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Response of the Pulmonary Vasculature to Hypoxia and H^+ Ion Concentration Changes *

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Considerable controversy regarding the effects of hypoxia on the pulmonary vasculature has arisen over the past few decades. The literature has been extensively reviewed by Fishman (1), and it is now generally accepted that hypoxia is a pulmonary vasoconstrictor. Much of the controversy has centered around the interpretation of a small elevation of pulmonary arterial pressure in the face of an increase in cardiac output related to the hypoxic stimulus. Some investigators calculated a small increase of pulmonary vascular resistance, whereas others could not confirm this observation. Most studies were performed in adult animals, or in adult humans, but more recently attention has been directed to hypoxic responses in the newborn animal, in view of the greater responsiveness of the pulmonary vasculature at this age.

The relationship between the degree of pulmonary vascular response and the level of hypoxia has received only little attention, and usually a constrictor response to a single low oxygen gas inhalation has been reported. Recently Thilenius, Hoffer, Fitzgerald, and Perkins (2) attempted to relate pulmonary vascular resistance change to the level of inspired gas oxygen tension, but no obvious relationship could be demonstrated. Liljestrand (3) in 1958 suggested that the pulmonary vascular response to hypoxia may be related to the production of local H^+ ion concentration changes in the lung. More recently Enson and associates (4) described a relationship between the response to hypoxia and the level of H^+ ion concentration.

The purpose of the present study was *1*) to attempt to delineate the effects of varying degrees of hypoxia induced by breathing low oxygen gas mixtures on the pulmonary vasculature of the newborn calf; *2*) to study possible interrelationships between pulmonary vascular response, hypoxia, and H^+ ion concentration; *3*) to assess the mechanism of the hypoxic response; and *4*) to study the general hemodynamic effects of hypoxia in the newborn animal.

Methods

Naturally born Holstein calves aged 9 to 36 hours were anesthetized with sodium Pentothal in doses of 15 to 20 ml of a 2.5% solution given intravenously. An endotracheal tube with an inflatable cuff was inserted perorally, and anesthesia was then maintained with a gas mixture containing ½ to 1% Fluothane and approximately 30% oxygen and 70% nitrous oxide. Spontaneous breathing was first allowed, while an incision was made through skin and muscle down to parietal pleura in the fourth left intercostal space. Positive pressure breathing was then administered with a Harvard respiratory pump by using a tidal volume of 350 to 500 ml and a frequency of 16 to 18 per minute. The expiratory tube from the pump was placed under 2 to 3 cm of water to slightly elevate endexpiratory pressure and so help to maintain expansion of the lungs with the chest open.

The ductus arteriosus was isolated and ligated twice with heavy suture material. An electromagnetic flowmeter probe was placed around the main pulmonary artery after minimal dissection. A polyvinyl tube with several side openings and a sealed tip was placed in the left atrium and the main pulmonary artery by direct puncture into these structures. Another catheter was passed through the internal mammary artery into the aorta. In two animals a multiple side-hole catheter was passed through a small branch of the middle pulmonary vein into the main pulmonary vein for sampling and pressure recording. The pericardium was closed; the chest was closed in layers, and the flowmeter connections and catheters were exteriorized. Air and fluid were carefully removed from the pleural cavity. A polyvinyl catheter was then passed through a hind-leg vein into the inferior

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TABLE I

*Effects of high and low oxygen concentrations in inspired air on pulmonary arterial pressure, pulmonary blood flow, and pulmonary vascular resistance at varying levels of blood H^+ ion concentration**

