Differential effect of recruitment manoeuvres on pulmonary blood flow and oxygenation during HFOV in preterm lambs

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Polglase GR, Moss TJ, Nitsos I, Allison BJ, Pillow JJ, Hooper SB. Differential effect of recruitment manoeuvres on pulmonary blood flow and oxygenation during high-frequency oscillatory ventilation in preterm lambs. J Appl Physiol 105: 603–610, 2008. First published June 5, 2008; doi:10.1152/japplphysiol.00041.2008.—The effects of lung volume recruitment manoeuvres on pulmonary blood flow (PBF) during high-frequency oscillatory ventilation (HFOV) in preterm neonates are unknown. Since increased airway pressure adversely affects PBF, we compared the effects of two HFOV recruitment strategies on PBF and oxygenation index (OI). Preterm lambs (128 ± 1 day gestation; term ~150 days) were anesthetized and ventilated using HFOV (10 Hz, 33% t1) with a mean airway pressure (Pao) of 15 cmH2O. Lung volume was recruited by either increasing Pao to 25 cmH2O for 1 min, repeated five times at 5-min intervals (Sigh group; n = 5) or stepwise (5 cmH2O) changes in Pao at 5-min intervals incrementing up to 30 cmH2O then decrementing back to 15 cmH2O (Ramp group; n = 6). Controls (n = 5) received constant HFOV at 15 cmH2O. PBF progressively decreased (by 45 ± 6%) and OI increased (by 15 ± 6%), indicating reduced oxygenation in controls during HFOV, which was similar to the changes observed in the Sigh group of lambs. In the Ramp group, PBF fell (by 54 ± 10%) as airway pressure increased (r2 = 0.99), although the PBF did not increase again as the Pao was subsequently reduced. The OI decreased (by 47 ± 9%), reflecting improved oxygenation at high Pao levels during HFOV in the Ramp group. However, high Pao restored retrograde PBF during diastole in four of six lambs, indicating the restoration of right-to-left shunting through the ductus arteriosus. Thus the choice of volume recruitment manoeuvre influences the magnitude of change in OI and PBF that occurs during HFOV. Despite significantly improving OI, the ramp recruitment approach causes sustained changes in PBF.

preterm; lung volume recruitment; waveform analysis; pulmonary blood flow

Very preterm infants (<30 wk of gestation) have immature lungs with low compliance, a small surface area for gas exchange, a thick air-blood gas barrier, reduced capacity to clear airway liquid, and little or no surfactant (8, 22, 23). Consequently, these infants commonly suffer respiratory failure, requiring resuscitation at birth and assisted ventilation during their first postnatal weeks. Although necessary for survival, mechanical ventilation increases the risk of lung injury and the infant developing bronchopulmonary dysplasia (7), but the specific underlying mechanisms are unclear.

High-frequency oscillatory ventilation (HFOV) provides an alternative to conventional positive-pressure ventilation for critically ill infants with acute respiratory failure (19). HFOV uses ventilatory rates of 10–15 Hz and tidal volumes of less than the anatomical dead space volume of the lung to promote gas exchange. Although HFOV has short-term benefits compared with conventional ventilation (6, 13, 18, 30), meta-analyses of clinical trials have shown that any beneficial effects of HFOV on the incidence or severity of bronchopulmonary dysplasia are of borderline significance and are inconsistent across the different trials (19).

Lung volume recruitment manoeuvres are commonly used during the commencement of HFOV to overcome initial atelectasis within the lung and to counteract the progressive atelectasis that can result from ventilation with low tidal volumes (5, 30). These manoeuvres are considered essential for the success of HFOV and to protect the lung from ventilator-induced lung injury (1, 3). Recruitment manoeuvres involve increases in mean airway pressure, which improve lung compliance and oxygenation (1, 9, 25, 33, 38), but effects on pulmonary blood flow (PBF) are poorly understood.

