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Preterm growth restriction and bronchopulmonary dysplasia: The vascular hypothesis and related physiology

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Short title: Vascular hypothesis in growth restriction and BPD

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*Equal contributions

Key points

- Approximately 5-10% pregnancies are affected by fetal growth restriction.
- Preterm infants affected by fetal growth restriction have a higher incidence of bronchopulmonary dysplasia.
- This study is the first to measure pulmonary artery thickness and stiffness.
- It highlights that impaired vasculogenesis may be a contributory factor in the higher incidence of bronchopulmonary dysplasia in preterm growth restricted infants.
- The study addresses the mechanistic link between fetal programming and vascular architecture and mechanics.

Abstract

Bronchopulmonary dysplasia is the most common respiratory sequelae of prematurity and histopathologically features fewer, dysmorphic pulmonary arteries. The objectives of this study were to characterize pulmonary artery mechanics and cardiac function in preterm infants with fetal growth restriction (FGR) compared to those appropriate for gestational age (AGA) in the early neonatal period. This prospective study reviewed 40 preterm infants between 28 to 32 weeks GA. Twenty infants had a birthweight <10th centile and were compared with 20 preterm AGA infants. A single high resolution echocardiogram (ECHO) was performed to measure right pulmonary arterial and right ventricular (RV) and indices. The GA and birthweight of FGR and AGA infants were 29.8 ± 1.3 vs. 30 ± 0.9 weeks (p = 0.78) and 923.4g ± 168 vs. 1403g ± 237 (p<0.001), respectively. Assessments were made at 10.5 ± 1.3 days after birth. The FGR infants had significantly thicker right pulmonary artery inferior wall (843.5±68 vs 761±40μm, p<0.001) with reduced pulsatility (516±76μm vs

597±75 μm, p=0.001). The RV contractility (fractional area change [28.7%±3.8 vs 32.5%±3.1, p=0.001], Tricuspid Annular Peak Systolic Excursion (TAPSE) [5.2%±0.3 vs 5.9%±0.7, p=0.0002] and myocardial performance index [0.35±0.03 vs 0.28±0.02, p<0.001]) was significantly impaired in FGR infants. Significant correlation between RV longitudinal contractility (TAPSE) and Time to Peak Velocity/ Right Ventricular Ejection Time (measure of RV afterload) was noted (r^2=0.5, p<0.001). Altered pulmonary vascular mechanics and cardiac performance reflect maladaptive changes in response to utero-placental insufficiency. Whether managing pulmonary vascular disease will alter clinical outcomes remains to be studied prospectively.

Introduction

Fetal growth restriction (FGR) affects approximately 5-10% pregnancies worldwide and such infants have a 10 to 20-fold increased risk of perinatal morbidity and/or mortality such as bronchopulmonary dysplasia (BPD) compared to non-growth restricted preterm infants (Rosenberg, 2008). Data from our own institution (AS) noted that the incidence of FGR in gestation 28 to 32 weeks to be 27% (unpublished observations). BPD is the most common and most significant long term respiratory sequelae of prematurity, with an incidence of about 60% in infants'≤25 weeks gestational age (GA) (Chow, 2014). The incidence in infants 28 weeks GA was high (23%), progressively decreasing with GA. The overall incidence in infants 28-32 weeks was 10.6%. A proportion (15-58%) of these infants (<1000g birthweight and <32 weeks GA respectively) (Khemani *et al.* 2007 & Bhat *et al.* 2012) have associated pulmonary hypertension. The evolving pattern of BPD may imply an important pathogenic role arising from FGR. A recent study noted that at 27 weeks GA, 25% of infants without

FGR developed BPD compared to 60% of infants with moderate FGR and 90% with severe FGR (Bose *et al.* 2009). Several other large and contemporary studies on infants <32 weeks GA have also identified similar associations (Lal *et al.* 2003 & Reiss *et al.* 2003). Therefore, FGR increases the risk for BPD; adverse respiratory outcomes attributable to the FGR state, which are independent of the degree of prematurity (Bose *et al.* 2009 & Gortner *et al.* 2011). On a histopathological level, infants with BPD have pulmonary vascular changes with thicker-walled pulmonary arteries (and a more distal extension of the muscular arterioles) (Bhatt *et al.* 2001 & Coalson, 2006). Chronic hypoxaemia (as seen in chronic utero-placental insufficiency) leads to muscularization of precapillary 'resistance vessels' by way of proliferation of vascular smooth muscle and the adventitial fibroblasts (Rabinovitch *et al.* 1979). Disruption of angiogenesis during critical periods of lung growth (fetal programming) in turn can impair alveolarization, contributing to the pathogenesis of BPD (Thebaud & Abman, 2007; Janer *et al.*, 2008).

