HHS Public Access

Author manuscript

J Am Soc Echocardiogr. Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:

J Am Soc Echocardiogr. 2019 July ; 32(7): 884–894.e4. doi:10.1016/j.echo.2019.03.015.

Echocardiographic Assessment of Right Ventricle Afterload in Preterm Infants: Maturational Patterns of Pulmonary Artery Acceleration Time Over the First Year of Age and Implications for Pulmonary Hypertension.

Meghna D. Patel[1,2], **Colm R Breatnach**[3,4], **Adam T. James**[3], **Swati Choudhry**[1,6], **Patrick J McNamara**[7], **Amish Jain**[8], **Orla Franklin**[4], **Aaron Hamvas**[9], **Luc Mertens**[5], **Gautam K Singh**[1], **Afif EL-Khuffash**[3,10], and **Philip T. Levy**[1,11]

[1]Department of Pediatrics, Washington University School of Medicine, Saint Louis, MO. [2]Department of Pediatrics, Stanford University School of Medicine, Stanford, CA. [3]Department of Neonatology, The Rotunda Hospital, Dublin, Ireland. [4]Department of Cardiology, Our Lady's Children's Hospital Crumlin, Dublin, Ireland [5]The Labatt Family Heart Centre, The Hospital for Children, Toronto, Canada. [6]Section of Pediatric Cardiology, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas [7]Department of Paediatrics, University of Toronto and and Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada. [8]Department of Pediatrics, University of Iowa, Iowa City, Iowa, USA. [9]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. [10]School of Medicine (Pediatrics), Royal College of Surgeons in Ireland, Dublin, Ireland. [11]Department of Pediatrics, Harvard Medical School and Division of Newborn Medicine, Boston Children's Hospital, Boston, MA, USA

Abstract

Background: Assessment of pulmonary hemodynamics is critical in the diagnosis and management of cardiopulmonary disease of premature infants, but reliable non-invasive indices of pulmonary hemodynamics in preterm infants are lacking. Since pulmonary artery acceleration time (PAAT) is a validated non-invasive method to assess right ventricular (RV) afterload in infants and children, we investigated the maturational changes of pulmonary artery acceleration time (PAAT) measures in preterm infants over the first year of age, and discerned the impact of typical cardiopulmonary abnormalities on the measures.

Methods: In a prospective multi-center study of 239 preterm infants (<29 weeks at birth), PAAT was assessed at days 1, 2, 5–7, 32 and 36 weeks post-menstrual age, and at 1 year corrected age. To account for heart rate variability, PAAT was adjusted for right ventricular ejection time (PAAT/

Correspondence Address: Philip T. Levy MD, Division of Newborn Medicine, Division of Newborn Medicine, Boston Children's Hospital, 300 Longwood Avenue | Hunnewell 436, Boston, Massachusetts 02115, Phone: (617) 919 6682, philip.levy@childrens.harvard.edu.

RVET). Premature infants who developed bronchopulmonary dysplasia or had echocardiographic findings of pulmonary hypertension were analyzed separately. Intra- and inter-observer reproducibility analysis was performed.

Results: PAAT was feasible in 95% of the image acquisitions and there was high intra- and inter-observer agreement (intraclass correlation coefficients > 0.9 and coefficient variations < 6%). In uncomplicated preterm infants (n=103, 48%) PAAT and PAAT/RVET increased longitudinally from birth to 1 year corrected age ($p < 0.001$); and were linearly associated with gestational age at birth ($r=0.81$ and $r=0.82$, $p < 0.001$) and increasing postnatal weight and postnatal age ($r > 0.81$, $p<0.001$). PAAT measures were significantly reduced ($p < 0.001$) in infants with bronchopulmonary dysplasia and/or pulmonary hypertension (n=119, 51%) beyond one week of age.

Conclusions: PAAT measures increase in preterm infants from birth to 1 year corrected age that is reflective of the physiologic postnatal drop in RV afterload. Bronchopulmonary dysplasia and pulmonary hypertension leave a negative impact on PAAT measures. By demonstrating excellent reliability and establishing reference patterns of PAAT in preterm infants, this study suggests the PAAT and PAAT/RVET can be used as complementary parameters to assess physiologic and pathologic changes in pulmonary hemodynamics in neonates.

Keywords

Pulmonary hemodynamics; prematurity; echocardiography; pulmonary artery acceleration time; right ventricular afterload

INTRODUCTION

Premature birth disrupts the normal maturational process of the developing pulmonary circulation with impairments resulting in prolonged oxygen requirements, abnormal vasoreactivity, and pulmonary vascular disease, which in its most severe form will lead to pulmonary hypertension.[1] The diagnosis of pulmonary vascular disease and the true prevalence of pulmonary hypertension in preterm infants has been difficult to discern, in large part, due to a paucity of reliable non-invasive screening measures to comprehensively evaluate and track the main components of right ventricle (RV) afterload in these neonates.[1,2] Currently, echocardiographic assessment of pulmonary hemodynamics relies on a combination of qualitative evaluations (septal wall flattening, RV morphological changes) and quantitative estimates based on the tricuspid regurgitation velocity; these pressure-dependent measures may not be feasible in some preterm infants with significant cardiopulmonary disease.[3,4] In the early stages of preterm pulmonary vascular disease, a significant reduction in pulmonary arterial compliance accompanies the small increases in pulmonary vascular resistance. These initial responses will not cause an immediate rise in pulmonary arterial pressure, thus limiting the applicability of the current screening modalities that focus only on characterizing a rise in pulmonary arterial pressure or vascular resistance.[5] With more advanced stages of pulmonary vascular disease, as in established pulmonary hypertension, increases in pulmonary arterial pressure and vascular resistance are not associated with further reduction in compliance.[6] Therefore, a non-invasive index of RV afterload that captures maturational changes in compliance, vascular resistance, and pressure

along the spectrum of disease will provide more clinical insight into the (patho) physiology of pulmonary vascular development and growth than a measure that only reflects one of these elements.[7]

Pulmonary artery acceleration time (PAAT) is a quantitative method used to define the blood flow velocity characteristics in the RV outflow tract in response to changes in ventricular mechanical performance, pulmonary vascular load and compliance.[8,9] PAAT and its ratio adjusted to RV ejection time (PAAT/RVET) have been validated against right heart catheritization as a reliable estimate of invasive pulmonary hemodynamic measures in children and neonates[8], and maturational patterns have recently been established in healthy children.[9] However, PAAT is still not utilized in clinical practice to characterize RV afterload in preterm infants due to the lack of data regarding feasibility, reproducibility and reference patterns.[2] The influence of common prematurity associated cardiopulmonary conditions, such as bronchopulmonary dysplasia (BPD) and pulmonary hypertension, on the maturational patterns of PAAT has also not been fully explored, but is a necessary prerequisite for clinical adoption in preterm infants.[10–13]

Our group recently demonstrated the maturational patterns of global and regional right ventricular (RV) deformation patterns in extremely preterm infants increased throughout the neonatal period, but were negatively affected by the presence of BPD and/or pulmonary hypertension.[14] We therefore, hypothesized that PAAT would similarly increase in uncomplicated preterm infants, but prematurity-associated cardiopulmonary conditions may influence the maturational patterns of PAAT changes differently. The primary objectives of this study were to determine the maturational (age- and weight-related) changes in PAAT and PAAT/RVET in healthy uncomplicated preterm infants and establish reference patterns from birth through 1 year corrected age. The secondary aim was to discern the impact that BPD and pulmonary hypertension will have on the maturational patterns of the PAAT measures.

