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HYPOXIA AND PULMONARY ARTERIAL PRESSURE IN THE RABBIT

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SUMMARY

1. The effect of hypoxia on pulmonary arterial pressure was studied in young and adult rabbits.

2. In isolated perfused lungs, hypoxia caused no rise in pulmonary arterial pressure in rabbits on the day of birth. The size of the hypoxic response increased progressively until 9–11 days of age, when the adult response of a 20 % rise of pulmonary arterial pressure at constant flow was attained.

3. The intact adult rabbit responded to hypoxia with a 14–30 % rise in pulmonary arterial pressure, attributed to vasoconstriction and independent of frequency or tidal volume during positive pressure ventilation.

INTRODUCTION

The initial level of pulmonary arterial pressure and the absolute and percentage rise during exposure to low oxygen mixtures vary with age from birth and with species. In the new-born rabbit, hypoxia causes an increase in peak right ventricular pressure (Dennis, 1968); its effect on pulmonary arterial pressure in the adult is uncertain. Dirken & Heemstra (1948*a*, *b*, *c*) used measurements of arterial oxygen saturation to suggest that there might have been a pulmonary vasoconstrictor response to hypoxia, which reached a peak in 8 hr. Later Heemstra (1955) reported an early rise reaching a maximum in 15 min. Nisell (1950) observed an immediate rise in pulmonary arterial pressure in one isolated perfused rabbit lung, but the pressure failed to return to its control value after hypoxia. Duke & Killick (1952) confirmed the pressor response in three rabbits but no details were given. Recently Waaler, Hauge & Lunde (1966) described the pulmonary pressor response in isolated rabbit lungs as surprisingly small. It therefore seemed desirable to determine the magni-

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tude of the pulmonary pressor response to hypoxia in the living adult rabbit, and to compare this with the pressor response of the isolated perfused rabbit lung. Furthermore, we wished to study the post-natal development of the hypoxic pulmonary pressor response in the rabbit.

METHODS

Eighty-one rabbits, weighing 0·05–4·5 kg aged 12 hr to adult, were studied under light sodium pentobarbitone anaesthesia (Nembutal, Abbott), 30 mg/kg intravenously for adults and 15 mg/kg for rabbits < 1 month old. Further doses of pentobarbitone, 10 and 15 mg/kg respectively, were given at intervals of 45–60 min as needed. The area of incision in the neck was infiltrated with 10 ml. procaine (1 %, w/v) in saline solution (0·9 %, w/v). Each rabbit was placed on a warmed table, its rectal temperature was monitored and the trachea was cannulated.

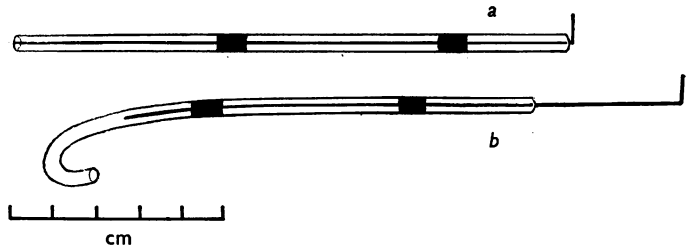

Fig. 1. Pulmonary artery catheter with wire introducer, fully advanced to facilitate catheterization of the right ventricle (*a*). Withdrawal of the wire allows the distal end to curve (*b*). The catheter diameter is not to scale.

Living rabbits. The left carotid artery was exposed and cannulated. Mean and phasic arterial pressures were measured with calibrated strain-gauge transducers. The right external jugular vein was exposed and cannulated using a catheter and introducer made of polyethylene chloride (Portex P.P. 90) and Nichrome wire $1{\cdot}8 \times 10^{-2}$ in. diam. (Fig. 1*a*). The catheter was advanced until visible pulsations suggested that the distal end was in the right ventricle. The wire introducer was then withdrawn leaving the curved portion in the ventricle (Fig. 1*b*). The catheter was connected to a strain-gauge transducer and phasic right ventricular pressure was recorded on a Schwarzer polygraph. The catheter was then advanced further until a characteristic record of pulmonary artery pressure was obtained. At the end of the experiment the catheter was slowly withdrawn from pulmonary artery to right ventricle and right atrium, its position being confirmed by inspection of the record.

