SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2022; 39 (2); e2022017 DOI: 10.36141/svdld.v39i2.12884

How We Do It: Whole Lung Lavage

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Abstract. Pulmonary alveolar proteinosis (PAP) is a rare pulmonary disorder characterized by the accumulation of surfactant in the alveolar spaces resulting in hypoxemic respiratory failure. Whole lung lavage (WLL), the preferred treatment for PAP, physically removes the lipoproteinaceous material from the alveolar spaces. Since its initial description in 1963, the WLL procedure has undergone various modifications. However, the procedure has not been standardized yet. After securing a double lumen endotracheal tube, we perform WLL under general anesthesia. One lung is ventilated, while the other is lavaged using one-liter aliquots of prewarmed saline. We use gravity-assisted drainage of the lavaged lung after each cycle till the milky white and opaque fluid becomes clear (usually 15-20 cycles). Herein, we describe the step-by-step procedure, precautions, and monitoring of WLL. We also provide videos demonstrating one-lung ventilation and bronchoscopic confirmation of lung isolation.

Key words: Pulmonary alveolar proteinosis; bronchoscopy; bronchoalveolar lavage; interstitial lung disease: diffuse parenchymal lung disease

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disorder characterized by surfactant accumulation in the alveolar spaces and terminal airways, resulting in hypoxemic respiratory failure (1). Since the initial description of PAP in 1958 (2), several treatment options were explored, including antibiotics, corticosteroids, dissolution by potassium iodide, streptokinase, trypsin, heparin, acetylcysteine, and others. Whole lung lavage (WLL) was described in 1963 and is currently the preferred treatment of primary PAP with respiratory failure (3). WLL physically removes the lipo-proteinaceous material from alveoli, thereby reversing the physiological defects.

Each institution has a different method for performing WLL (4, 5), and the procedure has not been standardized. Various modifications of WLL have been described (5-8). Several procedural aspects of WLL are tentative, including the number of sessions required, the interval between the two sessions, choice of the initial lung to be lavaged, performing lobar or whole lung lavage, patient position during the procedure, use of percussion device, chest physiotherapy, the amount of fluid used, the timing of extubation following lavage, and others (5). Herein, we provide a step-by-step description of WLL performed at our center.

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When to do WLL?

The initial steps are to confirm the diagnosis of PAP (Figure 1A and 1B) either on histopathology or bronchoalveolar lavage and exclude infective causes. We confirm the autoimmune basis for PAP using antibodies against granulocyte monocyte colony-stimulating factor (GM-CSF). We consider WLL if there is: (1) resting hypoxemia (PaO2 <65 mmHg), or (2) alveolar-arterial oxygen gradient of ≥40 mmHg, (3) severe symptoms, serially declining lung function, or exercise-induced desaturation (9-11).

While spirometry and imaging may identify a severe disease, we do not perform WLL solely on this basis. Elevated serum lactate dehydrogenase (LDH), surfactant protein D (SPD), or Krebs von Lundgren factor 6 (KL-6) may also indicate severity, but they are non-specific and not widely available (12, 13). Thus, treatment decisions should be individualized based on various factors including, symptoms (e.g. dyspnea severity score), limitation of daily activities, disease (clinical, radiological or spirometry) progression over time, exercise induced desaturation, the availability of alternative treatment options and patient preference.

When not to do?

The absolute contraindications are the lack of informed consent and hemodynamic instability. Active bacterial infections and significant lung fibrosis can be associated with decreased lung reserve and may also be regarded as absolute contraindications for WLL. Bleeding diathesis, heart failure, and recent myocardial infarction (<4 weeks) are relative contraindications.

How to do the procedure?

