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

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Effect of oxygen on breathing irregularities during haemodialysis in patients with chronic uraemia. J.C.H. Yap, Y.T. Wang, S.C. Poh. ©ERS Journals Ltd 1998.

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 (P_{a,O_2}) fell 1.9 (0.9) kPa ($p<0.001$) and mean minute ventilation (V'_E) fell 1.9 (1.1) L·min^{-1} ($p<0.01$) during dialysis. The arterial carbon dioxide tension (P_{a,CO_2}) 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 (f_R) and tidal volume (V_T) were 29.6 (11.9) and 38.2 (11.9)%, respectively. On D2, mean P_{a,O_2} remained stable (20.4 (4.1) kPa before, 21.3 (4.1) kPa during dialysis). There was no significant change in mean V'_E (6.4 (0.9) L·min^{-1} before, 5.5 (0.5) L·min^{-1} during dialysis). P_{a,CO_2} 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 f_R and V_T 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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A decrease in arterial oxygen tension has been noted in patients undergoing chronic haemodialysis. This dialysis-related hypoxaemia has been attributed mainly to alveolar hypoventilation and a ventilation-perfusion imbalance [1–12]. During dialysis the arterial oxygen tension (P_{a,O_2}) decreases by 1.3–2 kPa and returns to baseline after the procedure [4]. This fall in P_{a,O_2} may not be tolerated by patients with chronic renal failure who may also have cardiopulmonary disease [13]. Supplemental oxygen therapy may be required to correct the hypoxaemia [1, 14–15].

In a study by DE BACKER *et al.* [16], an irregular breathing pattern during haemodialysis was found. It is known that hypoxaemia is associated with periodic and irregular breathing in awake normal adults [17–20]. It was proposed that the extrapulmonary excretion of carbon dioxide into the dialysate resulted in carbon dioxide becoming less of a stimulus for respiration, causing in a shift of control to the hypoxic-sensitive peripheral chemoreceptors and a consequent unstable breathing pattern. In a subsequent study, HEYRMAN *et al.* [21] showed that the administration of oxygen abolished irregular breathing without any change in total ventilation. They explained that the restoration of stable breathing was due to the "switching off" of the peripheral chemoreceptor drive.

In this study, the role of P_{a,O_2} in the stability of breathing during haemodialysis was re-examined. It was felt that if low P_{a,O_2} was the major drive to ventilation, switching off the peripheral chemoreceptors by hyperoxia should also result in a further fall in total ventilation, besides removing the irregularity. Respiratory inductance plethysmography (RIP) was used to measure both qualitative and quantitative data and to overcome the problem of using a mouthpiece, which has been reported to influence the breathing pattern [22].

Patients and methods

Study subjects

Seven male patients, with chronic renal failure due to various causes, undergoing three times weekly 4 h haemodialysis for at least 6 months, were studied. All patients gave informed consent. Their mean (SD) age was 37.4 (8.1) yrs, with a range of 29–49 yrs. They had normal static and dynamic lung volumes and they remained clinically stable throughout the study. All had normal chest radiographs. There was no history suggestive of sleep apnoea syndrome in any of the patients.

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 m^2. The dialysate flow was kept constant at 500 $mL \cdot min^{-1}$ and the blood flow at 200 $mL \cdot min^{-1}$.

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 (P_{a,CO_2}), P_{a,O_2} and bicarbonate (HCO_3) 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 obtai-ned after each 15 min epoch. Analogue tracings 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 (S_{a,O_2}), 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 (V_T), minute ventilation (V'_E) and mean inspiratory flow (V_T/t_I). The other parameters were inspiratory time (t_I), expiratory time (t_E) and respiratory frequency (f_R). 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 V_T.

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 $L \cdot min^{-1}$.

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 P_{a,O_2} during haemodialysis ($p<0.001$; table 1). The mean (SD) decrease in P_{a,O_2} 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 P_{a,O_2} did not fall below 10.7 kPa during the 2 h of study. When intranasal oxygen at 4 $L \cdot min^{-1}$ was administered, their mean P_{a,O_2} was maintai-ned at a high level throughout haemodialysis (20.4 (4.1) kPa predialysis and 21.3 (4.1) kPa at the second hour) (table 2). P_{a,CO_2} did not show any significant decrease during the 2 h of the study on both days. However, the fall in P_{a,CO_2} 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, V_T and V_T/t_I 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) $L \cdot min^{-1}$ ($p<0.01$; table 1). On the day with oxygen administration, V'_E decreased from 6.4 (0.9) to 5.5 (0.5) $L \cdot min^{-1}$ (11.9 (14.1)% 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 V_T was also decreased on both days but

