



Impact of Prolonged Duration of Different Types of Renal Replacement Therapies on Serum Levels of Endothelin-1 and Pulmonary Function Tests

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Abstract

Introduction: This study was carried out to investigate the impact of duration of different renal replacement therapies such as hemodialysis and continuous ambulatory peritoneal dialysis on potential overproduction of endothelin-1 (ET-1) and pulmonary function tests in these patients.

Materials and methods: The study included 26 patients (14 males, mean age 54.9±16.2 years) with end stage renal diseases (ESRD) receiving regular hemodialysis (HD) and 23 patients (10 males, mean age 55.8±15.8 years) with ESRD treated with continuous ambulatory peritoneal dialysis (CAPD). The spirometry values were recorded before the onset of HD and prior to emptying the peritoneal cavity in CAPD patients and ET-1 was measured using the enzyme immunoassay (EIA) methodology. Two groups of patients (groups 1 and 2) were further divided into subgroups (group A and group B). Groups A (1-A and 2-A) included patients treated with any type of renal replacement therapy (RRT) (HD or CAPD) less than 5 years, and groups B (1-B and 2-B) included patients treated with any type of RRT (HD or CAPD) longer than 5 years.

Results: Patients treated with HD or CAPD for more than five years were found to have significantly higher serum levels of ET-1 (HD = 41.49±21.28 vs. 185.13±73.67, $p<0.01$; PD = 51.24±32.11 vs. 139.53±42.42, $p<0.01$, respectively). Values of most pulmonary function parameters differed significantly between groups treated longer or shorter than 5 years: FVC (HD = 108.4±13.34 vs. 80.82±11.26, $p<0.01$; CAPD = 97.20±18.99 vs. 73.25±10.73, $p<0.01$, respectively), FEV1 (HD = 108.33±15.8 vs. 76.73±4.9, $p<0.01$; CAPD = 100.67±18.31 vs. 66.75±6.25, $p<0.01$, respectively).

Conclusions: Prolonged duration of any type of renal replacement therapy is associated with higher serum levels of ET-1 and with lower pulmonary function tests in ESRD patients.

Keywords

CAPD, endothelin-1, hemodialysis, spirometry

INTRODUCTION

End stage of chronic renal disease (ESRD) known as uraemia is characterized by progressive, irreversible changes of kidneys and their function. Almost all organs and organic systems are affected at this stage of the disease and the negative effects of uremia are therefore seen in the lungs as well.¹⁻³ The ventilatory function disorder in this group patients mainly presents as an obstructive or restrictive pulmonary disease.⁴ In addition, treatment of ESRD patients with any type of renal replacement therapy (RRT) [RRT includes haemodialysis (HD), continuous ambulatory peritoneal dialysis (CAPD), and hemofiltration] ultimately leads to the development of complications in most major organs and organ systems including respiratory system.⁵⁻⁷ The most commonly described complications of uraemic syndrome and chronic RRT affecting respiratory system are: uraemic lung (pulmonary oedema), pulmonary hypertension, pleural effusions, disfunction of respiratory muscles, respiratory infections, uraemic pleuritis, and uraemic calcification. Post mortem findings in large number of patients indicate that changes appear at alveolar-capillary membrane: pathophysiologic changes that accompany ESRD along with RRT lead to thickening of alveolar-capillary membrane, which consequently affect the respiratory system function.⁸⁻¹⁰ Effects of chronic and long-term dialysis models (especially HD and CAPD) to respiratory function along with its complications have negative effects on pulmonary function tests (spirometry). Spirometry changes in observed population treated with chronic RRT have reversible character during the first years of the treatment.^{11,12} 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.^{13,14} Along with the progression of the disease, micro-inflammatory changes, which include activation of whole spectrum of mediators, develop.¹⁵ Consequently, complications of the same process lead to irreversible changes, which might explain the irreversibility of the pulmonary function tests changes after the RRT.^{4,12} Apart from these findings, a number of studies provide data which shows the existence of a vasoactive molecule imbalance in uremic patients, primarily endothelin-1 (ET-1).^{16,17} In addition to its powerful vasoactive effects, ET-1 causes bronchoconstriction as well.^{18,19} There is a small number of studies which investigated the connection of long-term RRT (HD and CAPD) and ET-1 overproduction and its effects on pulmonary function tests in these patients.

