Pediatric pulmonology year in review 2019: Physiology

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Abstract

Pulmonary physiologic assessments are critical for the care and study of pediatric respiratory disease. In 2019, there were numerous contributions to this topic in *Pediatric Pulmonology*.

1 INTRODUCTION

Physiologic measurements of the respiratory system constitute a core element of pediatric pulmonary medicine. In 2019, there were several reports published in *Pediatric Pulmonology* that advanced the field of pediatric pulmonary physiology.

2 FORCED OSCILLATORY BASED STUDIES

Many young children are unable to perform the maximal forced expiratory maneuver required for spirometry.^{1,2} Forced oscillometry (FO) is easier to perform than spirometry because measurements are obtained during tidal breathing.¹ FO calculates respiratory system impedance (Z) by measuring changes in pressure and flow in response to an oscillatory pressure wave introduced at the airway opening.² Z incorporates the in-phase and out-of-phase elements of pressure and flow, and it is the vector sum of resistance (R) and reactance (X), the latter of which represents the energy dissipated in the visco-elastic and inertive forces of the respiratory system. X and R measured at lower frequencies (ie, 5-8 Hz) are thought to reflect small airway function.^{2,3} The area under the reactance curve (AX) is another measurement that has been used to assess small airways function with FO.² Measurement of airway function by FO complements that obtained by spirometry. Several publications in 2019 applied impulse

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oscillometry (IOS) and other FO methods to the study of pediatric respiratory disease. A study performed by Evans et al⁴ compared FO results in children with asthma, cystic fibrosis (CF), and bronchopulmonary dysplasia (BPD) to determine if FO measurements varied with different pediatric respiratory diseases. FO measurements were significantly different from normal healthy control children in all the disease states, but the abnormalities differed depending upon the disease. This study indicates that different FO variables might need to be used depending upon the disease. Mondal et al⁵ performed a retrospective chart review to assess the capacity of IOS to diagnose asthma in children with sickle cell disease (SCD). They analyzed their data using receiver-operator characteristic curves and machine learning to assess the ability of spirometry and IOS to predict an asthma diagnosis. Both methods identified spirometry and IOS measurements predictive of asthma. These results suggest that IOS may be an alternative method to evaluate asthma in SCD in patients who cannot perform spirometry. However, this approach must still be validated in a prospective study. Bronchoprovocation is frequently used to identify physiologic markers of asthma.⁶ Jara-Gutierrez et al⁷ compared IOS to spirometry for the assessment of airway hyperresponsiveness (AHR) using three bronchoprovocation stimuli: mannitol, methacholine, and eucapnic voluntary hyperventilation. Changes in forced expiratory volume in 1 second (FEV1) were correlated with changes in IOS measurements of small airway function, with impedance at 5 Hz (Z5), resistance at 5 Hz (R5), and reactance at 5 Hz (X5) showing the greatest discriminatory capacity. The authors also calculated cutoff values for R5, X5, and AX. Their results suggest that IOS can be a substitute for spirometry to identify AHR, especially in patients who cannot perform spirometry. However, some children may have difficulty with the size of the mouthpiece or in using a facemask.

R and X are usually calculated as mean values over the entire breathing cycle and therefore incorporate both inspiratory and expiratory measurements. There may be clinically important differences between inspiratory and expiratory R and X. Two studies focused on within-breath versus whole breath analysis

of IOS signals. Sol et al⁸ hypothesized that analysis of inspiratory and expiratory IOS measurements would be more sensitive than whole-breath analysis in differentiating lung function in children with asthma compared with those without asthma. Whole-breath R5 and AX were significantly higher in asthmatic children compared with normal controls, while X5 was significantly lower. The absolute differences between inspiratory and expiratory R5, X5, and AX were significantly higher in asthma children compared with normal controls. These results demonstrate that IOS can identify differences in lung function between asthmatic and non-asthmatic children and that within-breath changes in IOS measurements can be useful in differentiating the two groups without needing to use a bronchodilator challenge. Zannin et al⁹ studied within-breath changes in IOS measurements in children with CF. R8 and X8, which reflect small airways function, correlated with FEV1 and residual volume/total lung capacity, but there was poor correlation between IOS measurements and both lung clearance index (LCI) and chest magnetic resonance imaging (MRI) scores. These results suggest that IOS can detect peripheral airway obstruction and dynamic airway narrowing, but it is not a sensitive measure of ventilation inhomogeneity or morphologic lung changes in CF.

