

## Decrease in haematocrit with continuous positive airway pressure treatment in obstructive sleep apnoea patients

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*Decrease in haematocrit with continuous positive airway pressure treatment in obstructive sleep apnoea patients. J. Krieger, E. Sforza, C. Delanoe, C. Petiau.*

**ABSTRACT:** Previous preliminary results have shown an overnight decrease in haematocrit and red cell count after the first night of treatment with nasal continuous positive airway pressure (CPAP) in obstructive sleep apnoea (OSA) patients. The present study was designed to confirm these preliminary data, and to analyse the long-term effects of CPAP.

The haematocrit and red cell count (RCC) were measured in 80 OSA patients on two consecutive mornings, after an untreated night and after a CPAP treatment night. The haematocrit and RCC significantly decreased with CPAP (from  $44.0 \pm 0.5$  to  $42.4 \pm 0.4\%$ ,  $p < 0.0001$  and from  $4.769 \pm 0.051$  to  $4.597 \pm 0.052 \times 10^{12}$  red cells  $l^{-1}$ ,  $p < 0.0001$ , respectively). Neither the decrease in haematocrit nor the decrease in RCC were correlated with the decrease in urine volume or flow which occurred with CPAP.

Thirty five of these patients remained untreated for  $45 \pm 4$  days, before home treatment with CPAP was initiated. The haematocrit and RCC had returned to values close to those before initial treatment and decreased again after the first treatment night.

Twenty one of the patients were re-evaluated after at least one year of home treatment with CPAP, again on two consecutive nights either with CPAP or untreated. The follow-up, post-CPAP haematocrit and RCC were slightly and nonsignificantly higher than after the baseline CPAP night, but still lower than after the baseline untreated night ( $p < 0.02$ ). After the untreated follow-up night, no significant change in haematocrit was observed.

We conclude that CPAP results in a decrease in haematocrit and RCC, which persists with long-term treatment. The overnight decrease in haematocrit and RCC does not appear to be related to the haemodilution resulting from the decrease in urine excretion.

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We have previously reported [1] an overnight decrease in haematocrit in obstructive sleep apnoea (OSA) patients after the first treatment night with nasal continuous positive airway pressure (CPAP). This preliminary study included only eight patients; in addition, the time course of the changes in haematocrit was not analysed beyond the first investigation night.

The present work was designed to confirm these preliminary findings, and to analyse the immediate and long-term effects of CPAP treatment on haematocrit in a larger patient group. We therefore took advantage of the standard investigation protocol in use at our Sleep Unit to prospectively repeat blood analyses at various times in the course of the CPAP treatment of our patients.

### Patients and methods

All patients diagnosed as having an unambiguous obstructive sleep apnoea (OSA) syndrome, defined as an apnoea+hypopnoea index  $>30$  episodes  $h^{-1}$  of sleep, were included. They were all informed that some of the blood and urine samples taken would be used for research purposes, and all gave consent.

They were all ( $n=80$ ) submitted to the same standard initial investigation, which included two polysomnograms on two consecutive nights, the first one serving to establish the diagnosis, the second one with CPAP aimed at determining the pressure to be used for home treatment.

During each night, the polysomnograms included recordings of the electroencephalograph (EEG),

electro-oculogram (EOG) and electromyogram (EMG) of chin muscles, according to usual standards [2]. Breathing was analysed using a pneumotachograph (Fleisch No. 2) with a Godart-Statham pressure transducer and electronic integrator. Respiratory efforts were measured using an oesophageal balloon and a Validyne MP 45 pressure transducer. Ear oximetry (Biox Ohmeda III) was used to analyse oxygen saturation.

During the CPAP-treatment night, continuous positive airway pressure was applied *via* a nasal mask, using a commercial device (Pression+, SEFAM). Treatment was started at a pressure of 3 cmH<sub>2</sub>O and increased until the apnoeas and snoring were eliminated and the intrathoracic pressure swings minimized.

A blood sample was taken on the morning after the untreated night and after the CPAP-treated night for standard red cell count and determination of the haematocrit and haemoglobin concentration. Urine was collected from bedtime until waking-up. Urine concentrations of sodium and chloride as well as cyclic guanosine monophosphate (cGMP) were determined, and the corresponding urine flow and excretion rates were calculated. These 80 patients will be termed the "immediate CPAP effect" group.

