Imaging the increase in pulmonary blood flow at birth

Lung aeration at birth stimulates a significant increase in pulmonary blood flow (PBF). This process is essential for taking over the role of gas-exchange from the placenta, as well as restoring the left ventricle preload to maintain cardiac output that is lost following umbilical cord occlusion [1]. The pulmonary transition into neonatal life is influenced by a number of stimuli, with the entry of air and clearance of liquid from the airways acting as the primary trigger for this process [2]. This is mediated through a range of vasoactive and mechanical factors to decrease pulmonary vascular resistance (PVR) and rapidly increase PBF [3]. Although much research has focused on understanding this process, the suggested mechanisms have been based on the assumption that, at birth, air entry stimulates a local increase in PBF to promote ventilation/perfusion matching. This assumption was based on the well-established relationship between regional ventilation and perfusion in the adult lung, largely because until recently we have not had the technology to investigate this relationship at birth.

Examining the regional distribution of pulmonary dynamics non-invasively during this transition period can only be achieved by imaging. However, real-time imaging of regional pulmonary ventilation has been difficult due to the low density of lung tissue. Development of phase-contrast (PC) X-ray imaging not only allows imaging of the lungs with high temporal and spatial resolution, down to the smallest air sacs, but can be combined with simultaneous microangiography. Utilizing such techniques with the high brilliance and collimation of monochromatic synchrotron radiation as an X-ray source, provides a unique insight into changes with aeration and perfusion in the lungs at birth with exceptional detail. The regional relationships between lung aeration and the increase in PBF are not well known and indeed, our previous studies have shown that perfusion is not spatially related to lung aeration, as partial lung aeration triggers a global increase in PBF [4]. The vasoactive and mechanical factors that normally contribute to an increase in PBF were not expected to be active in unaerated lung regions, yet PBF appeared to increase regardless of local aeration. In this study, we sought to isolate the effect of local oxygenation in this process and further investigate the mechanisms regulating the increase in PBF at birth.

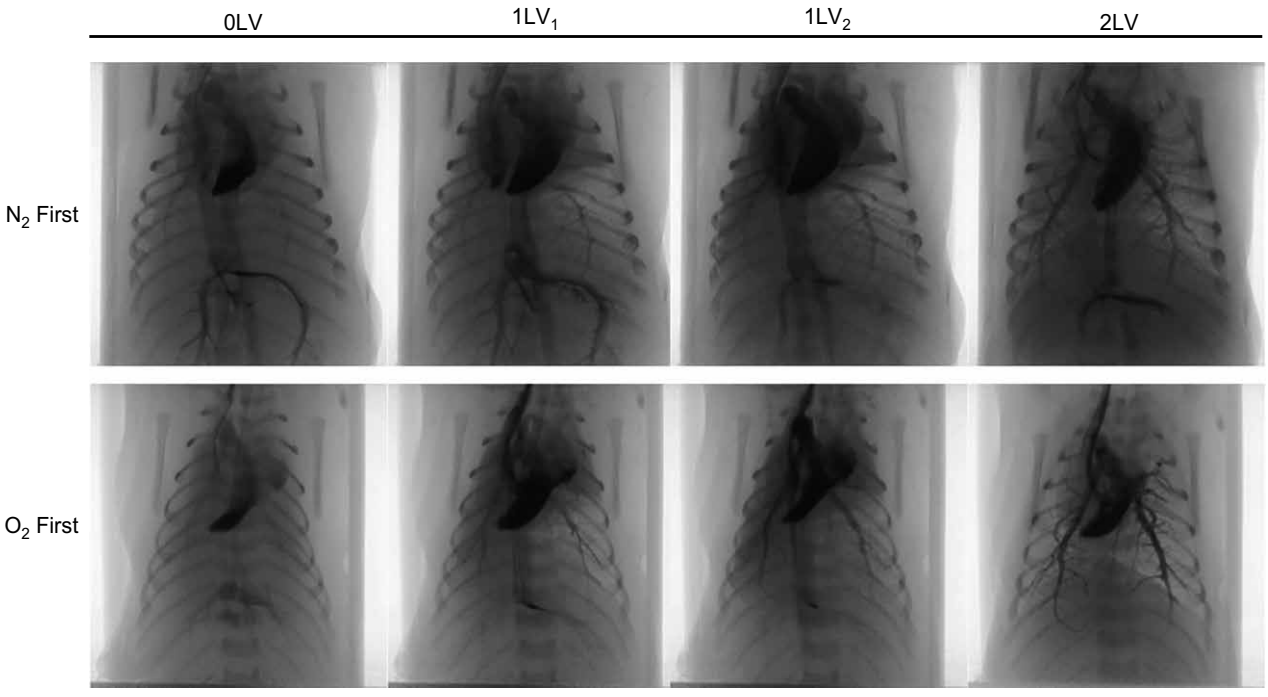

Fig. 1. Representative X-ray image sequences of newborn rabbits imaged prior to ventilation (0LV), following unilateral ventilation of the right lung ($1LV_1$) with either 100% N_2 or 100% O_2, subsequent ventilation with air (21% O2) in both kittens ($1LV_2$), and later ventilation of both lungs with air (2LV). Images were obtained 1–3 s following iodine bolus injection.