During fetal life, pulmonary vascular resistance (PVR) is high, and as a result PBF is low with most (~90%) of the right ventricular output bypassing the lungs and flowing directly into the systemic circulation (aorta) via the ductus arteriosus (DA), called right-to-left shunting. At birth, a large and rapid decrease in PVR causes a sizeable increase in PBF and the lungs begin to receive the entire output of the right ventricle; they can also receive blood flow from the systemic circulation via left-to-right shunting through the DA. Since the airway/capillary transmural pressure is a major determinant of PVR, respiratory manoeuvres that increase airway pressure can influence PVR as well as the degree and direction of shunting of blood through the DA. For instance, increases in end-expiratory pressures during conventional ventilation cause substantial reductions in PBF by increasing PVR in preterm lambs (34). Furthermore, the reduction in PBF persists after the end-expiratory pressures are reduced, indicating that elevated airway pressure can cause long-lasting changes to the pulmonary vasculature (34, 37). Thus we hypothesized that recruitment manoeuvres during HFOV would cause similar persistent reductions in PBF, which could lead to the restoration of right-to-left shunting of blood through the DA. Our aim was to compare the effects of two different recruitment strategies used during HFOV on systemic and pulmonary arterial pressures, arterial oxygenation, and PBF in preterm lambs.

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METHODS

The experimental protocol was approved by the animal ethics committees of the Department of Agriculture and Food, Western Australia; the University of Western Australia; and Monash University.

Surgery was performed on pregnant ewes (Merino) bearing single fetuses at 126 ± 1 days of pregnancy (term is ~150 days). The fetal head and neck were exposed for insertion of polyvinyl catheters (20 gauge), filled with heparinized saline, into a fetal carotid artery. A 4-mm ultrasonic flow transducer (Transonic Systems, Ithaca, NY) was placed around the left pulmonary artery (35). Pulmonary and carotid arterial pressures (DTX, Viggo-Spectramed, CA) and blood flow through the left pulmonary artery were recorded digitally (1 kHz; Powerlab, ADI, Castle Hill, Australia). Mean PBF was calculated electronically from the instantaneous PBF signal. The fetal chest was closed, the fetal trachea intubated orally, and the lung liquid was drained passively.

Lambs were anesthetized (ketamine IM, 30 mg; Parnell Laboratories, NSW, Australia), delivered, dried, weighed, and placed on intermittent positive-pressure ventilation (IPPV) for 15 min to allow birth-related changes in PBF to stabilize. Lambs were ventilated with warmed, humidified gas [inspired O2 fraction (FiO2) = 0.4 throughout, in N2]. Peak inspiratory pressure was set initially at 40 cmH2O, and positive end-expiratory pressure (PEEP) was 5 cmH2O; peak inspiratory pressure was subsequently altered to maintain a tidal volume of ~7 ml/kg body wt. Fifteen minutes after delivery, HFOV (10 Hz; Sensormedics 3100A, Viasys, CA) was initiated with a mean airway pressure at mouth opening (Pao) of 15 cmH2O. The lamb's well being was monitored throughout the procedure by measuring preductal arterial pressures (DTX, Viggo-Spectramed, CA) and blood flow through the left pulmonary artery were recorded digitally (1 kHz; Powerlab, ADI, Castle Hill, Australia). Arterial oxygenation was quantified using the oxygenation index [OI: FiO2 × mean airway pressure × (100/PaO2)]. HFOV amplitude was adjusted to maintain PaCO2 at 50–60 Torr. Postductal transcyanotic oxyhemoglobin saturation (SPO2) was monitored using a pulse oximeter (Masimo Radical, Masimo) positioned on a lower hind leg.

Lambs were randomized to Control (n = 6), or one of two recruitment strategy groups (Fig. 1) after the initial 15-min IPPV stabilization period. The Sigh group (n = 5) received five sigh manoeuvres, during which Pao was increased to 25 cmH2O for 1 min at 5-min intervals. A sigh Pao of 25 cmH2O was chosen because initial studies identified significant improvements in oxygenation at this pressure (33). The Ramp group (n = 6) received increments in Pao of 5 cmH2O at 5-min intervals to a Pao of 30 cmH2O, then 5 cmH2O reductions in Pao every 5 min to a Pao of 15 cmH2O. Controls received HFOV at a mean Pao of 15 cmH2O throughout the postnatal ventilation period. At the end of the ventilation period, Pao was reduced in all groups, including Controls, to 10 cmH2O for 5 min.

PBF waveform analysis. Changes in the contour of the PBF waveform were measured by selecting 10 consecutive cardiac cycles from each lamb at specific periods during the experiment: before birth, within the first 5 min after delivery, at 5-min intervals during HFOV in Control lambs, during each Pao increment in the Ramp group, and after each sigh in the Sigh group. Additionally, each 1-min sigh was separated into three 20-s blocks, with 10 consecutive waveforms analyzed from each block, to determine the acute effect on PBF. The waveform parameters analyzed were described previously (35): pulsatility index was calculated as (peak systolic flow – minimum flow after systolic flow)/mean peak systolic flow over five consecutive cardiac cycles.

