A vagal reflex mediates the lung aeration-induced increase in pulmonary blood flow at birth

At birth lung aeration not only allows pulmonary gas exchange to commence, but also stimulates a large increase in pulmonary blood flow (PBF) [1]. During fetal life, gas exchange occurs across the placenta and PBF is low due to a high pulmonary vascular resistance (PVR). Thus, PBF contributes little to the blood supply (preload) for the left ventricle in the fetus, whereas in the adult, PBF supplies 100% of this preload. Instead, in the fetus, preload for the left ventricle mostly comes from umbilical blood flow [2,3]. Following birth, umbilical venous return is lost with clamping of the umbilical cord and so PBF must rapidly increase to facilitate pulmonary gas exchange and supply preload for the left ventricle[2]. Thus, the increase in PBF is critical for the transition to newborn life and while it is clear that lung aeration is the trigger, the mechanism by which lung aeration stimulates PBF remains poorly understood.

Numerous factors are thought to contribute to the increase in PBF at birth, which include increased oxygenation, vasodilator release (e.g. nitric oxide (NO)) and mechanical factors. Increased oxygenation dilates pulmonary vessels through mediators such as NO, whereas air entry into the lung causes surface tension to develop at the air/liquid interface, which increases lung recoil and causes peri-alveolar capillaries to expand. Our recent studies have identified an additional, previously unrecognized, factor that contributes to the increase in PBF at birth [4,5]. These studies were conducted at SPring-8 using simultaneous angiography and phase contrast (PC) X-ray imaging and showed that partial lung aeration in the both presence and absence of O_2 increased PBF equally in both aerated and non-aerated lung regions [5]. These findings clearly demonstrated the existence of a previously unrecognized mechanism that could not be readily explained by any known mechanism [4].

As partial lung aeration triggers a global increase in PBF, we considered that a neural reflex may be responsible, which is triggered by the movement of liquid out of the airways and into the surrounding tissue during lung aeration. This is consistent with our previous studies performed at SPring-8 showing that during lung aeration liquid moves distally through the airways and eventually across the distal airway wall into lung tissue. It is also consistent with the finding that vagal stimulation causes pulmonary vasodilation in fetal sheep. In this study, we investigated the role of the vagus nerve in mediating the increase in PBF at birth using simultaneous PC X-ray imaging and angiography in newborn rabbits (Fig. 1). We hypothesized that, following partial lung aeration, vagotomy would disrupt vasodilation in non-aerated lung regions regardless of the O_2 content of the inspired gas.

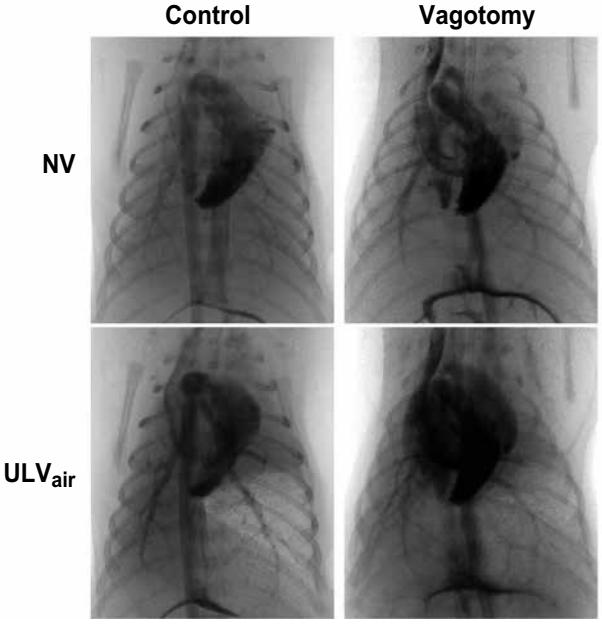

Fig. 1. Representative PC X-ray angiography image sequences of vagotomized and control newborn rabbits imaged prior to ventilation (NV) and following unilateral ventilation (ULV) of the right lung with air (ULV_{air}). Images were obtained 1–3 seconds following iodine bolus injection.

