

Acute effects of hemodialysis on lung function in patients with end-stage renal disease

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Akute Effekte der Hämodialyse auf die Lungenfunktion bei Patienten mit chronischem Nierenversagen

Zusammenfassung. Pathologische Veränderungen der Lungenfunktion bei Dialysepatienten können Folge einer zugrundeliegenden primären Lungenerkrankung sein. Der Einfluss der Urämie auf die Lungenfunktion und die Effekte der Dialyse sind jedoch nicht ausreichend geklärt. Ziel unserer Untersuchungen war es, akute Auswirkungen einer Bikarbonat-Hämodialyse unter Verwendung zweier Dialysemembranen mit unterschiedlicher Biokompatibilität auf die Lungenfunktion bei unselektierten chronischen Hämodialysepatienten nachzuweisen.

Vierzehn stabile Dialysepatienten ohne akute Lungenerkrankung nahmen an der Untersuchung teil. Acht Patienten hatten eine restriktive und ein Patient eine obstruktive Ventilationsstörung. Es wurde ein prospektiver Vergleich einer zelluloseischen low-flux Dialysemembran mit einer synthetischen high-flux Membran durchgeführt (2 Sitzungen pro Membran im Abstand von einer Woche). Die Spirometrie (VCmax, FEV1, FEF_{25–75%}, PEF) wurde vor und nach der Dialysesitzung durchgeführt. Der Atemwegwiderstand wurde vor, während und nach der Hämodialyse mittels der Unterbrecher Methode (Rocc) oder der Impuls-Oszillometrie (R5Hz, R20Hz) bestimmt.

Unabhängig von der Wahl der Dialysemembran hatte eine Hämodialysesitzung keinen akuten Einfluss auf die Lungenfunktion (Volumina, Atemwegwiderstand). Keiner unserer Patienten zeigte eine Bronchokonstriktion oder Verschlimmerung der obstruktiven Ventilationsstörung als Folge der geringen Biokompatibilität der Zellulosemembran. Weder die spirometrischen Daten noch die Messungen des Atemwegwiderstands mit zwei unterschiedlichen Methoden zeigten relevante Veränderungen der Lungenfunktion während der Dialyse. Veränderungen des Volumenstatus oder die Dauer an der Dialyse hatten keinen Einfluss auf die gemessenen Lungenfunktionsparameter.

Klinisch relevante Veränderungen der Lungenfunktion durch die Hämodialyse treten weder bei urämischen

Patienten mit normaler noch bei Patienten mit eingeschränkter Lungenfunktion auf. Die Dialyse ist ein sicheres Nierenersatzverfahren auch bei Patienten mit Lungenerkrankungen.

Summary. Impaired lung function in hemodialysis patients may be caused by an underlying pulmonary disease; however, the impact of uremia and the effects of dialysis treatment are not well understood. Our investigation aimed to characterize the acute effects of bicarbonate hemodialysis using membranes differing in biocompatibility on various parameters of lung function in unselected uremic patients maintained on regular hemodialysis.

Fourteen clinically stable hemodialysis patients without acute lung disease were included in the study. Restrictive lung disease was present in eight of 14 cases and obstructive lung disease in one patient. A cellulose dialyzer membrane and a synthetic high-flux dialyzer membrane were each tested twice (two sessions one week apart). Spirometry (VCmax, FEV1, FEF_{25–75%}, PEF) was carried out before and after hemodialysis. Resistance was determined with the interrupter technique and with the impulse oscillation system (R5Hz, R20Hz) before, during and after hemodialysis.

Our comparative investigation of two dialyzer membranes found that bioincompatibility of dialysis had no acute adverse effects on lung function in our heterogeneous population of dialysis patients. None of our patients experienced bronchoconstriction or aggravation of obstructive lung disease as a result of poor biocompatibility of the dialyzer membrane. Spirometric data and resistance measurements by two different methods showed no relevant changes during the dialysis procedure. There was no correlation between lung function parameters and interdialytic changes in body weight or duration on hemodialysis.