Statistical analysis. Data are presented as means ± SE. Comparisons within groups were performed using two-way ANOVA with repeated measures (Sigmastat version 3.0, SPSS). Post hoc comparisons were performed using Holm-Sidak method. The level of statistical significance was P < 0.05 for all analyses.

RESULTS

Umbilical arterial blood gas and acid/base status at delivery were normal for all lambs (pH, 7.31 ± 0.01; PaCO2, 50.7 ± 0.7 Torr; PaO2, 28.4 ± 1.6 Torr; SaO2, 86.1 ± 2.6%). Fetal body weights were not different between groups (Control, 2.8 ± 0.2 kg; Sigh, 2.8 ± 0.1 kg; Ramp, 2.6 ± 0.1 kg).

Heart rate and carotid arterial pressures were maintained in the Control and Sigh groups, but heart rates were reduced (P < 0.05) at high Pao in the Ramp group of lambs, relative to values during the initial IPPV period. Pulmonary arterial pressures were maintained, and were not different between groups (Table 1).

Temporal change in PBF. During the postnatal ventilation period in Controls, the mean PBF decreased from 86.5 ± 3.6 to 47.4 ± 1.8 ml·min⁻¹·kg⁻¹ (P < 0.05) and was reduced further (to 37.7 ± 2.6 ml·min⁻¹·kg⁻¹) when the Pao was reduced to 10 cmH2O (Fig. 2). A similar decrease in mean PBF was observed during the recruitment period in the Sigh group (from 79.0 ± 4.3 to 38.1 ± 2.1 ml·min⁻¹·kg⁻¹; P < 0.05); but there was no further change when Pao was reduced to 10 cmH2O (Fig. 2). In the Ramp group, mean PBF decreased during the recruitment period from 72.4 ± 8.0 (at a Pao of 15 cmH2O) to 31.3 ± 2.6 ml·min⁻¹·kg⁻¹ following the return of Pao to 15 cmH2O. This was significantly lower (P < 0.05) than PBF in both the Control and Sigh groups at the same airway pressure (15 cmH2O) and persisted beyond the completion of the recruitment maneuver (P < 0.05). There was no change in mean PBF in the Ramp group when Pao was reduced to 10 cmH2O (Fig. 2).

![Fig. 1. Diagrammatic representation of Control, Sigh, and Ramp protocols showing airway opening pressures (values in cmH2O). Periods of conventional ventilation (broken lines) and high-frequency oscillatory ventilation (HFOV; solid line) are indicated. IPPV, intermittent positive-pressure ventilation.](http://jap.physiology.org/content/105/3/604.full.sgm/604/F1.giff)
Table 1. Blood gas status and arterial pressures

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<td>167 ± 10*†</td>
<td>168 ± 11*†</td>
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Values are means ± SE. Pao, mean pressure at the airway opening; SAP, systemic arterial pressure measured at the carotid artery; PAP, main pulmonary arterial pressure. ‡At completion of 15 min conventional ventilation. §After 5 min on HFOV using same Pao as during conventional ventilation. Shaded columns indicate when recruitment maneuvers were being conducted. *Significantly different from HFOV at 15 cmH2O. †Significantly different from IPPV at 15 cmH2O.

Acute effects of recruitment maneuvers on PBF. Acute changes in mean PBF did not occur during the first or second recruitment maneuvers in the Sigh group, but reductions in mean PBF did occur during subsequent sighs (sigh 3 by 9.6 ± 3.7%; sigh 4 by 14.4 ± 4.9%; and sigh 5 by 15.4 ± 5.2%; all P > 0.05; see Fig. 5). Mean PBF was not different between the periods immediately before or after each sigh (Fig. 5). In the Ramp group, decrements in mean PBF (P < 0.05) occurred, and correlated, with each stepwise increase in Pao (mean decrease in PBF 53.3 ± 5.6%; range of reduction 29.3–69.3%; see Fig. 6).

