Maladaptive structural remodelling of the heart following preterm birth
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Preterm birth (delivery prior to 37 completed weeks of gestation) is the leading cause of perinatal deaths worldwide. Preterm infants are born when their hearts are structurally and functionally immature; as a result, maladaptive cardiac remodelling occurs in the neonatal period which may lead to cardiac dysfunction later in life. Hypotension is a common comorbidity of preterm birth in the neonatal period; however, hypertension often manifests in adulthood. Adults born preterm exhibit altered heart growth, which may in part be linked to their elevation in blood pressure. Clinical interventions used to facilitate lung function in preterm infants, including antenatal glucocorticoids and mechanical ventilation, may also impact cardiac growth early in life, with lifelong implications for cardiac structure and function.

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Current Opinion in Physiology 2018, 01:89–94
This review comes from a themed issue on Cardiac Physiology
Edited by Merry Lindsey and David Eisner
For a complete overview see the Issue and the Editorial
Available online 10th October 2017
https://doi.org/10.1016/j.cophys.2017.08.004
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Introduction
Preterm birth (delivery prior to 37 completed weeks of gestation) is the leading cause of perinatal deaths worldwide [1]. The survival rates of preterm neonates in developed countries have markedly improved over recent decades (particularly for those born extremely preterm), due to advances in neonatal care aimed at facilitating lung maturation and function. Along with the reduction in mortality rates, the adverse clinical consequences of preterm birth that emerge later in life are becoming increasingly apparent.

Hypotension is a common challenge faced by preterm neonates, and is clinically managed by volume replacement and/or vasopressor medications [2]. Later in life, however, it is of increasing concern that both children and adults born preterm are highly susceptible to developing hypertension [3], with a strong inverse correlation between gestational age at birth and blood pressure [4,5]. The later development of high blood pressure can be partly explained by the ‘developmental origins of health and disease’ hypothesis, which proposes that perinatal insults, such as preterm birth, result in compensatory mechanisms (including structural remodelling, physiological alterations and epigenetic changes), that are necessary for survival in the short term, but can program a later vulnerability to disease. In the case of the cardiovascular system, while the early postnatal adaptations are crucial for the neonate to increase systemic pressure for adequate organ perfusion, this short-term compensation can lead to impaired function later in life [6], thus increasing the risk of cardiovascular pathologies, such as heart failure [7] and hypertension [4,5,8]. This is true for all severities of preterm birth; even small reductions in gestational length are sufficient to induce long-lasting anatomical alterations [9]. Studying the underlying physiological mechanisms of preterm birth that result in cardiovascular sequelae is difficult, since the aetiologies of both preterm birth and cardiovascular disease are often multifactorial. This review will describe how maladaptive remodelling of the heart in preterm patients can influence cardiovascular physiology throughout life. The impact on the immature heart of clinical interventions (antenatal steroids and postnatal ventilatory support) used to improve postnatal respiratory function, and thus the survival of preterm infants, will also be discussed.

Structural remodelling of the heart following preterm birth
Before term birth, the total peripheral resistance of the foetal systemic circulation is low and hence systemic arterial pressure is relatively low [10]. Within minutes of umbilical cord occlusion at term birth, the peripheral resistance of the systemic circulation increases, primarily due to the loss of the placental vascular bed [11]. Thus, systemic arterial pressure is normally increased after term birth. In preterm infants, particularly those born very or extremely preterm, the immature heart cannot maintain cardiac output in the face of the sudden increase in systemic vascular resistance at birth, and these infants are consequently vulnerable to pathophysiological hypotension [2]. Compensatory structural remodelling of the heart and blood vessels may occur as a short-term adaptation to neonatal hypotension in infants born very or extremely preterm, but in turn could lead to the progressive development of high blood pressure later in life [4,5].
Indeed, preterm birth has been shown to be associated with the induction of hypertension in adulthood, with blood pressure inversely related to age at birth [4,5]. Individuals born preterm also demonstrate an elevated blood pressure stress response [8*]. Narrowing of conduit arteries in children born preterm is well-described [12,13,14*], and studies have also shown altered postnatal cardiac growth [15**,16,17,18]. A recent study found that preterm neonates had reduced heart mass to body weight ratio at birth compared to infants born at term [15**]. However, ventricular mass increased disproportionately in relation to body size within the first 3 months of life in the preterm infants, which was associated with cardiac dysfunction [15**]. Other studies have found that the interventricular septum remains flat for 9.5 days after preterm birth, resulting in a distorted ‘D’ shape in the transverse cross-section of the left ventricle (LV) (Figure 1a) [16–18]. While this phenotype is typical in the foetal heart where the right ventricle (RV) is dominant, the reduction in pulmonary vascular resistance (and thus a decrease in RV afterload) normally occurring at birth causes the intraventricular septum to bow into the RV, creating a circular LV by approximately 5 days after term birth (Figure 1b) [19]. However, the persistence of high pulmonary vascular resistance in preterm neonates is likely the reason why their septum remains flat after birth. This anatomical variation is associated with a reduction in the fractional shortening of the LV [18], and thus reduced LV diastolic filling [16]. Some studies found that within 12–14 days after preterm birth, the LV establishes a normal degree of circularity, and therefore an improvement in LV function [16,17]. One study, however, found that the shape of the ventricles was still abnormal in preterm infants after 51 days [18].