Abnormal angiogenesis (influenced by vascular endothelial growth factors and their receptors) appears to be a feature in the pathogenesis of BPD. Data from neonatal mice noted that chronic hypoxia during the first two weeks of life (a period of lung development corresponding to human fetal lung development during the third trimester), interferes with alveolar and pulmonary artery development and up-regulates transforming growth factor beta (Ambalavanan *et al.*2008). The dynamic component of this impaired angiogenesis most prominently affects the 'resistance' vessels; the effects of which can be assessed by measuring surrogates of pulmonary vascular resistance (PVR) by ultrasound and thickness of the major pulmonary arteries. The question for clinicians is whether there is a connection between FGR, its effects on pulmonary (vascular) development and the higher prevalence of BPD in human infants. There are no data linking *in-utero* events such as utero-placental insufficiency with structural pulmonary vascular changes, altered perinatal pulmonary

vasoreactivity, or the right heart mal-adaptive coupling in the preterm FGR infants. Given the available vascular cross sectional area is a critical determinant of PVR, it may be surmised that a reduction due to vascular remodelling (chronic hypoxaemia) may necessitate an increase in pulmonary artery pressure (and the consequent right ventricular [RV] hypertrophy) in order to maintain pulmonary blood flow. The effects of FGR on the *systemic vasculature* (aorta/carotid artery) in term neonates in the early postnatal period and children are well documented (Skilton *et al.* 2005; Crispi *et al.* 2010; Sehgal *et al.* 2018). These are thicker and stiffer in FGR neonates, the effect persisting in pediatric age groups (3-6 years) and adolescence. Evidence in these FGR cohorts has indicated altered cardiovascular function arising from suboptimal conditions, particularly chronic hypoxaemia (Crispi *et al.* 2010 & Sehgal *et al.* 2018). Impaired cardiac/vascular coupling has been previously demonstrated in the systemic and pulmonary circulation in adults (19-60 years and 51±24 year's old, and isolated canine ventricles respectively (Kelly *et al.* 1992; Sunagawa *et al.* 1983; Sanz *et al.* 2012). Arterial stiffening is an important index of disease progression and significantly contributes to increased afterload. Such changes in the pulmonary circulation in human preterm neonates have not been studied previously.

The objectives of this prospective study using high resolution ultrasound were to characterise in the early newborn period, the pulmonary artery and RV indices in a cohort of very preterm infants with FGR, compared to an AGA cohort. Important afterload and cardiac interactions arising from vascular stiffness in FGR infants may underlie the association with BPD, as normal angiogenesis is crucial to optimal alveolarization.

Methods

Ethical Approval

The study was approved by the Monash Health Research Ethics Board (approval number 14197B). Informed written parental consent was obtained and the study conformed to the standards set by the latest version of Declaration of Helsinki, except for registration in a database.

Twenty infants between 28 and 32 completed weeks of GA and weighing <10th percentile were recruited and were compared with 20 preterm AGA infants of similar GA. Infants <28 weeks were excluded as they are more likely to have a patent ductus arteriosus. Patency of the duct was an *a priori* exclusion criteria. Infants with perinatal depression (5 minute Apgar score <5), congenital malformations/heart disease or chromosomal abnormalities, or those born to diabetic mothers were excluded. Cohort characteristics were collected. The male/female ratio was comparable (11/9 vs 12/8 in FGR and AGA cohorts respectively). All echocardiographic (ECHO) assessments were performed in the second week of life by the same operator blinded to the group. The subjects in the control group were age matched to the FGR cohort. The infants were followed up for respiratory sequelae. This included total duration of respiratory support (including low flow), need for home oxygen, and incidence of BPD. In infants born <32 weeks GA, Australia and New Zealand Neonatal Network defines BPD as lung disease with ongoing requirement for supplemental oxygen therapy or ventilation support (high-flow oxygen, continuous positive airway pressure or mechanical ventilation) at 36 weeks post-menstrual age. **Table 1** depicts the ECHO assessments and their interpretation (Evans & Archer, 1999; Dyer *et al.* 2006; Koestenberger *et al.* 2011; Czernik *et al.* 2012). These were performed using the Vivid 7 Advantage Cardiovascular Ultrasound System (GE Medical Systems, Milwaukee, Wis., USA), with the infant in the supine position. Offline analysis was performed using *EchoPAC*^{TM} (Horten,

Norway) software without revealing group identity. All Doppler measurements were calculated from an average of three consecutive cardiac cycles, the angle of insonation being kept to $<15^0$.

The inferior wall of the right pulmonary artery (RPA) was assessed as previously described using the short axis view as it aligns perpendicular to the ultrasound beam (Dyer *et al.* 2006). The probe was aligned parallel to the RPA with gain settings and scaling adjusted to maximize the detail of the arterial walls. Colour m-mode tissue Doppler Imaging (TDI) allowed for higher resolution and sharper edges (**Figure 1**). RPA thickness was measured in end-diastole. Measurements were conducted offline by 2 independent observers masked to the grouping. The data was analyzed by Bland-Altman analysis. The average of two measurements for each observer were taken and then the average of the readings from both observers was used for analysis. Assessment of agreement using the Bland Altman techniques in readings between the two observers showed a small bias in measurements: 10.3 (95% limits of agreement from -38.87; 59.47). The intra-class correlation coefficient for overall assessment was 0.93 (95% confidence interval 0.86-0.96). The RPA thickness was also indexed to lumen diameter in diastole. Pulse diameter was calculated as the difference in diastole and systole from colour m-mode images.

