Changes in spirometry over time in uraemic patients receiving longterm haemodialysis therapy

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ABSTRACT

Complications of respiratory system in patients suffering from chronic renal failure who are treated with regular haemodialysis are well known. However, the influence of the duration of haemodialysis on pulmonary function is less understood. The aim of this study was to determine spirometry changes in patients on chronic haemodialysis over a five-year period.

We tested 21 patients, out of which 11 female and 10 male, mean age of 50 (±11) years. The mean duration of haemodialysis was 52.2 (±44.7) months at the time of the inclusion. We performed spirometry testings in all patients, one hour before start and one hour after completion of haemodialysis.

All parameters of spirometry recorded one hour after completion of haemodialysis (FVC, FEV_1, $FEF_{75, 50, 25,}$ % of predicted), improved significantly ($p<0,01$). After five years, only FVC demonstrated significant decline and none of the recorded spirometry parameters improved significantly one hour post haemodyalisys compared to pre-haemodialysis period. Analysis of post-dialysis parameters of spirometry at the study onset and following five years of haemodialysis showed that all parameters, except FEF_{50} ($p>0,05$), significantly deteriorated ($p<0,01$).

Patients who are on long term haemodialysis show a significant decline in FVC following five years of treatment. Although the spirometry changes in observed population treated with chronic haemodialysis have reversible character during the first years of renal replacement therapy, five years after these changes become irreversible.

Key words: *spirometry, uremia, haemodialysis.*

REZUMAT

Modificări spirometrice în timp la pacienții uremici tratați cu hemodializă cronică

Complicațiile în sfera respiratorie la pacienții suferind de insuficiență renală cronică sub tratament cu hemodializă sunt bine cunoscute. Totuși, influența duratei hemodializei asupra funcției pulmonare este mai puțin înțeleasă.

Am analizat 21 de pacienți, 11 femei și 10 bărbați, cu media de vârstă 50 de ani (±11). Durata medie a hemodializei a fost de 52,2 (±44.7) luni la momentul includerii în studiu. La toți pacienții s-a făcut spirometrie, o oră înainte de începutul și o oră după încheierea ședinței de hemodializă.

Toți parametrii spirometrici înregistrați la o oră după încheierea hemodializei (CVF, VEMS, FEF75, 50, 25 exprimate % din prezis) s-au ameliorat semnificativ comparativ cu măsurătoarea pre-hemodializă. Analiza parametrilor spirometrici post-dializă la începututl studiului și după o urmărire de 5 ani, a arătat că toți parametrii, cu excepția FEF50 ($p>0,05$), s-au deteriorat semnificativ ($p<0,01$).

Pacienții aflați pe hemodializă pe termen lung demonstrează un declin al CVF după 5 ani de tratament. Deși modificările spirometrice observate la populația tratată cu hemodializă cronică au caracter reversibil în primii ani de terapie de substituție, după cinci ani modificările devin ireversibile.

Cuvinte cheie: *spirometrie, uremie, hemodializă.*

Introduction

End stage of chronic renal disease known as uraemia is characterised with progressive and ireversible changes of kidneys and their function. Besides kidneys, almost all other organs and organic systems are affected at this stage of the disease.[1] Hence, the respiratory system is not spared from the complications of end-stage chronic renal disease, although chronic haemodyalisis itself may have the negative effect on lung function as well.[1,2] Most commonly described complications of uraemic syndrome involving respiratory system are: uraemic lung (pulmonary oedema), pulmonary hypertension, pleural effusions, disfunction of respiratory muscles, respiratory infections, uraemic pleuritis and uraemic calcification[3]. Post mortem findings in large number of patients indicate that changes also appear at alveolar-capillary membrane. Pathophysiologic changes that accompany end-stage chronic renal disease, as well as the haemodialysis itself, lead to thickening of this membrane, followed by all the consequences that could affect the respiratory system[1-4].

