Effect of oxygen on breathing irregularities during haemodialysis in patients with chronic uraemia

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ABSTRACT: Hypoxaemia and breathing irregularities have been shown to occur during haemodialysis in patients with chronic renal failure. This study examined the role of hypoxia in the genesis of the irregular breathing during haemodialysis.

The ventilatory patterns using respiratory inductance plethysmography and arterial blood gases were studied in seven males with chronic renal failure on long-term haemodialysis. The study was carried out before and during dialysis on one day without (D1) and another day with intranasal oxygen at 4 L·min⁻¹ (D2).

On D1, mean (SD) arterial oxygen tension (Pₐ,O₂) fell 1.9 (0.9) kPa (p<0.001) and mean minute ventilation (V̇E) fell 1.9 (1.1) L·min⁻¹ (p<0.01) during dialysis. The arterial carbon dioxide tension (Pₐ,CO₂) did not show a significant decrease (4.7 (0.2) kPa before and 4.6 (0.2) kPa during dialysis). Cumulative number of apnoeas was 64 and the coefficients of variation (COV) of respiratory frequency (fR) and tidal volume (Vₜ) were 29.6 (11.9) and 38.2 (11.9)%, respectively. On D2, mean Pₐ,O₂, remained stable (20.4 (4.1) kPa before, 21.3 (4.1) kPa during dialysis). There was no significant change in mean V̇E (6.4 (0.9) L·min⁻¹ before, 5.5 (0.5) L·min⁻¹ during dialysis). Pₐ,CO₂ decrease was not significant but the fall was greater (4.8 (0.1) kPa before, 4.5 (0.5) kPa during dialysis). Cumulative number of apnoeas was 94 and the COVs of fR and Vₜ were 35.8 (5.1) and 40.5 (11.3)% respectively.

Oxygen administration did not significantly affect the haemodialysis-induced changes in ventilation and breathing pattern, despite a significant protective effect from the fall in arterial oxygen tension. It was concluded that the fall in arterial oxygen tension is not the main determinant of breathing irregularities during haemodialysis.

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Study design

Dialysis was performed with an open, two-needle, single-pass system with a Single Unit Gambro AIC-10 machine. A cuprophane type membrane and an acetate containing dialysate were used. The surface area of the membrane was 1.2 m². The dialysate flow was kept constant at 500 mL·min⁻¹ and the blood flow at 200 mL·min⁻¹.

Blood specimens were collected in heparinized syringes from the arterial line before dialysis at time 0, and then 60 and 120 min after the onset of dialysis. Blood pH, arterial carbon dioxide tension (PₐCO₂), PₐO₂ and bicarbonate (HCO₃⁻) were measured with a Radiometer Copenhagen ABL 30 Acid Base Analyser.

The patients were studied in a semirecumbent position. RIP was carried out using a computerized system, Respigraph™. Approximately 15 min before the start of haemodialysis, the RIP was calibrated and validated during tidal breathing in a semirecumbent position using a previously validated method [23]. Calibration of RIP was performed for 10 min or a total of 250 breaths to obtain rib cage and abdominal gains. In a second procedure, the volume signal derived from RIP measurement was compared with the signal from the spirometer for 10 breaths to obtain new semiquantitative gains. Finally, the volume was validated with 10 breaths to obtain the mean percentage deviation of the Respigraph™ tidal volume from the Spirometer tidal volume. The quantitative calibration was only accepted if the validation per cent error was ±10%, and 90% of the breath-to-breath per cent error was ±15%. Once this was done, the semiquantitative RIP measurements were obtained after each 15 min epoch. Analogue recordings of the rib cage (RC), abdomen (AB) and sum components of the RIP were displayed on a screen. This could be converted to an envelope display which also showed the oxygen saturation (SₐO₂), recorded by an Ohmeda Biox 3 Pulse Oximeter (Ohmeda, CO, USA), and a wrist actigraph signal. The number, type and duration of apnoeas were also displayed. After every 15 min epoch, a compressed plot of the breathing pattern was printed out. The semiquantitative measurements that were taken were: tidal volume (Vₜ), minute ventilation (V'ₑ) and mean inspiratory flow (V't/l). The other parameters were inspiratory time (tᵢ), expiratory time (tₑ) and respiratory frequency (fₑ). The epochs at 0, 60 and 120 min were analysed. They were the average measurements of the last 15 min before each set interval time. The breathing pattern was also recorded on a eight-channel Gould Recorder 2800S. The breathing patterns on these recordings were analysed manually. At the end of the study, validation of semiquantitative measurements was repeated. The data were accepted only if the per cent error was ±10%, with 90% of the breath-to-breath validation ±15% different from the spirometric Vₜ.

