Review

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Review

Hemodynamic Melody of Postnatal Cardiac and Pulmonary Development in Children with Congenital Heart Diseases

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Simple Summary: Hemodynamics is the eternal theme of the circulatory system. Abnormal hemodynamics and cardiac and pulmonary development intertwine to form the most important features of children with congenital heart diseases (CHDs), thus determining these children's long-term quality of life. However, due to the lack of neonatal rodent models of CHDs, it is unclear how CHD-associated hemodynamics shape postnatal cardiac and pulmonary development. Here, we review the varieties of hemodynamic abnormalities that exist in children with CHDs, the recently developed neonatal rodent models of CHDs, and the inspirations these models have brought us in the areas of cardiomyocyte proliferation and maturation, and in alveolar development. Furthermore, current limitations, future directions, and clinical decision-making based on these inspirations are highlighted. Understanding how CHD-associated hemodynamic scenarios shape postnatal heart and lung development may provide a novel path to improving the long-term quality of life of children with CHDs, transplantation of stem cell–derived cardiomyocytes, and cardiac regeneration.

Abstract: Hemodynamics is the eternal theme of the circulatory system. Abnormal hemodynamics and cardiac and pulmonary development intertwine to form the most important features of children with congenital heart diseases (CHDs), thus determining these children's long-term quality of life. However, due to the lack of neonatal rodent models of CHDs, it is unclear how CHD-associated hemodynamics shape postnatal cardiac and pulmonary development. Here, we review the varieties of hemodynamic abnormalities that exist in children with CHDs, the recently developed neonatal rodent models of CHDs, and the inspirations these models have brought us in the areas of cardiomyocyte proliferation and maturation, and in alveolar development. Furthermore, current limitations, future directions, and clinical decision-making based on these inspirations are highlighted. Understanding how CHD-associated hemodynamic scenarios shape postnatal heart and lung development may provide a novel path to improving the long-term quality of life of children with CHDs, transplantation of stem cell–derived cardiomyocytes, and cardiac regeneration.

Keywords: volume overload; pressure overload; cardiomyocyte; maturation; proliferation; pulmonary alveolar dysplasia; pulmonary blood flow

1. Introduction

Since Harvey's discovery of the circulatory system in 1628, it has been recognized that the primary function of the circulatory system is to provide organs, including the heart and lungs, with well-oxygenated blood and nutrients, as well as to transport all types of harmful metabolites [1,2]. The hemodynamics resulting from blood flowing in the circulatory system inevitably becomes the eternal theme of the circulatory system [1,2]. Insufficient embryonic volume load is one of the main causes of left ventricular dysplasia, while adult volume overload (VO) or pressure overload (PO) leads to cardiac failure [3–7]. However, pediatric hearts and lungs are in a stage of active

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development. For example, 90% of alveoli form between the ages of 0 and 7 years, and there is an extensive cardiomyocyte maturation transition [8,9]. Hemodynamic modifications of embryonic or adult hearts and lungs are well established [3–7], but leave a vacuum to be filled of our understanding of the hemodynamic shaping of pediatric hearts and lungs.

Congenital heart diseases (CHDs) represent the most prevalent birth defect in the world [10,11]. With the progress in pediatric cardiac surgery, cardiology, and cardiac intensive care, most simple CHDs can be corrected, and the overall mortality shows a significant downward trend. However, the mortality of complex CHDs, such as hypoplastic left heart syndrome, Ebstein anomaly (EA), and tetralogy of Fallot (TOF), is still very high. Most of these cannot be physiologically corrected, leaving residual hemodynamic abnormalities, such as cardiac volume overload (VO), pressure overload (PO), pulmonary congestion, and reduced pulmonary blood flow (RPF), and therefore hemodynamic abnormalities dominate postnatal cardiac and pulmonary development in children with CHDs [12–17]. As a result, the long-term life quality of children with complex CHDs is poor, with significantly reduced exercise capacity and impaired cardiac performance, and some children ultimately require heart or lung transplantation [18,19].

In addition, cardiovascular therapies that are very effective in adults have limited effectiveness or even cause harm when treating infants and young children [20,21]. A possible reason underlying this phenomenon is that the extremely small size of a neonatal mouse heart challenges the creation of neonatal surgical mouse models of cardiovascular diseases. Consequently, clinicians or scientists generally use adult mouse models to explore mechanisms and pathophysiology and to obtain targets for pediatric cardiovascular diseases.

Here we reviewed the abnormal hemodynamics in children with CHDs and the recently developed neonatal surgeries for producing CHD-hemodynamic-associated animal models, which include neonatal aortic and inferior vena cava fistula (nACF) surgery, neonatal pulmonary artery banding (nPAB) surgery, neonatal pulmonary vein banding (nPVB) surgery, and neonatal transverse aortic constriction (nTAC) surgery [22–33]. nACF produces atrial and ventricular VO and pulmonary congestion; nPAB produces right ventricular (RV) PO and RPF; nPVB produces pulmonary vein stenosis (PVS), one of the most challenging issues of pediatric CHDs [34]; and nTAC produces left ventricular (LV) PO. These neonatal surgeries greatly inspire our understanding of the hemodynamic melody of postnatal cardiac and pulmonary development, such as cardiomyocyte proliferation and maturation, and pulmonary dysplasia.

2. Abnormal Hemodynamics in Children with CHD

2.1. Abnormal Hemodynamics in Ventricles

CHD usually leads to ventricular VO and PO, specifically RV VO, LV VO, RV PO, and LV PO. Table 1 summarizes each type of abnormal hemodynamic and its corresponding CHDs.

Table 1. Abnormal hemodynamic classification and their corresponding congenital heart diseases(CHDs).

