Longitudinal evaluation of myocardial function in preterm infants with respiratory distress syndrome

[1]Chuen Y Poon PhD MRCPCH, [2]Dirk G Wilson MB FRCP, [1]Suchita Joshi PhD MRCPCH, [3]Alan G Fraser MB FRCPE, [1]Sailesh Kotecha PhD FRCPCH

[1]Department of Child Health, School of Medicine, Cardiff University, Cardiff, Wales

[2]Children's Heart Unit, University Hospital of Wales, Cardiff, Wales

[3]Wales Heart Research Institute, School of Medicine, Cardiff University, Cardiff, Wales

Short title: Myocardial function in preterm infants with RDS

Corresponding Author:

Professor Sailesh Kotecha,

Department of Child Health,

School of Medicine,

Cardiff University,

Heath Park,

Cardiff CF14 4XN.

Tel: +44(0)29 20 74 3375

FAX: +44(0)29 20 74 4283

Email: KotechaS@cardiff.ac.uk

Keywords: Tissue Doppler echocardiography, Right ventricular function, left ventricular function,

Doppler myocardial imaging

Abstract

Aim:

Preterm births and respiratory distress syndrome (RDS) are associated with pulmonary vascular disease and altered myocardial function. We serially assessed up to one year of age the effects of RDS on global and regional myocardial function of preterm infants, compared to preterm and term controls using conventional echocardiography parameters, tissue Doppler velocities and deformation analysis.

Methods and results:

120 infants (30 preterm (PT) with RDS, 30 PT controls without RDS, and 60 term controls) underwent conventional and tissue Doppler echocardiography within 72 hours of birth, at corrected term age for the preterm infants, at one month corrected, and at one year corrected age. At birth, compared to preterm and term controls, the PT-RDS group had decreased right ventricular (RV) long-axis function, systolic velocity, peak systolic strain, shorter pulmonary arterial acceleration time (PAAT) and lower ratio of PAAT to RV ejection time (PAAT:RVET). Preterm infants had left ventricular (LV) diastolic dysfunction at birth (lower early diastolic myocardial velocity, mitral E velocity, and mitral E:A ratio), and reduced long-axis systolic velocities and shortening. Differences between groups disappeared by one month corrected age, except PAAT:RVET which remained lower in the PT-RDS group. At 1 year, RV function was normal in PT-RDS apart from systolic strain rate, and LV function was normal apart from lower stroke volume and shortening, relative to body weight.

Conclusion:

PT-RDS had lower left and right ventricular systolic and diastolic function at birth which improved over time, suggesting postnatal maturation of cardiac function and resolution of lung disease.

INTRODUCTION

Extremely preterm infants with severe respiratory distress syndrome (RDS) have evidence of pulmonary vascular disease[1] and LV dysfunction.[2] In addition to using conventional Doppler echocardiographic parameters such as tricuspid regurgitation (TR) and pulmonary systolic time intervals to assess pulmonary arterial pressure,[3-5] tissue Doppler imaging (TDI) has been used to measure myocardial function in healthy neonates.[6-8] TDI is feasible and reproducible in preterm infants[9-11] and has been used to assess myocardial function in extremely preterm infants during the transitional period and serially until 36 weeks postmenstrual age.[11-13] Myocardial function of extremely preterm infants has been reported to improve between serial studies after birth, suggesting postnatal maturation.[12,13] Myocardial dysfunction has been detected using TDI in neonates with pulmonary hypertension, asphyxia, and bronchopulmonary dysplasia (BPD).[14-16] Less is known about the effects of RDS on myocardial function and on the natural history of cardiac maturation.

Vitali and colleagues showed improved right ventricular (RV) systolic velocity, tricuspid annular plane systolic excursion (TAPSE) and the ratio of pulmonary artery acceleration time (PAAT) to right ventricular ejection time (RVET) 24 hours after surfactant administered to premature infants with respiratory distress syndrome.[17] James and colleagues reported that RV systolic tissue velocity, RV systolic strain rate, and TAPSE increased between day 1 and day 2 of life in extremely preterm infants.[11] The changes were attributed to the decrease in pulmonary vascular resistance. The same investigators also reported a lower RV strain in ventilated infants compared to infants on continuous positive airways pressure support. In contrast, the LV function of the extremely preterm infants did not change significantly during the first week of life.[11,12]

Infants with BPD and/or pulmonary hypertension had evidence of abnormal RV strain and RV fractional area change[18,19] but LV strain was not affected.[18] Levy and colleagues also reported maturation of RV, LV

and septal myocardial strains in uncomplicated preterm infants was associated with increasing weight and postnatal age.[18]

We undertook this prospective observational study to assess global and regional myocardial function of both ventricles serially in preterm infants with RDS using conventional echocardiography and TDI including strain and strain rate, and to compare results with preterm and term controls up to one year of age. We hypothesised that both global and regional right ventricular function are impaired in preterm infants with RDS compared to preterm infants without RDS and to infants born at term, and also their ventricular function would mature and improve over the first year of life.

METHODS

Population

120 infants were recruited: 60 term infants (≥37 weeks' gestation) (Term control), 30 preterm infants (≤34 weeks' gestation) without RDS (PT Control), and 30 preterm infants with clinical and radiological evidence of RDS requiring mechanical ventilation at birth (PT-RDS). All groups were serially assessed until one year corrected age. The study was approved by the research ethics committee, and written informed consent was obtained from the parents.

Echocardiographic assessment

All infants were scanned within 72 hours after birth, at corrected term age (preterm infants), at one month post-term, and at one year corrected age. Infants with congenital cardiac defects (other than patent arterial duct (PDA) or foramen ovale) were excluded. 3-beat loops were acquired using a commercial ultrasound machine (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway) with a 10 or 7.0 MHz transducer.

Standard echocardiographic views along with real-time pulsed tissue Doppler velocity profiles and color tissue Doppler loops were used to obtain images for measurements and calculations. LVOT diameter, VTI of LV outflow, mitral E and A velocities, TR and PR velocities, PDA velocity, RV systolic time intervals (PAAT, RVET and PAAT:RVET), LVOT area, LV and RV chamber lengths at end-diastole (Figure 1A), mitral annular velocity and other tissue Doppler parameters were recorded, according to consensus recommendations.[20,21] Off-line analysis was performed using commercial software (EchoPAC 7-00, GE Medical Systems). All parameters were measured from 3 beats and averaged. Long-axis shortening of the LV and RV were calculated as displacement of the basal lateral annuli (LV Ds' and RV Ds') as a percentage of respective diastolic chamber lengths.

Early diastolic velocity (Ve') was measured at the medial and lateral mitral annulus and averaged. Myocardial systolic velocity (Vs), early diastolic velocity (Ve) and velocity during atrial contraction (Va) were measured at the basal segments of the LV and RV lateral walls. When myocardial Ve and Va were fused due to rapid heart rate, a single diastolic velocity was recorded and noted as Ve. Annular displacement in systole (Ds') was measured at the lateral mitral and tricuspid annuli using tissue tracking (Figure 1B).

