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OXYGEN-EXCHANGE REACTION BETWEEN ARTIFICIAL LUNG DEVICE: THE HEME EMBEDDED IN POLYMERIZED LIPO LIPOSOME AS AN ARTIFICIAL OXYGEN CARRIER

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ABSTRACT

An oxygen-supplying medium (OSM), which was prepared by embedding a synthetic heme complex in a bilayer of polymerized lipid liposome (polylipid liposome/heme), could bind molecular oxygen reversibly under physiological conditions. The oxygen-exchange reaction of OSM with blood was examined by using a liquid/liquid artificial lung device. For example, deoxy-blood ($p_s(O_2) = 0$ torr) was passed countercurrent to oxy-OSM ($p_s(O_2) = 154$ torr) through hollow fibers of the device to provide oxy-blood ($p_b(O_2) = 57$ torr). The OSM was physicochemically and mechanically stable under strong shear stress during the passage through the hollow fibers and acted as the oxygen mediator to blood.

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INTRODUCTION

The primary functions of human lungs are to supply oxygen to blood and to remove carbon dioxide from blood. Artificial devices for the oxygenation of blood outside of the body, e.g., artificial heart-lung devices and artificial lung devices in a gas(oxygen)/liquid(blood) contact system, have been developed intensively during recent years [1-4]. Every heart-lung machine thus consists of a blood pump to replace the heart's function and a gas-exchange device to substitute for the natural lungs. For this gas/liquid artificial lung system, the device supplies oxygen to deoxy blood but cannot efficiently remove carbon dioxide, because carbon dioxide diffusion across the gas-liquid boundary is the rate-determinating step. Thus a liquid (oxygen-enriched medium)/liquid (blood) artificial lung system is expected to provide oxygen and remove carbon dioxide effectively and to act as a complete substitute for human lungs.

Recently, we found and reported that synthetic heme derivatives embedded in a bilayer of natural, synthetic, and polymerized lipid liposome (abbreviated as "liposome/heme") binds molecular oxygen under physiological conditions [5-7]. The oxygen-binding rate and affinity of the liposome/heme were similar to those of blood [6-9]. In the present work we prepared an oxygen-supplying medium (OSM) for a liquid/liquid artificial lung by embedding the 5,10,15,20-tetra(α,α,α,α-*o*-(2′,2′-dimethyl-20′-(2″-trimethylammonioethylphosphonatoxyeicosanamide)phenyl)porphinatoiron(II) complex (lipid-heme) of 1-laurylimidazole in a bilayer of the polymerized 1-(9′-(*p*-vinylbenzoyl)nonanoyl)-*O*-octadecyl-*rac*-glycero-3-phosphocholine (lipid monomer) liposome (see Scheme 1) and measured the oxygen-exchanging reaction between OSM and blood by using a hollow-fiber-type artificial lung device. The oxygen-supplying ability of the OSM will be compared with that of physiological salt solution (saline) and blood itself.

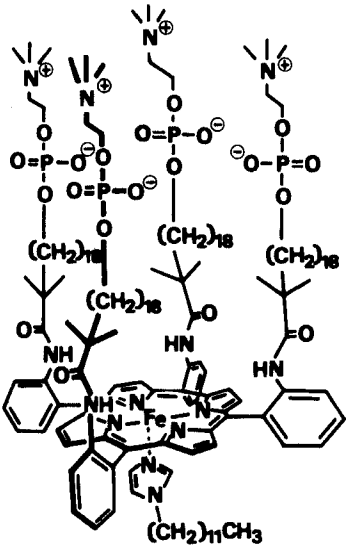
EXPERIMENTAL

Materials

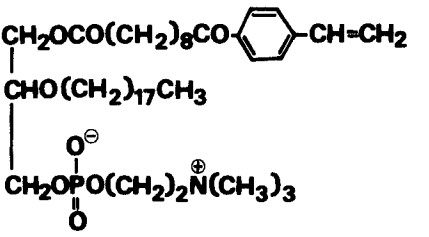
Lipid-heme, 1-laurylimidazole, and lipid monomer were prepared as reported in Refs. 5, 6, 10, 11.