The study was carried out on 3 days and at the same time each day. The time from the last dialysis to each study day was the same. The purpose of the study on the first day was to get the patients accustomed to the equipment, and the data were not analysed. On the second day (D1), the above measurements and breathing patterns were studied and analysed during 2 h of haemodialysis. This was repeated on the third day (D2) with intranasal supplemental oxygen at 4 L·min⁻¹.

Analysis of data

Statistical analyses of differences in measurements from the predialysis value, as well as between the days, were performed by analysis of variance (ANOVA). A multiple comparison test, Scheffe’s test, was used if the ANOVA was significant. The numbers of apnoeas on each study day were compared using a paired t-test.

Results

This study showed a highly significant fall in mean PₐO₂ during haemodialysis (p<0.001; table 1). The mean (sd) decrease in PₐO₂ was 1.9 (0.9) kPa by the second hour. This fall was 13.7 (6.2)% of the predialysis value (table 2). The individual PₐO₂ did not fall below 10.7 kPa during the 2 h of study. When intranasal oxygen at 4 L·min⁻¹ was administered, their mean PₐO₂ was maintained at a high level throughout haemodialysis (20.4 (4.1) kPa predialysis and 21.3 (4.1) kPa at the second hour) (table 2). PₐCO₂ did not show any significant decrease during the 2% of the study on both days. However, the fall in PₐCO₂ on D2 was greater (tables 2 and 3). The pH increased significantly by the second hour on both days (p<0.01 on D1 and p<0.05 on D2). The serum bicarbonate also showed a small rise with haemodialysis.

The mean V'ₑ, Vₑ and V'T/l were the average of measurements taken from five out of seven patients, as the calibration of semiquantitative data of the other two did not meet the criteria for acceptance. After 120 min of haemodialysis in D1, V'ₑ fell significantly from 7.4 (1.6) to 5.5 (0.9) L·min⁻¹ (p<0.01; table 1). On the day with oxygen administration, V'ₑ decreased from 6.4 (0.9) to 5.5 (0.5) L·min⁻¹ (11.9 (14.7)% fall compared with a 24.0 (11.3)% fall on D1) (tables 2 and 3). This fall in V'ₑ was not significant. The mean Vₑ was also decreased on both days but not significantly.

Table 1. Blood gases and ventilation parameters during haemodialysis on the second day (D1)

|                | 0 min | 60 min | 120 min |
|----------------|-------|--------|---------|
| PₐO₂ kPa       | 13.9  | 11.8   | 12.0    |
| (0.7)          | (0.9) | (0.6)  |
| PₐCO₂ kPa      | 4.7   | 4.8    | 4.6     |
| (0.2)          | (0.2) | (0.2)  |
| pH             | 7.393 | 7.399  | 7.418   |
| (0.023)        | (0.021) | (0.025) |**
| HCO₃⁻ mmol·L⁻¹ | 21.4  | 22.0   | 22.8    |
| (2.0)          | (1.2) | (1.4)  |
| V'E L·min⁻¹   | 7.4   | 6.2    | 5.5     |
| (1.6)          | (1.0) | (0.9)  |
| V'T mL         | 410   | 388.8  | 376.2   |
| (46.8)         | (22.1) | (31.0) |
| tᵢ breaths·min⁻¹ | 18.5 | 15.9   | 14.6    |
| (3.9)          | (3.0) | (2.4)  |
| V'T/l L·s⁻¹    | 358.4 | 327.8  | 297.0   |
| (59.5)         | (50.0) | (36.3) |
| t s            | 1.21  | 1.39   | 1.44    |
| (0.25)         | (0.37) | (0.28)  |
| tₑ s           | 1.98  | 2.39   | 2.57    |
| (0.46)         | (0.51) | (0.53)  |

