Evaluation of a disposable plastic, low volume, pumpless oxygenator as a lung substitute

A simple, disposable plastic device, with a total priming volume as low as 30 ml. (20 ml. per kilogram) has been tested as a lung substitute for prolonged periods. Primed with saline, it is interposed between a single femoral artery and vein, with cardiac action as the sole pumping mechanism. Asphyxiated puppies have been maintained for eight hours. Preliminary studies on moribund infants with the respiratory distress syndrome indicate sufficiently good chemical results to warrant further trial.

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THE TWO main functions of the lungs are to increase the oxygen content and to decrease the carbon dioxide content of the blood flowing through them. The clinical and chemical manifestations of pulmonary insufficiency may include such phenomena as lowered pH of the blood, a fall in arterial blood pressure, and physical exhaustion, but these changes are secondary to the oxygen–carbon dioxide exchange. In those clinical situations in which pulmonary function is severely impaired, it should be possible to carry out these prime functions of the lung artificially, and, if cardiac function is adequate, the heart's pumping action could be the driving mechanism for an extracorporeal lung. Severe degrees of arterial unsaturation could be corrected if an adequate external system were available and if a sufficient portion of the cardiac output could be directed through the device. In the studies described herein, a series of simple plastic disposable bubble type oxygenators was employed. Previous data of one of us[1] showed that 30 to 50 per cent of the total cardiac output could be made to flow through a single femoral arteriovenous fistula. A series of experiments was planned to evaluate the effects of interposing this extracorporeal lung between a single femoral artery and vein.

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GENERAL METHODS AND MATERIALS

The artificial lung. The extracorporeal lung was fabricated from concentric plastic cylinders as indicated in Fig. 1. The device was suspended 20 to 80 cm. above the right atrial level, the exact height determined as that level at which inflow and outflow balanced. One femoral artery and one

femoral vein were cannulated.* The arterial blood, under its own head of pressure, was mixed with a continuous stream of oxygen (flow rate, 2 to 4 L. per minute) and directed into the central cylinder of the external lung. The mixture then flowed over and under subsequent cylinders, was debubbled in the outer two cylinders with the aid of a plastic sponge coated with an antifoaming agent, and returned by gravity into the femoral vein.

In the early studies, the priming volumes were large and blood was used to fill the device. In the later studies, the size of the external lung was modified so as to limit the priming volume to 20 ml. per kilogram, and 0.85 per cent sodium chloride solution was used for priming. At the conclusion of the experiment, the entire volume of fluid in the external circuit was returned to the animal.

Measurements. Arterial blood pressure was measured with a capacitance electromanometer. Arterial oxygen saturation was measured by the cuvette oximeter by a modification of the method of Wood.[2] For continuous recording of arterial oxygen saturation, a cuvette oximeter was interposed between either a femoral artery and vein or a brachial artery and vein; this permitted continuous arterial flow through the cuvette. The output of the oximeter was amplified and recorded on a Grass oscillograph. An Instrumentation Laboratory Model 105 amplifier was used to measure pO_2,[3] pCO_2,[4] and ph with a glass electrode. Serum ketone levels were determined by the method of Michaels and associates.[5] Flow rates were ascertained either by a graduated cylinder-stopwatch method, or a gated sine-wave electromagnetic flowmeter† traced on a Sanborn direct-writing recorder.

General experimental procedures. Varying degrees of hypoxemia and hypercapnia were produced by tracheal obstruction in experimental animals. Total asphyxia was accomplished by completely enclosing the animals' heads in airtight polyethylene bags secured about the neck. Complete pulmonary capillary-alveolar block was produced by instilling outdated human blood into the trachea until: (1) arterial oxygen saturation was minimal, and (2) it was impossible to raise the arterial oxygen saturation with 100 per cent oxygen by positive-pressure endotracheal insufflation. Animals were maintained under very light anesthesia with thiopental, administered intermittently by vein. Normothermia was maintained by placing them on a simple heating pad.