Among these 80 patients, 35 had to wait from 6–120 days (45±4 days, mean±SEM) for administrative reasons before their CPAP device became available. They were then rehospitalized for one night on CPAP, during which they were taught how to use their device before home treatment was initiated. A blood sample was taken before and after the CPAP treated night, in order to test the reproducibility of the observed immediate effects of CPAP under more "natural" conditions than those of a polysomnographic recording. This subgroup will be termed the "repeat immediate CPAP effect" subgroup.

Of the initial 80 patients, 21 have so far undergone a follow-up reinvestigation after at least one year (451±12 days) of home treatment, in order to ascertain whether the pressure used was still adequate. During this reinvestigation, the same polysomnographic

and blood and urine analyses were performed as on initial investigation, with the important difference that the CPAP night was the first investigated night, and the untreated night the second investigated night. These 21 patients will be termed the "long-term follow-up" group.

The three subgroups (immediate, repeat immediate and long-term) were not significantly different from each other in terms of age, body mass index (BMI), apnoea or hypopnoea index, minimal arterial oxygen saturation (Sao<sub>2</sub>) during sleep, daytime arterial oxygen tension (Pao<sub>2</sub>) or arterial carbon dioxide tension (Paco<sub>2</sub>), or CPAP level used (table 1).

Comparisons between groups were made using the Student's t-test for unpaired values. Comparisons between situations (*i.e.* untreated vs CPAP-treated) were made using the Student's t-test for paired values when two situations were compared, or multiple analysis of variance for repeated measures followed by a Newman Keuls test for the localization of differences, when more than two situations were compared. In the repeat immediate effect subgroup and long-term follow-up subgroup, in which four measurements were available (*i.e.* two untreated, and two CPAP-treated) two-way analyses of variance (ANOVA) were performed with two factors (*i.e.* CPAP-treatment and time). Correlations were analysed using the Pearson's correlation coefficient. Results are given as means±SEM.

## Results

### Baseline data

Before treatment, the mean haematocrit in the 80 patients was 44.0±0.5%. Seven patients had a haematocrit greater than the upper limit of the normal range (38–50%) in our laboratory. Of these seven polycythaemic patients, four were hypoxaemic (*i.e.* daytime Pao<sub>2</sub> <65 mmHg). The mean Pao<sub>2</sub> in the polycythaemic group was not significantly different from that of the remaining patients (69.3±4.0 vs 75.3±1.1 mmHg, respectively p>0.10).

Table 1. – Main characteristics of the patients studied

	Immediate CPAP group n=80	Immediate repeat CPAP group n=35	Long-term CPAP group n=21 Baseline	Long-term CPAP group n=21 Follow-up	Follow-up vs baseline long-term CPAP group
Age yrs	53.4±1.0	54.2±1.5	52.6±1.9	53.8±1.9	
BMI kg·m <sup>-2</sup>	31.8±0.6	31.3±0.9	31.4±1.1	31.3±0.9	NS
Apnoea Index n·h <sup>-1</sup>	66.3±4.2	63.9±6.7	64.1±5.8	54.8±10.3	NS
Apnoea + Hypopnoea Index n·h <sup>-1</sup>	81.0±3.4	75.1±2.6	76.9±4.8	74.1±10.8	NS
Minimal Sao <sub>2</sub> %	76.4±1.6	75.1±2.6	75.4±3.1	80.2±1.7	p<0.05
Pao <sub>2</sub> mmHg	74.8±1.1	73.6±1.3	77.8±2.6	77.3±2.1	NS
Paco <sub>2</sub> mmHg	37.2±0.5	36.9±0.7	37.1±1.1	37.3±0.5	NS
CPAP cmH <sub>2</sub> O	9.8±0.4	9.0±0.4	10.9±0.6	9.2±0.7	p<0.02

Mean±SEM. CPAP: continuous positive airway pressure; BMI: body mass index; Sao<sub>2</sub>: arterial oxygen saturation; Pao<sub>2</sub>: arterial oxygen tension; Paco<sub>2</sub>: arterial carbon dioxide tension; NS: nonsignificant

### Immediate effects

In the 80 patients, the haematocrit decreased between the untreated and the CPAP-treated night from  $44.0 \pm 0.5$  to  $42.4 \pm 0.4\%$ , the red cell count decreased from  $4.769 \pm 0.051$  to  $4.597 \pm 0.052 \times 10^{12}$  red cells  $\cdot l^{-1}$ , and the haemoglobin concentration decreased from  $15.0 \pm 0.1$  to  $14.4 \pm 0.1$  g  $\cdot dl^{-1}$ . Figure 1 shows that individual values decreased in most patients. All of these changes were statistically significant ( $p < 0.0001$ ).

decrease in haematocrit, red cell count or haemoglobin concentration with either the level of CPAP used, the decrease in urine volume or flow, or the decrease in cGMP excretion (fig. 2).