Abnormal hemodynamic classification	RV VO	LV VO	RV PO	LV PO
CHD	ASD、PDA、PAPVD 、VSD 、TR 、	ASD+TS/RVOT 、 MR 、	PVS 、 VSD 、PDA 、 PAH 、MS、AS、TOF	BAV 、 IAA 、CAA 、 MS 、AS、HCM

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	EA 、 PVI 、 TOF 、 AVSD 、 PAH	MVI 、 AR 、 BAV	、 IAA 、 CAA 、 PAS、 PVS	

There are three types of CHDs that can result in RV VO. The first type is CHD with a left-to-right shunt, which includes atrial septal defect (ASD), patent ductus arteriosus (PDA), partial anomalous pulmonary vein drainage (PAPVD), atrioventricular septal defect (AVSD), and ventricular septal defect (VSD) [35–39]. The second type is right heart valve regurgitation-associated CHDs, which include tricuspid regurgitation (TR), EA, pulmonary regurgitation, pulmonary valve insufficiency (PVI), and TOF after patch enlargement of the RV outflow tract correction [40–44]. The third includes advanced pulmonary hypertension (PH), increased returning blood (e.g., in thyrotoxicosis), and functional univentricular conditions (e.g., hypoplastic left heart syndrome and Fontan surgery) [45–47].

Right-to-left shunting and left heart valvular regurgitation can lead to LV VO. Right-to-left shunting-associated CHDs include ASD with tricuspid stenosis (TS) or RV outflow obstruction (RVOT)[48]. These defects result in a high pressure in the right atrium compared to the left atrium, leading to a right-to-left shunt. Left heart valvular regurgitation includes congenital mitral regurgitation (CMR), acquired mitral regurgitation (rheumatic or calcific mitral valve), aortic valve calcification, and bicuspid aortic valve (BAV) [49–51]. In addition, increased venous return can lead to LV VO.

PH, left cardiac defects that cause PH at later stages, and RVOT obstructive diseases may cause RV PO. CHDs that cause PH include PVS, large VSD, and PDA [34,36,39,52]. Large VSD and PDA lead to increased pulmonary blood flow, resulting in pulmonary congestion and small vessel remodeling, which in turn causes PH. CHD with a left cardiac defect that causes PH includes mitral or aortic stenosis (MS or AS), and coarctation/interruption of the aortic arch (CAA/IAA) [50,51,53]. CHDs with RVOT obstruction includes TOF, isolated pulmonary artery obstruction or embolism, pulmonary artery stenosis (PAS), and pulmonary valve stenosis (PS) [54–57].

Hypertension and left ventricular outflow tract (LVOT) obstruction leads to LV PO. Hypertension is uncommon in children. CHD with LVOT obstruction includes BAV, CAA/IAA, mitral or aortic stenosis, and hypertrophic cardiomyopathy [50,51,53,58].

It is evident from Table 1 that various hemodynamic abnormalities, including both ventricular VO and PO, usually coexist in the same type of CHD. In addition, these hemodynamic abnormalities are closely associated with the disease progression, and sometimes one type of abnormal hemodynamic abnormality dominates a particular stage of disease progression. The extent of VO and PO often determines the performance of the RV and LV, as well as surgical approaches and the prognosis of children with CHDs. Therefore, gaining a comprehensive understanding of how VO and PO shape postnatal cardiac development may help establish a theoretical foundation for enhancing the quality of life in children with CHD.

2.2. Abnormal Hemodynamics in Lungs

A left-to-right shunt or increased venous return will induce increased pulmonary blood flow (IPF), which leads to pulmonary congestion, ultimately resulting in pulmonary hypertension and congestive heart failure. RVOT obstruction, such as TOF and PS, results in RPF, which leads to pulmonary dysplasia and reduced exercise endurance, and renders patients less susceptible to COVID-19 infection [25,29,59,60]. A deeper understanding of the mechanisms by which IPF and RPF regulate postnatal lung development may help improve lung function and exercise capacity in children with CHD.

PVS is another deadly CHD [28,34]. Stenosis of the pulmonary vein leads to remodeling of small pulmonary vessels, which in turn leads to PH, and ultimately right heart failure occurs. Despite advancements in surgical techniques, interventional procedures, and postoperative monitoring, the prognosis for children with PVS remains unfavorable, with 60% of children with PVS dying within 2

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years after diagnosis [34]. Moreover, due to stenosis, there may be oozing blood upstream of the pulmonary vessels, giving rise to hemoptysis and pulmonary infections, which further deteriorate the prognosis of children with PVS. Understanding how and why PVS occurs is crucial to treat children with PVS.

3. Immature Hearts and Lungs in Children

3.1. Immature Hearts in Children

Unlike adult mature hearts and lungs, children's hearts and lungs are immature and at an active stage of development [8,12].

To meet the physiological demands of pumping blood at adulthood, there are three main characteristic that immature cardiomyocytes need to develop (Figure 1) [8,61–67]: (1) sarcomere maturation, which includes sarcomere component maturation (an Myh7 to Myh6 and TnI1 to TnI3 switch), and arrangement maturation (disordered and irregular arrangement switched to a rod-like and orderly arrangement); (2) metabolism maturation, which is a shift from anaerobic glycolysis to oxidative phosphorylation due to mitochondrial maturation, with an increase in the number of mitochondrial and their ridges, as well as a closer proximity of mitochondria to sarcomeres; and (3) electrophysiological maturation, in which transverse tubules (T-tubules) form, with a gradually increased density and integrity, and are accompanied by a significant improvement in calcium handling and excitation-contraction coupling. Failure of cardiomyocyte maturation results in arrhythmias and heart failure.

