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Imaging Assessment of Partial Liquid Ventilation in Bronchopulmonary Dysplasia

Andrew J. Degnan, MD, MPhil[a,b,*], Xiaowei Zhu, MS[a], Colleen Flowers, RDMS[a], William W. Fox, MD[b,c], Huayan Zhang, MD[b,c], David Saul, MD[a,b]

[a] Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA
[b] Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
[c] Division of Neonatology and Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA

Partial liquid ventilation is proposed as an alternative ventilation strategy to reduce surface tension, increase alveolar recruitment, and decrease inflammation. Studied in acute respiratory distress and other indications, liquid ventilation is being revisited for infants with bronchopulmonary dysplasia. Perfluorooctyl bromide used for liquid ventilation is radiopaque, allowing radiographic visualization of lung liquid ventilation patterns that may provide additional insight into pulmonary pathophysiology. Current protocols utilize reduced liquid dosing, resulting in unique imaging features. We discuss optimal radiographic technique and report initial ultrasound evaluation results. With renewed interest in partial liquid ventilation, it may be helpful for pediatric radiologists to familiarize themselves with the clinical use and radiographic appearance of liquid ventilation material.

Introduction

Liquid ventilation was conceptualized in the 1960s using liquid capable of carrying oxygen and carbon dioxide to participate in gas exchange within alveoli.[1] Liquid ventilation agents such as perfluorooctyl bromide (PFOB) are inert volatile liquids denser than water, low in surface tension, and high in oxygen solubility.[2] In partial liquid ventilation (PLV), PFOB is administered via endotracheal tube and gas ventilation is also applied with a conventional mechanical ventilator.[2] Bromide in PFOB allows radiographic visualization and fluorine enables visualization by fluorine (^{19}F) MRI, previously inciting consideration as an MRI contrast agent.[3,4]

Experimental models showed improved compliance, oxygenation, and alveolar recruitment culminating in application of PLV to pediatric and adult clinical trials.[1] Despite some initial successes in infants with respiratory illnesses, industry support for PFOB withdrew after trials of acute respiratory distress syndrome failed to show benefit. A systematic review concluded that further study of PLV is needed to determine its clinical effectivness.[1,5] Two decades after initial trials, PLV is being revisited to potentially ameliorate bronchopulmonary dysplasia (BPD), a common long-term complication of prematurity, due to anti-inflammatory benefits of PFOB.[2,6] Others have proposed reinstating PLV for congenital diaphragmatic hernia.[7] The current application of PLV employs lower PFOB doses than earlier trials, which often filled the lungs to the level of the endotracheal tube, and this new approach poses specific challenges to assessing evaporation in lower weight-based dosing of PFOB.[8]

Assessment of ventilation patterns and evaporation of PFOB for repeat dosing and detection of any potential complication such as pleural leak are the main objectives of imaging in PLV.[9] An understanding of imaging approaches to evaluate PLV will be invaluable in better understanding altered lung physiology in BPD and PLV treatment considerations.

Methods

Study Participants

Preterm infants born earlier than 32 weeks gestational age with severe BPD (according to NIH criteria) enrolled in a prospective IRB-approved, FDA-regulated safety and feasibility randomized controlled trial of PLV using PFOB (up to 20 mL/kg) for up to 5 days in BPD (NCT03041740). Abbreviated inclusion criteria are: (1) under 6 months old, corrected for gestational age; (2) on conventional mechanical ventilation; (3) off steroids. Exclusion criteria are: (1) mechanical ventilation for acute disease; (2) severe pulmonary hypertension; (3) severe congenital heart disease or other major congenital anomalies; and (4) pneumothorax or active pulmonary hemorrhage. Medical records, treatment regimen and imaging studies were examined for determination of optimal imaging assessment of PLV.

Abbreviations: BPD, bronchopulmonary dysplasia; PFOB, perfluorooctyl bromide; PLV, partial liquid ventilation

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*Reprint requests: Andrew J. Degnan, MD, MPhil, Department of Radiology, Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, 3NW29, Philadelphia, PA 19104, USA.

E-mail address: degnana@email.chop.edu (A.J. Degnan).