### Repeat immediate effects

In the 35 patients, the immediate decrease in haematocrit, red cell count and haemoglobin concentration during the first evaluation was not different from that

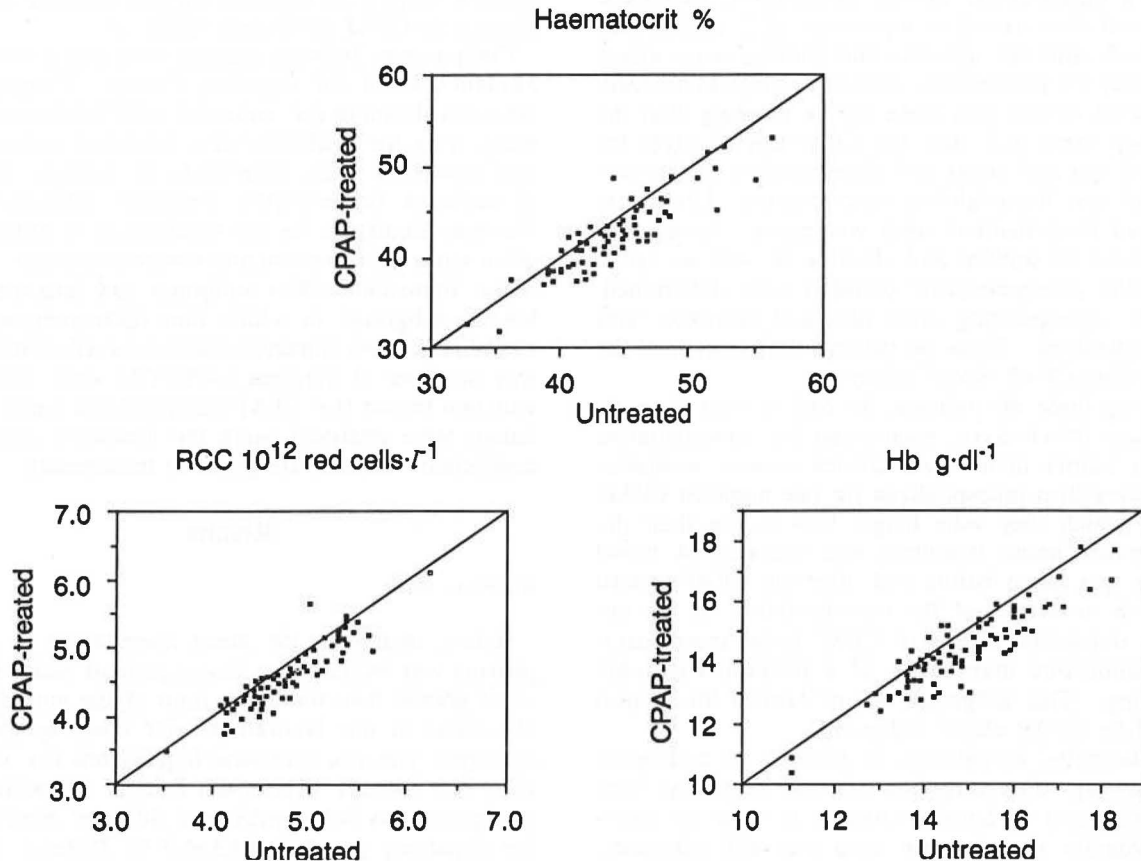


Fig. 1. - Immediate effects of continuous positive airway pressure (CPAP) on haematocrit, red cell count (RCC) and haemoglobin concentration (Hb) in the immediate CPAP group ( $n=80$ ). Values falling below the identity line indicate a decrease with CPAP.

Urine volume decreased from  $626 \pm 34$  to  $457 \pm 29$  ml, urine flow from  $1.22 \pm 0.04$  to  $0.86 \pm 0.01$  ml  $\cdot min^{-1}$ , sodium excretion from  $0.17 \pm 0.04$  to  $0.11 \pm 0.01$  mM  $\cdot min^{-1}$ , and cyclic guanosine monophosphate excretion from  $0.77 \pm 0.04$  to  $0.58 \pm 0.03$   $\mu M \cdot min^{-1}$  ( $p < 0.0001$  in all cases).

