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Bronchial reactivity in patients with chronic renal failure undergoing haemodialysis

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Bronchial reactivity in patients with chronic renal failure undergoing haemodialysis. A. Ferrer, J. Roca, R. Rodriguez-Roisin, J. López-Pedret, L. Revert.
ABSTRACT: We hypothesized that patients with chronic renal failure may present nonspecific bronchial hyperreactivity due to subclinical interstitial lung oedema. To assess lung function disturbances and methacholine (MTH) bronchial responsiveness in this condition, we studied 12 patients (9 men and 3 women; 41.8±13.3 yrs (SD)) with chronic renal failure undergoing regular haemodialysis (HD). Before HD, mean results of conventional lung function tests were within the normal range: forced expiratory volume in one second (FEV_1), 89±12.9% predicted; forced mid-expiratory flow (FEF_{25-75}), 81±36.7% predicted; total lung capacity (TLC), 94±14.6% predicted, but 3 subjects presented mild reduction in lung volumes and 5 individuals showed mild obstructive ventilatory impairment. After HD, maximal expiratory flow rates increased significantly (FEV_1, + 8.2±5.1% ($p<0.005$); FEF_{25-75}, +26.2±25.9% ($p<0.005$)). Interestingly, these increases in FEV_1 after HD correlated with body weight loss during HD ($r=0.74$, $p<0.01$). In contrast, pre-HD bronchial reactivity was within the normal range (mean % change in FEV_1 after MTH, -3.7±4.5%; range, +1– -14%) without significant changes in methacholine bronchial responsiveness after HD. We speculate that interstitial lung oedema may play a significant role in lung function impairment observed in patients with chronic renal failure. This study shows that nonspecific bronchial hyperreactivity is not present in clinically stable patients with this disorder.
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Increased extravascular lung water with a wide spectrum of clinical manifestations, from overt pulmonary oedema to subclinical disease, is a common finding in patients with chronic renal failure. Several studies carried out to assess pulmonary function disturbances in this condition [1–4] have documented a reduction in lung volumes and in maximal expiratory flow rates that usually reverse after haemodialysis, suggesting interstitial lung oedema as the underlying mechanism. The accompanying airways wall oedema may lead to nonspecific bronchial hyperresponsiveness. This hypothesis is supported by animal studies which suggest that oedema of the airways can produce a substantial increase in airways responsiveness [5, 6]. The incidence of bronchial hyperresponsiveness is increased among patients with impaired left ventricular function [7] and also in healthy subjects with reduced maximal expiratory flow rates [8]. In addition, nonspecific bronchial hyperreactivity has been induced in normal humans after rapid 0.9% saline infusion (30 $ml \cdot kg^{-1}$) [9].

We hypothesized that patients with chronic renal failure may show an exaggerated response to methacholine bronchial challenge due to the distension of peribronchial tissue caused by the accumulation of extravascular lung water. The present investigation was undertaken to examine this hypothesis. The study consisted of the analysis of routine pulmonary function tests and methacholine bronchial challenge before and immediately after regular haemodialysis in twelve subjects with chronic renal failure.

Materials and methods

Twelve patients (9 men and 3 women; 41.8±13.3 yrs) with clinically stable chronic renal failure undergoing regular haemodialysis (HD) three times per week (mean duration of each haemodialysis, 4 h), with normal chest X-ray films, and free from any concomitant disease were studied after giving oral consent according to the ethical standards of the Committee on Human Investigations of the Hospital Clinic. A membrane of polyacrilonitrile was always used as the dialyzer.

Conventional pulmonary function tests (PFT's) included: thoracic gas volume (Vtg) and specific airways conductance (sGaw) by body plethysmography (Body-Pneumotest, E. Jaeger, Würzburg, W. Germany); inspiratory capacity and expiratory vital capacity (Pulmonary

System, HP 47804A, Waltham, MA); single-breath carbon monoxide diffusing capacity (DLCO) (Model A, PK Morgan Ltd, Chatham, U.K.); and forced spirometry (HP 47804A). Single-breath DLCO measurements were corrected for haemoglobin concentration [10]. Lung function results, expressed as percentage of predicted values, were calculated using our own prediction equations [11–13].