Regardless of the membrane used, the hemodialysis procedure does not acutely affect lung function in uremic patients on maintenance hemodialysis. Hemodialysis is a

safe procedure even in uremic patients with pre-existing lung disease.

Key words: Lung function, biocompatibility, dialysis, impulse oscillometry, interrupter technique.

Introduction

End-stage renal disease is not simply the loss of renal functions but a complex syndrome which affects virtually every organ system. The excessive comorbidity of today's aged dialysis populations is related not only to the underlying renal disease and the dialytic intervention but also to the high prevalence of concomitant diseases. Chronic lung diseases are found by chest X-ray or at autopsy in the majority of patients maintained on non-transplant renal replacement therapies [3, 20, 25]. Numerous changes in pulmonary function, including restriction [17, 26], obstruction [2, 7, 8] and impaired diffusion capacity [11], have been described in this patient population. These pulmonary dysfunctions may be caused directly by an underlying primary pulmonary disease or the high incidence of smoking, but the influence of uremia and the effects of dialysis treatment with the artificial kidney are not well characterized [15].

Based on observations in experimental animals, it has been suggested that dialysis with bioincompatible cellulose membranes may cause increased release of elastase from activated neutrophils and reduced function of the inhibitory proteins in the presence of reactive oxygen species, resulting in breakdown of pulmonary elastin fibrils and perhaps an increased propensity for the development of emphysema [9]. It is unclear whether bioincompatibility of hemodialysis causes acute pulmonary dysfunction through the generation of inflammatory mediators with subsequent chronic lung disease. The few available clinical studies analyzing the effects of bioincompatible cuprophane hemodialysis membranes on pulmonary obstruction generated contradictory results [4, 5, 16, 23, 24], and there are theoretical concerns about the methods used to measure pulmonary function.

The aims of our investigation were to characterize the clinical relevance of acute effects of biocompatibility of two different dialyzer membranes and of changes in fluid overload on various parameters of lung function in unselected uremic patients maintained on regular hemodialysis.

Patients and methods

Study population

Fourteen clinically stable patients with end-stage renal disease (10 men, 4 women, aged 20 to 80 years; mean \pm SD 60 ± 16 years) maintained on regular hemodialysis for at least six months (range 7-255, median 45) were randomly selected from our outpatient clinic.

The causes of chronic renal failure, based on history, urine tests, radiologic signs or biopsy (in selected patients), were chronic glomerulonephritis in six patients, chronic tubulo-interstitial nephritis in five, polycystic kidney disease in one and unknown causes in two. None of the patients had signs or symptoms of acute lung disease. However, X-ray of the chest disclosed signs suggestive of previous tuberculosis (3 patients), chronic partial atelectasis (1 patient), pleural adhesions (3 patients), signs of chronic hyperinflation (3 patients), and cardi-

omegaly with pulmonary congestion (1 patient). Echocardiography showed left ventricular dysfunction in three patients. None of the patients was on antiobstructive medication. The major comorbidity in our dialysis patients was atherosclerotic vascular disease (peripheral vascular disease in 3 patients, coronary artery disease and cerebrovascular disease in 2 patients each). Chronic arterial hypertension was present in six patients but was controlled with angiotensin-converting enzyme inhibitors in four patients and betablockers in three. Renal anemia (hemoglobin 10.9 ± 1.0 g/dl) was documented in all study patients; 11 patients out of 14 received erythropoietin for partial correction of anemia. Three patients were current smokers (3-52 pack years), seven patients were ex-smokers (1-78 pack years) and four patients had never smoked.

Dialysis treatment

All patients underwent hemodialysis three times a week (3.5-5.0 hours) using machines with volumetrically controlled ultrafiltration (MTS 4008 H, Fresenius Medical Care, Bad Homburg, Germany). Ultrapure dialysis fluid was produced by on-line filtration. Bicarbonate buffer and first-use synthetic dialyzer membranes (polysulfone, Fresenius, FRG; acrylonitrile membranes AN69, Hospal, FRG) were used for all treatments prior to the study period. Blood flow rates ranged from 200-300 ml/min and dialysate flow rate was fixed at 500 ml/min. Dialysis dose, determined with single pool Kt/V, was greater than 1.2 in each patient. Dry weight was regularly judged by clinical investigation, chest X-ray and/or determination of the diameter of the inferior vena cava by ultrasound.

