0031-3998/92/3104-0349$03.00/0
PEDIATRIC RESEARCH

Vol. 31, No. 4, 1992
Printed in U.S.A.

The Influence of Pulsatile Perfusion on the Vascular Properties of the Newborn Lamb Lung

E. H. JOHNSON, S. H. BENNETT, AND B. W. GOETZMAN

Division of Neonatology, Department of Pediatrics, University of California, Davis, California 95616

ABSTRACT. It is not known how the mode of flow alters the resistance properties of the newborn pulmonary circulation. Therefore, we compared the pressure responses of the perfused left pulmonary circulation of 16 newborn lambs with step changes in either pulsatile or steady flow. The slope of the pressure-flow curve differed significantly according to mode of perfusion. The slope of the pressure-flow curve was 0.125 ± 0.115 mm Hg·mL^{-1}·kg·min for pulsatile flow and 0.484 ± 0.350 mm Hg·mL^{-1}·kg·min for steady flow perfusion ($p < 0.05$). The intercept pressure at zero flow was similar for both modes of flow, being 21.3 ± 4.9 mm Hg for pulsatile flow compared with 23.8 ± 11.3 mm Hg for steady flow perfusion. All perfusions with either mode of flow demonstrated flow-dependent decreases in pulmonary vascular resistance. However, the decreases in resistance were greater for pulsatile than for steady flow perfusion. In addition, the steady-perfused lungs demonstrated a significantly greater left lung wet/dry weight ratio than either the left lungs of pulsatile-perfused animals or the intact left lungs of 13 control animals not undergoing experimental perfusion ($p < 0.05$). Thus, the mode of flow appears to play a major role in modulating the magnitude and distribution of pulmonary vascular resistance. This factor must be considered when interpreting the physiologic significance of hemodynamic experiments. (*Pediatr Res* 31: 349–353, 1992)

Abbreviations

LA, left atrium
LPA, left pulmonary artery
MPA, main pulmonary artery
BP, blood pressure
P_{pa}, pulmonary artery pressure
P_{la}, left atrial pressure
R_s, slope of pressure-flow relationship
P_{alv}, alveolar pressure

Much of our understanding of the factors that control the pulmonary circulation has evolved from studies using nonpulsatile flow to perfuse isolated lung preparations using less than physiologic flow rates (1–6). Such studies support the concept that the newborn pulmonary circulation has a limited ability for recruitment and distension (7, 8). However, it is also known that the pulmonary circulation's apparent resistance to perfusion using steady flow is typically greater than that observed *in vivo* or when pulsatile pump perfusion is used (9–12). Under steady flow conditions in isolated lungs, physiologic flow rates result in pulmonary hypertension and edema formation (3, 13). This suggests that the mode of flow can influence the distribution of pulmonary vascular resistance. Therefore, the factors affecting the pressure response to increasing flow, and possibly lung edema, should differ for pulsatile and steady flow.

To determine whether blood flow and its mode can alter the resistive properties of the pulmonary circulation in the newborn, we analyzed and compared the mean pressure-flow relationships and the magnitude of edema formation in left lungs of newborn lambs that were perfused with either pulsatile or steady flow.

MATERIALS AND METHODS

Animals and surgical preparation. Newborn lambs (0–3 d of age) were blindfolded and placed on a warming pad to maintain their core temperatures between 38 and 40°C. Carotid artery catheterization, tracheostomy to provide mechanical ventilation (Baby-Bird Pediatric Ventilator, Bird Corp., Palm Springs, CA), and large-bore catheterization (12–14 F) of the right atrium via both external jugular veins were performed under α-chloralose anesthesia (50 mg/kg). Ligation of the ductus arteriosus, LA catheter placement, and ligation and cannulation of the LPA with a 12–14 F polyvinyl chloride catheter were performed via a left thoracotomy. Time from LPA ligation to the onset of artificial perfusion was limited to 5 min to avoid lung ischemia. Before placement of the LPA cannula, electromagnetic flow probes were placed on the MPA and LPA to obtain baseline flows.

