Subclinical pulmonary congestion is prevalent in nephrotic syndrome

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In patients with nephrotic syndrome (NS), the lung is considered an organ protected from the risk of edema. However, data on objectively measured lung water in NS patients is lacking. Here we measured lung water by an ultrasound (US) technique as well as by transthoracic impedance in 42 asymptomatic patients with active NS, in 14 stage G5D CKD patients on chronic hemodialysis, and in 21 healthy individuals. In patients with active NS, the median number of US-B lines (a metric of lung water) after 5 min in a supine position was significantly higher (12; interquartile range: 7–25) compared with that in healthy individuals (4; 2–9) but similar to that in hemodialysis patients (23; 10–39). The difference between NS patients and healthy individuals was significantly amplified (16; 10–35 vs. 4; 2–9) after 60 min of supine resting and significantly attenuated after 5 min of standing (10; 7–25 vs. 3; 1–6). Posture-dependent changes in lung water in patients with active NS were significantly accentuated compared with both hemodialysis patients and healthy individuals. After NS remission, the number of US-B lines was significantly reduced to 5 (4–18) at 5 min and to 6 (5–22) at 60 min approaching the normal range. Lung congestion in patients with active NS was confirmed by transthoracic impedance. Thus, asymptomatic pulmonary congestion is pervasive in patients with NS. A clinical trial is needed to assess the utility of lung US for the management of patients with NS.

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KEYWORDS: lung comets; lung congestion; lung ultrasound; lung water; nephrotic syndrome

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Edema, a cardinal feature of nephrotic syndrome (NS), is a pervasive phenomenon in this condition. Well beyond the integumentary system, edema can be extended to major organ systems including the intestinal wall[1] and the central nervous system[2] where it may have relevant pathophysiological and clinical consequences.

Because of the so-called lung safety factor, that is, the very low net filtration pressure at alveolar level (just 1 mm Hg), the lung is considered to be an organ uniquely protected from the risk of generalized edema.[3] Such a low pressure gradient is maintained by a continuous flow of lymphatic fluid from the lung interstitium to the systemic circulation as well as by a decrease in interstitial oncotic pressure, which parallels the decrease in plasma oncotic pressure. Furthermore, the high interstitial compliance of the lung allows accumulation of a large volume of fluid into this space with no or minimal pressure increase, a phenomenon preventing water accumulation at alveolar level.[3] This physiological knowledge accords with clinical experience because even in most severe cases of NS symptomatic pulmonary edema is conspicuously absent.[4–6] Even though the effect of hypoalbuminemia on fluid exchanges in the lung has been extensively studied in animal models, the complexity and cost of the methodology required for the quantification of lung water, lung water content, and lung water dynamics in patients with NS have never been systematically studied in patients with NS. The issue is important because the favorable resetting of hemodynamic and oncotic forces in the lung in hypoalbuminemia may be insufficient to prevent lung edema when NS is associated with LV systolic dysfunction and heart failure,[7] which are not rare comorbidities in patients with chronic kidney disease (CKD).

Chest ultrasound (US) is a novel technique that allows estimation of lung water and relevant lung alterations in various clinical settings.[8] The rationale of this technique is that in the presence of excessive lung water, the US beam is reflected by thickened interlobular septa, thereby generating US bundles, which are an equivalent of Kerley-B lines in standard chest X-ray radiograms.[9] Lung US has a high diagnostic accuracy for pulmonary congestion in intensive care patients[10] and in stage G5D CKD patients.[11,12] Furthermore, lung water can be estimated noninvasively also

Table 1 | Demographic and clinical characteristics of patients enrolled into the study

