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# Pulmonary Function in Patients with End-Stage Renal Disease: Effects of Hemodialysis and Fluid Overload

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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**Background:** Respiratory system disorders are one of the most prevalent complications in end-stage renal disease patients on hemodialysis. However, the pathogenesis of impaired pulmonary functions has not been completely elucidated in these patients. We designed a study to investigate acute effects of hemodialysis treatment on spirometry parameters, focusing on the relationship between pulmonary function and fluid status in hemodialysis patients.

**Material/Methods:** We enrolled 54 hemodialysis patients in this study. Multifrequency bioimpedance analysis (BIA) was used to assess fluid status before and 30 min after the midweek of hemodialysis (HD). Overhydration (OH)/extracellular water (ECW)% ratio was used as an indicator of fluid status. Fluid overload was defined as OH/ECW ≥7%. Spirometry was performed before and after hemodialysis.

**Results:** Forced vital capacity (FVC), FVC%, and forced expiratory volume in the first second (FEV1) levels were significantly increased after hemodialysis. FVC, FVC%, FEV1, FEV1%, mean forced expiratory flow between 25% and 75% of the FVC (FEF25–75), FEF25–75%, peak expiratory flow rate (PEFR), and PEFR% were significantly lower in patients with fluid overload than in those without. OH/ECW ratio was negatively correlated with FVC, FVC%, FEV1, FEV1%, FEF25–75, FEF25–75%, PEFR, and PEFR%. Stepwise multiple regression analysis revealed that male sex and increased ultrafiltration volume were independently associated with higher FVC, whereas increased age and OH/ECW ratio were independently associated with lower FVC.

**Conclusions:** Fluid overload is closely associated with restrictive and obstructive respiratory abnormalities in HD patients. In addition, hemodialysis has a beneficial effect on pulmonary function tests, which may be due to reduction of volume overload.

**MeSH Keywords:** **Electric Impedance • Renal Dialysis • Renal Insufficiency, Chronic • Respiratory Function Tests**

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## Background

Chronic kidney disease (CKD) is an irreversible and progressive disorder characterized by loss of kidney function. CKD gradually progresses to end-stage renal disease (ESRD). ESRD patients eventually need renal replacement therapy via dialysis (subdivided into hemodialysis and peritoneal dialysis) or kidney transplantation in order to survive. As the life expectancy of ESRD patients has increased with improvements in dialysis technology, systemic complications of kidney disease are likely to become increasingly important [1]. CKD, in fact, is not only a localized disease, but also affects virtually all organ systems, especially at the late stage of disease. Among these, respiratory system disorders are one of the most prevalent complications in ESRD patients [2]. A variety of pulmonary abnormalities, including pulmonary edema, pleural effusion, acute respiratory distress syndrome, pulmonary fibrosis and calcification, pulmonary hypertension, hemosiderosis, pleural fibrosis, and sleep apnea syndrome, have been documented in these patient cohorts [3–5]. Impaired pulmonary function may be the direct result of circulating uremic toxins or may indirectly result from fluid overload, anemia, immune suppression, extraosseous calcification, malnutrition, electrolyte disorders, and/or acid-base imbalances, which are common issues in ESRD patients [6].

It is known that fluid overload is a common and serious problem that leads to severe complications in HD patients. In the interdialytic period, weight fluctuations are commonly seen in patients with ESRD on regular hemodialysis program due to body fluid overload [7]. Fluid overload, together with a potential increase in pulmonary capillary permeability, can result in pulmonary edema and pleural effusion, abnormalities that could explain, at least in part, the decrease in pulmonary function [1,8,9]. Since hemodialysis removes excess body fluid, it can also lead to improvement in pulmonary functions by reducing water content of the lungs.

Relatively few studies have investigated the alterations of pulmonary function in ESRD patients undergoing hemodialysis treatment, and conflicting results have been reported. Also, the effects of hemodialysis are not well understood [5]. Therefore, we designed this study to investigate the acute effects of hemodialysis treatment on spirometry parameters. We particularly focussed on the relationship between pulmonary function and fluid status in ESRD patients on regular hemodialysis, using a novel bioelectrical impedance analysis device to measure the fluid status.

## Material and Methods

### Study population

The study design included 54 patients with ESRD receiving chronic HD therapy 3 times per week in Dicle University hospital's dialysis unit. This cross-sectional study was conducted at a tertiary care university hospital and among patients diagnosed with ESRD. The local Human Research Ethics Committee approved the study protocol, and informed consent was obtained from all patients at the time of study enrollment.

