygen flow rates varying from 0.4–2 l·min⁻¹. In seven patients the effectively administered oxygen treatment at home was checked by oxygen concentrator meter readings or pharmacy reports of delivered high
pressure compressed oxygen cylinders. In two patients no such controls were made and one patient did not comply with the prescribed oxygen treatment during a stay in a mental hospital during the observation period. Four patients used oxygen more than 15 h daily and four patients used oxygen less than 15 h.

Radioimmunoassay

A sensitive radio-immunoassay for s-Epo using labelled recombinant human erythropoietin (hEpo) and antiserum to urinary hEpo was used [4]. The specimens were frozen and sent to the Hormone laboratory at Akademiska Sjukhuset, Uppsala for analysis after the study period. The within-run imprecision expressed as coefficient of variation (CV) of this method was between 6-7% for s-Epo levels between 10-50 IU·l·1. The between-day CV varied between 11-19%. The reference range (mean±2sd) for healthy individuals was 3.3-13.5 IU·l·1 and the mean level 6.7 IU·l·1.

Statistics

The statistical significance of differences was tested using Wilcoxon’s signed rank test for paired data [5]. Single variable regression analyses were performed with a commercially available statistical package [6].

Results

All the patients were hypoxic when breathing air, with a mean arterial oxygen tension (Pao2) of 6.8 kPa (range 5.5-7.9 kPa). During oxygen breathing hypoxia improved to a mean value of Pao2 of 8.4 kPa (range 6.3-11.1 kPa) after 24 h of oxygen and 8.9 kPa (range 7.8-10.3 kPa) after 3 days of oxygen treatment. The mean arterial carbon dioxide tension (Paco2) rose from 6.5 to 6.9 kPa after 24 h and 3 days of supplementary oxygen (p<0.05). After one and three months of LTO the mean Paco2 diminished to 6.5 and 6.7 kPa, respectively (ns).

S-Epo decreased after breathing oxygen for 24 h in every patient. The initial s-Epo level was within the normal range (3.3-13.5 IU·l·1) in 7 of 10 patients before the start of LTO and within the normal range in all patients on the third day after LTO. The median s-Epo values were 11.3 IU·l·1 before LTO and 4.4, 5.5, 9.3 and 6.5 IU·l·1 at 24 h, 3, 30 and 90 days, respectively, after the start of LTO (fig. 1). The s-Epo levels fell significantly after 24 h and 3 days of supplementary oxygen therapy (p<0.01). The s-Epo values at 1 and 3 months were not significantly different from the values before the start of LTO. In three patients the s-Epo level was in the subnormal range after 24 h or on the third day of LTO. In one patient a very high level (184 IU·l·1) of s-Epo was found during a deterioration in the airways disease with hypoxia and hypercapnia during oxygen breathing. Markedly high s-Epo levels at the start of LTO were also found in one patient with hypoxia, hypercapnia and signs of cor pulmonale with ankle oedema.

The haemoglobin values (mean±sd) diminished from 151±80 g·l·1 before LTO to 144±10.6 g·l·1 after three months of LTO (p<0.05).

The relationship between s-Epo and the arterial oxygen tension, arterial carbon dioxide tension and haemoglobin value before and during LTO were calculated. There was a significant negative correlation between the value of arterial oxygen tension and the log value for the s-Epo level (r=0.40, p<0.005) (fig. 2). No significant relationships between s-Epo and haemoglobin or arterial carbon dioxide tension values were found (0.05<p<0.1).

![Fig. 1](image1) - S-erythropoietin (S-Epo) before and 24 h, 3, 30 and 90 days after the start of long-term oxygen therapy (n=10).

![Fig. 2](image2) - The relationship between s-erythropoietin (s-Epo) and arterial oxygen tension (Pao2) specimens taken before and 24 h, 3, 30 and 90 days after the start of long-term oxygen therapy (n=10).
In patients whose effective oxygen treatment exceeded 15 h, s-Epo was normal during follow-up except during exacerbation of the airways disease. The four patients who used oxygen less than 15 h had elevated values of s-Epo at 4 out of 8 control recordings during follow-up. S-Epo was within the reference range during the trial in the patient without theophylline medication.

**Discussion**

Erythropoietin (Epo) is the primary humoral regulator of erythropoiesis, acting by stimulation of the proliferation and differentiation of erythroid precursor cells. Its production in the renal cortex is stimulated by tissue hypoxia, which can be caused by anaemia and hypoxia. A considerable circadian variation of s-Epo has been observed with the lowest mean level at 08:00 h and a 60% increase to the highest level at 20:00 h [4]. A significant negative relationship between haemoglobin and log s-Epo values has also been shown [4].