Study design

The study was conducted according to the Declaration of Helsinki and the ICH GCP guidelines. All patients consented to participate in the clinical investigations. Two dialyzer membranes were tested, a first-use unregenerated cellulose hollow-fiber dialyzer (Discap 150 SE, cuprophane membrane, surface area 1.2 m^2 , ultrafiltration factor 5.3 ml/h/mmHg , Hospal, Meyzere, France) and a first-use synthetic high-flux hollow-fiber dialyzer (H 4, polyarylestersulfone membrane, surface area 1.4 m^2 , ultrafiltration factor 62 ml/h/mmHg , Hospal, Lyon, France), using a cross-over design. The potential of these two membranes to generate complement and activate cells has been shown to be very different [12, 22]. Each patient was evaluated for each membrane on two occasions one week apart, and on the same day of the week (short dialysis interval), at the same time and with the same dialysis regime. The only treatment change was the switch of the dialyzer membrane.

Lung function testing

Standard spirometric pulmonary function tests (Masterscope, Viasys Healthcare, Wuerzburg, Germany) were carried out immediately before and after clinical dialysis and included vital capacity (VC), forced expiratory volume in one second (FEV1), mean forced expiratory flow between 25% and 75% of FVC (FEF_{25-75%}) and peak expiratory flow (PEF). We conducted at least three tests of acceptable efforts and chose the best value to ensure a high reproducibility according to ATS criteria. Resistance was determined with the interrupter technique (Rint) (Masterscope, Viasys) before, during (15-20 minutes after initiation of the dialysis session) and after hemodialysis. Airway resistance (R5Hz, R20Hz) and reactance (X5) were measured with an impulse oscillation system (IOS) (Viasys Healthcare, Wuerzburg, Germany) during rhythmic breathing at 5 Hz and 20 Hz, according to the manufacturer's operating

instructions. Results of pulmonary function tests were expressed as percentage of predicted values (except for airway resistance).

Statistics

Data were analyzed using SPSS software (release 13.0, SPSS Inc., Chicago, IL, USA). Values are expressed as mean and standard deviation, median or range. Between-group differences were assessed with the non-parametric Wilcoxon test. The magnitude and direction of the association between lung function parameters and ultrafiltration rate or duration on hemodialysis was analyzed with the Spearman rho correlation. *P*-values of less than 0.05 were regarded as statistically significant.

Results

a) Pulmonary function tests

Pulmonary function tests varied in the 14 patients participating in the study. VC ranged from 1.9 l to 5.2 l, FEV1 from 0.9 l to 4.5 l and Rint from 0.31 kPa*s/l to 0.82 kPa*s/l. Eight of the patients had a reduction in VC before the dialysis session: the degree of restrictive lung disease was mild (70–90% predicted) in four patients; moderate (50–70% predicted) or severe (< 50% predicted) in two patients each. One patient had signs of severe obstructive lung disease (reduction of FEV1/VCmax < 50% predicted) before hemodialysis.

Repeated measurements of maximal VC and forced VC showed excellent reproducibility. The coefficients of variation for spirometric lung parameters were all below 4% for two measurements with the same membrane or for four measurements with all membranes before and after a dialysis session.