Statistics

A preliminary hypothesis was that cardiac and pulmonary artery indices in FGR are worse than those of an AGA cohort. Vascular and cardiac function indices were summarised as means ± standard deviation (SD). We assessed the effect of group (n=20 FGR vs. n=20 AGA) on vascular parameters via general linear regression models. Data were analysed using Stata software version 14 (StataCorp, College Station, Tex., USA) and SPSS version 18 (PASW Statistics for Windows; SPSS Inc., Chicago, Ill., USA). Correlations between the

vascular and cardiac parameters were assessed by Pearson's correlation. Statistical significance was regarded as $p<0.05$.

Results

The study cohort characteristics are depicted in **Table 2**. The GA in the two groups was comparable (FGR 29.8±1.3 vs 30±0.9 weeks, p=0.78) while birthweight was significantly lower (FGR 923±168 vs 1403±237g, p<0.001). Data regarding smoking was not available for most mothers. Preterm premature rupture of membranes (4 infants-2 in each group) and chorioamnionitis (2 infants-1 in each group) was seen in some infants. The two infants with chorioamnionitis were amongst the four who had premature rupture of membranes. None of the infants were intubated and mechanically ventilated. The duration of respiratory support (FGR 37 [14, 52] vs. AGA 8 [5, 21] days), median (interquartile) and the incidence of BPD (FGR 40% vs. AGA 5%) was significantly higher in the FGR infants. The GA at discharge was significantly greater in the FGR cohort (43±3.1 vs 40.2±2.8 weeks, p=0.0006). No infants had pulmonary hypertension necessitating nitric oxide therapy and none were administered postnatal steroids. The age at ECHO assessments in the FGR and AGA infants was 10.5 ± 1.3 vs 10.3 ± 1.3 days, respectively, p=0.55. **Table 3** depicts cardiac and pulmonary artery properties. The RPA inferior wall was significantly thicker in the FGR infants (Figure 2). The wall thickness to lumen ratio in diastole (%) was also significantly increased in the FGR cohort 11.1 ± 2 vs 8.6 ± 1.1, p=0.009. The pulsatile diameter was significantly lesser in FGR compared to AGA infants (516±76μm vs 597±75 μm, p=0.001). The RV fractional area change (FAC) and Tricuspid Annular Peak Systolic Excursion (TAPSE) were lower and the tissue Doppler imaging (TDI) Myocardial Performance Index was higher in the FGR infants indicating lower systolic and diastolic function. The

significance persisted after adjustment for GA. Significant correlation was noted between RV longitudinal contractility (TAPSE) and Time to Peak Velocity/ Right Ventricular Ejection Time (TPV/RVETc) (measure of RV afterload) in the overall cohort (r^2=0.5, p<0.001). **Figure 3** depicts individual cohort correlations. Lower TPV/RVETc (higher PVR) was associated with lower contractility. Correlation between tissue level performance (reflected by Myocardial Performance Index) and TPV/RVETc was r = -0.42, p=0.006; indicating higher PVR is associated with lower cardiac performance.

Discussion

There is a growing body of literature that supports FGR as an important factor contributing to the early developmental origins of impaired lung structure and function (Maritz *et al.* 2005; Morsing *et al.* 2012; Pike *et al.* 2012; Briana & Malamitsi-Puchner, 2013). Reduced fetal growth maybe a surrogate for abnormal intrauterine lung development, as the factors that control fetal somatic growth may significantly increase the vulnerability to lung injury in such affected fetuses. The chronic insufficiency of oxygen and nutrients impacts on the lung parenchyma, airways and vasculature (Maritz *et al.* 2005; Orgeig *et al.* 2010; Pike *et al.* 2012; Morsing *et al.* 2012), and possibly explains the higher incidence of BPD in such infants. Smooth muscle thickening of neonatal pulmonary vessels and changes in pulmonary vascular reactivity after chronic hypoxaemia support the role of utero-placental insufficiency. Similar to others, our study noted increased duration of respiratory support and incidence of BPD in FGR infants compared to GA matched AGA infants.

Our study builds on pre-existing literature using high-resolution ultrasound, and found that in preterm FGR infants, the pulmonary vasculature is thicker with reduced pulsatility. In addition, important physiological interactions between pulmonary vascular indices and RV

function were noted. The role of the proximal conduit arteries is to dampen the pressure oscillations originating form intermittent RV ejection. This cushioning capacity is in turn influenced by wall stiffness and distensibility. This concept is similar to the effect of aortic stiffness on the distal arterioles and the subsequent organ damage noted previously. This is the first study showing proximal pulmonary artery changes as possible contributors to respiratory morbidity in FGR cohort through its possible impact on the distal pulmonary vasculature.