3 MULTIPLE BREATH WASHOUT STUDIES

Another frequently utilized physiologic test in pediatric respiratory disease is multiple breath washout (MBW), which can identify ventilation inhomogeneity in CF lung disease.¹⁰ However, MBW is relatively time consuming and can require synchronization of the flow and gas concentration signals. This latter requirement is more challenging in infants and can potentially result in large measurement error. Two recent publications in *Pediatric Pulmonology* reported alternative strategies to overcome these limitations of MBW. Single breath washout (SBW) is much quicker to perform compared with MBW, and the slope of phase III (SIII) is thought to reflect emptying of the peripheral alveolar zones of the lung. However, the relationship between SBW measurements and structural changes in CF lung disease is not

known. Yammine et al¹¹ assessed the correlation between SBW and chest computed tomography (CT) in a cohort of children with CF. Although LCI as measured by MBW correlated with bronchiectasis observed on chest CT, SIII did not. These results indicate that SIII cannot be used as a substitute for MBW to detect structural lung disease in CF. In another report, Shawcross et al¹² described a novel method of infant MBW that avoids the need for signal synchronization and is more portable than conventional MBW using a mass spectrometer. They demonstrated high feasibility and reproducibility within maneuvers of their method. However, they were only able to successfully perform the technique on infants sedated with chloral hydrate, potentially limiting its use in infant respiratory physiology labs, and mass spectrometer data were only available for two infants, precluding any meaningful comparison with the novel method.

4 SPIROMETRY BASED STUDIES

Standard pulmonary function test (PFT) reference equations incorporate standing height as a variable, but this assumes normal thoracic growth.⁴ Childhood cancer survivors (CCS) have thoracic growth deficiency, which disproportionately affects their upper segment length (USL) compared with children without cancer. Dean et al¹³ hypothesized that CCS have a disparity in the ratio of USL to standing height that leads to overestimation of PFT abnormalities. To test this hypothesis, they compared PFT results in CCS to age-matched historical standards and also used double the USL as an alternative for standing height in calculation of predicted PFT values. They found that using double USL resulted in fewer patients classified with restrictive lung disease compared with using standing height. These results suggest that PFTs in CCS should be interpreted conservatively and future studies should be conducted using anthropomorphic variables other than standing height to derive predicted PFT values.

The global lung function initiative (GLI) contains predicted spirometric values for five different ethnic groups across a 3 to 95 year age range.¹⁴ However, there is a lack of data from Latin American

populations. The objective of a study performed by Aristizabal-Duque et al¹⁵ was to identify the most appropriate reference equations for healthy children and adolescents in Bogotá, Colombia. They performed spirometry on 326 children ages 6 to 17 years, and they found that Knudson and GLI-2012 provided the lowest median prediction error and narrowest limits of agreement in Bland-Altman plots. These results suggest using a combination of GLI-2012 and Knudson spirometry equations would be appropriate for the children living in Bogotá, Columbia and in other cities sharing a similar ethnic background and elevation above sea level.