The perfusion circuit (Fig. 1) consisted of a reservoir followed by valves that allowed selection of either a roller pump (PEMCO micropump; PEMCO Inc., Cleveland, OH) for steady flow or a pulsatile pump (Medical Engineering Consultants, Los Angeles, CA). Polyvinyl chloride tubing and siliconized blood chambers were used. A calibrated electromagnetic flow probe (C and C Instruments, Culver City, CA) was included in the circuit just proximal to the LPA cannula, and a precalibrated micromanometer (Camino Labs, San Diego, CA) was placed through the LPA cannula into the LPA distal to the tip of the perfusion cannula (Fig. 1).

Before initiation of artificial perfusion, the circuit was primed using heparinized fresh whole blood, 20 U/mL, from an anesthetized donor lamb. The experimental animal was given 500–800 U/kg of heparin before placement of the large-bore perfusion catheters.

The pulsatile pump was adjusted to have an upstroke time of 0.08–0.12 s and pulse rates ranging from 70–200/min. A typical pulsatile pump wave form is shown in Figure 2. The steady flow perfusion pump, when used with a depulsing chamber, resulted in no flow or pressure variations other than minor respiratory artifact. LA pressure, systemic BP, LPA pressure, LPA flow, and heart rate were continuously displayed and/or recorded on a multichanneled recorder (Gould 2200S; Gould Inc., Cleveland, OH). Arterial blood gas tensions were maintained in the normal range by changes in ventilation or fraction of inspired oxygen or by administration of sodium bicarbonate. The ventilator inspiratory pressures varied from 16 to 20 cm H_2O, and the end-

Received November 6, 1990; accepted November 15, 1991.
Correspondence: Boyd W. Goetzman, M.D., Ph.D., University of California, Davis, Division of Neonatology, TB 193, Davis, CA 95616.

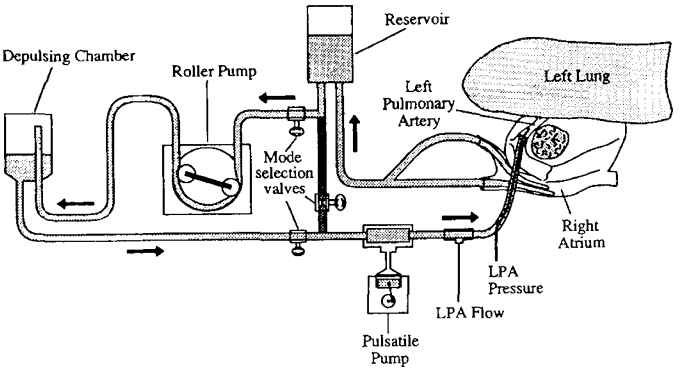

Fig. 1. Bypass circuit diagram.

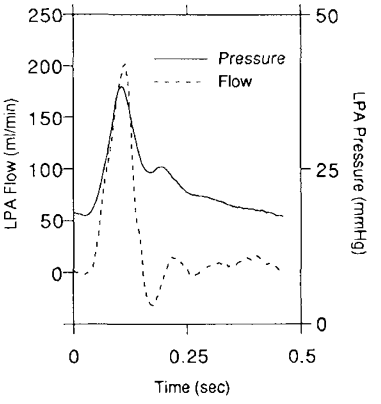

Fig. 2. Pressure and flow wave forms generated by the pulsatile pump.

expiratory pressure was always 4 cm H_2O. The ventilator rate varied from 12 to 20 min^{-1}, and the inspiratory time was maintained at 0.4 s. Once bypass was initiated, either steady or pulsatile flow to the LPA was begun and maintained for 10 to 20 min at about 10 $mL \cdot kg^{-1} \cdot min^{-1}$ before the experimental pressure and flow measurements were begun. Arterial blood gas values were measured before and after each set of pressure-flow measurements.

Experimental procedure. The procedure for obtaining the data composing the pressure-flow curve consisted of taking measurements of mean LPA pressure and mean LA pressure along with mean LPA flow at four to 10 different flow rates, which were increased stepwise for about a minute until the mean pressure reached a steady state. The pressures and flows at each steady state were then used to create pressure-flow curves over a flow range of 10 to 100 mL/kg/min. The duration of each experiment was limited to 2 h or less, at which time the anesthetized animal was euthanized with KCl. In five of the pulsatile pump perfused animals, six of the steady pump perfused animals, and 12 donor animals, the left lungs were removed at the end of the experiment and weighed before and after drying at 84°C for 48 h.