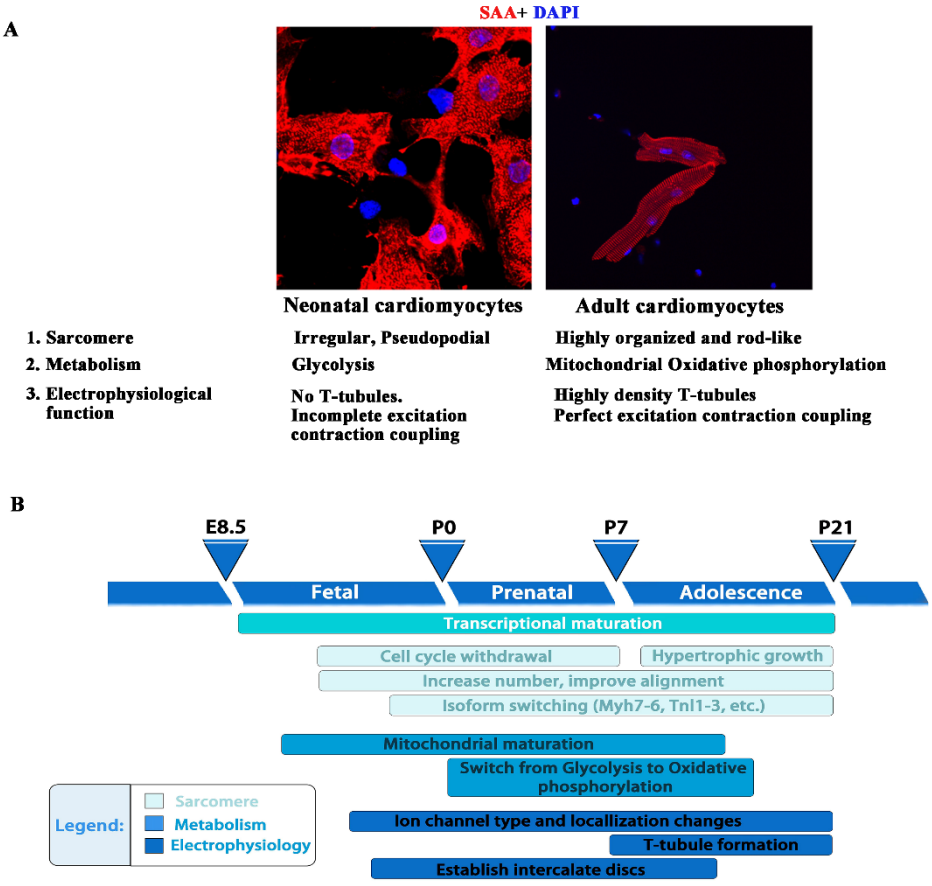

Figure 1. Illustration of three main characteristics that immature cardiomyocytes require for development. (**A**) Neonatal and adult cardiomyocytes have differences in sarcomere, metabolism, and electrophysiological functions. (**B**) Three main characteristics that immature cardiomyocytes need to develop, and the presumed key time points in rodents.

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3.2. Immature Lungs in Children

There are five developmental stages of human lungs (Figure 2) [68–71]: (1) Embryonic stage (pulmonary bud stage): Occurring between the third and sixth weeks of gestation, this stage marks the appearance of precursor cells and epidermal cells known as pulmonary buds. (2) Pseudoglandular stage (bronchial stage): Taking place between the sixth and 16th weeks of gestation, this stage is characterized by bronchial formation. The pulmonary buds proliferate and migrate to the visceral mesenchyme, forming airways and peripheral acinar buds, eventually developing into alveoli. (3) Tubular phase (alveolar tubular phase): This stage occurs from 16–26 weeks of gestation and involves the differentiation of intra-airway epithelial cells, including basal cells, cupped cells, ciliated cells, and other secretory cells. (4) Vesicular phase (terminal vesicular phase): Spanning from 26–36 weeks of gestation, the differentiation of peripheral glandular alveoli characterizes this phase, including cubic type 2 alveolar (AT2) cells and squamous type 1 alveolar (AT1) cells. At this stage, alveoli gradually expand and are covered by AT1 cells, and AT2 cells differentiate to produce alveolar surfactant. (5) Alveolar phase: This phase, which extends from 36 weeks of gestation to adolescence, is the main stage of alveolar formation, with over 90% of alveoli forming at ages 0–7 years. Bronchopulmonary dysplasia, a major complication of prematurity, occurs when the immature lungs fail to develop due to various damaging factors such as hyperoxia, toxicity, and inflammation. Therefore, the lungs of children are immature and in a critical stage of alveolar development, while adult lungs have completed their development. Consequently, many drugs effective in treating adult lung diseases have limited efficacy in addressing lung diseases in infants and children [72,73].

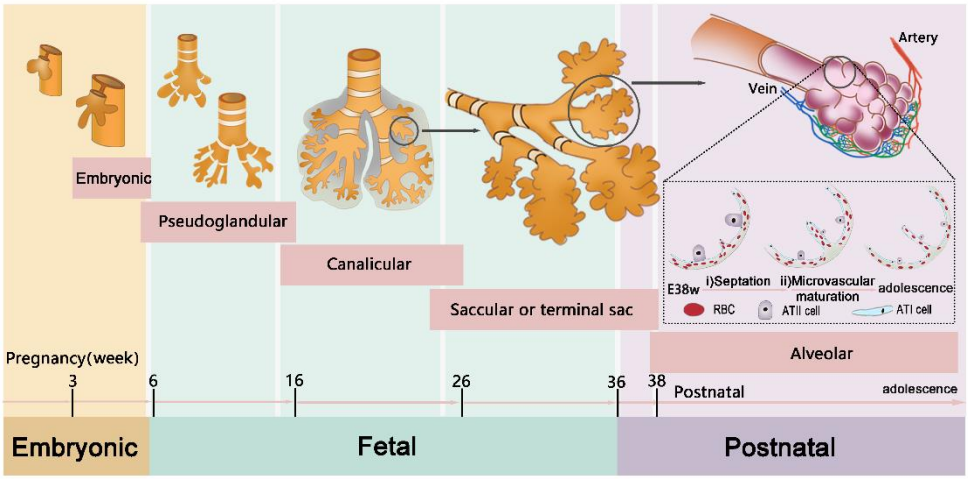

Figure 2. Five developmental stages of human lungs. Note that 90% of alveoli are formed at ages 0 – 7 years.