Methacholine (MTH) bronchial challenge was carried out by intermittent aerosol generation according to recommended standardized procedures [14]. Specific details of the standardization in our laboratory have been reported elsewhere [15]. In each test, increasing MTH concentrations (0.1–25 $mg \cdot ml^{-1}$) were used until 305 cummulative breath units (cbu) were reached. Delivery of methacholine was always done by the same observer (AF) in all patients using a hand-grip non-dosimeter nebulizer (DeVilbiss No 42, DeVilbiss Co, Somerset, PE). Spirometric measurements were determined using a water-sealed spirometer (7*L*-Stead Wells spirometer, WE Collins, Baintree, MA).

Conventional PFT's were performed before and after haemodialysis (pre-HD and post-HD, respectively) in 12 patients. In contrast, only 9 subjects completed the MTH study (pre-HD and post-HD). The remaining 3 subjects did not collaborate to perform the post-HD MTH challenge. All post-HD lung function measurements were carried out within 1 h after 4 h of HD. A preliminary study in our laboratory (unpublished data) has shown that the residual effects of MTH challenge, such as a mild reduction in maximal expiratory flow rates, may last for more than 4 h (equivalent to the mean duration of HD), particularly in patients with bronchial hyperreactivity. Consequently, the MTH study was designed as follows: each patient was studied on two consecutive sessions of HD (2 days apart) named A and B. The order of A and B was decided at random. On day A, PFT's and MTH were carried out only before HD. On day B, PFT's were carried out twice, before and after HD, but MTH was performed only after HD. Thus, while the residual effects of MTH were avoided, baseline pulmonary function tests were always known and thus comparable.

Results are expressed as mean values ± standard deviation (SD). Changes in PFT's after HD were analyzed using data sets of day B. Analysis of MTH was carried out comparing pre-HD MTH on day A with post-HD MTH on day B. Pre and post-HD data were compared using paired Student's t-test. Relationships between lung function changes after HD and loss of body weight during HD were examined using Pearson's correlation test. Probability values lower than 0.05 were considered significant in all cases.

Results

Age, sex, anthropometric data, smoking habits, type of renal disease and duration of the haemodialysis in the patients studied are reported in table 1. Mean results of pulmonary function tests pre-HD were within the normal range (table 2). Three patients presented mild reduction in static lung volumes (total lung capacity was 78%, 77% and 75% of predicted in subjects 1, 8 and 12, respectively) and 5 individuals (1, 2, 5, 7 and 12) showed a mild obstructive ventilatory impairment defined as forced mid-expiratory flow (FEF_{25-75}) lower than the 95% confidence interval. In addition, 6 individuals (1, 2, 6, 8, 9, and 12) presented mild to moderate reductions in DLCO (range 60–78%) that became normal after correction for single-breath helium total lung capacity in all but one individual (carbon monoxide transfer coefficient (KCO) was 73% of predicted in subject 9).

Table 1. – Population studied

Patient	Age yr	Sex	Height cm	Weight kg	Tobacco	Renal disease	HD yr
1	46	M	164	51	Yes	Haemolytic uraemic syndrome	5
2	22	M	160	51	No	Cystic medullary disease	1
3	26	M	177	60	No	Chronic pyelonephritis	1
4	43	M	161	61	Yes	Focal & segmental glomerulonephritis	5
5	40	M	170	58	Yes	IgA nephropathy	1
6	29	F	156	49	Yes	Primary amyloidosis	2
7	64	M	168	61	Yes	Unknown aetiology	1
8	36	M	161	61	No	Unknown aetiology	11
9	60	M	170	82	Ex-S	Uric nephropathy	4
10	34	F	162	51	No	Transplant rejection	15
11	48	F	158	63	No	Cortical necrosis	3
12	54	M	165	72	Yes	Nephroangiosclerosis	6
Mean±SD	42±13		165±6	60±10			4.6±4.4

Body weight measured post-HD; Ex-S: ex-smoker; HD: years of haemodialysis; M: male; F: female.