Examinations of patients on HD were performed during the middle of the week. The dialyses were carried out using Fresenius 4008S machines. All patients were dialyzed with using 1.6 $m^2$ surface area high-flux polysulphone dialyzers (Fresenius, Bad Homberg, Germany) with bicarbonate-based dialysate (Glucose 1 mmol/L, $Na^+$ 140 mEq/L, $HCO3^-$32 mEq/L, $K^+$ 2.0 mEq/L, $Ca^{2+}$ 1.25 mmol/L, $Mg^{2+}$ 0.5 mEq/L). The prescribed duration was 5 h with a blood flow rate of 250–350 ml/min and dialysate flow rate of 500 ml/min.

The exclusion criteria were: (1) hemodynamically unstable patients; (2) patients with lung disease, such as chronic obstructive pulmonary disease, asthma, or pleural disease; (3) known cardiovascular disease; (4) patients who had limb amputation, pacemakers, metallic intravascular devices, any malignant disease, or pregnancy; and (5) patients who have been receiving diuretic treatment.

### Clinical and laboratory investigations

All patients' demographics and baseline clinical characteristics were obtained from patient registries and the patients themselves. Body mass index (BMI) was calculated as the ratio weight/height$^2$ (kg/$m^2$). Blood samples were collected from all patients for the biochemical and hematological parameters. We collected 24-h urine samples to determine urine volume.

### Spirometry

Standard spirometric pulmonary function tests (Easy-On PC, True Flow by ndd, Medizintechnik AG CH-8005 Zurich, Switzerland) were performed immediately before and after the midweek hemodialysis session. All patients were able to perform acceptable and re-producible forced expiratory maneuvers with the same physician. The patients were studied in sitting posture while wearing a nose clip using standard methodology. This spirometer meets the spirometry standards determined by the ATS/ERS guideline [10]. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), peak expiratory flow rate (PEFR), mean forced expiratory flow between 25% and 75% of the FVC (FEF25–75), and the FEV1/FVC ratio were measured and calculated as%predicted using normal values determined on the basis of age, race, height, and sex (FVC%, FEV1%, PEFR%, and FEF 25–75%).





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**Table 1.** Demographic, clinical, and laboratory characteristics of patients included in the study.

| Parameters | |
|---|---|
| Age (years) | 49.51±15.08 |
| Sex (M/F) | 28/26 |
| Dialysis vintage (months) | 62.25±14.30 |
| Body mass index (kg/m$^2$) | 24.08±5.44 |
| Residual urine (l/day) | 0.02±0.01 |
| Ultrafiltration volume (ml) | 2381±415 |
| Duration delivered (hours) | 5.0 |
| Urea (mg/dl) | 150.96±36.63 |
| Creatinine (mg/dl) | 9.03±2.04 |
| Albumin(g/dl, pre-HD) | 4.66±1.20 |
| Hemoglobin (g/dl, pre-HD) | 12.00±1.64 |

### Bioelectrical impedance analysis

In recent years, multifrequency bioelectrical impedance analysis (BIA), which is a simple, safe, novel, rapid, noninvasive, and promising method, has been used to determine fluid status in patients on dialysis therapy [11,12]. A multi-frequency BIA device (Body Composition Monitor, BCM, Fresenius Medical Care D GmbH), which measures 50 different frequencies from 5 to 1000kHz, was used to assess fluid status by the same operator. BIA was performed just before (pre-HD) and 30 min after (post-HD) the midweek dialysis session. The following parameters were obtained: overhydration (OH), extracellular water (ECW), and OH/ECW% ratio. OH/ECW% ratio was used as an indicator of fluid status. Fluid overload was defined as a OH/ECW ≥7%, corresponding to the value of the 90th percentile for the reference cohort [13,14].

### Statistical analysis

Data analyses were performed using the Statistical Package for Social Sciences (SPSS), Version 18.0 for Windows (SPSS Inc., Chicago, IL). The variables were investigated using visual (histograms and probability plots) and analytical (Kolmogorov-Smirnov test) methods whether or not they were normally distributed. Normally distributed variables are presented as means and standard deviations, and non-normally distributed variables are presented as median and range (maximum and minimum). Comparisons between groups were performed using the Student's t-test. The paired Student's t-test was used to compare the pre-HD and post-HD measurements. The chi-square test was used to compare proportions in different groups. The Pearson correlations were used for simple regression analysis. Stepwise multiple linear regression analyses were performed to identify the independent determinants of FVC. P values <0.05 were considered statistically significant.

## Results

The mean age of the study population (n=54) was 49.51±15.08 years and 51.8% were male. The baseline demographic and clinical characteristics and relevant laboratory parameters of the patients are presented in Table 1.