Data analysis and interpretation. The pressure and flow data for each perfusion were used to create a pressure-flow pulmonary vascular function curve. This curve was determined by plotting the pressure corresponding to each flow over the flow range studied. Each curve was characterized by a slope, R_s, and a zero flow pressure intercept, P_{int}, by calculating the least-squares regression line for the pressure-flow data over the flow range of interest (1, 3).

To examine whether the mode of perfusion affected the vascular function curves, the averages of the P_{int} and R_s for steady flow perfusion were compared with the respective averages for pulsatile flow perfusion using a two-sample *t* test. Statistical significance was taken as being a *p* value of less than 0.05. The results are reported as the mean ± SD.

To examine whether the lung perfusions resulted in edema, the wet-to-dry ratios of the left lungs of 12 donor lambs were compared with the wet-to-dry ratios of steady and pulsatile pump perfused left lungs using a two-sample *t* test with the Bonferroni correction. Thus, a *p* value of 0.025 for an individual *t* test was chosen as the level of significance to adjust for the consequences of two comparisons (14).

RESULTS

The experimental model was established in 16 newborn lambs with a mean weight of 5.9 ± 1.0 kg. The blood flows in both the MPA and LPA before cannulation and pump perfusion were measured in 10 of the animals and averaged 185 ± 49 $mL \cdot kg^{-1} \cdot min^{-1}$ in the MPA and 42 ± 11 $mL \cdot kg^{-1} \cdot min^{-1}$ in the LPA. The preperfusion and postperfusion maneuver blood gas data are presented in Table 1. The pH, arterial CO_2 tension, and arterial O_2 tension values were the same for each mode of perfusion and were not influenced by the perfusion maneuver. The mean airway pressure required to maintain these blood gases varied from 5.3 to 6.7 cm H_2O (4–5 mm Hg). This was considered to be our range of alveolar pressures, P_{alv}. The systemic BP was similar in both groups of animals before perfusion, being 56 ± 21 mm Hg for the animals in the steady flow group and 63 ± 24 mm Hg for those in the pulsatile flow group.

The systemic BP was also similar in both groups after the lungs were perfused by a given mode of flow, being 49 ± 24 mm Hg for the steady flow perfused group and 69 ± 21 mm Hg for the pulsatile flow perfused group. Examples of pressure-flow curves, each determined from single animal perfusions with either pulsatile or steady flow, are shown in Figure 3.

The average flows, pressures, slopes, and intercepts observed during the pressure-flow studies are presented in Table 2. The average intercept for steady flow (23.8 ± 11.3 mm Hg) was not different from that for pulsatile flow (21.3 ± 4.9 mm Hg). Greater R_s were observed for steady (0.484 ± 0.350 mm $Hg \cdot mL^{-1} \cdot kg \cdot min$; $n = 8$) than for pulsatile flow perfusion (0.125 ± 0.113 mm $Hg \cdot mL^{-1} \cdot kg \cdot min$; $n = 8$).

The average wet-to-dry weight ratio for the left lungs of control animals was 4.97 ± 1.13, for steady flow perfused animals it was 6.70 ± 1.50, and for pulsatile perfused lungs it was 5.75 ± 1.83. The ratio for steady flow perfused lungs was significantly greater ($p < 0.025$) than that for either the control or pulsatile perfused lungs. The wet-to-dry ratio for pulsatile perfused lungs was not statistically different from that for control lungs ($p < 0.10$).

DISCUSSION

We have shown that both the magnitude of flow and its mode influence the resistive properties of the newborn lung. Our data demonstrate that, during both pulsatile and steady flow perfusion, pulmonary vascular resistance decreases with increasing flow, *i.e.* it is flow dependent. However, with a steady mode of perfusion, the pulmonary vascular resistance was always greater than that experienced with a similar magnitude of pulsatile flow. In addition, steady perfusion was more edemagenic, suggesting that the distribution of vascular resistance was also affected by this mode. It remains to be shown whether these effects are active or passive. However, the magnitude of the changes induced by steady flow make extrapolation from studies using this mode to the *in vivo*, pulsatile state problematic.