4. Creation of Neonatal Surgical Rodent Models of CHDs

4.1. Challenges in Constructing Neonatal Surgical Rodent Models of CHDs

The lack of neonatal rodent models for cardiac VO, PO, IPF, and RPF limits our understanding of how hemodynamics regulates postnatal heart and lung development [23,28,30,31]. Consequently, managing CHD primarily relies on surgical intervention, and thus the long-term quality of life for children with complex CHD remains poor [74,75]. The challenges of creating neonatal rodent CHD models are: (1) the size of the neonatal rodent heart is extremely small, with limited operation space; (2) the neonatal anesthesia is ice cooling, limiting the surgical time to no more than 20 min; and (3) cannibalization may account for additional post-surgical mortality in the neonatal surgery. The above three challenges require superb cardiac microsurgical skills.

As the largest pediatric heart center in the world, the heart center of Shanghai Children's Medical Center has about 4,000 open-heart surgeries per year; as a result, surgeons at Shanghai Children's Medical Center are very skillful in cardiac surgery. Thus, in recent years they have successfully

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developed a series of neonatal CHD models (Figure 3), including models of nACF, nPAB, nPVB, and nTAC [23,28,30,31,76].

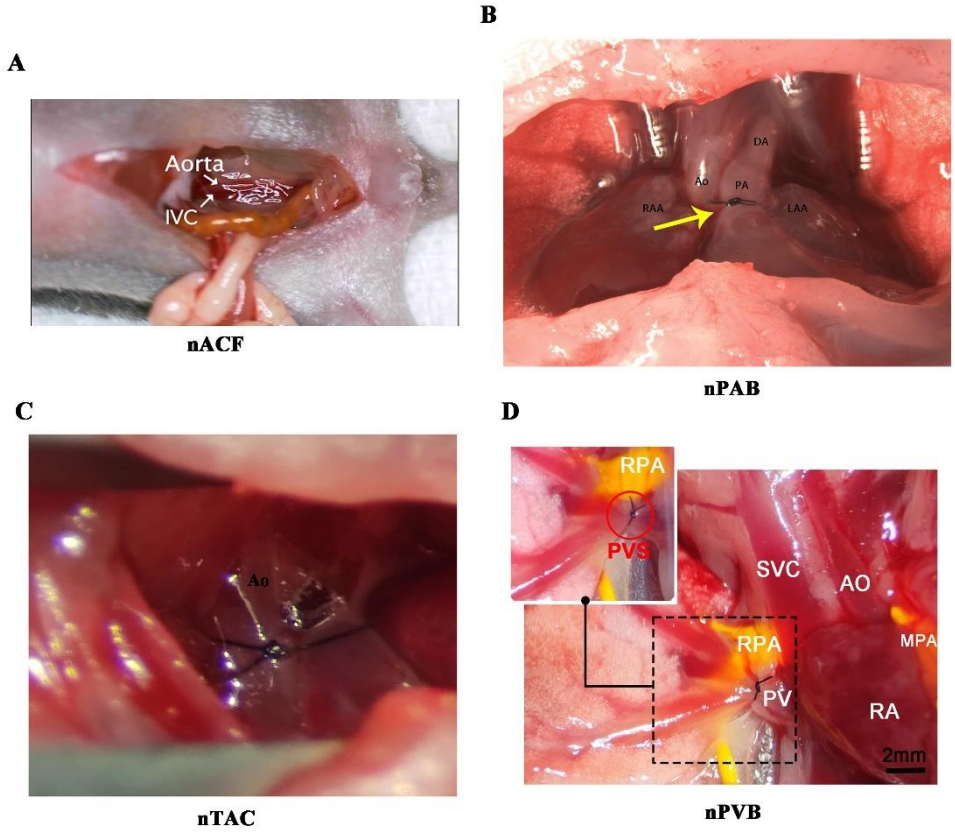

Figure 3. Neonatal surgical rodent models of CHDs. (**A**) nACF produces RA VO, RV VO, LA VO, LV VO, and IPF. (**B**) nPAB produces RV PO and RPF. (**C**) nTAC produces LV PO. (**D**) nPVB produces PVS and IPF. IVC: inferior vena cava; PA: pulmonary artery; DA: ductus arteriosus; Ao: aorta; RPA: right pulmonary artery; PV: pulmonary vein; SVC: superior vena cava; RA: right atrium; MPA: main pulmonary artery. Figure 3A was adopted from the JAHA journal (Sun S, et al. J Am Heart Assoc. 2021 Aug 17;10(16):e020854) under a Creative Commons Attribution-NonCommercial-NoDerivs License; Figure 3B was adopted from the JTCVS journal (Wang S, et al. J Thorac Cardiovasc Surg. 2017 Nov;154(5):1734-1739) with the permission of the publisher.