Calf	Age	Time	Oxygen in inhaled gas	Pressures: Aorta S	Aorta D	Aorta M	PA S	PA D	PA M	LA M	Pulmonary blood flow	Pulmonary vascular resistance	P_{O_2}	P_{CO_2}	pH
			%	mm Hg							L/minute	mm Hg/L/minute	mm Hg		
Calf no. 1 (12 hours)		7:21	50	180	125	153	89	27	50	8	3.9	10.8	245		7.19
Buffer infusion		7:25	50	165	115	145	88	25	50	9	4.0	10.2	260	28	7.23
Buffer infusion		7:37	50	145	110	130	88	27	50	9	4.8	8.1	260	26	7.29
		7:45	50	150	115	130	90	27	55	11	4.4	10.0	250	21	7.25
		8:02	10	160	120	130	100	40	60	6	3.1	17.5	24	34	7.21
		8:09	10	137	105	120	110	45	75	4	2.9	24.5	16	34	7.19
		8:19	50	145	115	129	75	25	40	4	2.8	12.8	270	37	7.19
Buffer infusion		8:26	10	160	120	125	90	27	50	3	2.9	16.3	14		7.27
Buffer infusion		8:30	10	105	55	65	97	30	58	8	4.8	10.4	11	23	7.34
Lactic acid infusion		8:36	10	140	95	115	125	45	85	8	3.8	20.3	20		7.19
		8:46	100	145	110	125	83	28	50	8	3.3	12.7	600	38	7.18
Calf no. 2 (10 hours)		5:26	100	90	45	60	68	15	40	11	6.6	4.4	434	15	7.42
Buffer infusion		5:30	10	95	60	75	63	20	40	13	6.1	4.4	18	16	7.38
		5:37	100	110	75	95	68	23	43	13	6.3	4.8	400	21	7.32
		5:47	10	125	90	110	100	40	63	12	6.6	7.5	18	22	7.33
		5:55	100	150	105	125	78	20	47	13	6.8	5.0	420		7.36
Lactic acid infusion		5:57	100	145	100	120	80	18	45	13	5.2	6.2	450	22	7.29
		6:10	100	155	105	125	88	20	48	11	5.2	7.1	450		7.28
Lactic acid infusion		6:15	100	150	105	125	85	25	50	11	4.6	8.5	450	25	7.25
		6:21	100	140	90	115	90	20	50	11	4.6	8.5	540	28	7.25
Lactic acid infusion		6:26	100	142	90	115	95	20	55	11	4.8	9.2	420		7.22
		6:33	10	135	90	115	155	70	105	10	4.4	23.0	20	29	7.20
		6:34	10	125	75	102	150	70	102	12	4.1	22.0	17	23	7.22
		6:40	100	145	105	125	80	25	50	10	4.6	8.7	415		7.25
Lactic acid infusion		6:54	100	140	100	115	125	55	80	15	5.2	12.5	450		7.14
		6:59	10	120	70	100	150	60	105	10	4.2	22.6	18	36	7.16
Buffer infusion		7:13	100	135	55	75	98	23	60	14	9.2	5.0	460	15	7.31
		7:20	10	135	60	80	115	30	65	11	8.1	6.7	18	15	7.33
		7:25	100	135	65	92	100	25	62	13	9.2	5.3	450	16	7.32
Calf no. 3 (12 hours)		5:35	100	88	68	80	48	25	35	9	3.8	6.9	430	20	7.26
Buffer infusion		5:47	100	75	50	60	45	30	35	11	5.7	4.2	530	14	7.40
		5:52	10	83	60	70	57	30	40	11	5.4	5.3	32	20	7.31
Buffer infusion		5:56	10	70	40	50	47	33	35	11	6.6	3.6	19	15	7.40
		6:06	100	90	65	80	50	28	39	12	4.8	5.6	560	20	7.32
Lactic acid infusion		6:21	100	150	110	125	65	33	42	11	4.0	7.8	300	34	7.24
		6:25	10	110	75	85	98	55	70	8	4.1	14.7	25	37	7.25
		6:27	10	112	82	95	110	65	82	9	4.1	17.3	21	37	7.24
		6:33	100	90	65	72	57	33	40	7	4.8	6.7	350	32	7.25
Lactic acid infusion		6:45	100	120	90	110	60	30	42	7	3.8	9.0	270	46	7.22
		6:49	10	110	85	88	105	72	82	5	3.0	24.6	24	46	7.19
		6:54	10	110	85	90	113	80	90	3	2.6	32.2	21	44	7.19
Lactic acid infusion		7:07	100	110	85	95	87	50	67	7	3.4	17.2	415	50	7.14
		7:12	10	110	85	95	118	72	90	3	3.2	26.8	35	41	7.18
		7:17	10	102	85	88	125	80	98	3	2.7	34.5	23	41	7.17
		7:24	100	100	72	85	72	42	55	7	2.9	16.6	390	39	7.18
Both vagosympathetic		7:29	100	80	60	72	68	40	50	6	2.6	16.9	420	39	7.20
trunks cut		7:35	10	68	52	60	83	58	66	5	1.4	41.8	27	37	7.20
Calf no. 4 (10 hours)		5:48	100	140	110	120	45	18	30	4	3.4	7.7	590	15	7.32
		6:15	100	130	115	125	47	18	35	4	3.8	7.6	550	14	7.30
		6:23	12	160	120	135	59	23	35	4	2.8	10.4	44	14	7.30
Lactic acid infusion		6:32	12	170	145	156	85	48	70	4	3.5	19.7	42	21	7.22
Lactic acid infusion		6:40	12	155	135	130	95	55	80	5	3.6	20.9	42	20	7.16
Buffer infusion		6:59	12	150	120	120	53	27	40	4	4.3	8.4	43	12	7.33
		7:10	100	125	110	115	40	22	29	5	2.8	8.6	410	13	7.30
Lactic acid infusion		7:18	100	100	85	90	50	30	38	8	2.8	10.7	390	19	7.18
		7:23	100	145	125	132	53	25	43	7	3.2	11.3	510	19	7.21
		7:32	12	200	160	175	97	58	75	5	3.0	23.4	45	17	7.25
Lactic acid infusion		7:39	12	190	150	165	95	53	80	5	3.0	25.5	45	16	7.22
		7:50	12	200	150	175	98	55	73	5	3.0	22.8	43	16	7.26
Lactic acid infusion		8:05	100	140	120	135	50	23	38	4	3.0	11.5	500	20	7.19
Buffer infusion		8:11	100	125	100	115	45	18	33	6	3.3	8.2	500	16	7.23
		8:20	100	120	105	112	43	23	35	5	3.2	9.4	550	16	7.31
		8:26	12	140	120	130	67	35	48	6	2.7	15.6	35	14	7.30

* Abbreviations: PA = pulmonary artery; LA = left atrium; S = systolic; D = diastolic; M = mean; P_{O_2} and P_{CO_2} = oxygen and carbon dioxide tension.

vena cava. An additional vinyl catheter was inserted into a front-leg vein; succinyl choline chloride in doses of 1 to 2 mg per minute was then infused continuously into the catheter in the front leg in five calves. After 3 to 4 minutes, anesthesia was stopped and ventilation was maintained with room air or 30% oxygen in nitrogen by using positive pressure administered by the Harvard pump.

Pressures were measured in the pulmonary artery, aorta, and left atrium, and in some cases in a major pulmonary vein, by means of Statham P 23 Db pressure transducers. Mean pressures were obtained by electrical integration. Pulmonary arterial flow was measured with a gated sine-wave electromagnetic flowmeter.[1] The velocity tracing so obtained was integrated electrically to record stroke volume of the right ventricle. Recording of each beat was made in some experiments, whereas the totalized integration was recorded in others. Calibrations of the electromagnetic flowmeter and probes *in vitro* showed that the response was linear with flow. The flowmeter was calibrated *in vivo* from the average of several indicator dilution curves with injection into the left ventricle and sampling from the aorta, performed while the calf breathed 100% oxygen. Right-to-left shunt at the time of recording of cardiac output was excluded by injection of indicator into the inferior vena cava and sampling in the aorta. Indicator dilution curves were performed by using indocyanine green with continuous sampling through a Waters X-300 cuvette densitometer, by means of a Harvard continuous withdrawal pump.

Two groups of experiments were conducted: *a*) In four calves, aged 6 to 20 hours, the responses of the various hemodynamic parameters were observed when arterial oxygen tension (Po_2) was changed acutely from high levels to very low levels at varying levels of blood H^+ ion concentration. The inhaled gas mixtures used were 100% oxygen and 10% oxygen in nitrogen in three calves and 12% oxygen in one calf. The blood pH was changed by infusion of lactic acid or amine buffer (Tris) into the right atrial catheter. Two types of experimental procedures were performed. The effect of lowering arterial Po_2 was examined after blood pH had been changed to varying degrees, and also the effect of changing pH at fixed high and fixed low Po_2 was examined (Table I).

b) Various gas mixtures of oxygen in nitrogen were administered, with oxygen concentrations varying from 8 to 100% (8, 9, 10, 12, 15, 21, 37, 50, and 100%). After measurement of pressures and pulmonary arterial flow and sampling of blood for Po_2, Pco_2, and pH from the aorta, and in some cases pulmonary artery and pulmonary vein, lower percentages of oxygen were administered until a steady level of pulmonary arterial pressure was maintained for several minutes. After successive decreases in oxygen concentration, similar studies were performed as oxygen was increased.