BPD-The vascular hypothesis

Perinatal factors including FGR predict persistent respiratory disease at one year of life just as accurately as the diagnosis of BPD (Keller *et al.* 2017). BPD pathophysiology is multifactorial and FGR severity can affect alveolarization as well as angiogenesis. The role of arterial stiffness seems crucial as the lack of waveform cushioning by the major arteries affects the heart by way of back pressure changes (hypertrophy/dilatation) (known as pulsatile afterload) but more importantly, exposes the pulmonary resistance vessels to higher pulsatile stress, thereby accelerating microvascular disease (Wang & Chesler, 2011). Stiffness of conduit pulmonary arteries increases distal strain damage (increased smooth muscle cell proliferation, leukocyte adhesion, inflammatory gene expression) (Li *et al.* 2009). This effect mirrors changes in the systemic circulation where aortic stiffening caused renal arteriolar damage (O'Rourke & Safar, 2005 & O'Rourke *et al.* 2007). The deleterious effects of the exposure to such high pulsatile stress on the kidneys (systemic circulation) have been demonstrated in children previously (Takenaka *et al.* 2005). In the FGR cohort, the urinary microalbumin and albumin–creatinine ratio were noted to be significantly higher at 18 months, indicating microvascular glomerular damage (Zanardo *et al.* 2011). Our data noted significantly thickened pulmonary vasculature with markedly reduced pulsatility. In terms of dynamics, a lower TPV/RVETc indicated elevated PVR. We postulate that high pulsatile

stress may be similarly deleterious to the pulmonary arterioles and lead to microvascular leakage which may contribute to pulmonary oedema. The resultant decreased compliance may contribute to a longer duration of respiratory support and a higher incidence of BPD in preterm FGR infants. These vascular effects (coupled with the effects on the heart) are possibly related to vascular arterial remodelling.

FGR and alterations in pulmonary vasculature: Mechanisms

The following section details possible mechanisms linking utero-placental insufficiency and pulmonary vascular changes. **Figure 4** summarizes the various mediators of the effects of FGR on the pulmonary vasculature and the putative clinical effects. Human epidemiological and clinical studies and data from animal experiments (sheep; 129-141 days gestation) have noted a significant burden of respiratory illnesses following FGR (Morrison, 2008 & Orgeig *et al.* 2010). The hypoxia signalling cascade regulates normal fetal lung angiogenesis, vascular remodelling, surfactant maturation and alveolarization. The vascular endothelial growth factor expression plays a crucial role (Gebb & Jones, 2003; Groenman *et al.* 2007; McGillick *et al.* 2016). In FGR sheep, decreased fetal pulmonary alveolarization and reduced pulmonary vessel density, pulmonary artery endothelial cell function and eNOS signalling has been noted. This adverse impact is evidenced by reduced pulmonary vessel density compared to the AGA cohort in this study in which the FGR fetuses were created by exposing pregnant ewes to elevated ambient temperatures (40°C for 12 h; 35°C for 12 h) from 33.4±0.3 days GA until 115.3±0.4 days GA (Rozance *et al.* 2011). Angiogenesis in turn regulates alveolarization during pulmonary development (Jakkula *et al.* 2000; Le Cras *et al.* 2002; Stenmark & Abman, 2005; Thebaud & Abman, 2007). Work on the sheep model also noted the effects of FGR on lung architecture that were apparent at 8 weeks after birth, and were still evident at 2 years (Maritz *et al.* 2005). In neonatal mice, chronic hypoxaemia during the first two weeks of life, interferes with both alveolar *and* pulmonary artery

development by way of increased endothelial permeability, heightened smooth muscle tone and an enhanced thrombotic state. Of concern, even a short period (two weeks) of hypoxaemia seems enough to induce extracellular matrix thickness in these rodents (Ambalavanan *et al.* 2008). In summary, studies from various animal models indicate the impact of FGR on pulmonary vasculature.

The perinatal period is also associated with significant elastin production in the pulmonary trunk (Leung *et al.* 1977), and is particularly sensitive to modulation by hypoxaemia during this time of rapid growth. Reduced elastin content in large pulmonary arteries predisposes to elevated RV pressures and hypertrophy (Shifren *et al.* 2008). Since the rates of elastin synthesis increase to a maximum in the perinatal period; our cohort of FGR infants born between 28-32 weeks may be particularly vulnerable. Thus, *in utero* disruption in the synthesis and deposition of adequate amounts of elastin and its replacement with collagen (100 times greater stiffness than elastin) in fetal life may lead to low arterial compliance (Martyn & Greenwald, 1997).

Exposure to adverse environmental conditions during certain stages of fetal development may be crucial. The physiological consequences of the changes include increased arterial resistance/stiffness and decreased compliance, contributing to increased RV afterload. These parameters have prognostic implications as RV functional status and cardiac index are strong predictors of survival (Ghio *et al.* 2001).