4.2. Key Points of Constructing Neonatal Surgical Rodent Models of CHDs

4.2.1. nACF Surgery

The nACF surgery [33] (Figure 3A) includes the following four steps: (1) anesthesia and fixation; (2) abdominal aorta (AA) and inferior vena cava (IVC) exposure; (3) fistula creation, and (4) abdominal closure. There are two key points of nACF surgery: (1) During fistula creation, a mixing of arteriovenous blood in IVC should be observed under a microscope to make sure a successful fistula was created. (2) When exposing the AA and IVC, the small intestine and large intestine should be moved with a cotton swab slowly to prevent bleeding.

4.2.2. nPAB Surgery

The nPAB surgery [30] (Figure 3B) includes the following four steps:(1) anesthesia and fixation; (2) pulmonary artery (PA) exposure; (3) PA banding; and (4) closure of the thoracic cavity. There are two key points of nPAB surgery: (1) The PA should be exposed with a small incision as much as possible to reduce the total time for the thoracotomy surgery, which is critical for the neonatal pups' recovery from anesthesia. (2) The PA should be separated from its adjacent small vessels with a blunt needle to avoid bleeding.

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4.2.3. nTAC Surgery

The nTAC surgery [32] (Figure 3C) includes the following four steps:(1) anesthesia and fixation; (2) ascending aorta exposure; (3) aorta banding; and (4) closure of the thoracic cavity. There are two key points of nTAC surgery: (1) Blunt needles should be used to prevent intraoperative bleeding, which is a primary cause of postoperative mortality. (2) During the surgery, the pericardium must be carefully separated from the aortic surface to expose the aortic site for banding. The pericardium should be kept intact as much as possible to avoid postoperative adhesion.

4.2.4. nPVB Surgery

The nPVB surgery [28] (Figure 3D) includes the following four steps:(1) anesthesia and fixation; (2) pulmonary vein (PV) exposure; (3) PV banding; and (4) closure of the thoracic cavity. There are two key points of nPVB surgery: (1) The right upper and right middle PVs, which are thicker than the other PVs, are selected for banding to replicate PVS. (2) The chest is closed layer by layer to avoid postoperative pneumothorax.

In summary, nACF surgery, which does not require opening the thoracic cavity, is easier to perform than the other three neonatal surgeries. All neonatal surgeries required ice-cooling anesthesia to reduce the operation time as much as possible, which increases the rate of neonatal pup recovery from anesthesia. A blunt needle is required to avoid intraoperative bleeding. For thoracotomy surgery, preventing postoperative adhesions and pneumothorax is a key for the neonatal pups' long term survival. The surgical videos for each neonatal cardiac surgery can be found at public access websites, summarized in Table 2.

Table 2. Neonatal cardiac surgery teaching videos.

Surgery	Website	ref
nACF	https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.020854	23
nTAC	https://www.nature.com/articles/s41596-020-00434-9	32
nPAB	https://www.jtcvs.org/article/S0022-5223(17)31192-3/fulltext#supplementaryMaterial	30
nPVB	https://cellandbioscience.biomedcentral.com/articles/10.1186/s13578-023-01058-8	28

5. Hemodyn

5.1. Cardiomyocyte Proliferation

Promoting cardiomyocyte proliferation is a fundamental method for treating heart failure, which not only improves heart failure caused by myocardial infarction [77,78], but also improves pediatric heart failure caused by CHDs [79,90]. A previous study demonstrated that children with TOF have impaired RV cardiomyocyte proliferation due to reduced expression of epithelial cell transforming 2 (ECT2) [79]. The study also found that beta blockers can promote cardiomyocyte proliferation by enhancing the expression of ECT2 [79]. Thus, beta blockers have been recommended to treat TOF [79]. The New England Journal of Medicine highlighted the study, commenting that the treatment of CHDs may not rely on surgical correction; this study opened a new approach for treating CHDs [80].

However, this study lacked a nPAB model to match the TOF most important clinical feature–RVOT obstruction, which produces RV PO–and made its conclusion based on an increase in the percentage of polyploidic cardiomyocytes in children with TOF [79]. An increased percentage of polyploidic cardiomyocytes could be a consequence of cardiomyocyte proliferation (Figure 4). Increasingly more studies showed that PO promoted neonatal cardiomyocyte proliferation, in both RV and LV [31,81–85]. We also found that PO promoted RV cardiomyocyte proliferation in children

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with TOF [31]. Therefore, it is inappropriate and unwise to ignore the contribution of PO to cardiomyocyte proliferation when studying pediatric TOF. Moreover, CHD is a polygenic disease, and mutations of ECT2 have rarely been reported in TOF patients [79]. Thus, it is more reasonable to open a new field for CHD treatment focused on abnormal hemodynamics than a single gene modification.