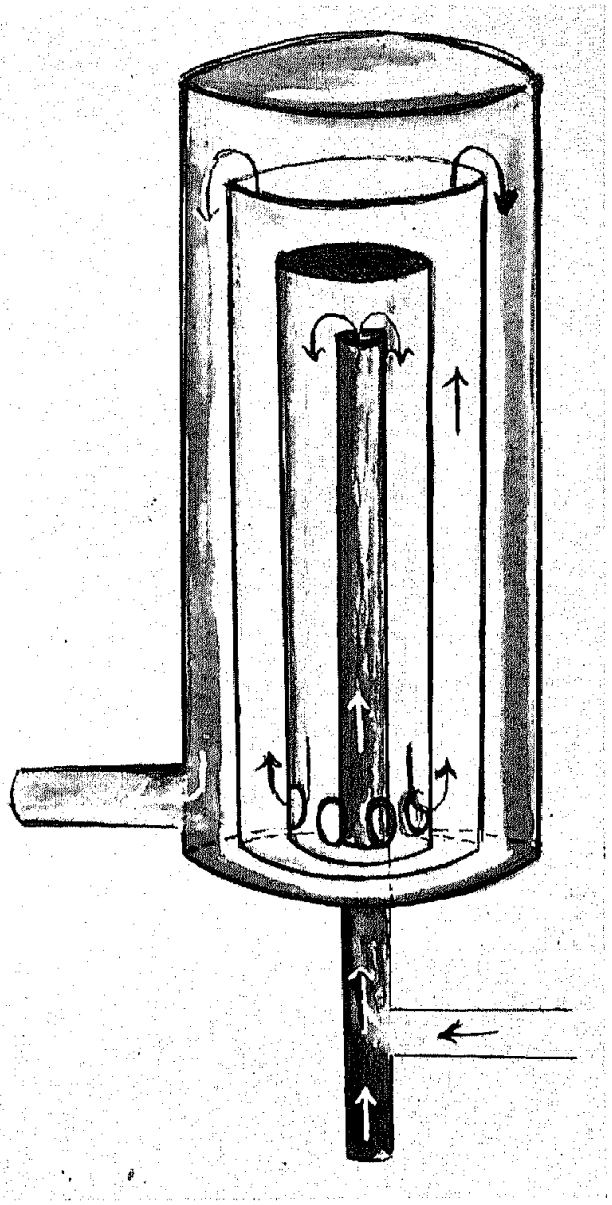

Fig. 1. Diagram of the oxygenator.

*This is the critical part of the technique. In order to obtain the flow for successful use, it is essential to use the largest-caliber, thinnest-wall cannula that can be inserted.

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Table I. Parameters of oxygenator function

Flow rate (ml./min./kg.)	*pO_2 change*		*pCO_2 change*		*pH change*	
	Inflow	*Outflow*	*Inflow*	*Outflow*	*Inflow*	*Outflow*
7	44	572				
46	119	420				
48	74	466	40	26	6.880	6.985
55	56	220	66	48	6.790	6.850
55	72	652	58	40	6.760	6.815
56			59	46	7.170	7.250
56			57	46	7.140	7.210
57	43	260				
68			58	50	7.107	7.160
68			60	53	7.040	7.095
85	34	91				
90	93	325	70	44	7.175	7.230
90			85	50	7.165	7.230
100	27	59				
Mean 65	59	343	61	45	7.025	7.092

Table II. Effects of temperature changes between 28.0 and 37.7° C. on CO_2 removal

Temperature		*pCO_2*		
Blood in oxygenator	*Rectal*	*Inflow*	*Outflow*	*% Change*
28.0	28.2	70.5	47.5	32.6
32.0	31.6	70.0	45.8	34.6
32.7	32.9	48.0	34.3	28.6
37.7	38.5	58.7	39.2	33.3

Table III. Effect of intermittent occlusion of the oxygenator on arterial oxygen saturation (38 experiments)

	Oxygenator on (% saturation)	*Oxygenator off (% saturation)*
Maximum change	8 to 85	90 to 20
Average change	31 to 73	72 to 31

RESULTS

Flow through external lung.

Single femoral artery. Two methods were used to measure the flow from a femoral artery through the oxygenator: (1) interposing a flowmeter in the return line, and (2) performing total cardiopulmonary bypass* and comparing the flow through the oxygenator to total flow. When the first method was employed, 30 measurements of 4 animals showed a mean oxygenator flow of 61 ml. per minute per kilogram. With the use of the second method, 26 measurements of 2 animals showed a mean oxygenator flow of 42 ml. per minute per kilogram, or 43 per cent of the controlled total arterial flow.