Longitudinal peak systolic strain (Ss) at end-systole was measured within the middle segments of the LV (Figure 2) and RV free walls, using a region of interest of 6x3mm and a strain length or computation distance of 6mm as we found previously that that was most reproducible.[10] Systolic (SRs), early diastolic (SRe) and late diastolic (SRa) strain rates were measured at the same sites. Superimposed event timings were derived from LVOT and RVOT pulsed Doppler traces. We have previously published our results on feasibility and reproducibility in preterm infants.[9]

Statistical analysis

Data were analyzed using SPSS version 20.0 (SPSS Inc, Chicako, IL, USA). Results are presented as mean ±

2SD or median (range) as appropriate. Shapiro-Wilk test ascertained normality, and non-parametric data were compared using Mann-Whitney U-test. One-way analysis of variance (ANOVA) with Tukey HSD post-hoc multiple comparisons was used to compare the three groups at individual time-points. Since the term and preterm groups had three or four echocardiographic assessments respectively, repeated measures ANOVA was inappropriate. Chi-square tests (or Fisher exact tests as appropriate) were used to assess associations between categorical variables. $P<0.05$ was considered significant.

RESULTS

Demographics

General characteristics are summarized in Tables 1 and 2; the PT-RDS group had the lowest gestation, birth-weight, and systolic and diastolic blood pressures. There were 8 preterm control infants and 11 preterm RDS infants who did not have their term corrected age assessment. 7 infants died in the preterm RDS group and the other preterm infants who were lost to follow up were either transferred out to their local neonatal units for follow on care or discharged prior to 36 weeks corrected age and were unable to return for the assessment. 10 out of 19 infants in PT-RDS group, who were assessed at term corrected age, fulfilled the criteria for BPD as defined by the 2001 National Institute of Health BPD workshop.[22] PDA was detected at birth in many infants in all three groups, but none was deemed hemodynamically significant or received pharmacologic or surgical treatment; no residual shunts were detected at one month corrected age.

Infants in both preterm groups were assessed at a slightly younger chronological age compared to term counterparts, at “term” and at one month and one year of corrected age. Correspondingly, LVOTd, and LV and RV chamber lengths were smaller in the preterm groups at term, but these differences had disappeared by one month and at one year, despite a lower mean weight in the PT-RDS group at one year. Differences in blood pressure had resolved by one month.

Left ventricular function

LV measurements are summarized in Tables 3 and 4. The PT-RDS group had the lowest values at birth for stroke volumes, long-axis shortening, myocardial systolic velocities and peak systolic strain, but these differences had resolved by one month of corrected age. Both preterm groups had lower LV early diastolic myocardial velocity, mitral E velocity and E:A ratio compared to Term Controls. There were no difference in LV peak systolic and diastolic strain rates across all time points; peak early diastolic strain rate was higher in the preterm groups but the difference disappeared when comparisons were adjusted for differences in heart rate.

Right ventricular function

RV global and regional systolic function, as indicated by long-axis shortening and systolic velocity, were lower at birth and at corrected term age in the PT-RDS group than in both control groups (Table 5). RV systolic strain (RV Ss), pulmonary acceleration time (PAAT) and the PAAT:RVET ratio were also lower in PT-RDS at birth (Table 6). By one month corrected age, there was no difference in RV strain between the groups but PAAT:RVET ratio was still lower in PT-RDS group. RV early diastolic velocity was lower in the preterm groups at birth and the differences resolved by one month corrected age. There were no differences in RV systolic and diastolic strain rate between groups at birth, at one month and one year corrected age.

At birth, 25 PT-RDS infants (83%) had tricuspid regurgitation, compared with 12 Preterm Controls (40%). Pulmonary regurgitation (PR) was measurable in only 8 infants in each group (27%). The velocities recorded were comparable (TR 2.0 (0.8) m/s in PT-RDS, 2.0 (0.8) m/s in Preterm Controls, p=0.99; and PR 0.6 (0.4) and 0.7 (0.4)m/s, p=0.78). No differences were noted between the groups for tricuspid and pulmonary regurgitation respectively at any period.

Maturation of myocardial function

Parameters for LV global and regional systolic and diastolic function were lower in preterm groups at birth than in term controls, apart from LV systolic and diastolic strain rates (Tables 2-4). These differences disappeared by term corrected age but stroke volume remained lower in preterm groups whereas heart rate, long-axis shortening and cardiac output were higher. At one year, PT-RDS group had lower stroke volume (by 12%, $p<0.05$) and LV long-axis shortening (by 9%, $p<0.025$) than control groups despite having comparable ventricular size. All markers of LV regional myocardial function matured over the first year.

A similar pattern was observed for RV global and regional function where differences disappeared at one month and at one year corrected age (Tables 4-5).

DISCUSSION

In this study, we used conventional echocardiography and myocardial velocity and deformation imaging (or tissue Doppler imaging, TDI) to assess global and regional myocardial function of both ventricles in preterm infants with RDS, and compared the results with preterm and term control infants during serial examinations recorded up to one year of age. Our main findings are that PT-RDS infants had lower LV and RV systolic function at birth that improved over time such that there were no measurable difference by one month corrected age, and that their cardiac function continued to mature during the first year of life. We used TDI-derived strain and strain rate to assess regional ventricular function in the extremely preterm infants, rather than speckle tracking, because of their much higher temporal resolution which is necessary for studying function at fast heart rates.[23] Overall, the detailed echocardiographic parameters were obtained in more than 95% of the studies.

LV function and maturation in the first year of life

Other investigators have also reported a progressive increase in LV systolic function[24,25] but in our study the changes cannot be explained solely by differences in body weight, because long-axis shortening of the LV remained lower in PT-RDS group after adjustment for ventricular size. All infants in that group required

mechanical ventilation and 20% required inotropic support with a low-dose dopamine infusion. Preterm myocardium, which lacks sarcoplasmic reticulum, relies mainly on the L-type calcium channels to trigger a weaker muscle contraction compared to the more mature infants.[26] Additionally, the immature myocardium contains a higher proportion of non-contractile collagen, which impairs relaxation and ventricular filling during diastole.[27] Breatnach and colleagues reported that infants who received inotropes had lower LV and septal early myocardial velocities whereas a hemodynamically significant PDA (hsPDA) had the reverse effect on the same parameters.[13] In our study, the comorbidities associated with extreme prematurity may have contributed to the myocardial dysfunction.

The mitral E:A ratio was lower in our preterm groups than in the Term Controls; a similar pattern was observed for fetal cardiac function.[28,29] When assessed at term, the mitral E:A ratio normalized and became comparable to term infants. Two other groups also reported that the mitral E velocity continued to increase up to one year[30,31] implying that ventricular diastolic function continues to evolve during infancy. The E/e' ratio is a non-invasive correlate of mean LV filling pressure in adults that to our knowledge has not been validated against invasive measurements in infants. It was similar in all groups at birth, which may suggest that LV preload was normal despite the lung disease in the PT-RDS group. Left ventricular filling in preterm infants was more dependent on atrial systole.

