

# Pediatric Pulmonology Year in Review 2020: Physiology

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## Abstract

Pulmonary physiology is a core element of pediatric pulmonology care and research. This article reviews some of the notable publications in physiology that were published in Pediatric Pulmonology in 2020.

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*Abstract*

Pulmonary physiology is a core element of pediatric pulmonology care and research. This article reviews some of the notable publications in physiology that were published in *Pediatric Pulmonology* in 2020.

### *Introduction*

Physiology is one of the foundations of pediatric pulmonology, and in 2020 there were several important articles focused on pediatric pulmonary physiology published in *Pediatric Pulmonology*.

### *Forced Oscillometry*

Forced oscillometry (FO) uses measurement of pressure and flow in response to an oscillatory pressure wave introduced at the airway opening to measure respiratory system impedance (Z) [1]. Z is a generalized concept of resistance that incorporates the in phase and out of phase relationships between pressure and flow. The in phase element of Z is resistance (R), while the out of phase element is represented by reactance (X). R is composed of the forces associated with frictional losses in the airways and the lung parenchyma. X is composed of an inertive element (Xi), which represents the inertive forces of the respiratory system, and a capacitance element (Xc), which reflects the visco-elastic properties of the lung. At low frequencies, Xc predominates over Xi. Because FO does not require a maximal forced expiratory maneuver, it is easier to obtain measurements from young children compared to spirometry. X and R at low frequency may also reflect small airways function better than spirometric measures such as the forced expiratory volume in 1 second (FEV1).

There is increasing evidence that the lungs are affected by diabetic microangiopathy. Anik, et al performed FO and spirometry on children with type 1 diabetes mellitus (T1DM) and compared the results to data from age matched healthy controls [2]. R at 5, 10, and 20 Hz (R5, R10, and R20 respectively) was significantly higher in children with T1DM compared to controls, and the forced expiratory flow at 75% of forced vital capacity (FEF<sub>75</sub>) and between 25-75% of forced vital capacity (FEF<sub>25-75</sub>) were both significantly lower. Lung function was worse in children with poorly controlled T1DM compared to well-controlled T1DM. These results demonstrate subclinical impairment of lung function in children with T1DM and suggest that monitoring of lung function in T1DM should be a part of T1DM care.

Zheng, et al studied whether impulse oscillometry (IOS), a form of FO, and the fraction of exhaled nitric oxide (FeNO) could be used to predict future asthma exacerbations in preschool children [3]. They were able to identify a cutoff value for the area under the reactance curve (AX), a measure of total low frequency X, that predicted future loss of asthma control, while FeNO did not have strong predictive value in this patient population. Their report suggests that IOS could be used to monitor preschool children for future risk of asthma exacerbation.

Lundberg, et al investigated the feasibility and correlation between spirometry and IOS in 6 year old children born extremely premature [4]. The success rate of IOS was significantly higher in both term and preterm children compared to spirometry (93% vs 60%). There was moderate correlation between spirometry measurements and IOS measurement, suggesting that IOS could be considered as an alternative test in children who cannot perform spirometry.

Veneroni, et al used FO to compare respiratory mechanics in preterm infants treated with continuous positive airway pressure (CPAP) versus CPAP with sustained inflations of 25 cmH<sub>2</sub>O for 15 seconds [5]. Infants presented with highly heterogeneous degrees of lung aeration at birth, limiting their ability to use FO to assess ventilation strategies. However, this pilot study did demonstrate the feasibility of obtaining FO measurements at birth in preterm infants.

### *Multiple Breath Washout*

The multiple breath washout (MBW) technique can be used to assess ventilation inhomogeneity, which can be seen in a variety of pediatric lung diseases, most notably cystic fibrosis (CF) [6]. MBW can be performed either by washing in a tracer gas, such as sulfur hexafluoride, and then washing the tracer gas out with

ambient air or washing out the resident nitrogen ( $N_2$ ) in the lungs with 100% oxygen. The lung clearance index (LCI) is the most commonly used measure derived from  $N_2$  MBW, and it represents the number of lung turnovers required to washout resident  $N_2$  from the lungs down to 2.5% of the original concentration; a higher LCI indicates increased ventilation inhomogeneity. In addition to LCI, other measures derived from MBW include  $LCI_{5,0}$ , where  $N_2$  is washed out to 5% of the original concentration, slope of phase III indices, and moment ratio analysis.