Blood was analyzed for pH, Pco_2, and Po_2 within 5 minutes of collection. Blood pH was measured with a Radiometer capillary electrode, Po_2 with a Beckman electrode, and Pco_2 with a Severinghaus electrode, using a Beckman 160 physiological gas analyzer. The oxygen electrode was calibrated throughout the whole range of Po_2 measurements from 0 to about 700 mm Hg by blood samples equilibrated in a tonometer at 37° with gases of measured oxygen concentration in nitrogen. The response of the electrode was linear within the whole range. In two experiments, a Harris needle oxygen electrode was inserted into a carotid artery and continuous Po_2, pulmonary arterial pressure, and pulmonary blood flow were recorded during inhalation of 100% oxygen after breathing 8% oxygen. All recordings were made on a Grass 8 channel polygraph or an Offner recorder. Pulmonary vascular resistance was expressed in resistance units of millimeters Hg per liter per minute and was calculated from the equation, resistance = PA mean − LA mean pressure/pulmonary flow, where PA = pulmonary arterial, and LA = left atrial. The pressures are expressed in millimeters Hg, and pulmonary flow is expressed in liters per minute.

[1] Kolin-Kado type, Kado, Los Angeles, Calif.

Results

The results in the two groups of experiments will be presented separately.

1) Effect of H^+ ion concentration changes during 100% oxygen inhalation (Table I, Figure 1). The blood pH was reduced to levels of 7.19 to 7.32 in all four calves as a result of the surgical procedure. Administration of amine buffer increased pH and resulted in an increase in pulmonary blood flow in all animals. Lactic acid reduced pH

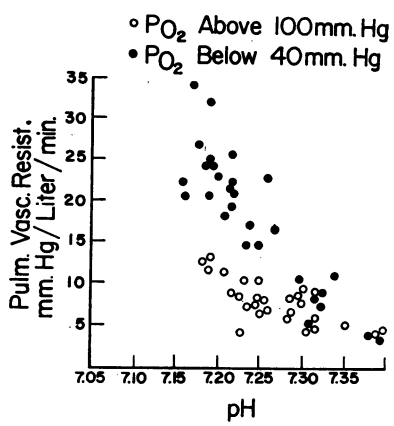

FIG. 1. RESPONSE OF PULMONARY VASCULAR RESISTANCE TO CHANGES IN BLOOD pH AT DIFFERENT LEVELS OF OXYGEN TENSION. Data from four calves in Table I are plotted. Open circles show observations made when oxygen tension (Po_2) in arterial blood was above 100 mm Hg, and solid circles show observations during hypoxia when arterial Po_2 was below 40 mm Hg.

TABLE II

Effects of varying oxygen concentrations in inspired air on pulmonary arterial pressure, pulmonary blood flow, and pulmonary vascular resistance and blood oxygen tension

Calf	Age	Time	Oxygen in inhaled gas	Pressures							Pulmonary blood flow	Pulmonary vascular resistance	Blood Po_2*			Blood Pco_2	Blood pH
				Aorta			PA			LA							
				S	D	M	S	D	M	M			SA	PV	PA		
			%	*mm Hg*							*L/minute*	*mm Hg/ L/minute*	*mm Hg*				
Calf no. 5	(9 hours)	6:49	37	95	75	85	43	18	28	3	1.75	14.9	148	157		37	7.13
		7:30	21	100	65	78	45	20	31	2	1.83	15.8		83		31	7.14
		8:03	12	98	75	83	48	28	35	1	1.63	21.4	36	42		29	7.13
		8:15	9	102	78	87	78	47	59		1.61	36.3	28	30		29	7.11
		8:32	9	100	78	87	84	55	67		1.17	57.1	29	32		29	7.10
		8:43	12	98	76	86	48	30	35	1	2.03	16.8	37	43		30	7.12
		9:11	9	100	76	88	78	47	60		1.33	45.1	25	26		29	7.13
		9:22	15	95	78	85	42	22	33	1	1.89	17.5	44	57		29	7.14
		9:29	21	92	70	80	42	19	28	1	2.09	13.4	49	78		31	7.12
		9:35	100	95	70	83	38	19	27	1	2.09	12.9	340	480		31	7.13
Calf no. 6	(18 hours)	4:32	50	105	84	96	42	24	33	5	2.6	10.8	101		57	49	7.12
		4:38	10	120	92	108	93	54	70	5	2.4	27.1	22		20	39	7.12
		4:48	10	126	96	108	123	72	90	4	2.3	37.4	18		16	42	7.15
		4:57	50	102	80	90	51	30	39	4	2.5	14.0	109		56	41	7.14
		5:05	50	96	76	88	45	24	32	3	2.4	12.1	118		54	42	7.13
		5:12	21	102	76	84	47	24	36	3	2.4	13.8	68		48	41	7.16
		5:20	21	96	72	84	45	21	34	3	2.6	12.0	66		39	37	7.16
		5:28	50	96	72	84	45	24	33	4	2.6	11.1	122			42	7.16
		5:33	8	102	75	90	99	60	78	4	2.2	33.8	21			37	7.15
		5:36	8	115	84	102	120	69	90	5	2.1	42.2	17			37	7.12
		5:41	8	120	84	102	125	65	95	4	2.0	45.5	16		14	37	7.12
		5:49	50	92	68	84	48	22	36	3	2.3	14.3	108			43	7.16
		6:03	15	102	78	92	105	66	81	5	2.3	33.1	33		24	40	7.16
Calf no. 7	(18 hours)	9:47	50	130	108	120	43	22	32	3	1.55	18.7	165			49	6.96
		9:57	21	137	115	125	46	23	34	2	1.42	22.5	53			48	7.06
		10:08	15	155	125	135	52	28	40	3	1.50	25.0	36			42	7.07
		10:21	21	148	95	128	44	22	23	3	1.42	21.2	42			45	7.07
		10:38	9	145	115	123	100	62	75	4	1.37	50.6	19			44	7.07
		10:42	9	133	102	113	98	60	75	5	1.39	50.2	18			43	7.06
		10:49	12	138	105	115	87	58	69	5	1.50	42.8	22			43	7.03
		10:57	15	138	112	120	66	40	52	5	1.34	35.0	31			44	7.03
		11:04	21	122	100	108	50	28	37	4	1.29	25.5	39			44	7.03
		11:09	100	110	88	98	47	25	36	4	1.37	23.4	375			45	7.04

* Abbreviations: SA = systemic arterial; PV = pulmonary venous.