METHODS

Patients

In this prospective multi-center study, 239 extreme preterm infants were recruited at birth and longitudinally followed until 1 year corrected age between August 2011 and January 2016 at hospitals affiliated with two academic institutions (Washington University School of Medicine, Saint Louis Children's Hospital, n=137, and Royal College of Surgeons in Ireland, Rotunda Hospital, n=102). The preterm infants enrolled from the Washington University site were among infants participating in the Prematurity and Respiratory Outcomes Program (PROP, Clinical Trials number: NCT01435187).[15] Infants with any suspected congenital anomalies of the airways, congenital heart disease (except atrial septal defects), chromosomal anomalies, intrauterine growth restriction or small for gestational age (birth weight < 10th centile for gestation) were excluded from the healthy uncomplicated cohort arm of the study. Reference values and maturational patterns of RV fractional area of change (FAC)[16,17] and deformation (strain)[14,18–20] from these cohorts have been published. Comparisons of PAAT measures at 1 year corrected age only between term and preterm-born infants have been reported from the PROP group,[21] but complete PAAT measures from

birth through 1 year corrected age have not been detailed for the entire cohort. The institutional review board of Washington University and the ethical committee on human research at Royal College of Surgeons approved the protocol. Written informed consent was obtained from the parents or guardians of all participants.

Inclusion Criteria for the Uncomplicated Cohort

We utilized a previous published approach to define a cohort of uncomplicated preterm infants (supplemental material).[14,17]. We assessed for the contributions of BPD (using a modified definition of the 2001 National Institutes of Health BPD workshop) and respiratory disease syndrome in a sub-analysis.[22] We have provided a list of terms (Appendix 1) that describe the definitions for length of gestation and age in the perinatal period based on the policy statement from the American Academy of Pediatrics.[23]

Preterm infants with any of the following echocardiographic signs of late onset pulmonary hypertension, identified at any time point beyond day 5–7 of age through 1 year corrected age were excluded from the reference cohort: an estimated RV systolic pressure (RVSP) > than 40 mm Hg, a ratio of RVSP to systemic systolic blood pressure > 0.5, any cardiac shunt with bidirectional or right-to-left flow, unusual degree of right ventricular hypertrophy or dilatation, or ventricular septal wall flattening.[24]

The wide scope of the clinical manifestations arising due to the ductus arteriosus, i.e. systemic circulatory insufficiency, hypotension, pulmonary overcirculation, and ventricular failure, are of significant concern in relationship to the evaluation of RV afterload and PAAT measures. We accounted for the ductus arteriosus and followed the same exclusion criteria for the presence of a hemodynamics significant ductus arteriosus (hsDA) or patent ductus arteriosus (PDA) as the original study (supplemental material).[14]

Echocardiography

Prospective echocardiograms were performed at six time points from birth to 1 year corrected age, as previously described by our group and detailed in Figure 1.[14] At Washington University School of Medicine site, the echocardiograms were performed serially at day 1 (n=30), day 2, (n=30), 32 weeks PMA (n=117), 36 weeks PMA (n=117), and 1 year corrected age (n = 81). At the Royal College of Surgeons in Ireland site, echocardiograms were performed at day 1 (n=102), day 2, (n=102), days 5–7 (n=98), and 36 weeks PMA (n=47).[14] The infants' antenatal, delivery and demographic characteristic were obtained.

Two-dimensional and color Doppler echocardiography images in the parasternal and apical standard views were acquired in the infants in the supine position as per the American Society of Echocardiography guideline.[25] We utilized a published protocol for PAAT image acquisition and post-processing data analysis.[8] A spectral Doppler image was obtained by placing a pulsed Doppler sample volume at the pulmonary valve annulus in the parasternal short-axis view. We achieved maximal alignment of Doppler interrogation with blood flow direction with the placement of the sample volume at the annulus of the pulmonary valve. We calculated PAAT as the time interval between the onset of systolic pulmonary arterial flow (onset of ejection) and peak flow velocity. To account for the potential impact of heart

rate variability, PAAT was adjusted for RVET with a ratio of PAAT/RVET.[8] Since we and others have previously failed to demonstrate a correlation between PAAT or PAAT/RVET ratio and R-R interval in neonates,[8] both PAAT and PAAT/RVET were not corrected for R-R interval in the analysis.

Ventricular function.—As PAAT measures detect the triad of elevated pulmonary vascular disease, decreased pulmonary arterial compliance, and RV dysfunction,[8] we assessed RV function using previously acquired and described measures of speckle-tracking echocardiography-derived free wall longitudinal systolic strain[14,18–20], FAC[16,17], and tricuspid annular plane systolic excursion (TAPSE).[17] Since cut-off values to determine normal vs. abnormal RV function do not yet exist in this cohort, we incorporated the measures as confounders in the linear regression models to determine their influence on maturational patterns.

Feasibility and Reproducibility

Intra- and inter-observer variability for PAAT and PAAT/RVET were measured in 50% of the infants by two investigators at each center, both of whom were blinded to the clinical and demographic data. Each observer utilized the same measurement protocol[8] and was blinded to the other's results. Equal distributions of studies were chosen at each time point and coefficient of variation and intraclass correlation coefficient were used to assess the reproducibility.

Statistical Methods

All data are expressed as mean ± standard deviation or as percentages. Continuous variables of PAAT were tested for normality using the Kolmogorov-Smirnov test and a histogram illustration of the data. Analysis of variance and student t tests were used to compare the changes in PAAT values from birth to 1 year corrected age in the preterm infants and to compare the patterns between uncomplicated preterm infants and those with BPD, pulmonary hypertension, and/or a PDA, respectively. All outcome variables with non-normal distributions were analyzed in simple comparisons using Wilcoxon rank sum tests or Kruskal-Wallis one-way analysis of variance for tests with more than two independent groups. Chi-square tests (or Fisher Exact test as appropriate) were used to assess the association between categorical variable. Two-way analysis of variance with repeated measures was used to compare change over time between infants with and those without BPD and pulmonary hypertension. Percentile charts (mean ± standard deviation) were created using linear regression to assess the independent effect of postnatal age (in weeks) and postnatal weight (at time of echocardiogram) on each PAAT measurement, while adjusting for gestational age at birth and gender. Univariate analysis was used to determine the best predictors to enter in the model and then backward step-wise regression was performed to assess the independent effect of gestational age, gender, total oxygen days, length of stay, and common neonatal morbidities (necrotizing enterocolitis, intraventricular hemorrhage, and retinopathy of prematurity), while adjusting for weight at examination.[21] As the incidence of pulmonary hypertension ranges from 14–44% of infants with BPD, we performed stepwise regression to analyze the influence of pulmonary hypertension and BPD on PAAT patterns.[24,26] Since we previously determined that measures of RV function[14,17]

performed better in preterm infants without BPD or pulmonary hypertension, pairwise comparison was conducted using the Bonferroni method to detect any difference in PAAT in a) preterm infants with and without BPD, b) with and without late pulmonary hypertension at 32 weeks PMA c) and with and without pulmonary hypertension at 36 weeks PMA. Finally, receiver operating characteristic curves were constructed to determine cutoff values for PAAT and PAAT/RVET in the first week of age and 32 weeks PMA with the best sensitivity and specificity to predict pulmonary hypertension at 36 weeks PMA. The statistical analysis was performed using SPSS version 14.0 (SPSS, Chicago, IL).

RESULTS

Clinical Data

The maternal and infant clinical data has been previously described[14] and summarized in Table 1 and the supplemental material as comparisons between uncomplicated preterm infants and infants classified with cardio-respiratory disease. In addition the clinical and demographic characteristics of the preterm patients compared by time points are represented in Appendix 2.