AIM

The aim of this study was to investigate the impact of duration of different RRT (HD and CAPD) on potential overproduction of ET-1 and pulmonary function tests values in ESRD patients.

MATERIALS AND METHODS

This study was performed as prospective observational study. Two groups of patients were included in this study. The first group (group 1) consisted of 26 ESRD patients treated with HD three times per week at the Institute for Nephrology of the University hospital (14 males, mean age 55.4 ± 16.4 years). Duration of each HD procedure was between 180 and 240 minutes. Hemodialysis machines were produced by Gambro and Fresenius with controlled ultrafiltration and with usage of acetate and bicarbonate module. Haemodialysis was performed using the following dialysers: E4H, F6, F60, F60s. Heparinization was continuous with 4000-5000 IU of heparin per patient. A second group (group 2) included 23 patients (10 males, mean age 56.3 ± 16.2 years) who were treated with CAPD at the Institute for Nephrology of the University Hospital. Dialysis solution was changed three times per day and patients were trained to do it by themselves or it was carried out at the Institute under the supervision of a member of the medical staff.

All patients involved in this study had to meet the following inclusion criteria: be older than 18 years of age, with end-stage renal disease treated with HD or CAPD, at beginning of this study without any cardio-respiratory diseases. Every patient was thoroughly examined and chest X-ray was used to exclude the presence of any pulmonary disease. We also did not find any other co-morbidities that could induce ventilatory failure in studied patients. None of these patients had haemodynamic instability during HD or CAPD.

Two studied groups of patients (groups 1 and 2) were further divided to subgroups (group A and group B). Groups A (1-A and 2-A) included patients treated with any type of RRT (HD or CAPD) less than 5 years, and groups B (1-B and 2-B) included patients treated with any type of RRT (HD or CAPD) longer than 5 years.

Spirometry parameters were recorded using a portable spirometer (Microlab - micro medical limited 2003). In group 1, spirometry was performed before the start of HD, when the interdialytic weight gain (fluid overload) was at its highest; while in group 2, spirometry was performed when the abdominal cavity was filled with dialysis fluid, just before emptying. This way, both groups of patients were equalized in fluid balance. At the time of measurement both groups of patients had the highest levels of harmful substances in the blood along with the highest interdialytic weight gain. Spirometry procedure was performed by trained technician at bedside on each patient three times consecutively and the best result was used. All studied patients were in a sitting position during spirometry measurements.

Blood for analysis was obtained by venipuncture of the cubital vein. All principles of asepsis were followed during blood sampling. A total sample of 2 millilitres of blood was taken from each patient. Serum was separated from the whole blood using heated bath at 37°C. Activity

of serum ET-1 was measured with the EIA methodology which is based on an immunometric assay, the so called “sandwich technique”. Measurement was performed using a computer-based ELISA reader (EL_x 800 Universal Microplate Reader Biotek Instruments, INC) with a wavelength of 405 nm. We used a prepared enzyme kit (Endothelin-1; EIA kit - IBL Hamburg, Germany).

The results were analysed using a standard statistical method (Student’s t-test for small independent samples) and results were shown as mean ± standard deviation. We tested the significance of differences in mean values between studied groups with the aim of monitoring changes in respiratory function parameters as well as enzymatic activity. We considered the value of $p < 0.05$ as statistically significant.

RESULTS

Basic demographic and clinical characteristics of 49 individuals with ESRD treated with some types of dialysis are presented in **Table 1**. The age and sex distribution, as well clinical characteristics (primary disease which led to ESRD) were similar for the observed groups.

Comparison of spirometry parameters (% of predicted values) in correlation with duration (less and longer than five years) of RRT (HD and CAPD) as well as serum levels of ET-1 (in correlation with duration of RRT) are presented in **Tables 2, 3, 4, and 5**.

Table 2 shows the serum levels of ET-1 and values of pulmonary function tests in patients with end stage renal disease treated by HD. All observed patients were divided into two groups according to length of dialysis. Serum ET-1 levels were significantly higher, while all values of ventilatory function parameters were significantly lower in patients treated by HD longer than five years.

Table 3 displays the serum levels of ET-1 and values of ventilatory function parameters in patients with end stage renal disease treated by CAPD. All observed patients were

divided into two groups according to length of dialysis. Serum ET-1 levels were significantly higher, while all values of pulmonary function tests were significantly lower in patients treated by CAPD longer than five years.

