



# Pulmonary Artery Pressures in School-Age Children Born Prematurely

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**Objectives** To test the hypothesis that pulmonary artery pressures were higher in school aged children born extremely premature than those born at term. We also wanted to assess whether pulmonary artery pressures differed between children born prematurely with or without bronchopulmonary dysplasia (BPD) or between those randomized in the neonatal period to different ventilation modes.

**Study design** Transthoracic echocardiography was performed on 193 children born extremely premature (106 had BPD) and 110 children born at term when they were 11-14 years of age. Ninety-nine children born extremely premature had been supported by high-frequency oscillation and 94 by conventional ventilation. Tricuspid regurgitation was assessed in the apical 4-chamber and modified parasternal long-axis views. Continuous-wave Doppler of the peak regurgitant jet velocity was used to estimate the right-ventricular-to-right-atrial systolic pressure gradient.

**Results** Tricuspid regurgitation was measurable in 71% (137/193) of the children born preterm and 75% (83/110) of the children born at term ( $P$  .23). The children born prematurely compared with the children born at term had a greater peak tricuspid regurgitation velocity (2.21 vs 1.95 m/s,  $P$  < .001) and the children born prematurely who had BPD vs those without BPD had a greater peak tricuspid regurgitation velocity ( $P$  = .023). There were no significant differences in pulmonary artery pressures according to neonatal ventilation mode.

**Conclusions** Pulmonary artery pressures were estimated to be greater in 11- to 14-year-old children born extremely prematurely compared with those born at term and in those born prematurely who developed BPD compared with those who did not but did not differ significantly by neonatal ventilation mode. (*J Pediatr* 2017;191:42-9).

**P**ulmonary hypertension appears to be common in infants of very low birth weight. In one series, 18% of infants had pulmonary hypertension during their time in the neonatal intensive care unit.<sup>1</sup> Those with bronchopulmonary dysplasia (BPD) or who were born small for gestational age were most likely to be affected. In certain infants, high pulmonary pressures persisted beyond discharge from the neonatal intensive care unit.<sup>1-4</sup> There is, however, conflicting evidence regarding whether pulmonary hypertension persists into later childhood in those born prematurely. In one study, children who had had BPD, when assessed at 2-4 years of age, had a decreased pulmonary artery acceleration time and left and right ventricular myocardial performances consistent with greater pulmonary artery pressures and impaired biventricular systolic and diastolic function.<sup>5</sup> Mourani et al evaluated 10 patients who had had BPD and found elevated mean pulmonary artery pressures (MPAP) at cardiac catheterization at a median age of 10 years.<sup>6</sup> There are limited data on pulmonary artery pressures of children born prematurely, particularly those who did not develop BPD.

An aim of this study was to test the hypothesis that pulmonary artery pressures at 11-14 years of age would be greater in those born extremely prematurely (that is, <29 weeks of gestation) compared with those born at term. In addition,

BPD	Bronchopulmonary dysplasia
FEF <sub>25</sub>	Forced expiratory flow at the 25% of exhaled forced vital capacity
FEF <sub>25-75</sub>	Mean forced expiratory flow between 25% and 75% of the forced vital capacity
FEF <sub>50</sub>	Forced expiratory flow at the 50% of exhaled forced vital capacity
FEF <sub>75</sub>	Forced expiratory flow at the 75% of exhaled forced vital capacity
FEV <sub>1</sub>	Forced expiration volume of air exhaled in the first second
FVC	Forced vital capacity
HFO	High-frequency oscillation
IVC	Inferior vena cava
LVEF	Left ventricle ejection fraction
MPAP	Mean pulmonary artery pressure
RA	Right atrial
RAP	Right atrial pressure
RV	Right ventricular
SPAP	Systolic pulmonary artery pressure
TAPSE	Tricuspid annular plane systolic excursion
UKOS	United Kingdom Oscillation Study
VMAX	maximum velocity

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we wished to determine whether pulmonary artery pressures differed between those who had or did not have BPD. Among children born extremely prematurely, we have demonstrated that a neonatal ventilation mode, high-frequency oscillation (HFO), was associated with better lung function at 11-14 years of age.<sup>7</sup> The children had been entered into a randomized trial of 2 neonatal ventilation modes, the United Kingdom Oscillation Study (UKOS).<sup>8</sup> There is a significant interaction between pulmonary blood vessels and branching airways during lung development.<sup>9</sup> Hence, we further aimed to test the hypothesis that the HFO group would have lower pulmonary artery pressures than the group supported by conventional ventilation.

## Methods

Term and preterm groups of children were assessed separately, at 11-14 years of age. The children born prematurely were part of the UKOS.<sup>7,8</sup> Children born at term were recruited from local schools in South London. All participants were assessed at a single center (King's College Hospital NHS Foundation Trust, London, United Kingdom). Assessments of children born preterm were done in the time period from the end of July 2011 until the end of February 2013, but echocardiography was only possible from November 2011 (Figure 1; available at [www.jpeds.com](http://www.jpeds.com)). Children born at term were assessed from June 2013 until the end of February 2014 (Figure 2; available at [www.jpeds.com](http://www.jpeds.com)). Children were excluded from analysis if found to have a structural congenital heart or lung condition, or if they were acutely unwell at the time of assessment. The study was approved by the South West London National Research Ethics Service Committee, and parents gave informed, written consent for their child to take part. At assessment, the children's height, weight, and blood pressure were measured. Blood pressure was measured by the use of a vital signs monitor with a pediatric blood pressure cuff of appropriate size. Oxygen saturation assessments were obtained by pulse oximetry.