Maturational patterns of PAAT and PAAT/RVET in the uncomplicated reference cohort

In uncomplicated preterm infants (n=103), PAAT increased from a median of 43 msec (IQR: 38–47) and PAAT/RVET ranged from 0.28 (0.23–0.30) on day 1 to a median PAAT of 78 msec (IQR:67–84) and PAAT/RVET of 0.32 (0.28–0.38) by 1 year corrected age ($p < 0.001$ for both measures, Figure 2). PAAT and PAAT/RVET at birth significantly correlated with gestational age (r=.81 and .82, p=.001) in uncomplicated infants and infants with BPD and pulmonary hypertension (r=.80 and .81, p=.001, Figure S3, Appendix 3). Time-specific maturational patterns revealed that the most rapid rise of PAAT and PAAT/RVET occurred between day 1 and days 5–7 (Table 2). In the uncomplicated preterm infants, step-wise regression analysis of the effects of gender, birth weight, respiratory support at birth, and selected maternal characteristics, revealed that the relationship of decreased PAAT and PAAT/RVET existed with lower gestational age at birth. A similar statistical approach that also accounted for common neonatal morbidities (necrotizing enterocolitis, intraventricular hemorrhage, and retinopathy of prematurity) revealed that at all time points the maturational patterns of PAAT and PAAT/RVET were associated with both increasing postnatal weight gain (r = .84, .83. $p < .001$, Table 3) and postnatal age (r = .81, .74, $p < .001$, Table 4).

Confounding cardiopulmonary factors.

We evaluated the affect of BPD and pulmonary hypertension on the PAAT measures, presented below. In addition, we also accounted for the affect of the PDA, ventricular function, respiratory distress syndrome, antenatal and postnatal administration of steroids, caffeine, and diuretic use. These analyses are presented in the supplemental material.

BPD.—In infants diagnosed with BPD (n = 116, 52%), the PAAT and PAAT/RVET increased from day 1 through days 5–7 ($p<0.001$ for both). Infants with BPD had a lower day 2 PAAT and PAAT/RVET when compared with infant without BPD (44 ± 8 vs. 47 ± 6, p = .005 and 0.25 ± 0.02 vs. 0.27 ± 0.01, p=.01). The differences did not exist on day 1 (p=.

34) or day 5–7 (p=.56), but returned by 32 weeks PMA (p < .01) and persisted through 36 weeks PMA (p<.001) to 1 year corrected age (p<.001). Although overall, PAAT and PAAT/RVET increased from birth to 1 year corrected age (p<.001) in infants with BPD, PAAT and PAAT/RVET remained stagnant (p=.36 and .45, respectively) from days 5–7 through 36 weeks PMA. PAAT then significantly increased from 36 weeks PMA to 1 year corrected age (P<.01), but PAAT/REVT did not rise (p=.56) over the same period. Difference in PAAT measures between infants with BPD and uncomplicated infants persisted even after adjusting for surfactant, antenatal, and postnatal steroids treatments. Receiver operating characteristic curve analysis was unsuccessful at determining specific cutoff values of PAAT or PAAT/RVET during the first week of age in predicting BPD.

Pulmonary hypertension.—Based on echocardiographic evidence, we found an overall incidence of pulmonary hypertension of 15% (n=17) at 32 weeks PMA, 9% (n=17) at 36 weeks PMA, and 0 at 1 year corrected age. There was no difference in PAAT measures between infants with and with **out** pulmonary hypertension during the first week of age. Receiver operating characteristic curve analysis was unsuccessful at determining specific cutoff values of PAAT or PAAT/RVET during the first week of age in predicting late pulmonary hypertension at 32 and/or 36 weeks PMA. In contrast to the first week of age, all the infants with pulmonary hypertension at 32 weeks PMA and/or 36 weeks PMA had decreased PAAT and PAAT/RVET when compared to those infants without pulmonary hypertension at both time points (p < .001 for both measures at each time point), even after adjusting for the presence of BPD on regression analysis ($\beta = 2.1$, p=.002). Infants with pulmonary hypertension at 32 and/or pulmonary hypertension at 36 weeks also had lower values PAAT and PAAT/RVET at 1 year corrected age than those without pulmonary hypertension, even after adjusting for the common maternal variables that may affect pulmonary vasculature growth and development.[21] For detection of late pulmonary hypertension at 36 weeks PMA, a PAAT < 47 msec and PAAT/RVET < 0.28 at 32 weeks PMA resulted in sensitivity of 91% and specificity of 95%, with an area under the receiver operating characteristic curve of 0.93 (95% CI, 0.88–0.97).

Feasibility and Reproducibility

The measurements were feasible in 95% of the obtained images using the methods previously described by our group.[8] There was high degree of intra-observer agreement for PAAT measurement (coefficient of variation: 5.6%, intraclass correlation coefficient: 0.96 (0.935–0.98) and inter-observer agreement (coefficient of variation: 5.0%; intraclass correlation coefficient: 0.94 (0.89–0.97). PAAT/RVET had similar results, (Appendix 4).

DISCUSSION

In a prospective multi-center longitudinal study of a large cohort of premature infants (≤ 29 weeks at birth), we evaluated PAAT and PAAT/RVET to determine the maturational patterns of RV afterload and the dynamic interaction between RV mechanical performance, pulmonary vascular load and arterial compliance.[8] This study establishes reference patterns for PAAT and PAAT/RVET in preterm infants with a linear maturational increase for each value from birth to 1 year corrected age. PAAT measures are positively correlated with

gestational age at birth in both healthy uncomplicated preterm infants and preterm infants that develop BPD and/or pulmonary hypertension. Preterm infants with BPD and/or pulmonary hypertension have decreased PAAT and PAAT/RVET that track lower to those in uncomplicated preterm infants beyond 1 week of age and remain stagnant through the late neonatal period to 1 year corrected age.

Feasibility and Reproducibility

To our knowledge, this is the largest multi-center study to systemically perform and demonstrate excellent reproducibility analysis with multiple intra- and inter-reliability tests on PAAT measures in preterm infants. The clinical performance of PAAT as a quantitative parameter in neonates is dependent on two critical aspects: feasibility and reproducibility. PAAT and PAAT/RVET, have been utilized in neonatal research studies[10–13,19,27–41] to characterize pulmonary hemodynamics, but are rarely used clinically because they lacked proper validation in neonates with structurally normal cardiac anatomy.[31,33,41] Evans and Archer demonstrated good inter-observer agreement only between two pairs of measurements of PAAT/RVET with a correlation coefficient of 0.92.[31] Subhedar et al. only performed intra-observer variability, but found large limits of agreement and high coefficient of variability.[33] In this study we employed a published protocol on PAAT image acquisition and post-processing data analysis, performed both intra- and inter-observer testing three months apart at two centers to minimize recall bias, and utilized multiple reproducibility testing to complement and confirm the results.[8] The measurements were feasible in 95% of the image at all times points over the first year of age. In comparison, the tricuspid regurgitation velocity was only present in 17% (17/98) at days 5–7, 15% (17/117) at 32 weeks of age, 9% (17/164 at 36 weeks PMA and 11% (9/164) of preterm infants at 1 year corrected age. This degree of feasibility with PAAT measures is in line with commonplace practices within neonatal echocardiography.[18]

Maturational Patterns of PAAT and PAAT/RVET

Birth transition is characterized by hemodynamic alterations during the switch from fetal to post-natal circulation,[17,19,27] and this study demonstrates that PAAT and PAAT/RVET physiologically increase in uncomplicated preterm infants during this period. Both PAAT and PAAT/RVET are linearly associated with increasing gestational age at birth in uncomplicated preterm infants and infants that later develop BPD and/or late pulmonary hypertension. The measures are also associated with both increasing postnatal weight and postnatal age through 1 year corrected age. Other studies have also demonstrated the increase in PAAT values in the transitional period from day 1 to day 2 in both preterm (42 ± 10 to 45 ± 15, $p = 0.04$) and term infants (49 ± 17 to 59 ± 15, $p < 0.001$).[19,27,42] These changes reflect the physiological decrease in afterload, but the rate of increase is slower in preterm infants when compared to term infants, reflective of the immature lung development.[30]

Beyond the first week of age, PAAT has been shown to increase in both term[9] and preterm infants.[10,11,34,43] The increase in PAAT over the first year of age mirrors the postnatal developmental patterns described in term infants,[9] but as expected, the values track lower in preterm infants at comparable time points.[9,21] The expected physiological rapid decrease in

postnatal pulmonary vascular disease may be delayed in the preterm pulmonary vasculature with the resulting time to peak acceleration of flow in the pulmonary outflow tract shortened secondary to the persistence of elevated RV afterload.

