Impact of renal replacement therapy on the respiratory function of patients under mechanical ventilation

**ORIGINAL ARTICLE**

**INTRODUCTION**

Renal failure is an independent predictor of mortality in intensive care unit (ICU) patients, despite the technological advances in the management of critically ill patients and the new techniques of renal replacement therapy (RRT). The mortality of renal failure remains high, especially when associated with the dysfunction of other organs, such as acute lung injury (ALI). Patients with multiple organ dysfunction in need of dialysis and ventilatory support are common in the intensive care environment.

For a long time, certain alterations in the chest radiographs of patients with kidney injury have been attributed to the increased permeability of pulmonary...
capillaries, known as the “uremic lung”. However, recent studies on experimental models of acute kidney injury that preserve body volume have demonstrated that the increased interstitial pulmonary edema correlates with the dysregulation of proteins involved in water and electrolyte transport, and these changes take place within a few hours. In the past 50 years, the mortality of patients with acute kidney injury has remained high despite the advances in intensive therapy, where the abnormalities observed in the lungs, which can also develop in the heart, brain, bone marrow and gastrointestinal tract, might not be completely reversible after the institution of dialysis therapy.

Only a few studies have evaluated respiratory function after performing RRT. Furthermore, an obvious limitation of these studies was the use of less biocompatible dialysis membranes (such as cuprofan), thus causing pulmonary inflammation and worsening respiratory function.

Recently, patients under mechanical ventilation (MV) and on conventional intermittent hemodialysis (IHD) or sustained low-efficiency dialysis (SLED) were evaluated. No changes in the oxygenation or ventilatory mechanics were observed upon dialysis support. However, that study evaluated only 31 patients and did not indicate how long after the dialysis therapy that the analyses were performed.

Thus, given the lack of information on this subject, the objective of the present study was to evaluate the oxygenation behavior and the ventilatory mechanics after hemodialysis in patients under ventilatory support.

**METHODS**

The present study was performed in the general ICU of the Hospital Geral Roberto Santos (HGRS), in Salvador (Bahia State, Brazil), a tertiary hospital of high complexity from the personal service network of the Brazilian Unified Health System (Sistema Único de Saúde - SUS). The general ICU has 22 beds and assists adult clinical or surgical patients, and there are 7 beds that are preferentially occupied by renal failure patients with a referral for dialysis.

Patients over 18 years of age on MV who required dialysis support (IHD or SLED) were included. Only those patients for whom the informed consent form was signed by the responsible person were included, according to the ethical aspects of the 196/96 resolution of the National Health Council. This project was approved by the Research Ethics Committee of the HGRS under the protocol No 07/11.

The data acquisition was performed by one of the authors, who used a structured and pre-approved evaluation form especially developed for this survey that was composed of questions regarding the demographic and clinical data, the cardiovascular and ventilatory parameters, the ventilatory mechanics, the laboratory evaluation and the dialysis procedure.

Initially, all patients were positioned in the dorsal decubitus position, with the head section inclined at an angle above 30° or according to the medical prescription. To avoid interference with the measured variables, no lung expansion therapy was performed at least 30 minutes prior to the data acquisition and up to the last measurement recorded (1 hour after dialysis). The patients were evaluated by a physiotherapist with respect to the need for bronchial clearance measures, which was confirmed by the presence of snoring in the lung auscultation and/or the presence of a jagged pattern in the flow-volume curve; if confirmed, a tracheal aspiration was performed according to the recommendations of the American Association for Respiratory Care. Immediately prior to the beginning of dialysis, the first collection of data was performed and a blood sample was drawn for the arterial blood gas analysis. Because of the recirculation rate, all variables were re-evaluated, and a new blood sample was drawn 1 hour after the end of the dialysis procedure. Each patient was submitted to 2 evaluations (pre- and post-dialysis).

The cardiovascular parameters, assessed with a DX 2022 multiparameter monitor (Dixtal Biomédica, Manaus, Brazil), were the heart rate (HR), in beats/min, and the mean blood pressure (MBP), the systolic blood pressure (SBP) and the diastolic blood pressure (DBP), in mmHg.

