

## Research Article

# Echocardiographic Right Ventricular Pressure Ratio Correlates with Prolonged Oxygen Therapy in Patients with Moderate to Severe Bronchopulmonary Dysplasia

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Submitted: 26 August 2015

Accepted: 23 October 2015

Published: 27 October 2015

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**OPEN ACCESS****Keywords**

- Bronchopulmonary dysplasia
- Oxygen
- Prematurity
- Pulmonary hypertension

**Abstract**

**Objective :** To characterize the incidence of pulmonary hypertension in a cohort of patients with bronchopulmonary dysplasia [BPD] and to correlate echocardiographic markers of pulmonary artery pressure [PAP] with prolonged oxygen supplementation, blood oxygen saturation [SpO<sub>2</sub>], pH and pCO<sub>2</sub>. **Study design:** We prospectively studied 29 infants admitted to a level 3 Neonatal Intensive Care unit [NICU] between February 2006 and August 2007. Neonates born at less than 28 weeks of gestation and requiring oxygen supplementation at 34-36 weeks of postmenstrual age were included. Echocardiographic estimation of pulmonary arterial pressure [PAP] was done with interventricle septal motion, tricuspid regurgitation jet velocity, right ventricular pre-ejection period/ejection time ratio [RVPEP/RVET] and right ventricular acceleration time/ejection time ratio [RVAT/RVET] at weeks 0, 1, 4 and 6 of study. These echocardiographic measurements were assessed for correlation with duration of oxygen therapy, SpO<sub>2</sub>, pH and pCO<sub>2</sub>.

**Results:** Twenty-nine patients were enrolled at a mean postmenstrual age of 35 weeks and 3 days [±6 days [SD]]. BPD was moderate in 62% and severe in 38%. Twenty-four patients required prolonged oxygen therapy [oxygen needed past 44 weeks postmenstrual age]. RVPEP/RVET ratio was 0.21 in these patients compared to 0.13 [p=0.02] in those that did not require prolonged oxygen therapy. RVPEP/RVET ratio correlated with low pH [p=0.02] and high pCO<sub>2</sub> [p=0.04]. It did not correlate with SpO<sub>2</sub> levels. **Conclusion:** In infants with BPD, the RVPEP/RVET ratio at 34-42 weeks of postmenstrual age was higher in infants requiring prolonged oxygen therapy, and correlated with pH and pCO<sub>2</sub>. This RVPEP/RVET ratio could help with early identification of patients that will require prolonged oxygen therapy.

**ABBREVIATIONS**

BPD: Bronchopulmonary Dysplasia; CPAP: Continuous Positive Airway Pressure; FiO<sub>2</sub> : Fraction of inspired Oxygen; IUGR : Intrauterine Growth Restriction; NICU : Neonatal Intensive Care Unit; PAP : Pulmonary Artery Pressure; PDA : Patent Ductus Arteriosus; PHT: Pulmonary Hypertension; PPROM: Prolonged Premature Rupture of Membranes; RVAT/RVET: Right Ventricular Acceleration Time to ejection time ratio; RVPEP/RVET: Right Ventricular Preejection Period to ejection time ratio; SC: Septal Curvature; SpO<sub>2</sub>: blood oxygen saturation measured by pulse oximetry; TAPSE: tricuspid annular plane

systolic excursion; TR: Tricuspid Regurgitation; VLBW: Very Low Birth Weight

**INTRODUCTION**

Bronchopulmonary dysplasia [BPD] is a chronic lung disease affecting premature infants and especially those with a very low birth weight [VLBW]. Oxygen dependence at 36 weeks of post-menstrual age is the commonly accepted definition for BPD [1]. It is associated with worse long term respiratory and neurodevelopmental outcomes and serves as a marker of BPD severity [2]. The incidence varies from 35 to 57% in newborns of less than 1500g [3].

Increased survival of very premature newborns has given rise to a BPD disease, which involves both the alveolar architecture and the pulmonary vascular bed [4]. Multiple factors are implicated in the pathogenesis of BPD; including oxygen toxicity, trauma due to mechanical ventilation and inflammation. The net result of these factors is a decreased alveolar surface area and vascular bed [4, 5], leading to reduced cross-sectional area and alveolar hypoxia, causing structural remodelling of the pulmonary vasculature, abnormal vasoreactivity and subsequent development of pulmonary hypertension [PHT] [6]. Despite that PHT has been shown to be associated with significantly increased mortality and morbidity among patients with BPD, systematic screening of PHT is not established in this patient population.