Interaction of pulmonary afterload and cardiac function

A recent ECHO study on the effects of hypoxaemia in rats noted pulmonary hypertension, as indicated by decreased pulmonary artery time to peak velocity and increased dilatation of RV diameter compared with age and sex-matched controls. Pregnant rats were exposed to hypoxia (12% O_2) or normoxia (21% O_2) between day 15 and 21 of pregnancy. Assessments at 12 months of age noted signs of left ventricular hypertrophy, diastolic dysfunction and

pulmonary hypertension (Rueda-Clausen *et al.* 2009). Prenatal hypoxaemia (in the mouse model exposed to chronic hypoxia for 4 weeks and assessments made at 40 weeks) also led to greater thickness of the muscularis media, which together with adventitial proliferation, decreased the luminal diameter (Pietra *et al.* 2004 & Bonnet *et al.* 2006). This remodelling, and the consequent stiffness in turn regulates pressure and flow wave velocities in the pulmonary bed and affect afterload (Milnor *et al.* 1969 & Weinberg *et al.* 2004). We found similar effects in the specific parameters. Similar interactions between *systemic* afterload and cardiac forces have been previously demonstrated in newborns with FGR and 3-18 year old children (Rowland & Gutgesell, 1995 & Sehgal *et al.* 2018). Such important correlations between *pulmonary* forces however, especially in FGR infants, have not been demonstrated before. This afterload/contractility relationship may be ideal for longitudinal studies monitoring disease progression. The altered RV function is likely related to pressure overload and intrinsic myocardial issues, as a maladaptive response. These include exposure to increased myocardial workload in-utero (Tintu *et al.* 2008; Verburg *et al.* 2008; Fouzas *et al.* 2014), alterations in arterial structure and vascular tone (Rouvet *et al.* 2002) and altered muscle fibre architecture (Greenbaum *et al.* 1981). Decreased cardiac sarcomeric proteins, a compensatory increase in glycogen and collagen deposition (Sohn *et al.* 1997 & Tintu *et al.* 2008), with interstitial fibrosis are also noted in the presence of FGR (Menendez-Castro *et al.* 2011).

The TPV/RVETc ratio is the commonly used Doppler assessment of pulmonary artery dynamics and allows semi-quantitative measure of PVR; the lower the ratio the higher is the PVR (ratio <0.1 signifies greater severity). It is a reliable surrogate of RV afterload and PVR (1/TPV: RVETc) (Evans & Archer, 1999 & Howard *et al.* 2012). Its application in infants with chronic neonatal lung disease previously noted a significant and negative correlation between TPV/RVETc and invasive PVR index (Milnor *et al.* 1969 & Ziino *et al.* 2010).

While measured in the main pulmonary artery, TPV/RVETc is more reflective of changes in the pulmonary resistance vessels. Infants in our study possibly have pulmonary vascular disease rather than frank pulmonary hypertension. Invasive assessments, while providing new insights into the pulmonary capacitance and vaso-reactivity, are impractical in such small FGR infants. Non-invasive measures of proximal pulmonary artery compliance in the form of vessel morphometery and beat to beat pulsatility (pulsatile diameter), are best placed to fill this void.

The main pulmonary artery, while a great vessel for Doppler studies due to its orientation, is not conducive for the above assessments where the vessel needs to be perpendicular to the ultrasound beam. The RPA overcomes this limitation. Using non-invasive colour TDI ECHO, Dyer (2006) *et al* recently studied diameter and compliance in the RPA in a pediatric population ranging from 0.6 to 17 years of age. The assessments correlated well with invasive intravenous pulmonary artery catheter measurements and patients with pulmonary hypertension had lower compliance (Dyer *et al.* 2006). This study is the first assessment of RPA thickness and dynamics in the neonatal age group. It gives useful physiologic information in settings where ventricular-arterial coupling may be of relevance. Compared to conventional ECHO, TDI is a relatively recent addition to the neonatal literature, allowing direct measurement of regional myocardial velocities. It has a greater sensitivity compared to conventional measures, and is relatively preload-independent (Sohn *et al.* 1997 & Sehgal *et al.* 2016). Feasibility of TDI for assessing fetal (30±3weeks GA and neonatal (term ~39 weeks GA) cardiac function in FGR cohorts has been previously reported (Comas *et al.* 2010; Altin *et al.* 2012; Sehgal *et al.* 2017). In this study, we noted impairment of cardiac function in FGR infants compared to GA and post-natal age matched AGA controls. TAPSE is also a relatively recent addition to RV assessments (Koestenberger *et al.* 2011). It is a simple and highly reproducible measure of longitudinal RV function, and is less

likely to be influenced by imaging artefacts. Its clinical relevance was recently noted in a cohort of infants >35 weeks GA with persistent pulmonary hypertension of the newborn, where the sensitivity/specificity for ECMO/death when TAPSE was <4 mm was 56 and 85%, respectively (Malowitz *et al.* 2015).

Our data is presented adjusted for GA. While the effect of prematurity is important, a previous study (Cheung *et al.* 2004) compared systemic arterial stiffness and blood pressure among children who were born preterm and FGR, or preterm appropriate for GA, or term appropriate for GA. The preterm FGR cohort was delivered at 32.3±2 weeks (GA comparable to our cohort). On assessments performed at 8.2±1.7 years, only children born preterm FGR had increased arterial stiffness and elevated mean blood pressure. Unfortunately, there is no comparable data in the early postnatal period.