No significant correlation could be demonstrated between the haematocrit, red cell count, or haemoglobin concentration before treatment and the apnoea or apnoea+hypopnoea index, the patients' age, body mass index, minimal  $Sa_{O_2}$  during sleep, or daytime  $Pao_2$ .

The decrease in haematocrit and haemoglobin concentration was weakly correlated with the baseline haematocrit and haemoglobin concentration ( $r=0.31$ ,  $p < 0.01$  and  $r=0.34$ ,  $p < 0.005$ , respectively). No significant correlation could be demonstrated between the

observed in the entire group (*i.e.* haematocrit from  $43.2 \pm 0.7$  to  $41.8 \pm 0.7\%$ ; red cell count from  $4.655 \pm 0.84$  to  $4.498 \pm 0.083 \times 10^{12}$  red cells  $\cdot l^{-1}$ ; haemoglobin concentration from  $14.7 \pm 0.2$  to  $14.3 \pm 0.2$  g  $\cdot dl^{-1}$  (fig. 3). After  $45 \pm 4$  days without treatment, the haematocrit increased to  $43.8 \pm 0.7\%$  and decreased again after the repeat CPAP-treatment night to  $42.5 \pm 0.7\%$ . The overall ANOVA indicated that the four haematocrit readings were different at the  $p < 0.001$  level, with the untreated values differing from the CPAP-treated values, and the two untreated and the two post-treatment values not differing between each other (Newman Keuls). Factorial analysis showed a significant CPAP-treatment effect ( $p < 0.001$ ), but no time effect for treatment by time interaction. The same evolution was observed for the red cell count (fig. 3) and the haemoglobin concentration.

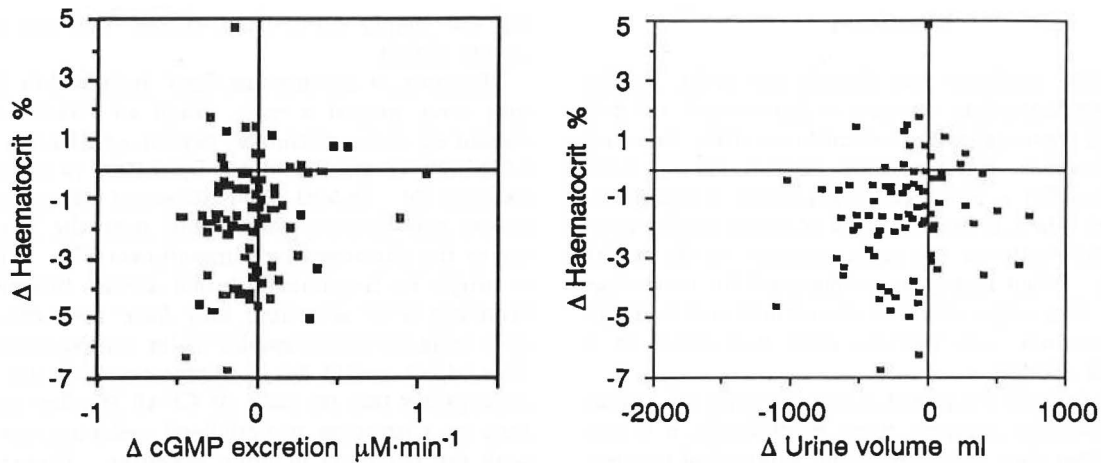


Fig. 2. - Change in haematocrit vs change in urine volume and in cyclic guanosine monophosphate (cGMP) excretion with continuous positive airway pressure (CPAP) treatment in the immediate CPAPM group (n=80), showing the absence of correlation between these variables.

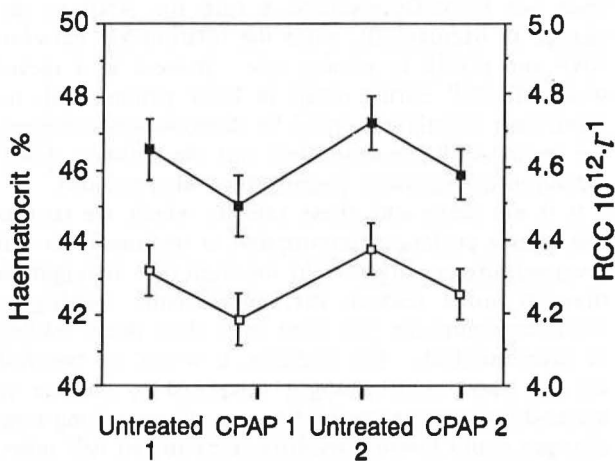


Fig. 3. - Evolution of the haematocrit (—□—) and red cell count (—■—) in the repeat immediate continuous positive airway pressure (CPAP) subgroup (n=35). Untreated 1: after the baseline untreated night; CPAP 1: after the baseline CPAP-treated night; Untreated 2: after 45 days without CPAP; CPAP 2: after a second single CPAP-treated night.