Step 1. Ensuring facilities and personnel: We perform WLL in the operating room (OR) under general anesthesia (GA). Our team includes cardiac anesthesiologists, pulmonologists, nurses, cardiothoracic surgeons, perfusionists, and bronchoscopy technicians. The required instruments include a double-lumen endotracheal tube (DLT; ≥26 F size was preferred in a survey (5)), flexible bronchoscope (FB, compatible with DLT), equipment for GA, blood warmer, cardiopulmonary bypass (CPB) machine, and hemodynamic monitor. The operating table should allow manipulation for Trendelenburg and reverse-Trendelenburg position. At our OR, we use a temperature control mechanism to optimize the operating table and mattress temperature.

Step 2. Intubation with DLT and confirmation of position: We intubate our patients with a left-sided DLT under GA (Figure 2), and confirm the position using FB (outer diameter, 2.8 mm; working channel, 1.2 mm). While either a right or left-sided DLT can be used, we prefer a left-sided DLT owing

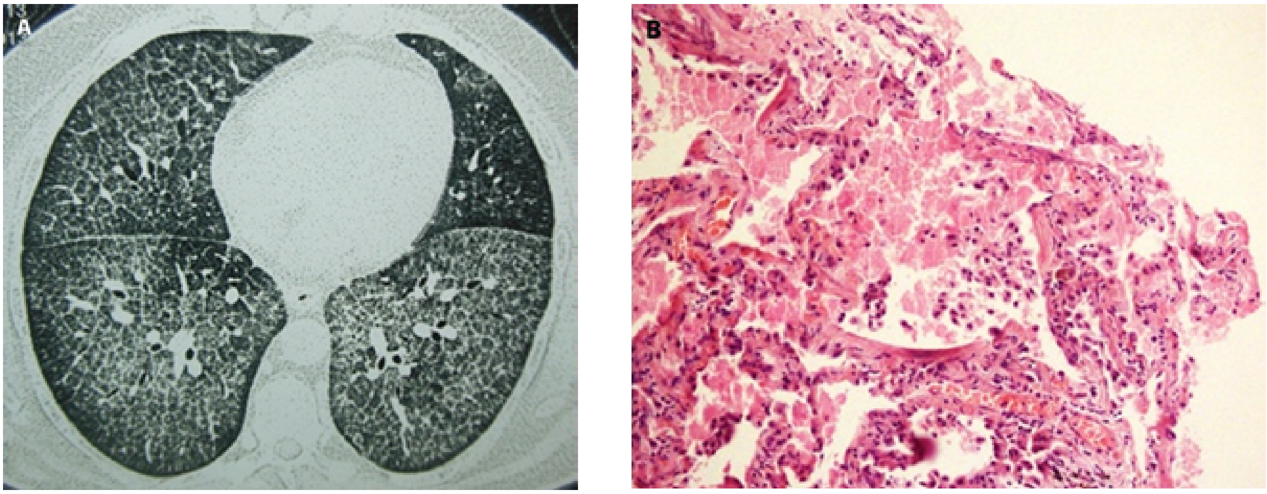

Figure 1. High resolution computed tomography of a patient with pulmonary alveolar proteinosis (left panel), showing diffuse ground-glass opacities, smooth interlobular and intralobular septal thickening ("crazy-paving" appearance), and the right panel showing intra-alveolar accumulation of eosinophilic material in the transbronchial lung biopsy specimen. The intra-alveolar material was strongly positive on periodic acid-Schiff staining (not shown here).

Figure 2. Left-sided double-lumen tube (DLT) with bronchial (blue) and tracheal limb (white), before (left panel), and after endotracheal intubation (right panel). Image B shows the bronchoscope inside the bronchial limb of the left-sided DLT.

to the longer left main bronchus. Also, a right-sided DLT may occlude the opening of the right upper lobe bronchus. We reserve right-sided DLT for situations where a left-sided DLT cannot be used due to anatomical reasons. The bronchial and the tracheal cuffs should be inflated to isolate the lungs. Apart from bronchoscopy, lung isolation can additionally be checked by ventilating one lung and observing for air leak (after submersing the external opening of the endotracheal tube lumen from the non-ventilated lung into saline). The absence of air bubbles from the non-ventilated lung confirms appropriate lung isolation (14). While a negative saline immersion maneuver suggests lung isolation, the bronchial cuff may still lie at the opening of the main bronchi (Figure 3). During WLL, the bronchial cuff may displace into the trachea, thereby compromising lung isolation. Hence, we always confirm the DLT position and lung isolation using FB (Video 1 - see Supplementary file online). The ideal position would be to visualize the tracheal carina and the inflated bronchial cuff lying at least 2 cm beyond the carina in the left main bronchus.