The strengths of this study include focussed cardiac and vascular assessments using conventional and newer but validated TDI ECHO parameters and the demonstration of afterload/cardiac forces coupling. This is a preliminary prospective hypothesis generating study involving a small number of infants. A larger multi-centric cohort studying possible intervention strategies is better suited to have greater understanding on the topic. In summary, this study builds on the current understanding of BPD as being multifactorial in pathogenesis with FGR an important etiopathologic factor. The vascular hypothesis we propose, mimics the vascular affliction of the systemic vasculature, which has been commented upon in multiple studies across age groups (newborn to adolescence) in FGR cohorts.

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Additional information

Competing interests

None of the authors has any conflicts of interests

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Author contributions.

The study was performed at Monash Newborn, Monash Children's Hospital, Melbourne, Australia

This section must state the laboratory where the experiments were performed and list the contribution (in words) of each author (using their initials) to the below aspects of the study. Authors must have contributed to:

AS-conception of the study, data acquisition, analysis and interpretation. Wrote the first draft and revised critically.

SMG-conception and design of the work. Data analysis and interpretation. Revised draft for important intellectual content

SM- conception and design of the work. Data interpretation and draft revision for important intellectual content

BA- conception and design of the work. Data interpretation and draft revision for important intellectual content

SLM- conception and design of the work. Data interpretation and draft revision for important intellectual content

GRP- conception and design of the work. Data interpretation and draft revision for important intellectual content

All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Figure legends

Figure 1.

A. 2D image from modified short axis view showing the right pulmonary artery.

B. Colour Doppler showing the right pulmonary artery.

C. m-mode tissue Doppler of right pulmonary artery

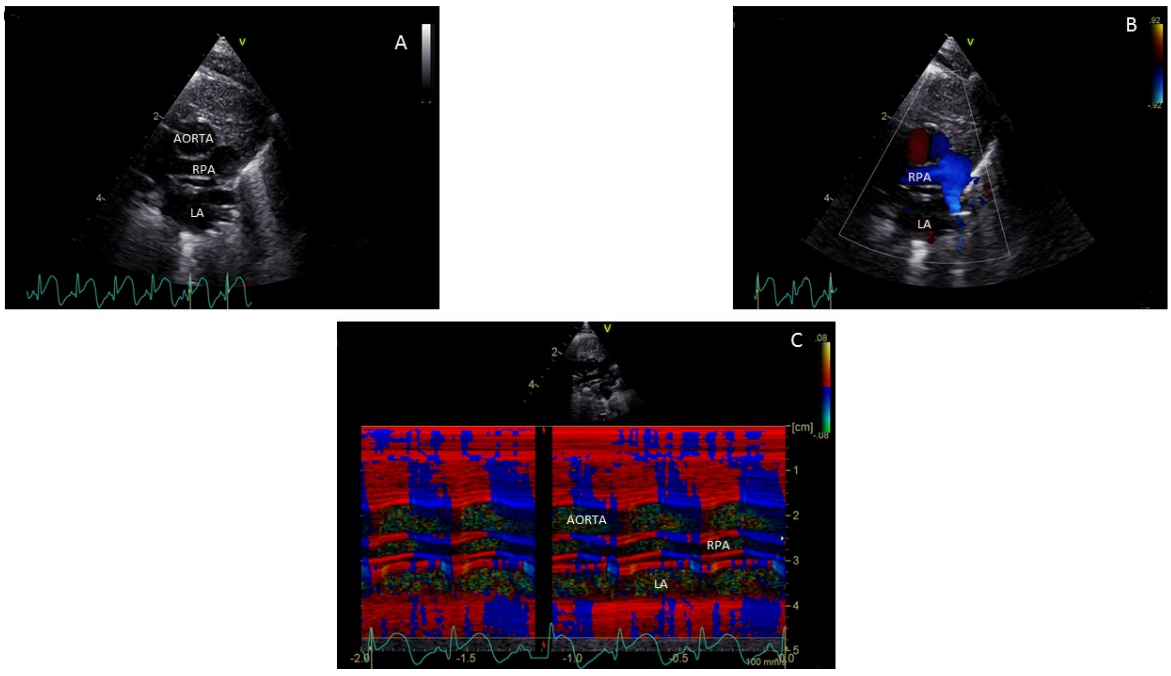

Figure 2.