Parisi, et al performed MBW and spirometry in a group of childhood cancer survivors and matched healthy controls [7]. They found that LCI was higher in these children compared to healthy controls, but this difference was not statistically significant; and there was no difference in spirometry measurements. There was a significant correlation between years following chemotherapy and increased LCI. Their results suggest that the chemotherapy used to treat childhood tumors may have less pulmonary toxicity than previously expected, at least during childhood. The increase in LCI over time suggests that LCI could be used to non-invasively assess pulmonary fibrosis but larger prospective studies are needed.

Gambazza, et al evaluated the association of LCI with exercise capacity in patients with CF [8]. LCI was significantly higher in patients with exercise intolerance, but it was also higher in some patients with normal exercise tolerance and normal to moderate airflow obstruction. No association was found between predicted peak work and LCI, but there was a significant association between peak work and nutritional status, airflow obstruction, and chronic *Pseudomonas aeruginosa* infection. Based on these findings, providers should not assume that patients with normal exercise tolerance do not have early lung disease.

Irving, et al compared MBW results between children with severe treatment resistant asthma (STRA), difficult asthma (DA) and healthy controls [9]. LCI was significantly higher in the patients with STRA compared to those with DA and controls but there was no difference between DA and controls. FeNO and LCI showed significant improvement following parenteral steroids. These results suggest that distal airways disease is worse in patients with STRA and can sometimes be improved with parenteral steroids. The improvement in FeNO and LCI suggests these patients with STRA may have distal airway eosinophilic inflammation that may not respond to inhaled corticosteroids. These results suggest that FeNO and LCI may be useful in monitoring treatment response in patients with STRA.

Other studies of MBW focused on use of outcome measures other than LCI and comparison of difference MBW devices. Arigliani, et al compared the conduction-dependent contribution to ventilation inhomogeneity ( $S_{cond}$ ), the diffusion-convection interaction-dependent inhomogeneity ( $S_{acin}$ ), LCI, spirometry, and transfer capacity of the lung to carbon monoxide (TLCO) in children born at <28 weeks gestational age (GA) [10].  $S_{cond}$  was abnormal in about one third of children while LCI and FEV1 were only abnormal in 18% and 14% respectively. They did not identify any significant difference in  $S_{cond}$  between infants born prematurely with BPD compared to those without BPD. No significant difference was observed in  $S_{acin}$  between the premature infants and the control group and no significant difference was found when comparing those with BPD to those without BPD. Finally, extremely preterm children had lower TLCO compared to controls, although moment ratios correlated with pulmonary symptoms, high variability limits its utility in the clinical setting. These results suggest that  $LCI_{5,0}$  can be used to track disease progression in young children with CF. Compartment analysis (CA) allows partitioning of MBW data into slower and faster ventilating units. Skov, et al applied CA to MBW testing in children with CF [12]. Because CA requires an extremely regular breathing pattern, it could only be successfully performed in 53% of children with CF. However, CA did correlate with other MBW measurements, such as LCI. Further research is needed to determine the clinical value of CA. Isaac, et al used a lung model to compare functional residual capacity (FRC) and LCI measured with 2 different MBW devices and body plethysmography [13]. Not only were there differences in these measurements using these 3 different methods, but for one device LCI decreased with age. These results indicate that MBW data obtained on one device cannot be directly compared to data from other devices.

### Reference Equations

Normal reference values are critically important for interpreting the results of pulmonary function tests

(PFTs), but data in non-White populations are lacking. Several reports in *PediatricPulmonology* this past year sought to fill this knowledge gap. Al Querem et al. evaluated the applicability of the 2012 Global Lungs Initiative (GLI) reference equations in 582 Jordanian children ages 6-13 year-old [14]. The GLI equation for Caucasians demonstrated a reasonable fit to the data collected in this study and was more suitable than the GLI equation for other ethnic groups, and equations derived from other studies conducted in Arabic counties. These results differ from previously reported values in Jordanian adults which showed that the GLI equations for other ethnicities rather than GLI Caucasian equation were better correlated, and demonstrate the importance of identifying age-specific reference equations.