Different tools are used to measure pulmonary artery pressure [PAP] in neonates. The most reliable, but also the most invasive is cardiac catheterization. Echocardiography can indirectly estimate PAP by using septal curvature [SC], tricuspid regurgitation [TR], right ventricular acceleration time/ejection time ratio [RVAT/RVET] or right ventricular pre-ejection period/ejection time ratio [RVPEP/RVET] [7-12].

The purpose of this study is to determine the incidence and evolution of pulmonary hypertension in extremely preterm infants with BPD between 34 and 42 weeks of postmenstrual age. This study will also assess correlations of different echocardiographic indices of PAP with duration of oxygen therapy and with clinical variables known to be associated with variations in PAP, including blood oxygen saturation measured by pulse oximetry [ $SpO_2$ ], pH and  $pCO_2$ .

## METHODS

### Study population

This was a prospective observational study of infants born at or admitted to CHU Ste-Justine's Neonatal Intensive Care Unit [NICU] between February 2006 and August 2007. During that period, the level 3 NICU had 57 beds and over 1000 admissions per year including 85 infants weighing less than 1000g. The institutional ethics review board at CHU Sainte-Justine approved this study.

Patients were eligible for the study if they were born at less than 28 weeks of gestation, had been receiving oxygen therapy for at least 28 days and still required supplemental oxygen at 34 to 36 weeks of postmenstrual age. As we wanted to include all infants that would fit the BPD criteria at 36 weeks postmenstrual age, we preferred to recruit patients between 34 and 36 weeks postmenstrual age who still required supplemental oxygen. In practice, this 2 weeks time range allowed us to collect consent from parents and to notify the cardiologist as he could organize the first echocardiography at an appropriate timing. Despite this "imperfect" type of recruitment strategy, all infants included in the study had oxygen requirements at 36 weeks postmenstrual age. Oxygen was administered by continuous positive airway pressure [CPAP] using nasal mask, prongs or cannula, with a minimum fraction of inspired oxygen [ $FiO_2$ ] of 0.25 or 0.02 L/min, respectively, to maintain a mean  $SpO_2$  between 85 and 92%. Prolonged oxygen therapy was defined as need for supplemental oxygen at four weeks of corrected age [44 weeks

postmenstrual age]. Exclusion criteria included: necessity of invasive mechanical ventilation [judged to be too unstable to undergo repeated echocardiography]; presence of complex congenital cardiac disease; actual proven or suspected sepsis; acute pneumonia; ongoing necrotising enterocolitis [stage 2 or 3 according to the modified Bell's classification]; and type 1 retinopathy of prematurity as defined by the ETROP study [zone I, any stage with plus disease; zone I, stage 3 without plus disease; zone II, stage 2 or 3 with plus disease] [13].

### Data Collection

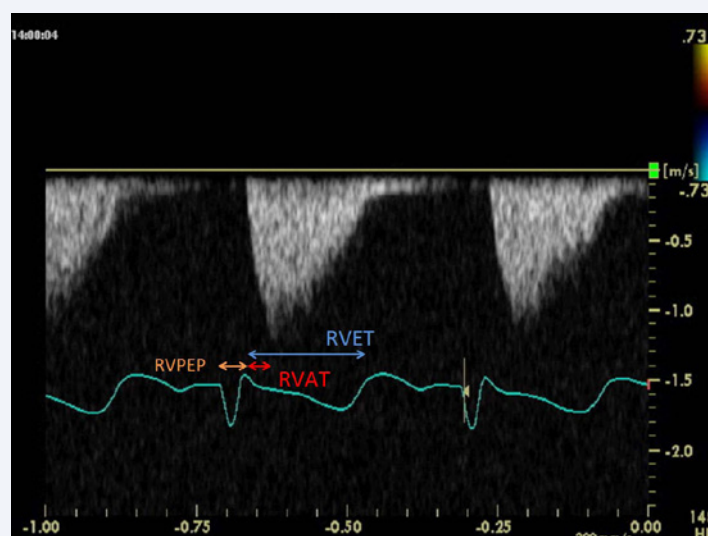
After obtaining consent, baseline patient characteristics were collected from chart review including gestational age at birth, birth weight, gender, postmenstrual age at enrolment, length of hospitalisation, presence of prenatal risk factors [intra-uterine growth restriction [IUGR], chorioamnionitis, oligohydramnios, preterm and premature rupture of membranes [PPROM], and details of hospital course [including use of postnatal systemic steroids and duration of oxygen therapy].