### Echocardiography

Two-dimensional echocardiography was performed with a Philips iE33 ultrasound device (Koninklijke Philips NV, Amsterdam, The Netherlands), equipped with standard 5- and 8-MHz transducers. Multiple views were recorded, including subcostal long axis, apical 4-chamber, parasternal long axis, parasternal long axis angulated for tricuspid valve, and parasternal short axis views. In the apical 4-chamber and the parasternal long axis angulated views, color Doppler was used to look for tricuspid regurgitation. The reproducibility of the measurements was assessed on 20 scans and reviewed independently by a pediatric cardiology consultant and the research fellow. If present, continuous-wave Doppler was used to look at the tricuspid regurgitation Doppler profile. In the presence of a complete tricuspid regurgitation envelope throughout systole, the time-velocity integral was traced to obtain the peak and mean systolic right ventricular-right atrial (RV-RA) gradients via the modified Bernoulli equation.<sup>10</sup> Two pulmonary artery pressure indices, the systolic pulmonary artery

pressure (SPAP) and MPAP, were derived from the peak and mean systolic RV-RA gradients.

To assess the right atrial pressure (RAP), the inferior vena cava (IVC) diameter was measured 2 cm from the IVC-RA junction. The child was asked to perform one brief rapid inspiration, and IVC collapse was recorded. When the IVC diameter was <2 cm, the RAP was estimated as 5 mm Hg when the collapsibility was >50% and as 10 mm Hg when the collapsibility was <50%. When the IVC diameter was >2 cm, the RAP was estimated as 15 mm Hg when the collapsibility was >50% and as 20 mm Hg when the collapsibility was <50%.<sup>10</sup>

Measurements of the IVC diameter in children have been found to correlate with RAP when measured by cardiac catheterization; however, the IVC collapsibility has no significant association with RAP.<sup>11</sup> Hence, the SPAP was calculated by adding to the peak systolic RV-RA gradient assuming an RAP of 5 mm Hg in all cases. The MPAP was calculated as the mean RV-RA gradient plus RAP was assumed to be 5 mm Hg in all cases.<sup>12</sup> Measurements of RAP from the collapsibility and diameter of the IVC were compared between groups independently from the tricuspid regurgitation measurements.

Pulmonary artery hypertension was defined as SPAP >36 mm Hg, calculated from the peak tricuspid regurgitation velocity, which was  $\geq 2.8$  m/s, as per the European Respiratory Society guidelines.<sup>13</sup> The children with an SPAP of  $\leq 30$  mm Hg were divided into 2 groups; those with a SPAP <25 mm Hg (low SPAP) and those with an SPAP of 30-25 mm Hg (moderate SPAP).

Additional measurements of the pulmonary artery pressure, independent of tricuspid regurgitation velocity, were undertaken, that is, the pulmonary end-diastolic pressure estimated from pulmonary regurgitation jet and the pulmonary artery acceleration time.<sup>14</sup> RV systolic function was estimated by calculating tricuspid annular plane systolic excursion (TAPSE) with the M-mode measurement of the systolic long axis motion of the RV free wall in the apical 4-chamber view.<sup>15-17</sup>

To exclude secondary pulmonary hypertension caused by left atrial hypertension, a number of left-sided measurements were made. These included left atrium dimensions measured in the apical 4-chamber view at the end of ventricular systole. Mitral valve inflow velocities, the ratio of the early filling, and atrial filling velocities of the left ventricle (E/A wave ratio) were determined. The end-diastolic diameter of the left ventricle, left ventricle ejection fraction (LVEF), and end-diastolic diameter of the interventricular septum were measured from the M-mode recorded at the tip of the mitral valve leaflets in the long parasternal view. The parasternal short-axis views were inspected and recorded at the level of mitral valve leaflets to exclude RV dilatation.<sup>12,18</sup>

### Spirometry

Large-airway and small-airway function was assessed by spirometry. Measurements of forced expiratory flow in the first second (FEV<sub>1</sub>) and at 25%, 50%, and 75% (FEF<sub>25</sub>, FEF<sub>50</sub>, FEF<sub>75</sub>) of the expired vital capacity (FVC) were obtained. A Jaeger MS-PFT Analyzer Unit (Jaeger, Würzburg, Germany) was used. The measurement was considered reproducible if 3 technically sat-

isfactory volume-time loops were obtained with FEV<sub>1</sub> and FVC measurements within 6% of each other.<sup>19</sup> The results were expressed as the percentage predicted for height and weight with the use of established reference ranges and converted into z scores as appropriate.<sup>20</sup>

The sample size for the cohort born prematurely was fixed, as the children were followed up at age 11-14 years from the UKOS trial.<sup>7</sup> Post hoc power calculation for the differences in pulmonary pressures was performed for the peak velocity of the tricuspid regurgitation (tricuspid regurgitation v<sub>max</sub> [m/s]), assessed by continuous-wave Doppler as the primary outcome. The achieved sample size of 110 children in each group allowed a difference of 1 SD to be detected with 90% power at the 5% significance level. Difference in pulmonary pressure of 3 mm Hg (equal to difference in velocity of 0.9 m/s) is considered significant in predicting the clinical outcome.<sup>13,21,22</sup>

### Statistical Analyses

Differences were assessed for statistical significance with the Student *t* test, the Mann-Whitney *U* test, or  $\chi^2$  test as appropriate. A sensitivity analysis was performed for birth weight and gestational age for all echocardiographic parameters. Because the perinatal data of the term children were incomplete, a separate analysis was performed to compare the children born at term and preterm with available data on gestational age and birth weight. All echocardiographic and spirometry results were adjusted in the regression analysis for observed baseline imbalances at the time of assessment, that is, the differences in age and height between the group born preterm and the group born at term; ANCOVA was performed. Three group comparisons were performed for all echocardiographic measurements (children born preterm with previous BPD, children born preterm without BPD, and chil-

dren born at term). One-way ANOVA was used to assess the influence of BPD diagnosed as oxygen requirement at 36 weeks' corrected gestational age. The analysis was performed with SPSS, 22 version (SPSS GmbH Software, IBM Corp, Armonk, New York).