PBF waveform analysis. All PBF parameters (mean, mean systolic, mean diastolic, peak-systolic; postsystolic minimum, end-diastolic; Fig. 3, A–D) increased immediately after delivery but declined throughout the postnatal ventilation period in all groups. These changes in PBF parameters coincided with increases in pulsatility index (Fig. 3F), which is a measure of downstream resistance to blood flow. The PBF pulse amplitude was similar throughout the protocol in control lambs but was significantly reduced in Ramp lambs during the recruitment maneuver, suggestive of cardiovascular constraint. Interestingly, the pulse amplitude in Sigh lambs was significantly decreased from control after the fourth and fifth sigh maneuver (P < 0.05 for both; Fig. 3E). Pulse amplitude was not different between the groups when Pao was reduced to 10 cmH2O.

Negative values of postsystolic minimum PBF, reflecting retrograde flow and right-to-left shunting through the DA, were observed in Controls when Pao was reduced to 10 cmH2O at the end of the control ventilation period and in four of six lambs in the Ramp group at high Pao during recruitment maneuvers (Fig. 3D). In addition, each of these four lambs, and one other lamb (also from the Ramp group), had a mismatch between the SpO2 (measured on the hind limb) and SaO2 at higher Pao, further indicating left-to-right shunting through the DA. The contour of the PBF waveform in Ramp group lambs ventilated with a high Pao had negative flows during the beginning of diastole, similar to that seen in the fetus (Fig. 4); these negative flow during diastole persisted, despite subsequent reductions of Pao (Figs. 3D and 4).

Oxygenation. SaO2 was maintained throughout the recruitment period in Controls, gradually declined (P = 0.15) in the Sigh group, but increased in the Ramp group (P < 0.05 vs. Control and Sigh groups; Fig. 7A). The OI gradually increased, reflecting a deterioration of oxygenation during the postnatal ventilation period in Controls (from 24.9 ± 3.9 to 33.0 ± 6.5; P < 0.05) (Fig. 7B), but did not change during the recruitment period in the Sigh group. On the other hand, the OI decreased (P < 0.05), reflecting an improvement in oxygenation, in the Ramp group during the recruitment period. Although the SpO2 tended to decrease when the Pao was reduced to 10 cmH2O, the OI did not change in any group.

Fig. 2. Mean pulmonary blood flow (PBF) measured through the left main pulmonary artery relative to body weight in Control (shaded circles), Sigh (filled circles), and Ramp (open circles) groups. Data are means ± SE. *P < 0.05 Ramp vs. Control and Sigh. #P < 0.05 vs. Control. Dark shaded region represents decrease in mean airway pressure (Pao) below starting Pao to 10 cmH2O.
In five of six lambs in the Ramp group, SpO₂ (measured at the hind limb) was lower than SaO₂ (measured from carotid arterial blood) at high Pao (\(P < 0.001; \) Fig. 8); this did not occur at lower Pao or in Control or Sigh groups.

**DISCUSSION**

HFOV is an increasingly common mode of ventilatory support for neonates with respiratory failure despite the fact that cardiovascular effects of this ventilatory modality in neonates are not completely understood. Ventilation immediately following a lung volume recruitment strategy improves arterial oxygenation and is commonly referred to as “ventilation on the deflation limb of the pressure-volume curve.” However, we have shown that, despite improving the OI, progressive step-wise increases in airway pressure to recruit lung volume cause persisting reductions in PBF and can restore right-to-left shunting in the pulmonary circulation of preterm neonates. The effect on PBF of sustained increases in airway pressure of 1-min duration (sigh maneuvers) during HFOV was substantially less than that of the ramp maneuver. Although the finding that PBF is intrinsically linked to mean airway pressure at mouth opening is consistent with previous findings in newborns (10, 34) and adults (43, 44), the finding that it persists after airway pressures have been restored appears unique to the immature lung.

We have shown that diastolic components of the PBF waveform are sensitive indicators of blood flow changes caused by increasing airway pressure during HFOV as well as during IPPV (31). During diastole, PBF is largely determined by PVR, which is responsible for generating the backward-travelling compression and expansion waves that reflect off the pulmonary vascular bed and influence the PBF waveform during middle-to-late systole in the fetus (14). Other influences on PBF during diastole include the elastic recoil of the main pulmonary arteries as well as flow through the DA. The latter is determined by the pressure gradients that exist across this vessel, which is influenced by downstream resistance in both the pulmonary and systemic circulations. Since changes to PBF during diastole in this study were very sensitive to sustained increases in Pao, particularly in the Ramp group of lambs, it is likely that changes in PVR were a major contributor to the observed changes in PBF caused by increases in Pao. Systolic flow was also significantly influenced by increases in Pao causing reductions in both peak- and end-systolic PBF compared with the initial conventional ventilation period. During systole, PBF must be influenced by ventricular contractility as well as the stiffness of the main pulmonary trunk, the resistance to flow through the DA (including downstream resistance in the systemic circulation), and downstream PVR (40). How these factors combined to influence systolic PBF in our study is unknown, but most could play a role, especially those influenced by alterations to Pao during HFOV. Consequently, we believe that diastolic PBF more accurately reflects PVR and that monitoring it, in addition to
blood oxygenation, may help to determine optimal Pao for neonates treated with HFOV.

