Whole-Lung Lavage: A Successful Treatment for Restoring Acinar Ventilation Distribution in Primary Acquired Pulmonary Alveolar Proteinosis

E. Vanderhelst^a S. Hanon^a S. Verbanck^a D. Schuermans^a K. Wissing^b
F. Bonella^c W. Vincken^a

^aRespiratory Division and ^bDepartment of Nephrology, University Hospital Brussels, Brussels, Belgium;

^cAbteilung Pneumologie, Ruhrlandklinik, Essen, Germany

Established Facts

- Whole-lung lavage is the common interventional treatment for pulmonary alveolar proteinosis. Standard follow-up methods include lung function parameters and radiological exams.

Novel Insights

- In addition to the standard tests, we used a state-of-the-art analysis of the multiple-breath nitrogen washout test, yielding the indices S_{cond} and S_{acin} as measures of ventilation heterogeneity at the level of the conductive and acinar air spaces, respectively. These parameters showed markedly abnormal acinar ventilation distribution at baseline, which returned to within the limits of normal immediately after lavage.

Key Words

Ventilation distribution · Pulmonary alveolar proteinosis · Whole-lung lavage

Abstract

A 51-year-old active smoker with primary acquired pulmonary alveolar proteinosis (PAP) diagnosed by biopsy and anti-GM-CSF antibodies was treated safely with whole-lung lavage (WLL). This resulted in a rapid improvement of symptoms and arterial blood oxygenation, but not of standard lung function parameters. However, we also performed the multiple-breath nitrogen washout (MBW) test to determine

the lung clearance index (LCI) as well as indices of acinar ventilation heterogeneity (S_{acin}) and conductive ventilation heterogeneity (S_{cond}). At baseline, a distinct abnormality was seen for S_{acin} and LCI, while S_{cond} was at the upper limit of normal for this subject. S_{acin} , in particular, was in excess of the S_{acin} abnormality corresponding to a 20-pack-year smoking history. Immediately after WLL, S_{acin} and S_{cond} both fell to within a normal range while LCI also decreased but remained abnormal. The S_{acin} decrease was much greater than the S_{cond} decrease, which was to be expected after 1 week of smoking cessation at the hospital (smoking was resumed after release from hospital). A follow-up visit 7 weeks after WLL revealed a spectacular improvement on CT scan and im-

provements in standard lung function. Another follow-up visit 14 weeks after WLL showed further improvements in standard lung function, and both S_{acin} and S_{cond} remained well within the normal range, and LCI was above the upper limit of normal. We conclude that in this patient, removal of excess surfactant by WLL resulted in a restored ventilation distribution in most of the distal air spaces.

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Introduction

Pulmonary alveolar proteinosis (PAP) is an uncommon disease characterized by the accumulation of PAS-positive lipoproteinaceous material in the distal air spaces with preserved alveolar architecture [1].

We present a case of primary acquired PAP in a patient, known to have end-stage renal failure and factor V Leiden deficiency, successfully treated with whole-lung lavage (WLL). The outcome was quantified with lung function tests, including a multiple breath washout (MBW) to study ventilation distribution [2]. In the adult human lung, this test distinguishes between ventilation heterogeneity in the conductive lung zone (S_{cond} ; induced by purely convective gas transport) and ventilation heterogeneity in the acinar lung zone (S_{acin} ; induced by diffusion-convection interaction beyond the acinar entrance).

Case Report

A 51-year-old male patient, on peritoneal dialysis because of end-stage renal failure due to biopsy-proven nephrosclerosis and known to have factor V Leiden deficiency, presented for a work-up prior to a kidney transplantation. He was an active smok-

er with a 20-pack-year smoking history. Laboratory tests showed renal failure and an elevated LDH level (556 U/l). Chest CT scan revealed ground-glass opacification with a thickening of intra-lobular and interlobular structures, in a crazy-paving pattern (fig. 1a) and with no signs of emphysema. Pulmonary function tests showed a mild restriction (TLC = 79% predicted), but neither obstruction (FEV₁/FVC 78%) nor air-trapping (FVC = 98% pred.) (table 1). Diffusing capacity was reduced [TLCO adjusted for hemoglobin (Hb_{adj}) = 57% pred.; Hb_{adj} = 13.3 g/dl]. VATS biopsy revealed preserved alveolar architecture with accumulation of lipoproteinaceous material in the air spaces (fig. 2). Anti-GM-CSF antibodies were identified in a referral lab (40 µg/ml, n < 10 µg/ml), confirming the diagnosis of primary acquired PAP. Given the high rate of spontaneous remission in PAP and because the patient was asymptomatic, we decided not to start any treatment at the time of diagnosis.