Scatterplot illustrating thickness of the right pulmonary artery

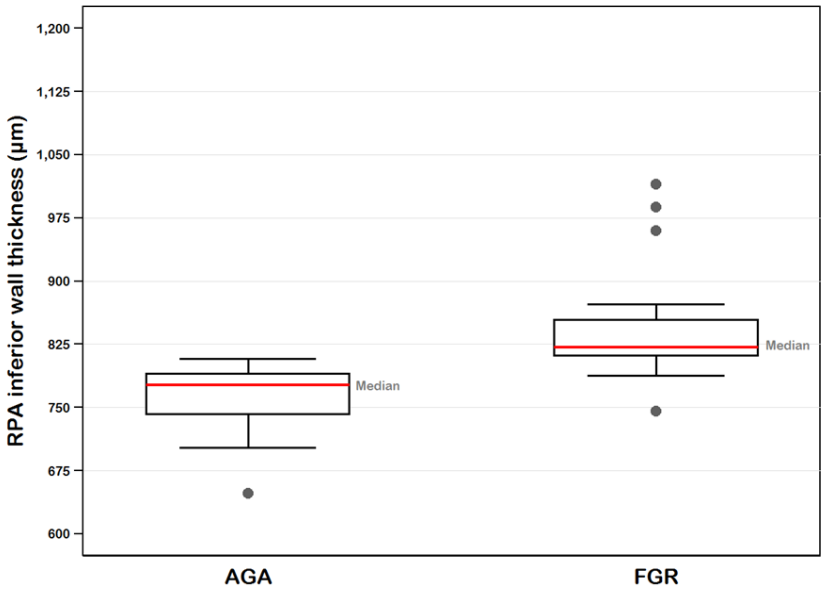

Figure 3.

Correlation between right ventricular contractility (TAPSE) and afterload (TPV/RVETc).

Panel A-fetal growth restriction, Panel B-appropriate for gestational age

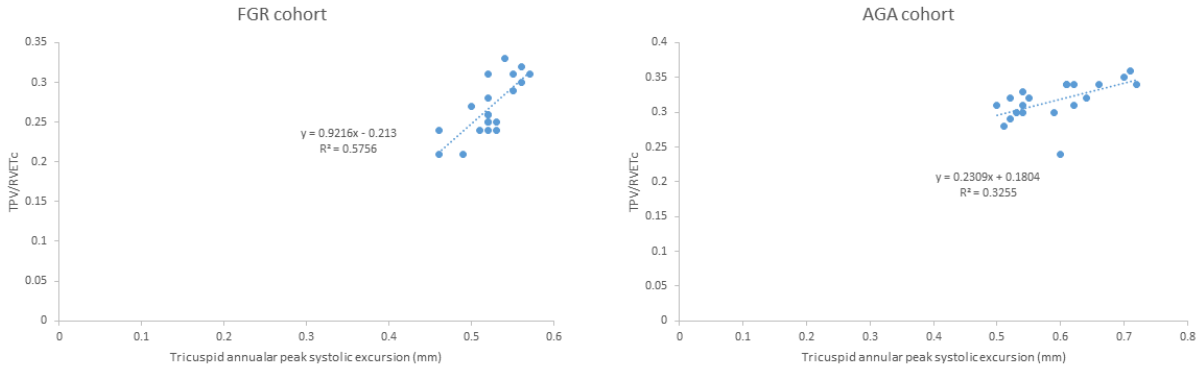

Figure 4.