## Results

Two hundred children born prematurely were assessed. Seven were excluded from the analysis. One child had a large atrial septum defect, 1 had a clinically significant persistent ductus arteriosus, 1 was diagnosed with hypertrophic cardiomyopathy at the time of screening, 2 had severe scoliosis, and 2 had a poor window quality on echocardiography assessment. One hundred six of the children born prematurely had had BPD, defined as oxygen dependency beyond 36 weeks' postmenstrual age. One hundred thirteen children born at term were assessed. Three were excluded from the analysis: 1 child had had a congenital diaphragmatic hernia, 1 had severe nephrotic syndrome with a pericardial effusion, and 1 was discovered at assessment to have been born prematurely.

At assessment, the children born prematurely compared with the children born at term had a lower age ( $P = .02$ ) and height ( $P < .001$ ), (Table I). The mean oxygen saturation, although in the normal range in both groups, was greater in the children born at term ( $P = .008$ ), and the systolic and the diastolic blood pressure lower in the children born prematurely ( $P < .001$ ) (Table I).

The tricuspid regurgitation velocity jet was present and measurable in 71% (137/193) of children born preterm and 75% (83/110) of children born at term,  $P = .23$ . There was moderate to substantial agreement on the assessment of tricuspid regurgitation between the 2 assessors (kappa statistic 0.69). In the population born preterm, 1 child had an SPAP of 36 mm

**Table I. Demographics by maturity at birth**

Demographics	No. participants with results	Children born preterm n = 193	Children born at term n = 110	Mean difference, term-preterm (95% CI)	P value
Gestational age at birth, wk	Term 110 Preterm 193	26.9 (1.33)	39.9 (1.48)	13.1 (12.8-13.4)	<.001
Birth weight, g	Term 110 Preterm 193	894 (203)	3510 (434)	2616 (2533-2699)	<.001
Male sex	Term 110 Preterm 193	99 (51.3%)	63 (57.3%)	6.0% (-5.6, 17.6)	.316
Age, y	Term 110 Preterm 193	12.1 (0.7)	12.3 (1.1)	0.23 (0.03-0.44)	.02
Weight, kg	Term 110 Preterm 193	44.9 (11.9)	46.4 (11.4)	1.88 (0.88-4.6)	.181
Height, cm	Term 110 Preterm 193	151.9 (8.7)	157.3 (9.7)	5.36 (3.2-7.5)	<.001
Hb, g/dL, median (IQR)	Term 110 Preterm 193	12.5 (11.8-13.1)	12 (11.4-12.9)	-0.5 (9, -2.1)	.001
Oxygen saturation (%), median (IQR)	Term 110 Preterm 193	98 (97-99)	99 (98-99)	1 (0-5)	.008
Systolic blood pressure, mm Hg, median (IQR)	Term 110 Preterm 193	116 (97-148)	119 (90-140)	3 (58-8)	.023
Diastolic blood pressure, mm Hg, Median (IQR)	Term 110 Preterm 193	73 (42-100)	79 (60-102)	6 (60-2)	<.001

Data are shown as n (%), median (IQR), or mean (SD).

Hg, and 4 children had an MPAP  $\geq 25$  mm Hg, but none of the children born at term were so affected ( $P < .001$ ). There were also significant differences in the proportions of children born preterm and children born at term with a low SPAP ( $< 25$  mm Hg) (51% preterm vs 87% term) or a moderate SPAP (25–30 mm Hg) (40% preterm vs 13% term) ( $P < .001$ ,  $P < .001$ , respectively).

The peak tricuspid regurgitation velocity, the peak and mean RV-RA gradient, the estimated RA pressure, and the calculated SPAP and the MPAP were significantly greater in the children born prematurely (**Table II**). The mean TAPSE was significantly lower in the children born prematurely compared with the children born at term, although the ranges in both groups were within normal limits. The LVEF was greater in the children born prematurely in comparison with the children born at term (68.7% vs 64.8%,  $P = .001$ ) (**Table II**).

There were no significant differences in left atrial size, left ventricle end-diastolic diameter, or the diastolic function of the left ventricle (E/A ratio) between the group born prematurely and group born at term born (**Table II**). There was, however, a significantly lower interventricular septum end-diastolic diameter in the children born prematurely (**Table II**). In addition, there was significantly greater end-diastolic velocity of the pulmonary regurgitation in the children born prematurely ( $P = .046$ ) (**Table II**). Pulmonary artery acceleration time was shorter in children born preterm; however, this was not statistically significant after we adjusted for age and height at the time of assessment (**Table II**). When the sensitivity analysis for birth weight and gestational age was performed, the differences between the group born preterm and group born at term remained statistically significant for all the cardiac results except the LVEF (%) (**Table II**).

All the lung function results of the children born prematurely were significantly lower than the children born at term (**Table II**). A mean difference in FEV<sub>1</sub> z score of  $-0.78$  SD was found between term and preterm groups,  $P < .001$ . There was also significantly reduced FEV<sub>1</sub>/FVC z score in children born prematurely (mean difference 1.06 SD,  $P < .001$ ) and reduced peak expiratory flow percentage predicted (mean difference 12.7%,  $P < .001$ ) (**Table II**). Children born prematurely also had lower small and medium airway function, with significant differences in FEF<sub>25</sub> z score, FEF<sub>50</sub> z score, FEF<sub>75</sub> z score, and FEF<sub>25-75</sub> z score (ie, mean difference in FEF<sub>25-75</sub> z score 0.9 SD,  $P < .001$ ) (**Table II**).

Children born prematurely who had had BPD had a significantly lower mean gestational age at birth and birth weight and lower oxygen saturation levels at assessment than children born prematurely without BPD (**Table III**). Comparison of the results of those born prematurely who did or did not develop BPD demonstrated those who had BPD had significantly greater mean tricuspid regurgitation v<sub>max</sub> ( $P = .023$ ) and significantly lower mean LVEF ( $P = .006$ ) (**Table IV**). In addition, children who had developed BPD had significantly lower FEF<sub>50</sub> ( $P = .04$ ) and FEF<sub>25-75</sub> z-scores ( $P = .04$ ) (**Table IV**). There were no significant differences in the demographics or the echocardiographic results between the children born prematurely who had been supported by HFO ventilation or

conventional mechanical ventilation (**Table V**; available at [www.jpeds.com](http://www.jpeds.com)).