5 OTHER PULMONARY MEASUREMENT TECHNIQUES

Electrical impedance tomography (EIT) uses measurement of thoracic electrical bioimpedance to generate a tomographic image of the lungs.¹⁶ EIT has mainly been used in adult critical care units, and there is little published data on its use in infants. Jardine et al¹⁷ describe a fatal case of an infant with chest wall mesenchymal hamartoma where EIT was used to evaluate the dynamic impact of the lesion on regional lung ventilation. Their results suggest that EIT can be used as an alternative imaging modality to chest CT or MRI when evaluating a space occupying lesion. EIT also provides the added benefit of being able to measure trends in regional lung ventilation which could further benefit clinical care.

6 GAS DIFFUSION BASED STUDIES

The carbon dioxide diffusion coefficient (DCO_2) is used as a measure of CO_2 removal in patients receiving high frequency oscillatory ventilation (HFOV) through an endotracheal tube, but the feasibility of using DCO_2 to estimate CO_2 clearance in patients supported by noninvasive HFOV (nHFOV) has not been reported. Schäfer et al¹⁸ hypothesized that DCO_2 reflects CO_2 removal during nHFOV and the presence of a leak does not affect this measurement. To test this hypothesis, they used a neonatal airway model of nHFOV with an adjustable leak and measured pressure and gas flow at the prongs, trachea, and leak.

They found that DCO_2 was strongly correlated with pCO_2 even in the presence of a moderate leak. These results suggest that DCO_2 may be a clinically useful measure of ventilation efficacy in nHFOV.

7 STUDIES IN PRETERM INFANTS AND OTHER PATIENT POPULATIONS

Physiologic instability induced by brief respiratory pauses in preterm infants using noninvasive respiratory support (NIRS) has not been well characterized. Marshall et al¹⁹ studied hypoxemia and bradycardia after apneic pauses in preterm infants receiving NIRS. They found that hypoxemia and bradycardia occur commonly with prolonged apneic events ≥ 10 seconds. However, even shorter episodes of apnea were associated with physiologic instability and since they were more common they contributed substantially to the total amount of instability. These results suggest that brief apneic pauses in preterm infants receiving NIRS are potentially deleterious, and they should potentially be monitored and treated.

Noninvasive ventilation (NIV) can fail to provide adequate respiratory support and gas exchange due to CO_2 retention.²⁰ In two separate papers, a research group led by Eichenwald investigated the effect of different modifications to NIV on airway pressure and CO_2 clearance. Rub et al²¹ used a premature infant lung model to study the effect of high frequency pressure oscillation (HFPO) on airway pressure delivered by high flow nasal cannula (HFNC). Superimposition of HFPO significantly reduced mean airway pressure while increasing CO_2 clearance. These results suggest that superimposition of HFPO may be beneficial to preterm infants receiving HFNC. In a complementary study, Sivieri et al²² assessed the effect of HFPO on end tidal CO_2 (ET-CO_2) in an infant model of nasal continuous positive airway pressure (NCPAP) by applying a flow interrupter in the ventilator circuit. HFPO applied to either bubble or variable-flow CPAP resulted in significantly reduced ET-CO_2 concentration, and this effect was frequency dependent. HFPO may reduce the amount of NIV failure by improving CO_2 clearance while maintain

airway distending pressure in infants receiving NCPAP. However, the results from both of these studies were derived from models, and these interventions must still be confirmed in a clinical trial.

Infants with ventilator-dependent type 2 severe BPD have increased airway resistance and long expiratory time constants, but these abnormalities are heterogeneously distributed throughout the lung.²³ This can result in dynamic hyperinflation and intrinsic positive end-expiratory pressure (PEEPi). The conventional method to measure PEEPi in a ventilated infant is to impose an expiratory pause and measure the end-expiratory pressure after alveolar and airway opening pressures equilibrate. However, this method requires pharmacologic muscle paralysis to prevent spontaneous inspiratory effort during the breath hold. Napolitano et al²⁴ studied the feasibility and utility of an alternative approach that does not require muscle paralysis by simultaneously measuring pressure in the esophagus and flow at the airway opening. They studied a cohort of 12 infants, and PEEPi was successfully measured in all 12. Furthermore, setting ventilator-determined PEEP based on achieving the lowest PEEPi led to less wasted inspiratory effort and lower FiO₂ in eight of the infants. The results of this pilot study demonstrate that PEEPi measurement in infants with type 2 severe BPD is feasible without the need for muscle paralysis and suggests that incorporating PEEPi measurements into ventilator management can lead to improvement in respiratory mechanics and oxygenation. A larger, prospective study is required before being able to incorporate this into regular clinical practice.