TABLE II—(*Continued*)

Calf	Age	Time	Oxygen in inhaled gas	Pressures: Aorta S	Aorta D	Aorta M	PA S	PA D	PA M	LA M	Pulmonary blood flow	Pulmonary vascular resistance	Blood P_{O_2}*: SA	Blood P_{O_2}*: PV	Blood P_{O_2}*: PA	Blood P_{CO_2}	Bloop pH
			%	*mm Hg*							*L/minute*	*mm Hg/ L/minute*	*mm Hg*				
				Rapid sampling changing from 9% O_2 to 21% O_2													
		11:35	9			90			87	4	1.34	61.9	19				
		11:37				103			70	4	1.45	45.6	20				
		11:38				110			65	4	1.57	38.8	24				
		11:39				110			60	4	1.57	35.6	27				
		11:40				105			58	4	1.57	34.4	31				
		11:41	21			103			55	4	1.57	32.5	33				
Calf no.	8 (36 hours)	4:20	50	102	80	90	38	21	29	6	2.4	9.6	65		51	55	7.11
		4:43	8	120	80	90	68	38	54	5	2.0	24.5	22		20	62	7.11
		4:55	37	108	75	90	35	18	26	6	2.3	10.0	74			52	7.08
		5:06	15	102	72	80	51	30	45	5	2.2	19.1	36		24	58	7.10
		5:13	37	96	72	82	33	15	25	5	2.3	8.7	81		54	58	7.10
		5:24	10	116	72	84	78	45	62	3	2.1	28.0	22		19	57	7.11
		5:31	10	90	72	84	90	45	63	4	2.0	29.5	24		16	52	7.11
		5:40	37	100	66	84	40	21	33	4	2.3	12.7	95		61	57	7.11
		5:48	21	102	69	86	48	30	40	5	2.3	15.2	46		30	58	7.08
		5:55	100	90	62	78	37	18	30	4	2.4	10.8	325		48	57	7.12
Calf no.	9 (36 hours)	6:55	100	94	62	77	50	18	30	1	3.9	7.4	430	500	55	50	7.20
		7:01	21	103	75	88	60	22	40		3.6	11.1	56	59	45	57	7.18
		7:11	15	103	75	88	78	41	60		3.2	18.7	53	55	36	57	7.16
		7:19	12	115	87	100	100	60	77		3.1	24.6	32	32	25	52	7.14
		7:33	9	88	50	68	105	60	76		3.0	24.7	18	18	14	51	7.16
		7:55	9	65	30	40	90	58	70		3.1	22.6	18	20	11	56	7.11
Calf no.	10 (4 days)	12:22	21	120	90	102	45	21	30				62		30	38	7.16
		12:38	8	118	74	93	70	33	45		3.8	11.8	16		10	31	7.19
		12:47	21	120	90	102	36	12	21		2.6	8.1	53			32	7.21
		1:05	15	132	102	114	43	15	30		3.2	9.4	43			33	7.16
		1:10	21	138	96	114	45	19	30		3.4	8.8	61			44	7.18
		1:24	10	128	98	110	66	36	51		3.8	13.4	28		14	35	7.19
		1:36	21	116	84	102	37	14	25		3.2	7.8	58			35	7.16
		1:52	100	112	84	98	27	8	18		2.8	6.5	500			41	7.18

and caused a consistent, often marked, fall in pulmonary blood flow in three calves (no. 1, 2, 3) but did not affect the pulmonary blood flow significantly in one calf (no. 4).

Resting pulmonary arterial mean pressures while the calf was respired with high oxygen mixtures and pH was near normal levels ranged between 30 and 42 mm Hg. When pH was lowered there was a significant increase in pulmonary arterial mean pressure to levels of 33 to 80 mm Hg. Both left and right atrial mean pressures decreased significantly when pH was lowered, and in one calf (no. 3) marked reductions of 4 to 5 mm Hg were recorded.

Calculated pulmonary vascular resistance was increased by reduction of pH. Moderate increases were observed when arterial blood pH dropped below 7.3, and a progressive increase was noted as pH dropped further (Figure 1).

Response to hypoxia at variable pH levels. Hypoxia produced minor but inconsistent small decreases in pulmonary blood flow when pH levels were above 7.3 to 7.35. When hypoxia was induced in the presence of acidosis, a consistent decrease in pulmonary blood flow occurred during inhalation of 10% oxygen.

Pulmonary arterial pressure was dramatically increased by hypoxia when pH was below 7.3, whereas only minor changes were noted when pH was above 7.3. Left and right atrial pressures did not change significantly when hypoxia was induced at higher pH levels, but further reductions in mean pressures were noted over and above the already reduced levels when pH was lowered.

Pulmonary vascular resistances were affected either minimally or not at all by changing the oxygen concentration of inspired air when pH was above 7.3. However, below this level dramatic increases of pulmonary vascular resistance occurred when hypoxia was induced. The lower the pH, the greater was the response of pulmonary vascular resistance to hypoxia (Figure 1).

The responses of pulmonary arterial pressure, pulmonary blood flow, and pulmonary vascular resistance to changes in inspired air oxygen tension were examined at two levels with varying H^+ ion concentrations. With the calf breathing 50 to 100% oxygen, arterial or left atrial Po_2 levels of 245 to 600 mm Hg were accomplished. With 10% oxygen inhalation in three calves, Po_2 levels of 11 to 32 were constantly achieved, and in one calf breathing 12% oxygen Po_2 levels of 35 to 45 were produced. Pco_2 levels in arterial or left atrial blood varied from 14 to 50 mm Hg. The maximal changes in Pco_2 were observed soon after lactic acid or buffer infusion. No relationship could, however, be established between the changes in pulmonary blood flow, pulmonary arterial pressure, and pulmonary vascular resistance and variation in Pco_2.

2) Responses at different levels of hypoxia (Table II, Figures 2, 6, 7). The resting pulmonary arterial mean pressures when the calves were ventilated with gas mixtures with an oxygen concentration of 21% or greater ranged from 20 to 36 mm Hg except in one calf aged 4 days (no. 10), in which resting pressure was 18 mm Hg. Respiration with 15% oxygen resulted in a mild increase of pulmonary arterial mean pressure to levels of 30 to 44 mm Hg. Further reduction of inspired air oxygen levels resulted in a precipitous increase of pulmonary arterial pressure, and with 8% oxygen, levels of 45 to 95 mm Hg were achieved (Figure 2). The responses of pulmonary arterial pressure were greater in those calves under 24 hours of age; in the 4-day-old calf the response was least striking, but the same general pattern of response was noted.

