Extracorporeal partial bypass with the use of fluorocarbon liquid-membrane oxygenator

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There are many effective methods of respiratory support for the various types of lung disorders. However, there are a number of acute lung diseases with severe hypoxemia that are refractory to the conventional modes of therapy, such as intermittent positive pressure ventilation, positive end-expiratory pressure, and continuous positive airway pressure. Clinicopathologic conditions in which a stable arterial hypoxemia is the main cause of death are severe pneumonia, shock-lung syndrome, respiratory distress syndrome, fat, thrombus, or amniotic fluid embolism, noxious gas inhalation and others.

Clinical experience has shown extracorporeal membrane oxygenation to be the most effective method in the management of acute respiratory insufficiency in these cases, since a membrane oxygenator permits prolonged respiratory support to several weeks in patients with minimal lung function.[1-4] However, extracorporeal membrane oxygenation is not widely used yet because of the short term of "membrane lung" life, as the gas permeability through a stable membrane decreases during prolonged bypass, the persistent hazard of systemic microembolization with blood cell aggregates, the design complexity of the membrane lung, and the high cost of commercially available membrane oxygenators.

A new approach in the development of extracorporeal membrane oxygenation is the design of a liquid-membrane oxygenator[5–11] where blood and gas are separated by a thin liquid film. Different fluorocarbons are used to generate liquid membranes in this type of "artificial lung."

This report deals with the development and experimental study of the fluorocarbon liquid-membrane oxygenator.

Methods and materials

Fifty experiments were undertaken on mongrel dogs, each weighing 22 to 30 kg (*Table 1*). In Group I, 40 dogs underwent vein-to-vein bypass with the use of the fluorocarbon liquid-membrane counterflow oxygenator. The time of bypass was as long as 24 hours. In Group II (controls), 10 dogs underwent the same bypass circle with the conventional bubble oxygenator. Duration of the bypass was as long as 9 hours. The experimental conditions were the same in both groups.

The dogs were anesthetized with hexethal intravenously, 1.0 to 1.5 mg/kg/hr. In all experiments, the animals breathed spontaneously. After the infusion of heparin, 4 mg/kg, the right ventricle was cannulated through the right femoral vein. The blood was drained by gravity from caval veins, cannulated through the jugular vein and the left femoral vein. The cannulas were connected to the apparatus for artificial blood circulation. The bypass circle was primed with serum substitutes (dextran, lactasol, 5% glucose). The priming volume did not exceed 1000 ml. Hemodilution was 30% to 45%. The body temperature of 37 C was maintained by a heat exchanger on the arterial line. The bypass was conducted with a roller pump. The blood flow rate was about 40 to 55 ml/kg/min. During bypass 5% glucose, 60 to 80 ml/hr, and heparin, 1.5 mg/kg/hr, were administered intravenously. After bypass heparin was neutralized by protamine sulphate (1:1). The hemodilution was eliminated by diuretics (furosemid, 1 mg/kg). All the experiments were performed under sterile conditions.

Design and performance of the oxygenator

The oxygenator unit consists of three main parts: a chamber of liquid-membrane formation, a gas-exchange chamber, and a liquid-membrane collapsing chamber. Perforated cylinder, diverting tube, and vizor are intended to prevent irruption of fluorocarbon to the organism with blood. An oxygen bubble when passing through fluorocarbon is covered with a thin film of the given liquid (the phase of liquid-membrane formation) and enters the gas-exchange chamber, where diffusion of O_2 through the liquid membrane to the blood and

Table 1. Mortality in experiments

Type of oxygenator	No. of experiments	Survived	Died	Cause of death
Fluorocarbon liquid-membrane oxygenator (bypass time to 24 hr)	40	34	6	Bleeding Anesthesiologic mistake Perforation of heart
Bubble oxygenator (bypass time to 9 hr)	10	0	10	High rate of hemolysis

of CO_2 vice versa (gas-exchange phase) takes place. In the liquid-membrane collapsing chamber, the bubbles collapse; CO_2 and remaining O_2 pass through the holes in the chamber to atmosphere, and fluorocarbon drains down the diverting tube. Then the cycle is repeated.

Fluorocarbon

The fluorocarbon $C_{12}F_{26}O$ was taken for liquid-membrane formation. It is a colorless, odorless, biologically inert fluid with a specific gravity of 1.89 g/cc. Fluorocarbon is not miscible with blood and can dissolve great amounts of O_2 (to 50v%) and CO_2 (to 190v%).

