Membrane diffusion of the lungs in patients with chronic renal failure

J. Moinard, H. Guenard

ABSTRACT: Patients with chronic renal failure (CRF) and haemodialysis treatment usually have a reduced CO transfer factor. The aim of this study was to evaluate the effects of alveolar wall fibrosis and of anaemia on gas diffusion in the lungs.

The NO and CO transfer factors of the lung (TLNO and TLCO) were measured, simultaneously, in 15 patients haemodialysed three times a week for 1–10 yrs. Assuming that NO is highly reactive with blood, TLNO is thus directly proportional to the membrane diffusion factor (Dmco). The lung capillary blood volume (Vc) was derived from the set of the two transfer equations. Transfer factors were measured between haemodialysis sessions.

All patients but one were anaemic, with haemoglobin concentrations ranging 61–151 g·l⁻¹. All had decreased Vc, and a decreased Dmco was observed in 14 patients. However, after correction for the anaemia, Vc values were normal with the exception of three patients. The percentage decrease in Dmco with respect to normal was correlated with the time elapsed since the first haemodialysis.

These results support the idea of a progressive development of haemodialysis-induced chronic lung disease, that may be related to a mechanism of complement activation by a bio-incompatible membrane (Cuprophane). Accordingly, patients with compromised cardiopulmonary functions should be dialysed with a bio-compatible membrane.

Keywords: Chronic renal failure, diffusion, haemodialysis, hypoxaemia, transfer factor

Patients and methods

All 15 patients with CRF had been treated by haemodialysis three times a week over the previous 1–10 yrs. The dialysis session used a Cuprophane membrane and bicarbonate in the dialysate. Patients were examined and pulmonary function tests were performed on the day before a haemodialysis session. All patients were free from previous respiratory diseases and had no history of cough, sputum production, wheezing, haemoptysis or orthopnoea, apart from some exercise dyspnoea. All were nonsmokers or light smokers (less than two cigarettes a day). None had evident lung disease, including pulmonary oedema, on a plain chest radiograph. Patient details are listed in table 1.

Procedure

The method used to perform the apnoea manoeuvre and the calculations of both CO and NO transfer
Morphological characteristics, blood gases and functional data of the 15 patients with chronic renal failure

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>56±19</td>
<td>54±18</td>
<td>55±18</td>
</tr>
<tr>
<td>Ht m</td>
<td>1.62±0.04</td>
<td>1.60±0.10</td>
<td>1.61±0.08</td>
</tr>
<tr>
<td>Wt kg</td>
<td>52.6±6.1</td>
<td>61.5±13.8</td>
<td>57.9±12.2</td>
</tr>
<tr>
<td>Hb g/l</td>
<td>83±16</td>
<td>101±25</td>
<td>90±22</td>
</tr>
<tr>
<td>Pao 2 kPa</td>
<td>11.3±1.9</td>
<td>9.9±1.6</td>
<td>10.5±1.9</td>
</tr>
<tr>
<td>Paco 2 kPa</td>
<td>5.2±0.2</td>
<td>4.4±0.3</td>
<td>4.9±0.4</td>
</tr>
<tr>
<td>pH</td>
<td>7.38±0.02</td>
<td>7.37±0.02</td>
<td>7.38±0.02</td>
</tr>
<tr>
<td>VC l</td>
<td>2.94±0.29</td>
<td>2.90±0.51</td>
<td>2.92±0.44</td>
</tr>
<tr>
<td>TLC % pred</td>
<td>82±4</td>
<td>101±8</td>
<td>93±14</td>
</tr>
<tr>
<td>FEV/VC %</td>
<td>76±10</td>
<td>78±12</td>
<td>76±10</td>
</tr>
<tr>
<td>Dmco</td>
<td>5.1±0.3</td>
<td>4.9±0.5</td>
<td>4.93±0.47</td>
</tr>
</tbody>
</table>

Pao 2: arterial oxygen tension; Paco 2: arterial carbon dioxide tension; VC: vital capacity; % pred: percentage predicted; FEV/VC: forced expiratory volume in one second as a percentage of vital capacity; TLC: total lung capacity.