Our results with steady flow were similar to the results of others in which pressure-flow relationships in newborn lambs were constructed using steady flow perfusion (Table 3). To extrapolate to the total lung from our studies of the left lung, we assumed that when the lamb is in the right recumbant position, the left lung receives one fourth of the total pulmonary blood flow (15). In our study, the lung was perfused under zone II conditions ($P_{pa} > P_{alv} > P_{la}$), and the mean MPA flow was similar to that observed in lambs of comparable age studies *in vivo* (16). In addition, the mean blood flow to the left pulmonary artery in

Table 1. *Arterial blood gas values, mean ± SD, before (pre) and after (post) obtaining pressure and flow data for each mode of perfusion**

	pH		$PaCO_2$		PaO_2	
Flow mode	Pre	Post	Pre	Post	Pre	Post
Steady ($n = 7$)	7.37 ± 0.04	7.34 ± 0.09	33.6 ± 5.5	37.6 ± 11.1	178 ± 78	126 ± 70
Pulsatile ($n = 8$)	7.38 ± 0.05	7.38 ± 0.08	32.5 ± 5.4	29.9 ± 7.2	210 ± 100	191 ± 79

* $PaCO_2$, arterial CO_2 tension in torr; PaO_2, arterial O_2 tension in torr (1 torr = 0.133 kPa).

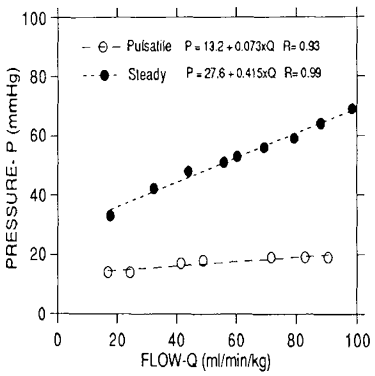

Fig. 3. Sample pressure-flow data for two different lamb lungs with different modes of perfusion. *P*, pulmonary artery pressure-left atrial pressure; *Q*, flow/kg; *R*, correlation coefficient.

our experimental group was consistent with that when unanesthetized, awake lambs were positioned in the right recumbant position (15). Interestingly, the R_s during the steady flow perfusion was similar to that in those experiments that take into account vascular tone and the nonlinear hysteresis properties of the pulmonary circulation perfused under zone III conditions ($P_{pa} > P_{la} > P_{alv}$), where it is implicitly assumed that all pulmonary vessels are recruited (17). For example, Raj and Chen (1) preconditioned lung vessels by exposing them to a nonspecific vasodilator, papaverine, in addition to using a low-viscosity perfusate. Gordon *et al.* (18) preconditioned the lungs in their study with repetitive standpipe perfusions until a pressure-flow limit was reached. Thus, for steady flow perfusion, the R_s, or incremental resistance, appears to be the same regardless of whether the lung is perfused in zone II conditions, where it is still theoretically possible for recruitment to occur, or in zone III, where further decreases in resistance must change by decreases in tone or by distension (17). Thus, Table 3 shows that the R_s for steady flow in the newborn lambs approach a constant value despite the fact that differing flow ranges and techniques were used to generate the data. By design, they may represent the minimum attainable slopes for each experimental approach. It is therefore curious that the pulsatile perfused lungs demonstrated a resistance to perfusion that was significantly less than that of steady flow perfused lung, which was theoretically fully recruited. If the differences in slope are due to differences in the level of recruitment in isolated and intact lung systems, then it may be more appropriate to examine the active and/or passive mechanisms responsible for modulating the capacity for recruitment. Furthermore, because the newborn period is associated with significant changes in pulmonary vascular resistance with increasing age, changes in vascular responses to humoral stimuli, changes in vessel structure, and increases in pulmonary blood flow, it may be possible to modulate these changes in a nonlinear way using external factors, such as flow or pressure conditioning.

If a pressure-flow relationship represents an accurate assay of the mechanical properties of the intact pulmonary circulation, it would be reasonable to expect that the same pressure-flow response curve should be obtained regardless of the mode of flow used to construct it. However, because steady and pulsatile flow modes of perfusion resulted in pressure-flow curves with different slopes, the question is raised as to which pressure response to increasing flow simulates that of the intact pulmonary circulation. This question was addressed by comparing the predicted P_{pa} with a fixed physiologic flow rate using the pressure-flow relationships from our experiment and those of others, shown in Table 3. Table 3 indicates the predicted P_{pa} response to a flow of 250 $mL \cdot min^{-1} \cdot kg^{-1}$ as calculated from the corresponding regression equations. For purposes of comparison, reported values of cardiac output vary from 250–425 $mL \cdot min^{-1} \cdot kg^{-1}$, whereas the P_{pa} range from 12 to 35 mm Hg in the first week of postnatal life in the lamb (19, 20). Thus, it can be seen that the steady flow models, including ours, tend to predict higher pressures, consistent with pulmonary hypertension in structurally normal vessels, whereas our pulsatile perfused model predicts pressures that are consistent with normal newborn cardiovascular characteristics.