Table. 2. – Pulmonary function tests pre-HD and changes in PFT's after HD

	FVC	FEV_1	FEV_1/FVC %	FEF_{25-75}	$\dot{V}max_{50}$	$\dot{V}max_{75}$	TLC	Vtg	RV/TLC %	sGaw	DLco	DL/VA
pre-HD	86 (11.3)	89 (12.9)	81 (7.5)	81 (36.7)	95 (24.5)	89 (41.6)	94 (14.6)	92 (16.6)	34 (6.0)	0.144 (0.057)	84 (16.0)	92 (14.8)
% change after HD	+4.5 (4.8)	+8.2 (5.1)	+3.7 (5.8)	+26.2 (25.9)	+19.3 (21.5)	+35.4 (35.9)	-0.5 (4.9)	+6.2 (6.7)	+2.2 (26.7)	+2.1 (31.3)	-2.6 (6.7)	-5.2 (8.1)
p	<0.05	<0.005	<0.05	<0.005	<0.005	<0.005	NS	<0.01	NS	NS	NS	NS

All measurements were performed on day B. Results are expressed as mean±(SD); pre HD: before haemodialysis, except for FEV_1/FVC ratio (actual %), RV/TLC ratio (actual %) and sGaw ($cmH_2O^{-1}\cdot min^{-1}$), all pre-HD measurements are expressed as % of predicted values; % change after HD was calculated as follows: ((post-HD - pre-HD)/pre-HD) ×100; p values correspond to paired Student's t-tests. NS: not significant. For abbreviations see Materials and methods.

Table 3. – Methacholine challenges pre and post-HD

	% change FVC		% change FEV_1		% change FEF_{25-75}	
	pre-HD	post-HD	pre-HD	post-HD	pre-HD	post-HD
Mean (SD)	-3.7 (4.3)	-0.6 (3.4)	-3.7 (4.5)	-1.0 (2.5)	-4.0 (13.8)	-5.3 (11.5)

% change FVC, % change FEV_1, and % change FEF_{25-75} indicate the percentage change from baseline after each methacholine bronchial challenge. For abbreviations see Materials and methods.

Mean body weight loss during HD on day B was 2.47±0.86 kg (range 1.5–4.1 kg). After HD, maximal expiratory flow rates (forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio, FEF_{25-75}, maximal flow at 50% and 75% of FVC ($\dot{V}max_{50}$ and $\dot{V}max_{75}$)) and FVC significantly increased (table 2). Mean thoracic gas volume increased by 6.2% ($p<0.01$) without accompanied changes in residual volume. Total lung capacity and maximal expiratory flow rates were within the normal range in all subjects after HD. In contrast, no changes were observed in DLco nor in Kco. Interestingly, there were significant correlations between loss of body weight during HD and % of increase in FEV_1 ($r=0.74$, $p<0.01$).

Table 3 indicates that methacholine bronchial hyperreactivity before HD was not present (mean % change in FEV_1, after the inhalation of 305 cbu of MTH in each individual, was -3.7±4.5%, range +1– -14%). In addition, no differences between pre-HD and post-HD values were shown in the percentage of change of the spirometric variables after MTH. Body weight loss between pre-HD on day A and post-HD on day B (2.13±1.11 kg) was not different from body weight loss during HD on day B. Baseline (pre-HD) measurements carried out on days A and B showed less than 5% variability in both FVC and FEV_1. No differences between days A and B were shown in baseline (pre-HD) spirometric variables.

Discussion

The present study demonstrates moderate but significant increases in maximal expiratory flow rates and in FVC after haemodialysis (HD) (table 2). These results are in keeping with different investigations on patients with chronic renal failure that reported improvement in small airways dysfunction [1–4] and in ventilation-perfusion ($\dot{V}A/Q$) relationships after HD [16]. In addition, although direct measurement of extravascular lung water was not carried out, the correlation between weight loss during HD and increase in FEV_1 after HD is consistent with the hypothesis that interstitial lung oedema may be the underlying mechanism of lung function impairment in our patients. Such a pathophysiological mechanism has also been formerly suggested by most of the studies on patients with chronic renal failure [1–4, 16]. The mild but significant increase in thoracic gas volume (Vtg) after HD may also be interpreted as a reflection of a reduction of elastic recoil caused by the loss of extravascular lung water during HD.