Table 1. Lung function parameters before and after dialysis using biocompatible or bioincompatible membranes

| | Biocompatible membrane | Bioincompatible membrane |
|-----------------------|------------------------|--------------------------|
| VC [l] | | |
| before dialysis | 3.3 ± 1.0 | 3.4 ± 1.2 |
| after dialysis | 3.2 ± 1.0 | 3.3 ± 1.0 |
| VC [%predicted] | | |
| before dialysis | 88.5 ± 24.0 | 89.1 ± 26.0 |
| after dialysis | 86.9 ± 25.7 | 86.7 ± 22.7 |
| FEV1 [l] | | |
| before dialysis | 2.6 ± 1.0 | 2.7 ± 1.1 |
| after dialysis | 2.5 ± 0.9 | 2.7 ± 1.1 |
| FEV1/VC [%predict.] | | |
| before dialysis | 99.6 ± 17.9 | 105.4 ± 11.5 |
| after dialysis | 103.1 ± 17.5 | 105.2 ± 15.0 |
| PEF [%predict.] | | |
| before dialysis | 87.7 ± 21.0 | 94.4 ± 22.9 |
| after dialysis | 86.7 ± 28.3 | 94.1 ± 21.6 |
| FEF _{25–75%} | | |
| before dialysis | 2.7 ± 1.3 | 2.9 ± 1.4 |
| after dialysis | 2.5 ± 1.3 | 2.9 ± 1.5 |

Values are given as mean ± standard deviation.

Table 2. R_{int} and R5Hz and R20Hz (IOS) before, during and after dialysis with biocompatible and bioincompatible membranes

| | Biocompatible membrane | Bioincompatible membrane |
|----------------------------|------------------------|--------------------------|
| R _{int} [kPa*s/l] | | |
| before dialysis | 0.47 ± 0.14 | 0.48 ± 0.13 |
| during dialysis | 0.52 ± 0.14 | 0.51 ± 0.15 |
| after dialysis | 0.48 ± 0.13 | 0.48 ± 0.15 |
| R at 5Hz [kPa*s/l] | | |
| before dialysis | 0.48 ± 0.16 | 0.51 ± 0.23 |
| during dialysis | 0.48 ± 0.14 | 0.48 ± 0.19 |
| after dialysis | 0.47 ± 0.16 | 0.48 ± 0.18 |
| R at 20Hz [kPa*s/l] | | |
| before dialysis | 0.34 ± 0.10 | 0.36 ± 0.14 |
| during dialysis | 0.32 ± 0.08 | 0.33 ± 0.10 |
| after dialysis | 0.34 ± 0.10 | 0.33 ± 0.09 |

Values are given as mean ± standard deviation.

b) Effect of bioincompatibility of dialyzer membrane on lung function

There were no significant differences in lung volumes between the two dialyzer membranes tested immediately before hemodialysis. VC and FEV1 values measured at the end of hemodialysis did not differ from pre-dialysis values. There were no significant differences between the mean values for the two membranes (Table 1).

Measurements of resistance with Rint and IOS showed no relevant changes before, during or after hemodialysis in patients treated using either biocompatible or bioincompatible membranes (Table 2).

Hemodialysis did not worsen abnormal lung function in nine patients (Table 3) and had no impact on lung function of the other patients.

c) Relationship between changes in volume status and lung function

The interdialytic weight gain (volume which needed to be ultrafiltered) did not differ between the four study days, independent of the percent change in body weight (Table 4). Patients gained 2–6% of body weight between the dialysis sessions. There were no significant differences in pre- and post-dialysis values of VC (%), FEV1/VC (%) or Rint among the four study days (Table 4). When patients were stratified according to the amount of ultrafiltration (4–6% vs 2–3%) there were no significant differences in the lung function parameters tested (Table 5). The Spearman rho correlation test did not reveal a significant relationship between fluid removal and lung function.

d) Relationship between duration on maintenance hemodialysis and lung function

There was no correlation between duration on hemodialysis and a restrictive pattern of impaired lung function.

Table 3. Effects of dialysis on lung function in hemodialysis patients with pre-existing abnormal lung function

| Pattern | Number of patients | VC [%predicted] | FEV1/VC [%predicted] | Rint [kPa*s/l] |
|-------------|--------------------|-----------------|----------------------|------------------|
| Restrictive | 8 | pre 68 ± 14 | pre 104 ± 15 | pre 0.46 ± 0.18 |
| | | post 69 ± 16 | post 98 ± 31 | post 0.47 ± 0.12 |
| Obstructive | 1 | pre 98 | pre 49 | pre 0.48 |
| | | post 106 | post 46 | post 0.53 |

pre pre-dialysis; *post* post-dialysis. Values are given as mean ± standard deviation.