Long-term effects

In the 21 patients who were reinvestigated after one year of home treatment with CPAP, the apnoea syndrome after the single night treatment interruption was less severe than before treatment, in that the apnoea index was substantially (but not statistically significantly) less than on baseline and the minimal  $SaO_2$  during sleep was higher; the level of CPAP required to normalize breathing during sleep was also lower (table 1).

In these patients, the initial decrease in haematocrit, red cell count and haemoglobin concentration during the first evaluation was not different from that observed in the entire group (i.e. haematocrit fell from  $44.8 \pm 0.7$  to  $42.4 \pm 0.6\%$ , red cell count from  $4.833 \pm 0.091$  to  $4.600 \pm 0.086 \times 10^{12}$  red cells· $l^{-1}$ , and

haemoglobin concentration from  $15.3 \pm 0.3$  to  $14.4 \pm 0.2$  g· $dl^{-1}$ ).

After one year of home treatment, the haematocrit following the CPAP treatment night was  $42.9 \pm 0.7\%$ , the red cell count  $4.727 \pm 0.085 \times 10^{12}$  red cells· $l^{-1}$  and the haemoglobin concentration  $14.8 \pm 0.2$  g· $dl^{-1}$ . After the untreated night they were  $42.4 \pm 0.7\%$ ,  $4.600 \pm 0.085 \times 10^{12}$  red cells· $l^{-1}$ , and  $14.4 \pm 0.2$  g· $dl^{-1}$  ml, respectively. The overall ANOVA indicated that the four haematocrit readings were different at the  $p < 0.001$  level; the haematocrit values with CPAP on baseline and on follow-up were significantly lower than the values before initial treatment ( $p < 0.01$  and  $p < 0.05$ , respectively), but the values after the second untreated night were not different from values on any other night (fig. 4). Again, the factorial analysis showed a CPAP effect ( $p < 0.001$ ), but no time effect, or CPAP by time interaction. The same evolution was observed for red cell count (fig. 4) and haemoglobin concentration.

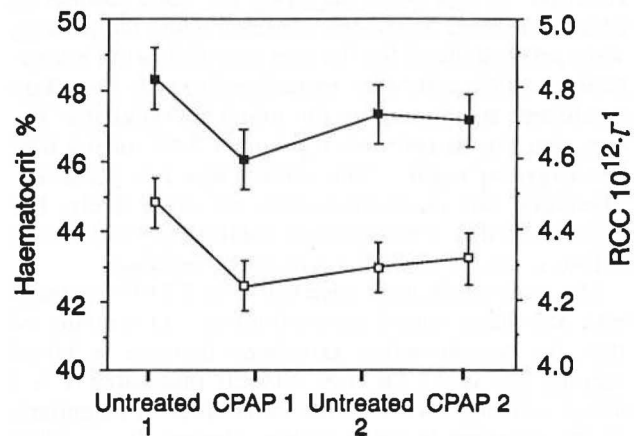


Fig. 4. - Evolution of the haematocrit (—□—) and red cell count (—■—) in the long-term follow-up group (n=21). Untreated 1: after the baseline untreated night; CPAP 1: after the baseline CPAP-treated night; CPAP 2: after the one-year follow-up CPAP-treated night; Untreated 2: after the follow-up untreated night.

### Discussion

This study confirms and extends our earlier results showing an immediate decrease in haematocrit, red cell count and haemoglobin concentration after the first CPAP treatment night in OSA patients [1]. It also shows that after a prolonged interruption in treatment, the values return to baseline and a repeat single treatment night produces the same changes as the initial treatment. When treatment is continued for more than one year, the initial effect is maintained and a single night treatment interruption does not result in a significant change.