Patients were enrolled prospectively at 34-36 weeks of postmenstrual age and were followed for a period of 6 weeks. Clinical and biochemical data were collected on a weekly basis and included: average vital signs over the preceding 24 hours [heart rate, respiratory rate, blood pressure and temperature which were measured every 1 to 4 hours according to patient status and then averaged over a 24 hour period], average  $FiO_2$  and  $SpO_2$  over the preceding 24 hours [calculated similarly to vital signs], number of apneas and bradycardias over the preceding 24 hours, growth parameters [head circumference and weight], complete blood count, blood pH and  $pCO_2$  measured by capillary gas [as part of the weekly routine blood work]. Twelve hours overnight  $SpO_2$  recordings validated the reliability of  $SpO_2$  recorded in patient charts.

On weeks 0, 1, 4 and 6 of the study, echocardiographic assessments [Vivid 7, GE, Waukesha, USA] were performed and interpreted offline by a single pediatric cardiologist. Various Doppler measurements were done in order to estimate PAP. Pulsed wave Doppler was applied at the level of the pulmonary valve. The slope obtained was used to measure the right ventricular pre-ejection period [RVPEP], the right ventricular acceleration time [RVAT] and the right ventricular ejection time [RVET] [Figure 1]. The mean of three repeated measures was calculated. From these measurements, we obtained two ratios [RVPEP/RVET and RVAT/RVET], which have been previously correlated with PAP [9,10,12]. Other echocardiographic measurements included assessment of shunt direction [PDA, atrial septal defect, ventricular septal defect] and the septal motion. Systemic systolic and diastolic blood pressures were recorded using a blood pressure cuff. Qualitative measures of PHT were also recorded. These included visual and M-mode assessment of right atrial enlargement and right ventricular hypertrophy and/or dilatation.

### Statistical Analysis

Statview was used to analyze the data. Unpaired t tests [for continuous variables], without assuming equality of variances, and chi-square [for categorical variables] were done



**Figure 1** Measurement of pulmonary artery echocardiographic indices.

to contrast patients requiring prolonged oxygen therapy from those who did not. The following variables were compared: echocardiographic indices of PHT; gestational age at birth and at enrolment; birth weight; sexe; prenatal history of IUGR, chorioamnionitis, oligohydramnios and PPROM; antenatal corticosteroid use; history of PDA; surgical treatment for PDA; duration of mechanical ventilation [including conventional and high frequency oscillation ventilation], and oxygen therapy; and severity of BPD [graded as mild, moderate or severe, according to the NICHD 2001 definition] [1]. Linear regressions using the Pearson correlation [as data were normally distributed] were performed correlating two echocardiographic ratios, RVPEP/RVET and RVAT/RVET, with pH,  $p\text{CO}_2$  and  $\text{SpO}_2$ .

## RESULTS

### Population

118 premature infants of less than 28 weeks of gestational age were born at or admitted to CHU Sainte-Justine during the study period. Of those, 80 required oxygen therapy at 34 to 36 weeks of postmenstrual age and 29 infants met the inclusion criteria for the study (Figure 2). The study population included 13 [45%] males and 16 [55%] females. The mean gestational age at birth was 26 weeks and 2 days [ $\pm 7$  days [SD]] and mean postmenstrual age at enrolment was 35 weeks and 3 days [ $\pm 6$  days]. The mean birth weight was 814 g [ $\pm 153$  g]. BPD severity was categorised as moderate in 18 [62%], and severe in 11 [38%] patients. Baseline characteristics of the patients are presented in table 1. In this study population, despite moderate to severe BPD, no patient had signs of significant PHT according to SC or TR.