Similar changes were seen in the LV lateral wall systolic velocity and strain which increased over time in the PT-RDS group where the differences between the groups disappear by one month corrected age. Fetal studies have shown the LV lateral wall velocities increases from mid-trimester to term[29,32] and Klitsie and colleagues reported that LV systolic and diastolic function increased up to 7 weeks after birth in healthy term infants.[33] These studies suggest that LV systolic function and relaxation improve with fetal maturity and continue to improve postnatally.

LV myocardial strain was lowest in the PT-RDS group at birth with no measurable reduction in preload or evidence of increased afterload as their blood pressure was lower than the control groups. This suggests an inherent reduction in LV systolic function as a result of prematurity. LV peak systolic strain of PT-RDS group increased and became similar to the control groups by one month of corrected age. Our finding is slightly different from those published by other groups where LV strain had remained stable from birth through to 28 days and 36 weeks post-menstrual age.[12,34] Levy and colleagues used 2D speckle tracking method to assess LV global strain reported an initial increase in LV strain in the first 7 days of life but thereafter the LV strain value stabilized until 1 year corrected age.[18] One possible reason for this discrepancy between our finding and other published data could be to the timing of the assessments. Our study assessed these infants within the first 72 hours of life and the second follow assessment occurred at term corrected age. Another possible explanation could be underestimation of the LV strain in the smallest hearts with our tissue Doppler technique and the difficulty in maintaining a small insonation angle. However, the LV strain of 23±4% in the larger Term Controls at birth in our study is comparable to other reports.[6,7,35] The increases in LV strain in all groups were not as high as those seen in the RV and this is due to the difference in myocardial fiber architecture between LV and RV.[36,37] Levy and colleagues reported infants with hsPDA have higher LV global strain but no difference in LV, RV, and septal wall strains in infants with PDA that did not require treatment compared to those without PDA. [18] Strain rate was similar in all groups at every time interval, implying that the preterm infants had normal intrinsic contractile function across all time points and is not affected by cardiac growth.[33,38]

Pulmonary artery pressure assessment, right ventricular function and its maturation in the first year of life

We did not detect any difference in pulmonary arterial pressure based on TR jet findings between PT-RDS and the control groups at birth. TR jet can be difficult to be detected and was only detected in less than 50% of infants with CLD and pulmonary hypertension in one study.[5] Even if this is detected, TR jet correlates poorly with the pulmonary arterial pressure measured by right heart catheterization (RHC).[39]

The TR measurements in PT-RDS infants were most likely under-estimated in our study as PAAT:RVET in the same group was significantly lower (0.27) than controls (0.31) , implying they had increased pulmonary arterial pressures.[4,40,41] PAAT:RVET <0.31 has been validated against RHC to have 97% sensitivity and 95% specificity at detecting pulmonary hypertension in children.[4] These time intervals could be measured in all infants, unlike tricuspid regurgitation which was detectable in approximately two thirds of the preterm infants in our study.

Vitali and colleagues assessed the changes in PAAT:RVET, myocardial velocities, right and left ventricular output and TAPSE at 2 and 24 hours post surfactant administration in a small cohort of preterm infants. They found an improvement in all the parameters measured following surfactant administration but only after 24 hours post surfactant administration.[17] Our PT-RDS infants had significantly low systolic displacement of the tricuspid annulus (RV Ds') and RV long axis shortening, both markers of RV global systolic function, at birth. A similar reduction in regional function represented by RV systolic velocity and strain, and late diastolic velocity were also noted at birth in the background of raised pulmonary arterial pressure in the PT-RDS group compared to the two control groups. These parameters improved by term corrected age compared to preterm controls implying improvement of RV function despite evidence of increased pulmonary arterial pressure. PAAT:RVET in the PT-RDS group remained significantly lower at the term corrected age and persisted until one month corrected age. 10 infants from PT-RDS group fulfilled the BPD criteria and it is possible that the pulmonary pressures remained elevated. We did not detect any residual RV systolic dysfunction in our PT-RDS group after term corrected age. Helfer and colleagues found that infants who developed BPD had significantly lower RV free wall longitudinal strain on days 14 and 28 of life[34]. Levy and colleagues found in their study, infants with BPD and pulmonary hypertension have persistent RV dysfunction on 2D speckle tracking derived strain measurements up to one year corrected age despite being clinically free from lung disease and oxygen dependency.[18] This potentially could help identify infants who are at higher risk of developing BPD. In both these studies, the RV longitudinal strain increased with age but the rate of increase is slower in BPD infants. Levy and colleagues also report that

10% of infants without BPD had detectable pulmonary hypertension at 36 weeks corrected age also had decreased RV longitudinal strain.[18] This suggests a primary vascular injury that may occur in some extremely preterm infants, independent of lung disease. We reported that children aged 8-12 who had BPD had normal myocardial function and responses to hypoxia[42] but had increased pulmonary arterial stiffness during hypoxia.[43] Children who had BPD have increased pulmonary vascular reactivity to hypoxia thus may be at risk of developing pulmonary hypertension at an earlier age compared to healthy preterm infants despite normal cardiovascular function at rest during normoxia.

The preterm groups showed postnatal adaptation during their neonatal period and a significant improvement in their RV systolic function (RV Ds', RV long axis shortening, RV longitudinal systolic strain and RV systolic strain rate) and RV diastolic function (RV Vebl and RV Vabl) at term corrected age compared to the term controls at birth. This progressive increase in RV systolic function could be due to the fall in the pulmonary vascular resistance and also suggest an increase in RV contractile function in the postnatal period. It is reassuring to note that both RV systolic and diastolic function of the preterm infants continue develop in line with the term infants when assessed at one month and one year corrected age respectively. This observation was also noted by other investigators who used speckle tracking echocardiography to assess ventricular functions of the preterm infants.[2,18]

Clinical application of the study

Our study adds TDI myocardial velocities and TDI-derived strain and strain rate data to the growing literature in this population. We have successfully used tissue Doppler echocardiography and TDI-derived strain and strain rate to assess the both regional and global ventricular function in the preterm population. TDI-derived strain measurement of the RV can be used to monitor longitudinally cardiopulmonary disease in the first year especially in infants with moderate and severe BPD where conventional echocardiographic parameters may not be sensitive to detect. In cases where TR jet is absent or the envelope is incomplete, PAAT:RVET is a good surrogate marker for pulmonary artery pressure or compliance. LV myocardial

velocities at the lateral mitral annulus were sensitive and easily reproducible measurements for serial follow-up of LV systolic and diastolic function in preterm infants. Additionally, we have also shown in our previous study that LV lateral wall mid-segment longitudinal peak systolic strain, mitral E, mitral A, and E:A ratio were highly reproducible.[9,10]

Limitations

We started the study with 120 infants in three groups but follow-up rates at one month and one year represented 64% and 55% of the 120 subjects. We performed analysis comparing infants who attended follow ups at one month or one year corrected age and those who dropped out and found no difference in baseline characteristics or in the parameters of cardiac function at the first assessment (Supplementary table 1). We are satisfied that those followed up were representative of the group. A subgroup analysis comparing BPD infants and non-BPD infants within the RDS group at term corrected age only showed a difference in RV longitudinal axis shortening (p=0.037) in a small cohort that is insufficiently powered (Supplementary table 2). Even though the 2:1:1 ratio between groups was preserved, the relatively small sample size at one month and one year assessments may not be sufficiently powered to detect differences between the groups. However, our findings are comparable to other published studies as discussed above.