One year after establishing the PAP diagnosis, the patient presented with progressive dyspnoea. He was an active smoker at the time. His LDH level was 841 U/l and chest CT revealed more pronounced reticulonodular opacities. On pulmonary function tests, both ventilatory restriction and diffusion impairment had worsened [TLC = 62% pred.; TLCO (Hb_{adj}) = 39% pred.]. Arterial oxygen saturation was 86%. From figure 3, it can be inferred that the most marked degree of abnormality in ventilation heterogeneity was observed for most of the distal air spaces (S_{acin} = 184% pred.) as opposed to that in the conductive air spaces (S_{cond} was at the level of its upper limit of normal for a 52-year-old never-smoker). The predicted normal S_{acin} , S_{cond} and LCI values and limits of normal were based on a local cohort of 120 never-smokers (50% males) evenly distributed across the age range 25–65 years [3].

Because of the progression of the disease, we decided to perform a WLL, using a double-lumen endotracheal tube. Twenty-one 1-liter aliquots of normal saline (warmed to body temperature) were used for the left lung. The initial effluent was very milky in appearance and became progressively less opaque. The weight gain of the patient was limited and he did not need ultrafiltration. Three days after the first procedure, WLL of the right lung was performed using a total of 17 liters of normal saline. No bleeding complications occurred.

Three days after WLL, standard lung function parameters had not yet changed [TLC = 61% pred., TLCO (Hb_{adj}) = 38% pred.],

Fig. 1. CT scanning of the chest before (a) and after (b) WLL.

Color version available online

Fig. 2. VATS biopsy shows preserved alveolar architecture with accumulation of lipoproteinaceous material in the air spaces.

Table 1. Lung function values at diagnosis and up to 14 weeks post whole lung lavage

	PAP diagnosis	Pre-WLL	1–3 Days ^b post-WLL	7 Weeks post-WLL	14 Weeks post-WLL
PaO ₂ , mm Hg	92	64	90		
SaO ₂ , %	94	86	94	98	98
LDH, U/l	556	841	972	575	
FEV ₁ , % pred.	95	71	70	75	86
FEV ₁ , liters	3.63	2.69	2.63	2.83	3.24
FVC, % pred.	98	66	66	73	85
FEV ₁ /FVC, %	78	86	84	83	81
TLC, % pred.	79	62	61	75	79
TLC, liters	5.82	4.59	4.49	5.55	5.80
FRC, % pred.	68	72	69	74	77
FRC, liters	2.45	2.60	2.49	2.69	2.80
TLCO, % pred.	57	39	38	56	65
S _{cond} ^a		0.056	0.016	0.029	0.042
S _{acin} ^a		0.20	0.08	0.11	0.12
LCI ^a		7.45	7.10	6.90	7.20

^a Predicted values for a 52-year-old male never-smoker: S_{cond} = 0.036/liter, S_{acin} = 0.110/liter and LCI = 6.43.

^b LDH was measured on day 1 after the WLL and all other parameters were measured on day 3 after WLL.

while S_{acin} and S_{cond} had already decreased, by 60 and 29% of respective baseline values in this patient, to within the normal range. The PaO₂ and oxygen saturation had also returned to normal immediately after WLL. Nine days after WLL, the patient was discharged from the hospital, no longer in need of any oxygen supplements. While he was subject to the smoking ban within the hospital, he returned to being an active smoker after hospital discharge.