Step 3. Confirming successful one-lung ventilation (OLV): Once the position of DLT is confirmed, OLV is achieved by clamping the limb of the DLT lumen, which ventilates the lung to be lavaged (Video 2 - see Supplementary file online). For instance, in a left-sided DLT, clamping the tracheal lumen ventilates the left lung and vice versa. We perform OLV for about 5-10 minutes (before starting WLL) to ensure adequate oxygenation and estimate the patient's respiratory reserve. Meanwhile, a cardiothoracic surgeon secures a femoral arterial and venous access to establish CPB, which would be used if the need arises for extracorporeal oxygenation. A partial cardiopulmonary bypass may be useful in patients experiencing dangerous or refractory hypoxemia (15, 16) or those who fail to tolerate OLV (decline in oxygen saturation or rise in end-tidal CO_2 concentration resulting in respiratory acidosis). While we secure access for cardiopulmonary bypass, we use them only in selected cases of severe hypoxemia or when lung isolation is not possible (7, 17, 18). Most patients, especially those undergoing lavage of one lung, do not require extracorporeal oxygenation and

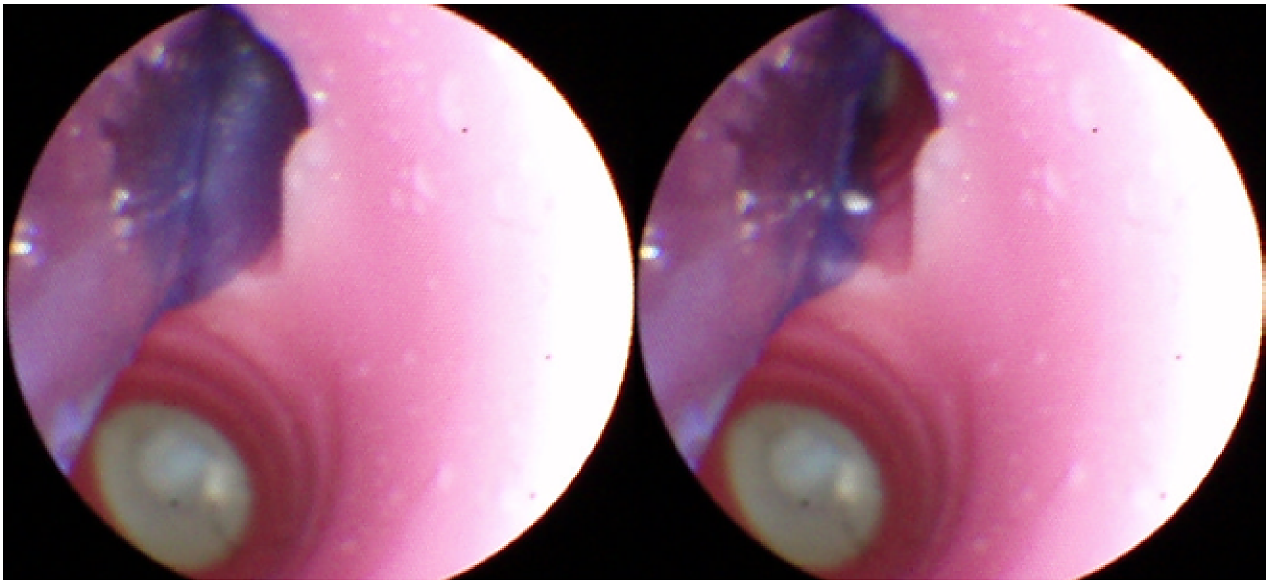

Figure 3. Confirmation of the double-lumen tube (DLT) and cuff using a flexible bronchoscope (FB). FB inserted through the tracheal limb (white) of the left-sided DLT shows the cuff (inflated [left panel] and deflated cuff [right panel]) of the bronchial limb to be present at the opening of the left main bronchus (LMB). The cuff should ideally be placed 1-2 cm (beyond the carina) into the LMB.

worldwide most centers do not follow this practice (4, 5, 19).