### Prolonged oxygen therapy

Of our study group, 24 had prolonged oxygen therapy, compared to 5 who did not. Clinical characteristics according to whether or not subjects required or not prolonged supplemental oxygen are described in table 2. The mean birth weight was  $796 \pm 141$  g for the prolonged oxygen therapy group and  $899 \pm 198$  g in the second group [ $p = 0.32$ ]. The proportion of each group

who had a PDA was similar, but twelve patients [50%] with prolonged oxygen therapy had a surgical closure, compared to none in the group of patients without prolonged oxygen therapy [ $p = 0.06$ ]. In patients who needed prolonged oxygen, mechanical ventilation was used for a mean of  $42 \pm 18$  days as compared to  $10 \pm 5$  days for patients without prolonged oxygen [ $p < 0.001$ ]. All of the patients in the group with prolonged oxygen therapy received surfactant therapy, compared to 4 of the 5 in the other group [ $p = 0.03$ ]. The proportion of moderate and severe BPD was respectively 54% [ $n = 13$ ] and 46% [ $n = 11$ ] in patients with need of prolonged oxygen therapy compared to 100% [ $n = 5$ ] and 0% [ $n = 0$ ] in patients without oxygen therapy.

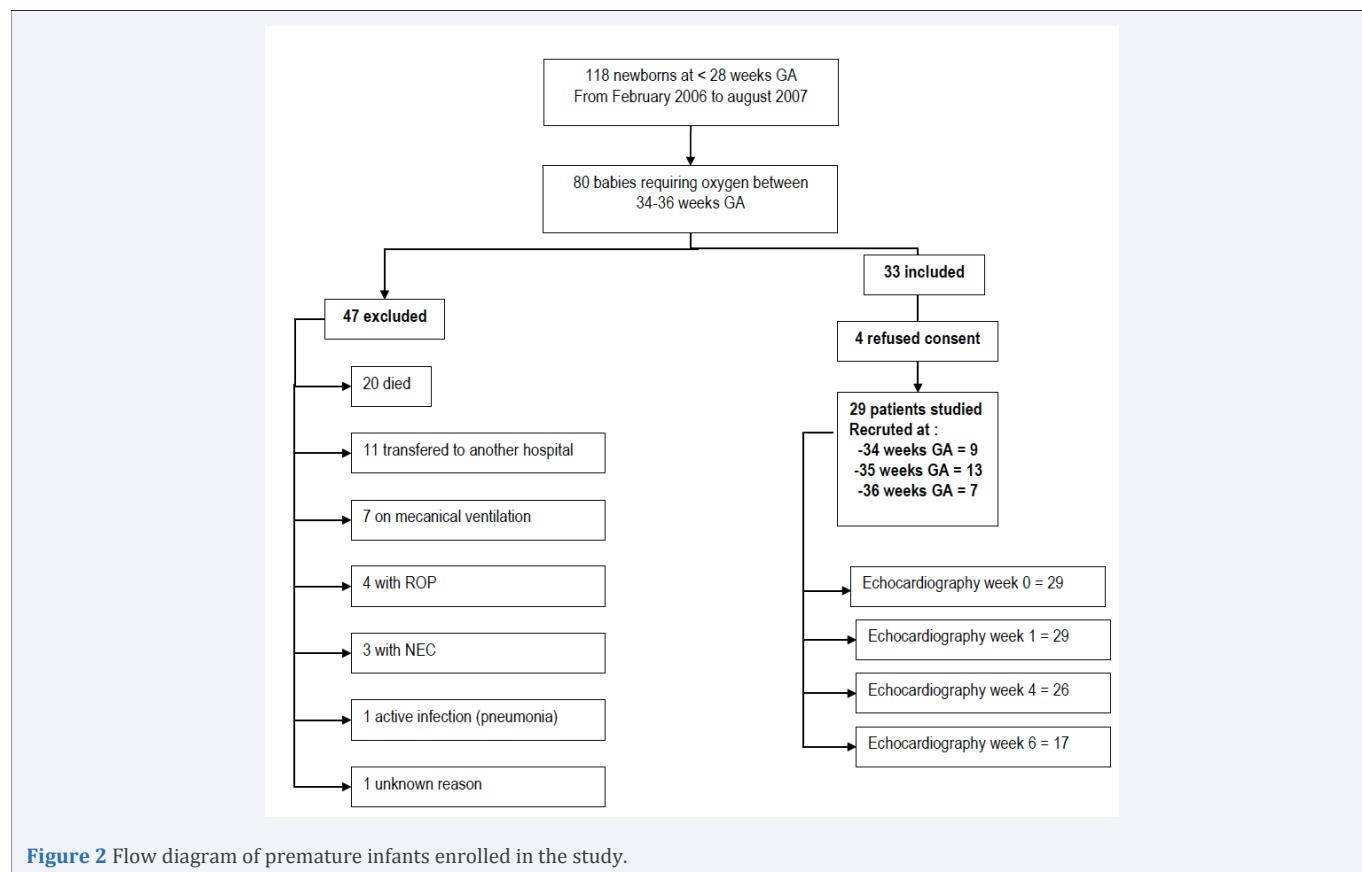
The average RVPEP/RVET ratio, measured between 34 and 42 weeks of postmenstrual age, was 0.21 [0.05] vs. 0.13 [0.05] [ $p = 0.02$ ] in patients requiring prolonged oxygen therapy compared to patients without such need. However, there was no significant difference between those two groups when comparing RVAT/RVET ratio.