The assessed ventilatory parameters were as follows: the inspiratory pressure (Pins) and positive end-respiratory pressure (PEEP), in cm H2O; the tidal volume (Vt), in mL; the respiratory rate (RR), in breaths/min (bpm); the minute volume (Vm), in L/min; and the fraction of inspired oxygen (FiO2), as a percent. The values from the display of the mechanical ventilator were recorded.

The laboratory evaluation consisted of the following: the potential of hydrogen (pH); the partial pressure of oxygen in arterial blood (PaO2) and the partial pressure of carbon dioxide in arterial blood (PaCO2), in mm Hg; bicarbonate (HCO3) and base excess (BE), in mEq/L; the arterial oxygen saturation (SaO2), as a percent; hemoglobin, in g/dL; lactate, sodium and potassium, in mEq/L; and the PaO2/FiO2 ratio, calculated by dividing the PaO2 by the FiO2 utilized by the patient. The blood gas analyses and the determination of the acid-base balance were performed with an automatic pH and blood gas analyzer (ABL 700 and ABL 800 - Radiometer, Copenhagen, Denmark), as were the quantifications of hemoglobin, lactate and electrolytes (sodium and potassium).
All patients who participated in the study were ventilated with the Vela ventilator machine (Viasys Healthcare, Critical Care Division, California, USA). For the measurement of the ventilatory mechanics, the patients had their ventilatory modality changed to volume-controlled ventilation (VCV) with a Vt of 8mL/kg, a constant flow of 60L/min (square wave), a base PEEP and a RR of 15 bpm, along with the performance of a manual inspiratory pause of 3s. The hyperventilation technique was applied to exclude spontaneous breathing efforts (RR>30bpm for 2 minutes).

The evaluated parameters of the ventilatory mechanics were as follows: the peak pressure (Ppeak), considering the value from the display of the mechanical ventilator; the intrinsic PEEP (PEEPi), obtained by performing a manual occlusion of the expiratory valve of the ventilator for 3s at the end of expiration; the plateau pressure (Pplateau), obtained from the display of the ventilator by means of a manual occlusion of the airways for 3s at the end of inspiration; the resistive pressure (Pres), obtained by calculating the difference between the Ppeak and the Pplateau; the static compliance (Cstat), calculated by dividing the Vt by the Pplateau minus the PEEP and PEEPi; the dynamic compliance (Cdyn), calculated by dividing the Vt by the Ppeak minus the PEEP and PEEPi; and the resistance of the respiratory system (Rrs), calculated by dividing the Pres by the flow. The Ppeak, PEEPi, Pplateau and Pres were measured in cm H₂O. The Cstat and Cdyn were calculated in mL/cm H₂O, and the Rrs was calculated in cm H₂O/L/s.

All ventilatory mechanics measurements were performed by a single physiotherapist.

**Renal replacement therapy**

The patients were divided into 2 groups according to the type of renal failure: acute or chronic. Acute renal failure (ARF) was defined as an acute change in serum creatinine levels (a total increase >0.3mg/dL or a relative increase of 50% with respect to base levels) or urinary output (a reduction to <0.5mL/kg/min for more than 6h), according to the criteria of the Acute Kidney Injury Network (AKIN). Chronic renal failure (CRF) was defined as proposed by the Kidney Disease Outcomes Quality Initiative (KDOQI), which establishes that any adult individual exhibiting glomerular filtration (GF) <60mL/min/1.73m² or, in the cases of GF ≥60mL/min/1.73m², a marker of structural kidney injury (for example albuminuria) for ≥3 months suffers from CRF.

Dialysis was prescribed by a nephrologist according to the patient’s need and hemodynamic condition. There was no interference from the authors regarding the referral or the dialysis method selected by the nephrologist. The patients who were submitted to RRT were divided according to the methods: SLED and IHD. A blood flow (Qa) varying from 150 to 300mL/min and a dialysate flow (Qd) of 300 to 500mL/min was used. Ultrafiltration was calculated as the difference between the volume of the ultrafiltered fluid and the infused dialysis fluid. The patients with no contraindications for anticoagulation used heparin. The Polyflux 8 LR polysulfone capillary dialyzer (Gambro Dialysatoren GmbH, Hechingen, Germany) was used for both methods.