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

	0 min	60 min	120 min
P_{a,O_2} kPa	13.9 (0.7)	11.8 (0.9)***	12.0 (0.6)***
P_{a,CO_2} kPa	4.7 (0.2)	4.8 (0.2)	4.6 (0.2)
pH	7.393 (0.023)	7.399 (0.021)**	7.418 (0.025)**
HCO_3 $mmol \cdot L^{-1}$	21.4 (2.0)	22.0 (1.2)	22.8 (1.4)
V'_E $L \cdot min^{-1}$	7.4 (1.6)	6.2 (1.0)**	5.5 (0.9)**
V_T mL	410 (46.8)	388.8 (22.1)	376.2 (31.0)
f_R $breaths \cdot min^{-1}$	18.5 (3.9)	15.9 (3.0)***	14.6 (2.4)***
V_T/t_I $L \cdot s^{-1}$	358.4 (59.5)	327.8 (50.0)	297.0 (36.3)
t_I s	1.21 (0.25)	1.39 (0.37)	1.44 (0.28)*
t_E s	1.98 (0.46)	2.39 (0.51)***	2.57 (0.53)***

All values are expressed as mean (SD). P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; V'_E: minute ventilation; V_T: tidal volume; f_R: respiratory frequency; V_T/t_I: mean inspiratory flow; t_I: inspiratory time; t_E: expiratory time. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$ *versus* time 0 min.

Table 2. – Blood gases and ventilation parameters during haemodialysis with intranasal oxygen on the third day (D2)

	0 min	60 min	120 min
P_{a,O_2} kPa	20.4 (4.1)	22.9 (7.0)	21.3 (4.1)
P_{a,CO_2} kPa	4.8 (0.1)	4.7 (0.4)	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 (3.1)	15.6 (2.8)	14.9 (4.5)
V_T/t_I L·s^{-1}	311.0 (45.0)	314.0 (81.4)	308.6 (22.2)
t_I s	1.31 (0.34)	1.37 (0.37)	1.44 (0.56)
t_E s	2.15 (0.42)	2.40 (0.44)	2.70 (0.79)*

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

statistical differences were not observed (p=0.09 on D1 at the second hour). Mean V_T/t_I 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 V'_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_{a,O_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_{a,O_2} (table 3).

The breathing patterns were analysed manually from the Gould recordings. Breathing was found to be irregular

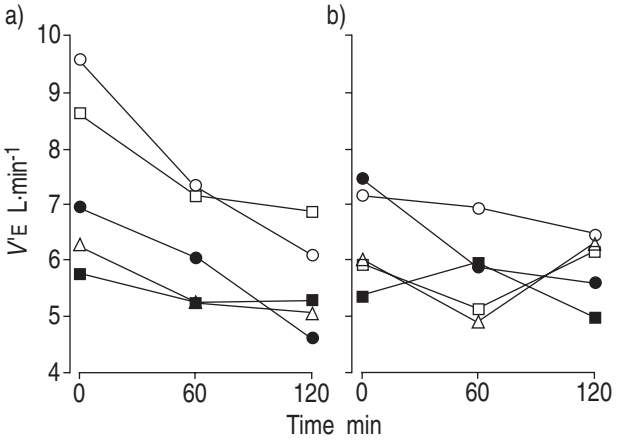

Fig. 1. – Individual minute ventilation (V'_E) data on a) D1 (second day dialysis) and b) D2 (third day dialysis intranasal oxygen).

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

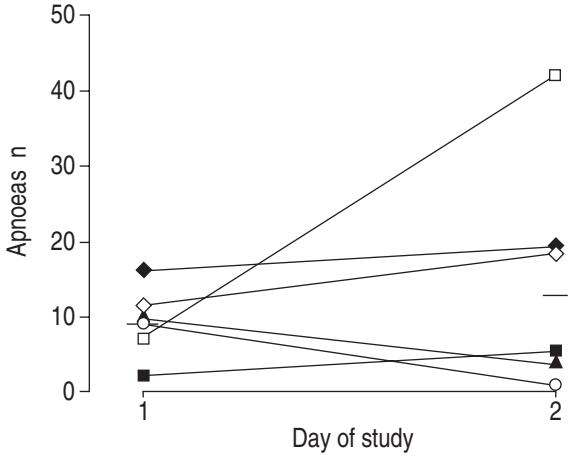

Fig. 2. – Number of central apnoeas for each individual on the two study days (D1 and D2). Horizontal line at each day indicates mean.