## Discussion

We have demonstrated that at 11–14 years of age, the mean pulmonary pressures of children born extremely preterm were greater than those of children born at term. Only 1 of the children born prematurely, however, had a systolic pulmonary pressure of 36 mm Hg, measured by SPAP and, therefore, fulfilled the diagnosis of pulmonary hypertension according to European Respiratory Society guidelines.<sup>13</sup>

In addition to the pulmonary pressures being greater in children born prematurely, they also had lower RV systolic function as measured by TAPSE. The differences remained significant after we adjusted for differences in age and height between those born at term or prematurely. Our results suggest that greater pulmonary pressures in the children born prematurely had affected the systolic function of their right ventricle, even in the absence of pulmonary hypertension.

It is interesting that the greater pulmonary artery pressure and RV afterload did not cause an increase in RV septal wall thickness. Indeed, the children born prematurely had a thinner septum, although still within normal z score range. A possible explanation is the lower blood pressures of the children born prematurely. In addition, the systolic afterload of the left ventricle is a more important determinant of septal thickness.

Our results contrast with those of Joshi et al.<sup>22</sup> In their study, no significant differences at 8–12 years of age were found in right and left ventricular function between 90 children born either at term or prematurely. Sixty of the children were born at  $< 33$  weeks of gestation, but only 28 had had BPD. No significant differences were found in right and left ventricular function between those with or without BPD. The sample size, however, was based on a difference in the response of the pulmonary artery pressures to hypoxia.<sup>22</sup>

There is evidence that preterm birth is associated with global myocardial structural and functional differences in adult life, with potentially clinically significant impairment in RV systolic function.<sup>23,24</sup> In a study of 102 young adults born prematurely, smaller RV size was found on cardiovascular magnetic resonance compared with individuals born at term. Furthermore, 21% of the young adults had ejection fractions of the right ventricle below the lower limit observed in adults born at term.<sup>24</sup> The changes in the right ventricle were greater than those previously observed in the left ventricle.<sup>20</sup> Unfortunately, the aforementioned study did not provide simultaneous data on the pulmonary pressures. It is possible, however, that the structural changes detected in adulthood could be a consequence of an increase in pulmonary artery pressures. In a recent study by Aye et al, TAPSE was found to be reduced at birth and at 3 months of age in children born moderately premature, that is, born at a gestational age of 34 weeks.<sup>25</sup>

The main finding of the study was a disproportionate increase in the ventricular mass in the children, suggesting that preterm birth had altered the growth pattern of cardiomyocytes from hyperplastic to hypertrophic. It was, however, not

**Table II.** Echocardiographic measurements and lung function measurements according to gestation groups, including pulmonary pressure measurements based on the tricuspid valve velocity and IVC diameter, left atrial size, diastolic and systolic function of the left ventricle, left ventricle and interventricular septum diameter and systolic function of the right ventricle, pulmonary valve velocity, systolic gradient across pulmonary valve, end-diastolic velocity of pulmonary regurgitation and pulmonary artery acceleration time, and spirometry measurements of large and small airway function

Measurements	No. participants with results <sup>†</sup>	Children born preterm n = 193	Children born at term n = 110	Mean difference (term-preterm) (95% CI)	P value*
TR peak velocity, m/s	Term 83 Preterm 137	2.21 (0.21)	1.95 (0.23)	-0.25 (-0.31, -0.19)	<.001
Maximum RV-RA gradient, mm Hg	Term 83 Preterm 137	19.77 (4.04)	15.46 (3.26)	-4.3 (-5.34, -3.27)	<.001
Mean RV-RA gradient, mm Hg	Term 54 Preterm 86	13.9 (2.86)	11.5 (2.38)	-2.39 (-3.32, -1.47)	<.001
IVC diameter	Term 108 Preterm 190	1.79 (0.30)	1.69 (0.24)	-0.09 (-0.15, -0.02)	.001
Estimated RAP	Term 108 Preterm 190	7.82 (4.26)	5.75 (2.64)	-2.08 (-2.97, -1.18)	<.001
SPAP, <sup>‡</sup> mm Hg	Term 83 Preterm 137	24.8 (4.1)	20.2 (3.5)	-4.6 (-5.6, -3.53)	<.001
MPAP, <sup>§</sup> mm Hg	Term 54 Preterm 86	18.9 (2.8)	16.6 (2.1)	-2.31 (-3.2, -1.4)	<.001
LA diameter, cm <sup>2</sup>	Term 110 Preterm 193	11.7 (1.8)	12.0 (1.49)	0.32 (-0.72, 0.84)	.75
E/A	Term 103 Preterm 180	1.74 (0.27)	1.80 (0.23)	0.06 (-0.03, 0.12)	.062
LVEDD z score	Term 109 Preterm 188	-0.05 (2.03)	-0.14 (0.98)	-0.09 (-0.5, 0.32)	.37
LVEF, %	Term 109 Preterm 188	68.7 (8.0)	64.8 (7.1)	-3.87 (-5.69, -2.04)	.001 <sup>¶</sup>
EDIVS z score	Term 109 Preterm 188	-0.14 (0.69)	0.31 (0.67)	0.45 (0.29, 0.61)	<.001
PAAT, ms	Term 108 Preterm 181	142 (21.4)	149 (16.4)	-6.66 (-11.4, -1.93)	.21 <sup>**</sup>
PI end diast. v, m/s	Term 41 Preterm 58	0.9 (0.15)	0.82 (0.14)	-0.06 (-0.12, -0.01)	.046
PV v max, m/s	Term 109 Preterm 191	0.93 (0.2)	0.86 (0.12)	0.07 (0.04, 0.12)	.004
TAPSE z score	Term 104 Preterm 178	0.03 (1.94)	0.98 (1.16)	0.95 (0.54, 1.36)	.001
FEV <sub>1</sub> z score	Term 187 Preterm 108	-0.77 (1.1)	-0.11 (1.0)	-0.78 (-1.03, -0.51)	.003
FVC z score	Term 187 Preterm 108	-0.35 (1.0)	-0.10 (0.9)	-0.36 (-0.6, -0.12)	<.001
FEV <sub>1</sub> /FVC z score	Term 187 Preterm 108	-1.5 (1.8)	-0.3 (1.4)	-1.06 (-1.5, -0.6)	<.001
FEF <sub>25</sub> z score	Term 187 Preterm 108	-1.03 (0.9)	-0.16 (1.1)	-0.9 (-1.1, -0.6)	<.001
FEF <sub>50</sub> z score	Term 187 Preterm 108	-1.2 (0.9)	-0.3 (1.0)	-0.95 (-1.2, -0.7)	<.001
FEF <sub>75</sub> z score	Term 187 Preterm 108	-1.06 (0.9)	-0.5 (1.0)	-0.6 (-0.8, -0.35)	<.001
FEF <sub>25-75</sub> z score	Term 187 Preterm 108	-1.4 (1.1)	-0.5 (1.1)	-0.9 (-1.2, -0.7)	<.001
PEF, %	Term 187 Preterm 108	82.9 (16)	93.7 (20)	-12.7 (-17.1, -8.2)	<.001