FVC, FVC%, and FEV1 levels were significantly increased after the hemodialysis session (p<0.05). As regards the BIA parameters, OH/ECW% were significantly lower in post-HD patients compared to pre-HD patients (p<0.05). Table 2 depicts

**Table 2.** Comparison of respiratory function tests and OH/ECW% ratio before and after hemodialysis.

| Parameters | Pre-dialysis | Post-dialysis | P |
|---|---|---|---|
| FVC | 2.61±1.22 | 2.80±1.12 | **0.002** |
| FVC% | 77.03±24.32 | 81.61±23.33 | **0.002** |
| FEV1 | 2.08±0.99 | 2.20±0.93 | **0.011** |
| FEV1% | 73.45±24.00 | 75.59±25.68 | 0.335 |
| FEV1/FVC | 0.79±0.08 | 0.78±0.07 | 0.412 |
| FEF25–75 | 2.07±0.74 | 2.08±0.82 | 0.858 |
| FEF 25–75% | 57.88±16.25 | 56.41±17.84 | 0.575 |
| PEFR | 4.53±1.14 | 4.58±1.92 | 0.792 |
| PEFR% | 63.14±22.06 | 63.13±21.53 | 0.996 |
| OH/ECW% | 9.92±2.25 | 4.18±1.65 | **<0.001** |

FVC – forced vital capacity; FEV1 – forced expiratory volume in the first second; FEF25–75 – mean forced expiratory flow between 25% and 75% of the FVC; PEFR – peak expiratory flow rate; OH – overhydration; ECW – extracellular water.





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**Table 3.** Respiratory function test results of the groups.

| Parameters | Patients with fluid overload (n=15) | Patients without fluid overload (n=39) | p |
|---|---|---|---|
| FVC | 1.81±0.90 | 3.17±0.96 | **<0.001** |
| FVC% | 60.00±24.48 | 89.92±16.83 | **<0.001** |
| FEV1 | 1.44±0.33 | 2.49±0.80 | **<0.001** |
| FEV1% | 50.53±17.31 | 84.58±18.25 | **<0.001** |
| FEV1/FVC | 0.79±0.08 | 0.77±0.07 | 0.672 |
| FEF25–75 | 1.46±0.48 | 2.32±0.72 | **0.014** |
| FEF25–75% | 42.35±13.83 | 61.73±18.53 | **0.026** |
| PEFR | 3.51±1.36 | 4.99±1.78 | **0.009** |
| PEFR% | 49.42±15.60 | 68.41±17.38 | **0.003** |

FVC – forced vital capacity; FEV1 – forced expiratory volume in the first second; FEF25–75 – mean forced expiratory flow between 25% and 75% of the FVC; PEFR – peak expiratory flow rate.

**Table 4.** Correlations between OH/ECW and respiratory function tests.

| Variable | r | p |
|---|---|---|
| FVC | –0.411 | **0.002** |
| FVC% | –0.530 | **<0.001** |
| FEV1 | –0.395 | **0.003** |
| FEV1% | –0.491 | **<0.001** |
| FEV1/FVC | 0.032 | 0.816 |
| FEF25–75 | –0.307 | **0,024** |
| FEF25–75% | –0.272 | **0.047** |
| PEFR | –0.302 | **0.027** |
| PEFR% | –0.425 | **0.001** |

FVC – forced vital capacity; FEV1 – forced expiratory volume in the first second; FEF25–75 – mean forced expiratory flow between 25% and 75% of the FVC; PEFR – peak expiratory flow rate.

comparison of pulmonary function tests and BIA characteristics in pre-dialysis and post-dialysis patients.

FVC, FVC%, FEV1, FEV1%, FEF25–75, FEF2575%, PEFR, and PEFR% were significantly lower in patients with fluid overload than in those without fluid overload ($p<0.05$). Table 3 shows pulmonary function test results of the groups after hemodialysis.

There were significant negative correlations between OH/ECW and FVC, FVC%, FEV1, FEV1%, FEF25–75, FEF25–75%, PEFR, and PEFR% (Table 4).

Further, we modelled a stepwise multiple regression analysis to define the independent determinants of post-hemodialysis FVC. Sex, age, OH/ECW% ratio, and ultrafiltration volume were included into the model. Male sex and increased ultrafiltration volume were independently associated with higher FVC, whereas increased age and OH/ECW% ratio were independently associated with lower FVC ($R^2=0.569$, $p<0.001$, Table 5).

## Discussion

CKD, which can lead to ESRD, is a worldwide public health problem and is associated with increased morbidity, mortality, and diminished quality of life. Unfortunately, the prevalence of ESRD is increasing with the rise in diabetes, hypertension, obesity, and the aging population [15]. Almost all systems of the body are adversely affected as the patient approaches ESRD; therefore, these patients suffer from serious respiratory, cardiovascular, and metabolic complications. The respiratory system is especially affected due to the pulmonary complications commonly encountered in ESRD patients receiving hemodialysis treatment [9]. However, respiratory symptoms are usually either underestimated or overlooked in clinical practice [16].