The toxicity of the given type of fluorocarbon was evaluated in the in vitro study for its effects on cell proliferation in a controlled cell-culture of lung fibroblasts of the china hamster. Mutagenic effects of fluorocarbon were determined on human leukocytes. The consequences of contact of fluorocarbon with blood and isolated rat liver mitochondria were studied in vitro. We evaluated K^+ permeability of erythrocyte membranes, the rate of K^+ output by erythrocytes and the content of K^+ in erythrocytes at the first, second, third, and fifth minutes of the blood-fluorocarbon contact.

The oxidation rate of NAD-dependent substrates and succinate in states three and four[12] and the rate of uncoupled oxidation were determined. Ca^{2+}, K^+, and Cl^- conductivity of a bilayer membrane after its contact with fluorocarbon were also studied on rat liver mitochondria.

Arterial pressure, venous pressure, and electrocardiograms were monitored during bypass. In blood samples pH, pO_2, pCO_2, oxygen circulation, and plasma bicarbonate of venous and arterial blood were registered before, after, and during bypass. For hematological and biochemical analyses, the following studies were performed: hemoglobin concentration; cell volume; erythrocyte, leukocyte and platelet counts, stability of erythrocytes to acid hemolytics; plasma-free hemoglobin; total protein; blood urea nitrogen; uric acid; bilirubin; fibrinogen; blood glucose; serum lactic dehydrogenase; and serum electrolytes (K^+, Ca^{2+}, Na^+). With a K^+-selective electrode, the K^+ content in erythrocytes, the rate of the valinomycin-stimulated and ouabain-sensitive K^+ output of erythrocytes were studied. The distribution of monospiral and bispiral nucleotic acids between nucleus and cytozolum was determined in blood lymphocytes histochemically. The shape and surface of erythrocytes were studied with the scanning microscope. Seven to 14 days after the experiment the dogs were killed and internal organs were taken for a morphologic and chromatographic study.

Results

The experiments have demonstrated that the liquid-membrane oxygenator at a blood flow rate of 800 to 1000 ml/min ensures a stable and adequate level of gas exchange throughout the experiments.

P_vO_2 in the blood entering the oxygenator was 45.5 ± 4.2 torr. P_aO_2 in the outlet of the oxygenator was 230 ± 11.5 torr ($p < 0.05$). ΔpO_2 in blood varied around 187 ± 3.47 torr. Hemoglobin saturation in the outlet blood was about 100% in all the experiments.

The liquid-membrane oxygenator ensures an adequate CO_2 elimination. P_vCO_2 was 36.1 ± 4.25 torr at the inlet and 32.6 ± 0.9 at the outlet of the oxygenator. $\Delta\ pCO_2 = 4.02 \pm 0.12$ torr. If pCO_2 in venous blood was at a high level, the pCO_2 gradient increased correspondingly and $PaCO_2$ was at a normal level.

$\Delta pO_2, \Delta pCO_2$ has been shown to be a function of blood flow rate. A liquid-membrane oxygenator gives adequate oxygenation and eliminates CO_2 at a blood flow rate of 0.8 to 1.7 L/min with a fixed O_2 flow of about 0.8 L/min. In all experiments, the pH of arterial and venous blood remained at physiologic levels (*Table 2*).

The changes in hematologic values such as hemoglobin, cell volume, and erythrocyte count are typical of the bypass with hemodilution without the use of donor's blood (*Table 3*). At the beginning of the bypass, because of hemodilution, there was a decrease of all parameters. During the following hours on bypass the decrease slowed and continued only due to bleeding, which was compensated for by serum substitutes. The same changes were observed in the control group, where the bypass was carried out with a conventional type of bubble oxygenator. The decrease in platelets was different from that of the control group. In the first 2 hours of the bypass with a bubble oxygenator, the number of platelets decreased from 30.1 $\pm$ 1.32 $\times$ 10^4 to 7.55 $\pm$ 0.9 $\times$ 10^4 ($p < 0.05$), which is almost four times lower than the initial number, whereas on bypass with the liquid-membrane oxygenator it fell only two times lower (from 25 $\pm$ 0.33 $\times$ 10^4 to 12.2 $\pm$ 0.29 $\times$