The effects of hypoxia were studied in ten rabbits (closed chest) during positive pressure ventilation through a tracheal cannula using a neonatal ventilator (Bourns Life Systems Ames, Iowa, U.S.A.). Tidal volume was recorded as the electrical analogue of the output of a variable resistance attached to the piston of the ventilator pump (Owen-Thomas, Ulan & Swyer, 1968). Observations were repeated in these ten rabbits during positive pressure ventilation with the chest widely opened to atmosphere through a median sternotomy.

Isolated perfused lungs. In preparations from rabbits aged under 1 month, the perfusion fluid used was blood collected from the carotid of a heparinized parent (Heparin 10 mg/kg, Boots Pure Drug Co.) into a Perspex reservoir (volume 100 ml.) at 38° C in a heated water-bath. Either blood from donor rabbits or the animal's own blood was used for adult isolated perfused lungs. Care was taken to keep the animal at 38° C (Daly, Michel, Ramsay & Waaler,

1968). A median sternotomy was performed and the pericardium was incised. The lungs always remained in the chest. In rabbits less than 4 days old the ductus arteriosus was visualized through a dissecting microscope and was ligated. The pulmonary artery was cannulated through an incision in the right ventricle. Blood from the reservoir (haematocrit 34 %, S.E. ±1 %) was pumped at constant flow by a Dale–Schuster or rotary pump through an electromagnetic flowmeter (Wyatt, 1961) to the pulmonary artery. The blood returned from the lungs to the reservoir via a cannula in the left atrium. A flow was selected which gave a pulmonary artery pressure comparable to that in the intact rabbit. Pulmonary arterial pressure was measured with a calibrated strain-gauge transducer. The ventilation mixture was changed from 5 % CO_2 in O_2 to 5 % CO_2 in N_2 for periods of 4–6 min.

In twenty-one initial experiments, no consistent pressor response during hypoxia was obtained in perfused lungs of infant and adult rabbits. Following the work of Duke & Vane (1968) we repeated the experiments and substituted silicone rubber tubing for polyvinyl chloride (Portex) tubing in the perfusion circuit, whereupon hypoxic pressor responses were obtained. In six of seven rabbits (9 days to adult) addition of polyvinyl chloride tubing to the blood reservoir abolished or reduced the hypoxic pressor response. In three animals addition of polyvinyl chloride tubing was followed by a progressive rise of pulmonary arterial pressure and pulmonary oedema. For all subsequent lung perfusions we used silicone rubber tubing, glass connectors and a Perspex blood reservoir.

In rabbits less than 7 days old, the pulmonary pressor responses tended to diminish with repeated hypoxic tests. The largest single pressor response was selected for inclusion in the results. In the older rabbits (9 days to adult) reproducible hypoxic pressor responses were obtained as long as pulmonary arterial pressure remained stable during oxygen breathing. For each rabbit the average of two to seven hypoxic responses was used. Occasionally after 1-2 hr perfusion, pulmonary arterial pressure during oxygen ventilation began to rise. Hypoxia then caused an exaggerated pulmonary pressor response and the pulmonary pressure did not return again to control levels after oxygen ventilation was restored. In such animals the gross examination of the cut lung surface and of histological sections revealed evidence of oedema, which is known to occur in perfused rabbit lungs (Hauge, Lunde & Waaler, 1966; Lunde, 1967; Lunde, Waaler & Walloe, 1968).

Blood samples (0·2–0·4 ml.) were drawn anaerobically either from a carotid artery (living rabbit) or left atrium (perfused lungs) into siliconed glass syringes, whose dead space had been filled with heparin. They were analysed immediately for pH, P_{CO_2} and P_{O_2} using a Radiometer (Copenhagen) micro-electrode assembly at 38° C. The electrodes were calibrated frequently with gas mixtures and buffer solutions of known composition.

The doses of acetylcholine perchlorate (British Drug Houses) and noradrenaline bitartrate (Winthrop Laboratories) are given in terms of salt.

RESULTS

Isolated lungs perfused at constant flow. In the lungs of five rabbits studied on day 0 (less than 24 hr old) hypoxia caused no pulmonary arterial pressure change (three rabbits), a 1 mm Hg pulmonary arterial pressure rise (one rabbit) or a 1 mm Hg pressure fall (one rabbit). Seven of nine rabbits 2–3 days old showed 1 or 2 mm Hg pulmonary arterial pressure rises during hypoxia. None showed a pressure fall. All rabbits, 4–7 days, 9–11 days, and adult showed a rise in pulmonary arterial pressure during hypoxia (Table 1). The magnitude of the hypoxic pressor responses increased with age up to 11 days; the lungs were perfused at comparable

TABLE 1. Effect of hypoxia on isolated perfused rabbit lungs (means ± S.E.)