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Radiographic Technique

Clinical portable frontal and cross-table lateral chest radiographs were obtained throughout the trial to assess filling and distribution of liquid ventilation material, in accordance with prior evidence showing dependent distribution of PFOB.[2] Low kV (kV = 40) technique was chosen over conventional standard kV (kV = 58-60) technique for frontal radiographs on the basis of the low k-edge of bromine (13.483 keV) present in PFOB that confers its radiopaque density. Phantom radiographic studies performed at this institution using an anthropomorphic newborn dosimetry model with PFOB material in the phantom lung cavity showed greater contrast on the basis of visual inspection between PFOB material and background simulated lung parenchyma and soft tissue (unpublished data). Standard kV radiography (kV = 62) was performed for lateral views due to poor penetration with greater soft tissue thickness in the lateral plane.

Sonographic Technique

While tested as an intravenous sonographic contrast agent,[3] PFOB has never been evaluated using chest ultrasound in humans, to our knowledge. Phantom studies using a sponge to simulate lung in PFOB bath and clinical patients were imaged with grayscale ultrasound (GE LOGIQ E9, 8 MHz transducer). Clinical chest ultrasound was performed using grayscale ultrasound (GE LOGIQ E9, 8 MHz transducer) in conjunction by both a board-certified pediatric radiologist (DS) and sonographer with greater than 10 years experience in chest ultrasound examinations. Chest ultrasound was performed with the patient in the supine and semilateral decubitus positions due to support devices.

Results

Included in this initial report are a total of 6 infants (4 male and 2 female) with severe BPD requiring mechanical ventilation from birth to PLV initiation at 43-49 weeks corrected gestational age.

Radiographic Assessment of Liquid Ventilation

Phantom evaluation of PFOB revealed low kV radiography to be optimal to improve contrast between PFOB and background lung and

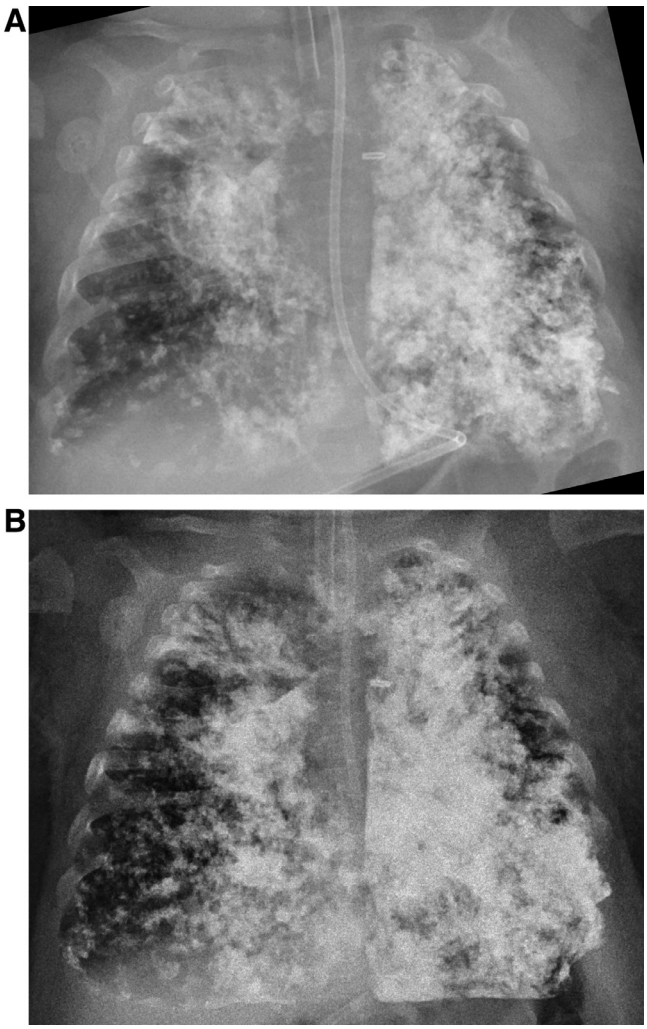

FIG 1. A 5-month-old, ex-24-week gestational age male with BPD on the PLV trial received radiographs using different kiloVo settings (A: 58 kV, 200 mA, 4 ms; B: 40 kV, 160 mA, 5 ms) at the same dosing of 10 mL/kg PFOB. Heterogeneous opacification of PFOB is demonstrated, more extensive in the left lung compared to the right, with a central predominance. The liquid ventilation material appears slightly more conspicuous on the lower kV radiograph, particularly at the edges of PFOB-filled regions (B). BPD, bronchopulmonary dysplasia; PFOB, perfluorooctyl bromide; PLV, partial liquid ventilation.