Table 4 shows the serum levels of ET-1 and values of pulmonary function tests in patients with end stage renal disease treated by HD or CAPD. We compared serum levels of ET-1 and values of pulmonary function tests between patients treated by HD and patients treated by CAPD, both shorter than five years. There were no significant differences in observed values between tested groups of patients, except in FEF25-75 and FEF50.

Table 5 gives the serum levels of ET-1 and values of pulmonary function tests in patients with end stage renal disease treated by HD or CAPD. We compared serum levels of ET-1 and values of pulmonary function tests between patients treated by HD and patients treated by CAPD, both longer than five years. There were no significant differences in observed values between tested groups of patients, except in FEV1, FEF75 and FEF50.

Table 2. The impact of length of HD to serum levels of ET-1 and values of spirometry parameters

Parameter	Group 1-A	Group 1-B	P
ET-1	41.49±21.28	185.13±73.67	<0.01
FVC	108.4±13.34	80.82±11.26	<0.01
FEV1	108.33±15.8	76.73±4.9	<0.01
FEF25-75	124.53±41.98	59.18±14.37	<0.01
FEF75	98.93±21.61	70.82±9.82	<0.01
FEF50	92.20±29.43	45.64±12.22	<0.01
FEF25	95.27±22.75	47.45±20.15	<0.01

Group 1-A: less than 5 years of HD; Group 1-B: longer than 5 years of HD

Table 1. Basic demographic and clinical characteristics of the studied patients

	Hemodialysis – HD N=26	Peritoneal dialysis – CAPD N=23	P
Sex (male)	14	10	0.469
Age (years)	55.4±16.4	56.3 (±16.2)	0.841
Length of dialysis treatment (months)	52.5 (±36.9)	46.8 (±32.7)	0.571
Primary diseases:			
Diabetic nephropathy	9 (34%)	8 (35%)	
Hypertensive nephropathy	5 (19%)	6 (26%)	
Polycystic kidney disease	3 (12%)	2 (9%)	0.965
Chronic pyelonephritis	2 (8%)	1 (4%)	
Unknown	7 (27%)	6 (26%)	

Table 3. Impact of length of CAPD to serum ET-1 levels and values of spirometry parameters

Parameters	Group 2-A	Group 2-B	P
ET-1	51.24±32.11	139.53±42.42	<0.01
FVC	97.20±18.99	73.25±10.73	<0.01
FEV1	100.67±18.31	66.75±6.25	<0.01
FEF25-75	90.80±30.24	51.88±5.94	<0.01
FEF75	85.73±19.51	52.50±8.88	<0.01
FEF50	73.73±27.03	33.38±7.73	<0.01
FEF25	64.87±15.62	36.75±8.79	<0.01

Group 2-A: less than 5 years of CAPD; Group 2-B: longer than 5 years of CAPD

Table 4. Serum levels of ET-1 and values of spirometry parameters in patients treated by different types of dialysis (HD and CAPD) less than 5 years

Parameters	Group 1-A	Group 2-A	P
ET-1	41.49±21.28	51.24±32.11	0.335
FVC	108.4±13.34	97.20±18.99	0.07
FEV1	108.33±15.8	100.67±18.31	0.23
FEF25-75	124.53±41.98	90.80±30.24	<0.05
FEF75	98.93±21.61	85.73±19.51	0.09
FEF50	92.20±29.43	73.73±27.03	0.08
FEF25	95.27±22.75	64.87±15.62	<0.01

Group 1-A: patients on HD less than 5 years; Group 2-A: patients on CAPD less than 5 years

Table 5. Serum levels of ET-1 and values of spirometry parameters in patients treated by different types of dialysis (HD and CAPD) longer than 5 years

Parameters	Group 1-B	Group 2-B	P
ET-1	185.13±73.67	139.53±42.42	0.136
FVC	80.82±11.26	73.25±10.73	0.16
FEV1	76.73±4.9	66.75±6.25	<0.01
FEF25-75	59.18±14.37	51.88±5.94	0.19
FEF75	70.82±9.82	52.50±8.88	<0.01
FEF50	45.64±12.22	33.38±7.73	<0.05
FEF25	47.45±20.15	36.75±8.79	0.17

Group 1-B: patients on HD longer than 5 years; Group 2-B: patients on CAPD longer than 5 years

DISCUSSION

The main finding of this study is that ET-1 levels are significantly higher in patients subjected to RRT (HD or CAPD)

longer than 5 years. Different models of dialysis do not have significant impact on serum ET-1 levels in observed patients.