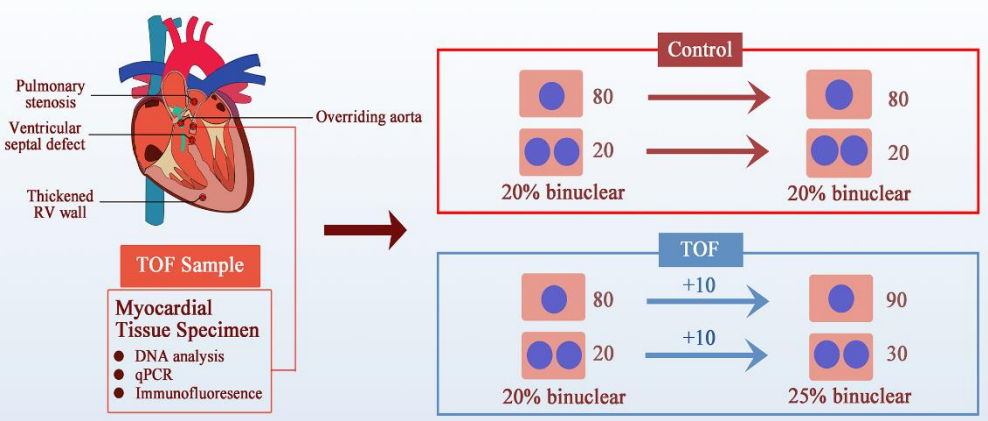

Figure 4. Possible mechanism of an increased percentage of polyploid cardiomyocytes in TOF children. (**A**) Four clinical features of TOF: RVOT obstruction, ventricular septal defect, thickened RV, and aortic riding, the most important of which is RVOT obstruction, which leads to RV PO and RV failure. (**B**) Illustration of increased binuclear cardiomyocytes generated in TOF patients. Greater numbers of binuclear cardiomyocytes do not indicate failure of cytokinesis. For example, in the beginning of a study, if both the control group and TOF group had 80 mononucleated and 20 binucleated cardiomyocytes (CMs), the proportion of binucleated CMs was 20%. Under PO conditions, both mononucleated and binucleated CMs in the TOF group increased by 10, and the proportion of binucleated CMs was 25%. Therefore, an increase in the proportion of binucleated CMs does not necessarily mean impaired cytokinesis and proliferation.

Nevertheless, the effect of PO on promoting proliferation of cardiomyocytes decreases with age, and PO cannot re-induce proliferation of differentiated and mature cardiomyocytes [31]. However, interestingly, VO re-induces proliferation of prepubertal cardiomyocytes in both the LV and RV [22,23], but does not promote proliferation of neonatal cardiomyocytes [86]. In contrast, with heart failure and at an adult stage, pressure unloading promotes cardiomyocyte proliferation [87]. These results show the complex roles of forces generated by abnormal hemodynamics on cardiomyocyte proliferation.

Force is one of the foundations of matter [88,89], and the maintenance of many life phenomena depends on a balance of forces [88,89]. How force regulates cardiac regeneration remains elusive, and perhaps changing a single mechanoreceptor can promote cardiac regeneration. In fact, a recent study demonstrated that Plxnd1 is a necessary and sufficient condition for endothelial cells to sense force for regulating cardiovascular pathophysiology [90]. We also found that Plxnd1 significantly increased in prepubertal cardiomyocytes under VO conditions (Figure 5). The introduction of neonatal ventricular PO and VO models provides a platform for us to explore the regulation of cardiac regeneration by forces, and the role of Plxnd1 may be one of the future directions.

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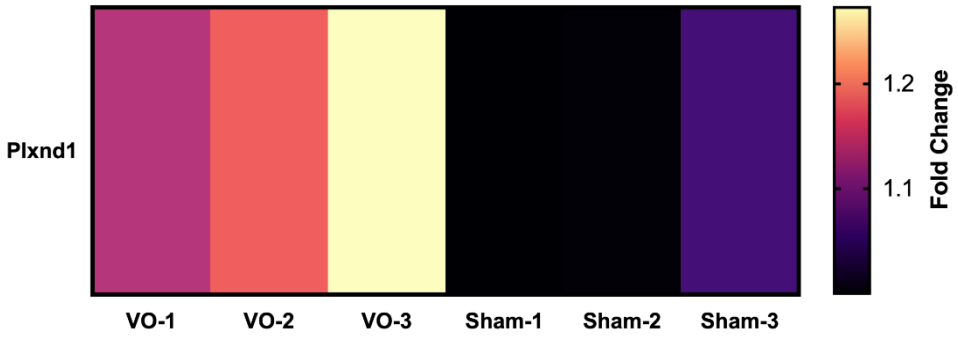

Figure 5. Plxnd1 significantly increased in prepubertal cardiomyocytes under VO. Raw data have been deposited in NCBI's Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo) with accession number GSE157396.

5.2. Cardiomyocyte Maturation

Maturation is the most important event of postnatal cardiomyocyte development in mammals [91,92]. Although the underlying mechanisms of cardiomyocyte maturation are largely unknown, the switch from pediatric to adult hemodynamics is undoubtedly an important contribution [91,92]. Due to the increase in body size, the preload and afterload faced by the adult heart is significantly greater than that of children [91,92]. In other words, it may be the force generated by the increasing preload and afterload that guide the maturation of cardiomyocytes.

The immaturity of cardiomyocytes derived from pluripotent stem cells (iPS-CMs) and their failure to mature in vivo limits their clinical use [93,94]. Therefore, in vitro experiments with various stimuli, including electrical rhythm, force, and 3D culture, were used to promote the maturation of iPS-CMs [93,94]. Although their maturity has increased, there is still a large gap between stimuli-enhanced iPS-CMs and mature adult cardiomyocytes [93,94]. The differences between in vivo and in vitro conditions, as well as an insufficient understanding of force, may account for the limited effect of force on cardiomyocyte maturation in studies.

Recent studies indicated that cardiomyocyte proliferation and maturation are two opposite processes [95,96]. Because VO and PO promote cardiomyocyte proliferation at neonatal or prepubertal stages [23,31], it is not surprising to find that cardiomyocyte maturation was impaired because of VO [22,23]. We also found that VO impeded cardiomyocyte maturation (Figure 6). The purpose of iPS-CM transplantation is to treat patients with heart failure, the hemodynamic characteristic of which is VO. Thus, the finding that VO impedes cardiomyocyte maturation may further deter the transplantation of iPS-CMs into patients with heart failure.