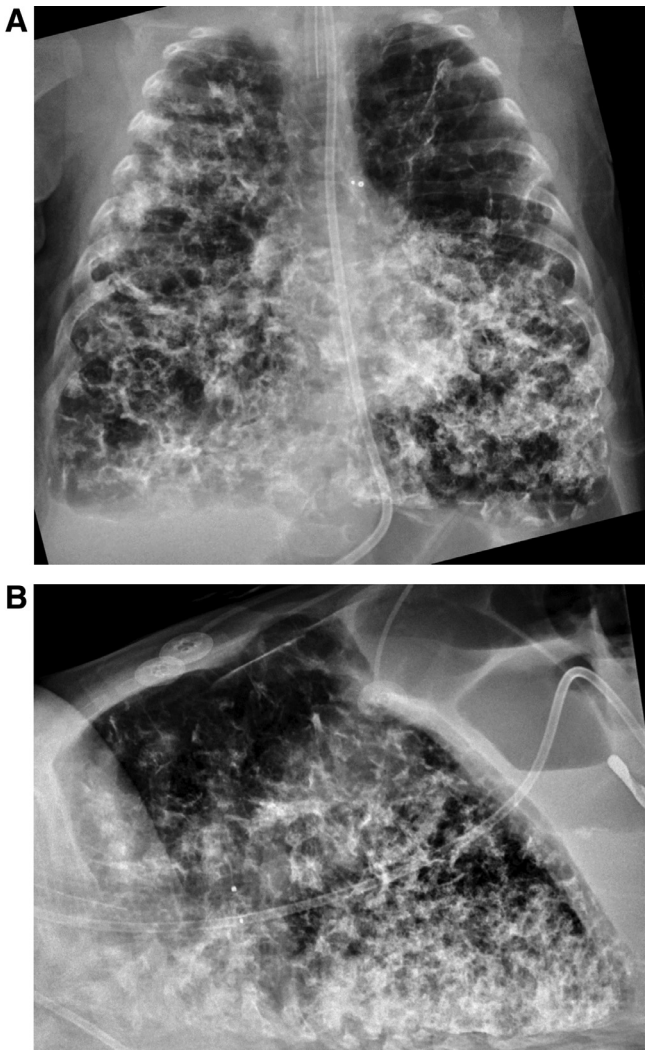

FIG 2. 4-month-old male, ex-25-week gestational age infant with bronchopulmonary dysplasia. Frontal (A) and cross-table lateral (B) chest radiographs following administration of 5 mL/kg PFOB show heterogeneous accumulation within the dependent lungs and substantially less opacification of the peripheral and anterior lungs. There is also absent filling within the left upper lobe that did not fill with additional dosing and was found to be related to left upper lobe bronchus narrowing by bronchoscopy. PFOB, perfluorooctyl bromide.

soft tissue. Clinical radiographs using low kV showed improved visualization of lower PFOB concentration, especially in the periphery (Fig 1). In general, lower dose PFOB yielded heterogeneous radiographic distribution.

Cross-table lateral radiography confirmed prior reports of dependent PLV accumulation (Fig 2).[2] PFOB first fills centrally in perihilar regions and dependently before extending more peripherally and in a posterior-anterior direction. At maximum weight-based dosing, there was nonfilling and decreased filling of segments with air-trapping or peripheral dilated airspaces. In one case, an area of lobar nonfilling corresponded with bronchoscopic findings of narrowing of the respective lobar bronchus. Other cases demonstrated abnormal distribution of PFOB with delayed evaporation from atelectatic lung segments seen on serial radiographs weeks after the end of the PLV protocol.