Increases in airway pressure in the Ramp group reduced heart rate, systemic (carotid) arterial pressure (Table 1), systolic pulmonary waveform variables, and PBF pulse amplitude, suggestive of impaired cardiac function. High airway pressure can modify PVR, and thus right ventricular afterload, in a number of ways (27). Critically, as Pao is increased and total lung capacity is approached, PVR increases due to compression of intra-alveolar vessels. This increases right ventricular afterload, which, combined with re-establishment of right-to-left shunting, results in decreased pulmonary venous return and inflow to the left ventricle; subsequently, left ventricular output is compromised. The result is impaired cardiac output and transient hypotension, as evidenced by a reduction in heart rate and a fall in carotid arterial pressure; this may signify a fall in cerebral perfusion, as has been shown by others (16, 28).

Furthermore, peak systolic flow, mean systolic pulse flow, and PBF pulse amplitude were all decreased at high Pao (Fig. 6, A and C) in the Ramp group, indicating that right-ventricular output is also reduced by this maneuver, perhaps due to direct mechanical constraint on the heart, further exacerbating the influence of PVR on cardiac output.

In the mature lung, the decrease in PBF and increase in PVR caused by increasing airway pressure is thought to be primarily due to an elevation in alveolar pressure above capillary pressure, resulting in compression of peri-alveolar capillaries (11, 12, 26, 32, 34, 39, 42, 46). In support of this concept, our previous study showed that changes in positive end-expiratory pressures during conventional ventilation correlated with changes to PVR and PBF in preterm lambs (34). The correlation between PBF and Pao during ramp recruitment suggests the same mechanism occurs during HFOV. Our data support those from a previous study showing that the interaction between the heart and lungs during HFOV is largely mediated by airway pressure (44). The correlation between Pao and PBF is consistent with findings from other studies in immature fetal sheep, showing correlation between intraluminal pressure and PBF: during changes in lung liquid volumes; during acute changes in intraluminal pressure associated with Valsalva-like maneuvers; and during fetal breathing movements (36, 44, 48). It is possible that increased vasoconstriction of muscularized arterioles also contributes to the Pao-related reduction in PBF (11, 21, 24, 45, 46), but the improved oxygenation that occurs...
with increasing Pao would be expected to oppose increased vasoconstrictor activity (21, 42, 43) and facilitate vasodilation. Failure of PBF to increase when Pao was reduced after the recruitment maneuvers, even after the Pao was reduced to 10 cmH2O, indicates that these procedures have persisting effects on PBF. This finding is consistent with suggestions of a volume hysteresis effect of increasing airway pressure on PBF (11, 34), but the mechanisms involved are unknown. It is possible that recruitment maneuvers cause relatively greater over-distension of the already-opened and aerated alveolar units rather than recruiting collapsed units. This would favor capillary collapse in overinflated regions and divert blood flow to atelectatic areas or promote increased right-to-left shunting through the DA (47). This speculation is supported by findings in normal and surfactant-deficient newborn piglets, which showed lung overdistension at high Pao during HFOV (17, 49). Whatever the cause, our findings indicate that sustained reductions in PBF, pulmonary hypertension, and right-to-left shunting of blood are possible consequences of lung volume recruitment maneuvers in very preterm infants during HFOV. Sighs of 1 min in duration caused only minor changes in PBF, which returned to control values after the sigh.

Restricting lung volume recruitment maneuvers to <1 min in duration may limit the detrimental effect that they have on the pulmonary vascular bed. A further consideration is that the lower Pao used for the sighs (25 cmH2O) was insufficient to cause sustained overdistension of alveoli or to elicit a pulmonary “vasomotor” response. If the decrease in PBF caused by high positive-pressure ventilation is due to capillary compression, subatmospheric extrathoracic pressure ventilation (negative pressure ventilation) may be able to recruit lung volumes, reduce lung injury, and improve oxygenation, as has been recently shown (15), without compromising PBF.