Left atrial pressure. Left atrial pressure ranged from 0 to 6 mm Hg (mean) while the calves were ventilated with oxygen or air. Only small changes of 0 to 2 mm Hg were noted in left atrial mean pressure with variations of inhaled oxygen; there was no specific relationship between the change in left atrial pressure and the gas inhaled.

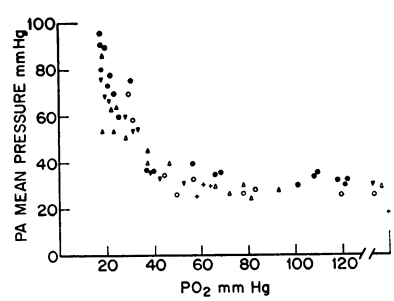

FIG. 2. RELATIONSHIP BETWEEN PULMONARY ARTERIAL (PA) MEAN PRESSURE AND ARTERIAL Po_2 IN SIX CALVES IN TABLE II. Data on different calves are represented by different symbols.

Aortic pressure. Aortic mean pressures were between 80 and 90 mm Hg during air or oxygen breathing in all except one calf (no. 7) in which a resting level of 125 mm Hg was observed. As oxygen concentration in inspired air was reduced, no significant changes in aortic pressure were observed. Increases or decreases of 5 to 10 mm Hg occurred at random as oxygen concentration was changed, but no consistent pattern was observed.

Pulmonary blood flow. In previous experiments, attempts were made to measure pulmonary blood flow with indicator-dilution techniques by injecting indocyanine green into the right or left atrium or pulmonary artery and sampling from the aorta. It became apparent that this method was not valid due to shunting, and it was necessary to measure pulmonary flow directly by means of a flowmeter on the main pulmonary artery.

Actual levels of total pulmonary blood flow varied considerably but were lower in the younger calves (under 24 hours). During inhalation of air or oxygen, pulmonary blood flows of 1.35 to 2.09 L per minute were observed in the younger calves, and 3.9 to 5.6 L per minute in the older calves (over 24 hours). Reduction of oxygen concentration in inspired air resulted in a consistent decrease of pulmonary blood flow of 10 to 35% of the flow during air or oxygen inhalation. An interesting change in the pattern of blood flow through the main pulmonary artery was observed. The blood velocity as recorded by the electromagnetic flowmeter showed a smooth rounded contour during ejection while the animal breathed air, but during low oxygen inhalation the ejection was more rapid, and a sharper rise and fall with a higher peak velocity were observed. In spite of an increase in peak velocity, the total area under the velocity curve was decreased, indicating a decrease in stroke volume (Figure 3).

Indicator dilution curves (*Figure 4*). Ductal shunting was obviated by surgical ligation of the ductus arteriosus. During air or oxygen breathing indicator dilution curves with indocyanine green injected into the pulmonary artery or left atrium with sampling from the aorta revealed a change in slope on the descending portion of the curve with a delayed descent, indicating the presence of a left-to-right shunt. Since no other defects were present (the ductus having been ligated), it was assumed that this shunt was occurring at the atrial level through the foramen ovale. Injection of indicator into the left ventricle with sampling in the pulmonary artery showed very late appearance, whereas injection into the left atrium with sampling from the pulmonary artery revealed the early appearance of a small amount of indicator, confirming that the left-to-right shunt was at the atrial level. The magnitude of the left-to-right shunt varied from one animal to the other

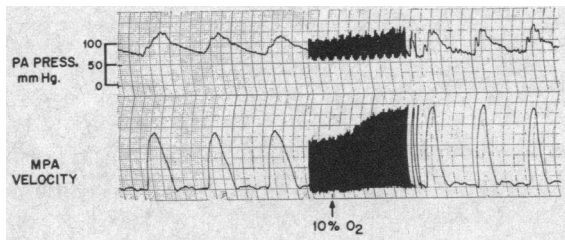

FIG. 3. PULMONARY ARTERIAL PRESSURE AND BLOOD VELOCITY IN MAIN PULMONARY ARTERY (MPA) AS MEASURED BY AN ELECTROMAGNETIC FLOWMETER IN CALF NO. 2. Marked increase in peak velocity in main pulmonary artery occurs, but stroke volume, as represented by the area under the flowmeter curve, is actually reduced. Slow tracing started 5 minutes after initial rapid recording.

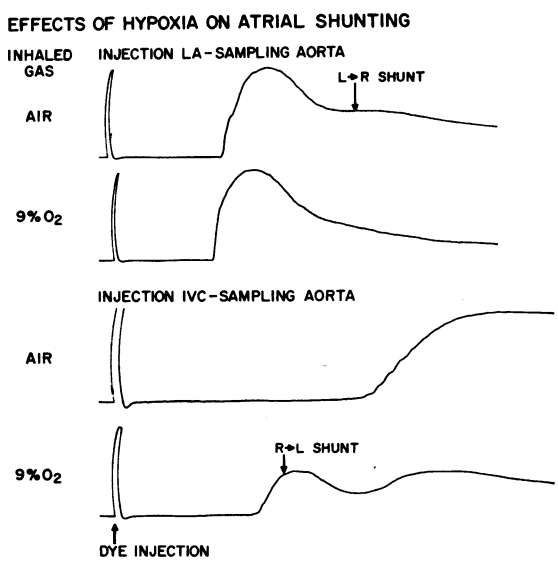

FIG. 4. INDICATOR DILUTION CURVES SHOWING LEFT-TO-RIGHT SHUNT IN UPPER TRACING AND ABSENCE OF RIGHT-TO-LEFT SHUNT (THIRD TRACING) WHEN CALF BREATHES ROOM AIR. During inhalation of 9% oxygen, left-to-right shunt disappears and large right-to-left shunt is noted in lower tracing. LA = left atrium; IVC = inferior vena cava.

and was absent in the 4-day-old calf. When hypoxia was induced, the atrial left-to-right shunt disappeared.

Injection of indicator into the inferior vena cava with sampling in the aorta showed an early appearance of indicator with a small preliminary hump, demonstrating the presence of a small right-to-left shunt, while the animal was ventilated with air or oxygen. This right-to-left shunt was markedly accentuated during inhalation of low oxygen gas mixtures and in some animals appeared to account for as much as half the systemic blood flow. It was presumed that the right-to-left shunt was through the foramen ovale, and this was confirmed in two animals in which sampling from the left atrium when indicator was injected into the inferior vena cava showed the same double hump type of curve.