Sonographic Assessment of Liquid Ventilation

Ultrasound evaluation performed on a phantom consisted of a plastic bag containing PFOB with a small sponge immersed in the liquid ventilation material (Fig 3A). PFOB appears anechoic without any complexity, and appears indistinguishable from simple fluid. The sponge, despite being saturated with PFOB demonstrated an echogenic appearance, likely reflecting its internal architecture. It was expected that PFOB might be difficult to visualize sonographically in small alveoli with surrounding lung parenchyma and admixed with air from superimposed gas ventilation.

Clinical ultrasound of PLV patients was unable to discretely detect PFOB as anechoic fluid (Fig 3B). Lung parenchyma containing a greater quantity of PFOB compared with the contralateral lung in 1 patient demonstrated absence of A-lines, although findings are likely nonspecific given background parenchymal disease as expected in BPD. No patient had clear sonographic visualization of PFOB in a small subset of patients. None of the patients in this study had pleural leak or effusion.

Discussion

After losing favor in the late 1990s, liquid ventilation is experiencing renewed interest in BPD, prompting consideration of optimal imaging approaches. Ventilation patterns are uneven in this new clinical population of severe BPD patients and lower dose PLV. Understanding

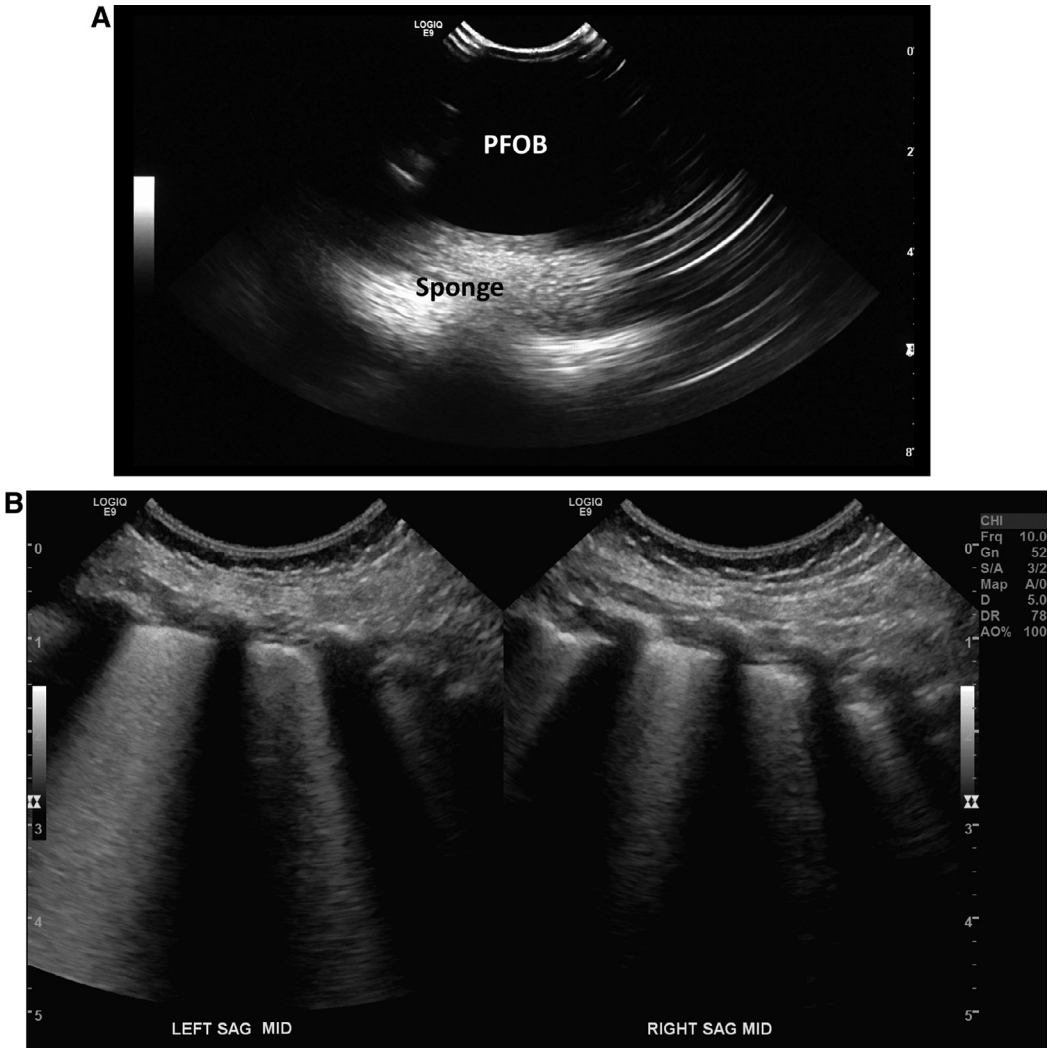

FIG 3. Ultrasound evaluation of liquid ventilation material (A) demonstrated an anechoic appearance, whereas a sponge immersed in PFOB demonstrated persistent hyperechogenicity. Chest ultrasound performed in a 5-month-old, ex-24-week GA male (B) (same patient as shown in Fig 1) demonstrated no hypoechoic material to directly visualize PFOB. Lung parenchyma demonstrated absence of expected A-lines and diffuse hyperechogenicity bilaterally but greater on the left side, which had higher PFOB accumulation on radiographs (Fig 1). These findings may also represent underlying parenchymal disease, which is expected in BPD and potentially complicates sonographic assessment of liquid ventilation. BPD, bronchopulmonary dysplasia; PFOB, perfluorooctyl bromide.

and optimizing radiographic assessment of PLV is helpful for clinicians to assess distribution to adjust dose and ventilation parameters.

Our findings highlight the heterogeneous radiographic appearance in severe BPD patients. Radiographic assessment of PFOB demonstrated a predominantly central and dependent lung distribution in these patients, emphasizing the importance of lateral chest radiography to estimate the amount of lung filling. Information regarding relative lung filling in PLV is used by neonatologists to determine whether additional PFOB should be added and ventilation parameters changed; therefore, serial radiography is clinically useful in guiding PLV management.