Reference values for infant PFT's have been reported but there is a lack of information about racial or ethnic differences. The aim of a study by Kosma et al was to estimate the extent to which previously published reference equations for infant spirometry could be implemented in a cohort of Swedish term, healthy infants [15]. Tidal volume and raised volume rapid thoracoabdominal compression (RVRTC) maneuvers were performed on 91 term infants. Height and weight in Swedish infants were above average compared to other infant PFT reference cohorts, and this led to an underestimation of lung function measured by infant spirometry in the youngest age group and an overestimation in the older infants using previously published infant PFT reference data.

Not only spirometry reference values but also reference equations to calculate diffusing capacity of carbon monoxide (DLCO) have been tested for their applicability in different racial groups. A study by Dridi et al. measured nitric oxide/carbon monoxide transfer in 118 healthy Tunisian males ages 8-14 [16]. They confirmed previous observations that height and body weight are key individual predictors of DLCO and that alveolar volume (VA) was related with both height and weight. Their values for DLCO and VA were similar to those found by Kim et al in both Caucasian and African American populations [17].

Normal reference data for maximal voluntary ventilation (MVV) in children have only been reported for limited ethnic and racial populations. Silva et al. obtained MVV data from children in São Paulo, Brazil [18]. MVV in their cohort differed from results obtained in other populations, highlighting the need and importance to obtain normal reference data for multiple different populations.

Although not the focus of studies published in *PediatricPulmonology* in 2020, the issue of incorporating race into PFT reference equations has grown in prominence and importance in the past few years. Although genetic ancestry contributes to differences in PFT values in different populations, race is a complex construct that incorporates more than just genetic ancestry, and includes cultural and social factors [19]. Furthermore, race serves as a proxy for social determinants of health that may affect lung function. It is likely that in the future, we will see studies in *PediatricPulmonology* that more directly incorporate genetic ancestry into predictive equations rather than phenotypic race [20].

### *Tidal Breathing Studies*

Tidal breathing analysis (TBA) is an attractive method of respiratory function testing because it can be done without the need for sedation or the requirement of forced expiratory maneuvers [21]. TBA can be performed using a face mask and pneumotachometer, but this can be challenging to apply in infants since it requires the infant to maintain a seal over the nose and mouth with the mask, which can also potentially alter infant breathing patterns. Electromagnetic inductance plethysmography (EIP) measures changes in the electromagnetic field created by tidal breathing while wearing a metallic vest through which a low voltage is applied. Sautter, et al used EIP to perform TBA in a cohort of 36 infants with bronchiolitis [22]. EIP was successfully performed in 80% of the infants, and a significant increase in the ratio of the total expiratory time over the inspiratory time ( $T_e/T_i$ ) was observed after inhalation of normal saline. The ratio of the time to peak expiratory flow over total expiratory time ( $T_{ptef}/T_e$ ) decreased after administration of nebulized normal saline, but this change was not statistically significant. This study demonstrates the feasibility of using EIP for TBA and suggests that further study of the physiologic effects of inhaled normal saline in bronchiolitis are warranted. Traditionally TBA has been done manually, which is a time consuming and laborious process. A study by Gomes et al. compared two computing systems, AutoCAD and MATLAB,

in their ability to obtain automated TBA data [23]. Thoracoabdominal area averages calculated with both systems were comparable, but MATLAB required less time and less user training to complete. They suggest that it could be used in the clinic setting to calculate or derive tidal volume measurements.

### *Physiologic Outcomes of Prematurity*

Bronchopulmonary dysplasia (BPD) is the most common short-term complication of premature birth, and infants with BPD can continue to have impaired lung function into adulthood [24]. Although there have been studies comparing lung function between infants with BPD and those without this diagnosis, there are limited data in preterm infants who are born small for gestational age (SGA). Kim, et al investigated the differences in airway obstruction in term, healthy neonates and preterm neonates with and without BPD using MBW and TBA [25]. No significant differences in  $T_{pef}/T_e$  were observed between the term infants, preterm infants with mild/moderate BPD, and preterm infants with severe BPD. However,  $T_{pef}/T_e$  was significantly lower in the severe BPD infants compared to the mild/moderate BPD infants, consistent with worse airway obstruction in the former group. LCI was significantly increased in preterm infants compared to term ones, but it did not vary between the infants with no BPD, mild BPD, or severe BPD, even when accounting for SGA status. SGA infants with BPD had a significantly lower  $T_{pef}/T_e$  than average for GA matched infants, showing a negative effect of SGA in BPD. These results suggest that SGA status is a risk factor for worse airway obstruction in infants with BPD.