Table 4. Effects of interdialytic weight gain (ultrafiltration rate) on lung function

| Day | Weight gain [kg] | Weight gain [%] | VC [%predicted] | FEV1/VC [%predicted] | Rint [kPa*s/l] |
|-----|------------------|-----------------|-----------------|----------------------|------------------|
| 1 | 2.9 ± 0.9 | 4.3 ± 1.3 | pre 88 ± 24 | pre 100 ± 19 | pre 0.47 ± 0.14 |
| | | | post 87 ± 28 | post 100 ± 29 | post 0.49 ± 0.13 |
| 2 | 2.9 ± 0.8 | 4.2 ± 1.0 | pre 92 ± 23 | pre 102 ± 14 | pre 0.43 ± 0.10 |
| | | | post 91 ± 24 | post 105 ± 10 | post 0.45 ± 0.12 |
| 3 | 2.7 ± 0.9 | 4.1 ± 1.2 | pre 89 ± 25 | pre 105 ± 12 | pre 0.45 ± 0.13 |
| | | | post 87 ± 24 | post 106 ± 11 | post 0.48 ± 0.13 |
| 4 | 2.7 ± 0.8 | 4.0 ± 1.2 | pre 89 ± 28 | pre 106 ± 12 | pre 0.44 ± 0.13 |
| | | | post 86 ± 22 | post 104 ± 24 | post 0.47 ± 0.17 |

pre pre-dialysis; *post* post-dialysis. Values are given as mean ± standard deviation.

Table 5. Effects of ultrafiltration on lung function in patients stratified according to interdialytic body weight gain (%)

| Group | Weight gain | VC [%predicted] | FEV1/VC [%predicted] | Rint [kPa*s/l] |
|---------|-------------|-----------------|----------------------|------------------|
| 1 (N=9) | 4–6% | pre 93 ± 22 | pre 100 ± 23 | pre 0.53 ± 0.14 |
| | | post 89 ± 21 | post 100 ± 24 | post 0.54 ± 0.13 |
| 2 (N=5) | 2–3% | pre 79 ± 29 | pre 99 ± 11 | pre 0.38 ± 0.08 |
| | | post 84 ± 41 | post 100 ± 40 | post 0.41 ± 0.07 |

pre pre-dialysis; *post* post-dialysis. Values are given as mean ± standard deviation.

However, only two patients had been receiving hemodialysis for longer than 10 years, therefore possible effects could have been missed.

Discussion

Our comparative investigation demonstrated that hemodialysis with membranes of different biocompatibility had no acute adverse effects on lung function in our heterogeneous population of dialysis patients, even in the presence of pre-existing alterations of lung function suggesting restrictive lung disease in the majority of cases. None of our patients treated using new cuprophane membranes experienced bronchoconstriction or aggravation of obstructive lung disease as a result of poor biocompatibility of the dialyzer membrane. Spirometric data and resistance measurements with two different methods showed no relevant changes during the dialysis procedure.

The restrictive pattern of lung function was assessed with spirometry. We used spirometry plus IOS and Rint to pick up changes in airway caliber during hemodialysis. Spirometric data obtained with a conventional pneumo-

tachygraph typically have a repeatability of 5% (FEV1, FVC) to 12% (PEF) [6] but may be less reliable in children or in the frail elderly. The IOS and Rint techniques are particularly attractive for use in immobilized dialysis patients as they require only passive cooperation from the patients. Comparative measurements in children and adults show that IOS is a useful test for the assessment of bronchial hyper-responsiveness when compared with spirometry and can be used for bronchial challenge testing [13, 18, 19]. A direct comparison of IOS with body plethysmography showed that differences in airway resistance obtained with the two methods were small and that only high resistance values were markedly underestimated by IOS [10].