Seven weeks later the patient presented for follow-up. He had not experienced any respiratory symptoms, and standard lung

function parameters showed an improvement [TLC = 75% pred., TLCO (Hb_{adj}) = 56% pred.]. While S_{acin} and S_{cond} had increased slightly, both values were still in the normal range and very close to the predicted values for this subject (table 1, fig. 3). Arterial oxygen saturation on room air was 98%. CT scan of the chest showed a spectacular decrease of the interstitial pattern (fig. 1b). After another 7 weeks, standard lung function was seen to be further improved, while S_{acin} remained stable and only S_{cond} continued to slightly increase, nevertheless remaining within the normal range.

Fig. 3. **a** S_{acin} at time of PAP diagnosis and at 3 time points during a 14-week follow-up; the grey area delimits the zone of normality (upper and lower limit of normal for a male subject of the same age based on a local database). **b** S_{cond} during a 14-week follow-up. **c** LCI during a 14-week follow-up. In **b** and **c** the representation is the same as in **a**.

Discussion

PAP is an uncommon disease characterized by the accumulation of PAS-positive lipoproteinaceous material in the distal air spaces, with negligible inflammation [1]. This case of primary acquired PAP in a patient with end-stage renal failure was safely treated with WLL.

First performed in 1960, the success of WLL is presumed to be due to the physical removal of the excess surfactant, allowing for functional improvement. A review of 47 patients showed a favorable therapeutic response in PaO_2 , $P(A-a)O_2$ gradient, FEV_1 and TL_{CO} in 85% of the patients [1]. Signs of improvement are radiographic clearing, decreased LDH levels and increased

ventilation/perfusion matching. A review of 38 cases in Korea and of 21 in Italy showed consistent improvements in PaO_2 , $(A-a)O_2$ and TL_{CO} after WLL, while FVC and TLC responses were variable [4, 5]. In our patient, we saw an improvement of TLC, TL_{CO} and PaO_2 . The parameters for ventilation distribution, S_{acin} and S_{cond} , showed an early improvement at a time when standard lung function had not yet signaled any notable change.

Lung volumes (FRC and TLC) showed a delayed improvement and, in fact, remained low throughout the observation period. This could possibly be due to an engorgement of the lymphatic vessels after WLL and to the presence of some residual fluid in the alveolar spaces affecting lung compliance. Abnormal compliance of rela-

tively large lung units may also be at the basis of the relatively high LCI values throughout the study, yet LCI could also be enhanced due to irreversible smoking-induced small airway dysfunction. Since the quantitative effect of smoking history on LCI has not been documented and it is intrinsically impossible to attribute LCI to large or small lung units, we cannot speculate on the likelihood of either explanation.

The difficulty with establishing abnormality of small airway function in this patient was that he was an active smoker. Based on a previous MBW study in smokers [2], typical S_{acin} and S_{cond} values in a smoker with 20 pack-years amount to 125 and 132% of their normal predicted value, respectively. So for this particular patient, his personal best values for S_{acin} and S_{cond} could be estimated as 0.138/liter and 0.048/liter respectively, i.e. close to the S_{acin} and S_{cond} value obtained after 14 weeks (fig. 3). We cannot exclude the possibility that part of the initial S_{acin} and S_{cond} decrease may have been due to an episode of

reduced smoking during the hospital stay. However, the expected effect of 1 week of complete smoking cessation on S_{acin} and S_{cond} is 16 and 13%, respectively [6], which is considerably smaller than the 60 and 29% decrease seen in figure 3a and b. While it could be argued that the increasing trend of S_{cond} between 7 and 14 weeks was still in part associated with resumed smoking (after only 1 week of smoking cessation), the stabilization of S_{acin} over the same time interval (fig. 3a) suggests a sustained recovery of ventilation distribution in most of the distal airway spaces of this patient.

There are no demographic or disease-related predictors of successful response to WLL [1] and approximately 15% of the patients will relapse. The observed abnormality of ventilation heterogeneity in most of the distal lung spaces and its marked response after WLL suggest that the MBW test may be a helpful additional noninvasive tool for monitoring PAP patients during follow-up in various intervention strategies.

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