In the "bypass" experiments, 18 measurements of 2 animals indicated a mean flow-rate of 71 ml. per minute per kilogram, or 65 per cent of the controlled flow, while 23 measurements of 2 animals showed a flow of 101 ml. per minute per kilogram when the "non-bypass" method was used.

Effect of using both femoral arteries. The use of both femoral arteries increases the flow through the oxygenator by approximately 50 per cent. The effect of this increased flow on arterial pO_2 and pCO_2, is small. In 10 determinations of pO_2 on 3 animals, there was a 9 per cent increase; in 7 measurements on 2 animals there was no change in pCO_2.

Function of the oxygenator.

General parameters. The differences between the blood flowing into and out of the oxygenator are summarized in Table I. Measurements were made at various flow rates. The higher flow rates were obtained by cannulating the aorta via a carotid artery and returning the blood to an external jugular

*Total venous return is diverted through one of the oxygenators described here and pumped by an occlusive roller pump into a carotid artery at a constant rate of flow.

vein. Inflow pO_2 varied from 27 to 119 mm. Hg and outflow pO_2 from 59 to 654 mm. Hg, with a mean increment of 284 mm. Hg across the oxygenator (59 to 343 mm. Hg). In all studies except the one measurement at 100 ml. per minute per kilogram flow, the outflow oxygen saturation was raised to 98 per cent or higher.

The pCO_2 of the inflow blood varied from 40 to 85 mm. Hg, and the outflow blood from 26 to 53 mm. Hg. The mean fall in pCO_2 across the oxygenator was 16 mm. Hg (61 to 45 mm. Hg). The pH changes paralleled the pCO_2 changes, averaging an increment of 0.07 (7.025 to 7.092). The hemolysis rate averaged 0.054 gm. per 100 ml. per hour.

The effect of cold on CO_2 removal. A puppy weighing 5.4 kilograms was subjected to total cardiopulmonary bypass; one of the oxygenators described here was used as the pulmonary portion of the bypass. Flow was maintained at a constant rate of 318 ml. per minute. Temperature was monitored at two sites: the outer column of the oxygenator and the dog's rectum. Temperatures were altered by cooling or warming the skin; the animal was apneic. The effects of temperature changes between 28.0 and 37.7° C. on CO_2 removal are summarized in Table II.

Oxygenator function in vivo.

Effects of intermittent use.

EFFECT ON ARTERIAL OXYGEN SATURATION. Fig. 2 shows the effect of the intermittent use of the external lung on a hypoxic puppy. The upper tracing is arterial pressure and the lower is per cent oxygen saturation of arterial blood. This animal was subjected to asphyxia by means of a plastic bag. Without the external lung, arterial oxygen saturation fell to 0 to 10 per cent. When perfusion was restarted, saturations of 70 to 80 per cent were obtained.

In 38 experiments, arterial oxygen saturation was increased from a mean value of 31 per cent to a mean value of 73 per cent by perfusion. The maximum change was 8 to 85 per cent. Stopping the perfusion resulted in a mean fall of arterial oxygen saturation from 72 to 31 per cent, with a maximum change from 90 to 20 per cent (Table III).

EFFECT ON ARTERIAL pCO_2. Fig. 3 shows two typical studies on the effect of the external lung on CO_2 removal. In 22 experiments, the mean fall in arterial pCO_2 was 72 to 44 mm. Hg.

Treatment of asphyxiated animals.