Another finding of this study suggests that the length of dialysis has a negative effect on spirometry parameters (% of predicted values) since it was significantly lower in patients subjected to RRT (HD or CAPD) longer than 5 years. Patients with significantly higher ET-1 levels (RRT longer than five years) had significantly lower values of spirometry parameters. We showed that groups of patients treated with different types of RRT (HD or CAPD) had similar spirometry parameters (% of predicted values). Due to the fact that number of studies which tested the influence of length of dialysis to ET-1 levels is small, comparison of our data to other publications is quite difficult.

Some earlier studies showed that patients treated with regular HD and CAPD had significantly higher levels of ET-1 compared to healthy subjects.²⁰⁻²³ In our study, serum levels of ET-1 in HD patients in higher than in CAPD group of patients (Table 5), but this difference is without statistical significance. Reason for this difference can be shear stress who acts at the apical cell surface and deform cells in the direction of blood flow; wall distention tends to deform cells in all directions and consequently produce more ET-1. Today it is not well known whether the augmented plasma levels of ET-1 and big ET-1 in dialyzed patients are caused by increased production or decreased degradation, or both. In addition, it is unclear whether different type of dialysis (HD or CAPD) reduces or increases plasma concentrations of ET-1 and big ET-1, because previous studies, which only studied HD-induced changes in ET-1, have demonstrated conflicting results.^{24,25}

On the other hand, the role of ET-1 in lung diseases is significant and the number of respiratory tract disorders in which pathophysiology of this molecule holds a crucial role is rising.¹⁹ Apart from pulmonary hypertension where ET-1 has a considerable effect, obstructive pulmonary diseases as well as pulmonary fibrosis should be also considered. In both dialysis groups of patients, we got results which suggest obstructive and restrictive (reduction of pulmonary volume) lung diseases. Results by other authors who have studied spirometry parameters in different dialysis modules are similar.⁴ Apart from all previously listed complications of uremia and its treatment with [one of] dialysis modules, pulmonary hypertension should also be taken into account. Studies show that 40% of this population usually develop the above-mentioned complications.²⁶ Pulmonary hypertension is accompanied by ventilatory disorders which is reflected in the changes in spirometry parameters.²⁷ One possible reason for the obtained results in this study is the pathophysiological mechanism by which progression of pulmonary hypertension associated with pulmonary fibrosis leads to a reduction in spirometry results. The first link in this pathophysiology chain is a phenomenon called "microinflammatory state" which is present in this population.²⁸ The most commonly described causes of this condition were: postsynthetic protein modification, oxidative stress a type of dialysis membrane or

dialysis module, dialysis quality or infection.

It is well known that tumor necrosis factor (TNF- α) is one of the leading mediators of inflammation. On the other hand, this inflammation mediator plays a significant role in releasing ET-1 from smooth muscle cells of the bronchial tree. This cascade of inflammation mediators can affect respiratory function and consequently spirometry parameters. ET-1 can have a twofold effect, bronchoconstriction and vasoconstriction on one side and proinflammatory effect on the other, creating a vicious circle of pathophysiologic events. Cumulative effects on the bronchial tree can be viewed as bronchoconstriction and inflammation accompanied by fibrosis.²⁹ This fact is supported by studies which showed that patients in a terminal state of uremia who are treated with regular HD had ET-1 levels two to six times higher compared to those of the healthy population (reported plasma concentrations of ET-1 in healthy human subjects vary considerably with mean values ranging between 0.1 and 5.0 fmol/mL).²⁰⁻²³ Knowing the effects of ET-1 on the pathogenesis of pulmonary hypertension as well as its effects on respiratory function, a series of studies demonstrates that 40% of patients treated with regular HD have pulmonary hypertension. In addition to the listed pathophysiologic events, the endothelin molecule itself along with its physiology can cause such events, as all three forms of ET can cause respiratory bronchoconstriction of the bronchial tree smooth muscle cells, but ET-1 stands out with its bronchoconstrictory effect. The work carried out by a group of authors who studied the effects of endothelin in isolated bronchial model show that ETB receptors placed on the smooth muscles of the bronchial tree have the highest affinity for ET-1. These findings are supported by the fact that ET_A receptor blockers do not highlight the bronchodilatory effect, while ET_B receptor agonists potentiate the bronchoconstrictor effects.³⁰