BPD and pulmonary hypertension.—There was no difference in PAAT and PAAT/RVET between day 1 and day 2 in preterm infants who required mechanical intervention and those that required non-invasive respiratory support (p=.56). These findings are in contrast to Evans and Archer who demonstrated in the pre-surfactant era, that PAAT measures are decreased in the acute and recovery phases of infants with respiratory disease syndrome.[28,40] We likely found no difference in our study because 93% of the infants received surfactant replacement therapy and 96% of the mothers received antenatal steroids. Hamden and Shaw demonstrated that PAAT/RVET increased, reflective of a drop in afterload, after the administration of surfactant replacement therapy in preterm infants.[35] The decline of oxygen support and the resolution of respiratory disease syndrome in the first month of age in preterm infants has further been shown to correlate to a physiological increase in the corrected ratio of PAAT/RVET.[11] We were unable to properly investigate the effect of mechanical ventilation on PAAT changes beyond the first week of age because 10/12 (85%) of the mechanically ventilated infants at 32 weeks PMA and all infants mechanically ventilated at 36 weeks PMA developed BPD.

In this study, PAAT and PAAT/RVET were lower at day 2 in infants without BPD, but similar by day 5–7. In most preterm infants we would expect pulmonary vascular resistance to be elevated on day 1, but begin to dramatically fall by day 2–3. Multivariate analysis showed that PAAT and PAAT/RVET on day 1 were directly related to gestational age at birth in both uncomplicated preterm infants and those with BPD and/or pulmonary hypertension onset beyond the first week of age, consistent with previous reports.[21,31,34] By days 5–7 the PAAT values were the same between cohorts. We suspect that the influence of the ductus arteriosus and cardiac shunting at one week of age may wash out the ability to detect true differences in PAAT measures between cohorts. The pathogenesis of pulmonary vascular disease in BPD is multifactorial, resulting from complex interactions between maternal, genetic, epigenetic susceptibility, and environmental factors (both prenatal and postnatal).[1] By 32 weeks PMA (1–3 months of age), PAAT and PAAT/RVET were indeed lower in infants with BPD and/or pulmonary hypertension, which is in agreement with previous literature.[10–13] The decline of PAAT and PAAT/RVET in infants with BPD from 32 to 36 weeks PMA is likely reflective of either a failure of the physiologic drop in afterload or their progressive rise in these parameters from birth.[1,21]

PDA.—In this study we found no association between PAAT measures and the presence of a hsDA in the first week of age or any PDA through 1 year corrected age (supplemental material), similar to previous work.[12] Prolonged patency may be associated with numerous adverse outcomes, but the extent to which these adverse outcomes are attributable to the hemodynamic consequences of ductal patency, if at all, has not been established.[44] The ductus arteriosus has a multifaceted biological role in the context of hemodynamic instability in preterm infants and its relationship to PAAT measures cannot be explained solely on the basis of presence of hemodynamic significance, size, or even length of

exposure.[45] In the case of a significant cardiac shunt causing increased volume to the right heart, i.e. PDA or a large ASD, PAAT may be also falsely increase**d**, and be inaccurate. PAAT should therefore be utilized in conjunction with measures of right heart function and assessed cautiously in the setting of high shunt volumes. Prospective studies that test the reliability of PAAT measures at different points along the pulmonary trunk and main pulmonary arteries to isolate the different components of RV afterload from the influence of a hsDA with left to right flow are needed to fully characterize the influence of the ductus arteriosus on PAAT measures in extreme preterm infants.[46]

Clinical implications

These findings may have important clinical implications in preterm infants. In the early stages of pulmonary vascular disease a small increase in pulmonary vascular resistance is accompanied by a large reduction in compliance “to accommodate the entire cardiac output at low arterial pressure with large microcirculatory reserve.”[5] This initial microcirculation loss in early pulmonary vascular disease is not accompanied by a change in pulmonary arterial pressure. Unfortunately, many of the current screening modalities are dependent only on detecting a rise in pulmonary arterial pressure, and the evaluation of pulmonary arterial pressure with Bernoulli’s equation (and pulmonary vascular disease with the Abbas equation[47]) relies on the tricuspid regurgitation velocity that at times imprecisely correlates with cardiac catheterization indices in infants and children.[3] PAAT, as non-invasive index that more broadly captures alterations in components of RV performance and afterload (compliance, vascular resistance, and pressure) may prove to be more informative than pressure estimates alone.[8] In this study we even demonstrated that a PAAT < 47 msec and PAAT/RVET < 0.28 beyond the transitional period detected pulmonary hypertension at 36 weeks PMA.

A systematic review on the use of echocardiography in the assessment of pulmonary hypertension in infants with BPD suggests that in the absence of a reliable tricuspid regurgitation velocity, PAAT and the ratio of PAAT/RVET could be complementary indices for screening and follow up.[2] Similarly, a recent systematic review and meta analysis also suggested that PAAT is useful to identify and monitor pulmonary hypertension and pulmonary vascular disease in adults.[48] The argument that PAAT is limited in clinical practice by a paucity of large prospective studies is no longer valid as two recent studies established PAAT as a non-invasive index of afterload in infants and children with normative values and maturational patterns.[8,9] PAAT is relatively easy to perform, highly reproducible, and unlike pressure estimates based on tricuspid regurgitation velocity and right atrial pressures, Doppler recordings from the RV outflow tract are available in almost in all patients.[29] In our current study, an interpretable tricuspid regurgitation velocity was present in less than 10% of patients during the first week of age, at 32 weeks PMA, and 36 weeks PMA. In a similar cohort of preterm infants, Mourani et al. evaluated tricuspid regurgitation velocity at one week of age and 36 weeks PMA as an early echocardiographic sign of pulmonary vascular disease to the subsequent development of BPD and found tricuspid regurgitation velocity to be present in 8% of all patients at one week and 6% at 36 weeks PMA.[24] Furthermore, the other conventional echocardiographic indices of pulmonary arterial pressure (i.e. septal flattening) have been recognized with low sensitivity and

specificity for detecting mild to moderate manifestations of pulmonary hypertension in preterm infants.[4] By demonstrating excellent reliability and establishing reference patterns of PAAT in preterm infants, our study provides a clinically applicable non-invasive tool that captures the main elements of afterload and may be useful in evaluating pulmonary hypertension in preterm infants.