This study was not aimed at investigating the causes of the observed changes; more specifically, it is not clear whether they were due to the elimination of sleep apnoeas or to a direct effect of CPAP. This would have required a parallel study of the effects of CPAP in non-sleep-apnoeic subjects under the same conditions, which would have been difficult to achieve. In addition, it would not have been helpful, since the sleep disturbing effects of CPAP on sleep in normal subjects would have introduced an additional confounding factor, rather than clarifying the situation.

A short-term (*i.e.* 7 day) decrease in haematocrit from 47 to 43% has been reported after tracheostomy in ten OSA patients [3]. An intermediate-term (*i.e.* 22–59 day) decrease has also been reported with CPAP treatment [4] and was ascribed to a reduced red cell mass, secondary to a supposedly decreased haematopoiesis consecutive to improved daytime and/or night-time oxygenation. The observation of an overnight decrease in haematocrit after a single treatment night demonstrates that a change in red cell mass cannot be responsible for the observed changes, given the half-life of red cells of about 120 days; the only possible mechanism is haemodilution.

Haemodilution might be due to an uncompensated water load, such as that resulting from increased fluid intake; more specifically, the patients may have increased their drinking upon admission to hospital. However, if this were the case, the same change in behaviour could have been expected when the patients were rehospitalized for the one year follow-up examination, which otherwise reproduced exactly the same conditions and timing as the initial investigation, except that the patients were put on CPAP on the first investigation night. This effect was not observed. Therefore, this mechanism does not seem likely, but requires further investigations controlling fluid intake before it can be excluded with more certainty.

The reduced diuresis observed with CPAP treatment may also have caused haemodilution. As a matter of fact, the corresponding calculated increase in blood volume [5] is 4.17%, *i.e.* 208 ml (assuming a 5 l blood volume); this is of the same order of magnitude as the decrease in urine volume during sleep, which was 169 ml in these 80 patients. However, there was no significant correlation between the change in either haematocrit or red cell count and the change in urine volume, suggesting that the observed haemodilution

did not simply result from excess fluid not excreted by the kidney.

Therefore, it appears that fluid shifts within the body may have played a role. Such an effect might be caused by atrial natriuretic peptide (ANP), the release of which is known to be increased in some OSA patients [6]. Indeed, ANP increases vascular permeability and favours a fluid shift from the intravascular to the extravascular compartment [7]. Therefore, it might be hypothesized that CPAP treatment, by reducing ANP secretion, may have favoured a fluid shift from the extravascular to the intravascular space. This effect would be in agreement with the clinical observation that the start of CPAP is often accompanied by a decrease in peripheral oedemas, contrasting with the reduction in urine excretion. However, this mechanism is not supported by the lack of a correlation between cGMP excretion and change in haematocrit, since cGMP excretion has been shown to be a marker of ANP release [8]; this lack of a correlation does not formally exclude a role for ANP in the change in haematocrit, since the relationship between ANP and cGMP is a loose one. Indeed, in a recent study of ANP during sleep in OSA patients [6], no significant correlation could be demonstrated between the mean ANP concentration and the urinary cGMP excretion during sleep (unpublished observation).

It is not clear why these effects, which are reversible after a prolonged interruption in treatment, are not reversed after a single night interruption. It might be that for some reason, the mechanisms leading to haemoconcentration are more inert than those leading to haemodilution. For instance, it would be possible for the short-term changes observed to be due to haemodilution, as suggested above, whereas long-term changes could involve modifications in red cell mass, which would be expected to be more inert. Another possible explanation would be that because the sleep apnoea severity was less after a single night treatment interruption than on the initial investigation, the mechanisms leading to haemoconcentration, whatever their nature, are less active.

These observations also lead us to question the mechanism of the "polycythaemia", which is classically described as part of the clinical features of obstructive sleep apnoea [3, 9, 10], although it has been reported as being infrequent (7% of patients, once associated lung diseases had been eliminated) [11]; this result is in the range of the 9% in our study, in which no attempt has been made to exclude the contribution of associated lung diseases. The polycythaemia in OSA is generally ascribed to increased red cell volume due to hypoxaemia-induced increased haematopoiesis; however, recent studies have failed to demonstrate increased plasma erythropoietin concentrations either during sleep or during daytime in OSA patients [12] or a difference in morning and evening plasma erythropoietin between hypoxaemic and normoxaemic OSA patients [13]. In view of the present observations, a contribution of haemoconcentration to the observed increased haematocrit may be postulated.

Clearly, investigations measuring the actual plasma volume and globular mass, as well as extravascular volumes are required to clarify these points.

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