In addition, this initial investigation noted the importance of identifying nonfilled segments that may suggest bronchial obstruction or narrowing, as seen in one patient in this small sample. Bronchial atresia or mucus plugging may prevent the entrance of PFOB during the filling phase of PLV. In similar fashion, atelectasis or airway obstruction may also prevent prompt evaporation of PFOB in some patients with retention of PFOB in atelectatic lung on follow-up radiographs. This additional information afforded by liquid ventilation patterns on chest radiographs may prompt further investigation such as bronchoscopy or CT to identify findings otherwise not apparent on conventional radiographs in the absence of PLV.

Our initial experience provides support for the use of low kV radiography to improve visualization of the PFOB liquid ventilation agent. Lower kV radiography provides suitable X-ray penetration for frontal infant chest examinations but may not be useful in older populations and lateral views. Both phantom and clinical radiographs of liquid ventilation material supported the use of a lower kV to enhance contrast between bromine in PFOB and background soft tissue density. However, lower kV radiographs may be suboptimal in the assessment of the remainder of the chest anatomy including the lung parenchyma and for detection of pneumothorax. As this study did not perform detailed assessment of the diagnostic performance of lower kV technique for purposes other than PLV assessment, patients may require conventional kV technique radiographs for other clinical indications.

This report is also the first to have performed chest ultrasound in patients on PLV and observed nonspecific asymmetrical appearance of absent A-lines in 1 case with asymmetrical filling but did not discretely visualize PFOB within the lungs. Our experience with phantom assessment and clinical evaluation supports that lung parenchyma contains too many air and fluid interfaces to allow detection of liquid ventilation material by ultrasound at partial filling concentrations. As such, this modality appears presently confined to the detection of pleural fluid in selected patients since assessment of liquid ventilation material distribution is not feasible on ultrasound. While CT and MRI are capable of visualizing PFOB, radiographic assessment will likely remain the mainstay for infants on PLV due to diagnostic, logistical, and cost considerations. Uneven filling patterns and delayed clearance in these patients highlights markedly abnormal ventilation in severe BPD. Analysis of radiographic PLV filling patterns in these patients may offer novel insights into this important lung disease affecting many preterm infants and could potentially prompt rethinking of BPD classification.

Continued work will examine differential filling patterns on PLV with long-term pulmonary outcomes. Clinical trials are proposed to examine longer use of PFOB and use in other conditions. In revisiting liquid ventilation, these new trials conducted in a responsible manner will provide information regarding the clinical relevance of this technique for infants with severe pulmonary disease.

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