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

		60 min from baseline				120 min from baseline			
		D1		D2		D1		D2	
P_{a,O_2}	%	14.6	(7.6)	-11.1	(12.8)***	13.7	(6.2)	5.1	(12.6)**
P_{a,CO_2}	%	-1.6	(5.6)	2.3	(7.2)	3.1	(6.8)	6.5	(8.6)
pH	%	-0.1	(0.2)	-0.06	(0.5)	-0.4	(0.3)	-0.5	(0.5)
HCO_3	%	-3.2	(6.8)	1.3	(4.6)	-7.3	(11.6)	-1.4	(7.4)
V'_E	%	16.1	(5.4)	9.4	(13.2)	24.0	(11.3)	11.9	(14.1)
V_T	%	4.5	(7.9)	4.9	(13.2)	7.7	(8.3)	1.8	(13.0)
f_R	%	13.3	(9.3)	7.7	(8.4)	20.1	(7.8)	13.2	(15.4)
V_T/t_I	%	7.6	(13.6)	-0.7	(19.9)	16.1	(12.0)	-0.8	(15.3)
t_I	%	-15.1	(18.7)	-4.7	(8.8)	-19.7	(16.7)	-10.1	(33.4)
t_E	%	-22.0	(17.2)	-12.4	(12.1)	-30.9	(12.0)	-24.3	(22.2)

All values are expressed as mean±SD. For definitions see legend to table 1. **: p<0.01; ***: p<0.001 between D1 and D2.

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

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

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

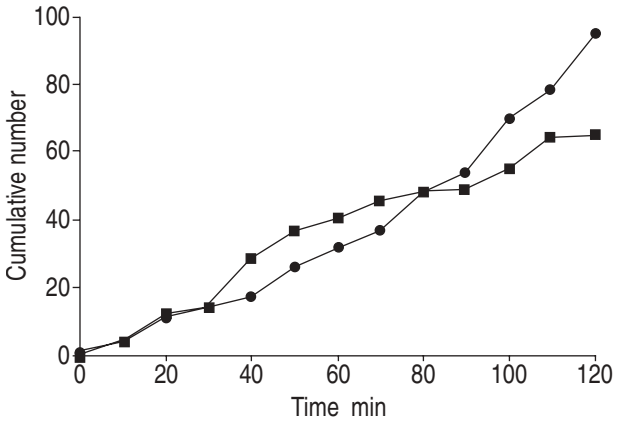

Fig. 3. – Cumulative number of central apnoeas >10 s with time on D1 (■) and D2 (●) study days.

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 no difference in the coefficient of variation of f_R (29.6 (11.9)% on D1 *versus* 35.8 (5.1)% on D2) or V_T (38.2 (11.9)% on D1 *versus* 40.5 (11.3)% on D2) on both days at the second hour of the study.

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 and V_T/t_I). 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.

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} ð6.7 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

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_{a,CO_2} may be up to 1.3 kPa below the resting level, but with wide individual variation. The threshold level of P_{a,CO_2} needed to eliminate spontaneous breathing depends on P_{a,O_2} and breathing terminates at a lower level of P_{a,CO_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 eliminated 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_{a,CO_2} and P_{a,O_2}, resulting in irregular breathing and central apnoeas. When P_{a,O_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_{a,CO_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_{a,O_2}. Berssenbrugg *et al.* [19] found that hypoxaemia-induced periodic breathing required the presence of hypocapnia and that hypocapnia, even in the absence of hypoxaemia, continued to elicit irregular breathing. Furthermore, irregular breathing could be improved by the inhalation of carbon dioxide [18, 20] and it is postulated that the peripheral chemoreceptor response to P_{a,CO_2} may be more important in causing these breathing patterns. Another study with car-bon dioxide and oxygen administration should be underta-ken to determine whether regular breathing can be restored.

The finding that oxygen administration did not eliminate the irregular breathing pattern was in contrast to that in a similar study by Heyrman *et al.* [21]. However, the design of their study was different from that of the present study. Their subjects were given 30 min of oxygen administration after 130 min of dialysis, while the present subjects had 120 min from the start of haemodialysis. The mean onset of central apnoeas was 42.7 (44.4) min after the start of haemodialysis on the third study day compared with 16 (17) min on the second study day. The present subjects were given a longer duration of oxygen, which could have accounted for the differences in the results.

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