**Statistical analysis**

The data were analyzed with the Statistical Package for Social Sciences (SPSS) Software, version 11.0 for Windows. The quantitative data were expressed as the mean±standard deviation (SD), and the rate data were expressed as the number of individuals (N) and percent cases (%). The normality of the distribution of the variables was assessed by means of the Kolmogorov-Smirnov test. In the comparisons between groups, an ANOVA was performed to assess the difference between the means among more than 2 variables, and the Pearson's chi-squared or Fisher's exact test was performed to assess the association between the qualitative variables. The paired Student's t test was used for the paired samples (pre- and post-dialysis periods), according to the type of renal failure and the blood volume reduction. Differences were considered as statistically significant at p<0.05.

**RESULTS**

Eighty patients were included. Eight patients were excluded for the following reasons: 2 suffered from previous chronic pulmonary diseases (chronic obstructive pulmonary disease and asthma), 1 suffered from congestive heart failure, 3 patients exhibited incidents during dialysis (cardiorespiratory arrest and hemodynamic instability with the need to interrupt dialysis), 1 used PEEP >10cm H₂O and 1 was tracheostomized.

Table 1 displays the general patient characteristics sorted by the type of renal failure. The mean urea and creatinine levels of the CRF group were significantly higher than those of the ARF group. The groups also differed with respect to the reason for admission; the CRF group exhibited a higher ratio of clinical treatment as the reason for admission compared to the ARF group. Table 2 itemizes the characteristics of the dialysis sessions and indicates that there were no differences between the groups.
Table 1 - General patient characteristics

| Characteristics       | Total       | Type of renal failure |     |     |     |     |     |     |
|-----------------------|-------------|-----------------------|-----|-----|-----|-----|-----|-----|
|                       |             | Acute (N=43)          |     |     |     |     |     |     |
|                       |             | Chronic (N=37)        |     |     |     |     |     |     |
|                       |             | p value               |     |     |     |     |     |     |
| Gender                |             |                       |     |     |     |     |     |     |
| Male                  | 38 (47.5%)  | 21 (48.8%)            |     |     |     |     |     |     |
|                       |             | 17 (45.9%)            |     |     |     |     |     |     |
| Female                | 42 (52.5%)  | 22 (51.2%)            |     |     |     |     |     |     |
|                       |             | 20 (51.4%)            |     |     |     |     |     |     |
| Age (years)           | 52±18       | 53±18                 |     |     |     |     |     |     |
|                       |             | 52±19                 |     |     |     |     |     |     |
| Origin                |             |                       |     |     |     |     |     |     |
| Emergency             | 44 (55.0%)  | 21 (48.8%)            |     |     |     |     |     |     |
|                       |             | 23 (62.2%)            |     |     |     |     |     |     |
| Infirmary             | 16 (20.0%)  | 8 (18.6%)             |     |     |     |     |     |     |
|                       |             | 8 (21.6%)             |     |     |     |     |     |     |
| Surgical center       | 20 (25.0%)  | 14 (32.6%)            |     |     |     |     |     |     |
|                       |             | 6 (16.2%)             |     |     |     |     |     |     |
| Length of hospital stay (days) | 21±23       | 23±25                 |     |     |     |     |     |     |
|                       |             | 18±20                 |     |     |     |     |     |     |
| Length of stay in the ICU (days) | 7±6         | 8±6                   |     |     |     |     |     |     |
|                       |             | 6±5                   |     |     |     |     |     |     |
| Reason for hospitalization |          |                       |     |     |     |     |     |     |
|                       |             | 0.033                 |     |     |     |     |     |     |
|                      | Clinical    | 53 (66.2%)            |     |     |     |     |     |     |
|                      | Surgical    | 27 (33.8%)            |     |     |     |     |     |     |
|                      |            | 19 (44.2%)            |     |     |     |     |     |     |
|                      | Diabetes mellitus | 28 (35.0%) |     |     |     |     |     |     |
|                      |             | 13 (30.2%)            |     |     |     |     |     |     |
|                      | APACHE II   | 29±8                  |     |     |     |     |     |     |
|                      | Time under MV (min) | 6±4       |     |     |     |     |     |     |
|                      |             | 7±5                   |     |     |     |     |     |     |
|                      | Hemoglobin (g/dL) | 7.9±1.3 |     |     |     |     |     |     |
|                      |             | 8.1±1.3               |     |     |     |     |     |     |
|                      | Urea (mg/dL) | 161±73                |     |     |     |     |     |     |
|                      |             | 147±74                |     |     |     |     |     |     |
|                      | Creatinine (mg/dL) | 6.0±4.8 |     |     |     |     |     |     |
|                      |             | 4.3±3.5               |     |     |     |     |     |     |
|                      |             | 8.2±5.4               |     |     |     |     |     |     |
|                      |                      |                       |     |     |     |     |     |     |