The factor most likely responsible for our finding of lower R_s under pulsatile conditions is that of a greater capacity for vascular recruitment with increasing flow. In theory, the increased slope under steady flow conditions can be explained by a vascular network with vessels that remain occluded when flow is increased from low flow to a higher flow (21). Under these circumstances, the occurrence of edema can be explained as a consequence of the increased hydrostatic pressure experienced by the vessels that are being perfused (3, 13, 22). This inference appears to be independent of whether the pressure-flow curve is interpreted in terms of a Starling resistor or whether it is interpreted as a vascular network of distensible vessels (17, 23, 24). In our experiments, if the pulmonary circulation is viewed as a Starling resistor in zone II conditions, the decrease in resistance seen with pulsatile flow could be explained by vascular recruitment because the critical pressure, as indicated by the intercept pressure of the pressure-flow relationship, was greater than the P_{la}. Alternatively, the vascular recruitment to flow can be enhanced if the vessels of a network possess nonlinear distensibility (13). A vascular distensibility that is nonlinear not only implies that the relationship between transmural pressure and vessel diameter will not be a straight line (25), but also implies that the pressure-diameter relationship and the resulting pressure-flow relationship of a vascular bed display hysteresis (26). That is, both the diameter and the vessel distensibility are functions of the magnitude and rate of change of stress, such as pressure or volume flow, and will be dependent upon the previous stress history (27). Therefore, repetitive pulsations may recruit more vessels and vascular volume than steady flow at similar mean pressure (26, 28–30).

Table 2. *LPA pressure and flow data and the parameters determined from the pressure-flow curves**

Flow mode	Q (mL/min/kg)	P_{pa} (mm Hg)	P_{la} (mm Hg)	R_S (mm Hg/mL/min/kg)	P_{int} (mm Hg)
Steady ($n = 8$)	48.5 ± 24.3	39.2 ± 12.8	1.0 ± 0.7	0.484 ± 0.35†	23.8 ± 11.3
Pulsatile ($n = 8$)	42.6 ± 25.1	24.5 ± 7.0	1.2 ± 0.7	0.125 ± 0.113	21.3 ± 4.9

* Values expressed as mean ± SD. Q, flow; P_{int}, intercept pressure.

† Significant difference from pulsatile mode, $p < 0.05$.

Table 3. *Prediction of P_{pa}, at a flow of 250 mL/min/kg from pressure-flow relationships reported for newborn lambs**

Study	Age (d)	R_S (mm Hg/L/min/kg)	$P_{int} + P_{la}$ (mm Hg)	P_{pa} (mm Hg)
Pulsatile (current study)	0–3	0.031	21.3	29.1
Steady				
Current study	0–3	0.121	23.8	54.1
Gordon *et al.* (18)	2–4	0.110	8.2	36.7
Raj and Chen (5)				
No tone	8	0.112	15.7	43.7
Tone	8	0.187	16.9	63.6

* P_{int}, intercept pressure of pressure-flow relationship. R_s for whole lung was estimated from average intercepts, P_{int}, and average slope, R_s, divided by 4; $P_{pa} = 250 \times R_s + (P_{int} + P_{la})$.

In this regard, pulse wave-form characteristics such as the fast upstroke and the slower diastolic decay of the normal pulse wave may prove to be important factors in vascular recruitment.

The characteristics of phasic changes in BP during pulsatile flow are considered to be responsible for mechanically altering the pulmonary vasculature (31). Chronic changes in vessel wall tension have been shown to cause vascular mesenchymal cells to produce collagen, elastin, or smooth muscle, and hemodynamic drag causes changes in vascular caliber (31). More acute changes can probably be induced in the vasculature as well. Endothelial cells can release or modify mediators of vasoreactivity such as endothelin, endothelium-derived relaxing factor, prostacyclin, platelet activating factor, and others (32, 33). Pulsatile pressure changes have been shown to stimulate release of some of these agents (34, 35). Such responses may also be responsible for at least part of the differences that we observed between pulsatile and steady flow perfusion.