Simultaneous PC X-ray imaging and angiography was performed at SPring-8 **BL20B2** to compare aeration and perfusion in newborn rabbit kittens as previously described [4,5]. We imaged kittens first while the lungs remained unaerated and liquid filled, then with a single lung ventilated with either 100% N_2 (0% O_2), air (21% O_2) or 100% O_2. Kittens were further imaged with the ventilated gas switched to air, then with both lungs ventilated. We were able to demonstrate changes in PBF before and after ventilation of a single lung (Fig. 1). We consistently found that, in all parameters measured, the greatest change occurred between the pre-ventilation and the initial unilateral ventilation periods, with relatively minor changes occurring thereafter. This confirmed that partial lung aeration induces a widespread increase in PBF, which is mediated by a potent mechanism that is unrelated to oxygenation levels, as these changes occurred even following partial ventilation with 100% N_2. Perfusion of vessels rapidly increased and pulmonary transit time rapidly decreased in both lungs following aeration of a single lung (Fig. 2). These changes are indicative of downstream vasodilatation, vessel recruitment and an associated fall in PVR. Additionally, high oxygen concentration appeared to have an additive effect on pulmonary vasodilatation and PBF, which was localized to aerated lung regions. This suggests that there are a number of factors that work independently to increase PBF at birth.

In summary, PC imaging and microangiography can be utilized to demonstrate that partial lung aeration triggers a global increase in PBF, leading to a potential mismatch between pulmonary ventilation and perfusion. Furthermore, we show that a highly potent stimulus unrelated to oxygenation or local aeration can initiate these changes but is not fully explainable with our current knowledge of this process. We conclude that regionalized inhomogeneous aeration of the lung, as is common in preterm newborn infants during the onset of air breathing, may result in these widespread changes in PBF and occur regardless of inspired oxygen. The underlying mechanisms remain to be investigated, but could relate to a neural reflex as indicated by the rapid and global nature of PBF changes caused by air entry into the lungs.

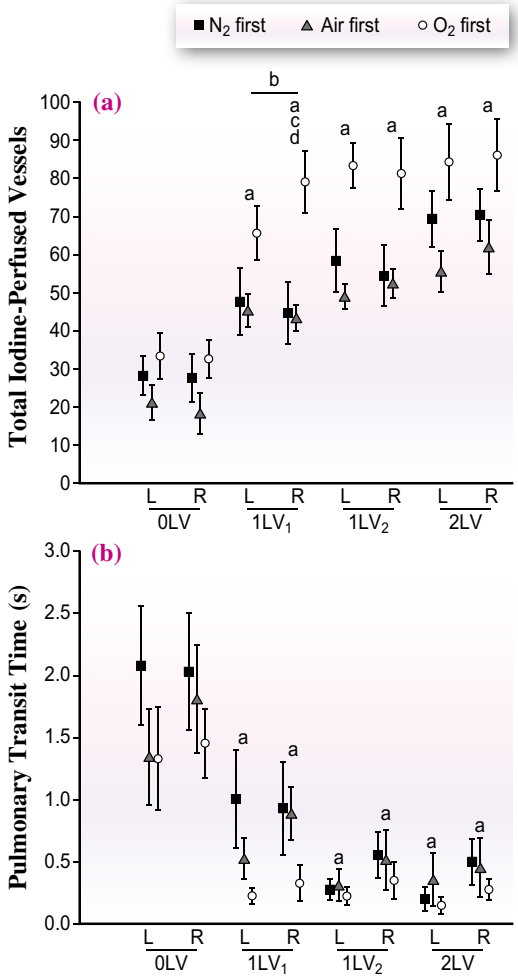

Fig. 2. **(a)** Mean iodine-perfused vessel number (±SEM) in the left and right lungs. **(b)** mean arterial transit time (s ± SEM) in the left and right lungs. Data shown are at each ventilation period (0LV, $1LV_1$, $1LV_2$ and 2LV) in N_2 first (solid squares), air first (crosses) and O_2 first (open circles) groups. [a]$P<0.05$ compared to baseline (0LV) in the same lung in the same group; [b]$P < 0.05$ left lung *vs.* right lung in O_2 first; [c]$P<0.05$ air first *vs.* O_2 first; [d]$P < 0.05$ N_2 first *vs.* O_2 first.

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