Methacholine bronchial hyperresponsiveness has been induced in healthy subjects after fluid overload (rapid 0.9% saline infusion, 30 $ml\cdot kg^{-1}$) [9]. Although different mechanisms, such as stimulation of J receptors by peribronchiolar wall oedema, increased sensitivity of irritant lung receptors or increased passage of methacholine to

the cholinergic receptors on smooth muscle have been suggested, how interstitial lung oedema could increase bronchial reactivity in these subjects remains controversial. Animal studies have shown that oedema of the airways can produce an important increase in airways responsiveness to histamine [5, 6]. This finding is consistent with the hypothesis that a swollen submucosa may explain an abnormal airways narrowing in the presence of a normal airways smooth muscle [17]. A study performed on clinically stable patients with chronic congestive heart failure has failed to demonstrate methacholine bronchial hyperreactivity in this condition [18]. However, a recent study performed on patients with coronary heart disease showed that while patients with normal left ventricular function did not have bronchial hyperresponsiveness, patients with impaired left ventricular function showed bronchial hyperresponsiveness probably due to bronchial wall oedema caused by increased pulmonary venous pressure [7]. The present investigation was specifically designed to assess whether or not nonspecific bronchial reactivity is increased in patients with chronic renal failure. Both the normal pre-HD methacholine challenge and the lack of significant changes in the MTH testing after HD (table 3) clearly indicate that bronchial hyperresponsiveness was not present. Our data therefore demonstrate that bronchial hyperresponsiveness is not a significant determinant of lung function disturbances in clinically stable patients with chronic renal failure. However, nonspecific bronchial hyperreactivity cannot be ruled out in acute or chronic renal failure where body fluid overload may be greater than that observed in this study. Further studies are needed to investigate the role of fluid overload on bronchial responsiveness in patients with underlying hyperreactivity.

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Réactivité bronchique chez des patients avec insuffisance rénale chronique au cours de l'hémodialyse. A. Ferrer, J. Roca, R. Rodriguez-Roisin, J. López-Pedret, L. Revert.

RÉSUMÉ: Nous avons émis l'hypothèse que les patients en insuffisance rénale chronique pourraient présenter une hyperréactivité bronchique aspécifique due à un oedème pulmonaire interstitiel subclinique. Douze patients (9 hommes et 3 femmes; 41.8±13.3 ans), atteints d'une insuffisance rénale chronique et subissant des hémodialyses régulières, ont été étudiés pour déterminer les anomalies fonctionnelles pulmonaires et la réactivité bronchique à la methacholine. Avant hémodialyse, les résultats moyens des tests fonctionnels pulmonaires conventionnels restent dans la norme (VEMS, 89.0±12.9 des valeurs prédites; FEF_{25-75}, 81.1±36.7 des valeurs prédites: TCL, 94.1±14.6 des valeurs prédites). Chez 3 sujets, l'on a observé une réduction légère des volumes pulmonaires; et chez 5 individus, une atteinte ventilatoire obstructive légère. Aprés hémodialyse, l'on observe une augmentation significative des débits expiratoires maximaux (VEMS, + 8.2±5.1 ($p<0.05$);

FEF_{25-75}, + 26.2±25.9 (p<0.005)). Ces augmentations du VEMS après hémodialyse sont en corrélation avec la perte de poids corporel au cours de l'hémodialyse (r=0.74, p <0.01). Par contre, la réactivité bronchique de base avant hémodialyse est dans les limites normales (modification moyenne du VEMS après methacholine, -3.7±4.5%; extrêmes +1 et -14%); apres hémodialyse, il n'y a pas de modification significative de la réactivité bronchique à la methacholine. Nous supposons que l'oedème pulmonaire interstitiel pourrait jouer un rôle significatif dans l'atteinte fonctionnelle pulmonaire observée chez les patients en insuffisance rénale chronique. Cette étude montre qu'il n'y a pas d'hyperréactivité bronchique non spécifique chez les patients cliniquement stables atteints de cette affection.
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