Recently, it has become apparent that altered cardiac growth following preterm birth continues into childhood and later life. One study found that the interventricular septum was thicker and left ventricular end-diastolic diameter was reduced in preterm-born children at 5 years of age, compared to age-adjusted population reference values [20]. This altered cardiac morphology, combined with increases in systolic blood pressure, are indicative of increased cardiac afterload in preterm individuals [20]. Increased cardiac afterload and elevated blood pressure may reflect reduced distensibility in the large arteries [21], and importantly in this regard, abdominal aortic wall distensibility and whole-body arterial compliance has been shown to be reduced in very low birth weight preterm infants examined at 7 weeks of age [22].

Cardiac and vascular remodelling can also occur following moderate to late preterm birth (between 32 and 36 weeks' gestation) even though hypotension is not an issue in babies born at this gestational age. Indeed, it may be the premature exposure of the immature heart and vasculature to the increase in blood pressure that normally occurs at birth that leads to the cardiac and vascular remodelling following moderate or late preterm birth [23]. At the cellular level, we have shown through experimental studies that preterm birth leads to an increase in collagen deposition and alterations in cardiomyocyte maturation and size within the myocardium, early in life [9,23]. Bensley et al. [9] found that cardiomyocyte volume was markedly increased in both the LV and RV of 11 week old lambs born preterm, as compared to term-born lambs, despite no differences in absolute or relative heart weight, wall thickness, or luminal areas of the RV or LV. The accelerated cardiomyocyte hypertrophy was accompanied by findings of altered cardiomyocyte nuclearity and increased cardiomyocyte ploidy in the preterm myocardium [9]; polyploidy is common in hearts subjected to pathological hypertrophy, and is linked to impaired cardiac function [24]. Furthermore, preterm-born lambs were shown to have narrowing of the ascending aorta and altered cellular composition of the aortic and pulmonary artery walls, with some animals exhibiting significant aortic intimal injury [25].

Anatomical alterations in the hearts of people born preterm have also been reported in adulthood. Lewandowski et al. [6,26] used magnetic resonance imaging (MRI) to analyse cardiac structure in 25-year-old adults. Cavity size was significantly reduced in the LV and, to a greater extent, the RV of adults born preterm compared to those born at term, which was associated with decreased stroke volume and ejection fraction [6,26]. Preterm-born adults also had significantly greater ventricular mass, with ventricular mass inversely associated with gestational age at birth (−0.98 g/m² LV mass and −0.67 g/m² RV mass per additional week of gestation) [6,26]. Importantly, LV mass in the young adults born preterm was disproportionately increased relative to blood pressure [6]. It may be speculated that the LV hypertrophy observed in preterm-born adults occurs due to the increased cardiac afterload.
and increased peripheral vascular resistance reported in preterm infants and children [20,22].

Notably, in contrast to the MRI findings of Lewandowski et al. [6] a recent echocardiography study conducted in 18 year-old adults born preterm, by Kowalski et al. [27**, showed that although preterm-born adults had a reduced left ventricular volume compared to those born at term, there was no significant difference in LV wall thickness. Furthermore, they found that LV mass was significantly reduced in adults born preterm compared to those born at term (preterm = 75 ± 14 g/m², term = 81 ± 16 g/m², P = 0.02).

There are a number of differences in these studies that may account for the disparity in findings. Firstly, different imaging techniques were used; Lewandowski et al. [6,26] used MRI, which may be more accurate in estimating tissue mass than echocardiography [28] used by Kowalski et al. [27**]. Secondly, Lewandowski et al. [6,26] included a mixed cohort of adults born moderately (31%), very (55%), and extremely (14%) preterm, with 31% of participants also intrauterine growth restricted (IUGR), whereas Kowalski et al. [27**] only included adults born extremely preterm (<28 weeks gestation) or weighing <1000 g at birth, the vast majority of whom were non-IUGR. Certainly, it is well described in animal models that IUGR, independent of preterm birth, leads to altered cardiac growth [29] and to a reduced complement of cardiomyocytes at birth [30,31]. Clinical studies have also shown that IUGR leads to alterations in vascular and cardiac morphology, and cardiac dysfunction in neonates [29]. Given the limited proliferative capacity of cardiomyocytes after birth, it is likely that IUGR as a co-morbidity of preterm birth would further impact postnatal cardiac growth, particularly in the setting of accelerated catch-up growth which often occurs in IUGR infants [32]. Therefore, the combined effect of preterm birth and IUGR could have a greater influence on ventricular mass, and ultimately, cardiac function, than preterm birth alone.