Blood oxygen tension. Oxygen tensions of aortic and left atrial blood measured simultaneously were essentially similar in all the observations made. During inhalation of 100% oxygen, arterial Po_2 levels reached only 325 to 500 mm Hg, indicating the presence of some right-to-left shunt, either intracardiac or possibly intrapulmonary. There was considerable variation in the levels of arterial Po_2 reached during inhalation of various gas mixtures, presumably due to some variation in the degree of ventilation accomplished and to variability of right-to-left shunting. During ventilation with room air, arterial Po_2 levels ranged from 50 to 68 mm Hg; with 15% oxygen, the levels were 36 to 47 mm Hg; with 12% oxygen, 32 to 38 mm Hg; and with 8% oxygen, 16 to 22 mm Hg.

Simultaneous Po_2 determinations were made in pulmonary venous and left atrial blood samples in three calves. During inhalation of high oxygen gas mixtures, a large difference in Po_2 favoring pulmonary venous blood was noted, whereas when oxygen in inspired air diminished there was a progressively smaller difference in Po_2. When pulmonary venous Po_2 was below 35 mm Hg, only minimal differences were observed (Figure 5). In three calves simultaneous pulmonary arterial and aortic or left atrial blood Po_2 measurements were made. A progressive decrease in pulmonary arterial Po_2 was noted as inspired oxygen concentration decreased. When arterial Po_2 was below 35 mm Hg, the levels of pulmonary arterial Po_2 were only slightly lower than those in the systemic artery.

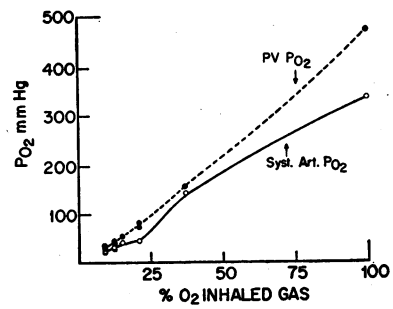

FIG. 5. PULMONARY VENOUS (PV) AND SYSTEMIC ARTERIAL Po_2 DURING INHALATION OF VARIOUS CONCENTRATIONS OF OXYGEN (CALF NO. 5). During breathing of low oxygen mixtures, in spite of large right-to-left shunt, only small differences exist.

Hydrogen ion concentrations were allowed to remain at the levels present after the surgical procedure with no attempt at regulation. In all animals pH was below 7.2, and in one animal it was as low as 7.0. In each individual animal there was, however, a variation of no more than 0.1 pH unit throughout the experimental period.

Arterial Pco_2 levels were quite variable from one animal to another, and the levels were largely dependent on the state of ventilation maintained. In spite of this wide range, there was, however, little variation of Pco_2 within an individual animal.

Pulmonary vascular resistance and oxygen tension. A very striking relationship has been demonstrated between the calculated pulmonary vascular resistance and the level of arterial Po_2. When Po_2 levels were maintained above 100 mm Hg, pulmonary vascular resistance ranged from 6.5 to 23.4 mm Hg per L per minute. This resting level of pulmonary vascular resistance was dependent on the age and the blood pH of the animals, being higher in the younger and more acidotic animals. As Po_2 was lowered to 45 to 50 mm Hg, there was only a small increase in pulmonary vascular resistance, but with further decrease of Po_2 there was a much more precipitous rise of resistance. In the range of arterial Po_2 of 15 to 30 mm Hg there was an extremely marked increase in pulmonary vascular resistance response to small changes of Po_2. Although the resting levels of pulmonary vascular resistance were variable, the patterns of response to Po_2 changes were quite comparable (Figure 6).

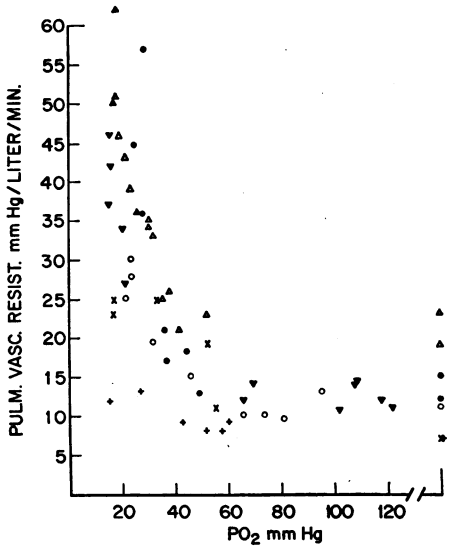

FIG. 6. RELATIONSHIP BETWEEN CALCULATED PULMONARY VASCULAR RESISTANCE AND ARTERIAL Po_2 IN SIX CALVES IN TABLE II. Each calf is represented by a different symbol.

In view of the fact that only minimal differences in pulmonary venous and systemic arterial Po_2 levels occurred at low Po_2 values, whereas a wide separation occurred at higher levels, the general pattern of pulmonary vascular resistance change shown in Figure 7 would be essentially similar if plotted against pulmonary venous Po_2. The

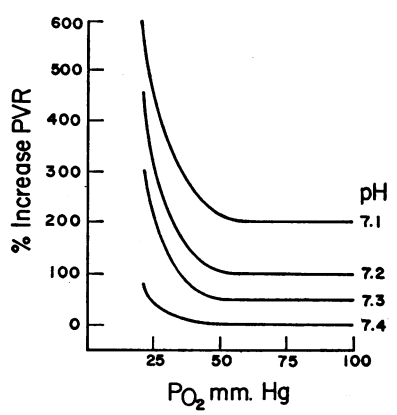

FIG. 7. PATTERN OF PULMONARY VASCULAR RESPONSES TO CHANGES OF pH AND Po_2. In this figure, the average increases of pulmonary vascular resistance (PVR) are expressed as a per cent of the level at pH 7.4 and Po_2 100 mm Hg. The changes in pulmonary vascular resistance with changes in Po_2 have been related at different levels of pH. This information has been derived from a compilation of the measurements made in all the animals studied.

steep portion of the curve would be displaced minimally to the right, and the flat portion would not be changed. Thus if the response of pulmonary vasculature is related to a direct local response of the vessels to Po_2 change, the pattern demonstrated would be essentially similar.

In two animals bilateral section of the vagosympathetic trunks did not alter the pulmonary vascular response to acidosis and hypoxia.