E/A, ratio of left ventricle inflow velocities; EDIVS, interventricular septum end diastolic diameter; LA, left atrium; LVEDD, left ventricle end-diastolic diameter; PAAT, pulmonary artery acceleration time; PEF, peak expiratory flow; PI end diast. v, end-diastolic velocity of the pulmonary regurgitation; PV v max, pulmonary maximum outflow velocity; TR, tricuspid regurgitation. Data are presented as mean (SD) or n (%).

\*All echocardiographic results were adjusted in the regression analysis for observed baseline imbalances at the time of assessment (age and height), by performing an analysis of covariance.

<sup>†</sup>n is the number of children in whom the results of the measurement were available.

<sup>‡</sup>SPAP was calculated by adding a minimal RAP of 5 mm Hg to the peak RV-RA gradient.

<sup>§</sup>MPAP was calculated by adding a minimal RAP of 5 mm Hg to the mean RV-RA gradient.

<sup>¶</sup>P = .063 after sensitivity analysis.

\*\*P value (unadjusted) <.001.

**Table III. Demographics by BPD status in children born prematurely**

Demographics	Children born preterm with BPD, n = 106	Children born preterm without BPD, n = 87	Mean difference (no BPD – BPD) (95% CI)	P value
Gestational age at birth, wk	26.6 (1.3)	27.2 (1.3)	0.63 (0.27-0.99)	.001
Birth weight, g	833 (198)	966 (185)	134 (79-188)	<.001
Male sex	61/106 (58.5%)	39/89 (44.8%)	13%	.056
Antenatal steroids, %	93/106 (88%)	80/87 (92%)	4%	.86
Received surfactant, %	104/106 (98%)	86/87 (99%)	1%	.66
Postnatal systemic steroids, %	41/193 (39%)	13/87 (15%)	24%	<.001
Age at assessment, y	12.2 (0.7)	12.01(0.8)	−0.2 (−0.4, 0.1)	.16
Weight, kg	42.86 (10.0)	46.3 (13.8)	3.5 (0.0-6.9)	.05
Height, cm	151.1 (8.2)	152.7 (9.1)	1.6 (−0.9, 4.1)	.20
Hb, g/dL, median (IQR)	12.6 (11.7-13)	12.5 (11.8-13.2)	0.1 (7.9-0.1)	.9
Oxygen saturation, %, median (IQR)	98 (97-99)	99 (98-100)	1 (0-5)	.008
Systolic blood pressure, mm Hg, median (IQR)	116 (110-123)	118 (111-126)	2 (2-50)	.45
Diastolic blood pressure, mm Hg, median (IQR)	73 (67-78)	75 (69-83)	2 (0-58)	.09

Hb, hemoglobin.

Results are presented as mean (SD) or %, unless otherwise stated.

possible to exclude maternal hypertension during pregnancy as a potential influencing factor on the myocardium.<sup>25</sup>

Similar to our findings, a smaller study has found significantly thinner intraventricular septum in infants born preterm (31-34 weeks' GA) compared with infants born at term. In addition, there was reduced ventricular diastolic function when measured by tissue Doppler imaging.<sup>26</sup>

Reduced RV function can potentially indicate the severity and chronicity of increased pulmonary artery pressure. The possible mechanism underlying the decrease in systolic function of the right ventricle secondary to increased pulmonary artery pressure has been described previously.<sup>27-29</sup>

Injury to the small airways in infants born extremely preterm has been described previously.<sup>30</sup> Our study showed significantly reduced small airway function in children born extremely preterm when compared with those at term, with children who had previously had BPD more affected. Greater pulmonary pressures may imply that small pulmonary arteries also were affected, suggesting a common underlying mechanism of injury such as inflammatory process, including perivascular and interstitial inflammation.<sup>31</sup> In addition, abnormal pulmonary vessels potentially could affect the function of their adjacent airways.<sup>32</sup>

Previous studies of children born prematurely usually have concentrated on those children with BPD.<sup>6,33</sup> In our study, 55% of the children born prematurely had had BPD. We demonstrated that the children who had BPD, compared with those who did not, had significantly greater tricuspid regurgitation v<sub>max</sub>. Those findings are supported by previous results showing that infants with severe BPD, when examined at a median age of 12 months, had increased pulmonary vascular resistance.<sup>34</sup> It is important, however, to note that in our study, both groups born prematurely had significantly worse mean tricuspid regurgitation v<sub>max</sub>, SPAP, MPAP, and TAPSE than the children born at term, demonstrating it is important to follow up children born extremely prematurely regardless of a previous diagnosis of BPD.