Effects of chronic and especially long term haemodialysis on respiratory function along with its complications are less

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Table I.
% predicted values of spirometry parameters before and after haemodialysis during the study year zero

	Before haemodialysis	*After haemodialysis*	*p - value* **
FVC (% predicted mean value ± SD)	83,99 (17,7)	103,3 (11,29)	p < 0.01
FEV1 (% predicted, mean value ±SD)	88,55 (18,15)	103,8 (10,6)	p < 0.01
FEV1/FVC (%mean value ± SD)	88,3 (9,7)	86,3 (10,1)	n.s.
FEF 75 (% predicted, mean value ± SD)	81,3 (25,1)	100,8 (25,9)	p < 0.05
FEF 50 (% predicted, mean value ± SD)	79,9 (25,1)	98,2 (27,2)	p < 0.05
FEF 25 (% predicted, mean value ± SD)	83,1 (27,3)	109,9 (27,6)	p < 0.05

** Student t-test; n.s. = non significant

Table II.
% predicted values of spirometry parameters before and after haemodialysis after five years of study

	After haemodialysis, year zero	*After haemodialysis*	*p - value* **
FVC (% predicted mean value ± SD)	76,7 (17,1)	77,1 (16,5)	n.s.
FEV1 (% predicted mean value ± SD)	83,3 (18,1)	84,9 (14,7)	n.s.
FEV1/FVC (%mean value ± SD)	89 (7,2)	90,9 (7,8)	n.s.
FEF 75 (% predicted mean value ± SD)	79,3 (20,3)	78,9 (18,5)	n.s.
FEF 50 (% predicted mean value ± SD)	78,6 (26,4)	85,1 (20,4)	n.s.
FEF 25 (% predicted mean value ± SD)	90,5 (27.6)	105,1 (31,4)	n.s.

known. [4-9] Literature data on this topic are insufficient and contradictory. [1, 4-5, 9-15]

Technical improvement in haemodialysis process is followed by prolonged survival of this patients' population, hence uremic as well as the treatment complications are more expressed. Regarding all stated above, this study was designed with the aim to follow the effects of long term haemodialysis on respiratory function (spirometry tests).

Methods

Initially 30 patients were included in this study, out of whom 9 died during the five year time period. Twenty one patient was analysed, including 11 female and 10 male patients. All patients were treated at the International dialysis centre Banja Luka and they all signed the informed consent for the participation in this study. All patients were non-smokers. In this study we included patients without the presence of any acute or chronic lung disease, cardiac or any chest disease, connective tissue disease and without any immunosupresive treatment (eg cyclophosphamide).

Patients were treated with haemodialysis three times per week, but were never treated with peritoneal dialisys or had renal transplantation. Duration of haemodialysis per one visit was individually tailored according to patients' needs and it was between 180 and 240 minutes.

Haemodialysis was performed using Gambro and Fresenius machines with controlled ultrafiltration. Bicarbonate module was used as well. Dialisators used were as follows: E_4H, F_6, F_{60}, $F_{60s.}$ 4000-5000 IU of heparin were given to each patient continuously during haemodialysis.

Study design

Medical history of all patients was noted at screening. Basic spirometry testing was performed to all patients along with physical examination. We measured following spirometry parameters: forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), forced expiratory flow at 75%, 50%, 25% VC ($FEF_{75, 50, 25}$).

Three consecutive spirometry testings were performed one hour before and three consecutive spirometry testings were performed one hour after hemodialysis, during the year zero (2003) of the study as well as five years later (2008). Out of each three consecutive testings, the best result was included in analysis. We used Micro Medical Ltd portable spirometer for lung function testing in our study. Quality control of used spirometer was assured by regular testing which was performed according to ATS/ESR criteria in order to gain valuable results. [16]

Student t-test was used for statistical analysis. Results are presented using descriptive statistical measures such as mean and standard deviation; $p < 0,05$ was taken as statistically significant.