SLED - sustained low efficiency dialysis; Qa - blood flow; Qd - dialysate flow. The results are expressed as number (%) or the mean±standard deviation. ANOVA or chi-squared test (type of dialysis and referral for dialysis) and Fisher’s exact test (anticoagulation).

Table 2 - Characteristics of the dialysis sessions

| Dialysis               | Total       | Type of renal failure |     |     |     |     |     |     |     |
|-----------------------|-------------|-----------------------|-----|-----|-----|-----|-----|-----|-----|
|                       |             | Acute (N=43)          |     |     |     |     |     |     |     |
|                       |             | Chronic (N=37)        |     |     |     |     |     |     |     |
|                       |             | p value               |     |     |     |     |     |     |     |
| Type of dialysis       |             |                       |     |     |     |     |     |     |     |
| SLED                  | 39 (48.8%)  | 22 (51.2%)            |     |     |     |     |     |     |     |
|                       |             | 17 (45.9%)            |     |     |     |     |     |     |     |
| Conventional          | 41 (51.2%)  | 21 (48.8%)            |     |     |     |     |     |     |     |
|                       |             | 20 (51.4%)            |     |     |     |     |     |     |     |
| Referral for dialysis |             |                       |     |     |     |     |     |     |     |
| Uremia                | 49 (61.2%)  | 27 (62.8%)            |     |     |     |     |     |     |     |
|                       |             | 22 (59.5%)            |     |     |     |     |     |     |     |
| Hypervolemia          | 31 (38.8%)  | 16 (37.2%)            |     |     |     |     |     |     |     |
|                       |             | 15 (40.5%)            |     |     |     |     |     |     |     |
| Qa (mL/min)           | 195±32      | 195±36                |     |     |     |     |     |     |     |
|                       |             | 195±28                |     |     |     |     |     |     |     |
| Qd (mL/min)           | 362±93      | 355±90                |     |     |     |     |     |     |     |
|                       |             | 370±96                |     |     |     |     |     |     |     |
| Ultrafiltration (mL)  | 1,738±912   | 1,732±918             |     |     |     |     |     |     |     |
|                       |             | 1,745±916             |     |     |     |     |     |     |     |
| Anticoagulation       |             |                       |     |     |     |     |     |     |     |
| Yes                   | 10 (12.5%)  | 7 (16.3%)             |     |     |     |     |     |     |     |
|                       |             | 3 (8.1%)              |     |     |     |     |     |     |     |
| No                    | 70 (87.5%)  | 36 (83.7%)            |     |     |     |     |     |     |     |
|                       |             | 34 (91.9%)            |     |     |     |     |     |     |     |

DISCUSSION

In the present study, an increase in the Cstat and a reduction in the Pplateau were observed after dialysis when the mechanical properties of the respiratory system were analyzed.

Another relevant finding was that the significant improvement in the ventilatory mechanics provided by dialysis in both patient groups did not lead to an improvement in oxygenation (the PaO₂ and the PaO₂/FiO₂ ratio). This result was observed even in the cases where a reduction in blood volume occurred upon ultrafiltration. These results are in agreement with the data observed in other studies(8,10,11) and can be explained by the increased blood pH and the resulting left-shift of the oxyhemoglobin (HbO₂) dissociation curve.