After a full exhalation, the patient inhaled the test gas mixture to total lung capacity (TLC), held the breath for a given time (Tinh) and then expired rapidly. An alveolar sample of 900 ml was withdrawn after a 900 ml wash-out. The total duration of apnoea (TTOT) was taken as the sum of the inspiratory time, Tinh and expired time up to the start of the sampling period. The measurement of fractional inspiratory NO, CO and He (FINO, FICO and FHE), fractional alveolar NO, CO and He (FANO, FACO and FAH) and TTOT enabled calculation of TLCO and TINO. Dmco and Vc were derived from the following two equations [8]:

\[
Dmco = \frac{TINO}{a} \quad (1)
\]

\[
I/Vc = \theta co \times \left(\frac{1}{TLCO - a/TINO}\right) \quad (2)
\]

with a = \sqrt{\left(\frac{MWNO}{MWCO}\right) \times \left(\frac{TLCO}{\theta co}\right)}

MW is the molecular weight and \( \theta \) the solubility for each gas. Solubility for NO and CO in plasma at 37°C are, respectively, 0.0439 and 0.0215 [9]. Given MW are, respectively, 30 and 28, and a=1.97, \( \theta co \) is the rate of reaction of CO with haemoglobin at a given Hb concentration, with \( 1/\theta co=1.30 + 0.0041 \) oxygen tension (Pao 2) [10].

Five of the fifteen patients performed the tests twice with different Tinh and FINO fractions in order to check the validity of a short Tinh in these patients with CRF. Fifteen ppm FINO was necessary for an 8 s Tinh, as 8 ppm FINO was found to be sufficient to obtain a measurable fraction of NO in alveolar gas with a 3 s Tinh. All of the other patients (10 out of 15) inhaled an 8 ppm NO fraction and performed a 3 s Tinh. Measurements were made in duplicate, and considered valid if they did not differ by more than 10%. Mean values were calculated. Arterial blood gases were analysed in a Corning 167 apparatus (USA), the accuracy of which was checked with blood samples tonometered with gas tank mixtures. The effect of anaemia on these determinations was also checked.

Statistical analysis

The values of TLCO were corrected using Cote's equation [11] or by altering the value of \( \theta co \) for haemoglobin concentration. Results in patients performing both tests with 3 s and 8 s Tinh were compared with a paired t-test. All results obtained with the 3 s Tinh were compared to the reference values given by Georges et al. [12]. Regression analysis were performed using standard formulae. The significant baseline value for the probability (p) was chosen at 0.05. Data are expressed as mean±sd.

Results

These patients were not troubled by respiratory symptoms. The time elapsed since the last haemodialysis session was 2.3±0.5 days. Weight gain was 3.3±0.7 kg (5.5±3.2%). Only two had a, just-detectable, degree of ankle oedema.

All patients but one (no. 4) were anaemic. The mean arterial oxygen tension (Pao 2) was normal (10.5 kPa), although the standard deviation (1.9) indicated that some of the patients were hypoxaemic.

Because of the fast NO uptake kinetics of lungs and the low inspired NO concentration (8 ppm), five patients performed 3 s and 8 s Tinh. Reduction of the breathing duration did not affect TLCO (t=1.3; p>0.2). Both Dm and Vc were not different between the two times (Dm=27.6±5.6 ml·min⁻¹·mmHg⁻¹ and Vc=51.±8.3 ml for 3 s; Dm=29.±8.2 ml·min⁻¹·mmHg⁻¹ and Vc=51.±6.7 ml for 8 s). Experiments were conducted using the shorter Tinh.