Preparation of OSM

The solution of lipid-heme, 1-laurylimidazole, and lipid monomer (molar ratio, lipid-heme/1-laurylimidazole/lipid monomer 1/3/50) in methanol/



Lipid heme and laurylimidazole



Lipid monomer

SCHEME 1.

benzene (1/20 vol/vol)) was freeze dried in vacuo to give a brownish powder. The powder was solubilized with saline to give a suspension. The suspension was homogenized and ultrasonicated (50 W × 20 min, probe-type sonicator, Nihon-Seiki UP-600) under nitrogen to yield a red, transparent solution. The solution thus prepared was allowed to polymerize under nitrogen by ultraviolet irradiation (32 W, 50°C, 1 h with a low-pressure Hg 1 amp, Riko-Kagaku, UV-32B), giving the deoxy-OSM solution (λ_{max} 535 and 562 nm (sh)). Then the deoxy-OSM solution was concentrated (until the concentration of heme, [heme], reached 1.0-5.0 mmol/L and the concentration of lipid, [lipid], reached 4.0-20 wt%) by an ultrafiltration method (Millipore, Pericon Lab. XX42-OLC-KO). Dextran (0.82 wt%, $\bar{M}$ 40 000) was added to give a colloidal osmotic pressure comparable to that of blood. The volume of oxygen dissolved in the OSM solution ([heme] = 5 mmol/L) was volumetrically measured to be ~10.3 mL O_2/100 mL solution (92% of the theoretical value, at $p(O_2)$ = 154 torr (in air) and 25°C), which is about 20 times larger than that of water and saline.

Preparation of Blood

Bovine blood was used after addition of sodium citrate solution to suppress coagulation (blood/3.8% sodium citrate solution = 1000/12 vol/vol). Deoxy-blood was obtained by a carbon dioxide flow method with an artificial lung device of the gas/liquid phase type. pH was controlled at 8.0.

Oxygen-Exchange Reaction with Artificial Lung Devices

An oxygen-exchange flow circuit with an artificial lung device was set up as shown in Fig. 1. The hollow-fiber-type artificial lung (HF/AL) device was purchased from Kawasumi Medical Co. (hollow fiber dialyzer, Kawasumi; i.d. of hollow fiber 200 μm, membrane thickness 5 μm, average pore size 2.5 nm, length 175 mm, number of hollow fiber 2040, useful area 0.24 m^2). The deoxy-blood was passed through the inside of the hollow fibers at a flow rate, v_b, of 15 mL/min. OSM, saline, or bovine blood was passed countercurrent past the outside of the fibers in the device at a flow rate, v_s, of 400-500 mL/min, returning to a storage tank of oxygen supplying medium to be used repeatedly. The oxygen-exchange efficiency was measured by an oxygen-probe method (Yellow Spring Institute, oxygen electrode YSI 5331) and visible absorption spectroscopy (Hitachi, spectrophotometer UV-320).

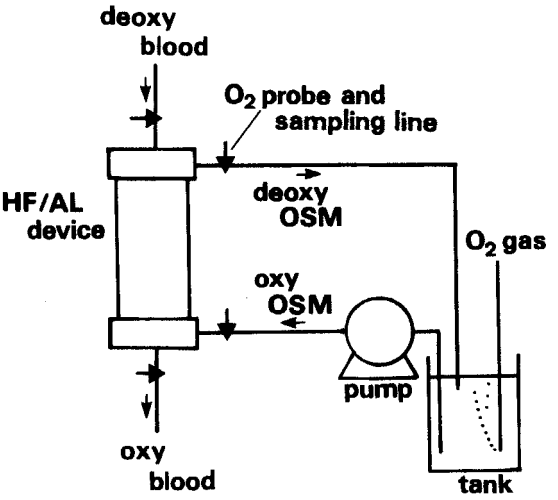


FIG. 1. Schematic of the oxygen-exchanging flow circuit with an artificial lung device.

RESULTS AND DISCUSSION

The oxygen-exchange profile from OSM to deoxy-blood was monitored with an oxygen probe. The oxygen pressure of the deoxy-blood ($p_b(O_2)$ = 0-7 torr) increased to 57 torr after passing through the artificial lung device and contacting the OSM. On the other hand, the oxygen pressure of the OSM ($p_s(O_2)$ = 154 torr) decreased to 141 torr with a time dependence symmetrical to that of blood.

The oxygen-exchange was also estimated spectroscopically (Fig. 2). The visible absorption spectrum of the deoxy-blood (λ_{max} 555 nm) changed to that of oxy-blood (λ_{max} 546 and 570 nm) after passing through the artificial lung device. On the other hand, the oxy spectrum (λ_{max} 543 nm) of OSM changed to the deoxy one (λ_{max} 540 nm).