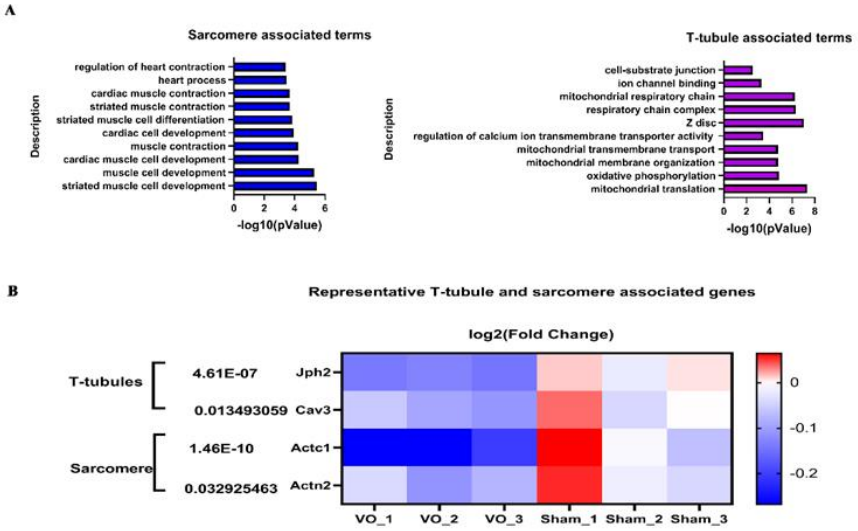

Figure 6. VO impeded cardiomyocyte maturation. (**A**) Enrichment of sarcomere- and T-tubule-associated terms in the Gene Ontology (GO) analysis of downregulated genes under VO. (**B**) Heat

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map of representative sarcomere and T-tubule genes. Raw data have been deposited in NCBI's Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo) with accession number GSE186968.

Another issue is whether VO or PO affects cardiomyocyte maturation temporarily or permanently. In other words, when VO or PO is released, can the cardiomyocytes still mature? This is the situation that exists in children with CHD. When the structural defects of the heart of children with CHDs are corrected, will the maturity of their adult cardiomyocytes be affected? Clinical investigations have found that even with perfect anatomic correction in childhood, patients with TOF are still at a high risk of arrhythmia [97], one feature of cardiomyocyte immaturity, suggesting that cardiomyocyte maturation may be permanently impaired.

In summary, some force is helpful for cardiomyocyte maturation in vitro, and force generated by age-increased preload and afterload may guide cardiomyocyte maturation in vivo. However, excessive force due to VO and PO impairs postnatal cardiomyocyte maturation. A key question is how force regulates cardiomyocyte maturation. Does maturation share the same mechanoreceptor(s) used in proliferation? After mechanoreceptor activation, different pathways involved in maturation and proliferation may be subsequently activated. In fact, we found that VO initiated an immune response at neonatal and prepubertal stages in both the RV and LV, including macrophage activation [22,23,86]. Consistently, activation of the mechanoreceptor Plxnd1 in endothelial cells led to expression of macrophage chemokines, which recruited macrophages from the peripheral blood to the heart [90]. These interesting studies are a good foundation for us to understand how force, a basic component of the material world, affects cardiovascular pathophysiology.

5.3. Lung Development

The interplay of the heart and lung profoundly, functionally, and anatomically determine a person's quality of life [98–100]. About half a century ago, an autopsy study revealed a decrease in lung volume and pulmonary dysfunction in patients with RPF-associated CHDs [101]. However, the underlying mechanisms remained elusive until recent nPAB surgery was developed, which showed that RPF caused alveolar dysplasia, angiogenesis impairment, and inflammation [28,29]. RPF also impaired cell–cell communication and axon guidance, two critical events of late alveolar formation [29,102]. Axon guidance is required for the coronavirus infection, which may explain why children with RPF-associated CHDs are relatively insensitive to COVID-19 infection [29,103]. RPF reduces the intravascular pressure and gas exchange rate, which means a reduced force in the vessels of the lung. It is possible that force is the basic cause of RPF-induced pulmonary dysplasia. Interestingly, RPF also induces inflammation [25], similar to that of VO-induced cardiomyocyte proliferation, further suggesting that there may be a force-mediated regulation.

Current bronchopulmonary dysplasia (BPD) animal models for premature infants include models of hyperoxia, pulmonary ventilation, and lipopolysaccharide [104,105], all of which aim to induce inflammation, yet yield poor targets for improving lung development of premature infants[106,107]. This may be because inflammation is not the initiating factor. Complications of premature infants often include PH and PDA [107,108], both of which induce RPF. Thus, RPF may account for premature BPD, and the nPAB model provide a new window into the study of BPD.

In contrast to RPF, IPF, which increases intravascular pressure, leads to pulmonary congestion and thickening of pulmonary small blood vessels, a characteristic of PH, which in turn increases intravascular pressure, and ultimately a vicious circle forms. A nPVB model showed a similar presentation as children with PVS, which included PV thickening, pulmonary small vessels thickening, pulmonary congestion, PH, and RV failure [28]. Consistently, the nACF model causing IPF also showed thickening of pulmonary small blood vessels, but to a lesser extent [33]. The mechanoreceptors in lungs are less studied in lungs than in hearts, including their regulation of force in lungs.

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6. Summary and Prospects

Force, a basic component of our world and generated by abnormal hemodynamics in CHDs, produces profound effects on postnatal heart and lung development, which we were previously unaware of due to the lack of neonatal rodent animal models. Nevertheless, we now know that both VO and PO promote prepubertal cardiomyocyte proliferation and impede cardiomyocyte maturation, and we also know that RPF leads to pulmonary dysplasia and IPF leads to thickening of pulmonary blood vessels.