All values are expressed as mean (sd). PₐO₂: arterial oxygen tension; PₐCO₂: arterial carbon dioxide tension; V'E: minute ventilation; V'T: tidal volume; tᵢ: respiratory frequency; V'T/l: mean inspiratory flow; tₑ: inspiratory time; tₑ: expiratory time. *: p<0.05; **: p<0.01; ***: p<0.001 versus time 0 min.
statistical differences were not observed (p=0.09 on D1 at the second hour). Mean VT/t fell by 61.4 (53.1) L·s⁻¹ on the day of haemodialysis without oxygen supplement (p=0.054; table 1). On D2 it did not decrease with the progress of haemodialysis.

The mean \( t_e \) was markedly increased on D1, from 1.98 (0.46) to 2.57 (0.53) s (p<0.001). This was due to both a decrease in \( f_r \) (p<0.001; table 1) and the occurrence of apnoeas. There was also an increase in \( t_e \) on the day with oxygen administration. Mean \( t_e \) was 2.15 (0.42) s before dialysis, rising to 2.7 (0.79) s by the second hour (p<0.05). Mean \( t_i \) increased from 1.21 (0.25) to 1.44 (0.28) s by 120 min (p<0.05) on D1.

All predialysis ventilation parameters were similar on the two study days. It was noted, however, that the baseline VT/e on D2 was lower than that on D1 (tables 1, 2 and fig. 1). One possible explanation was that the amount of fluid overload was less on D2. Besides \( P_{aO_2} \), there was no statistical difference in predialysis blood gas measurements between the two days. The percentage differences from baseline of all ventilation parameters and blood gases were compared between the two days and no significant difference was found, except for \( P_{aO_2} \) (table 3).

The breathing patterns were analysed manually from the Gould recordings. Breathing was found to be irregular with episodes of apnoea during the 2 h study on D1. On D2, periodic breathing and apnoeas were still present. All apnoeas were of the central type and analysed only when they were >10 s in duration. Four out of the seven patients had more apnoeas on D2 (fig. 2). There was no significant difference in the number of apnoeas between the two days (table 4), although the mean number was higher on the day with oxygen administration. However, one of the patients had a large increase in the number of apnoeas (7 on D1 to 42 on D2) on the day with oxygen administration and this may have biased the mean result. The range of

| Table 2. – Blood gases and ventilation parameters during haemodialysis with intranasal oxygen on the third day (D2) |
|----------------------------------------------------------------------|
| Parameter          | 0 min   | 60 min | 120 min |
| \( P_{aO_2} \) kPa    | 20.4 (4.1) | 22.9 (7.0) | 21.3 (4.1) |
| \( P_{aCO_2} \) kPa   | 4.8 (0.1)  | 4.7 (0.2)  | 4.5 (0.5)  |
| \( pH \)             | 7.399 (0.026) | 7.403 (0.02) | 7.433 (0.034)* |
| \( HCO_3 \) mmol·L⁻¹ | 22.2 (1.3) | 21.9 (1.1) | 22.4 (1.4) |
| \( V_e \) L·min⁻¹   | 6.4 (0.9)  | 5.7 (0.8)  | 5.5 (0.5)  |
| \( V_t \) mL         | 382.0 (43.2) | 361.2 (48.8) | 379.0 (86.4) |
| \( f_r \) breaths·min⁻¹ | 17.0 (45.0) | 15.6 (81.4) | 14.9 (22.2) |
| \( V_t/n \) L·s⁻¹    | 311.0 (3.1) | 314.0 (2.8) | 308.6 (4.5) |
| \( t_e \) s          | 2.15 (0.34) | 2.40 (0.37) | 2.70 (0.56) |
| \( t_i \) s          | 1.30 (0.34) | 1.37 (0.37) | 1.44 (0.56) |

All values are expressed as mean±SD. For definitions see legend to table 1. *: p<0.05 versus time 0 min.