Table 2, and figures 1 and 2, pool the data obtained from the 15 patients, with reference values [12]. TLCO and carbon monoxide transfer coefficient (Kco) (TLCO/ alveolar volume (VA)) were decreased in all patients. Dmco, which depends only on TINO, and is assumed to be independent of haemoglobin concentration (Equation 1), was decreased in all patients but one (no. 14).
Table 2. Data obtained from the 15 patients with reference values [12] in parentheses

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>TLCO ml·min⁻¹·mmHg⁻¹</th>
<th>Kco ml·min⁻¹·mmHg⁻¹·t⁻¹</th>
<th>TLNO ml·min⁻¹·mmHg⁻¹</th>
<th>Dmco ml·min⁻¹·mmHg⁻¹</th>
<th>Vc ml</th>
<th>Hb g·l⁻¹</th>
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<tr>
<td>1</td>
<td>13.3 (18.9)</td>
<td>3.8 (5.8)</td>
<td>54.9</td>
<td>27.8 (35.2)</td>
<td>40.8 (68.0)</td>
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</tr>
<tr>
<td>2</td>
<td>16.7 (26.1)</td>
<td>4.3 (6.7)</td>
<td>70.1</td>
<td>35.5 (51.0)</td>
<td>50.4 (89.5)</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>11.0 (20.5)</td>
<td>3.0 (5.6)</td>
<td>35.8</td>
<td>18.1 (38.0)</td>
<td>44.8 (74.5)</td>
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<td>4</td>
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<td>3.9 (5.0)</td>
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<td>29.7 (37.3)</td>
<td>64.5 (72.0)</td>
<td>151</td>
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<td>5</td>
<td>15.1 (19.1)</td>
<td>4.1 (5.9)</td>
<td>52.6</td>
<td>26.7 (35.4)</td>
<td>55.6 (69.2)</td>
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<td>4.0 (5.5)</td>
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<td>15</td>
<td>10.4 (11.6)</td>
<td>3.3 (5.7)</td>
<td>48.2</td>
<td>24.5 (28.0)</td>
<td>28.8 (33.9)</td>
<td>86</td>
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</tbody>
</table>

Mean *13.4 (20.5) *3.6 (5.8) 59.9 *30.4 (40.1) *40.5 (70.8) 90
sd 2.7 (4.1) 0.6 (0.5) 14.1 7.2 (7.7) 12.0 (15.3) 23

Dmco is directly proportional to TLNO; Kco is TLco divided by alveolar volume. TLco, TLNO, Vc figures are corrected to STPD and BTPs but not for anaemia. *: p<0.001, comparison measured versus reference values. TLco: transfer factor of the lung for carbon monoxide; Kco: carbon monoxide transfer coefficient; TLNO: transfer factor of the lung for nitric oxide; Dmco: membrane diffusion factor for carbon monoxide; Vc: lung capillary blood volume; STPD: standard temperature and pressure dry; BTPs: body temperature and pressure saturated.

Fig. 1. - A) TLco values before and after correction either by Cotes equation (TLco=10.22 + Hb/ (1.7 x Hb) or by correcting Vc values (Vcc) for a normal haemoglobin concentration (Hb = 14.6 g·100ml⁻¹). B) Vc before and after correction for anaemia. ns: not significant; *: p<0.01; †: p<0.001; comparison measured versus reference values. Data are mean, bars are sd. TLco: transfer factor of the lung for carbon monoxide; Vc: lung capillary blood volume; Ref: reference values [12].

Fig. 2. - Mean and sd of Dmco and Vc data either corrected (Vcc) or not, and the ratio Dmco/Vc and Dmco/Vcc expressed as percentages of reference values [12]. ns: not significant; *: p<0.02; †: p<0.01; ‡: p<0.001, comparison measured versus reference values Dmco: membrane diffusion factor for carbon monoxide; Vc: lung capillary blood volume.
In most patients (10 out of 15), the ratio DMCO/Vc was higher than normal, suggesting that the decrease in haemoglobin concentration or true capillary blood volume was greater than the decrease in DMCO. After correction for haemoglobin concentration (Vce = Vc × 14.6/Hb), DMCO/Vcc was found to be lower than normal with the exception of four cases (nos. 1, 6, 11 and 14). Patients nos. 1 and 6 had reductions in both Vcc and DMCO, while in patient nos. 11 and 14, the reductions were greater in Vcc than in DMCO.