6.1. Clinical Decision Making

VO- and PO-impaired cardiomyocyte maturation are associated with arrhythmias and weakened cardiac systolic function [93,94], suggesting that childhood correction of VO or PO or the promotion of cardiomyocyte maturation may improve adult cardiac performance. However, VO and PO promote prepubertal cardiomyocyte proliferation, which is fundamental to heart failure treatment [96,97], suggesting that VO and PO should be enhanced. Clearly, these two suggestions are contradictory. An in-depth understanding of how force regulates cardiomyocyte proliferation and maturation is a prerequisite for us to precisely regulate proliferation and maturation via VO and PO for improving the quality of life of children with CHD.

RPF and IPF are both detrimental to pulmonary performance, suggesting that it should be corrected as early as possible. If RPF or IPF cannot be corrected, mechanoreceptor blockers, axon guidance molecules, or vessel thickening inhibitors are suggested to be used as early as possible to improve pulmonary performance of children with CHD.

6.2. Limitations and Future Directions

Currently, the neonatal surgical rodent models only help us obtain a very primitive observation, leaving an abundance of unanswered questions: (1) Do mechanoreceptors for VO or PO promote cardiomyocyte proliferation or impede cardiomyocyte maturation? Apart from Plxnd1, other mechanoreceptors have also been revealed. Sdc4 is upregulated, while Itga11 is downregulated in the neonatal PO RV (Figure 7). The expression pattern of neonatal Sdc4 and Itga11 is different from that of adults, in whom both are upregulated [109,110]. How PO or VO regulates cardiomyocyte proliferation and maturation via Plxnd1, Sdc4, and Itga11 might be a future direction of research. Whether there are other mechanoreceptors that play a crucial role in regulating postnatal heart and lung development also needs to be explored. (2). Metabolic reprogramming also occurred under the condition of neonatal PO and VO (Figure 8). Is metabolic reprogramming the cause or result of cardiomyocyte proliferation? How do PO and VO initiate metabolic reprogramming of cardiomyocytes? (3) The chromatin openness of many genes associated with heart and lung development has been changed greatly by PO, VO, IPF, and RPF (data not shown). Epigenetics of hemodynamics should also be a future direction.

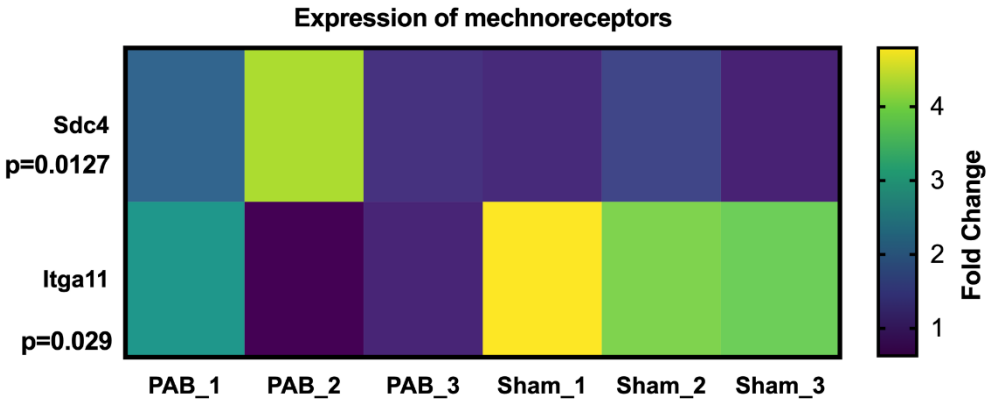

Figure 7. Sdc4 is upregulated and Itga11 is downregulated in the neonatal PO RV. Raw data have been deposited in NCBI's Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo) with accession number GSE139561.

 doi:10.20944/preprints202402.1403.v1

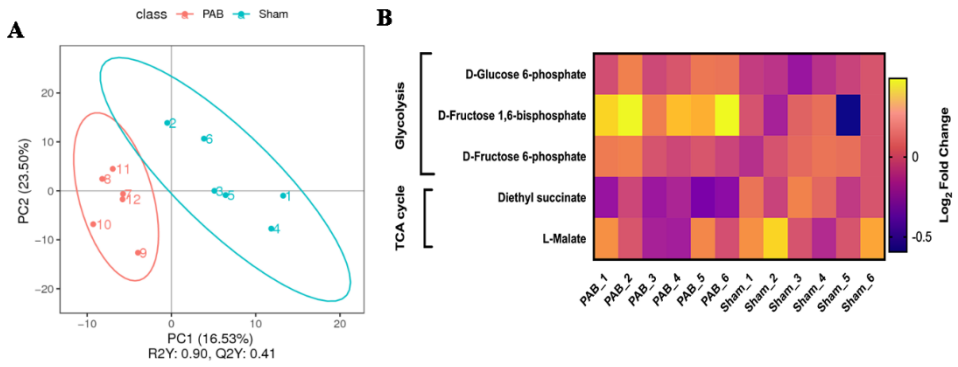

Figure 8. Metabolic reprogramming occurred with neonatal PO or VO. (**A**) Principal component analysis of RV metabolic reprogramming under neonatal PO. (**B**) Heat map of metabolites under neonatal PO. Note that glycolysis was upregulated, while the TCA cycle was downregulated under PO. Raw data have been deposited in NCBI ' s Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo) with accession number GSE139561.

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Data Availability Statement: We encourage all authors of articles published in MDPI journals to share their research data. In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Where no new data were created, or where data is unavailable due to privacy or ethical restrictions, a statement is still required. Suggested Data Availability Statements are available in section "MDPI Research Data Policies" at https://www.mdpi.com/ethics.

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