Studies in adult dogs support our findings of higher vascular resistance and more edema formation during steady flow perfusion than during pulsatile perfusion (9, 10). In one of these reports, nephrectomy, autonomic nervous system blockade, carotid sinus denervation, and bilateral vagosympathetic nerve section did not alter these responses (9). The mechanisms responsible for the observed differences in edema production are therefore unclear. Vessel permeability changes due to differences in blood-borne substances between modes of perfusion are not a likely explanation for our edema differences, inasmuch as the circuits for each mode were essentially the same. A more likely explanation is that differences in the longitudinal distribution of resistance, and therefore microvascular pressures, were induced by the different modes of perfusion. Steady flow conditions possibly resulted in higher microvascular hydrostatic pressure and, thus, greater edema formation.

In our attempt to focus on newborns, we studied only lambs from 0 to 3 d old. Even so, we recognize that this sample may not be representative of the time-dependent pressure and flow patterns observed immediately after birth (33, 36). Other studies often classify older animals ranging from 4 to 16 d of age as "newborns" (3, 5, 6, 37, 38). Results from animals with this larger range of older ages could obscure findings because of inherent variability. In addition, they may not be applicable to younger animals because of the age-related pulmonary vascular changes mentioned above.

One advantage of our experimental model, in which the perfusate circulates through the remainder of the body, is the deactivation of humoral substances produced by the lung (39). On the other hand, there is a major source of cellular blood elements in our system. Preliminary studies in our model show progressive leukopenia similar to that found by Zach *et al.* (40) during extracorporeal membrane oxygenation in human newborns. These cellular elements may play a role in determining differences in pulmonary vascular responses (2, 4, 38, 39). Other factors related to establishing the perfusion model may also be important. In related studies, the reported ischemia time, the time from cessation of normal perfusion to the time of onset of artificial perfusion, varies from 5 to 45 min (1, 3–6, 41). To avoid undesirable effects of such prolonged ischemia, we restricted time from LPA ligation to reperfusion to less than 5 min. However, even this short time allows the intravascular volume to change while there is no flow and the transvascular pressure is low.

The advent of cardiopulmonary bypass and organ transplantation has stimulated studies comparing pulsatile and steady flow perfusion in other organs. Donor organ viability is prolonged by pulsatile perfusion before transplantation (42–44). In the majority of such studies, vascular resistance increases more dramatically in response to steady flow perfusion (9, 11, 42, 45, 46). Also, lymph flow and edema increase more during steady flow than during pulsatile flow (12, 42, 45). Differences in hormonal responses between pulsatile and steady flow perfusion, including those to catecholamines, renin, antidiuretic hormone, prostaglandins, thyrotropin-releasing hormone, and cortisol, have been reported (11, 42, 45, 47, 48). Their physiologic importance deserves further study, and they could have clinical implications for infants undergoing cardiopulmonary bypass.

Conclusion. The mode of perfusion affects the magnitude, and probably the distribution, of the resistive properties of the pulmonary circulation. Flow dependence of resistance and edema formation are affected. Our analysis raises questions about the assumption of a fully recruited pulmonary vasculature during steady flow perfusion under zone III conditions. Furthermore, under typical experimental conditions, the mechanical properties of the *in vivo* pulmonary vasculature cannot be accurately predicted from steady flow experiments.

Speculation. Pulsatility of pressure and flow are important in determining both active and passive responses of the pulmonary vascular bed. Whether the capacity of the neonatal pulmonary circulation for recruitment is modulated by these factors requires further investigation. Learning how and where these mechanical factors are transduced into these responses may allow us to understand vascular remodeling and certain pathologic conditions of the transitional circulation, such as pulmonary hypertension in the newborn, as well as pulmonary edema.

Acknowledgment. The authors thank Jay Milstein and Carolyn Getman for their advice and technical assistance in the completion of these studies.