Limitations

In this study, we elected not to create PAAT z-scores. Indexing PAAT to birthweight, body length, or BSA in neonates and young infants must be interpreted with caution, because of the high variability in body size, pulmonary blood flow, and pulmonary vascular disease in this particular age group.[8,9] Furthermore, recent work demonstrated that sex specific centile curves using left ventricular M-mode echocardiographic values indexed to weight alone were actually similar to curves generated using length and body surface.[49] We therefore elected to present percentile charts (mean +/− standard deviation) using linear regression to assess the independent effect of postnatal age (in weeks) and weight (at the time of echocardiography) on each PAAT measurement, while adjusting for gestational age at birth and gender. There are many approaches to interpret these measures, but understanding both the advantages and limitations will serve to inform the clinician on how PAAT could be an important variable during follow-up investigations of neonates at risk to develop pulmonary hypertension, as it has been shown for pediatric[8,50] and adult patients.[48]

Some additional important considerations should be undertaken when using PAAT and PAAT/RVET as a measure of pulmonary hemodynamics. The confounding variables for interpretation of the PAAT measures are imaging acquisition techniques and post-processing analysis, influence of RV dysfunction, the presence of large left to right shunts, and heart rate.[31] The image acquisition and post process analysis uncertainties were identified in a previous study and quantified in the published protocol.[8] Although we accounted for RV function in our model, as poor myocardial function will prolong PAAT and PAAT/RVET, there is still discussion about what constitutes normal RV function using emerging quantitative measures such as deformation, FAC, and TAPSE.[8] Previous studies have only utilized qualitative assessments of RV function,[29,35] but this is the first study to assess the contribution of these quantitative measures to characterize RV function. Finally, we determined cut-off values of PAAT and PAAT/RVET at 32 weeks to detect pulmonary hypertension at 36 weeks PMA. These measures should be considered to be a “best case” scenario since we determined the cut off value from this same population that we tested. Future research is needed test how these cut-off values perform in an independent population.

CONCLUSION

This prospective multi-center study establishes reference patterns for PAAT and PAAT/RVET measures in preterm infants, and tracks their maturational changes during postnatal development. These measures increase from birth to 1 year corrected age, and are associated with both increasing postnatal weight and age that reflects the postnatal decrease in pulmonary vascular disease and pulmonary arterial pressure, and increase in pulmonary

arterial compliance. BPD and pulmonary hypertension leave a negative impact on PAAT measures. This study suggests the PAAT and its ratio to RVET can be used as complementary modalities to assess physiologic and pathologic changes in pulmonary hemodynamics in neonates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Support:

This study was supported by grants from Premature and Respiratory Outcomes Program (NIH 1U01 HL1014650, U01 HL101794), and Postdoctoral Mentored Training Program in Clinical Investigation (NIH UL1 TR000448). Afif EL-Khuffash is funded by multiple sources: EU FP7/2007–2013 grant (agreement no. 260777, The HIP Trial); the Friends of the Rotunda Research Grant (Reference: FoR/EQUIPMENT/101572); Health Research Board Mother and Baby Clinical Trials Network Ireland (CTN-2014–10).

Abbreviations:

BPD	bronchopulmonary dysplasia
FAC	fractional area of change
FWLS	free wall longitudinal strain
hsDA	hemodynamically significant ductus arteriosus
PAAT	pulmonary artery acceleration time
PDA	patent ductus arteriosus
PMA	post-menstrual age
RV	right ventricle
RVET	right ventricle ejection time
TAPSE	tricuspid annular plane systolic excursion

REFERENCES

1. Mourani PM, Abman SH. Pulmonary Hypertension and Vascular Abnormalities in Bronchopulmonary Dysplasia. Clin Perinatol 2015; 42:839–55. [PubMed: 26593082]
2. Nagiub M, Lee S, Guglani L. Echocardiographic assessment of pulmonary hypertension in infants with bronchopulmonary dysplasia: systematic review of literature and a proposed algorithm for assessment. Echocardiography 2015;32:819–33. [PubMed: 25231322]
3. Groh GK, Levy PT, Holland MR, Murphy JJ, Sekarski TJ, Meyers CL, et al. Doppler echocardiography inaccurately estimates right ventricular pressure in children with elevated right heart pressure. J Am Soc Echocardiogr 2014;27:163–71. [PubMed: 24183542]
4. Mourani PM1, Sontag MK, Younoszai A, Ivy DD, Abman SH. Clinical Utility of Echocardiography for the Diagnosis and Management of Pulmonary Vascular Disease in Young Children With Chronic Lung Disease. Pediatrics 2008;121:317–25. [PubMed: 18245423]

5. Lau EMT, Manes A, Celermajer DS, Galie N. Early detection of pulmonary vascular disease in pulmonary arterial hypertension: time to move forward. Eur Heart J. 2011;32:2489–98. [PubMed: 21616950]
6. Ghio S, Schirinzi S, Pica S. Pulmonary arterial compliance: How and why should we measure it? Glob Cardiol Sci Pract 2015;4:58
7. Levy PT, Keller RL. Pulmonary Vascular Disease in Premature Infants: Early Predictive Models of Late Respiratory Morbidity. Am J Respir Crit Care Med 2018 (Article in Press).
8. Levy PT, Patel MD, Groh G, Choudhry S, Murphy J, Holland MR, et al. Pulmonary Artery Acceleration Time Provides a Reliable Estimate of Invasive Pulmonary Hemodynamics in Children. J Am Soc Echocardiogr 2016;29:1056–65. [PubMed: 27641101]
9. Koestenberger M, Grangl G, Avian A, Gamillscheg A, Grillitsch M, Cvirn Get et al. Normal Reference Values and z Scores of the Pulmonary Artery Acceleration Time in Children and Its Importance for the Assessment of Pulmonary Hypertension. Circ Cardiovasc Imaging. 2017;10:e005336 17. [PubMed: 28003222]
10. Gill AB, Weindling AM. Raised pulmonary artery pressure in very low birth weight infants requiring supplemental oxygen at 36 weeks after conception. Arch Dis Child Fetal Neonatal Ed 1995;72:F20–2. [PubMed: 7743278]
11. Gill AB, Weindling AM. Pulmonary artery pressure changes in the very low birthweight infant developingchronic lung disease. Arch Dis Child 1993;68:303–7. [PubMed: 8466267]
12. Subhedar NV, Hamdan AH, Ryan SW, Shaw NJ. Pulmonary artery pressure: early predictor of chronic lung disease in preterm infants. Arch Dis Child Fetal Neonatal Ed 1998;78:F20–4. [PubMed: 9536835]
13. Su BH, Watanabe T, Shimizu M, Yanagisawa M. Doppler assessment of pulmonary artery pressure in neonates at risk of chronic lung disease. Arch Dis Child Fetal Neonatal Ed 1997;77:F23–7. [PubMed: 9279178]
14. Levy PT, El-Khuffash A, Patel MD, Breatnach CR, James AT, Sanchez AA, et al. Maturational patterns of systolic ventricular deformation mechanics by two-dimensional speckle tracking echocardiography in preterm infants over the first year of age. J Am Soc Echocardiogr 2017; 30:685–98. [PubMed: 28433214]
15. Pryhuber GS, Maitre NL, Ballard RA, Cifelli D, Davis SD, Ellenberg JH, et al. Prematurity and respiratory outcomes program (PROP): study protocol of a prospective multicenter study of respiratory outcomes of preterm infants in the United States. BMC Pediatr 2016;10;15:37.
16. James AT, Corcoran JD, EL-Khuffash AF. Clinical utility of right ventricular fractional area change in preterm infants. Early Hum Dev 2016;92:19–23. [PubMed: 26619069]
17. Levy PT, Dioneda B, Holland MR, Sekarski TJ, Lee CK, Mathur A, et al. Right Ventricular Function in Preterm and Term Neonates: Reference Values for Right Ventricle Areas and Fractional Area of Change. J Am Soc Echocardiogr 2015;28:559–69. [PubMed: 25753503]
18. Levy PT, Holland MR, Sekarski TJ, Hamvas A, Singh GK. Feasibility and reproducibility of systolic right ventricular strain measurement by speckle-tracking echocardiography in premature infants. J Am Soc Echocardiogr 2013;26:1201–13. [PubMed: 23880052]
19. James AT, Corcoran JD, Jain A, McNamara PJ, Mertens L, Franklin O, et al. Assessment of myocardial performance in preterm infants less than 29 weeks gestation during the transitional period. Early Hum Dev 2014;90: 829–35. [PubMed: 25463828]
20. James AT, Corcoran JD, Breatnach CR, Franklin O, Mertens L, El-Khuffash A. Longitudinal assessment of left and right myocardial function in preterm infants using strain and strain rate imaging. Neonatology 2015; 109:69–75. [PubMed: 26583602]
21. Levy PT, Patel MD, Choudhry S, Hamvas A, Singh GK. Evidence of Echocardiographic Markers of Pulmonary Vascular Disease in Asymptomatic Preterm Infants at One year of Age. J Pediatr 2018;18: S0022–3476.
22. Poindexter BB, Feng R, Schmidt B, Aschner JL, Ballard RA, Hamvas A, et al. Comparisons and Limitations of Current Definitions of Bronchopulmonary Dysplasia for the Prematurity and Respiratory Outcomes Program. Ann Am Thorac Soc 2016: 12:1822–30.
23. Engle WA. Age Terminology During the Perinatal Period. Pediatrics 2004;114:1362–4. [PubMed: 15520122]

