Review Article

Imaging the increase in pulmonary blood flow at birth

Introduction

Before birth the human fetus lives in a liquid environment with liquid-filled lungs that play no role in the exchange of oxygen and carbon dioxide [1]. Instead, gas exchange occurs across the placenta and the fetal lungs receive only a small fraction of the blood flow they receive after birth [2]. However, at birth the airways are cleared of liquid to allow the lungs to take over the role of gas exchange. Fetal vascular shunts close to separate the pulmonary and systemic circulations and, as a consequence, blood flow through the lungs markedly increases to equal blood flow through the entire body [3]. Undertaking these changes is a major physiological challenge for the infant that is unparalleled by any other event that the infant may experience during of its life. Thus, it is truly amazing that most infants make these changes with an apparent ease that belies the magnitude of the changes.

Fetal circulation

The fetal circulation is very different to adults. Adults have two circulations; the pulmonary, which circulates blood through the lungs and the systemic, which circulates blood through the rest of the body. These two circulations are separated by the heart, allowing them to work at very different pressures (mean of ~15 mmHg *vs* ~100mmHg, respectively), but are connected in series. As such, flow through both circulations must always be equal so that blood doesn't pool in either circulation. The right ventricle pumps blood through the lungs (pulmonary circulation) whereas the left ventricle pumps blood around the body (systemic circulation) (Fig. 1). Blood returning from the body supplies blood for the right ventricle to pump (called preload) whereas the supply of blood for the left ventricle comes from the lungs.

In the fetus, the pulmonary and systemic circulations are interconnected by the presence of vascular shunts, making it very different from the adult. Both ventricles contribute to blood flow in the systemic circulation, with the left ventricle supplying blood to the upper body and the right ventricle supplying blood to the lower body and placenta [3]. Most of the blood pumped by the right ventricle (~90%) by-passes the lungs and directly enters the descending aorta, through a shunt called the ductus arteriosus. This is largely because the resistance to blood flow through the lungs is very high during fetal life (Fig. 1) and pulmonary blood flow (PBF) is low. As a result, the volume of blood returning to the left ventricle (preload) from the lungs is small and is unable to supply the left ventricle with sufficient blood to pump [3]. Instead, the left ventricle receives most of its preload from the highly oxygenated blood returning from the placenta (Fig. 1). This blood passes from the umbilical vein through a shunt (ductus venosus) into the inferior vena cava and then passes through another shunt (foramen ovale) to enter the left atrium, before entering the left ventricle (Fig. 1) [4]. As the left ventricle receives a high proportion of oxygenated blood from the placenta and, as its output is directed mainly towards the brain, the brain receives blood that is more highly oxygenated than organs in the lower body (Fig. 1).

Changes to the fetal circulation at birth

At birth, the resistance to blood flow through the lungs massively decreases (30-50 fold) so that it can accept the entire output of the right ventricle [3]. The fetal vascular shunts (ductus arteriosus, ductus venosus and foramen ovale) must close to separate the pulmonary and systemic circulations, allowing them to work at very different pressures (see above). All of these changes are precipitated by two seemingly innocuous events; (i) the baby taking its first few breaths and (ii) clamping and cutting of the umbilical cord.

Phase contrast X-ray imaging experiments at SPring-8 BL20B2, demonstrated in newborn's breathing efforts are overwhelmingly responsible for clearing the airways of liquid and aerating the lung [5,6]. This, in turn, stimulates a large decrease in the resistance to blood flow through the lungs and a big increase (30-50 fold) in PBF, allowing the lungs to accept the entire output of the right ventricle. Clamping the umbilical cord disconnects the low resistance placental circulation from the fetal circulation, causing a large increase in resistance [3]. As a result, pressure in the systemic circulation rapidly increases and, combined with the large decrease in pulmonary vascular resistance, blood flow through the

ductus arteriosus reverses during diastole (between heart beats) [7]. Thus, blood begins to flow from the aorta and into the lungs, contributing up to 50% of PBF for ~30 minutes after birth (called left-to-right shunting) [8]. However, blood flow gradually diminishes with time after birth as the ductus arteriosus narrows and then eventually closes [8].