Table 3. – Comparison of per cent difference from baseline between the second and third days (D1 and D2)

| Parameter | 60 min from baseline | 120 min from baseline |
|-----------|----------------------|-----------------------|
| \( P_{aO_2} \) % | -1.6 (5.6) | -11.1 (12.8)*** |
| \( P_{aCO_2} \) % | -0.1 (0.2) | -0.06 (0.5) |
| \( pH \) | -3.2 (6.8) | 1.3 (4.6) |
| \( HCO_3 \) | 16.1 (5.4) | 9.4 (13.2) |
| \( V_e \) % | 4.5 (7.9) | 4.9 (13.2) |
| \( f_r \) | 13.3 (9.3) | 7.7 (8.4) |
| \( V_t/n \) | 7.6 (13.6) | -0.7 (19.9) |
| \( t_e \) | -15.1 (18.7) | -4.7 (8.8) |

All values are expressed as mean±SD. For definitions see legend to table 1. **: p<0.01; ***: p<0.001 between D1 and D2.
number of apnoeas was wide on D2. Therefore, the cumulative number of apnoeas (64 on D1 versus 94 on D2 over the 2 h study) was also studied and, as shown in figure 3, the curves were similar and no statistical difference was obtained when the areas under the two curves were compared. The onset of apnoea on each study day was also examined. On D1, the mean onset was 16 (17) min, while that on D2 was 42.7 (44.4) min after the start of haemodialysis. The difference was not significant. The mean duration of apnoea was similar on both days, with the longest duration being 15 s on D1 and 29 s on D2. Breathing was irregular on both days and this was further confirmed by the length of the duration of apnoea because of a decreased hypoxic sensitivity of the peripheral chemoreceptors as well as an increased cycle time of oscillation [18, 20]. On D2, with \( P_{a,O_2} \) maintained above 20 kPa, the hypoxic drive was removed. Extrapulmonary excretion of carbon dioxide continued during haemodialysis. The breathing pattern remained unstable. There was also a fall in \( V_{E} \), although this was not significant.

Excess carbon dioxide and hydrogen ions affect respiration mainly by excitatory effects on the respiratory centre itself, whereas oxygen acts almost entirely on the peripheral chemoreceptors. These peripheral chemoreceptors also respond to carbon dioxide and hydrogen ions. The mechanisms of both carbon dioxide and hydrogen ion action are more important in the control of respiration. The effect of \( P_{a,O_2} \) changes on respiratory control is opposed by both the carbon dioxide and the hydrogen ion control mechanisms. This is because the increase in ventilation that occurs when the \( P_{a,O_2} \) falls, reduces the \( P_{a,CO_2} \) and, at the same time, decreases the hydrogen ion concentration. The latter two therefore exert inhibitory effects that oppose the excitatory effect of the diminished \( P_{a,O_2} \) [24]. The peripheral chemoreceptors become very sensitive to changes in \( P_{a,O_2} \) only when it is below 8 kPa.

In this study, it was unlikely that hypoxaemia played a major role in producing the irregular breathing pattern with central apnoeas, as the \( P_{a,O_2} \) did not fall below 10.7 kPa throughout the 2 h of study in all subjects. The carbon dioxide response could have played a more important role in causing the irregular breathing.

The lower end of the carbon dioxide response curve is flattened into a “dogleg” region in which carbon dioxide responsiveness is greatly reduced or absent [25–27]. At the junction of the “dogleg” and the steep point of the carbon dioxide response curve, breathing is not stable and central apnoeas occur. It could be explained that during haemodialysis with extrapulmonary carbon dioxide unloading, the patients were breathing at this junction. However, the “dogleg” region in the \( V_{E}-P_{a,CO_2} \) curve occurs only in the presence of hypoxaemia with a \( P_{a,O_2} \) of 6.7 kPa [24, 25, 28]. Thus, this could not have explained the irregular breathing found in these patients.

In humans, apnoeas or unstable breathing patterns can be induced by small reductions in \( P_{a,CO_2} \) below the resting

### Table 4. Number and duration of apnoeas during the 2 h study

|       | D1          | D2          |
|-------|-------------|-------------|
| Number| Mean (s)    | 9.1 (4.2)   | 13.4 (14.5) |
|       | Median      | 9           | 5           |
|       | Range       | (2–16)      | (1–42)      |
| Duration(s) | Mean (s)    | 15.8 (4.3)  | 15.8 (4.6)  |

D1: second study day; D2: third study day (with intranasal oxygen).