Studies on individual animals. Nine dogs with a mean weight of 4.6 kilograms (range, 1.4 to 11.0 kilograms) were asphyxiated or subjected to total pulmonary capillary-alveolar block as described under "General Methods." Each animal was kept alive by the external lung for the duration of perfusion (2 to 8 hours). All died within 10 minutes after perfusion was stopped. Fig. 4 shows the results obtained in one such experiment. On the upper channel of each pair of tracings is a record of the arterial blood pressure, on the lower a record of the arterial oxygen saturation expressed in per cent. Pulmonary capillary-alveolar block resulted in a fall in arterial oxygen saturation to 8 per cent, and at *A* asystole occurred. External cardiac massage and endotracheal insufflation with 100 per cent oxygen did not result in any rise in

Table IV. The effect of the extracorporeal lung on compliance compared with the effect of anesthesia alone

	Experimental puppy			*Control puppy*		
	Before perfusion	*During perfusion*	*After perfusion*	*Before perfusion*	*During perfusion*	*After perfusion*
Pair I	7.7*	4.3	3.4	10.8	9.5	10.6
Pair II	5.7	5.1	6.2	9.6	7.0	Not measured
Pair III	9.8	6.8	8.9	6.9	8.3	6.2
Pair IV	2.5	2.9	2.9	8.3	8.9	7.3
Mean	6.4	4.8	5.4	8.9	7.4	8.0

*All figures are the means of at least three measurements.

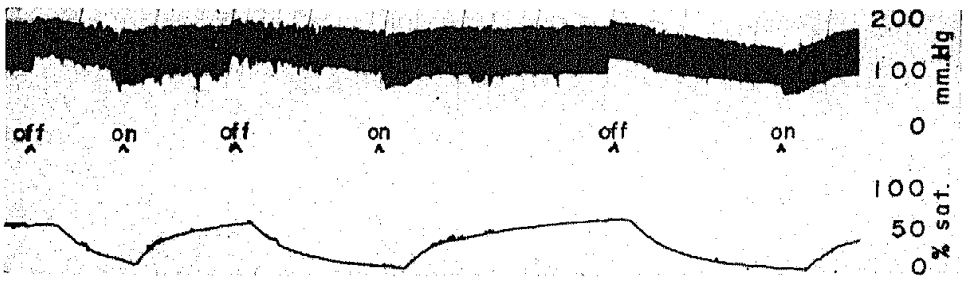

Fig. 2. Effect of intermittent occlusion of the oxygenator.

arterial oxygen saturation. When the oxygenator was turned on, *(D)* the arterial oxygen saturation promptly rose and stabilized at 80 per cent. Ketone levels were measured in two of these animals; they rose from 1.05 to 3.34 mg. per 100 ml. in one, and 2.8 to 12.9 mg. per 100 ml. in the other.

Studies on littermates. Four pairs of littermate puppies were subjected to total pulmonary capillary-alveolar block by the method described above. One of each pair served as a control (in one group, two littermates served as controls), and the remaining puppy was connected to the external lung. All control animals died within 20 minutes of the production of the block. The experimental animals survived as long as the perfusion was maintained (2, 4, 6, and 8 hours). Within 5 minutes after cessation of perfusion, all animals died.

Effect of extracorporeal oxygenation on lung-thorax compliance. Four pairs of puppies were studied. Each pair were either littermates or closely paired as to size and weight. All were lightly anesthetized with intravenous thiopental. Occlusive endotracheal tubes were inserted into the tracheas of all animals. Compliance of the lung-thorax was measured by the method of Richards and Bachman.[6] One animal from each pair was subjected to extracorporeal oxygenation by the technique described above. Measurements of compliance were made, in both control and experimental animals, immediately prior to extracorporeal oxygenation, during the procedure, and after removal of the external lung. The effect of the extracorporeal lung on compliance (expressed as milliliters per millimeter of mercury) is compared to the effect of anesthesia alone in Table IV.

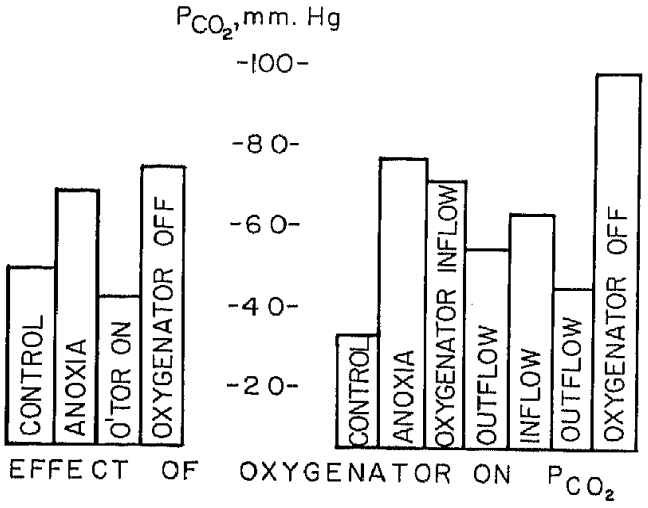

Fig. 3. Effect of the oxygenator on arterial pCO_2.