The ramp recruitment maneuver used in this study improved oxygenation and arterial oxygen saturation, consistent with findings in preterm neonates and adult animals receiving similar recruitment strategies during HFOV (2, 5, 19, 31, 41). Although the correlation between arterial oxygenation and mean airway pressure has been well established (29), the influence on PBF and the negative correlation between Pao and PBF have not. This apparent incongruity of PBF and oxygenation has been observed previously during IPPV of preterm neonatal lambs (34). It may be due to a reduction in intrapulmonary shunting (caused by perfusion of nonventilated alveoli) leading to an improvement in the ventilation-to-perfusion ratio and to an increase in gas-exchange efficiency. The increase in oxygenation may appear to be a desirable outcome in the short term, but the long-term consequences of reduced PBF are unknown: they may be detrimental for the developing pulmonary vascular bed. However, the progressive increase in OI we observed in control lambs suggests progressive collapse of the lung and a worsening ventilation-perfusion ratio, confirming that recruitment maneuvers are vital for maintenance of oxygenation during HFOV.

All lambs were ventilated with a FIO2 of 0.4, which was not varied during the recruitment maneuvers despite significant improvements to systemic oxygenation at high Pao levels. It is interesting that preductal Sao2, measured in the carotid artery, correlated with postductal SpO2, measured on the hind limb of the lamb, except during high Pao recruitment maneuvers. This likely indicates increased right-to-left shunting of blood through the ductus during (and after) high Pao maneuvers,
resulting in an oxygenation differential between pre- and post-ductal circulations. Although coincident vasoconstriction of blood vessels within the skin of the hind limb could account for the observed oxygenation differential, the development of the difference was associated with re-establishment of negative PBF during diastole in four of six lambs in the Ramp group; the latter is indicative of DA patency (40). Consequently, we consider that our data provide evidence that sustained and inappropriately high Pao levels during recruitment procedures enhance right-to-left shunting of right ventricular blood, thereby counteracting beneficial effects of alveolar recruitment.

PBF gradually decreased in lambs within the Control and Sigh groups, which were maintained at 15 cmH2O Pao for ~1 h, similar to the changes in PBF observed previously during constant positive-pressure ventilation with 4-cmH2O PEEP (34). The mechanisms responsible are unknown but may include a gradual decrease in the release of vasodilators (e.g., bradykinins and prostaglandins) that promote pulmonary vasodilation at birth (45), a gradual increase in the proportion of overdistended regions of the lung with high vascular resistance, or a gradual deterioration of preterm lambs born without exposure to antenatal glucocorticoids, surfactant administration, or fluid administration. A recent study suggests that the gradual reduction of blood flow through the left main pulmonary artery can also result from a decrease in the contribution of left-to-right flow through the DA, that is, blood flowing from the systemic circulation into the pulmonary circulation via a patent DA (4). Thus the progressive decline in PBF in Control lambs may, in part, reflect a progressive closure of the DA. In the preterm lamb, left-to-right shunting is established almost immediately at the onset of air-breathing, contributing substantially to the increase in PBF at birth. Ductal flow progressively decreases over the first hour, becoming nonpulsatile and contributing little to PBF. This process takes much longer in human neonates and is likely due to species developmental differences. However, these findings also confirm that caution should be used when using high Pao during recruitment maneuvers since the resumption of right-to-left shunting maybe a contributing factor to the maintenance of a patent DA.

In conclusion, we have demonstrated that lung volume recruitment maneuvers using high Pao during HFOV can have significant, long-lasting adverse effects on pulmonary hemodynamics in very premature lambs. In particular, high airway pressures in the Ramp group were associated with marked reductions in PBF that were not restored when Pao was lowered at the end of the recruitment maneuver. In four of six lambs, this caused fetal PBF characteristics to re-emerge, including right-to-left shunting through the DA. The mechanisms by which increases in Pao cause sustained changes in PBF are currently unknown. Analysis of the PBF waveform is a sensitive indicator of pulmonary homeostasis in the preterm neonate during HFOV, confirming our previous findings during conventional ventilation. Further studies are required to determine whether the failure to restore PBF to initial values after recruitment maneuvers are a consequence of permanent changes to the pulmonary vasculature.

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