Comparison of pulmonary artery pressure results demonstrated no statistical differences between children who had been supported by conventional mechanical ventilation or HFO ventilation. There also were no significant differences in left atrial dimensions, intraventricular septum diameter, left ventricular systolic and diastolic function, or RV systolic function between the 2 ventilation groups. A possible explanation is that although there were highly significant differences in the lung function of the 2 groups at 11-14 years, the difference was relatively small.<sup>7</sup> It may be, however, as these children go through puberty, differences in lung function may become greater and then are associated with differences in pulmonary pressures and other echocardiographic results. It is possible that any differences in lung function postpuberty will be particularly marked in the female patients.<sup>35</sup> Among young adults who had had BPD, female but not male young adults had worse lung function and more respiratory symptoms than control subjects born at term. The authors suggested this was due to greater chest wall growth in boys during puberty.<sup>35</sup>

This study should be interpreted in the context of both strengths and limitations. The study is the largest to date to measure pulmonary artery pressures in children born very preterm at school age. The feasibility of the tricuspid regurgitation measurement was consistent with the literature, and an extensive suite of assessments was undertaken. As the children born at term were recruited after the assessments of the group born preterm had finished, the sonographers were not blinded to whether the children were term or preterm. They were, however, blinded to all the perinatal factors of the children born prematurely, including their ventilation group and BPD status.

In our study, the children did not undergo cardiac catheterization, and this may be considered to be a limitation. Examination by echocardiography can underestimate or overestimate SPAP in comparison with the gold standard cardiac catheterization<sup>10,36,37</sup>; nevertheless, it has been suggested to be a valuable screening tool. The clinical utility of

**Table IV.** Comparison of echocardiographic parameters according to prematurity and BPD status

Parameters	Group 1, preterm (BPD) Mean (SD) n	Group 2, preterm (no BPD) Mean (SD) n	Group 3, term Mean (SD) n	P values
Peak TR velocity, m/s	2.25 (0.23) n = 82	2.15 (0.23) n = 55	1.95 (0.2) n = 83	<i>P</i> (1,2) <b>.023</b> <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) < <b>.001</b>
Max RV-RA gradient, mm Hg	20.4 (3.97) n = 82	18.9 (4.03) n = 55	15.2 (3.54) n = 83	<i>P</i> (1,2) .07 <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) < <b>.001</b>
Mean RV-RA gradient, mm Hg	14.1 (2.6) n = 59	13.4 (3.3) n = 27	11.6 (2.1) n = 54	<i>P</i> (1,2) .5 <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) <b>.008</b>
SPAP,* mm Hg	24.4 (4.0) n = 82	23.9 (4.0) n = 55	20.2 (3.5) n = 83	<i>P</i> (1,2) .07 <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) < <b>.001</b>
MPAP,† mm Hg	19.1 (2.6) n = 59	18.4 (3.3) n = 27	16.6 (2.1) n = 54	<i>P</i> (1,2) .49 <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) <b>.008</b>
IVC RV-RA gradient, cm	1.79 (0.35) n = 103	1.79 (0.25) n = 87	1.70 (0.24) n = 108	<i>P</i> (1,2) .99 <i>P</i> (1,3) .06 <i>P</i> (2,3) .07
LA, mm <sup>2</sup>	11.5 (1.7) n = 106	11.9 (2.0) n = 87	12.0 (1.5) n = 110	<i>P</i> (1,2) .20 <i>P</i> (1,3) .12 <i>P</i> (2,3) .98
TAPSE z score	-0.11 (1.86) n = 96	0.23 (2.02) n = 82	0.97 (1.17) n = 104	<i>P</i> (1,2) .37 <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) <b>.01</b>
LVEDD z score	0.15 (1.9) n = 103	-0.27 (2.13) n = 85	-0.16 (0.98) n = 109	<i>P</i> (1,2) .23 <i>P</i> (1,3) .41 <i>P</i> (2,3) .89
LVEF %	67 (7.9) n = 103	71 (7.7) n = 85	65 (7.1) n = 109	<i>P</i> (1,2) <b>.006</b> <i>P</i> (1,3) .1 <i>P</i> (2,3) < <b>.001</b>
EDIVS z score	-0.06 (0.7) n = 103	-0.28 (0.7) n = 85	0.31 (0.7) n = 109	<i>P</i> (1,2) .08 <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) < <b>.001</b>
PV v max, m/s	0.93 (0.2) n = 104	0.92 (0.2) n = 87	0.86 (0.12) n = 109	<i>P</i> (1,2) .78 <i>P</i> (1,3) <b>.001</b> <i>P</i> (2,3) <b>.01</b>
PI end diast. v, m/s	0.88 (0.16) n = 33	0.91 (0.13) n = 25	0.82 (0.14) n = 41	<i>P</i> (1,2) .58 <i>P</i> (1,3) .27 <i>P</i> (2,3) <b>.04</b>
PAAT, ms	140 (21) n = 101	144 (22) n = 80	149 (16) n = 108	<i>P</i> (1,2) .38 <i>P</i> (1,3) <b>.04</b> <i>P</i> (2,3) .22
FEV <sub>1</sub> z score	-0.93 (1.1) n = 99	-0.59 (1.1) n = 88	-0.12 (1.0) n = 108	<i>P</i> (1,2) .07 <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) <b>.006</b>
FVC z score	-0.43 (1.0) n = 99	-0.28 (0.96) n = 88	-0.11 (0.94) n = 108	<i>P</i> (1,2) .56 <i>P</i> (1,3) <b>.05</b> <i>P</i> (2,3) .43
FEV <sub>1</sub> /FVC z score	-1.75 (2.0) n = 99	-1.19 (1.68) n = 88	-0.33 (1.4) n = 108	<i>P</i> (1,2) .06 <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) <b>.001</b>
FEF <sub>25</sub> z score	-1.20 (0.9) n = 99	-0.83 (0.96) n = 88	-0.16 (1.1) n = 108	<i>P</i> (1,2) .27 <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) < <b>.001</b>
FEF <sub>50</sub> z score	-1.37 (0.9) n = 99	-1.05 (0.92) n = 88	-0.34 (0.95) n = 108	<i>P</i> (1,2) .04 <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) < <b>.001</b>
FEF <sub>75</sub> z score	-1.21 (0.8) n = 99	-0.91 (0.96) n = 88	-0.50 (0.97) n = 108	<i>P</i> (1,2) .11 <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) <b>.008</b>
FEF <sub>25-75</sub> Z score	-1.62 (1.1) n = 99	-1.24 (1.0) n = 88	-0.46 (1.1) n = 108	<i>P</i> (1,2) <b>.04</b> <i>P</i> (1,3) < <b>.001</b> <i>P</i> (2,3) < <b>.001</b>

Data are presented as mean (SD), and the number in each group with results of the measurement. n is the number of children with each result.