Step 4. Lavage procedure: We perform WLL of both the lungs at the same sitting, owing to technical and logistic reasons (longer waiting time for OR, financial constraints, and others). We perform lavage of the more diseased lung, followed immediately by the less affected one. Bilateral lung lavage in the same session is associated with a longer procedure time, and patient tolerance must be assessed before WLL. Transient metabolic acidosis (20), prolonged mechanical ventilation, and complications related to anesthesia may be higher in patients undergoing bilateral lung lavage. While there are no trials comparing lung lavage in the same session versus two sessions, most centers prefer performing WLL in two separate sessions, usually spaced three weeks apart (range 1 day to 6-12 weeks) (5). Pre-warmed (37^0 C) sterile bags of normal saline are used for the lavage procedure to avoid inadvertent hypothermia. A closed circuit is established, as shown in Figure 4. The three wide bore IV tubes with stopcock are connected using a Y adapter to complete the circuit to separate lavage and drainage limbs (Figure 4). The vertical limb is used for the inflow of saline. The lavage limb is attached to DLT, and the drainage limb is directed into collecting jars.

While instilling saline through the DLT, the lung to be lavaged is made dependent. The patient is placed in the reverse-Trendelenburg position to establish a free saline flow (gravity-dependent). The patient positioning also varies at several centers. While most employ a supine position as described here, a lateral decubitus position has also been used by some (5, 21). In a lateral decubitus position, the dependent lung is ventilated, and the non-dependent lung is washed. The lateral decubitus position allows easy access for chest percussion and probably provides a favorable ventilation-perfusion ratio (19, 21).

We usually instill 1000 mL saline aliquots in one cycle (except for the first cycle, where we use >1000 mL to fill the functional residual capacity [FRC] of the lung). Some centers determine the volume of fluid instilled based on the pre-procedure FRC (3/5 and 2/5 of FRC for the right and left lung, respectively)(20) or total lung capacity (750 mL for lavage if TLC < 2.5L) (22). We avoid squeezing the bags to pump in more fluid, as it increases the hydrostatic pressure and possibly leads to pulmonary edema and pleural effusion. Further, the excess pressure applied during squeezing can compromise lung isolation, causing a fluid leak into the contralateral side. Once the saline stops flowing, we clamp the inflow part of the circuit and release the clamp on the outflow.

Figure 4. Closed circuit prepared for WLL along with bronchoscope. A Y-adapter connects the inflow and outflow tubes regulated by clamps to ensure lavage and drainage, respectively.

Further, we tilt the operating table to the Trendelenburg position, which facilitates gravity-aided drainage of the milky effluent that gets collected in the graduated glass bottles (Figure 5). Once the effluent stops, we clamp the outflow circuit and elevate the head end back to the reverse-Trendelenburg position.