	Active nephrotic syndrome (no. 42)	Patients seen only during partial or total remission ($n=5$)	Hemodialysis patients ($n=14$)
Age (years)	49 ± 20	47 ± 17	65 ± 16
Males, *n* and (%)	22 (52%)	3 (60%)	8 (57%)
BP (syst/diast) (mm Hg)	131 ± 20/75 ± 11	109 ± 10/65 ± 10	118 ± 21/60 ± 13
Heart rate (beats/min)	73 ± 13	65 ± 6	67 ± 6
eGFR (ml/min per 1.73 m^2)	76 (IR: 52–106)	82 (I.R. 50–98)	
Serum sodium (mmol/l)	136 ± 5	140 ± 2	140 ± 2
Proteinuria (g/24 h)	5 (IR: 3.3–6.1)	0.24 (IR: 0.19–0.39)	
Serum albumin (g/l)	2.2 ± 0.6	3.9 ± 0.1	3.8 ± 0.7
Serum cholesterol (mg/dl)	265 ± 74	170 ± 34	139 ± 38
Hb (g/dl)	12.1 ± 1.9	14.0 ± 0.9	10.7 ± 1.9
Edema			
No edema (*N* and %)	4 (10%)	5 (100%)	13 (93%)
Mild edema (*N* and %)	14 (33%)	–	1 (7%)
Moderate edema (*N* and %)	15 (36%)	–	–
Severe edema (*N* and %)	9 (21%)	–	–
Renal histology			
Minimal change	8 (19%)	2 (40%)	–
Focal glomerulosclerosis	8 (19%)	1 (20%)	–
Membranous nephropathy	17 (41%)	–	–
Proliferative glomerulonephritis	5 (12%)	2 (40%)	–
Amyloidosis	4 (9%)	–	–
History of cardiovascular events	5 (12%)	0	7 (50%)

Abbreviations: BP, blood pressure; diast, diastolic; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IR, interquartile range; syst, systolic.
Eleven of the patients with active nephrotic syndrome were also studied during the remission phase of the disease. Five patients were studied during the remission phase only.

by thoracic impedance, a technique that has been frequently applied in patients with heart failure.[12,13] We have therefore taken the opportunity offered by lung US to perform a dynamic study of lung water in patients with NS. Furthermore, we adopted thoracic impedentiometry as an independent confirmatory test of our findings based on lung US. The aim of this study was to test whether lung water is increased in an incident series of patients with full-blown NS as compared with well-matched healthy subjects and to study the dynamics of lung water in response to postural changes in these patients.

RESULTS

The demographic and clinical data of the patients enrolled in the study are shown in Table 1. All patients had a diagnosis based on renal histology.

Forty-two patients had full-blown, active NS. Twenty-six of these had still not received steroids or other immunosuppressant drugs, whereas the remaining 16 patients had already started steroid treatment ($n=8$) or other immune suppressants ($n=4$) or an association thereof ($n=4$). Twenty-nine patients were already being treated with angiotensin-converting enzyme inhibitors or angiotensin II blockers or a combination of these drugs and five were on calcium-channel blockers. Twenty-seven patients were being treated with furosemide (dose range: 25–375 mg per day). Among these patients, four (10%, all on furosemide) had no edema, whereas edema was of mild degree in 14 (33%), moderate in 15 (36%), and severe in 9 (21%). Eleven of these patients were studied twice, during the active phase of the disease and after partial or total remission. Five patients had had previous cardiovascular events (myocardial infarction in 1, transient ischemic attack in 1, angina in 1 and arrhythmia in 1, and peripheral vascular disease in 1). In these patients, left ventricular ejection fraction ranged from 57 to 68% (systolic dysfunction, ejection fraction $<50\%$)[14] and pulmonary pressure as estimated by echo-Doppler ranged from 19 to 35 mm Hg (pulmonary hypertension:estimated pulmonary pressure >40 mm Hg),[15] excluding systolic dysfunction and frank pulmonary hypertension.

Five patients, all edema free, were seen while in partial ($n=1$) or total remission only. Two of these patients were still receiving steroids. Three were being treated with angiotensin-converting enzyme inhibitors or angiotensin II blockers, one with a channel blocker and only one was on furosemide.

None of these patients complained of dyspnea before hospitalization and all remained dyspnea-free during hospitalization.

Among stage G5D CKD patients on hemodialysis, seven patients had a history of cardiovascular disease. In particular, one patient had had five cardiovascular events (myocardial infarction, stroke, transient ischemic attack, angina, and arrhythmia), one patient had two cardiovascular events (myocardial infarction and angina), and the remaining five