Survival experiments. Fifteen puppies, 14 of which weighed less than 3 kilograms (mean weight, 2.3 kilograms; range, 1.1 to 5.2 kilograms) were subjected to the technique for periods varying from 1 to 8 hours. Five animals were subjected to hypoxia, 10 were not; 11 recovered completely without detectable sequelae. Four died, 3 within 12 hours of cessation of perfusion and 1 immediately at the end of the perfusion. The cause of death in the first 3 animals was not determined; the fourth had inadvertent massive oxygen embolization. The results are given in Table V.

Clinical Trials.

Respiratory crisis secondary to cystic fibrosis. Four children with respiratory insufficiency secondary to cystic fibrosis were treated with the extracorporeal lung. All were comatose and unresponsive at the start of the procedure. Patient 2 was so moribund that intravenous epinephrine was required

to obtain an arterial pressure level sufficient to perform perfusion. Patients 1 and 2 were each perfused for five hours; the pCO_2 was lowered markedly and they awakened and became alert and responsive. Endotracheal aspiration was attempted, at which point both had sudden irreversible cardiac arrest. Patients 3 and 4 were perfused for four and eight hours, respectively. Both were markedly improved clinically; they awakened, answered questions, and had the chemical changes indicated in Table VI. Patient 3 died 48 hours, and Patient 4 eight days, after perfusion. Until the terminal comas, neither demonstrated neurologic or cardiovascular sequelae from the perfusion. Postmortem examinations of all four patients failed to reveal any alterations other than those due to the primary disease. Patient 4 had a plasma hemoglobin of 0.063 Gm. per 100 ml. at the end of 8 hours and a mean hemolysis rate of 0.008 Gm. per 100 ml. per hour.

Respiratory distress syndrome. Four critically ill newborn infants were perfused for 1, 12, 16, and 27 hours. All had had periods of apnea and their condition had deteriorated to the point that positive pressure ventilation was required to sustain life. Despite this type of ventilation assistance, severe changes in the arterial pO_2, pH, and pCO_2 were found. These changes, and the subsequent changes produced, are summarized in Table VII. All of these infants died and showed massive atelectasis on postmortem examination. One of the infants (27 hour perfusion) became apneic as soon as positive pressure ventilation was discontinued (synchronous with onset of perfusion) and remained completely apneic throughout the perfusion.

Cyanotic congenital heart disease. A 5-year-old child with severe cyanosis was maintained by the technique for 30 minutes while a subclavian-pulmonary artery anastomosis was made. The child died without awakening. Postmortem examination revealed splenic agenesis syndrome, with a single ventricle.