However, previous studies with a similar methodology have identified a different behavior of ventilatory mechanics after dialysis. Steinhorst et al.(8) have studied 31 renal failure patients (acute and chronic) on a dialysis program (IHD or SLED) and have observed no significant changes in the Rs, the Cdyn or the Cstat, ascribing the obtained results to the low blood volume reduction. Huang et al.(10) have evaluated 14 patients and have observed an improvement in the Ppeak, Pplateau, auto-PEEP and Rs values and have reported that the reduction in the Rs was correlated with a loss of blood volume (r=0.71;
The authors suggest that the negative balance produced by hemodialysis could lead to a decrease in peribronchial edema. In the present study, a reduction in the $P_{\text{plateau}}$ and an increase in the $C_{\text{stat}}$ after hemodialysis were observed. This behavior can be explained by the redistribution of pulmonary ventilation that occurs after volume removal by ultrafiltration and, perhaps, by the improvement of uremia through hemodialysis, thereby allowing the ventilation of alveoli that were previously filled with fluid. These findings might also suggest that the dialysis procedure favors the fluid dynamics occurring within the interstitial and intravascular spaces, resulting in a reduction of the edema. Notably, an improvement of the $C_{\text{stat}}$ was observed in the present study, independent of the blood volume loss provided by ultrafiltration. However, the group of patients with a volume loss >2,000mL also exhibited a reduced $P_{\text{peak}}$, which suggests that the volume reduction provided by ultrafiltration generates a significant reduction of the airway resistance component. The group with no blood volume loss exhibited an increase in the $P_{\text{res}}$ and the $R_{\text{rs}}$, most likely due to the maintenance of a positive hydric balance.

The beneficial effects of hemodialysis on the ventilatory mechanics were most evident in the ARF patients, who also exhibited a reduction in the $P_{\text{peak}}$ and an increase in the $C_{\text{dyn}}$. Of note, these patients exhibited better prognostic indexes (Acute Physiology and Chronic Health Evaluation II - APACHE II).
Table 5 - Ventilatory mechanics and oxygenation, pre- and post-dialysis, according to blood volume reduction

| Blood volume reduction | No loss (N=8) | Up to 1,000mL (N=12) | >1,000 to 2,000mL (N=38) | >2,000mL (N=22) |
|------------------------|--------------|----------------------|--------------------------|-----------------|
| Pre-dialysis | Post-dialysis | p value | Pre-dialysis | Post-dialysis | p value | Pre-dialysis | Post-dialysis | p value | Pre-dialysis | Post-dialysis | p value |
| Ventilatory mechanics | | | | | | | | | | | | |
| Ppeak | 29.2±4.5 | 28.7±7.8 | 0.770 | 32.1±7.7 | 30.3±6.1 | 0.109 | 30.5±6.8 | 30.4±6.9 | 0.852 | 34.1±10.5 | 31.7±8.3 | 0.027 |
| Pplateau | 23.5±5.6 | 19.6±4.7 | 0.015 | 22.2±7.6 | 19.5±6.0 | 0.014 | 21.4±7.7 | 19.2±5.5 | 0.000 | 22.6±7.1 | 20.9±6.5 | 0.002 |
| Pres | 5.7±2.6 | 7.8±2.3 | 0.010 | 9.9±3.0 | 10.8±3.5 | 0.224 | 9.8±6.1 | 11.3±5.0 | 0.070 | 11.0±5.4 | 10.8±4.4 | 0.815 |
| Cstat | 34.2±8.7 | 41.6±8.8 | 0.008 | 36.8±17.2 | 46±19.8 | 0.002 | 35.7±10.8 | 42.5±17.1 | 0.000 | 38.5±19.1 | 42.3±20.7 | 0.015 |
| Cdyn | 23.1±3.5 | 23.3±5.3 | 0.857 | 20.4±8.2 | 22.3±7.7 | 0.110 | 21.0±6.7 | 21.6±8.2 | 0.441 | 20.5±9.2 | 21.2±8.1 | 0.396 |
| Rs | 8.0±4.2 | 11.1±4.2 | 0.020 | 13.9±4.8 | 14.9±5.0 | 0.307 | 14.0±9.9 | 15.6±8.1 | 0.172 | 15.7±8.5 | 15.3±6.9 | 0.756 |
| Oxygenation | | | | | | | | | | | | |
| PaO₂ | 137±28.7 | 128±31.9 | 0.440 | 108±25.3 | 133±39.2 | 0.093 | 126±33.9 | 125±29.0 | 0.930 | 132±32.9 | 129±29.5 | 0.553 |
| PaO₂/FiO₂ | 385±82 | 366±57 | 0.521 | 301±113 | 351±87 | 0.062 | 369±104 | 380±117 | 0.564 | 369±116 | 362±102 | 0.655 |