Table 2. Blood gases and acid-base state in prolonged bypass

Time of bypass, hr		pH		pCO_2 torr		BE mEkv/L		pO_2 torr		SO_2%	
		L-M oxyg	Bubble oxyg	L-M oxyg	Bubble oxyg	L-M oxyg	Bubble oxyg	L-M oxyg	Bubble oxyg	L-M oxyg	Bubble oxyg
Before	V	7.27 ±0.08	7.29 ±0.07	44.2 ±2.3	45.1 ±1.44	−4.5 ±0.7	−3.2 ±0.3	55.1 ±5.2	45.0 ±2.3	78.0 ±0.36	71.0 ±0.49
	A	7.31 ±0.05	7.34 ±0.01	40.1 ±2.2	41.3 ±1.21	−3.4 ±0.4	−2.3 ±0.2	90.3 ±4.8	89.5 ±3.1	96.8 ±0.21	96.7 ±0.54
1	V	7.36 ±0.015	7.35 ±0.016	38.1 ±1.25	37.6 ±2.5	−4.7 ±0.6	−2.5 ±0.3	56.8 ±3.1	46.2 ±4.7	78.6 ±0.82	73.4 ±0.61
	A	7.41 ±0.016	7.45 ±0.025	33.8 ±1.13	30.5 ±2.4	−3.4 ±0.6	−1.2 ±0.3	228 ±10.5	546 ±8.1	100 ...	100 ...
6	V	7.37 ±0.01	7.34 ±0.018	34.9 ±1.04	40.0 ±2.6	−3.6 ±0.5	−1.4 ±0.35	54.0 ±2.2	36.4 ±1.73	76.0 ±0.86	70.6 ±0.58
	A	7.41 ±0.009	7.45 ±0.007	31.6 ±1.6	30.4 ±1.6	−2.6 ±0.5	−1.0 ±0.35	235 ±9.9	479 ±10.1	100 ...	100 ...
12/9	V	7.39 ±0.01	7.45 ±0.02	36.1 ±0.88	34.8 ±2.7	−2.9 ±0.6	+2.44 ±0.4	53.0 ±2.5	38.8 ±1.4	80.0 ±1.23	74.3 ±0.69
	A	7.43 ±0.01	7.60 ±0.025	28.2 ±1.3	20.2 ±1.3	−1.7 ±0.6	+3.5 ±0.2	244 ±5.5	442 ±9.1	100 ...	100 ...
18	V	7.38 ±0.008	... ...	37.0 ±1.29	... ...	−2.7 ±0.3	... ...	55.0 ±2.4	... ...	76.5 ±0.98	... ...
	A	7.43 ±0.009	... ...	33.6 ±1.23	... ...	−1.7 ±0.3	... ...	242 ±6.9	... ...	100 ...	... ...
24	V	7.33 ±0.02	... ...	40.1 ±3.6	... ...	−3.2 ±1.4	... ...	45.0 ±3.0	... ...	69.0 ±1.47	... ...
	A	7.38 ±0.017	... ...	35.7 ±3.0	... ...	−1.3 ±0.7	... ...	218 ±2.1	... ...	100 ...	... ...

L-M oxyg = liquid-membrane oxygenator

Table 3. Hematologic parameters in prolonged bypass

Time of bypass, hr	Hemoglobin, g/dl		Platelet count × 10^4		Cell volume, %		Free plasma hemoglobin, mg%	
	L-M oxyg	Bubble oxyg	L-M oxyg	Bubble oxyg	L-M oxyg	Bubble oxyg	L-M oxyg	Bubble oxyg
Before	13.8 ±0.12	17.5 ±0.98	25.1 ±0.33	30.1 ±1.32	40.0 ±0.33	55.1 ±1.58	0 ...	0 ...
1	11.5 ±0.21	12.5 ±0.12	12.2 ±0.29	7.55 ±0.9	34.0 ±0.42	39.2 ±1.1	0 ...	0 ...
6	9.4 ±0.13	10.1 ±0.25	6.3 ±0.13	2.8 ±0.22	26.0 ±0.36	30.9 ±0.89	0 ...	77.3 ±1.18
12/9	8.7 ±0.37	9.3 ±0.08	4.1 ±0.16	2.01 ±0.06	24.0 ±0.57	28.4 ±0.73	0 ...	177.5 ±1.65
18	8.2 ±0.37	... ...	3.5 ±0.16	... ...	21.0 ±0.72	... ...	0 ...	... ...
24	7.2 ±0.6	... ...	2.0 ±0.22	... ...	20.0 ±1.83	... ...	0 ...	... ...

L-M oxyg = liquid-membrane oxygenator.

10^4 ($p < 0.05$). The lowest number of platelets ($2.0 \pm 0.22 \times 10^4$) was seen at the eighth to ninth hour of the bypass in the control, and at the 24th hour in the experimental group. There was no free plasma hemoglobin throughout the experiments (to 24 hr). In the control group the free plasma hemoglobin was observed at the seventh hour of the bypass (77.3 ± 1.88 mg/dl) and increased quickly to reach 1000 mg/dl in the next 2 to 3 hours. Among the biochemical data, the changes in fibrinogen and total protein content are of particular interest (*Table 3*). During the 24 hours of the bypass, the total protein concentration decreased from 7.2 ± 0.12 to 6.34 ± 0.3 g/dl ($p < 0.05$), whereas in the control group it decreased from 7.14 ± 0.09 to 3.51 ± 0.02 g/dl ($p < 0.05$) in 9 hours.