We used TDI-derived strain to assess LV and RV free wall function. TDI-derived strain is able to capture images at higher temporal resolution compared to 2D speckle tracking in the assessment of strain in this population consisting extremely preterm infants who have high heart rate. We decided to place the sampling area in the middle segment to avoid adjacent structures affecting the measurements as the ventricular size of the PT-RDS group is approximately 18mm.[6] By placing the sampling area in the middle segment of the LV free wall, in the smallest preterm infants, this actually sampled almost the whole of the free wall. It has been suggested that measuring strain in the middle segment more reliable for serial follow ups in this population.[6] We have reported good reproducibility measuring LV strain at this site using our sampling size and strain length.[10] We are aware of the limitations associated with TDI and tried to minimize

the deviation between the wall segment and ultrasonic beam to below 20^{o}. Assessment of myocardial function in the fetus and neonate using 2D speckle tracking[44,45] is both feasible and more reproducible, in addition to allowing the assessments of both regional and global strain. However, 2D speckle tracking may have disadvantages due to smoothing and limited temporal resolution. In our study, signal noise are likely to have affected strain rate measurements, which could explain why they were less sensitive for demonstrating subtle differences between groups, especially in the LV free wall.

CONCLUSION

Preterm infants with RDS have lower left and right ventricular systolic and diastolic function at birth compare to the larger preterm and term control groups. These improve with time, suggesting postnatal maturation of cardiac function and resolution of their lung disease.

Acknowledgement

We thank Mrs. Julie Edwards for performing the echocardiograms and contacting patients for follow up assessments.

Statement of Ethics

Written informed consent was obtained from the parents prior to enrolment into the study.

The study was approved by the South East Wales research ethics committee.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contribution

Sailesh Kotecha conceived and designed the study, supervised the study, contributed to the interpretation of the results, revised and approved the paper.

Alan Fraser conceived and designed the study, technical supervision of echocardiography and contributed to the interpretation of the results, revised and approved the paper.

Dirk Wilson designed the study, technical supervision of echocardiography, and contributed to the interpretation of the results, revised and approved the paper.

Suchita Joshi undertook the study, performed echocardiograms on the infants, and revised and approved the paper.

Chuen Y Poon undertook the study, analyzed the echocardiogram images, interpreted of the results, and drafted and revised the paper.

REFERENCES

1. Mourani PM, Sontag MK, Younoszai A, et al. Early Pulmonary Vascular Disease in Preterm Infants at Risk for Bronchopulmonary Dysplasia. *Am J Respir Crit Care Med.* 2015;191(1):87-95.
2. Schubert U, Müller M, Abdul-Khaliq H, Norman M. Preterm birth is associated with altered myocardial function in infancy. *J Am Soc Echocardiogr.* 2016;29(7):670-678.
3. Skinner JR, Stuart AG, O'Sullivan J, Heads A, Boys RJ, Hunter S. Right heart pressure determination by Doppler in infants with tricuspid regurgitation. *Arch Dis Child.* 1993;69(2):216-220.
4. Levy PT, Patel MD, Groh G, et al. Pulmonary artery acceleration time provides a reliable estimate of invasive pulmonary hemodynamics in children. *J Am Soc Echocardiogr.* 2016;29(11):1056-1065.
5. Benatar A, Clarke J, Silverman M. Pulmonary hypertension in infants with chronic lung disease: non-invasive evaluation and short term effect of oxygen treatment. *Arch Dis Child Fetal Neonatal Ed.* 1995;72(1):F14-F19.
6. Pena JLB, Silva MGd, Faria SCC, et al. Quantification of regional left and right ventricular deformation indices in healthy neonates by using strain rate and strain imaging. *J Am Soc Echocardiogr.* 2009;22(4):369-375.
7. Nestass E, Stoylen A, Brunvand L, Fugelseth D. Tissue Doppler derived longitudinal strain and strain rate during the first 3 days of life in healthy term neonates. *Pediatr Res.* 2009;65(3):357-362
8. Pena JLB, da Silva MG, Alves JMS, Jr., et al. Sequential changes of longitudinal and radial myocardial deformation indices in the healthy neonate heart. *J Am Soc Echocardiogr.* 2010;23(3):294-300.
9. Joshi S, Edwards JM, Wilson DG, Wong JK, Kotecha S, Fraser AG. Reproducibility of myocardial velocity and deformation imaging in term and preterm infants. *Eur J Echocardiogr.* 2010;11(1):44-50.
10. Poon CY, Edwards JM, Joshi S, Kotecha S, Fraser AG. Optimization of myocardial deformation imaging in term and preterm infants. *Eur Heart J Cardiovasc Imaging.* 2011;12(3):247-254.
11. James AT, Corcoran JD, Jain A, et al. Assessment of myocardial performance in preterm infants less than 29 weeks gestation during the transitional period. *Early Hum Dev.* 2014;90(12):829-835.
12. James AT, Corcoran JD, Breatnach CR, Franklin O, Mertens L, El-Khuffash A. Longitudinal Assessment of Left and Right Myocardial Function in Preterm Infants Using Strain and Strain Rate Imaging. *Neonatology.* 2016;109(1):69-75.
13. Breatnach CR, El-Khuffash A, James A, McCallion N, Franklin O. Serial measures of cardiac performance using tissue Doppler imaging velocity in preterm infants <29weeks gestations. *Early Hum Dev.* 2017;108:33-39.
14. Patel N, Mills J, Cheung M. Use of the myocardial performance index to assess right ventricular function in infants with pulmonary hypertension. *Pediatr Cardiol.* 2009;30(2):133-137.
15. Wei Y, Xu J, Xu T, Fan J, Tao S. Left ventricular systolic function of newborns with asphyxia evaluated by tissue Doppler imaging. *Pediatr Cardiol.* 2009;30(6):741-746.
16. Yajamanyam PK, Negrine RJS, Rasiah SV, Zamora J, Ewer AK. Assessment of myocardial function in preterm infants with chronic lung disease using tissue Doppler imaging. *Arch Dis Child Fetal Neonatal Ed.* 2016;101:F527-F532.
17. Vitali F, Galletti S, Aceti A, et al. Pilot observational study on haemodynamic changes after surfactant administration in preterm newborns with respiratory distress syndrome. *Ital J Pediatr.* 2014;40(1):26.
18. Levy PT, El-Khuffash A, Patel MD, et al. Maturational Patterns of Systolic Ventricular Deformation Mechanics by Two-Dimensional Speckle-Tracking Echocardiography in Preterm Infants over the First Year of Age. *J Am Soc Echocardiogr.* 2017;30(7):685-698.e681.
19. Haque U, Stiver C, Rivera BK, et al. Right ventricular performance using myocardial deformation imaging in infants with bronchopulmonary dysplasia. *J Perinatol.* 2016;37:81.
20. Lopez L, Colan SD, Frommelt PC, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: A report from the pediatric measurements writing

group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr.* 2010;23(5):465-495.

21. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28(1):1-39.e14.
22. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2001;163(7):1723-1729.
23. D'hooge J, Heimdal A, Jamal F, et al. Regional Strain and Strain Rate Measurements by Cardiac Ultrasound: Principles, Implementation and Limitations. *Eur J Echocardiogr.* 2000;1(3):154-170.
24. Negrine RJS, Chikermane A, Wright JGC, Ewer AK. Assessment of myocardial function in neonates using tissue Doppler imaging. *Arch Dis Child Fetal Neonatal Ed.* 2012;97(4):F304-F306.
25. Saleemi MSH, El-Khuffash A, Franklin O, Corcoran JD. Serial changes in myocardial function in preterm infants over a four week period: the effect of gestational age at birth. *Early Hum Dev.* 2014;90(7):349-352.
26. Noori S, Seri I. Pathophysiology of newborn hypotension outside the transitional period. *Early Hum Dev.* 2005;81(5):399-404.
27. Friedman WF. The intrinsic physiologic properties of the developing heart. *Prog Cardiovasc Dis.* 1972;15(1):87-111.
28. Harada MDK, Rice MDMJ, Shiota MDT, et al. Gestational age- and growth-related alterations in fetal right and left ventricular diastolic filling patterns. *Am J Cardiol.* 1997;79(2):173-177.
29. Chan LYS, Wing YF, John THW, Cheuk MY, Tse NL, Tze KL. Reference charts of gestation-specific tissue Doppler imaging indices of systolic and diastolic functions in the normal fetal heart. *Am Heart J.* 2005;150(4):750-755.
30. Schmitz L, Xanthopoulos A, Koch H, Lange PE. Doppler flow parameters of left ventricular filling in infants: How long does it take for the maturation of the diastolic function in a normal left ventricle to occur? *Pediatr Cardiol.* 2004;25(5):482-491.
31. Elkiran O, Karakurt C, Kocak G, Karadag A. Tissue Doppler, strain, and strain rate measurements assessed by two-dimensional speckle-tracking echocardiography in healthy newborns and infants. *Cardiol Young.* 2013;24(02):201-211.
32. Elmstedt NN, Johnson JJ, Lind BB, et al. Reference values for fetal tissue velocity imaging and a new approach to evaluate fetal myocardial function. *Cardiovasc Ultrasound.* 2013;11:29.
33. Klitsie LM, Roest AAW, Haak MC, Blom NA, Ten Harkel ADJ. Longitudinal follow-up of ventricular performance in healthy neonates. *Early Hum Dev.* 2013;89(12):993-997.
34. Helfer S, Schmitz L, Bührer C, Czernik C. Tissue Doppler–Derived Strain and Strain Rate during the First 28 Days of Life in Very Low Birth Weight Infants. *Echocardiography.* 2014;31(6):765-772.
35. Jain A, El-Khuffash AF, Kuipers BCW, et al. Left ventricular function in healthy term neonates during the transitional period. *J Pediatr.* 2017;182:197-203.e192.
36. Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. *Br Heart J.* 1981;45(3):248.
37. Levy PT, Holland MR, Sekarski TJ, Hamvas A, Singh GK. Feasibility and Reproducibility of Systolic Right Ventricular Strain Measurement by Speckle-Tracking Echocardiography in Premature Infants. *J Am Soc Echocardiogr.* 2013;26(10):1201-1213.
38. Perles Z, Nir A, Gavri S, Rein AJJT. Assessment of fetal myocardial performance using myocardial deformation analysis. *Am J Cardiol.* 2007;99(7):993-996.
39. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126(1 Suppl):14S-34S.
40. Fitzgerald D, Evans N, Van Asperen P, Henderson-Smart D. Subclinical persisting pulmonary hypertension in chronic neonatal lung disease. *Arch Dis Child Fetal Neonatal Ed.* 1994;70(2):F118-F122.

41. Evans NJ, Archer LN. Doppler assessment of pulmonary artery pressure during recovery from hyaline membrane disease. *Arch Dis Child.* 1991;66(7 Spec No):802-804.
42. Joshi S, Wilson DG, Kotecha S, Pickerd N, Fraser AG, Kotecha S. Cardiovascular function in children who had chronic lung disease of prematurity. *Arch Dis Child Fetal Neonatal Ed.* 2014;99(5):F373-F379.
43. Poon CY, Watkins WJ, Evans CJ, et al. Pulmonary arterial response to hypoxia in survivors of chronic lung disease of prematurity. *Arch Dis Child Fetal Neonatal Ed.* 2015(101):F309-F313.
44. Jain A, Mohamed A, El-Khuffash A, et al. A comprehensive echocardiographic protocol for assessing neonatal right ventricular dimensions and function in the transitional period: Normative data and 'Z' Scores. *J Am Soc Echocardiogr.* 2014;27(12):1293-1304.
45. Schubert U, Muller M, Norman M, Abdul-Khaliq H. Transition from fetal to neonatal life: Changes in cardiac function assessed by speckle-tracking echocardiography. *Early Hum Dev.* 2013;89:803-808.

Table 1: Maternal and infant characteristics

	Term Control (A)	PT Control (B)	PT RDS (C)	p-value
Number	60	30	30	
Male : Female (n)	31:29	18:12	21:9	-
Gestation (weeks)	39.8 (1.2)	32.7 (1.4)	28.2 (2.7)	<0.001[§, §§, §§§]
Birth weight (kg)	3.4 (0.5)	1.8 (0.4)	1.2 (0.4)	<0.001[§, §§, §§§]
Antenatal corticosteroids (n)	-	26 (87%)	22 (73%)	0.197
Multiple births (n, %)	2 (3%)	10 (33%)	5 (17%)	0.001
Caesarean section (n, %)	10 (17%)	16 (53%)	9 (30%)	0.001
Maternal smoking (n, %)	11 (18%)	12 (40%)	11 (37%)	0.05
Maternal fever (n, %)	2 (3%)	3 (10%)	1 (3%)	0.349
Prolonged rupture of membranes (n, %)	3 (5%)	10 (33%)	6 (20%)	0.002
Inotropic support (n, %))	-	-	6 (20%)	-
Patent ductus arteriosus (n, %)	27 (45%)	7 (23%)	19 (63%)	0.008
Ventilation / respiratory parameters				
Surfactant therapy (n, %)	-	-	30 (100%)	
Conventional ventilation:HFOV (n)	-	-	26:4	
Highest peak pressure (cmH_20)	-	-	21.8 (3.9)	-
Duration of ventilation (days)	-	-	14.0 (17.5)	-
Duration of O_2 dependency (days	-	4.4 (7.9)	57.9 (83.6)	<0.001
Postnatal steroids (n, %)	-	-	0 (%)	
Bronchopulmonary dysplasia* (n, %)	-	-	10 (33%)	-
Necrotising enterocolitis (n, %)	-	-	4 (13%)	-
ROP threshold (Stage 2 plus or above) (n, %)	-	-	4 (13%)	-
IVH (grade 3 or 4)	-	-	3 (10%)	-