Clamping of the umbilical cord at birth causes the ductus venosus to close due to a loss of blood flow, but it also removes umbilical venous return as a source of blood supply for the left ventricle (via the foramen ovale) [3]. As a result, if umbilical cord clamping occurs before the infant has aerated its lungs and its PBF has increased, then the left ventricle is deprived of blood to pump and cardiac output markedly decreases (by 30-50%) [3]. This can have serious consequences for the infant, potentially contributing to hypoxic/ischemic injury to the brain. On the other hand, if lung aeration precedes umbilical cord clamping, the increase in PBF can immediately replace umbilical venous return as the primary source of preload for the left ventricle, thereby preventing a reduction in cardiac output after birth [7]. In addition, the increase in pulmonary venous return to left atrium increases left atrial pressure above right atrial pressure, causing the foramen ovale to close, which eventually fuses with the intra-atrial septa.

Increase in Pulmonary blood flow at birth

With respect to infant survival after birth, the increase in PBF plays two critical roles. It facilitates the switch to pulmonary gas exchange by directing a high rate of blood flow across the lung's gas exchange surface to meet the infant's oxygen uptake requirements. The increase in PBF is also vital for maintaining cardiac output after birth, as it takes over from umbilical venous return as the primary source of preload for the left ventricle. Thus, a persisting high pulmonary vascular resistance is a major cause of death and disease in newborn infants [9], which reinforces the need to understand the mechanisms by which PBF increases after birth.

Although the precise mechanisms are unknown, lung aeration is the primary trigger for the increase in PBF after birth. It was widely believed that increased release of vasodilators, particularly nitric oxide (NO) in response to an increase in oxygenation associated with lung aeration, is the primary mechanism for the increase in PBF [2]. Increasing oxygen levels in the fetus stimulates an increase in PBF, although the increase is not sustained [2]. Furthermore, ventilation of the lung with a gas devoid of oxygen (with 100% nitrogen) or with low oxygen levels that do not increase oxygenation, can stimulate a large increase in PBF [10]. However, as the increase in PBF is greater with higher oxygen levels, increased oxygenation levels likely contributes to the increase in PBF at birth, but is not the primary mechanism [3,10]. Other potential mechanisms include an increase in lung recoil caused by the formation of an air/liquid interface and the creation of surface tension within the lung following aeration [11]. An increase in recoil within adjacent alveoli decreases the pressure within the interstitial tissue separating the alveoli, as it does in the intrapleural space (space between lung and chest wall). As such, the capillaries located within lung tissue would be expected to expand leading to an increase in vessel caliber and a reduction in resistance. Although simulating the increase in lung recoil induced by lung aeration increases PBF, the increase is considerably smaller than the increase at birth [11]. As such, additional, as yet undefined, mechanisms likely also contribute to the increase in PBF at birth.

Experiments at SPring-8 BL20B2 has discovered what is likely to be the primary underlying mechanism