A moribund 6 pound infant, with com-

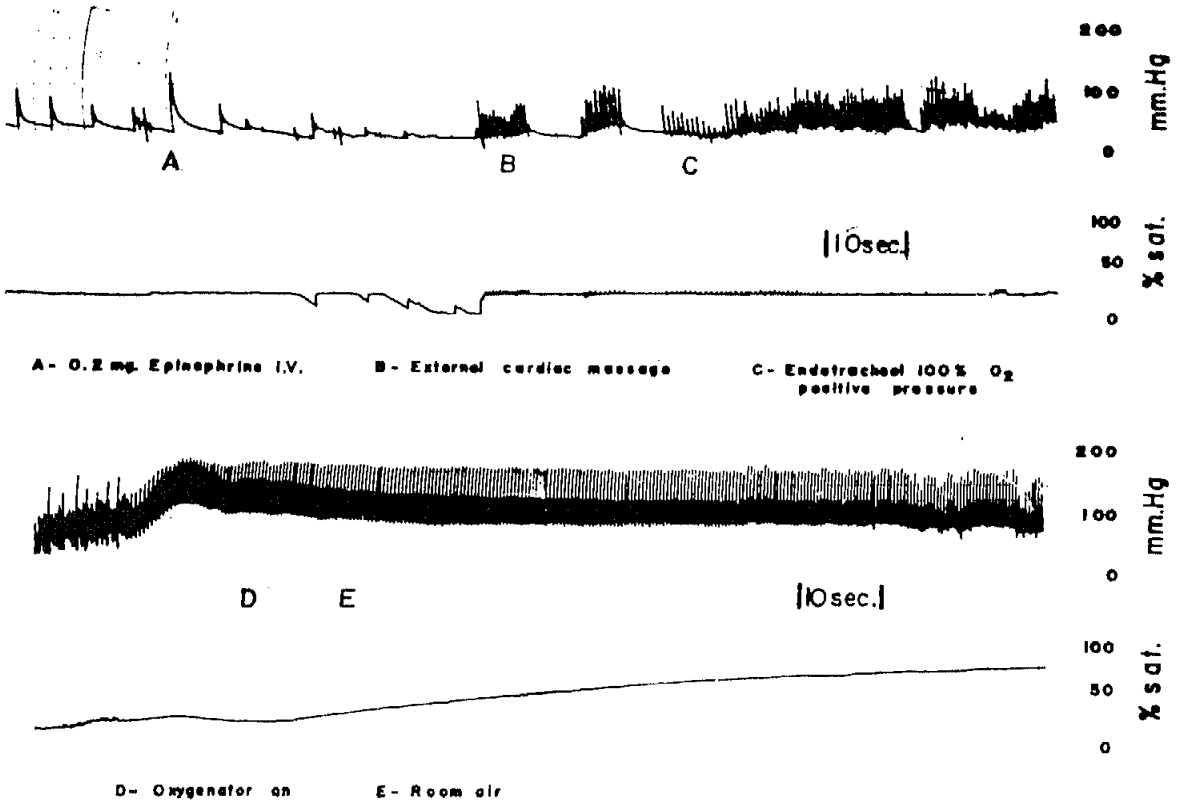

Fig. 4. Effects of the oxygenator on an animal with complete pulmonary capillary alveolar block. (See text for details.)

Table V. Survival experiments on 15 puppies*

Recovered	11
Died	4
Weight range	1.1 to 5.2 kilograms
Mean weight	2.3 kilograms

*Fourteen of the 15 puppies weighed less than 3 kilograms.

plete transposition of the great vessels, was placed on the external lung to assist oxygenation during an attempt to create, surgically, an atrial septal defect by the Blalock-Hanlon technique. Perfusion was performed for one hour. No measurements were made, but the operation was completed successfully. Now, 18 months after the operation, the child leads a normal life, and has had normal development, and satisfactory, but slow, growth. There are no clinical neurologic abnormalities detectable.

DISCUSSION

Extrapulmonic respiration has been attempted in various ways. Cole[7] has reviewed the method of intravenous oxygen bubbling. Other reports of intravenous, intra-arterial, intraperitoneal, and intraintestinal oxygen or hydrogen peroxide administration are too numerous to be catalogued. None of these techniques has been capable of maintaining long-term respiration. Extracorporeal pump-oxygenator systems have been used for variable periods of time, primarily as aids to intracardiac surgery, but also as treatment for experimental pulmonary insufficiency.[8, 9] Small-volume systems have been used on puppies,[10] but artificial pumping was required. The technique described here obviates the need for an extracorporeal pump and permits the use of a small priming volume and readily accessible blood vessels.

The success of the method is dependent upon whether or not a sufficient portion of the cardiac output can be caused to flow through the external lung. In early studies, flows of approximately 45 ml. per kilogram per minute were obtained from a single femoral artery. With improved cannulas and cannulation techniques, this was increased to approximately 60 ml. per kilogram per minute. In those studies in which the cardiac output was known, 43 per cent of the total arterial input was obtained from one femoral artery. Assuming a total cardiac output of 150 ml. per kilogram per minute in the "non-bypass" group, 40 per cent of the cardiac output was obtained from one femoral artery. Flows of this order of magnitude were sufficient to maintain total respiratory func-