Results

From all data that were collected in this study, only results obtained from 21 patients who finished the study were analysed. Mean age of patients included in this study was 51 years (± 11). Mean time spent on haemodialysis at beginning of the study (year zero) was 52,2 (44,7) months. During the year zero, all patients had spirometry testings performed, one hour prior to and one hour after haemodialysis. Out of all patients observed in our study, during the year zero and five years after, only one patient had values of $FEV_1/FVC < 70\%$ (in pre-dialysis and post-dialysis period). During the year zero six patients had $FVC < 80\%$ prior to dialysis, which reversed to normal in all patients in our study. All recorded spirometry tests showed statistically significant recovery after haemodialysis ($p<0.1$) (Table I).

Five years after initial spirometry testing, $FVC < 80\%$ during pre-dialysis period was found in 13 patients while during the post-dialysis period, $FVC < 80\%$ was found in 12 patients. This time, none of measured spirometry parameters (FVC, FEV_1, $FEF_{75, 50, 25,}$ % of predicted values) showed statistically significant recovery (Table II).

In order to ilustrate decline in spirometry parameters five years after initial testings, we made comparison between pre-dialysis values during the year zero and pre-dialysis values five years after (Table III). Statistically significant decline in FVC was noted ($p<0.05$) while there was no significant difference in other spirometry parameters (Figure 1).

Similarly, we compared post-dialysis spirometry testings in the same way and found that all of them (FVC, FEV_1, FEV_1/ FVC, $FEF_{75, 50, 25,}$ % predicted values) show statistically significant decline ($p<0.01$) except for FEF_{50} ($p > 0.05$) (Table IV).

Table III.
Comparison of pre-dialysis spirometry parameters (% predicted mean values of spirometry parameters) during the year zero and year five of the study

	Before haemodialysis, year zero	*Before haemodialysis, year five*	*p - value* **
FVC (% predicted mean value±SD)	83.99 (17.7)	76.7 (17.1)	p < 0.01
FEV1 (% predicted mean value±SD)	88.55 (18.15)	83.3 (18.1)	n.s.
FEV1/FVC (%mean value±SD)	88.3 (9.7)	89 (7.2)	n.s.
FEF 75 (% predicted mean value±SD)	81.3 (25.1)	79.3 (20.3)	n.s.
FEF 50 (% predicted mean value±SD)	79.9 (25.1)	78.6 (26.4)	n.s.
FEF 25 (% predicted mean value±SD)	83.1 (27.3)	90.5 (30.7)	n.s.

** Student t-test; n.s. = non significant

Table IV.
Comparison of post-dialysis spirometry parameters (% predicted mean values of spirometry parameters) during the year zero and year five of the study

	After heamodialisys, year zero	*After haemodialisys, year five*	*p - value* **
FVC (% predicted srednja vrednost±SD)	103.3 (11.29)	77.1 (16.5)	p < 0.01
FEV1 (% predicted srednja vrednost±SD)	103.8 (10.6)	84.9 (14.7)	p < 0.01
FEV1/FVC (%srednja vrednost±SD)	86.3 (10.1)	90.9 (7.8)	p < 0.01
FEF 75 (% predicted srednja vrednost±SD)	100.8 (25.9)	78.9 (18.5)	p < 0.01
FEF 50 (% predicted srednja vrednost±SD)	98.2 (27.2)	85.1 (20.4)	n.s.
FEF 25 (% predicted srednja vrednost±SD)	101.9 (27.6)	105.1 (31.4)	p < 0.01

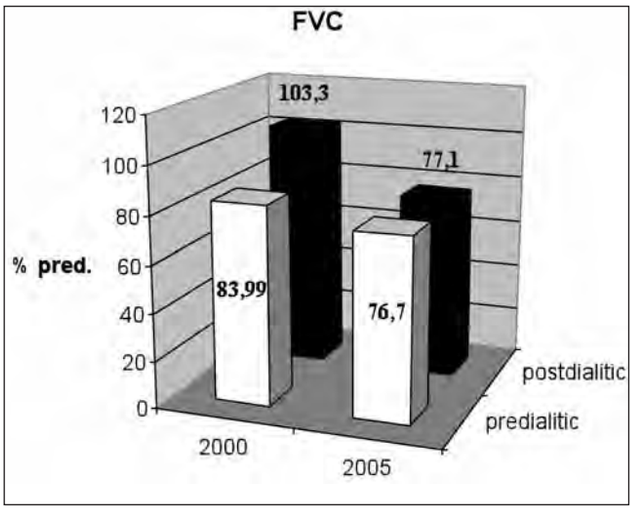
Discussion & conclusions

Results of our study show that both prolonged end stage chronic renal failure, as well as prolonged renal replacement tratment with haemodialysis have negative effects on spirometry parameters.