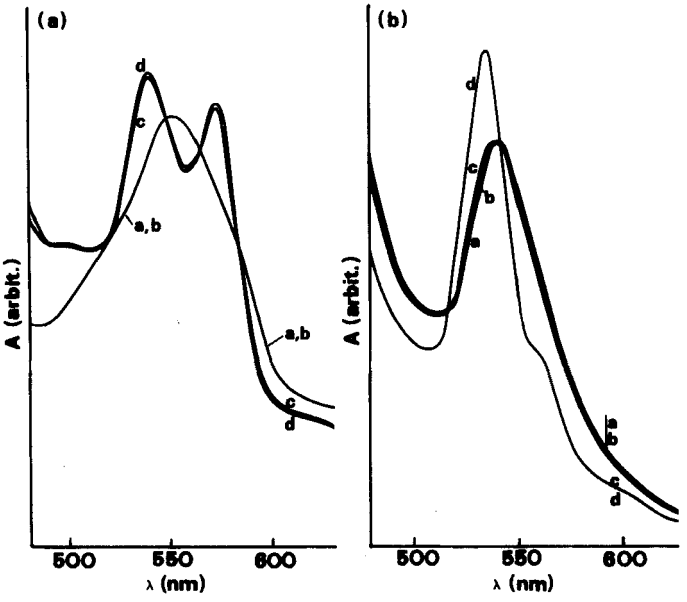


FIG. 2. Visible absorption spectra of the bovine blood (a) and the oxygen-supplying medium (OSM) (b) before and after passing through a liquid/liquid artificial lung device. The bovine blood; a, b, deoxy and before passage ($p_b(O_2)$ = 0 torr); c, after passage ($p_b(O_2)$ = 57 torr); d, oxy ($p_b(O_2)$ = 760 torr). OSM: a, oxy ($p_s(O_2)$ = 760 torr); b, before passage ($p_s(O_2)$ = 154 torr); c, after passage ($p_s(O_2)$ = 141 torr; d, deoxy ($p_s(O_2)$ = 0 torr).

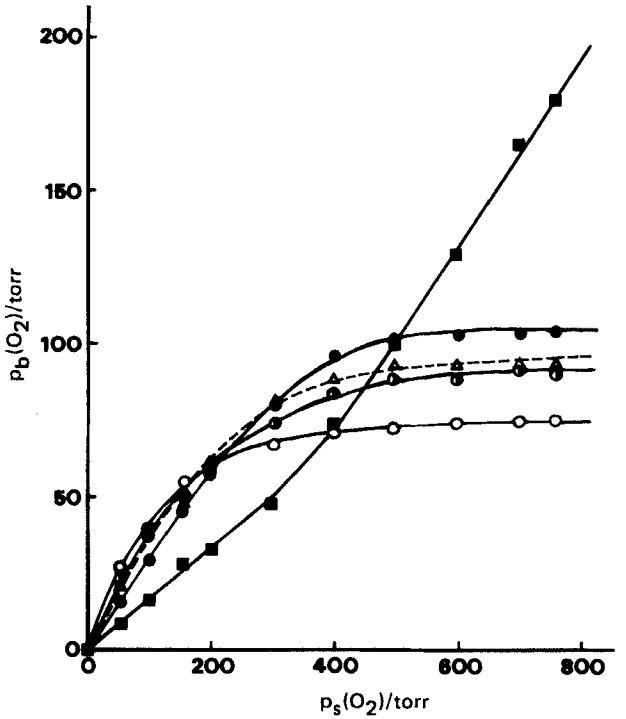


FIG. 3. Exchange of oxygen from OSM to blood at various oxygen partial pressures at 25°C. OSM, [heme] = 5.0 m*M* (○), 2.5 m*M* (◑), 1.0 m*M* (●), bovine blood (△), and saline (■). $p_s(O_2)$ is the oxygen pressure in the OSM; $p_b(O_2)$ is the oxygen pressure in the bovine blood.

At the same time, the carbon dioxide (CO_2) pressure of the deoxy-blood decreased from $p_b(CO_2) = 34.8$ to 30.7 torr, and that of OSM increased correspondingly.

Figure 3 shows the effect of the pressure of the oxygen which is bubbled through the OSM in the storage tank on the oxygen pressure of the deoxy-blood. The latter increases with the oxygen pressure in OSM and reaches saturation at ~90 torr at ~400 torr oxygen pressure in OSM. For bovine blood the oxygen supplying profile is similar to that of OSM. On the other hand, the oxygen in saline increases linearly with oxygen pressure. These results correspond to the oxygen dissolving capability of OSM, bovine blood, and

saline: OSM and bovine blood bind oxygen according to a Langmuir isotherm while saline dissolves oxygen physically according to Henry's law. Anyhow, when the oxygen pressure in the OSM is low or the OSM is saturated with air, the oxygen-supplying efficiency of OSM is superior to that of saline.

In Fig. 3, notice also that the oxygen-supplying efficiency of the OSM increases somewhat with decreasing liposome/heme concentration of the OSM. This suggests that oxygen diffusion across the exchange interface in the pores of the hollow fibers is one of the efficiency-determining steps and that the width of the boundary membrane at the liquid/liquid interface increases for a viscous solution, such as the highly concentrated OSM and bovine blood and cancels their higher oxygen supplying ability. Thus, better oxygen supplying efficiency was observed for the OSM with the lower liposome/heme concentration.

In any event, the aqueous solution of synthetic heme embedded in the polymerized lipid liposome has the potential to act as an oxygen-supplying medium to blood in a liquid/liquid artificial lung device.

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