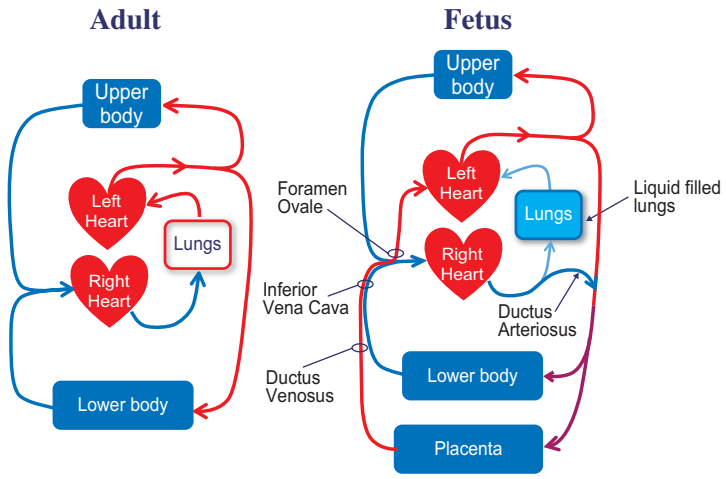

Fig. 1. Diagrammatic representation of the adult and fetal circulations. In the adult, the pulmonary and systemic circulations are separated by the heart and each ventricle provides blood flow through only one circulation; the left provides all systemic blood flow, whereas the right provides all pulmonary blood flow. In the fetus, the two circulations are interconnected by vascular shunts (foramen ovale and ductus arteriosus) that allow both the left and right ventricles to contribute to blood flow in the systemic circulation. Blood flow through the lungs is very low as most right ventricular output by-passes the lungs and flows through the ductus arteriosus. As such pulmonary blood flow provides little venous return for the left ventricle, which instead comes from the placenta via the ductus venosus and foramen ovale.

for the increase in PBF at birth [12-14]. By combining phase contrast X-ray imaging and angiography, the spatial relationship between lung aeration and the increase in PBF at birth was investigated. In view of the known effect that oxygenation and lung recoil has on PBF, it was hypothesized that the increase in PBF would be restricted to aerated lung regions [14]. However, contrary to this hypothesis, the experiments showed that partial aeration of the lung caused a global increase in PBF (Fig. 2). Furthermore, the increase in PBF occurred equally and simultaneously in all parts of the lung, irrespective of their state of aeration (Fig. 2 and Fig. 3). This effect of partial lung aeration on the global increase in PBF also occurred when the ventilation gas was changed to 100% nitrogen [12]. This discounted the suggestion that the increase in PBF in unaerated regions occurred in response to an increase in oxygenation caused by recirculation of well oxygenated blood from aerated regions into unaerated lung regions. On the other hand, partial lung aeration with 100% oxygen caused a larger increase in PBF in aerated regions compared to unaerated regions [12]. This indicates that increased oxygenation contributes to the increase in PBF, but the effect of oxygen is localized to aerated lung regions.

Realization that partial lung aeration causes rapid and global vasodilation of the lung, which occurs simultaneously and equally in both aerated and unaerated regions, led to the hypothesis that a neural reflex mediates the effect of lung aeration on PBF [13]. Studies in adult lung have previously described the juxta-capillary receptor (J-receptor), which is sensitive to lung edema and when activated triggers an increase in breathing rate (tachypnoea) [15]. The receptors are thought to be located within the juxta-capillary tissue between adjacent alveoli and to signal via afferent C-fibers passing within the vagal nerve trunk. As lung aeration at birth involves lung liquid leaving the distal airways and entering the peri-alveolar tissue, the accumulation of lung liquid within lung tissue simulates lung edema and may activates these J-receptors. The receptors signal the brain via the vagus which then initiates global dilation of the lung, presumably via efferent parasympathetic nerves. This hypothesis was tested by examining the effect of partial lung aeration on the global increase in PBF in newborn rabbits following bilateral trans-section of the vagus nerves [13]. Sectioning of the vagus nerves blocked the global increase in PBF caused by partial lung aeration (Fig. 3), which is consistent with the suggestion that signaling via the vagus nerve plays a vital role in the increase in PBF at birth. Interestingly, partial aeration of the lung with 100% oxygen increased PBF just in the aerated lung region, indicating that the increase in PBF at birth results from a hierarchy of mechanisms that either have global or localized effects. That is, the initial movement of liquid out of the airways into lung tissue activates receptors (possibly J-receptors) to initiate a global increase in PBF via a neural reflex. However, this increase in PBF is modulated at the local level by increased oxygenation, which is likely mediated by NO release.