Table VI. Studies on patients with cystic fibrosis

Patient No.	*Before perfusion*			*During perfusion*			*Comment*
	% sat. O_2	*pCO_2*	*pH*	*% sat. O_2*	*pCO_2*	*pH*	
1	100	96	7.215	89	79	7.265	Died after 5 hours of perfusion, during endotracheal aspiration
2	100	250	6.930	100	140	7.160	
3	95	218	6.900	95	71	7.300	Died 48 hours after 4 hour perfusion
4	98	141	7.180	95	97	7.392	Died 8 days after 8 hour perfusion; plasma hemoglobin was 0.063 Gm./100 ml. at end of perfusion
Mean	98	176	7.037	95	96	7.329	

Table VII. Studies on patients with neonatal respiratory distress syndrome

Perfusion duration (hours)	*Before perfusion*			*During perfusion*			*Weight (Kg.)*
	pO_2	*pCO_2*	*pH*	*pO_2*	*pCO_2*	*pH*	
1	31	44	7.07	65	45	7.05	1.8
12	24	93	7.01	50	67	7.12	2.6
16	25	100	7.02	47	63	7.20	2.7
27	28	112	6.93	52	53	7.16	3.6
Mean	27	87	7.01	54	57	7.13	

tion. The use of both femoral arteries allowed increased flow without appreciable effect on gas exchange. It is possible, particularly under clinical conditions, that if flow from one femoral artery is inadequate, the use of both vessels may be valuable.

In the over-all function of the external lung, oxygen exchange is accomplished easily. Carbon dioxide exchange is adequate, but somewhat more of a problem. It was postulated that a temperature drop might be a factor by facilitating CO_2 binding by hemoglobin. The studies described on the effect of temperature change on CO_2 removal show that this is not a factor. Animals and patients with prolonged anoxemia develop acidosis even when oxygenation is performed adequately. Part of this acidosis is metabolic, as reflected by a rise in ketone bodies at a mean rate of approximately 3 mg. per 100 ml. per hour and the pH–pCO_2 relationships. Even though the amount of $NaHCO_3$ theoretically required to overcome the metabolic component of the acidosis has been administered and the pCO_2 reduced to normal levels by the external lung, the pH remains low. This aspect of the procedure requires further investigation.

The hemolysis rate in the early animal studies was low. In the child with cystic fibrosis perfused for eight hours, the rate was negligible, 0.008 Gm. per 100 ml. per hour. Hemolysis has not presented any problem. Temperature drop, a factor in early studies, is now controlled with a simple heating pad and/or a 150 watt light bulb placed next to the artificial lung.

Since one of the prime targets for the clinical use of the technique is the respiratory distress syndrome, it was considered important to determine the effect of the procedure upon surface active lung material. Tooley[11] has reported surfactant washout during total cardiopulmonary bypass. Measuring lung compliance is a crude screening method for evaluation of surfactant washout. It may be noted that the compliance fall that occurred in the perfused animals was no greater than that in the controls. Partial bypass of this type apparently does not interfere with lung surface active material, since any significant reduction in surfactant should cause a marked decrease in compliance.

The early clinical trials have shown encouraging chemical improvement. It was apparent that the prognosis of the patients with cystic fibrosis and those with the respiratory distress syndrome was hopeless from the long-term point of view. The fact that there were no apparent neurologic sequelae in the short-term survivors, and that one child is now living 18 months after perfusion without apparent harm suggests that the procedure per se is safe. Further trials seem justified in patients with severe, life-threatening pulmonary insufficiency.

SUMMARY

1. A simple small volume, plastic disposable pumpless device has been designed which is capable of functioning as an artificial lung.

2. Interposition of this device between a single femoral artery and vein altered arterial pO_2 and pCO_2 to levels compatible with life, in the face of complete pulmonary capillary-alveolar block, in puppies.

3. Early trials of the technique on moribund infants with respiratory distress syndrome have produced encouraging chemical results, although clinical improvement was only temporary.

4. Two children with respiratory crises due to cystic fibrosis were improved by 4 and 8 hours of perfusion and survived 2 and 8 days beyond perfusion without apparent harm from the procedure.

5. A child with complete transposition of the great vessels, maintained on the device for one hour while operation was performed, is alive 18 months postoperation, without vascular or neurologic sequelae.

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