The inflow and outflow cycles are repeated till the effluent becomes clear. We do not use percussion devices to facilitate outflow. We employ manual percussion if the effluent is less than the instilled fluid. Most centers routinely use chest percussion (either manually or using a device) to facilitate drainage of the proteinaceous material (5, 19, 23, 24). Notably a previous study demonstrated manual chest percussion to be superior to no percussion (25). Employing manual hyperinflation and intermittent chest compression (while instilling the first 500 mL of saline and when the last 500 mL of saline is being drained) has also been shown to improve the efficacy of WLL in a recent study (22). However, cautious use of manual hyperinflation and modified ventilation techniques is required since they may be associated with higher chances of barotrauma (4). The initial effluent is milky and tends to sediment on standing (Figure 5). We maintain a chart documenting the amount of inflow and outflow during each cycle (Table 1). Usually, 15-20 cycles are required to obtain a clear effluent. After the lung lavage is completed, excessive fluid is aspirated using FB and suction. Lavage of the second may be challenging since it depends on adequate ventilation of the recently

Figure 5. Milky effluent drained after whole lung lavage. Serial effluent collected in glass bottles from left to the right shows clearing of turbidity.

Table 1. Monitoring of instilled and drained fluid during the procedure

Cycle	Instilled volume (mL)	Drained volume (mL)	Retained volume (mL)	Cumulative balance (mL)	Remarks
1					
2					
3					
4					
5					
6					
7					
8….					
Total Volume					

lavaged lung (which is usually stiff and may have a poor compliance). Both the lungs are now ventilated for a few minutes, followed by OLV of the recently lavaged lung. Once oxygenation is ensured with OLV, the lavage is begun in the contralateral lung as described above. A typical WLL of both the lungs takes approximately 3-6 hours.

During each cycle, the volume of infused saline varies greatly, ranging from 80 mL for single lobe bronchial lavage (SLBL) to 1,650 mL for WLL, with an average of 800 ± 331 mL (5). The total lavage volume also varies widely among different centers (mean of 15.4 L, range 5 to 40 L), with most centers using less than 18 liters per lung (5). SLBL or therapeutic lavage using FB has been used as an alternative to WLL; however, data is insufficient to support their use (26-28). They may be helpful in patients who are too ill to undergo WLL (29) or specific situations(28) where WLL is not possible (e.g., technical difficulties in children), or when the facilities are not available (30-32).

Intraoperative monitoring: Pulse oximetry (SpO_2), capnography, electrocardiogram, temperature, invasive arterial blood pressure, and arterial blood gases are routinely monitored. In patients undergoing therapeutic lavage, hemodynamic changes in the pulmonary circulation are known to occur (33, 34). Whether the routine use of invasive (pulmonary arterial catheters) or non-invasive monitoring of pulmonary arterial pressures improves the outcome of WLL is not known. At our center, we sometimes perform transesophageal echocardiography (TEE) to assess the functional status of both the ventricles and pulmonary artery pressure, especially if there is intraoperative hypoxemia. The use of transthoracic ultrasonography to look for serial improvement in B-lines and monitoring for the development of pleural effusion has also been described (35, 36). The use of echocardiography or ultrasonography is not essential while performing WLL and has not been described in the global survey of practices (5, 19).

When to stop the procedure?

We conclude the procedure once the lavage is successfully completed on both sides or when there is a complication such as pneumothorax, massive pleural effusion, hemodynamic instability, and others. We terminate the procedure based on the visual appearance of the fluid, like several other centers (5). Objective criteria for determining the efficacy of WLL such as estimation of the protein content (centrifuge at 1,720 g for 10 minutes and measurement of protein content in the supernatant), or spectrophotometric evaluation of the effluent fluid is also used by a few centers (22, 37). Recent studies have measured protein content and shown that nearly 91% of the total protein amount is removed after the third cycle of lavage (each cycle comprises 3 washes of 1L each) (22). Rapid turbidity assessment by measuring the effluent fluid's optical density (OD) using a spectrophotometer at 405 nm wavelength is simple and found to correlate with protein content estimation (38). An OD value of < 0.4 is considered to indicate the success of WLL (38).

How to monitor the patient in the post-operative period?

Once the procedure is completed, we resume double lung ventilation. After confirming oxygenation and ventilation by blood gas analysis, we exchange the DLT with a single lumen endotracheal tube. We continue post-operative care in our respiratory intensive care unit (ICU). We routinely perform chest radiograph to rule out complications (pleural effusion, pneumothorax, and others). Estimating the post-procedure hemoglobin and hematocrit can suggest intravascular volume expansion. Several centers performing single lung lavage extubate the patients soon after the procedure and proceed with lavage of the contralateral lung after an observation period of 24-48 hours (4, 35).