REFERENCES

1. Raj J, Chen P 1986 Micropuncture measurements of microvascular pressures in isolated lamb lungs during hypoxia. Circ Res 59:398–404
2. Patterson G, Rock P, Mitzner W, Adkinson Jr N, Sylvester J 1985 Effects of imidazole and indomethacin on fluid balance in isolated sheep lungs. J Appl Physiol 58:892–898
3. Raj J, Chen P 1987 Effect of edema on segmental vascular resistance in isolated lamb lungs determined by micropuncture. Circ Res 61:236–243
4. Krausz M, Utsunomiya T, Levine L, Dunham B, Shepro D, Hechtman H 1982 Adverse effects of prostacyclin used to perfuse isolated lung lobes. Am J Physiol 242:H745–H750
5. Raj J, Chen P 1986 Microvascular pressures by micropuncture in isolated perfused lamb lungs. J Appl Physiol 61:2194–2201
6. Fike C, Hansen T 1987 Hypoxic vasoconstriction increases with postnatal age in lungs from newborn rabbits. Circ Res 60:297–303
7. Tod ML, Yoshimura K, Rubin L 1991 Pulmonary vascular distensibility of arterial, middle, and venous regions in newborn lambs. J Appl Physiol 70: 1315–1322
8. Pitt BR, Lister G, Davies P, Reid L 1987 Correlation of pulmonary ACE activity and capillary surface area during postnatal development. J Appl Physiol 62:2031–2041
9. Mandelbaum I, Burns W 1965 Pulsatile and nonpulsatile blood flow. JAMA 191:657–660
10. Clarke C, Kahn D, Dufek J, Sloan H 1968 The effects of nonpulsatile blood flow on canine lungs. Ann Thorac Surg 6:450–457
11. Wilkens H, Regelson W, Hoffmeister F 1962 The physiologic importance of pulsatile blood flow. N Engl J Med 267:443–446
12. Mandelbaum I, Berry J, Silbert M, Burns W, Rothe C 1965 Regional blood flow during pulsatile and nonpulsatile perfusion. Arch Surg 91:771–774
13. Bshouty Z, Ali J, Younes M 1988 Effect of tidal volume and PEEP on rate of