Adenosine has been shown to modulate erythropoietin production [7]. Hypoxia increases the degradation of adenosine triphosphate (ATP) due to limited oxygen availability resulting in the formation of adenosine. Theophylline is a well-known adenosine receptor antagonist and has been shown to inhibit the enhancement of radio-iron incorporation induced by adenosine in combination with hypoxia in polycythaemic mice [7]. In man, theophylline has recently been shown to attenuate the production of erythropoietin both in normal subjects and in patients with erythrocytosis after renal transplantation [8]. We do not know whether theophylline medication attenuates the s-Epo production in chronic hypoxia in man. Our patient without theophylline had s-Epo values within the reference range during the observation period. Beta-adrenergics such as albuterol, on the other hand, enhance the radio-iron incorporation in polycythaemic mice after exposure to hypoxia [7]. Reduced renal blood flow can stimulate erythropoietin production by producing tissue hypoxia [9]. However, the production is also dependent on tubular sodium reabsorption and a regulation of Epo production that is independent from renal blood flow within a certain range has been suggested [10]. Whether a decrease in renal blood flow caused by hypcapnia and possibly hypoxia in decompensated cor pulmonale is an additional stimulus for erythropoietin release is unknown [11, 12].

Circulating s-Epo begins to rise approximately 1.5 h after the onset of acute hypoxia and reaches a maximum level after 1–3 days [13]. Once a secondary erythrocytosis is established s-Epo levels decrease down to the normal range during maintenance of erythrocytosis in some 75% of the cases [14].

In most patients with chronic cor pulmonale a low grade of stimulation of erythropoiesis by the chronic hypoxia is suggested by the findings of an elevated red cell mass which is usually masked by combination with an elevation of the plasma volume [15]. Frank erythrocytosis is found in a minority of these patients [1, 15]. Elevation of s-Epo has been found in approximately 25% of patients with chronic hypoxia [16].

We found that s-Epo levels were in the normal range in 7 of 10 patients with chronic hypoxia, thereby confirming earlier results [2, 3]. The reduction in the s-Epo levels after 24 h of oxygen breathing in all of our patients suggests that erythropoiesis is stimulated in these patients despite the normal s-Epo value.

Very high levels of s-Epo were found in two patients with hypoxia and hypercapnia at the time of blood sampling. Whether hypercapnia contributed to the s-Epo elevation is not known.

The investigation showed that, although the s-Epo decreased significantly after the administration of oxygen, the decrease was not sustained during domiciliary LTO at one and three months of follow-up. Elevated s-Epo levels were found during LTO in four patients on at least one occasion. The circadian variation of s-Epo or change of medication known to affect s-Epo production could not explain the rise of s-Epo during follow-up. Neither did the decrease in haemoglobin values, which was well within the normal range in all patients, explain these elevated s-Epo values. The arterial oxygen tension when breathing oxygen varied between 6.4 and 9.3 kPa at the time of blood sampling in these four patients. Hypoxia during oxygen breathing due to deterioration of the airways disease could explain the elevated values in two patients. Poor compliance with oxygen treatment is a possible explanation in the remaining two patients, who both used oxygen during less than 15 h. The fact that s-Epo levels were found to be normal in half of the measurements in patients using oxygen less than 15 h probably indicates that s-Epo measurements are not suitable as indicators of compliance with LTO.

**References**


RÉSUMÉ: Des déterminations successives de l'érythropoïétine sérique (s-Epo) ont été faites chez 10 patients atteints d'hypoxie chronique au moment du début de l'oxygenothérapie à domicile (LTO). Après 24 heures d'oxygenothérapie, on note une chute du niveau moyen de s-Epo de 16.2 IU/l à 7.1 IU/l (p<0.01). La diminution initiale de s-Epo en rapport avec le traitement à l'oxygène ne se maintient pas après 1 et 3 mois de LTO. Les niveaux de s-Epo au-dessus des valeurs de référence (3.3-13.5 IU/l) ont été trouvés chez trois patients avant et pendant LTO, et chez deux autres patients pendant LTO. Des niveaux fortement élevés de s-Epo ont été découverts chez deux patients souffrant d'hypoxie et d'hypercapnie au moment de la prise de sang. L'on a décelé une relation significative négative entre la tension d'oxygène artériel et le logarithme de la valeur du niveau de s-Epo (r = 0.40, p<0.005). Les niveaux de s-Epo s'avèrent normaux dans la moitié des mesures chez les patients qui utilisent l'oxygène moins de 15 heures par jour, un fait qui indique que les mesures de s-Epo ne sont probablement pas de bons indicateurs de la compliance à l'égard de l'oxygenothérapie.