24. Mourani PM, Sontag MK, Younoszai A, Miller JI, Kinsella JP, Baker CD, et al. Early Pulmonary Vascular Disease in Preterm Infants at Risk for Bronchopulmonary Dysplasia. Am J Respir Crit Care Med 2015; 191:87–95 [PubMed: 25389562]
25. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for chamber quantification. J Am Soc Echocardiogr 2015;28:1–39. [PubMed: 25559473]
26. Weismann CG, Asnes JD, Bazzy-Asaad A, Tolomeo C, Ehrenkranz RA, Bizzarro MJ. Pulmonary hypertension in preterm infants: results of a prospective screening program. J Perinatol 2017;37:572–77. [PubMed: 28206997]
27. Jain A, Mohamed A, El-Khuffash A, Connelly KA, Dallaire F, Jankov RP A Comprehensive Echocardiographic Protocol for Assessing Neonatal Right Ventricular Dimensions and Function in the Transitional Period: Normative Data and Z Scores. J Am Soc Echocardiogr 2014 12;27:1293–304 [PubMed: 25260435]
28. Evans NJ, Archer LN. Doppler assessment of pulmonary artery pressure and extrapulmonary shunting in the acute phase of hyaline membrane disease. Arch Dis Child 1991;6:6–11.
29. Evans N, Archer N. Non invasive assessment of pulmonary arterial pressure in healthy neonates. Arch Dis Child 1992;67:471.
30. Evans NJ1, Archer LN. Postnatal circulatory adaptation in healthy term and preterm neonates. Arch Dis Child 1990;65:24–6. [PubMed: 2306130]
31. Fitzgerald D1 Evans N, Van Asperen P, Henderson-Smart D. Subclinical persisting pulmonary hypertension in chronic neonatal lung disease. Arch Dis Child Fetal Neonatal Ed. 1994;70:F118–22. [PubMed: 8154904]
32. Evans N Cardiovascular effects of dexamethasone in the preterm infant. Arch Dis Child Fetal Neonatal Ed 1994;70:F25–30 [PubMed: 8117123]
33. Subhedar NV, Shaw NJ. Intraobserver variation in Doppler ultrasound assessment of pulmonary artery pressure. Arch Dis Child Fetal Neonatal Ed 1996;75:F59–61. [PubMed: 8795360]
34. Subhedar NV, Shaw NJ. Changes in pulmonary arterial pressure in preterm infants with chronic lung disease. Arch Dis Child Fetal Neonatal Ed 2000;82:F243–7. [PubMed: 10794795]
35. Hamdan AH, Shaw NJ. Changes in pulmonary artery pressure during the acute phase of respiratory distress syndrome treated with three different types of surfactant. Pediatr Pulmonol 1998;25:191–5. [PubMed: 9556011]
36. Murase M, Ishida A. Serial pulsed Doppler assessment of pulmonary artery pressure in very low birth-weight infants. Pediatr Cardiol 2000;21:452–7. [PubMed: 10982705]
37. Murase M1, Ishida A. Echocardiographic assessment of early circulatory status in preterm infants with suspected intrauterine infection. Arch Dis Child Fetal Neonatal Ed 200;91:F105–10
38. Akiba T, Yoshikawa M, Otaki S, Kobayashi Y, Nakasato M, Suzuki H. Prediction of Peak Pulmonary Artery Pressure by Continuous-Wave Doppler Echocardiography in Infants and Children. Pediatr Cardiol 1988;9:225–9. [PubMed: 3237507]
39. Villeneuve A, Bigras JL, Lachance C, Bérubé D, Barrington KJ, Lapointe A, et al. Echocardiographic Right Ventricular Pressure Ratio Correlates with Prolonged Oxygen Therapy in Patients with Moderate to Severe Bronchopulmonary Dysplasia. Ann Pediatr Child Health 2015;3:1087.
40. Evans NJ, Archer LN. Doppler assessment of pulmonary artery pressure during recovery from hyaline membrane disease. Arch Dis Child 1991;66:802–4. [PubMed: 1863127]
41. Skinner JR, Boys RJ, Heads A, Hey EN, Hunter S. Estimation of pulmonary arterial pressure in the newborn: study of the repeatability of four Doppler echocardiographic techniques. Pediatr Cardiol 1996;17:360–9. [PubMed: 8781085]
42. Jain A, Mohamed A, Kavanagh B, Shah P, Kuipers BCW, El-Khuffash A, et al. Cardiopulmonary Adaptation During First Day of Life in Human Neonates. J Pediatr 2018;200:50–57. [PubMed: 29803302]
43. Bokiniec R, Własienko P, Borszewska-Kornacka M, Szymkiewicz-Dangel J. Echocardiographic evaluation of right ventricular function in preterm infants with bronchopulmonary dysplasia. Echocardiography 2017;34:577–586. [PubMed: 28229480]

44. Weber SC, Weiss K, Bührer C, Hansmann G, Koehne P, Sallmon H. Natural History of Patent Ductus Arteriosus in Very Low Birth Weight Infants after Discharge. J Pediatr 2015;167:1149–51. [PubMed: 26239928]

45. Rios DR, Bhattacharya S, Levy PT, McNamara PJ. Circulatory Insufficiency and Hypotension Related to the Ductus Arteriosus in Neonates. Front. Pediatr 2018;6:F474.

46. Chaoui R, Taddei F, Rizzo G, Bast C, Lenz F, Bollmann R. Doppler echocardiography of the main stems of the pulmonary arteries in the normal human fetus. Ultrasound Obstet Gyneco 1998;11:173–9.

47. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. A simple method for noninvasive estimation of pulmonary vascular resistance. J Am Coll Cardiol 2003;41:1021–7 [PubMed: 12651052]