**Discussion**

In this study, ventilation parameters and blood gases were measured in patients during haemodialysis for 2 h. The validation of quantitative calibration was checked before the start and at the end of the study. The data from only five patients who had a mean validation per cent error of ±10%, and 90% of their breath-to-breath per cent error was ±15%, were used in the quantitative analysis of para-meters \( (V_{E}, V_{T}, \text{and } V_{T/n}) \). The data from all patients were included in the analysis of the other measurements. RIP was used to overcome the problem of using a mouthpiece, which has been reported to influence the pattern of breathing via oral respiration. Oral breathing has been found to increase \( V_{T} \) and reduce \( f/R \) [22].

The decrease in \( P_{a,O_2} \) of 1.9 kPa, or 13.7% from baseline, in this study was consistent with previous studies [3, 12] and was associated with a decrease in \( V_{E} \). An irregular breathing pattern with episodes of central apnoea was demonstrated. The patients were observed to be awake during the study and this was further confirmed by the presence of activity on their wrist actigraphs. None of them was taking any medicine that could have led to respiratory suppression.

Administration of oxygen prevented the fall in \( P_{a,O_2} \) but did not remove the irregular breathing. \( V_{E} \) continued to fall, although this was not significant. Percentage differences of change from baseline values were compared between the two days and no significant difference was shown. The breathing pattern remained irregular. The coefficient of variation of \( f/R \) and \( V_{T} \) did not decrease with oxygen administration. The cumulative number of apnoeas over the 2 h was higher (94 versus 64) on D2 than on D1. Some patients experienced more prolonged central apnoeas. Oxygen administration had been shown to lengthen the duration of apnoea because of a decreased hypoxic sensitivity of the peripheral chemoreceptors as well as an increased cycle time of oscillation [18, 20]. On D2, with \( P_{a,O_2} \) maintained above 20 kPa, the hypoxic drive was removed. Extrapulmonary excretion of carbon dioxide continued during haemodialysis. The breathing pattern remained unstable. There was also a fall in \( V_{E} \), although this was not significant.

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In humans, apnoeas or unstable breathing patterns can be induced by small reductions in \( P_{a,CO_2} \) below the resting
level both in sleep [29, 30] and sometimes in the awake state [26, 31–33]. Venous carbon dioxide unloading by haemodialysis [16, 27] and the ventilatory response to transient carbon dioxide pulses during recovery from voluntary overbreathing [34] suggested that the apnoeic threshold for \( P_aCO_2 \) may be up to 1.3 kPa below the resting level, but with wide individual variation. The threshold level of \( P_aCO_2 \) needed to eliminate spontaneous breathing depends on \( P_aO_2 \) and breathing terminates at a lower level of \( P_aCO_2 \) with hypoxaemia than with hyperoxia. The threshold level of chemical stimulation needed to initiate peripheral chemoreceptor activity may be less than that required to trigger central chemoreceptor discharge [20, 35, 36]. Increasing hypocapnia, nonetheless, eventually silences the peripheral chemoreceptors. A comparative study between the peripheral chemoreceptor stimulating agent almitrine and the mainly central stimulating acetazolamide showed that central chemoreceptor stimulation elicited periodic breathing, whereas peripheral stimulation enhanced breathing instability [37]. It may be postulated that with carbon dioxide unloading during acetate containing dialysate haemodialysis, the central chemoreceptors were inactivated, leaving the peripheral chemoreceptors responding to the changes in \( P_aCO_2 \) and \( P_aO_2 \), resulting in irregular breathing and central apnoeas. When \( P_aO_2 \) was raised with oxygen administration, this carbon dioxide apnoeic threshold may have been increased [25, 38]. The correction of acidosis also raised the threshold level [38]. The fall in \( P_aCO_2 \) on D2 was greater. One possible reason for the higher carbon dioxide unloading on D2 may be due to the blood flow. However, in this study, the dialysate flow and blood flow rates were kept constant on the two days. With a higher threshold value, more central apnoeas were encountered and an irregular breathing pattern continued despite an improvement in \( P_aO_2 \). Borsus-

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