Respiratory function in children with spinal muscle atrophy (SMA) receiving NIV is not well described.²⁵ Kapur et al²⁶ performed a series of PFTs in 25 children with SMA who had not been treated with nusinersen and assessed differences between those using NIV and those who were not. They found that children requiring NIV generally had more abnormal respiratory function as measured by a variety of methods, including polysomnography (PSG), spirometry, FO, LCI, and respiratory muscle strength testing. Based on their results, the authors suggest that children with SMA and an FVC Z score <-2.0 or

LCI >7 should have a PSG to assess their need for NIV. Their study is limited by the small patient number and single country study design, and larger, prospective studies should be performed to determine the best method to identify the need for NIV in SMA.

Chronic graft-vs-host disease (cGVHD) is a common complication of hematopoietic stem cell transplantation (HSCT), and in some cases results in severe small airway obstruction due to bronchiolitis obliterans syndrome (BOS).²⁷ Spirometry is not a sensitive test for detection of early small airway obstruction. Uhlving et al²⁸ studied the potential role of LCI in identifying or predicting pulmonary complications of cGVHD in a cohort of 30 children who received HSCT. Post-HSCT LCI was significantly higher in children who developed cGVHD, but LCI measured before and 3 months post-HSCT was not superior to spirometry in predicting BOS. Their results suggest that LCI may be a potential marker of cGVHD in HSCT recipients, but a larger study is required to define the clinical utility of LCI measurements in this patient population.

8 CARDIOPULMONARY EXERCISE TESTING

Chronic lung disease frequently affects exercise tolerance, and exercise testing can be a method to assess the degree of pulmonary impairment.²⁹ Cardiopulmonary exercise testing is the gold standard for assessment of exercise capacity, but it requires specialized, expensive equipment and cannot be performed in the field. There is a paucity of data from other exercise tests in children. To address this knowledge gap, Scalco et al³⁰ compared the 6 minute walk test (6MWT), modified shuttle walk test (MSWT), and a pediatric version of the multiple-task Glittre activities of daily life test (TGlittre-P) in healthy school-aged children. The TGlittre-P and 6MWT elicited similar physiologic responses consistent with submaximal exercise testing, whereas physiologic overload was greater with the MSWT. Based on these results, the authors recommend that these three exercise tests be used in a complementary

fashion, and the selection of the specific test should be based on the clinical condition and research objectives. One limitation of this study is the small sample size (N = 24).

The ventilatory efficiency index (VEI) during exercise increases with worsening cardiopulmonary disease, but there are few studies using this outcome measure in people with CF (PWCF).³¹ Kampouras et al³² investigated the relationship between VEI and disease severity in PWCF and correlated this with chest CT and LCI. There was no relationship between VEI and disease severity as measured by spirometry, CT, or LCI. However, the intercept of the index regression line, which reflects dead space ventilation, did increase with worsening FEV1. These findings differ from those from other lung diseases, such as chronic obstructive pulmonary disease, and the authors speculate that PWCF maintain their VEI by increasing their respiratory rate. However, this results in increased dead space ventilation, hence leading to an increase in the intercept of the index regression line.

9 CONCLUSION

Assessment of respiratory physiology will always be an important element of the care and study of pediatric respiratory diseases. Advances in physiology research reported in *Pediatric Pulmonology* in 2019 helped develop novel methods of physiologic measurement and increased our understanding of the physiologic basis of several pediatric respiratory diseases.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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