Spirometry changes in observed population treated with chronic renal replacement therapy (mostly with HD) have reversible character during the first years of renal replacement therapy.³¹ There is a small number of studies which investigated the connection of long-term CAPD and its effects on pulmonary function tests in these patients. Consequently, comparison of our data to other publications is quite difficult. On the other hand, along with the progression of the disease, microinflammatory changes which include activation of whole spectrum of mediators (ET-1) develop. Consequently, complications of the same process which have irreversible character develop in group of patients who were under the renal replacement therapy more than five years.¹²

Some limitations within our investigation should be noted, though. First of all, we did not measure the diffusion capacity of the lung for carbon monoxide (DLCO) in studied subjects. DLCO is a parameter which contributes to a better assessment of the pulmonary function tests. Secondly, we did not create a multicentre study, the number of included patients is quite low and patients did not screen for pulmonary hypertension.

CONCLUSIONS

From this study, it can be concluded that long term renal replacement therapy (HD and CAPD) has obvious effect on overproduction of ET-1 serum levels. On the other hand, along with the progression of the disease, microinflammatory changes which include activation of whole spectrum of mediators (especially ET-1) develop. Consequently, complications of the same process which have irreversible character occur, which might explain the worsening of the pulmonary function tests.

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Влияние длительной продолжительности различных видов заместительной почечной терапии на уровни эндотелина-1 в сыворотке крови и функциональные тесты лёгких

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Резюме

Введение: Это исследование было проведено для изучения влияния продолжительности различных методов заместительной почечной терапии, таких как гемодиализ и длительный амбулаторный перитонеальный диализ, на потенциальную гиперпродукцию эндотелина-1 (ЭТ-1) и исследования функции лёгких у этих пациентов.

Материалы и методы: В исследование были включены 26 пациентов (14 мужчин, средний возраст, которых составлял 54.9 ± 16.2 года) с терминальной стадией почечной недостаточности (ТСПН), находившихся на регулярном гемодиализе (ГД), и 23 пациента (10 мужчин, средний возраст, которых составлял 55.8 ± 15.8 года) с ТСПН, получавших длительный амбулаторный перитонеальный диализ (ДАПД). Значения спирометрии регистрировали перед началом ГД и перед опорожнением брюшной полости у пациентов с ДАПД, а ЭТ-1 измеряли с помощью иммуноферментного анализа (ИФА). Две группы пациентов (группы 1 и 2) были дополнительно разделены на подгруппы (группа А и группа В). Группа А (1-А и 2-А) включала пациентов, получавших любой тип заместительной почечной терапии (ЗПТ) (ГД или ДАПД) в течение менее 5 лет, а группа В (1-В и 2-В) включала пациентов, получавших лечение с любым типом ЗПТ (ГД или ДАПД) в течение более 5 лет.

Результаты: Пациенты, получавшие ГД или ДАПД в течение более 5 лет, имели значительно более высокие уровни ЭТ-1 в сыворотке (ГД = 41.49 ± 21.28 против 185.13 ± 73.67 , $p < 0.01$; ГД = 51.24 ± 32.11 против 139.53 ± 42.42 , $p < 0.01$, соответственно). Значения большинства параметров функции лёгких значительно различались между группами, получавшими FVC в течение более или менее 5 лет (соответственно ГД = 108.4 ± 13.34 против 80.82 ± 11.26 , $p < 0.01$; ДАПД = 97.20 ± 18.99 против 73.25 ± 10.73 , $p < 0.01$), FEV1 (соответственно ГД = 108.33 ± 15.8 против 76.73 ± 4.9 , $p < 0.01$; ДАПД = 100.67 ± 18.31 против 66.75 ± 6.25 , $p < 0.01$).

Заключение: Большая продолжительность любого типа заместительной почечной терапии связана с более высокими уровнями ЭТ-1 в сыворотке крови и с нарушением функциональных тестов лёгких у пациентов с ТСПН.

Ключевые слова

ДАПД, эндотелин-1, гемодиализ, спирометрия