Our patients were well instructed and highly motivated and all tests were made by the same experienced technician. Patients underwent spirometry, IOS and Rint for each membrane on two separate days, one week apart. The intrasubject repeatability was less than 5%, which gives values low enough to detect significant responses to removal of excess water or biocompatibility-induced airway hyper-reactivity.

Some studies investigating spirometric lung function in the dialysis population found no changes in VC, FEV1 and FEF25–75% before and at the end of a dialysis session using bioincompatible membranes [14, 17, 21], therefore it has been stated that in end-stage renal disease patients on hemodialysis lung volumes and flow rates are normal unless there is chronic pulmonary or chest-wall disease. However, in early studies on small numbers of patients, removal of marked excess body water, i.e. up to 9.6% of body weight [26], resulted in significant improvement or normalization of decreased lung volume [17, 21, 26]. The weight gain in our patients was significantly less (1.2–4.4 kg or 2–6% of body weight) and all patients with irreversible restrictive lung function had a history of severe pulmonary disease or heart failure. Moreover, the study by Alves et al. in 61 patients on long-term hemodialysis found only a weak correlation ($r = 0.6$, $P < 0.03$) between reduction of excess body weight ($-3.6\% \pm 0.2$) and lung function parameters [1].

We could not confirm the findings of Davenport and Williams, who measured PEF in 30 patients on regular hemodialysis with new cuprophane dialyzer membranes and acetate-buffered dialysate [4], and showed that mean PEF before a dialysis session was significantly reduced and during the first 30 minutes of a session decreased by 0–31.8% (mean 13%), with a second drop after five hours. The temporal relation in the fall of PEF and arterial oxygen tension during hemodialysis supported the authors' hypothesis that the change in PEF may be due to the activation of complement, neutrophils, monocytes and platelets following blood-membrane interactions, resulting in appreciable airway constriction. This hypothesis was further supported by data obtained by the same authors during hemodialysis with reused and more biocompatible cuprophane membranes [5]. The expected fall in PEF and arterial oxygen tension was much less than when the dialyzer was used for the first time. However, other investigators could not confirm these observations. Wu et al. studied the PEF of patients undergoing hemodialysis with new cuprophane membranes manufactured by two different companies [24] and found a small reduction of the PEF during the first 45 minutes of dialysis with one of the membranes but no change in this parameter with the other membrane. Moreover, Walshaw et al. [23] observed a small but sustained drop of less than 4% in peak flow (peak flow meter) after the start of the dialysis session using new cuprophane membranes in six long-term hemodialysis patients. These patients had stable chronic renal failure and underwent intermittent hemodialysis with no change in weight during the procedure. Musacchio et al. reported that spirometrically measured PEF and FEV1 had significantly fallen after one hour and at the end of hemodialysis with low-flux synthetic membranes [16].

The data published previously have one common methodological flaw, in that measurement of peak flow with simple peak flow meters is highly dependent on patient cooperation, on practice with the device and on the correct body position. Furthermore, diurnal variations up to 20% are considered clinically irrelevant in pulmonary patients. The fall in PEF during hemodialysis may well be related not only to the maximum of bioincompatibility reactions but also to the hemodialysis-induced re-

duction in the patient's ability to generate a concerted, maximal contraction of the respiratory muscles [15]. In contrast, we report measurements from several methods of lung function testing that are not dependent on maximal effort. We also made sure that postural influences and the expertise of the technician did not influence the results. No evidence for bronchial hyper-reactivity in central or peripheral airways was shown with IOS, Rint, PEF or FEV1/VC.

In conclusion, there is no convincing evidence that trapping of activated neutrophils in the lungs and release of toxic or inflammatory mediators by bioincompatibility reactions of the hemodialysis procedure causes acute pulmonary dysfunction in patients on maintenance dialysis, even in the presence of pre-existing lung disease or compromised cardiac function. Hemodialysis is a safe procedure even in uremic patients with pre-existing lung disease.

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