### Other echocardiographic findings

There was a correlation of the RVPEP/RVET ratio with blood pH [figure 3] and  $p\text{CO}_2$  [Figure 4] but not with  $\text{SpO}_2$ , with a correlation coefficient of  $R^2 = 0.109$  [ $p = 0.02$ ],  $R^2 = 0.086$  [ $p = 0.04$ ] and  $R^2 = 0.0025$  [ $p = 0.78$ ] respectively. There was no correlation of the RVAT/RVET ratio with blood pH,  $p\text{CO}_2$  and  $\text{SpO}_2$ .

## DISCUSSION

In this study, none of the 29 infants with moderate or severe BPD, assessed at a postmenstrual age between 34 and 42 weeks, was found to have echocardiographic signs of PHT [flattening of septal motion, significant TR or right ventricle hypertrophy and/or dilation]. We observed that RVPEP/RVET ratio measured at a gestational age between 34 and 42 weeks was higher in patients who needed prolonged oxygen therapy than in those who did not. Furthermore, increased RVPEP/RVET ratio correlated with low blood pH and with higher blood  $p\text{CO}_2$  levels but not with different levels of  $\text{SpO}_2$ .



**Figure 2** Flow diagram of premature infants enrolled in the study.

<b>Gestational age at birth [wks]</b>	26 ± 1
<b>Gestational age at enrollment [wks]</b>	35 ± 1
<b>Birth weight [g]</b>	814 ± 153
<b>Male Sexe [%]</b>	45
<b>Prenatal History</b>	
<i>IUGR [%]</i>	7
<i>Chorioamnionitis [%]</i>	14
<i>Oligohydramnios [%]</i>	14
<i>PPROM [%]</i>	38
<b>Antenatal Corticosteroids [%]†</b>	62
<b>PDA [%]</b>	76
<b>Surgical closure of PDA [%]</b>	41
<b>Respiratory parameters</b>	
<i>Mechanical Ventilation [days]</i>	37±20
<i>O2 Therapy [days]</i>	102±26
<i>Patients that received surfactant [%]</i>	97
<b>pH</b>	7.35 ± 0.25
<b>pCO<sub>2</sub> [mmHg]</b>	55.8 ± 6.5
<b>SpO<sub>2</sub> [%]</b>	92.7 ± 2.4
<b>Severity of BPD [%]</b>	
<i>Mild</i>	0
<i>Moderate</i>	62
<i>Severe</i>	38
<b>Post natal systemic corticosteroids [%]</b>	52

†Missing data in two patients

## Prevalence of PHT

Although PHT is now recognized as a significant problem in infants with BPD and is strongly associated with increased mortality and morbidity, its true incidence is still unknown [14]. In our study, none of the infants with BPD had echocardiographic signs of PHT. Previous studies have reported a prevalence of PHT in infants with BPD ranging from 25% to 37% [15,16]. PHT associated with BPD has been related to the degree of severity of BPD, a low birth weight, long-term ventilation care, oxygen supplementation, aggressive ventilator settings, infections and PDA [15,17,18]. Surprisingly, our cohort demonstrated an absence of PHT that could be explained by the exclusion of patients on invasive mechanical ventilation and with active sepsis. Furthermore, echocardiographic indices of PAP like TR and ventricular septal flattening have been recognized with low sensitivity and specificity for detecting mild to moderate manifestations of PHT [19]. This underlies the need for more sensitive echocardiographic markers that could detect PHT at an earlier stage, to allow treatment in order to prevent progression to more severe disease. New promising echocardiographic parameters such as tissue doppler velocities and tricuspid annular plane systolic excursion [TAPSE] are under study to measure more accurately PAP [20,21].