Since we perform bilateral lung lavage in the same session, we avoid immediate extubation. The patient is monitored closely and ventilated in the intensive care unit (ICU) postoperatively. We extubate the patients within 24 hours (usually 1-3 days) of the procedure. On the contrary, experience from other centers suggest that successful extubation is usually possible within few hours to less than 24 hours (mean time to extubation 5 hours)(5), even after bilateral lung lavage (20). Such patients are usually managed in the post-anesthesia care unit and seldom require ICU admission (4). The ICU stay may be required only in a few patients due to complications such as prolonged hypoxemia, pneumothorax, pneumonia, pleural effusion, and others (19, 39). The complication rate at our center is <10% (unpublished data over the last five years), the most common being hypoxemia (resolving over 24 hours), followed by pneumothorax.

How to follow-up the patients undergoing WLL?

We assess our patients' symptoms profile, oxygenation status, and exercise capacity (using a six-minute walk test), at discharge from the hospital. Additionally, we measure the lung functions and perform a computed tomography during the first visit (usually between 1-4 weeks after discharge). If there is no clinical deterioration, hypoxemia, or exercise-induced desaturation, we observe the patients with six-monthly spirometry and clinical assessment (including oximetry, and exercise testing). We then repeat a computed tomography annually or as and when required. The global survey of practices highlighted the variation in practice, with some centers routinely performing CT scans at eight months, biomarkers (including serum LDH, SPA, SPD, KL-6, and GM-CSF autoantibody levels) or quality of life questionnaires during follow-up (5).

The duration of benefit following WLL is variable (5, 40), with one series reporting that nearly 70% of their subjects experienced no recurrence following WLL (21). Data from two studies suggest that a repeat WLL procedure was required in approximately one-third of the subjects with PAP (5, 19). Usually two or three procedures were required in these patients during follow-up with a mean interval of eight months (range, one week to several years) after the first WLL (5).

Discussion

WLL improves the symptoms (dyspnea and improved exercise tolerance), lung function (85% of cases show improvement in lung function), and even provides long-lasting benefits in a few patients (41). The 5-year survival is higher in patients undergoing WLL than those without (94 $\pm$ 2% vs. 85 $\pm$ 5%) (41).

A uniform protocol for performing WLL is not available. Due to the rarity of the disease, conducting a randomized trial or evaluating the efficacy of the procedural details has not been possible. Last decade has witnessed the publication of experiences from several centers, and multiple procedural modifications have been described (5, 19, 22, 38). Herein we have described one such protocol of performing bilateral WLL, and there may be significant differences worldwide. More prospective multicenter, multinational studies are required to standardize the procedure and evaluate the efficacy of various approaches. As the procedure can have potential complications, we suggest that WLL be performed in experienced centers using a standardized protocol and a skilled team to ensure safety. More prospective studies and standardization of the procedure are required.

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Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Legends to videos (see the Supplementary file online)

Video 1: Bronchoscopic confirmation of the double lumen position in a mannequin. After the bronchoscope is inserted through the tracheal limb, we can observe the carina and the bronchial limb entering the left main bronchus. Here the cuff of the bronchial limb is seen just beyond the carina. Preferably, the cuff should lie at least 1-2 cm beyond the opening of the left main bronchus (which could not be demonstrated in the mannequin) to avoid inadvertent displacement of the tube during the lavage. Displacement of the cuff or poorly inflated cuff may compromise lung isolation while performing the lavage.

Video 2: Video demonstrating right lung ventilation in a mannequin after placing a left-sided double-lumen tube (DLT). Note the clamp applied on the bronchial limb (blue; left side), and the ventilation is performed through the tracheal limb (right side) of the DLT.

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