P values set in bold were considered significant.

\*SPAP calculated as peak RV-RA gradient plus minimal RAP of 5 mm Hg for all.

†MPAP calculated as mean RV-RA gradient plus minimal RAP of 5 mm Hg for all.

echocardiography in the diagnosis of the pulmonary vascular disease in children with BPD has been described by Mourani et al.<sup>33</sup> They assessed 29 patients with BPD who had an echocardiogram in the first 2 years after birth who subsequently underwent cardiac catheterization. Tricuspid regurgitation was detectable in 19 children, allowing estimation of the SPAP in 61% of the patients. Cardiac catheterization confirmed pulmonary hypertension in 23 of the 29 patients.<sup>33</sup> Because our study was limited to 2-dimensional echocardiography, it was not possible to measure the 3-dimensional size of the RV and LV, and therefore changes in the RV wall thickness could not be assessed. The literature suggests the difference of 3 mm Hg in pulmonary pressures could be potentially significant in determining the clinical outcomes.<sup>13</sup> We report a difference of 4 mm Hg obtained through measurements of the systolic RV-RA gradient. A limitation of our study is that we did not assess exercise tolerance and thus cannot comment on the clinical significance of our findings. Our recommendation for future follow-up of similar cohorts would be to formally assess exercise tolerance.

In conclusion, children born very prematurely have significantly greater MPAPs at school age compared with children born at term, but there was no influence of neonatal ventilator mode. In addition, the children born prematurely had lower systolic function of the right ventricle and thinner interventricular septum. The clinical significance of the increased pulmonary artery pressures in the children born prematurely and whether with increasing age the pulmonary artery pressures will further increase is not known. It is, therefore, crucial this cohort is re-examined after puberty. ■

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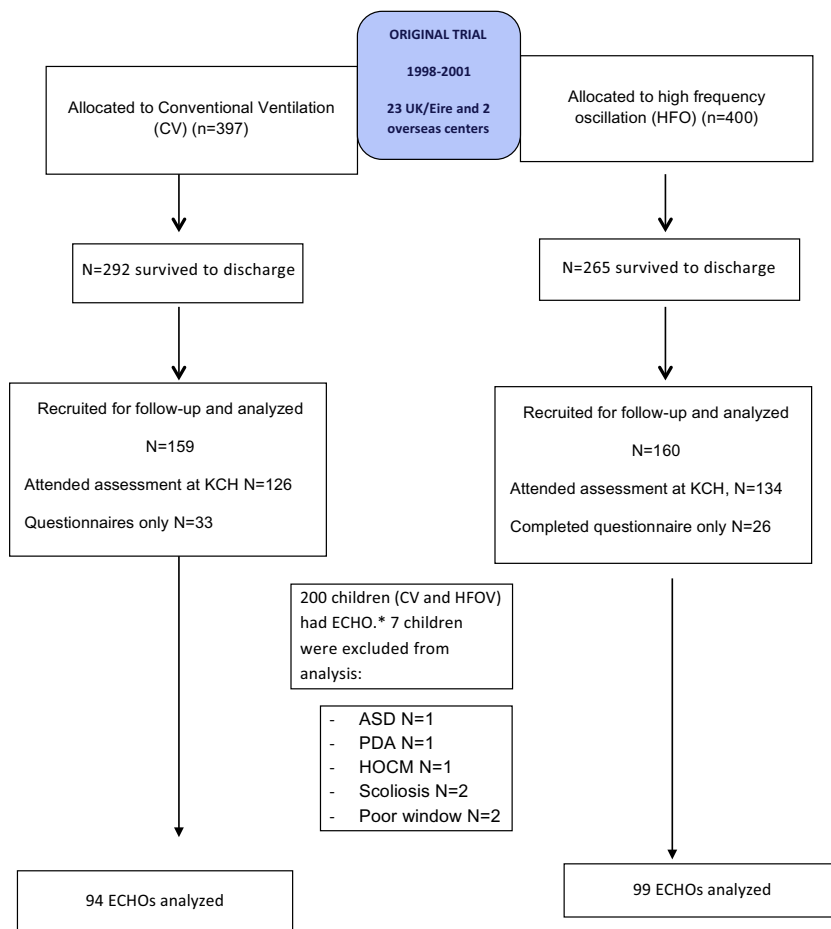
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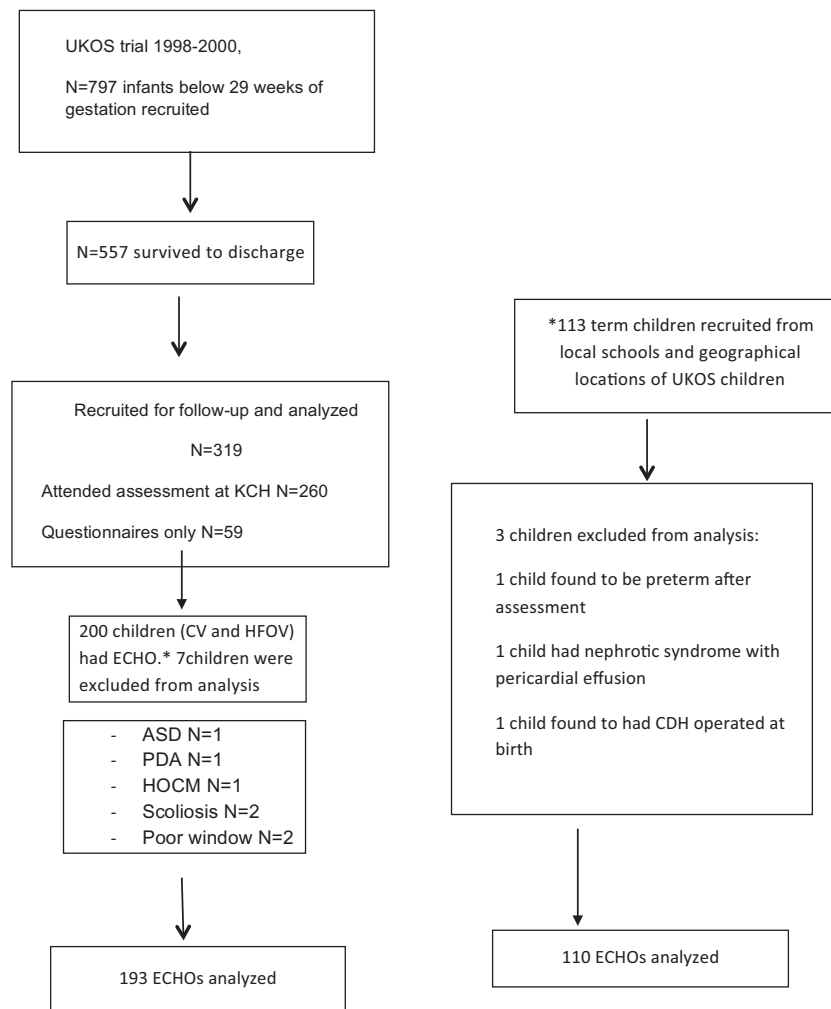
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**Figure 1.** UKOS recruitment flow diagram for echocardiographic analysis between ventilation groups. \*Echocardiograms obtained from children recruited from November 1, 2011, to March 1, 2013. ASD, atrial septal defect; HOCM, hypertrophic cardiomyopathy; KCH, King's College Hospital; PDA, patent ductus arteriosus.