higher serum hemoglobin (Hb) levels and lower urea and creatinine levels. The CRF group exhibited an increased Rs after dialysis, for which no explanation was found. Bianchi et al. (13) have reported that repeated lung injury due to an overload of fluid can damage the alveolar capillary membrane and induce a reduced diffusion capacity. These repeated episodes of subclinical edema that occur during each hemodialysis session might induce interstitial fibrosis in chronic renal patients who are under hemodialysis treatment for a longer period of time. (13) In addition to interstitial fibrosis, other abnormalities, such as hyperemia and bronchitis, are commonly found in the autopsies of patients on chronic hemodialysis, (14) explaining the increased Rs.

Renal failure can compromise respiratory function in many ways. Perhaps acute edema is the most common and severe pulmonary complication in renal failure patients. Furthermore, the presence of fluid in the pleural and abdominal compartments can restrict thoracic expansion, leading to changes in the ventilatory mechanics and gas exchange. The accumulation of fluid around the small airways can also be found, resulting in premature closing and air entrapment, thus leading to increased respiratory work and PEEPi. These pulmonary changes lead to reduced compliance and to increased airway resistance. (10) Finally, hypervolemia can determine the diminish of alveolar ventilation, with CO₂ retention and consequent acute respiratory acidosis, thus hampering the weaning from MV. (15)

The sequential evaluation of the ventilatory response during dialysis treatment suggests indicators for the progression of the disease and allows for an adequate adjustment of the ventilatory parameters within physiological limitations. Such evaluation aims to improve patient assistance, facilitate synchronization of the patient with the breather, assist in the MV removal program and provide a better quality of life to the patient.

The present study has some limitations that must be addressed. This study was a unicentric study with a small number of patients and no sample-size calculation. The clinical interventions during dialysis were not controlled. Furthermore, all pre- and post-dialysis evaluations were performed by an evaluator who knew to which group the patients belonged, thus raising the possibility of a bias in the analysis. The sample of CRF patients exhibited higher serum urea and creatinine levels than the ARF patients. This difference was because the CRF patient sample was from a hospital for dialysis referral through the Bahia State regulatory system; therefore, many patients were possibly admitted with no previous treatment of the disease and no possibility of previous dialysis and hence exhibited a dialysis urgency. This situation may have led to a bias in the present study.

**CONCLUSION**

Hemodialysis was able to change the mechanics of the respiratory system; specifically, hemodialysis reduced the Pplateau and increased the Cstat independent of a reduction in blood volume.
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RESUMO

Objetivo: Avaliar o comportamento da oxigenação e da mecânica ventilatória em pacientes com suporte ventilatório após a realização de hemodiálise.

Métodos: Estudo realizado na unidade de terapia intensiva geral de um hospital público terciário. Foram incluídos pacientes maiores de 18 anos, sob ventilação mecânica, com necessidade de suporte dialítico. Cada paciente foi submetido a duas avaliações (pré e pós-diálise) referentes a parâmetros cardiovasculares e ventilatórios, mecânica ventilatória e avaliação laboratorial.

Resultados: Foram incluídos 80 pacientes com insuficiência renal aguda e crônica. A análise da mecânica ventilatória demonstrou que houve redução da pressão de platô e aumento da complacência estática, após diálise, independentemente da redução da volemia. Pacientes com insuficiência renal aguda também apresentaram redução da pressão de pico (p=0,024) e aumento da complacência dinâmica (p=0,026), enquanto pacientes com insuficiência renal crônica apresentaram aumento da pressão resistiva (p=0,046) e da resistência do sistema respiratório (p=0,044). No grupo de pacientes sem perda volêmica, após diálise, observou-se aumento da pressão resistiva (p=0,010) e da resistência do sistema respiratório (p=0,020), enquanto no grupo com perda >2.000mL observou-se redução da pressão de pico (p=0,027). Não houve alteração na PaO\textsubscript{2} e nem na relação PaO\textsubscript{2}/FiO\textsubscript{2}.

Conclusão: A hemodiálise foi capaz de alterar a mecânica do sistema respiratório, especificamente reduzindo a pressão de platô e aumentando a complacência estática, independentemente da redução da volemia.

Descritores: Terapia de substituição renal; Respiração artificial; Insuficiência renal

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