Age (days)	Number of rabbits	Body weight (g)	Ventilating gas, with 5% CO_2	pH	P_{CO_2} (mm Hg)	P_{O_2} (mm Hg)	Pulmonary arterial pressure (mm Hg)		Flow (ml./kg/min)
							Control	Increase with hypoxia	
0*	5	68 ± 3	O_2	7·42 ± 0·04	35 ± 4	> 220	17 ± 2		33 ± 6
			N_2	7·41 ± 0·03	31 ± 3	13 ± 2		0 ± 0·2	
2–3	9	72 ± 5	O_2	7·39 ± 0·02	31 ± 2	> 220	15 ± 1		39 ± 3
			N_2	7·39 ± 0·02	30 ± 2	23 ± 4		1 ± 0·2	
4–7	5	100 ± 10	O_2	7·39 ± 0·02	32 ± 4	> 220	14 ± 1		30 ± 6
			N_2	7·39 ± 0·02	28 ± 4	15 ± 4		2 ± 0·3	
9–11	9	220 ± 20	O_2	7·34 ± 0·02	31 ± 2	> 220	18 ± 1		36 ± 4
			N_2	7·34 ± 0·02	31 ± 2	19 ± 3		3 ± 0·2	
Adult	8	3100 ± 190	O_2	7·34 ± 0·02	45 ± 3	> 220	15 ± 1		57 ± 4
			N_2	7·41 ± 0·03	36 ± 3	13 ± 3		3 ± 0·4	

* < 24 hr old.

flows. The adult lungs were perfused at higher flows. The pH and blood gas data were comparable for all groups.

Acetylcholine (2–5 μg) injected into the pulmonary artery of eight adult lungs increased pulmonary arterial pressure by 15 ± 3 mm Hg; 5–50 μg noradrenaline had little effect, confirming the observations of Euler (1932), Gilbert (1938), and Bohr, Goulet & Taquini (1961).

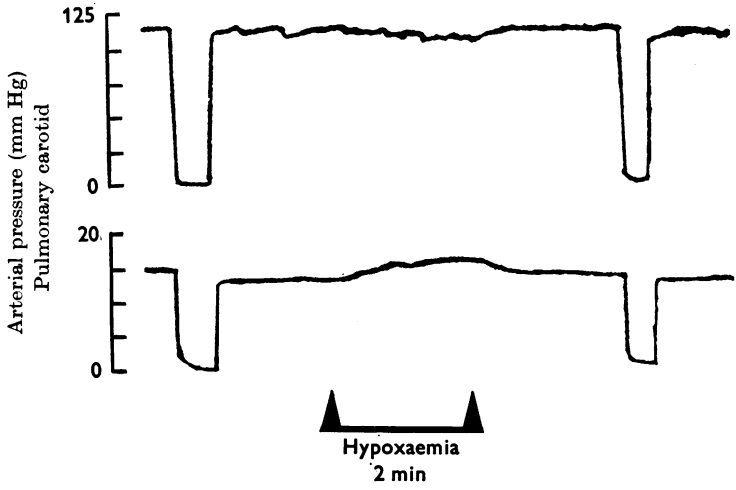

Fig. 2. Adult rabbit, 3·1 kg, breathing spontaneously under pentobarbitone anaesthesia. Hypoxia for 2 min, during which arterial P_{O_2} fell to 47 mm Hg, caused a rise in pulmonary artery pressure from 13 to 16 mm Hg, which returned to its control value on breathing air. There was little change in carotid pressure.

Living rabbits. Pentobarbitone anaesthesia decreased the respiratory rate from approximately 100–200 to 59 ± 4 breaths/min. Hypoxia (inhalation of 8–12% O_2) increased the rate to 74 ± 6 breaths/min. In each of fourteen rabbits (0·3–4·2 kg) hypoxia caused a rise in pulmonary arterial pressure (Fig. 2), which averaged 30%. Systemic arterial pressure and heart rate were unchanged. Intermittent positive pressure ventilation (67 ± 5 breaths/min and tidal volume 18 ± 2 ml.) with closed chest or open chest increased the control pulmonary arterial pressure slightly but did not abolish the pulmonary arterial pressure rise with hypoxia (Table 2). Varying tidal volume from 5 to 55 ml. and respiratory frequency from 20 to 120 breaths/min did not alter the hypoxic pressor response.