Discussion

Observations on the reactivity of the pulmonary circulation have most frequently been made in human adults and adult dogs. The pulmonary circulation in these species has demonstrated remarkably little response to most physiologic and pharmacologic influences. Since resting pulmonary arterial pressure is quite low and since only small changes in pressure occur, it has been difficult to separate pulmonary vasomotor effects from simple physical effects related to changes in cardiac output and pulmonary venous or left atrial pressure. Numerous techniques have been developed to overcome these difficulties in interpretation. Himmelstein, Harris, Fritts, and Cournand (5), by means of bronchospirometry, measured blood flow through each lung and demonstrated a reorientation of flow in response to hypoxia in one lung. Rudolph and Scarpelli (6) continuously measured flow through each lung of the dog by means of electromagnetic flowmeters.

The considerably greater response to the pulmonary circulation in the fetal or neonatal animal has been repeatedly described. The small pulmonary vessels of the fetus have thick muscular walls with relatively small lumina, and the pulmonary arterial pressure is at systemic arterial levels. After birth, the vessels rapidly lose this thick muscular medial layer and assume the characteristics of the adult circulation in 2 to 3 weeks (7, 8). This is associated with a rapid decrease of pulmonary arterial pressure toward adult levels, and also a loss of the marked physiologic response of the circulation over a similar period (9, 10). In view of this great reactivity of the pulmonary vasculature during the fetal and immediate postnatal periods, an excellent experimental model for the study of pulmonary vascular response is provided; physical factors such as changes in left atrial pressure and blood flow exert relatively small changes

compared with those produced by pulmonary vasomotion. An increase in viscosity could produce an increase in pulmonary vascular resistance as calculated from arterial pressure, as demonstrated in the Posseuille equation. There was, however, no significant increase in hematocrit during hypoxia, and the likelihood of hypoxemia producing an increased viscosity by other means is small. Greenberg, Kass, and Castle (11) have shown that little change in blood viscosity occurs when normal hemoglobin is reduced.

Although pulmonary vasoconstriction in response to inhalation of hypoxic gas mixtures has been unquestionably demonstrated in the adult, the changes in the fetal and neonatal animal are far more striking. Cook and associates (12) and Cassin and associates (13) have stressed the importance of a low Po_2 in maintaining pulmonary vasoconstriction in the fetus, and the immediate increase of pulmonary blood flow associated with ventilation of the lungs with gas containing oxygen. James and Rowe (14) demonstrated the marked increase in pulmonary arterial pressure resulting from administration of low oxygen mixtures to the neonatal human infant. Reeves and Leathers (15) have carefully delineated the normal changes in pulmonary arterial pressure and pulmonary vascular resistance with advancing age in the calf; the marked vascular response to hypoxia noted in the postnatal period rapidly decreased as resting pulmonary arterial pressure fell.

Although the greater reactivity of the pulmonary circulation in the newborn animal affords an excellent model to study the responses of the pulmonary vasculature, certain special aspects of the neonatal circulation have to be taken into account. Fetal shunting mechanisms may still be operative, thus making the measurement of pulmonary blood flow by either Fick or indicator dilution techniques most unreliable. During the first 24 hours after birth the ductus arteriosus may still be functionally patent, thus allowing left-to-right or right-to-left shunting, depending on the relationship between systemic and pulmonary vascular resistances. The absence of any ductal shunt during inhalation of room air does not preclude the possibility that the ductus may reopen with hypoxemia (16), thus introducing difficulties of interpretation of indicator curves and oxygen saturation data. The foramen ovale also does not provide a complete and competent separation of the left and right atria after birth. A small left-to-right shunt can be demonstrated very frequently both in the calf (Figure 4) and in the human infant. When pulmonary vascular resistance is elevated, as when right ventricular outflow obstruction occurs, a marked right-to-left shunt may occur through the foramen ovale. These considerations have been neglected in many studies relating to measurement of pulmonary vascular resistance and to shunting mechanisms in the newborn infant and experimental animals (15–18).

The difficulties in measurement of pulmonary blood flow and pulmonary vascular resistance imposed by these mechanisms were overcome in our preparation. Ligation of the ductus arteriosus prevented any shunting into or away from the pulmonary artery, thus assuring the accuracy of the electromagnetic flow probe around the main pulmonary artery in measuring pulmonary blood flow. Shunting through the foramen ovale also did not interfere with the measurement of pulmonary blood flow by the method applied.

The increase in pulmonary vascular resistance with acidosis at normal or high levels of arterial Po_2 confirms the observations of a number of previous studies. In our studies no attempt was made to distinguish between the effects of increase of Pco_2 or decrease of pH by fixed acid infusion. Bergofsky, Lehr, and Fishman (19) have shown that the pulmonary vascular response is related to a change of hydrogen ion concentration and that a similar response occurs either with respiratory or metabolic acidosis. These previous studies did not, however, establish any specific relationship between the level of pH and the pulmonary vascular response. Our observations indicate that pulmonary vasoconstriction occurs when pH falls below 7.30 to 7.35. As pH drops further, a large increase in pulmonary vascular resistance is observed below levels of 7.15 to 7.2. There thus appears to be a curvilinear relationship between pH and pulmonary vascular resistance.

Although many observations of a pulmonary vasoconstrictor response to hypoxia have been reported, little information is available regarding the relationship between the degree of hypoxia and the magnitude of the pulmonary vascular response. Several attempts to compare the pulmonary vascular resistance with the level of arterial oxygen

saturation have not shown any consistent relationship (2, 20, 21). A rise of pulmonary vascular resistance has usually been observed in patients with chronic pulmonary disease when arterial oxygen saturation falls to 80 to 85% representing a Po_2 of 46 to 50 mm Hg (1).

However, Reeves and Leathers (15) have shown a progressive increase in pulmonary arterial pressure with decreasing concentration in inhaled gases in unanesthetized newborn calves, and Cassin and co-workers (13) established a linear relationship between the conductance of the pulmonary circulation and the Po_2 of blood perfusing the lung. These latter studies were performed in the fetal lamb and show very wide scatter.