It is well-known that males born preterm are more susceptible to developing respiratory distress syndrome (RDS) than their female counterparts [33], likely due to delayed maturation of the pulmonary surfactant system [34]. To our knowledge, the limited number of experimental studies that have explored sex as a factor in cardiovascular physiology at the time of preterm birth have not reported any significant differences [35–37]; there is a lack of evidence regarding whether there are sex differences in the prevalence of long-term cardiovascular morbidities. In one study, female adults born preterm were shown to have a significantly greater RV mass to end-diastolic volume ratio compared to males (female: 0.33 ± 0.059 g/ml, male: 0.30 ± 0.060 g/ml) [26], however this was not associated with any differences in RV function. This area of research warrants further investigation, particularly given the known sex differences in the prevalence of cardiovascular disease, with males at greater risk than females prior to middle-age [38,39].

**Interventions directed at improving survival following preterm birth have the potential to adversely impact cardiac development**

Clinical approaches to preterm birth are primarily targeted towards improving respiratory function postnatally. Specifically, the use of antenatal glucocorticoids, postnatal surfactant, and assisted ventilation have become standard practice to maintain adequate respiratory function in preterm neonates and this has markedly decreased neonatal mortality and morbidity [40–42]. It has recently become apparent, however, that antenatal steroids and postnatal ventilation have the potential to adversely impact the immature heart, either independently of preterm birth, or additive to the respiratory outcomes of preterm birth.

**Antenatal glucocorticoids**

Glucocorticoids are a class of corticosteroids that play vital roles in the development and maturation of foetal organs. Cortisol, the major human glucocorticoid, is notable for stimulating pulmonary surfactant production in the foetal lungs. The developing foetus is unable to produce cortisol, and thus receives its supply from the maternal circulation [43,44]. Cortisol levels in the amniotic fluid peak in late gestation, and this is highly synchronised with the timing of lung maturation during the third trimester [45,46]. However, if birth occurs prior to the surge of cortisol in late gestation, lung development of the preterm neonate is severely impaired.

It is well-known that the prenatal administration of synthetic glucocorticoids to mothers at risk of delivering preterm accelerates foetal lung development, markedly improving short term survival [47]. Much like foetal lungs, structural and functional maturation of the foetal heart is highly dependent on glucocorticoid signalling [48]. However, glucocorticoid sensitivity varies between organs [49], and it is unknown whether the dosage of antenatal glucocorticoids necessary for foetal lung maturation is suitable for the developing heart.

The effects of antenatal glucocorticoids on cardiac development in preterm infants is not yet fully elucidated. Certainly, there are a number of studies that report a link between antenatal corticosteroids and the onset of hypertension and aortic stiffness later in life [50,51], and this can, in turn, lead to cardiac remodelling in the adult heart. Although there are some conflicting reports in sheep studies relating to the direct effects of steroid exposure on the growth of cardiomyocytes in early life, the majority of studies support the view that glucocorticoids accelerate cardiomyocyte maturation [37,52]; evidence of decreased cardiomyocyte proliferation and increased cardiomyocyte
hypertrophy and/or binucleation after glucocorticoid exposure (all of which are markers of mature cardiomyocytes) support this concept [37,53–56]. Premature cell cycle arrest following accelerated maturation may be particularly detrimental for the developing heart, as it may lead to a reduced cardiomyocyte endowment and thus, reduced cardiac functional reserve, rendering the heart susceptible to cardiovascular injury and dysfunction later in life.

Considering the widespread use of glucocorticoid therapy for mothers at risk of delivering preterm, it is necessary to develop a better understanding of the long-term effects on the developing cardiovascular system. Indeed, given that maternal antenatal glucocorticoids have only been used clinically in the past 40 years, the full extent of the long-term cardiovascular consequences may not have yet emerged.

**Neonatal ventilation**

Aeration of the neonatal lungs is one of the first obstacles of preterm life. Intermittent mandatory ventilation (IMV) is an invasive form of ventilation requiring endotracheal intubation, and it provides cycles of positive pressure during inspiration and expiration to prevent airway collapse [57]. IMV use has extended the limit of viability of preterm infants and significantly improved survival rates, particularly in neonates with RDS [58]. This form of ventilation may, however, cause volutrauma and atelectrauma due to over-inflation of the developing lungs, which can lead to chronic lung disease.