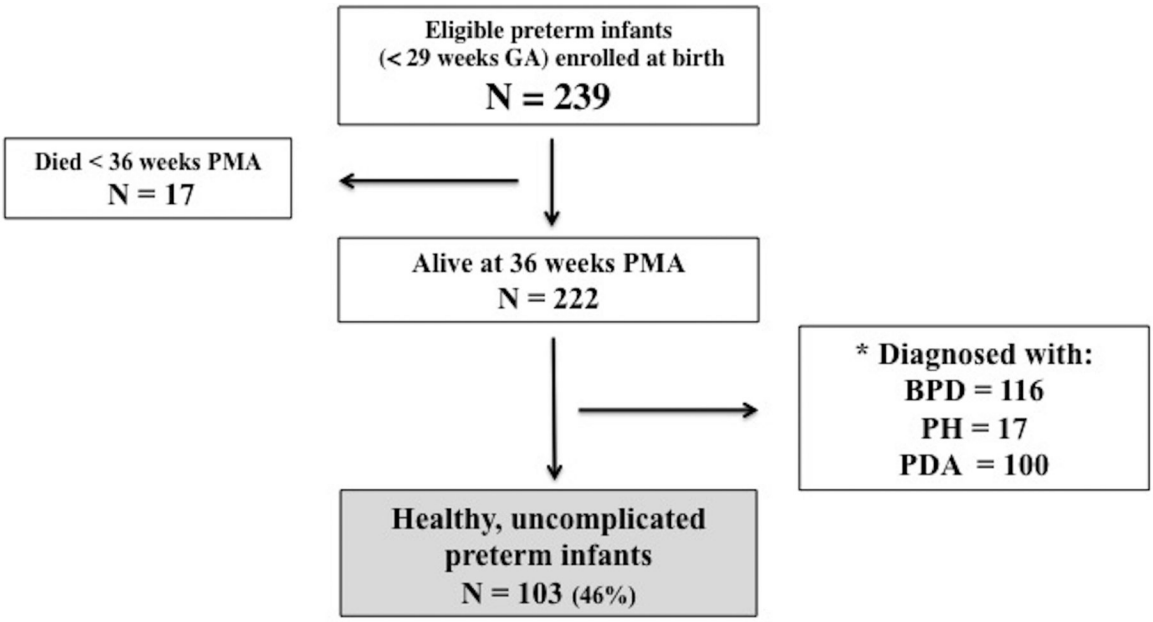
48. Wang YC, Huang CH, TU Y-K. Pulmonary Hypertension and Pulmonary Artery Acceleration Time: A Systematic Review and Meta-Analysis. J Am Soc Echocardiogr 2018;31:201–210. [PubMed: 29229495]

49. Choudhry S, Salter A, Cunningham TW, Levy PT, Nguyen HH, Wallendorf M, et al. Normative Left Ventricular M-mode Echocardiographic Values in Preterm Infants Up To Two Kilograms J Am Soc Echocardiogr 2017;30:781–9. [PubMed: 28599830]

50. Cevik A, Kula S, Olgunturk R, Tunaoglu FS, Oguz AD, Saylan B, et al. Assessment of pulmonary arterial hypertension and vascular resistance by measurements of the pulmonary arterial flow velocity curve in the absence of a measurable tricuspid regurgitant velocity in childhood congenital heart disease. Pediatr Cardiol 2013;3:646–55.

Highlights

- Pulmonary artery acceleration time (PAAT) measures provide a reliable non-invasive tool to characterize pulmonary hemodynamics in children,
- This study establishes PAAT measures as feasible and reproducible from a large cohort of extreme preterm infants followed from birth through one year corrected age.
- PAAT measures increase in uncomplicated preterm infants over the first year of age that is reflective of the physiologic postnatal drop in RV afterload.
- Common cardiopulmonary morbidities, such as bronchopulmonary dysplasia and pulmonary hypertension, appear to leave a negative impact on PAAT measures through the first year of age.
- With the establishment of the range of maturational patterns of PAAT measures and associated variations up to one year CA, PAAT may now be implemented in preterm infants as a means to non-invasively characterize changes in RV afterload in health and disease.



Timing of Echocardiograms	Day 1	Day 2	Day 5-7	32 weeks PMA	36 weeks PMA	1 year CA
Total # infants **	132	132	98	117	164	81
Uncomplicated preterm infants	65	65	36	48	67	30

Figure 1:

Study Flow Diagram of Uncomplicated Preterm Infants:

BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension; PDA, patent ductus arteriosus; PMA, postmenstrual age

*119/222 infants were excluded from the uncomplicated cohort because they either were: a) diagnosed with BPD[22] (n=116, 52%), b) had evidence of PH on echocardiogram at 32 weeks PMA (n=17, 15%) and/or 36 weeks PMA (n=17, 9%)[24] and/or c) had a PDA at or beyond one week (Day 5–7, n=57, 58%; 32 weeks PMA, n=19, 16%, and/or 36 weeks PMA, n=24, 16%). Therefore, after meeting all inclusion criteria, 103 patients (47%) infants were classified as “healthy uncomplicated preterm infants.” (Adapted from J Am Soc Echocardiogr 2017;30:685–98)[14] There was significant overlap between these four categories. ** There were 239 infants recruited for this study (137 infants from the Washington University School of Medicine site in Saint Louis, USA and 102 infants from the Royal College of Surgeons in Ireland site in Dublin, Ireland). Echocardiograms were performed at Day 1 (n=30), Day 2 (n=30), 32 weeks PMA (n=117), 36 weeks PMA (n=117), and 1 year corrected age (CA, n=81) in Saint Louis, USA. Echocardiograms were performed at Day 1 (n=102), Day 2 (n=102), Day 5 (n=98), and 36 weeks PMA (n=47) in Dublin, Ireland.

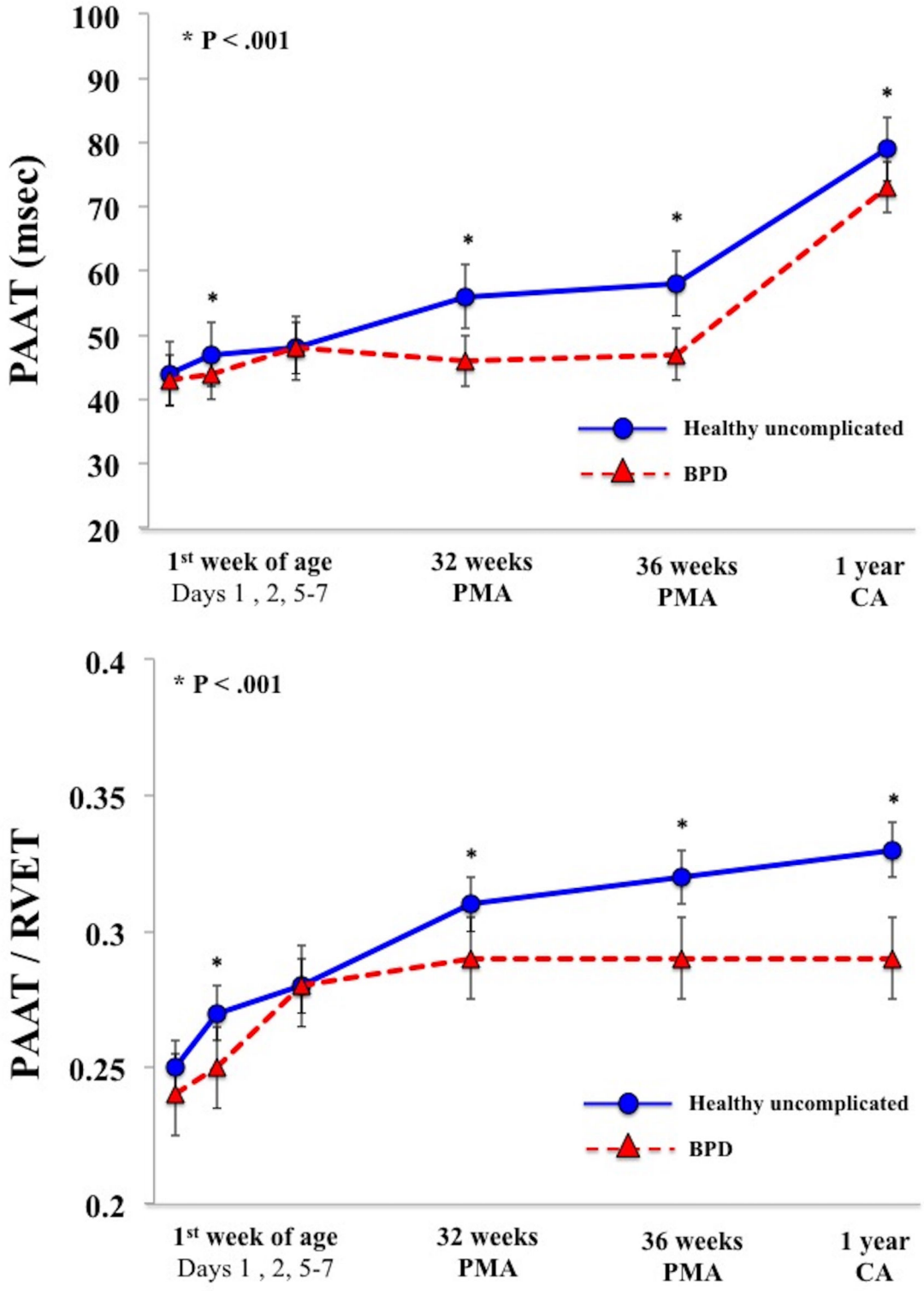


Figure 2:

Maturational patterns of (A) pulmonary artery acceleration time (PAAT) and (B) the ratio of PAAT to right ventricle ejection time (PAAT/RVET) in uncomplicated healthy preterm

infants without cardiorespiratory disease (blue circles) and preterm infants with bronchopulmonary dysplasia, BPD (red triangles).