HFOV, high frequency oscillation ventilation; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage.
Results are presented as mean (SD) or as number (percentage).
[§] p <0.001 (PT RDS V PT control), [§§] p <0.001 (PT RDS V Term control), [§§§] p <0.001 (PT control V Term control), [†] p <0.05 (PT RDS V PT control)
*Bronchopulmonary dysplasia as defined by 2001 National Institute of Health BPD workshop[19]

Table 2: General characteristics, blood pressure, and ventricular sizes

	Term Control	PT Control	PT-RDS	p-value
Numbers				
Birth	60	30	30	-
At term	60	22	19	-
1 month	45	17	15	-
1 year	33	18	16	-
Age (weeks)				
Birth	39.8(1.2)	32.7(1.4)	28.2(2.7)	<0.001§,§§,§§§
At term	"	37.3(1.9)	36.7(1.4)	<0.001§§,§§§
1 month	5.3(1.0)	4.6(1.8)	3.8(1.6)	0.002‡‡
1 year	53.0(2.3)	51.9(3.5)	49.2(4.2)	0.001§§,§§§
Weight (kg)				
Birth	3.4(0.5)	1.8(0.4)	1.2(0.4)	<0.001§,§§,§§§
At term	"	2.5(0.7)	2.3(0.4)	<0.001§§,§§§
1 month	4.5(0.6)	4.3(0.8)	4.1(0.5)	0.064
1 year	9.8(1.1)	9.5(1.2)	8.8(1.4)	0.041††
ANOVA (p-value)	<0.001	<0.001	<0.001	
Systolic BP (mmHg)				
Birth	66.9(11.7)	65.1(10.8)	49.3(7.8)	<0.001§,§§
At term	"	65.8(10.1)	49.1(6.7)	<0.001§,§§
1 month	95.6(14.0)	95.3(14.5)	99.1(20.7)	0.765
1 year	106.3(21.2)	107.8(18.7)	92.2(14.1)	0.058
ANOVA (p-value)	<0.001	<0.001	<0.001	
Diastolic BP (mmHg)				
Birth	41.3(9.9)	37.1(7.8)	30.8(7.5)	<0.001†,§§
At term	"	37.2(8.3)	29.1(6.0)	<0.001†,§§
1 month	60.7(11.0)	57.7(13.4)	58.6(13.3)	0.688
1 year	70.1(14.4)	71.5(13.3)	61.5(10.9)	0.095
ANOVA (p-value)	<0.001	<0.001	<0.001	
Heart rate (bpm)				
Birth	115(19)	136(15)	143(16)	<0.001§§,§§§
At term	"	159(16)	155(12)	<0.001§§,§§§
1 month	152(17)	160(21)	153(14)	0.276
1 year	125(15)	131(20)	127(17)	0.473
ANOVA (p-value)	<0.001	<0.001	<0.001	
End-diastolic left ventricular chamber lengths (cm)				
Birth	2.8(0.3)	2.1(0.2)	1.8(0.3)	<0.001§,§§,§§§
At term	"	2.5(0.4)	2.6(0.4)	<0.01††,‡‡‡
1 month	3.1(0.2)	3.1(0.2)	3.0(0.2)	0.263
1 year	4.0(0.2)	3.9(0.3)	3.9(0.2)	0.340
ANOVA (p-value)	<0.001	<0.001	<0.001	
End-diastolic right ventricular chamber lengths (cm)				
Birth	2.6(0.3)	2.0(0.2)	1.8(0.3)	<0.001§,§§,§§§
At term	"	2.3(0.4)	2.4(0.3)	<0.001‡‡,‡‡‡
1 month	3.0(0.2)	3.1(0.3)	2.9(0.2)	0.420
1 year	3.9(0.2)	3.9(0.3)	3.8(0.2)	0.636
ANOVA (p value)	<0.001	<0.001	<0.001	

Results are presented as mean(SD).
§p <0.001(PT-RDS v PTC), §§p <0.001(PT-RDS v TC), §§§p <0.001(PTC v TC),
‡p <0.01(PT-RDS v PTC), ‡‡p <0.01(PT-RDS v TC), ‡‡‡p <0.01(PTC v TC),
†p <0.05(PT-RDS v PTC), ††p <0.05(PT-RDS v TC), †††p <0.05(PTC v TC)

Table 3: Left ventricular global systolic and diastolic function

	Term Control	PT Control	PT-RDS	ANOVA p-value
LVOT_d (cm)				
Birth	0.66(0.07)	0.53(0.06)	0.45(0.08)	<0.001§,§§,§§§
At term	"	0.62(0.06)	0.58(0.06)	<0.001§§
1 month	0.77(0.07)	0.75(0.06)	0.73(0.07)	0.109
1 year	0.98(0.07)	0.96(0.07)	0.92(0.08)	0.097
ANOVA (p-value)	<0.001	<0.001	<0.001	
LVOT VTI (cm)				
Birth	12.5(2.4)	10.2(2.3)	8.6(2.5)	<0.001†,§§,§§§
At term	"	12.7(2.9)	13.2(2.0)	0.583
1 month	13.9(2.2)	15.0(2.0)	14.5(1.6)	0.206
1 year	17.2(1.7)	16.9(2.0)	16.8(2.8)	0.870
ANOVA (p-value)	<0.001	<0.001	<0.001	
Stroke volume (ml)				
Birth	4.3(1.2)	2.3(0.8)	1.4(0.6)	<0.001‡,§§,§§§
At term	"	2.5(0.7)	2.3(0.4)	0.014††
1 month	6.5(1.5)	6.7(1.3)	6.0(1.0)	0.314
1 year	12.8(1.6)	12.1(1.8)	11.3(2.3)	0.043††
ANOVA (p-value)	<0.001	<0.001	<0.001	
Cardiac output (ml/min)				
Birth	489(125)	305(114)	194(83)	<0.001‡,§§,§§§
At term	"	624(204)	541(142)	0.002‡‡‡
1 month	989(248)	1070(247)	909(151)	0.151
1 year	1600(290)	1590(262)	1420(221)	0.081
ANOVA (p-value)	<0.001	<0.001	<0.001	
LV Ds' (mm)				
Birth	4.6(1.0)	3.4(0.8)	2.6(1.0)	<0.001‡,§§,§§§
At term	"	5.8(1.3)	5.0(1.1)	<0.001†,§§§
1 month	7.5(1.2)	7.2(0.8)	6.6(0.9)	0.037††
1 year	9.5(1.2)	8.7(1.1)	8.5(1.0)	0.007††,†††
ANOVA (p-value)	<0.001	<0.001	<0.001	
LVbl long axis shortening (%)				
Birth	16.3(3.6)	15.7(3.5)	14.0(5.1)	0.047††
At term	"	22.6(3.0)	18.8(3.1)	<0.001‡,††,§§§
1 month	23.7(3.8)	23.0(2.6)	21.9(2.6)	0.200
1 year	24.0(3.0)	22.2(2.3)	21.9(2.3)	0.022††
ANOVA (p-value)	<0.001	<0.001	<0.001	
Mitral E (m/s)				
Birth	0.64(0.12)	0.52(0.11)	0.47(0.14)	<0.001§§,§§§
At term	"	0.96(0.24)	0.94(0.20)	<0.001§§,§§§
1 month	1.04(0.21)	1.08(0.18)	1.09(0.16)	0.649
1 year	1.18(0.15)	1.16(0.19)	1.11(0.09)	0.271
ANOVA (p-value)	<0.001	<0.001	<0.001	
Mitral A (m/s)				
Birth	0.57(0.11)	0.56(0.11)	0.52(0.13)	0.081
At term	"	0.92(0.22)	0.91(0.15)	<0.001§§,§§§
1 month	0.90(0.20)	1.00(0.22)	0.94(0.14)	0.270
1 year	0.88(0.16)	0.92(0.18)	0.79(0.19)	0.106
ANOVA (p-value)	<0.001	<0.001	<0.001	
Mitral E:A				
Birth	1.13(0.23)	0.95(0.18)	0.92(0.22)	<0.001§§,§§§
At term	"	1.03(0.13)	1.02(0.21)	0.054