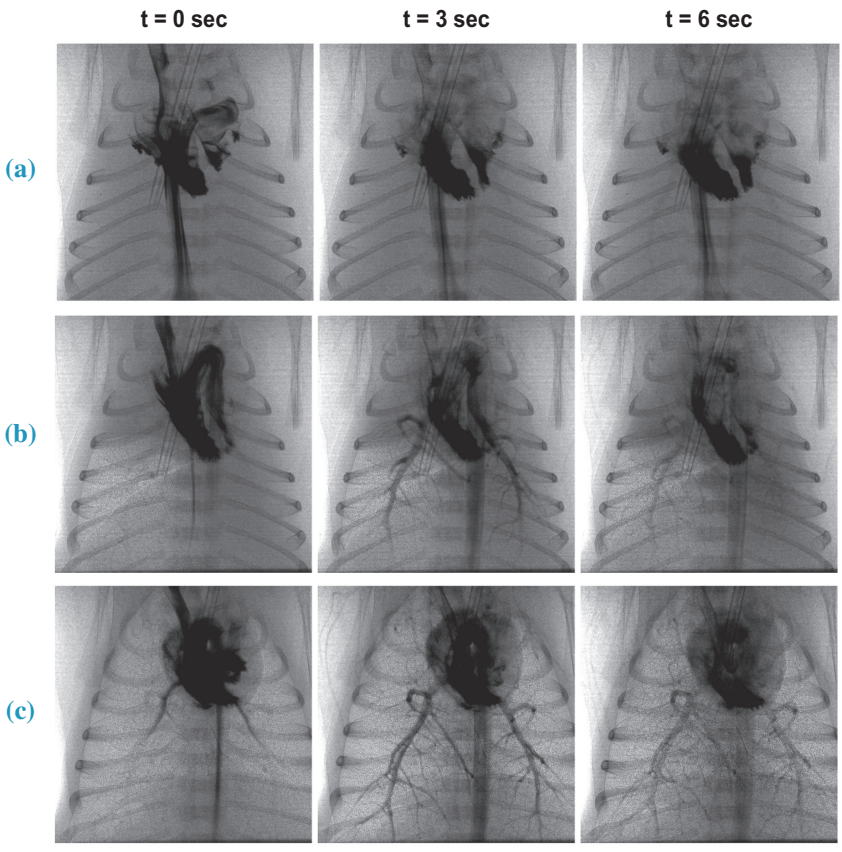

Fig. 2. Simultaneous phase contrast X-ray imaging and angiography of a newborn rabbit before lung aeration **(a)**, after aeration of one lung **(b)** and after aeration of both lungs **(c)**. An iodine solution was used as a contrast agent and was injected into a major vein leading to the heart. A series of images were acquired starting (t=0 sec) from the moment that iodine was first ejected from the heart to show the transit time of iodine through the pulmonary circulation; images displayed were acquired at t = 0, 3 and 6 secs. Aeration of the lung is clearly identified in the lung as regions of higher intensity with the presence of speckle. Note that before lung aeration (a), very little iodine enters the pulmonary circulation, but this markedly increases following aeration of one lung (b) with the increase occurring equally in both aerated and unaerated regions.

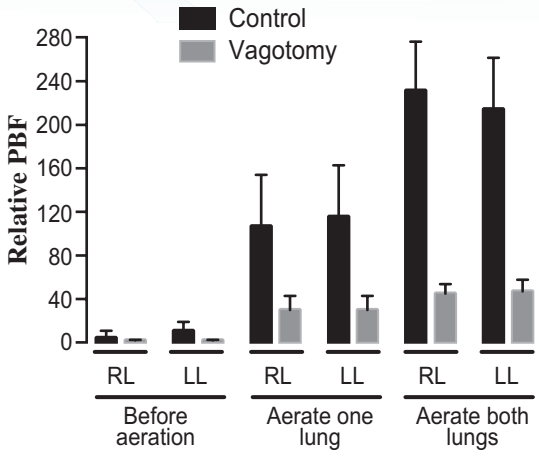

Fig. 3. Effect of vagotomy (cutting of both vagus nerves) on relative pulmonary blood flow before lung aeration, following aeration of one lung and following aeration of both lungs in newborn rabbits. Note that in controls (black bars) pulmonary blood flow increases in both lungs following aeration of only one lung. However, this increase in greatly reduced in vagotomized (gray bars) newborn rabbits. Data has been redrawn from [13].