Table 1:

Maternal and infant characteristics.[14]

	ALL N=222	Uncomplicated Cohort * N=103	Infants with either BPD, PH, and/or PDA N = 119	P-Value
Birthweight (g)	895 [767,1010]	960 [805,1130]	880 [750,980]	0.007
Birthweight strata (g)				
500 – 749 (n=43)	650 [595,698]	690 [650,700]	640 [578.685]	0.13
750 – 999 (n=90)	880 [820,950]	853 [809,940]	890 [830,950]	0.47
1000 – 1250 (n=89)	1125 [903,1255]	1140 [1052,1265]	1110 [1045,1217]	0.71
Gestational age	27 [26,28]	27 [26,28]	26 [25,27]	<0.01
Gender (female)	108 (49%)	60 (58%)	72 (60%)	0.22
Race				0.64
White	156 (70%)	91 (82%)	68 (57%)	
Black	63 (54%)	21 (20%)	39 (33%)	
Asian	2 (2%)	1 (1%)	1 (1%)	
Other	1 (1%)	0	1 (1%)	
Ethnicity				0.36
Hispanic or Latino	3 (3%)	2 (2%)	1 (1%)	
Not Hispanic or Latino	219 (97%)	101 (98%)	118 (99%)	
Maternal Smoking	28	11 (11%)	17 (14%)	0.67
Antenatal corticosteroids	197 (89%)	99 (96%)	98 (82%)	0.76
Surfactant Replacement Therapy	222 (100%)	103 (100%)	119 (100%)	0.84
Multiples	14 (6%)	3 (3%)	11 (9%)	0.23
Cesarean section	160 (72%)	75 (73%)	85 (71%)	0.56
Maternal complications				
Gestational DM	10 (5%)	7 (7%)	3 (3%)	0.57
Gestational HTN	35 (16%)	17 (17%)	18 (15%)	0.28
Prolonged rupture of membranes	38 (17%)	15 (15%)	23 (19%)	0.58
Chorioamnionitis	20 (9%)	10 (10%)	10 (8%)	0.51
Preeclampsia	56 (25%)	26 (26%)	30 (25%)	0.62
Placental Abruption	38 (17%)	17 (17%)	21 (18%)	0.89
Necrotizing enterocolitis	21 (9%)	11 (11%)	10 (8%)	0.53

	ALL N=222	Uncomplicated Cohort * N=103	Infants with either BPD, PH, and/or PDA N = 119	P-Value
ROP threshold (Stage 2 or higher)	43 (19%)	8 (9%)	35 (29%)	0.004
IVH (Grade 3 or 4)	28 (13%)	9 (9%)	19 (16%)	0.09
Total oxygen days (NICU)	84 [40,107]	34 [19,50]	92 [82,115]	< 0.001
Length of stay (NICU)	91 [76,114]	79 [64,89]	98 [87,119]	< 0.001

Data are presented as median [interquartile range], or number (Percentage)

BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension; PDA, patent ductus arteriosus; DM, diabetes mellitus;

HTN, hypertension; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage

*Healthy uncomplicated cohort, defined as preterm infants without BPD, echocardiographic signs of pulmonary hypertension at 32 or 36 weeks PMA, and/or a hemodynamically significant ductus arteriosus at day 5–7 or any size PDA at 32 or 36 weeks PMA.

Table 2:

Pulmonary artery acceleration time measures over the 1st week.

	Day 1	Day 2	Day 5 – 7	p
Entire cohort				
Number of infants	132	132	98	
PAAT (msec)	44 ± 4	46 ± 4 *†	48 ± 5 *†	0.001
PAAT/RVET	0.24 ± 0.02	0.26 ± 0.01 *	0.28 ± 0.03 *†	0.001
Healthy uncomplicated cohort				
Number of infants	65	65	36	
PAAT (msec)	44 ± 3	47 ± 3 *†	49 ± 6 *†	<0.001
PAAT/RVET	0.25 ± 0.02	0.27 ± 0.01 *†	0.29 ± 0.03 *†	<0.001

Values are presented as mean (standard deviation). One way ANOVA with repeated measures was used to assess the change in values over time. * = $p < 0.05$ compared with previous day measurement;

† = $p < 0.05$ compared with Day 1 measurement (with Bonferroni adjustment).

PAAT, pulmonart artery acceleration time

RVET, right ventricle ejection time

Table 3

PAAT measures in healthy uncomplicated preterm infants by weight

Weight (kg)	Infants* (*n*)	HR (beats/min)	PAAT (msec)	PAAT/RVET
0.5–0.9	66	172 ± 14	43 ± 4	0.27 ± 0.03
1.0–1.4	82	168 ± 12	52 ± 4	0.28 ± 0.01
1.5–1.9	62	163 ± 11	53 ± 5	0.29 ± 0.04
2.0–2.4	50	159 ± 15	54 ± 4	0.30 ± 0.02
2.5–2.9	21	161 ± 13	56 ± 6	0.30 ± 0.03
8.0–9.0	16	138 ± 17	77 ± 5	0.32 ± 0.03
10.0–12.0	14	135 ± 15	80 ± 8	0.33 ± 0.02

HR, Heart rate.

Data are expressed as mean ± SD.

*Healthy uncomplicated cohort, defined as preterm infants without BPD, echocardiographic signs of pulmonary hypertension at 32 or 36 weeks' PMA, and/or hemodynamically significant PDA at days 5 to 7 or any size PDA at 32 or 36 weeks' PMA. At day 1, $n = 65$; at day 2, $n = 65$; at days 5 to 7, $n = 36$; at 32 weeks' PMA, $n = 48$; at 36 weeks' PMA $n = 67$; and at 1-year corrected age, $n = 30$.

Table 4

PAAT measures in uncomplicated preterm infants by age beyond the 1st week

Age (wk)	Infants* (*n*)	HR (beats/min)	PAAT (msec)	PAAT/REVT
3–5	40	165 ± 12	51 ± 9	0.28 ± 0.01
6–8	57	163 ± 13	55 ± 5	0.29 ± 0.02
9–11	18	158 ± 10	58 ± 4	0.30 ± 0.04
60–79	26	138 ± 12	75 ± 4	0.32 ± 0.03
80–99	4	132 ± 11	78 ± 3	0.33 ± 0.02

Data are expressed as mean ± SD.

HR, Heart rate.

*Uncomplicated, defined as infants without BPD or echocardiographic signs of pulmonary hypertension at 32 or 36 weeks. There were 48 uncomplicated preterm infants at 32 weeks' PMA, 67 uncomplicated preterm infants at 36 weeks' PMA, and 30 uncomplicated preterm infants at 1 year corrected age. PMA and/or hemodynamically significant PDA at days 5 to 7 or any size PDA at 32 or 36 weeks' PMA.