The pathogenesis of impaired pulmonary functions has not been completely elucidated in HD patients, perhaps partly due to the small number of studies. To the best of our knowledge, this is the first study to investigate the relationship between fluid overload based on OH/ECW ratio measured by using BIA and pulmonary function in patients receiving regular HD.

Several alterations in pulmonary functions, including restriction [17], obstruction [18], and impaired diffusion capacity [19], have been reported in CKD patients. Despite some conflicting results, improvement of spirometry parameters after hemodialysis





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**Table 5.** Stepwise multiple linear regression analyses for the independent determinants of post-HD FVC.

| Independent variables | Beta coefficient | 95% CI | Standardized Beta coefficient | P |
|---|---|---|---|---|
| Sex (0=female, 1=male) | 0.762 | 0.29 to 1.22 | 0.341 | 0.002 |
| Age | –0.031 | –0.046 to –0.017 | –0.419 | <0.001 |
| OH/ECW% | –0.039 | –0.064 to –0.015 | –0.314 | 0.002 |
| Ultrafiltration volume | 0.204 | 0.010 to 0.398 | 0.218 | 0.040 |
| Constant | 3.636 | | | |

CI – confidence interval; Model: $p<0.001$; $R^2=0.569$. FVC – forced vital capacity; OH – overhydration; ECW – extracellular water.

is noteworthy. Kovacević et al. demonstrated that spirometry parameters (FVC, FEV1, FEF75, 50, 25,% of predicted) significantly improved at 1 h after a hemodialysis session [20]. In a study by Alves et al., including in 61 hemodialysis patients, spirometry parameters were examined before and after hemodialysis; they found a significant correlation between the improvement of pulmonary functions (FEV1 and FVC) and weight reduction after dialysis [21]. They also suggested that correction of volume overload after hemodialysis seems to be an important factor in the spirometric improvement. Moreover, a study by Kovelis et al. conducted in a relatively small number of patients (17 HD patients) showed an improvement in FVC after a hemodialysis session, and they also concluded that the pronounced weight gain in the interdialytic period is associated with worsening of pulmonary function, which is almost fully reversible by hemodialysis [9]. On the contrary, Myers et al. reported that the accumulation of body water between dialysis sessions did not significantly influence pulmonary function [17]. In a similar study, Lang et al. found no significant difference in pre- and post-dialysis values of VC (%), FEV1/VC (%), and correlation between lung function parameters and interdialytic changes in body weight in 14 patients receiving HD [22]. In the present study, we demonstrated that spirometry parameters (FVC, FVC%, and FEV1) were significantly improved after hemodialysis. Another finding of the present study is that pulmonary functions tests (FVC, FVC%, FEV1, FEV1%, FEF25–75, FEF25–75%, PEFR, and PEFR%) were significantly lower in patients with volume overload. Also, OH/ECW, which was used to assess volume overload, was negatively correlated with FVC, FVC%, FEV1, FEV1%, FEF25–75, FEF25–75%, PEFR, and PEFR%. Importantly, this study showed that volume overload, determined by OH/ECW ratio and ultrafiltration volume, is an independent predictor of FVC after HD.

Our study results support previous studies by demonstrating the improvement of spirometry parameters, which are mainly related to reduction of excess lung water, after a hemodialysis session. In addition, the findings of the present study demonstrated that volume overload is closely associated with restrictive and obstructive respiratory abnormalities. Volume overload is a frequently encountered problem among hemodialysis patients. Although excess fluid is removed by ultrafiltration during a dialysis session, patients still can be overhydrated. On the other hand, many hemodialysis patients also return to the pre-dialysis period with overhydration as a consequence of water overload [23]. One major consequence is the accumulation of fluid during the interdialytic period, which has a propensity to collect in the lungs and lead to progressive pulmonary congestion [24]. Pulmonary congestion is highly prevalent among patients with ESRD treated with hemodialysis and is associated with a mixed restrictive-obstructive pattern on pulmonary function tests [25]. Hemodialysis can lead to improvement in lung restriction, due to decreasing interstitial edema and bronchial wall decongestion. Liquid accumulation close to airways leads to obstruction and dysfunction [26]. Hemodialysis can remove the excess fluid from the body in overhydrated patients, which in turn reduces water content of the lungs and thus decreases the pressure on airways, and reduces obstruction [27].

A major limitation of the present study is the lack of a long-term follow-up. Remeasurement of pulmonary function tests after achievement of euvolemia in overhydrated patients is needed in a future prospective study.

## Conclusions

The present study indicates that fluid overload is closely associated with restrictive and obstructive respiratory abnormalities in patients with end-stage renal disease on maintenance hemodialysis treatment. In addition, hemodialysis has a beneficial effect on pulmonary function tests, which can attributed to reduction of volume overload. We suggest that intervention to reduce excess volume in hemodialysis patients with volume overload could result in better pulmonary functions.

**Conflict of interest**

The authors declare no conflicts of interest.





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