Actual values of DMCO were expressed as percentages predicted (% DMCO). The percentage decrease in DMCO was significantly correlated with the time elapsed since the patients were haemodialysed for the first time (fig. 3).

% DMCO was not correlated to age. Neither TLNO nor TLCO were correlated with haemoglobin concentration. However, indexed TLCO values (TLCO·m⁻²) were significantly correlated with Hb (r = 0.56; p < 0.05); although TLNO·m⁻² was not correlated with Hb.

![Graph showing the relationship between duration of dialysis and percent of predicted DMCO](image)

**Fig. 3.** Relationship between duration of dialysis and percentage of predicted DMCO (% DMCO). Regression line: % DMCO = 96.22 - 5.35 yrs, r = 0.788; p < 0.01. DMCO: membrane diffusion factor for carbon monoxide.

**Discussion**

Our results show that at a distance from haemodialysis, DMCO was reduced in patients with CRF, DMCO as percentage predicted was correlated to the time elapsed since the first haemodialysis. Since the methodology of the NO-CO method was developed only recently the specific problems due to the use of NO as transfer gas will be examined first.

The use of NO in the NO-CO method raises the problem of its toxicity and its potential haemodynamic effects. Fifteen ppm NO inhaled for 15 min has not been found to alter PaO₂, arterial carbon dioxide tension (PaCO₂), pH, alveolar-arterial diffusion

difference for O₂ (D(A-a)O₂), TLCO or methaemoglobin concentration [13]. The possible toxic effects of the amount of NO inspired during a single vital capacity in the present study are, thus, negligible.

NO has been suggested to be the endothelium-derived relaxing factor (EDRF), although in vivo biochemical data to substantiate this are lacking. S-nitrosocysteine has been proposed as a more likely candidate [14]. Nevertheless, NO itself, or a metabolite, has been proved to be a pulmonary vasodilator [15] and could, thus, be suspected to alter lung perfusion and the measurement of Vc. Meyer et al. [16], using a high inspired NO concentration (600 ppm) in dogs, failed to find any alteration in TLCO, suggesting a constancy of Vc. We tested the effect of a 10 min inhalation of 15 ppm NO on pulmonary arterial pressure in 10 patients with COPD and moderate pulmonary hypertension. We failed to demonstrate any effects during the first minute of inhalation, although there was a NO-induced fall in pulmonary vascular pressure and resistance over the subsequent minutes, without effect on alveolar/ventilation perfusion ratio (VA/Q) distribution [17]. As the effect of NO is not immediate, this suggests that NO could react in blood or tissue to produce an active metabolite. Whatever it is, NO inspired during a single-breath is unlikely to have a vasomotor effect on pulmonary circulation and to alter TLCO measurement.

Anaemia decreases TLCO [18, 19]. The correlation between TLCO expressed as % normal and Hb concentration is fair [19-21] but DMCO is not affected by the correction for haemoglobin concentration [19, 20]. The correlation between TLCO·m⁻² and Hb concentration in the present group of patients is in agreement with these previous data.

Whatever the correction for Hb concentration used in the calculation of TLCO, this parameter and DMCO are reported to be decreased in most patients with CRF. The present results were obtained using the NO-CO method, in which the value of DMCO depends only on NO transfer, whereas CO transfer depends on DMCO, 6CO, Vc and Hb concentration. We found that DMCO was reduced in all of our patients and was independent of Hb concentration. Two arguments are against the dependency of TLNO on Hb concentration.

A first theoretical argument concerns NO reactivity in blood. As the reactivity of NO for haemoglobin is high, the conductance for NO in the blood is much greater than the membrane conductance, and so a dependence of TLNO on Hb concentration would seem unlikely. For a TLNO/TLCO ratio of about 5, and assuming the values of DMCO and 6CO-Vc are equal, the value of 6NO determined from the conventional equations for both transfers is about 10 × 6CO. A second argument for the independence of TLNO on Hb concentration is that no significant difference was found between the two estimations of TLCO after correcting for anaemia either by Cote's equation or by correcting the value of Vc obtained from the NO-CO method for Hb concentration.