1 month	1.14(0.18)	1.06(0.18)	1.10(0.17)	0.293
1 year	1.36(0.22)	1.23(0.21)	1.44(0.22)	0.030[†]
ANOVA (p-value)	<0.001	<0.001	<0.001	

LVOT_d, left ventricular outflow tract diameter; LVOT_VTI, left ventricular outflow tract velocity-time integral; LV Ds', left ventricular lateral annular displacement; LVbl, left ventricular basal lateral.
Results are presented as mean(SD)
[§]p <0.001(PT-RDS v PTC), [§§]p <0.001(PT-RDS v TC), [§§§]p <0.001(PTC v TC),
[‡]p <0.01(PT-RDS v PTC), [‡‡]p <0.01(PT-RDS v TC), [‡‡‡]p <0.01(PTC v TC),
[†]p <0.05(PT-RDS v PTC), [††]p <0.05(PT-RDS v TC), [†††]p <0.05(PTC v TC)

Table 4: Left ventricular regional myocardial function (lateral wall)

	Term Control	PT Control	PT-RDS	ANOVA p-value
LV Vsbl (cm/s)				
Birth	3.0(0.8)	2.1(0.7)	1.7(0.8)	<0.001§§,§§§
At term	"	3.4(0.8)	3.1(1.0)	0.121
1 month	4.3(0.9)	4.3(1.2)	3.9(1.1)	0.481
1 year	4.8(1.0)	4.7(1.0)	4.7(0.7)	0.861
ANOVA (p-value)	<0.001	<0.001	<0.001	
LV Vebl (cm/s)				
Birth	4.5(1.1)	3.5(1.1)	2.5(1.2)	<0.001‡,§§,§§§
At term	"	6.8(1.5)	5.9(1.9)	<0.001§§,§§§
1 month	9.1(2.4)	8.3(2.6)	8.2(2.5)	0.292
1 year	11.7(2.1)	11.0(1.9)	10.8(1.2)	0.190
ANOVA (p-value)	<0.001	<0.001	<0.001	
LV Vabl (cm/s)				
Birth	3.7(1.4)	3.1(1.1)	2.8(1.2)	0.003‡‡
At term	"	4.9(1.0)	4.2(0.9)	0.015†††
1 month	5.2(1.1)	4.8(1.2)	4.0(1.9)	0.178
1 year	3.7(1.6)	3.6(1.0)	3.4(0.8)	0.850
ANOVA (p-value)	<0.001	<0.001	<0.001	
LV lateral wall mid-segment longitudinal peak systolic strain, Ssl (%)				
Birth	-22.8(3.9)	-21.2(3.8)	-18.9(4.9)	<0.001§§
At term	"	-25.5(5.1)	-22.8(4.7)	0.041†††
1 month	-27.7(5.3)	-27.2(3.1)	-27.5(4.7)	0.928
1 year	-31.7(4.0)	-31.0(3.6)	-29.1(3.2)	0.079
ANOVA (p-value)	<0.001	<0.001	<0.001	
LV SRsl (/s)				
Birth	-2.2(0.8)	-1.9(0.5)	-2.0(0.8)	0.116
At term	"	-2.4(0.7)	-2.3(0.9)	0.758
1 month	-2.5(1.1)	-2.9(0.6)	-2.4(1.0)	0.370
1 year	-3.4(1.2)	-3.1(1.0)	-3.3(1.1)	0.627
ANOVA (p-value)	<0.001	<0.001	<0.001	
LV SRel (/s)				
Birth	2.7(0.9)	3.1(0.9)	2.6(0.9)	0.172
At term	"	4.5(1.4)	3.8(1.3)	<0.001§§,§§§
1 month	5.0(1.3)	4.6(1.2)	5.4(1.2)	0.178
1 year	6.0(1.5)	5.6(1.1)	5.1(0.7)	0.068
ANOVA (p-value)	<0.001	<0.001	<0.001	
LV SRal (/s)				
Birth	2.4(1.0)	2.5(0.8)	2.8(0.9)	0.188
At term	"	3.0(0.8)	2.9(1.1)	0.123
1 month	3.5(1.2)	3.1(1.4)	2.9(1.3)	0.394
1 year	2.7(1.1)	2.3(0.7)	2.1(0.7)	0.135
ANOVA (p-value)	<0.01	0.121	0.104	

LV Vsbl, left ventricular myocardial systolic velocity at basal lateral wall; LV Vebl, left ventricular myocardial early diastolic velocity at basal lateral wall; LV Vabl, left ventricular myocardial late diastolic velocity at basal lateral wall; LV Ssl, left ventricular longitudinal peak systolic strain; LV SRs, left ventricular systolic strain rate; LV SRe, left ventricular early diastolic strain rate; LV SRa, left ventricular late diastolic strain rate.
Results are presented as mean(SD)
§p <0.001(PT-RDS v PTC), §§p <0.001(PT-RDS v TC), §§§p <0.001(PTC v TC),
‡p <0.01(PT-RDS v PTC), ‡‡p <0.01(PT-RDS v TC), ‡‡‡p <0.01(PTC v TC),
†p <0.05(PT-RDS v PTC), ††p <0.05(PT-RDS v TC), †††p <0.05(PTC v TC)