Acetylcholine in doses up to 1 μg injected into the jugular vein of eleven spontaneously breathing adult rabbits caused no significant change in pulmonary arterial pressure; systemic pressure fell by 25 ± 6 mm Hg. In three rabbits 2–5 μg acetylcholine caused a mean increase in pulmonary arterial pressure of 2 mm Hg from an initial value of 16 ± 1 mm Hg, while

TABLE 2. The effect of hypoxia in living rabbits (means ± S.E.)

	Number of rabbits	Inspired O_2 (%)	pH	P_{CO_2} (mm Hg)	P_{O_2} (mm Hg)	Heart rate	Systemic arterial pressure (mm Hg)	Pulmonary arterial pressure (mm Hg)
Spontaneous breathing	14	21	7·46 ± 0·01	30 ± 1	80 ± 3	290 ± 4	106 ± 3	10 ± 1
		8–12	7·48 ± 0·01	28 ± 1	40 ± 1	282 ± 6	100 ± 5	13 ± 1
Positive pressure ventilation, closed chest	10	21	7·45 ± 0·01	27 ± 2	112 ± 6	280 ± 6	111 ± 5	13 ± 1
		8–12	7·48 ± 0·02	27 ± 2	50 ± 2	278 ± 5	109 ± 5	15 ± 1
Positive pressure ventilation, open chest	10	21	7·39 ± 0·03	33 ± 3	85 ± 5	270 ± 10	118 ± 8	14 ± 1
		8–12	7·39 ± 0·02	32 ± 2	37 ± 2	245 ± 11	119 ± 7	16 ± 1

systemic pressure fell by 46 mm Hg. Atropine (10 mg I.V.) abolished the circulatory effects of these doses of acetylcholine, but during hypoxia pulmonary arterial pressure rose from a mean of 12–16 mm Hg.

DISCUSSION

Dennis (1968) found that in asphyxiated and hypoxic new-born rabbits the right ventricular systolic pressure showed a small increase irrespective of the direction of the change in systemic arterial pressure. She found that the magnitude of this hypoxic right ventricular pressor response increased with post-natal age. In particular, she reported a 10 % rise in right ventricular pressure during hypoxia in rabbits 0–2 days old and a 44 % rise at age 22–32 days. Interpretation of her results was made difficult by the absence of flow measurements and by the patency of the ductus arteriosus in rabbits < 3 days old.

The present experiments attempted to evaluate the hypoxic response in the isolated perfused new-born rabbit lung where pulmonary blood flow was controlled and the ductus arteriosus ligated. Perfusion of the new-born rabbits' lungs presented technical difficulties. The low pulmonary blood flow suggested the presence of vasoconstriction which in turn might obscure an hypoxic pulmonary pressor response. Vasoconstriction in small lungs might be due to substances released during surgical manipulation, or to the release of serotonin from the reservoir blood in quantities greater than could be metabolized. For example, two rabbits (3 days old), weighing 51 and 60 g respectively, failed to show any hypoxic response. However, it is unlikely that low pulmonary blood flow accounted for the poor hypoxic response in rabbits 3 days old, since rabbits 4–7 days and 9–11 days with clear pressor responses had comparable flows. Furthermore, when the lungs of five rabbits aged 3 days or less which had poor pulmonary pressor responses were replaced in the same circuit, using the same blood, by the lungs of rabbits 4–11 days old, larger (2–3 mm Hg) rises of pulmonary arterial pressure were obtained during hypoxia. The rise in pulmonary arterial pressure (20 %) in the adult isolated perfused lung during hypoxia was comparable to the rise in pulmonary arterial pressure (14 %) in the living rabbit (positive pressure ventilation with chest open, Table 2). The results obtained from the isolated perfused lung experiments are probably a true reflexion of changes in the pulmonary vasculature during hypoxia.

The present data together with Dennis's (1968) report indicate that the new-born isolated perfused rabbit lung has a poorly developed pressor response to hypoxia, and the magnitude of this response increases with post-natal age. It is possible that in the rabbit a strong hypoxic pulmonary pressor mechanism is not present in foetal life.

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