During the year zero values of spirometry tests, obtained post-dialysis, significantly improved compared to the pre-dialysis tests. Until nowdays, several studies were published which revealed effects of uraemia and hemodialysis to spirometry parameters[1,10,11,13,14,15]. Most of them show positive effect of haemodialysis on respiratory function which is the result of removal of fluid excess, better diffuse capacity of lungs and increase in ventilation of basal lung area[1,4,5,17-19]. All mentioned things could be the reason for initial improvement of respiratory parameters in our study.

Five years after initial testings none of the observed parameters measured one hour post-dialysis improved significantly. In accordance to slower improval of spirometry parameters after haemodialysis are results of post-dialysis testings obtained during year zero and year five of the study. These results show significant decline in post-dialysis spirometry parameters after five years, except for $FEF_{50.}$ Altough significant number of studies which aimed to perceive the effects of haemodialysis on respiratory function were published, literature data is deficient in revealing longterm effects of uraemia and haemodialysis on spirometry parameters, which makes our study unique. Possible pathophysiology mechanisms that explain gained results in our study are: progression of lung oedema known as uraemic lung, changes at alveolocapilar membrane and progression of pulmonary hypertension. First link of this pathophysiological chain is phenomenon of so called microinflammatory state which accompanies this population[20-28]. Mostly mentioned causes of this state are: postsintetic protein modification[29], oxidative stress[30], type of dialysis membrane or dialysis technique[31], haemodialysis quality[32,33] and infection[31]. It is well known that one of the leading mediators of inflammation is tumor necrosis factor (TNFα). On the other hand, this factor plays significant role in lung smoth muscle cells endotelin – 1 release (ET-1)[34,35,36]. This cascade of mediators of inflamation might affect respiratory function, and consenquently spirometry parameters. ET -1 has double effect, which is bronchoconstrictive and vasoconstrictive on one side and proinflammatory on the other side, which enables vicious circle of pathophysiological events. Summary effect of ET – 1 on bronchial tree might manifest as bronchoconstriction and inflammation accompanied by consequent fibrosis[37]. This fact is supported by the studies which claim that patients in terminal stage of uraemia treated by repeated haemodialysis have two to six times higher values ET-1 compared to healthy population [38-42].

Figure 1.
Dynamics of FVC spirometry parameter changes in time



Knowing the effect of ET – 1 on pathogenesis of pulmonary hypertension and all its effects on respiratory function, ilustrative are results of several studies which show that 40% of patients treated with repeated haemodialysis are diagnosed with pulmonary hipertension[7,8,20-27,36-42]. Besides all stated it is important to note that dialysis membrane is defined as cause of decline in respiratory function[12,14].

Our study has few limitations. We included relatively small number of patients. Reason for that lays in the fact that small number of patient gave their informed consent. Beside this, further testing of respiratory function (diffusion capacity for CO) was

impossible. We did not perform chest X-ray in patients included in our study which can be a bias because the decline in lung function due to inflammation can not be distinguished from those due to pleural problems.

In our calculations we did not include results obtained from 9 patients who died during the study period, but the mean values of all spirometry testing results were not significantly different from results of included patients at year zero.

To conclude, spirometry changes in observed population treated with chronic haemodialysis have reversible character during the first years of renal replacement therapy. On the other hand, along with the progression of the disease, microinflammatory changes which include activation of whole spectrum of mediators develop. Consequently, complications of the same process which have irrevesible character develop, which might explain the irreversibility of the spirometry changes after the renal replacement therapy.

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