During bypass, despite the constant level of serum K^+, the ion content in erythrocytes was reduced considerably. The K^+ loss rate was essentially lower in erythrocytes of animals who underwent bypass with the liquid-membrane oxygenator than in the control group. The distribution of monospiral and bispiral forms of nucleotic acids between nucleus and cytozolum of lymphocytes did not change. The blood urea nitrogen, uric acid, and total bilirubin levels changed analogically in both groups. The analysis of erythrograms of the first group demonstrated no considerable changes in stability of erythrocytes to the acid hemolytic after 10 to 24 hours of the bypass. In the scanning microscope we had not seen any shape and surface aberrations of erythrocytes, whereas all animals in the control group had considerable deformation and devastation of erythrocytes at the fifth to seventh hour of the bypass. All the animals of the experimental group were successfully taken off bypass. There were no signs of fluorocarbon intoxication. Six animals died of various causes other than the oxygenator (*Table 4*). All the animals of the second group died of massive hemolysis. The in vitro studies demonstrated that in rat liver mitochon-

Table 4. Biochemical parameters in prolonged bypass

Time of bypass, hr	Total protein g/dl		Residual nitrogen mg/dl		Total bilirubin mg/dl		Fibrinogen mg/dl	
	L-M oxyg	Bubble oxyg	L-M oxyg	Bubble oxyg	L-M oxyg	Bubble oxyg	L-M oxyg	Bubble oxyg
Before	7.20 ±0.12	7.14 ±0.09	29.0 ±0.11	30.0 ±0.27	0.45 ±0.015	0.46 ±0.03	355 ±4.57	520 ±3.8
1	6.95 ±0.1	5.05 ±0.15	29.0 ±0.15	29.03 ±0.19	0.45 ±0.012	0.49 ±0.06	200 ±2.6	210 ±2.5
6	6.83 ±0.19	4.04 ±0.4	30.0 ±0.26	29.0 ±0.19	0.49 ±0.017	...	170 ±2.55	70. ±1.8
12/9	6.80 ±0.28	3.51 ±0.02	30.0 ±0.18	28.5 ±0.15	0.58 ±0.015	...	164 ±1.67	64. ±2.4
18	6.74 ±0.12	...	31.0 ±0.24	...	0.57 ±0.018	...	158 ±2.58	...
24	6.34 ±0.33	...	30.0 ±0.52	...	0.59 ±0.017	...	145 ±4.49	...

L-M oxyg = liquid-membrane oxygenator.

dria after 15 to 40 minutes of contact with fluorocarbon there was an activation of succinate oxidation and a small inhibition of oxidation in NAD-depending substrates without any damage of the mechanism of oxidation phosphorylation coupling. The growth and proliferation of lung fibroblasts of hamsters were not altered by fluorocarbons. The Ca^{2+}, K^+, and Cl^- conductivity of bilayer membranes remained constant.

Discussion

The experiments have demonstrated the designed model of liquid-membrane oxygenator to be convenient and easy to operate. It has a small priming volume of about 1000 ml. The priming volume of fluorocarbon is 300 ml. The fluorocarbon losses in 24 hours of the bypass do not exceed 50 to 100 ml, which may be attributed completely to evaporation. The developed fluorocarbon trap works effectively. We did not find any signs of fluorocarbon irruption into the animal organisms at a blood flow rate to 1600 ml/min. Results of experiments demonstrated a stable performance of the oxygenator, adequate blood oxygenation, and CO_2 elimination throughout the bypass (to 24 hours). During and after the bypass there was no damage to erythrocytes, no reduction in their resistance, and no free plasma hemoglobin. Comparing the liquid-membrane oxygenator with a conventional bubble oxygenator, the advantages of the new oxygenator are a low rate of platelets destroyed, no hypoproteinemia or hypofibrinogenemia, and a lower rate of K^+ loss by erythrocytes.

We may regulate the gas exchange by changing the size of disperser holes. In the performance of the oxygenator there is a constant regeneration of liquid membranes and, therefore, the duration of service is unlimited.

The in vitro experiments have demonstrated that fluorocarbon is not toxic and does not interfere with oxidative processes in mitochondria.

In further experiments it would be

useful to study the performance of the oxygenator at a high flow rate and to undertake a thorough study of fluorocarbon-blood interaction in prolonged (to several days) bypass.

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