The results of our studies in calves have demonstrated a very definite pattern of pulmonary vascular response to hypoxia. Pulmonary arterial pressure and pulmonary vascular resistance showed only a slight increase as systemic arterial Po_2 dropped to 50 to 60 mm Hg. More significant increases occurred when Po_2 fell to 40 to 45 mm Hg, and below this level there was a very steep rise of pulmonary arterial pressure and pulmonary vascular resistance, indicating an exquisite sensitivity of the pulmonary vessels to Po_2 changes in the range below 35 to 40 mm Hg. It was not possible to maintain Po_2 levels of 18 to 20 mm Hg at low levels of pH for more than a few minutes because of the effect on the myocardium with resulting circulatory depression (22). However, it appeared that the pulmonary vascular response was maximal at Po_2 levels of 18 to 20 mm Hg, and no further increase occurred below this level.

The possibility that pulmonary arterial Po_2 determines the response of the pulmonary vessels has been considered. Our studies did not separate the relative roles of pulmonary venous and pulmonary arterial Po_2 in pulmonary vascular response, since pulmonary arterial Po_2 also decreased when oxygen concentration in inhaled air was reduced.

Enson and associates (4) reported a definite relationship between pulmonary vascular resistance and the levels of Po_2 and pH in a group of patients with chronic pulmonary disease. There was, however, wide scatter of the data and only little information relating to repeated studies in the same individual. The interrelationship between pulmonary arterial pressure and pulmonary vascular resistance and Po_2 and pH has been strikingly demonstrated in our studies. The mechanism of the enhanced pulmonary vasoconstrictor response to hypoxia in the presence of acidosis has not been elucidated.

Although it is possible that the presence of acidosis may result in an increased sensitivity of the vascular smooth muscle to hypoxia, the increased response of vascular resistance to hypoxia could be explained on a simple physical basis. The calculated pulmonary vascular resistance is an expression of total cross-sectional area of the pulmonary vascular bed; a given decrease in circumference or diameter produced by smooth muscular constriction will result in a relatively small decrease in cross-sectional area. However, if the same degree of smooth muscular constriction produces a similar reduction in diameter of the vessel already partly constricted from some other influence, this same reduction will cause a much greater decrease in cross-sectional area and thus a marked increase in pulmonary vascular resistance.

That a simple physical phenomenon is probably not the only mechanism involved is suggested by the fact that marked reduction in Po_2 to levels below 25 mm Hg could be produced in some instances and yet, when pH was normal, no increase in pulmonary vascular resistance occurred.

On the basis of our studies, the relationship between pulmonary vascular resistance, Po_2, and H^+ ion concentration may be represented diagrammatically as depicted in Figure 7. This extreme response of the pulmonary vasculature to small changes of Po_2 in the range 15 to 30 mm Hg at decreased pH may have an important role in the fetal circulation. Blood perfusing the lungs in the fetus has a Po_2 in this range, and this could provide a sensitive mechanism for distribution of blood flow in the fetus. An increase in pulmonary vascular resistance would divert blood away from the lungs and through the ductus arteriosus into the descending aorta and thus to the placenta. This mechanism could thereby result in an increase in blood flow to the placenta where gas exchange occurs, providing a means of adapting to stress situations interfering with oxygenation of the fetus.

In the neonatal period, the development of acidosis and hypoxia from any cause may produce pulmonary vasoconstriction, which may have seri-

ous consequences. An increase in pulmonary vascular resistance in the immediate neonatal period would reestablish a fetal pattern of circulation with right-to-left shunting through the ductus arteriosus and foramen ovale. Pulmonary blood flow would be reduced, and whereas this is of no consequence in the fetus where oxygenation is carried out in the placenta, it would result in a vicious cycle of events in the newborn animal or infant. Acidosis and hypoxia would increase pulmonary vascular resistance and decrease pulmonary blood flow, thus further reducing oxygenation and interfering with the respiratory compensating mechanism to correct acidosis by CO_2 elimination. This, combined with right-to-left shunting, would produce greater hypoxia and combined metabolic and respiratory acidosis, with more severe pulmonary vasoconstriction.

This sequence of events may be important in the respiratory distress syndrome of the newborn infant (hyaline membrane disease). Suggestive evidence for a decreased pulmonary blood flow has been presented by Chu and co-workers (23).

The pulmonary vasoconstrictor response to acidosis and hypoxia may also be important in the postoperative period in infancy, particularly after thoracic procedures. Acidosis develops quite readily in infants, and if ventilation is decreased and hypoxia superimposed, pulmonary vasoconstriction may result. In the absence of shunting mechanisms, total cardiac output may be decreased if the right ventricle is not capable of maintaining an adequate output. If the foramen ovale is still patent, right-to-left shunting could result.

The necessity of the presence of acidosis for a significant hypoxic vasoconstrictor response provides a relatively simple means of avoiding this mechanism. Rapid correction of acidosis by means of bicarbonate or amine buffer infusion can rapidly reverse the general hemodynamic effects resulting from pulmonary vasoconstriction.

This mechanism of pulmonary vascular response to hypoxia and acidosis was not conclusively established in this study. However, the fact that vagosympathectomy did not in any way alter the response in two animals studied suggests that it is not mediated through a central reflex pathway and that it is most likely a local reaction of the vessels. This is supported by Bergofsky and Weinberg (24), who have shown that strips of pulmonary artery suspended *in vitro* constrict on exposure to hypoxia.

Summary

The pulmonary vascular responses to variations in blood oxygen tension and H^+ ion concentration levels have been studied in the newborn calf. The difficulties in measuring pulmonary blood flow in the newborn animal are discussed. In this study, flow was measured directly with an electromagnetic flowmeter.

When arterial oxygen tension (Po_2) is 100 mm Hg or above, reduction of pH below 7.30 results in a small increase in pulmonary vascular resistance. A progressive and more dramatic increase in vascular resistance occurs as pH drops to lower levels.

At normal levels of blood pH (above 7.35) reduction of arterial Po_2 produced by inhalation of low oxygen gas mixtures resulted in minimal increases in pulmonary vascular resistance even when arterial Po_2 fell to 18 to 20 mm Hg. When pH was lowered, reduction of Po_2 produced an increase of pulmonary vascular resistance which was of significant degree when Po_2 fell below about 50 mm Hg. Further reductions of Po_2 resulted in very marked increases in pulmonary vascular resistance. A curvilinear relationship between pulmonary vascular resistance and Po_2 was established, with extreme sensitivity of pulmonary vascular resistance to Po_2 changes in the range 18 to 20 mm Hg. Also, the lower the pH, the greater was the pulmonary vascular resistance response to Po_2 reduction.

The importance of this relationship on shunting mechanisms through the ductus arteriosus and foramen ovale in the neonatal period is discussed, with particular reference to the respiratory distress syndrome and to postoperative complications of thoracotomy in infancy.

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