Table 5: Right ventricular global and regional (free wall) myocardial function

	Term Control	PT Control	PT-RDS	ANOVA p-value
RV Ds' (mm)				
Birth	7.6(1.3)	5.9(1.1)	4.4(1.3)	<0.001§,§§,§§§
At term	"	8.4(1.7)	8.4(1.2)	0.030
1 month	9.6(1.4)	10.4(1.7)	10.2(1.3)	0.119
1 year	14.4(1.8)	14.6(2.0)	13.4(2.0)	0.113
ANOVA (p-value)	<0.001	<0.001	<0.001	
RV long axis shortening (%)				
Birth	28.7(4.5)	29.2(4.4)	25.1(6.6)	0.003‡,‡‡
At term	"	35.6(4.3)	35.7(6.8)	<0.001§§,§§§
1 month	31.9(4.3)	34.1(3.6)	34.6(3.8)	0.037
1 year	37.0(4.9)	37.6(3.6)	34.8(4.6)	0.169
ANOVA (p-value)	<0.001	<0.001	<0.001	
RV Vsbl (cm/s)				
Birth	4.3(0.9)	3.7(0.8)	2.7(0.8)	<0.001§,§§,‡‡‡
At term	"	4.9(1.5)	4.7(1.1)	0.059
1 month	5.4(1.3)	6.0(1.1)	5.8(1.1)	0.283
1 year	7.7(1.9)	7.9(2.0)	7.2(1.9)	0.525
ANOVA (p-value)	<0.001	<0.001	<0.001	
RV Vebl (cm/s)				
Birth	6.1(1.8)	4.4(1.8)	4.3(2.3)	<0.001§§,§§§
At term	"	8.9(3.8)	7.4(3.0)	<0.001§§§
1 month	11.2(4.2)	9.7(3.1)	12.1(4.9)	0.257
1 year	12.9(4.0)	11.2(3.2)	12.6(4.4)	0.331
ANOVA (p-value)	<0.001	<0.001	<0.001	
RV Vabl (cm/s)				
Birth	5.7(1.2)	5.3(1.2)	4.5(1.4	0.002‡‡
At term	"	7.0(2.1)	6.1(1.8)	0.030
1 month	5.3(1.7)	6.5(2.0)	5.5(1.0)	0.238
1 year	6.4(2.5)	7.0(2.4)	6.3(1.4)	0.627
ANOVA (p-value)	<0.001	<0.05	<0.001	
RV free wall mid-segment longitudinal peak systolic strain, Ss (%)				
Birth	-27.6(5.8)	-25.0(5.5)	-23.2(6.7)	0.004‡‡
At term	"	-34.2(5.1)	-34.9(5.6)	<0.001§§,§§§
1 month	-34.2(4.4)	-34.2(3.7)	-34.4(5.3)	0.989
1 year	-40.9(3.9)	-40.3(3.2)	-39.1(4.5)	0.315
ANOVA (p-value)	<0.001	<0.001	<0.001	
RV SRs (/s)				
Birth	-2.4(0.7)	-2.3(0.7)	-2.2(0.8)	0.490
At term	"	-3.4(0.8)	-3.5(0.6)	<0.001§§,§§§
1 month	-4.1(0.9)	-3.9(1.0)	-3.5(0.9)	0.095
1 year	-4.4(1.0)	-4.5(1.0)	-3.7(0.9)	0.032†
ANOVA (p-value)	<0.001	<0.001	<0.001	
RV SRe (/s)				
Birth	2.7(0.9)	2.4(0.8)	2.8(1.2)	0.182
At term	"	5.0(1.6)	3.9(1.7)	<0.001†,‡‡,§§§
1 month	5.8(1.9)	5.0(1.6)	5.5(1.9)	0.359
1 year	6.2(1.2)	6.1(1.5)	5.4(1.1)	0.113
ANOVA (p-value)	<0.001	<0.001	<0.001	
RV SRa (/s)				
Birth	2.9(0.9)	3.1(0.8)	3.0(1.3)	0.556

At term	"	5.4(1.1)	4.2(0.9)	$<0.001^{‡,§§,§§§}$
1 month	4.6(1.7)	3.5(1.0)	3.6(1.6)	0.062
1 year	3.9(1.3)	3.4(1.4)	2.9(0.9)	0.077
ANOVA (p-value)	<0.001	<0.001	<0.05	

RV Ds', right ventricular lateral annulus displacement; RV Vsbl, right ventricular myocardial systolic velocity at basal lateral wall; RV Vebl, right ventricular myocardial early diastolic velocity at basal lateral wall; RV Vabl, right ventricular myocardial late diastolic velocity at basal lateral wall; RV Ssl, right ventricular longitudinal peak systolic strain; RV SRs, right ventricular systolic strain rate; RV SRe, right ventricular early diastolic strain rate; RV SRa, right ventricular late diastolic strain rate.

Results are presented as mean(SD).

§p <0.001(PT-RDS v PTC), §§p <0.001(PT-RDS v TC), §§§p <0.001(PTC v TC),

‡p <0.01(PT-RDS v PTC), ‡‡p <0.01(PT-RDS v TC), ‡‡‡p <0.01(PTC v TC),

†p <0.05(PT-RDS v PTC), ††p <0.05(PT-RDS v TC), †††p <0.05(PTC v TC)

Table 6: Surrogate measures of pulmonary arterial pressure

	Term Control	PT Control	PT-RDS	ANOVA p-value
PAAT (ms)				
Birth	70.3(11.9)	64.2(15.1)	52.6(11.3)	<0.001‡,§§
At term	"	57.3(10.2)	49.5(11.2)	<0.001§§,§§§
1 month	61.1(8.9)	54.8(6.5)	54.2(7.6)	0.005††,†††
1 year	79.5(10.9)	83.1(10.4)	84.7(15.8)	0.316
ANOVA (p-value)	<0.001	<0.001	<0.001	
RVET (ms)				
Birth	224.6(20.7)	208.2(19.7)	198.1(26.3)	<0.001§§,‡‡‡
At term	"	197.4(15.9)	202.0(15.8)	<0.001§§,§§§
1 month	199.2(16.0)	193.8(14.9)	197.4(13.5)	0.479
1 year	236.3(20.2)	234.6(19.0)	238.3(24.5)	0.874
ANOVA (p-value)	<0.001	<0.001	<0.001	
PAAT:RVET ratio				
Birth	0.31(0.04)	0.31(0.06)	0.27(0.04)	<0.001‡,§§
At term	"	0.29(0.06)	0.25(0.06)	<0.001†,§§
1 month	0.31(0.05)	0.28(0.03)	0.27(0.03)	0.015††
1 year	0.34(0.05)	0.35(0.03)	0.35(0.05)	0.287
ANOVA (p-value)	<0.001	<0.001	<0.001	

PAAT, pulmonary artery acceleration time; RVET, right ventricular ejection time
Results are presented as mean(SD).
§p <0.001(PT-RDS v PTC), §§p <0.001(PT-RDS v TC), §§§p <0.001(PTC v TC),
‡p <0.01(PT-RDS v PTC), ‡‡p <0.01(PT-RDS v TC), ‡‡‡p <0.01(PTC v TC),
†p <0.05(PT-RDS v PTC), ††p <0.05(PT-RDS v TC), †††p <0.05(PTC v TC)

Figure legends

Figure 1: Measurement of LV chamber length, LV annular displacement and derivation of LV long axis shortening.

On this static image, the endocardial border at the apex is not well defined but during analysis its position was determined by reviewing the cine loop.

Figure 2: LV strain measurement in the middle segment of the LV free wall.