## Prediction of prolonged oxygen therapy

In our institution, the proportion of infants with BPD needing home oxygen at discharge is estimated to be 52%. Criteria for discharge with home oxygen after NICU stay are highly variable between institutions. In our institution, discharge is considered

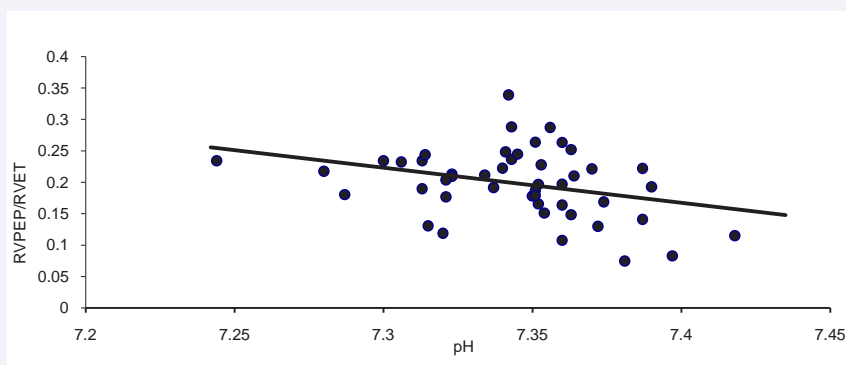


Figure 3 Variation of RVPEP/RVET ratio with pH.

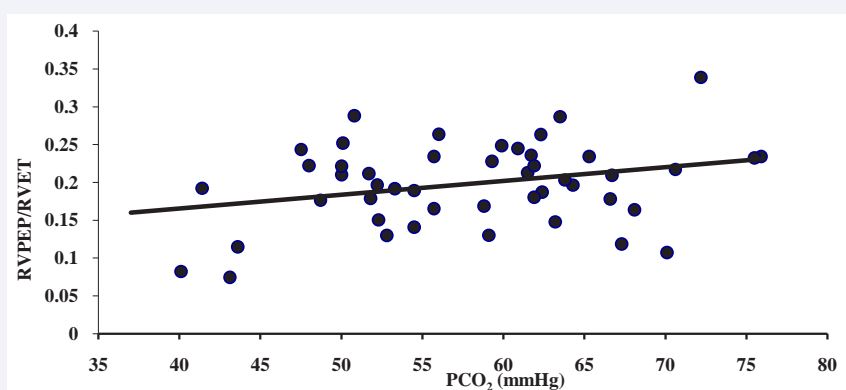


Figure 4 Variation of RVPEP/RVET ratio with pCO<sub>2</sub>.

Table 2: Clinical characteristics of infants requiring or not prolonged oxygen therapy.

	Prolonged oxygen therapy n =24	No prolonged oxygen therapy n =5	p
<b>Gestational age at birth [wks]</b>	26 ± 1	27 ± 1	<0.001
<b>Gestational age at enrolment [wks]</b>	35 ± 1	35 ± 1	0.43
<b>Birth weight [g]</b>	796 ± 141	899 ± 198	0.32
<b>Male Sexe [%]</b>	46	40	1.00
<b>Prenatal History</b>			
<i>IUGR [%]</i>	4	20	0.32
<i>Chorioamnionitis [%]</i>	17	0	1.00
<i>Oligohydramnios [%]</i>	17	0	1.00
<i>PPROM [%]</i>	33	40	1.00
<b>Antenatal Corticosteroids [%]<sup>†</sup></b>	58	80	0.62
<b>PDA [%]</b>	79	60	0.57
<b>Surgical closure of PDA [%]</b>	50	0	0.06
<b>Respiratory parameters</b>			
<i>Mechanical Ventilation [days]</i>	42±18	10±5	<0.001
<i>O<sup>2</sup> Therapy [days]</i>	111±18	59±5	<0.001
<b>Severity of BPD [%]</b>			0.13
<i>Mild</i>	0	0	
<i>Moderate</i>	54	100	
<i>Severe</i>	46	0	