Partial lung aeration and a global increase in PBF: What are the broader considerations?

In the healthy adult lung, ventilation (in and out movement of gas) of lung regions is closely "matched" with the level of blood flow (perfusion) through those lung regions. This is termed "ventilation/perfusion matching" and is regulated by changing oxygenation levels within localized lung regions. Ventilation/perfusion matching in the lung plays an important role in optimizing the lung's gas exchange potential by ensuring that when ventilation within a region changes, this region receives a matching change in blood flow. In the diseased lung, ventilation/perfusion matching can be reduced, resulting in a "mismatch". This is where lung regions with little or no ventilation receive large amounts of blood flow, which are commonly referred to as pulmonary shunts. Clearly, shunting blood through non-ventilated regions of the lung will greatly reduce the gas exchange efficiency of the lung.

While a ventilation/perfusion "mismatch" is thought to be problematic in adults, the presence of large pulmonary shunts in newborns immediately after birth should be viewed differently and may be beneficial for the infant. Indeed, while survival at birth depends on only part of the lung being ventilated, good cardiac output is essential for survival and to prevent brain injury, particularly when oxygenation levels are low. Thus, as a high PBF is essential to maintain left ventricular output, it is vital that the increase in PBF is not limited by whether or not the lung is fully aerated. Thus, it is logical that the increase in PBF at birth is not linked to the rate and degree of lung aeration, particularly as the lung can take some time to fully aerate [5,6].

Summary

The increase in PBF is vital for survival after birth as it enhances the efficiency of pulmonary gas exchange and is critical for maintaining cardiac output. However, until recently the primary mechanisms underpinning the increase in PBF were unclear. Imaging experiments at SPring-8 BL20B2 have provided a new understanding for how lung aeration triggers the increase in PBF at birth. By demonstrating that the increase in PBF is not spatially related to lung aeration and that the effect of oxygen is mediated locally, this implicated the involvement of a neural reflex. The role of this neural reflex was confirmed in subsequent experiments, but much further research is required to detail the specific pathways involved.

Stuart B. Hooper[a,b,*],
James T. Pearson[c]
and Marcus J. Kitchen[d]

[a] The Ritchie Centre, Hudson Institute of Medical Research, Australia
[b] Dept. of Obstetrics and Gynaecology, Monash University, Australia
[c] Department of Cardiac Physiology, National Cerebral and Cardiovascular Center Research Institute, Japan
[d] School of Physics and Astronomy, Monash University, Australia

*Email: stuart.hooper@monash.edu

References

[1] S.B. Hooper, R. Harding: Clin. Exp. Pharmacol. Physiol. **22** (1995) 235.
[2] Y. Gao, J.U. Raj: Physiol Rev. **90** (2010) 1291.
[3] S.B. Hooper *et al.*: Pediatr. Res. **77** (2015) 608.
[4] A.M. Rudolph: Ann. Rev. Physiology. **41** (1979) 383.
[5] S.B. Hooper *et al.*: FASEB J. **21** (2007) 3329.
[6] M.L. Siew *et al.*: J. Appl. Physiol. **106** (2009) 1888.
[7] S. Bhatt *et al.*: J. Physiol. **591** (2013) 2113.
[8] K.J. Crossley *et al.*: J Physiol. **587** (2009) 4695.
[9] E.M. Ostrea *et al.*: Pediatr. Drugs **8** (2006) 179.
[10] D.F. Teitel *et al.*: Pediatr. Res. **27** (1990) 372.
[11] S.B. Hooper: Exp. Physiol. **83** (1998) 833.
[12] J.A. Lang *et al.*: J. Physiol. **594** (2016) 1389.
[13] J.A. Lang *et al.*: J. Physiol. **595** (2017) 1593.
[14] J.A. Lang *et al.*: J. Appl. Physiol. **117** (2014) 535.
[15] A.M. Roberts *et al.*: Circ. Res. **58** (1986) 512.