Although cardiac and pulmonary physiologies are closely interconnected, interventions aimed at improving one, may negatively impact the other. IMV facilitates gas exchange by forcing air into the lungs during inspiration, thereby increasing intrathoracic pressure. Other intrathoracic structures are consequently affected, notably the heart and great vessels. Firstly, increased intrathoracic pressure causes right atrial pressure to increase, resulting in decreased venous return and cardiac output, with subsequently increased pulmonary vascular resistance and right ventricular afterload [59]. These outcomes contribute to increased workload in the right ventricle, causing maladaptive hypertrophy of the RV [60]. Indeed, Lewandowski et al. [26] found that increased duration of postnatal IMV following preterm birth was directly correlated with increased RV mass in adulthood. Additionally, increased intrathoracic pressure can also result in decreased LV afterload, venous return and cardiac output [61–63]. This LV dysfunction is associated with hypotension, and a leftward displacement of the interventricular septum occurs in adults requiring respiratory mechanical ventilation [63]; however, as yet no studies have examined whether postnatal ventilation affects the structure of the developing LV in preterm infants.

Ventilator-induced lung injury and its associated sequelae necessitates a reduction in the time that preterm infants spend on IMV. While gentler alternatives, such as nasal continuous positive airway pressure (nCPAP), have the potential to reduce the risk of lung disease [64], they are not effective in extremely preterm infants who cannot yet produce spontaneous breaths [65]. Furthermore, 46% of infants on nCPAP ultimately require subsequent intubation and IMV [65]. Although clinical approaches to neonatal ventilation have improved, the effects of assisted ventilation on the developing preterm heart warrant further investigation. Indeed, studies in sheep have shown that ventilation after birth reduces glomerular capillary growth in both preterm and term born lambs [66], thus suggesting that there are haemodynamic changes that may then influence cardiovascular growth.

**Conclusion**

With the first generation of medically treated preterm patients now approaching mid-adulthood, we are beginning to see the long-term cardiovascular consequences of being born early. There is substantial evidence to suggest that the immature preterm heart undergoes structural remodelling as a maladaptive response to the functional demands associated with postnatal life, and that these abnormal structural changes in cardiac growth persist into adulthood. It is important to also take into account that current clinical interventions used to treat preterm neonates may further exacerbate cardiac remodelling following preterm birth. Further research is required to fully understand the potential long-term pathophysiological consequences of these treatments.

**Funding**

Bianca Le was the recipient of an MBio Postgraduate Discovery Scholarship from the Biomedicine Discovery Institute, Monash University, and Megan Sutherland the recipient of a National Health and Medical Research Council (NHMRC) of Australia CJ Martin Early Career Fellowship.

**Conflict of interest statement**

None declared.

**References and recommended reading**

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


Preterm birth and cardiac remodelling


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8. Steen E, Bonamy AK, Norman M, Hellstrom-Westas L: Preterm birth may be a larger risk factor for increased blood pressure than intrauterine growth restriction. Acta Paediatr 2015, 104:1098-1103. In this study of adolescents born very low birth weight it was found that during a moderately stressful situation (an MFI scan), those born preterm and appropriately grown for gestational age exhibited a heightened and sustained elevated blood pressure response when compared to those that were intrauterine growth restricted. The findings suggest that extremely preterm birth may be a greater risk factor for the later onset of hypertension, compared to intrauterine growth restriction.


15. Aye CYL, Lewandowski AJ, Lamata P, Upton R, Davis E, Ohuma EO, Kenworthy Y, Boardman H, Wopperer S, Packham A, Advani S, McCormick K, Papageorghiou AT, Lessen P: Disproportionate cardiac hypertrophy during early postnatal development in infants born preterm. Pediatr Res 2017, 82:36-41. This cardiac ultrasound study conducted in 392 infants (from in utero to 3 months of age) showed that there is a disproportionate postnatal increase in right and left ventricular mass, relative to body weight, in infants born preterm. These differences were not present at birth, indicating abnormal growth of the preterm heart in the neonatal period.


28. Using echocardiography, Kowalski et al. found that adolescents born extremely preterm had decreased left ventricular mass and cavity size, but preserved left ventricular function. These findings differ from that of Lewandowski et al. [8], and may be attributed to the different demographics of the preterm individuals studied. In the Lewandowski study [8], a much greater proportion of the subjects were intrauterine growth restricted, and they were from a wider range of gestational ages at birth.