Alterations in gas exchange during haemodialysis are
well-documented [22]. The progressive obstruction of small airways leads to a heterogeneity in V/A/Q distribution, with reductions in vital capacity, TLC and lung compliance. These combined effects contribute to the hypoxaemia and the increase in (A-a)\textsubscript{O}_2. \textit{Ler et al.} [2] reported that recurrent haemodialysis in transplanted patients appears to lead to chronic lung disorders. In our patients examined between haemodialysis sessions, there was no evidence of spirometric abnormalities (table 1). Furthermore, the absence of a significant increase in TL\textsubscript{CO} when T\textsubscript{Bhu} was increased from 3 s to 8 s is not in favour of marked V/A/Q heterogeneities [7, 23]. Alterations in lung function during and between haemodialysis sessions should, therefore, be distinguished.

Dm\textsubscript{co}/Vcc was decreased in 11 of our 15 patients, and decreases in both Vcc and Dm\textsubscript{co} were found in 3 of the remaining 4. The decrease in Vcc may suggest a reduction in the pulmonary capillary network, which could be explained by the recurrent activation of white blood cells in these capillaries during haemodialysis. However, the main feature of these patients is the significant decrease in Dm\textsubscript{co}, with a mean reduction of 23.4% and a maximum of 47.6% observed in patient no. 3. This alteration in Dm\textsubscript{co} could be due to morphological alterations in the alveolocapillary membrane [4], or to interstitial oedema stemming from an increase in permeability [21], or release of mediators [24], and activation of the complement system [13, 25]. As our measurements were performed between haemodialysis sessions, it seems unlikely that the mediators released during haemodialysis were still activated at the time of the measurements. The decreased Dm\textsubscript{co} could thus be attributed to alterations in permeability from oedema and/or chronic damage to the alveolocapillary membrane. An argument supporting chronic damage is the fair correlation between the percentage decrease in Dm\textsubscript{co} and the time elapsed since the first haemodialysis.

Some of our patients, even the younger ones, were hypoxaemic. The decrease of Dm\textsubscript{co} could indicate that hypoxaemia was due to a reduction in alveolar surface and/or an increase in thickness of the membrane. Pao\textsubscript{2} is independent of morphological factors, and decreases with age. Although there was no correlation between Pao\textsubscript{2} and age in our patients, a multiple correlation analysis showed that Pao\textsubscript{2} was correlated to both % Dm and age (p=0.02). Other factors should be taken in account. A decrease in Dm\textsubscript{co}/Vcc favours hypoxaemia by hampering the rise in P\textsubscript{o}2 in capillaries. However, the mean decrease was small (-16.5%) and was not correlated with Pao\textsubscript{2}. Furthermore, the decrease in Hb concentration decreases blood capacitance and increases the rate of rise of P\textsubscript{o}2 in the capillaries. The patchy zones observed on pathological examination may have low membrane permeability, giving rise to diffusion/perfusion ratio (D/Q) mismatches, which could account for the hypoxaemia.

The use of Cuprophane as the dialysis membrane for our patients probably explains, in part, the alterations of transfer factors. This bio-incompatible membrane can activate the alternative pathway of the complement system, leading to intrapulmonary leucostasis. The release of multiple mediators by these activated leucocytes accounts for local inflammation and bronchoconstriction [25]. During haemodialysis, these cellular phenomena develop in parallel with spirometric and blood gas modification and reverse with cessation of dialysis. The repetition of this aggression with every dialysis (three times a week) could lead, by persistence of the inflammatory reaction in the pulmonary interstitium, to lesions of the alveolocapillary membrane, responsible for reduction in Dm\textsubscript{co}. The absence of variation of Vc could be explained by the transience of endovascular phenomena, limiting the deleterious effects of adherent granulocytes on the endothelium [25]. Thus, the patients should be dialysed with a bio-compatible and non-complement activating membrane (Polyacrylonitrile, for example), which, theoretically, could avoid the development of diffusion limitation.

References