These experiments were performed at SPring-8 **BL20B2** in newborn rabbit kittens as previously described [4,5]. Newborn kittens were either vagotomized or sham operated prior to delivery and then imaged at 20Hz. Image sequences were acquired before lung aeration and following aeration of a single lung ventilated with either 100% N_2 (0% O_2), air (21% O_2) or 100% O_2 in different groups of kittens (Fig. 1). Kittens were imaged again after the ventilation gas was switched to air, then again after ventilation commenced with both lungs [6]. In contrast to sham operated kittens, PBF in vagotomized kittens did not increase in response to unilateral ventilation of the lung with both 100% N_2 and air (Fig. 2). Interestingly, PBF was not reduced in vagotomized animals ventilated with 100% O_2, demonstrating the independent stimulatory effects of oxygen and autonomic innervation to the increase in PBF at birth. The PBF findings were consistent with the changes in vessel diameter and PBF transit times measured from the image sequences, demonstrating that the increase in PBF was primarily due to downstream vasodilation.

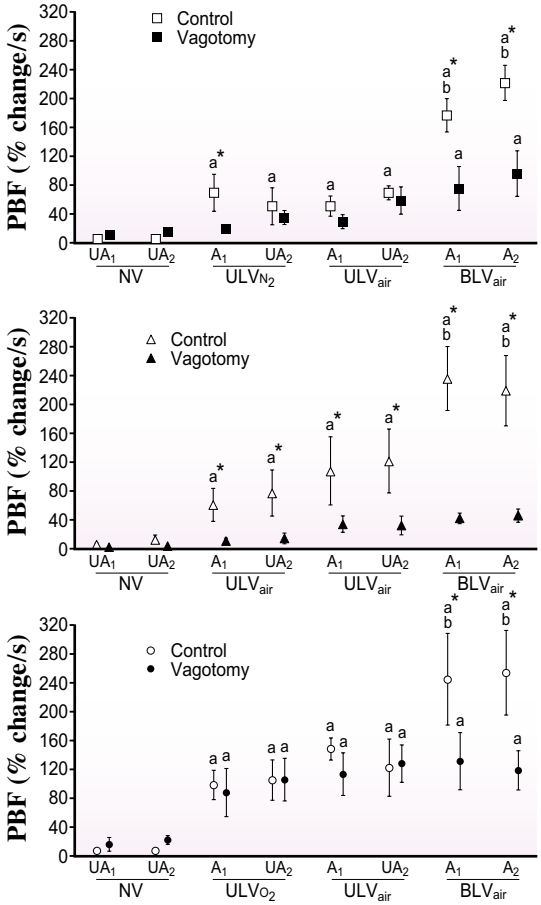

Fig. 2. Mean (±SEM) relative PBF (% change/s) levels in control (open symbols) and vagotomized (closed symbols) kittens initially ventilated with either 100% N_2 (squares; upper panel), air (triangles; middle panel) or 100% O_2 (circles; lower panel). Ventilation periods shown are non-ventilated (NV), unilateral ventilation ($ULV_{N_2/air/O_2}$), unilateral ventilation with air (ULV_{air}) and bilateral ventilation with air (BLV_{air}). Lungs are either unaerated (UA) or aerated (A) and ventilated first ($_1$) or second ($_2$). a: $p<0.05$ compared to the same lung at NV. *: $p<0.05$ control *vs.* vagotomy. Relative PBF was calculated by determining the maximum % change gray value in the main axial arteries divided by the arterial transit time.

The results of this study confirm that partial lung aeration induces a global increase in PBF across the entire lung, which is mediated by a neural reflex that signals via afferent nerve fibers that travel within the vagal trunk. Activation of these fibers are independent of oxygenation levels, which appears to act predominantly in localized manner to increased PBF only in affected tissues. While it remains unclear how lung aeration activates these nerve fibers and what receptors are involved, we speculate that the response involves activation of the lung's J-receptors. That is, during lung aeration, the movement of liquid out of the airways and into lung tissue causes lung tissue edema, which is known to activate J-receptors that signal via *c*-fibers within the vagal trunk. In summary, PC imaging and angiography can be utilized to demonstrate that partial lung aeration triggers a global increase in PBF, that is mediated via the vagal nerve. While this can lead to a potential mismatch between pulmonary ventilation and perfusion, at birth this is an advantage, not a disadvantage. That is, as the increase in PBF at birth is not dependent upon complete aeration of the lung, then the infant's cardiac output after birth (which depends on PBF for preload) is also not dependent upon complete lung aeration.

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