**Figure 2.** UKOS recruitment flow diagram for echo analysis between gestation groups (term vs preterm). \*Echocardiograms obtained from children recruited from June 1, 2013, to March 1, 2014.

**Table V.** Comparison of echocardiographic measurements according to ventilation status

Measurements	CMV n = 94	HFO ventilation n = 99	Mean difference (CMV – HFO ventilation) (95% CI)	P value
GA, wk	27.0 (1.2)	26.8 (1.4)	0.2 (–0.2, 0.6)	.34
Birth weight, g	898 (193)	890 (213)	8 (–50, 65)	.80
Weight, kg	44.0 (12.7)	45.0 (11.4)	–1.0 (–4.4, 2.5)	.56
Height, cm	152.4 (9.2)	151.3 (8.1)	1.1 (–1.4, 3.6)	.39
Hb, g/dL	12.6 (1.3)	12.54 (1.1)	0.16 (–0.22, 0.59)	.42
Oxygen saturation, %	98.3 (1.1)	98.3 (1.2)	0.03 (–0.3, 0.37)	.98
BP systolic, mm Hg	118 (9.4)	117 (11.0)	0.59 (–2.5, 3.7)	.71
BP diastolic, mm Hg	74.3 (8.9)	74.1 (9.5)	0.19 (–2.64, 3.02)	.89
TR peak velocity, m/s	2.22 (0.221)	2.20 (0.25)	0.02 (–0.06, 0.10)	.56
n	63	74		
Maximum RV-RA gradient, mm Hg	20 (3.8)	20 (4.3)	0.16 (–1.2, 1.65)	.81
n	63	74		
Mean RV-RA gradient, mm Hg	13.8 (2.63)	14.0 (3.382)	0.04 (–1.5, 1.0)	.69
n	39	47		
IC diameter, cm	1.77 (0.29)	1.80 (0.32)	–0.02 (–0.11, 0.06)	.61
n	94	96		
Estimated RAP, mm Hg	7.9 (4.1)	7.7 (4.4)	0.2 (–1.07, 1.4)	.75
n	94	96		
LA, cm <sup>2</sup>	11.56 (1.83)	11.86 (1.82)	–0.29 (–0.81, 0.22)	.26
n	94	99		
E/A	1.74 (0.28)	1.74 (0.25)	0.01 (–0.07, 0.08)	.090
n	86	94		
LVEDD z score	–0.08 (2.2)	–0.00 (1.10)	–0.08 (–0.78, 0.50)	.78
n	90	98		
LVEF, %	68.4 (8.325)	68.8 (8.07)	–0.41 (–2.7, 1.9)	.72
n	90	98		
EDIVS z score	–0.175 (0.74)	–0.15 (0.65)	–0.01 (–0.20, 0.18)	.87
n	90	97		
TAPSE z score	0.19 (1.87)	–0.07 (2.00)	0.26 (–0.10, 0.83)	.37
n	84	94		
PV max, m/s	92.1 (20.0)	93.6 (13.4)	–1.5 (–6.4, 3.3)	.53
n	91	99		
PV max PG, mm Hg	3.70 (1.29)	3.55 (1.09)	0.15 (–0.19, 0.49)	.37
N	91	99		
PI end diastolic velocity, m/s	89.3 (13.0)	89.1 (15.7)	0.11 (–7.9, 8.10)	.98
n	22	36		
PAAT	141.70 (20.13)	141.72 (22.7)	–0.103 (–6.295, 6.244)	.97
n	85	96		
SPAP, mm Hg*	24.9 (3.8)	24.7 (4.3)	–0.17 (–1.56, 1.22)	.81
n	63	74		
MPAP, mm Hg†	18.8 (2.3)	19.0 (3.3)	0.25 (–0.98, 1.49)	.69
n	39	47		

BP, blood pressure; CMV, conventional mechanical ventilation.

n is the number of children with each result.

Data are demonstrated as mean (SD) or n (%) unless otherwise stated.

\*SPAP calculated as peak RV-RA gradient plus minimal RAP of 5 mm Hg for all.

†MPAP calculated as mean RV-RA gradient plus minimal RAP of 5 mm Hg for all.