Sex differences in lung function and structure are well known, but studies of sex differences in lung mechanics of preterm neonates are lacking. Kim, et al measured airway pressure and flow in male and female neonates requiring mechanical ventilation for neonatal respiratory distress syndrome, and then used these data to generate a single compartment model to calculate specific elastance ( $E_S$ ) [26]. Male infants had higher  $E_S$  compared to female infants of matched gestational age and less breath-to-breath variability in  $E_S$ . This study suggests that ventilator strategies may need to take sex into account, but further studies with larger cohorts are needed.

0.5. There was no significant difference in any other forced expiratory flow measurements, FRC, or respiratory system compliance between the caffeine treated or untreated groups. When further stratified by BPD diagnosis, differences in lung function were only seen in infants without BPD who had received caffeine. These results indicate that caffeine may have beneficial effects on lung function in addition to its effect on reducing risk of BPD.

### *Other Physiologic Studies*

A study by Fabi et al. examined short- and long-term changes in respiratory mechanics after palliative or corrective surgery in 168 infants and toddlers with congenital heart disease [28]. They found that these patients demonstrated normal basal respiratory function but decreased exercise capacity. This decrease in exercise capacity was more pronounced in patients who underwent total cavopulmonary connection (TCPC) procedures. This suggests the need to conduct respiratory monitoring on patients with TCPC more closely and for longer than those with non-TCPC procedures. They also found that a higher age at surgery but prior to 24 months was associated with better respiratory outcomes which suggests that increased development of the lung parenchyma prior to intervention will lead to improved respiratory outcomes post-operatively.

Sivieri, et al used a preterm infant lung model to evaluate the effects on end tidal  $CO_2$  ( $ETCO_2$ ) when high frequency oscillation is superimposed on bubble CPAP (BCPAP) [29]. They found that there is improved  $CO_2$  clearance when high frequency oscillation is applied to BCPAP, and that this effect was more pronounced when the model mimicked lung disease in a preterm infant compared to normal infant lung mechanics. This improvement was not dependent on BCPAP pressure,  $CO_2$  clearance was significantly improved for both lung models as a function of increased frequency and lower respiratory rate. These results support conducting a clinical trial to assess the effect of superimposed high frequency oscillations in infants receiving BCPAP.

Extrathoracic high frequency chest compression (HFCC) using an inflatable vest is frequently used for airway clearance in patients with mucociliary abnormalities, such as CF. Weiner, et al sought to determine

if HFCC augments ventilation by measuring end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) after HFCC was performed at varying frequencies (Hz) in a cohort of 15 people with CF who were experiencing a pulmonary exacerbation [30]. ETCO<sub>2</sub> values were significantly lower at all Hz compared to no treatment. This remained the same when adjusting for patient specific factors such as age, sex, body mass index, baseline FEV<sub>1</sub> and respiratory rate. Increasing Hz produced a small, but significant improvement in ETCO<sub>2</sub> clearance. These results demonstrate that HFCC increases clearance of CO<sub>2</sub> in a frequency dependent manner. Further research is needed to determine the clinical importance of this finding.

Formulas used to calculate the appropriate pediatric tracheostomy or endotracheal tube (ETT) size have incorporated age, weight, and height, but there are no formulas that incorporate airflow resistance or cross-sectional area of the inner cannula. Since resistance varies by the 4<sup>th</sup> power of the radius, small changes in ETT lumen diameter can have marked effects on tube resistance (R) [31]. Khan and Baker applied the Hagen-Poiseuille equation for R under laminar flow conditions to calculate the R in different ETT and tracheostomy tubes based on tube inner diameter and cross-sectional area [32]. A large decrease in R was seen when tube diameter was increased by as little as 0.5mm in ETTs that would likely be used for patients <1 year of age. This effect was not as significant in larger tube sizes. When invasive mechanical ventilation is required, and a patient can safely tolerate upsizing of ETT or tracheostomy tube, this should be considered to lower airway resistance and improve airflow dynamics.

### Summary

Pulmonary physiology continues to play an important role in pediatric pulmonology care and research, and we anticipate that future issues of *Pediatric Pulmonology* will continue to contain reports of interest and importance on this topic.

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