edema formation in *in situ* perfused canine lobes. J Appl Physiol 64:1900–1907
14. Ware J, Mosteller F, Ingelfinger J 1986 P values. In: Balier III JC, Mosteller F (eds) Medical Uses of Statistics. New England Journal of Medicine Books, Waltham, MA, pp 149–169
15. Lock J, Hamilton F, Luide H, Coceiani F, Olley P 1980 Direct pulmonary vascular responses in conscious newborn lambs. J Appl Physiol 48:188–196
16. Tripp M, Drummond W, Heyman M, Rudolph A 1980 Hemodynamic effects of pulmonary artery infusion of vasodilators in newborn lambs. Pediatr Res 14:1311–1315
17. Mitzner W 1983 Resistance of the pulmonary circulation. Clin Chest Med 4:127–137
18. Gordon JB, Tod ML, Wetzel RC, McGeady ML, Adkinson Jr NF, Sylvester JT 1988 Age-dependent effects of indomethacin on hypoxic vasoconstriction in neonatal lambs. Pediatr Res 23:580–584
19. Schrieber M, Heyman M, Soifer S 1987 The differential effects of leukotriene C4 and D4 on the pulmonary and systemic circulations in newborn lambs. Pediatr Res 21:176–182
20. Juratsch C, Emmaniolides G, Thiebeault D, Baylen B, Jengo J, Laks M 1980 Pulmonary arterial hypertension induced by distension of the main pulmonary artery in conscious newborn, young and adult sheep. Pediatr Res 14:1332–1338
21. Bshouty Z, Younes M 1990 Distensibility and pressure-flow relationship of the pulmonary circulation. II. Multibranched model. J Appl Physiol 68:1514–1527
22. Homik LA, Bshouty Z, Light RB, Younes M 1988 Effect of alveolar hypoxia on pulmonary fluid filtration in *in situ* dog lungs. J Appl Physiol 65:46–52
23. Mitzner W, Huang I 1987 Interpretation of pressure-flow curves in the pulmonary vascular bed. In: Will J, Dawson C, Weir E, Buckner C (eds) The Pulmonary Circulation in Health and Disease. Academic Press, Orlando, FL, pp 215–230
24. Mitzner W, Chang HB 1989 Hemodynamics of the pulmonary circulation. In: Chang HK, Paiva M (eds) Respiratory Physiology: An Analytical Approach. Marcel Dekker, New York, pp 561–631
25. Bsouty Z, Younes M 1990 Distensibility and pressure-flow relationship of the pulmonary circulation. I. Single-vessel model. J Appl Physiol 68:1501–1513
26. Beck K, Hildebrandt J 1983 Adaptation of vascular pressure-flow-volume hysteresis in isolated rabbit lungs. J Applied Physiol 54:671–679
27. Dobrin P 1978 Mechanical properties of arteries. Physiol Rev 58:397–460
28. Fishman A 1963 Dynamics of the pulmonary circulation. In: Hamilton W, Dow P (eds) Handbook of Physiology: Circulation. American Physiological Society, Washington, DC, pp 1695–1699
29. Sarnoff S, Berglund E 1952 Pressure-volume characteristics and stress relaxation in the pulmonary vascular bed of the dog. Am J Physiol 171:238–244
30. Gregory T, Newell J, Hakim T, Levitzky M, Sedransk N 1982 Attenuation of hypoxic vasoconstriction by pulsatile flow in dog lungs. J Appl Physiol 53:1538–1588
31. Rodbard S 1974 Biophysical factors in vascular structure and caliber. In: Schettler G, Weizel A (eds) Atherosclerosis III. Proceedings of the Third International Symposium, pp 45–65
32. Vane J, Anggard E, Botting R 1990 Mechanisms of disease: regulatory functions of the vascular endothelium. N Engl J Med 323:27–36
33. Leffler C, Hessler J, Green R 1984 Onset of breathing at birth stimulates pulmonary vascular prostaglandin synthesis. Pediatr Res 18:938–942
34. Piper P, Vane J 1971 The release of prostaglandins from the lung and other tissues. Ann NY Acad Sci 180:363–385
35. Bhagyalakshmi A, Frangos J 1989 Mechanism of shear-induced prostacyclin production in endothelial cells. Biochem Biophys Res Commun 158:31–37
36. Riemenschneider T, Brenner R, Mason D 1981 Maturational changes in myocardial contractile state of newborn lambs. Pediatr Res 15:349–356
37. Custer J, Hales C 1986 Chemical sympathectomy decreases alveolar hypoxic vasoconstriction in lambs but not in sheep. J Appl Physiol 60:32–37
38. Hansen T, Le Blanc A, Gest A 1985 Hypoxia and angiotensin II infusion redistribute lung blood flow in lambs. J Appl Physiol 58:812–828
39. Said S 1982 Metabolic Function of the Pulmonary Circulation. Circ Res 50:325–333
40. Zach T, Steinhorn R, Georgieff M, Mills M, Green T 1990 Leukopenia associated with extracorporeal membrane oxygenation in newborn infants. J Pediatr 116:440–444
41. Gordon J, Hortop J, Hakim T 1989 Developmental effects of hypoxia and indomethacin on distribution of vascular resistance in lamb lungs. Pediatr Res 26:325–329
42. Mavroudis C 1978 To pulse or not to pulse. Ann Thorac Surg 25:259–271
43. Toledo-Pereyra L, Northrup W, Humphrey E, Najarian J 1975 Maintenance of lung viability for transplantation after long periods of hypothermic perfusion. J Surg Res 18:99–106
44. Barber WH, Deierhoi MH, Phillips MG, Diethelm AG 1988 Preservation by pulsatile perfusion improves early renal allograft function. Transplant Proc 20:865–868
45. Hickey P, Buckley M, Philbin D 1983 Pulsatile and nonpulsatile cardiopulmonary bypass: review of a counterproductive controversy. Ann Thorac Surg 36:720–737
46. Jacobs L, Klopp E, Seamone W, Topaz S, Gott V 1969 Improved organ function during cardiac bypass with a roller pump modified to deliver pulsatile flow. J Thorac Cardiovasc Surg 58:703–712
47. Taylor K, Wright G, Reid J, Bain W, Caves P, Walker M, Grant J 1978 Comparative studies of pulsatile and nonpulsatile flow during cardiopulmonary bypass II. The effects on adrenal secretion of cortisol. J Thorac Cardiovasc Surg 75:574–578
48. Taylor K, Wright G, Reid J, Bain W, Caves P, Walker M, Grant J 1978 Comparative studies of pulsatile and nonpulsatile flow during cardiopulmonary bypass III. Response of anterior pituitary gland to thyrotropin-releasing hormone. J Thorac Cardiovasc Surg 75:579–584