Relevant mediators in fetal growth restriction

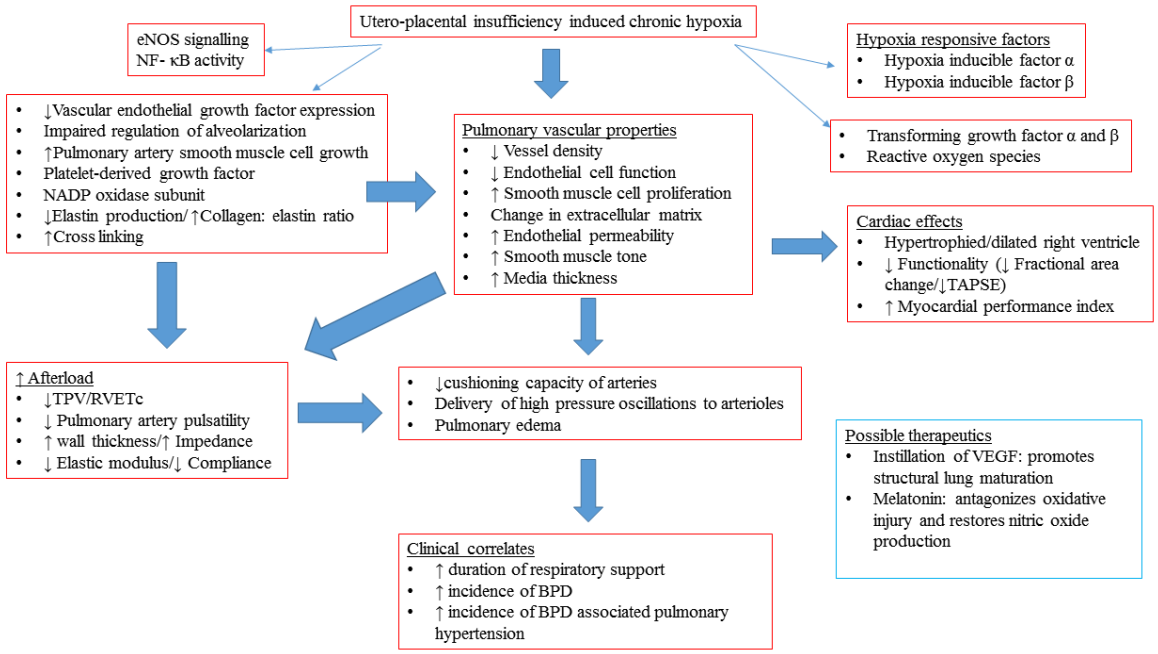

Table 1. Summary of haemodynamic assessments

	Technique	View	Cursor position	Comment
Ventricular function				
RV fractional area change	2D	Apical 4 chamber	Include full view of the right ventricle (base to apex)	[(RV four-chamber area at end-diastole – RV four-chamber area at end-systole)/RV four-chamber area at end-diastole] x 100%
Tricuspid annular peak systolic excursion	M mode	Apical 4 chamber	Tricuspid annulus	Measure of longitudinal contractility
Tricuspid MPI	TDI	Apical 4 chamber	Tricuspid lateral annulus	(IVCT + IVRT)/RVET

Pulmonary vascular dynamics				
TPV/RVETc	PWD	Long axis RVOT	Aligned with the flow, sample at tips of pulmonary leaflets	1/(TPV/RVETc) acts as a surrogate for pulmonary resistance
RPA inferior wall thickness in diastole	CCM TDI	Short axis	Perpendicular to RPA	Measured in end diastole
RPA Pulsatile diameter	CMM TDI	Short axis	Perpendicular to RPA	Difference between the RPA internal caliber in diastole and systole

PWD-pulse wave Doppler, CMM- colour m-mode, TPV-time to peak velocity, RVET-right ventricular ejection time, TAPSE-tricuspid annular peak systolic excursion,
RV-right ventricular, 2D-Two dimensional, RVOT-right ventricular outflow tract, TDI-tissue Doppler imaging, IVCT- iso volumic contraction time, IVRT- iso volumic relaxation time

Table 2. Demographics of the study population.

Variable	**FGR infants n=20** **Mean ± SD**	**AGA infants n=20** **Mean ± SD**	**P**
Mode of delivery (caesarean) n (%)	5 (25)	5 (25)	1
Antenatal steroids n (%)	19 (95)	20 (100)	0.9
Duration of respiratory support (days)	37 (14, 52)^	8 (5, 21)^	0.010
Total length of hospital stay (days)	73±21	50±16	<0.001
Home oxygen n (%)	4 (20)	0 (0)	0.1

Bronchopulmonary dysplasia n (%)	8 (40)	1 (5)	0.019
Ventilation at ECHO assessment			
Room air	7	9	0.6
CPAP/High flow	13	11	
$Pressure (cm of H_2O)/L/min	6±1	6±0.5	0.7
#Fraction of inspired oxygen	0.27±0.01	0.26±0.02	0.6

^median (interquartile), CPAP-continuous positive airway pressure, FGR-fetal growth restriction, AGA-appropriate for gestational age, #for those in oxygen, $for those on CPAP/high flow, SD-standard deviation.

Table 3. Echocardiographic assessments.

Variable	**FGR n=20 Mean ± SD**	**AGA n=20 Mean ± SD**	**Unadjusted difference (95% CI)**	**p**	**GA adjusted (95% CI)**	**P**
Heart rate (beats/min)	147±5	146±3	-1.25 (-4.08;1.58)	0.377	-1.32 (-4.19;1.54)	0.356
RV diastolic area (cm^2)	2.31±0.13	2.18±0.19	0.13 (0.03, 0.23)	0.016	0.13 (0.02, 0.23)	0.019
RV systolic area	2.02±0.14	1.86±0.18	0.17 (0.06,	0.002	0.16 (0.06,	0.003

(cm^2)			0.27)		0.27)	
RV fractional area change (%)	28.7±3.9	32.5±3.1	-3.8 (-6.0, -1.5)	0.002	-3.7 (-6.0, -1.4)	0.002
Tricuspid Annular Peak Systolic Excursion (mm)	5.2±0.3	5.9±0.7	-0.7 (-1.0, -0.4)	<0.001	-0.7 (-1.0, -0.3)	<0.001
Myocardial Performance Index	0.35±0.03	0.28±0.02	0.07 (0.05, 0.09)	<0.001	0.07 (0.05, 0.09)	<0.001
TPV/RVETc	0.27±0.04	0.32±0.03	-0.05 (-0.07, -0.03)	<0.001	-0.05 (-0.07, -0.03)	<0.001
RPA inferior wall thickness (µm)	843±68	761±40	82.1 (46.3, 117.8)	<0.001	84.0 (49.5, 118.5)	<0.001

FGR-fetal growth restriction, AGA-appropriate for gestational age, RV-right ventricular, TPV-time to peak velocity, RVET-right ventricular ejection time, RPA-right pulmonary artery, SD-standard deviation

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