<sup>†</sup>Missing data in two patients

when  $pCO_2$  is less than 60 mmHg, and oxygen delivered by nasal prongs is less than 0,3 litre per minute. Considering the burden of discharging an infant with oxygen therapy, infants close to discharge with very little oxygen needs [less than 0.05 litre per minute] tend to have their stay prolonged in a hope to completely withdraw oxygen therapy. Higher echocardiographic RVPEP/RVET ratio, an indirect measurement of PAP, could be an interesting predictive tool of the need of prolonged oxygen therapy and thus the need of home oxygen. This would help to avoid unnecessary prolonged hospitalization. A RVPEP/RVET ratio above 0.3 has been shown to be associated with increased mortality in infants suffering from respiratory distress syndrome or BPD [22]. To our knowledge, this is the first study that demonstrates a relationship of echocardiographic indices of PAP at 34 to 42 weeks of gestational age and the need of prolonged supplemental oxygen. However, this needs to be validated and confirmed in future prospective clinical studies with larger populations.

### Reactivity of PAP

Pulmonary vascular tone is a result of a complex interplay of biochemical pathways. Hypercapnia has been shown to induce pulmonary vasoconstriction and increase pulmonary vascular tone in healthy adult humans, contributing to the pathogenesis of PHT [23]. Also, an animal study using a rabbit lung model suggested that by controlling  $pCO_2$  at a constant level, acidemia, measured as a low blood pH, resulted in significant increase in PAP [24]. To our knowledge, this study is the first to correlate  $pCO_2$  and blood pH to echocardiographic indices of PHT in human preterm infants with BPD. It highlights that about 10% of the observed variation in the RVPEP/RVET ratio could be explained by pH and  $pCO_2$ , increasing with lower pH or higher  $pCO_2$ . Our data supports previous observations that PHT associated with BPD is partly reactive [11,25].

Oxygen is often considered the first line of PHT treatment. The balance between avoiding hypoxia, which can increase PAP, needs to be weighed against the associated risks of hyperoxia [25]. Animals and *in vitro* studies have shown that hyperoxia may induce injury to endothelial cells causing vascular remodelling and increased basal pulmonary tone by reactive oxygen species [26,27]. As in our study, clinical studies have not found any effect of increased  $SpO_2$  on PAP in patients with normal levels of PAP [11,28]. There might be two explanations for this observation. Either it might be that contrarily to infants with BPD and established PHT who have a reactive pulmonary vascular tone, infants with early-established BPD without PHT do not show the same variation of PAP when supplemental oxygen is provided. Or the echocardiographic measurement of RVPEP/RVET ratio is not sensitive enough to detect small variations of PAP.

### Strengths and limitations

This single center study is limited by its observational design. The small sample size, exclusion of ventilated patients and cessation of the study at an early age [44 weeks postmenstrual age] could explain the absence of detection of classical echocardiographic signs of PHT. This finding could also be explained by the previously discussed controversies surrounding the capability of echocardiography to diagnose PHT.

Despite these limitations, this study suggests an interesting clinical screening tool [RVPEP/RVET ratio] for patients that will require prolonged oxygen therapy, which needs to be validated in future studies. RVPEP/RVET ratio combined with right ventricle function measurements, such as TAPSE and tissue Doppler, could be more sensitive to detect PHT at an earlier stage when a treatment could prevent progression of the disease.

### CONCLUSION

In our population of extremely preterm infants with moderate to severe BPD, RVPEP/RVET ratio correlated with prolonged oxygen supplementation, pH and  $pCO_2$  but not with  $SpO_2$ . It might be an interesting predictor of patients who will require prolonged oxygen therapy. Further studies need to be oriented towards the natural history of pulmonary pressures and right ventricle function in a population of preterm infants with BPD in whom routine screening of PHT is implemented.

### ACKNOWLEDGEMENTS

The authors would like to send a special thought in memory of Dr Hardy Bard for inspiring young trainees and physicians into completing this study. They would also like to thank Dr Euloge Krammoh for his help in acquiring echocardiography images for this study.

### Conflict of Interest Statement

Villeneuve, A., Bigras, J-L., Lachance, C., Bérubé, D, Barrington, K, Lapointe, A. and Moussa, A. have no conflict of interest to declare.

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Villeneuve A, Bigras JL, Lachance C, Bérubé D, Barrington KJ, et al. (2015) Echocardiographic Right Ventricular Pressure Ratio Correlates with Prolonged Oxygen Therapy in Patients with Moderate to Severe Bronchopulmonary Dysplasia. *Ann Pediatr Child Health* 3(9): 1087.