Membranes used for blood oxygenation and blood plasma separation represent well-proven applications as artificial organs. Although the absolute consumption is much less compared with dialysis membranes, their relevance for medical devices and healthcare around the world does not hide behind the big brother. This chapter illustrates the cornerstones for production and application of these products. Blood oxygenation membranes produced by different methods, both symmetrical and asymmetrical, are discussed first. The second part describes hydrophobic and hydrophilic synthetic blood plasma separation membranes. For both types of membranes, membrane make-up and medical device implications are considered.

MEMBRANE FOR BLOOD OXYGENATION:

Currently, the vast majority of devices used for blood oxygenation use hollow fiber membranes. These hollow membranes permit sufficient blood gas diffusion in a small volume due to the large surface area and high permeability of these fibers. The high permeability of hollow fibers is due to the porous walls that comprise the membrane. This porosity allows oxygen traveling through the lumen of the fiber to come in direct contact with blood surrounding the fiber at the surface of the pores. Although the open, porous network permits very high blood gas permeability of the hollow fiber wall, it is responsible for problems that limit the time that current membrane oxygenators may be used. These include blood plasma leakage and gaseous emboli formation. Upon contact with blood, equilibrium is established between the forces of the surface tension and pressures acting on the blood. This equilibrium results in the formation of an interface between the blood plasma and sweep gas across the opening of the membrane's pore. This interface allows the superior gas exchange encountered in hollow fiber oxygenators. However, phospholipids in the blood act as a surfactant and disrupt the surface tension equilibrium.The hydrophobic portion of these molecules adhere to the wall of the micropore, leaving the hydrophilic portion oriented toward the middle of the pore. This action allows the plasma/sweep gas interface to advance in the direction of the center of the fiber. The interface between blood plasma and sweep gas then moves through the length of the pore until it reaches the inner surface of the fiber. At this point the lung is "wetted out" and is no longer capable of exchanging sufficient amounts of blood gasses with the blood flow on the outer surface of the fiber due to impaired diffusion through liquid filled micropores. Gaseous emboli formation occurs when the pressure difference between blood on the outer surface of the fiber and sweep gas on the inner surface is sufficient enough to change the force equilibrium at the blood plasma/sweep gas interface. If the interface is driven to the outside of the fiber by sufficiently high sweep gas pressures or low pressures on the blood side of the membrane, emboli may be formed. These bubbles, if transported into the body have the potential to cause serious harm by forming an embolism. Disruptions of blood flow into the oxygenator, resulting in low pressures on the outside of the fiber, are the most common cause of this dangerous condition. In addition to wetting and emboli formation, thrombus formation limits the use and longevity of current hollow fiber oxygenators. Upon contact with foreign surfaces, components of the blood coagulation systems are activated and a powerful signaling cascade is initiated, ultimately leading to thrombus formation. Although systemic anticoagulants are administered during the use of any blood oxygenation device, clot formation within the oxygenator remains an issue that may cause failure. Various attempts have been undertaken to create hollow fiber membranes capable of long term blood oxygenation. These approaches involve coatings applied to existing, porous membranes and the production of non-

porous membranes. Although substantial progress has been made recently, no hollow fiber membrane based blood oxygenator is approved for long term use by the United States Food and Drug Administration. Each of the approaches and techniques of developing long term blood oxygenation membranes has advantages and drawbacks. A disadvantage of each coating technique previously explored is the reliance on a very specific chemistry to form the coating. The reaction of human blood to foreign surfaces is very complex, for a composite long term blood oxygenation membrane to be viable the surface chemistry of this fiber must be as non-activating as possible. Another drawback involves the lack of strong chemical bonds anchoring the coating to the exterior surface of the fiber. A common failure mechanism of medical coatings is delamination and undesired degradation and leaching, all of which are unacceptable during long term blood oxygenation.

MEMBRANE FOR PLASMA SEPERATION:

Introduction

Continuous plasma separation was developed by Nosé et al [1] and first used in humans for the treatment of hepatic coma in 1976 and 1977 [2, 3]. Since 1978 hollow fibre devices have largely replaced centrifuges for plasma separation. With these devices plasma is separated from blood by filtration through microporous membranes.

Plasma separation is an effective method to eliminate high molecular substances and will be used increasingly for a number of reasons: elimination of antibodies and immune complexes, protein bound hormones and toxins and other foreign serum components.

At our institution we have used this procedure since May 1979 and since then performed more than 100 separations on seven patients without complications (one patient with Goodpasture's Syndrome, one with systemic lupus, one with immune complex vasculitis, three with rapidly progressive glomerulonephritis and one with transplant rejection.

Material and methods

The filters were either from Asahi Med. Co. (surface: $0.65m^2$, and pore width 0.2μ) or from MTS Co., St Wendel (surface $0.8m^2$, pore width 0.2μ).

According to the manufacturers both have a cut-off point at 3 mill. daltons. Balancing and substitution of the filtered plasma was done with the haemofiltration machine of Dialyse Tecknik Co., Karlsruhe. Immune globulins were determined using a laser nephelometer (FA, Behring, Marburg).

Substitution Balancing and substitution of the filtered plasma should be done by using a haemofiltration machine to avoid side effects from volume variations.

In the acute phase of Goodpasture's Syndrome fresh frozen plasma should be used. With this regime clotting factors are available and diminish the chance of

bleeding into the lung.

For the other indications we used a substitution solution based on a haemofiltration solution with the addition of 20% human serum albumin (HSA) with the following composition listed as 1 in Table I.

TABLE I

	Na	K	Ca	Cl	P	Fe	Cu	Zn	Mg	
1	159	2.2	3.0	88	0.4	9.8	7.5	12.18	1.1	mmol/L
2	145	3.5	2.5	105	1.0	15	15	13	1.5	mmol/L

During all treatments serum electrolytes were within normal limits.

A more desirable composition of replacement fluid is listed as 2 in Table I. But this is not yet available.

Heparinisation

For heparinisation the patients were given heparin by an initial IV dose and then by continuous infusion. Dosage should be flexible and coagulation should be controlled by measuring activated partial thromboplastin time (APTT). Generally the initial dose (about 2500–4000IU) and the maintenance dose (1200–2300IU) is 2–3 times higher than in haemodialysis. However the consumption of heparin decreases during the procedure because of loss of clotting factors. For one plasma separation about 4500–7500IU heparin is necessary. If heparinisation is done according to the actual APTT value, APTT values can be held within narrow limits (47–75 sec) without clotting. With this procedure bleeding due to overdosage is avoidable. This is especially useful in patients with bleeding tendencies as with Goodpasture's Syndrome.

Effectiveness of the procedure

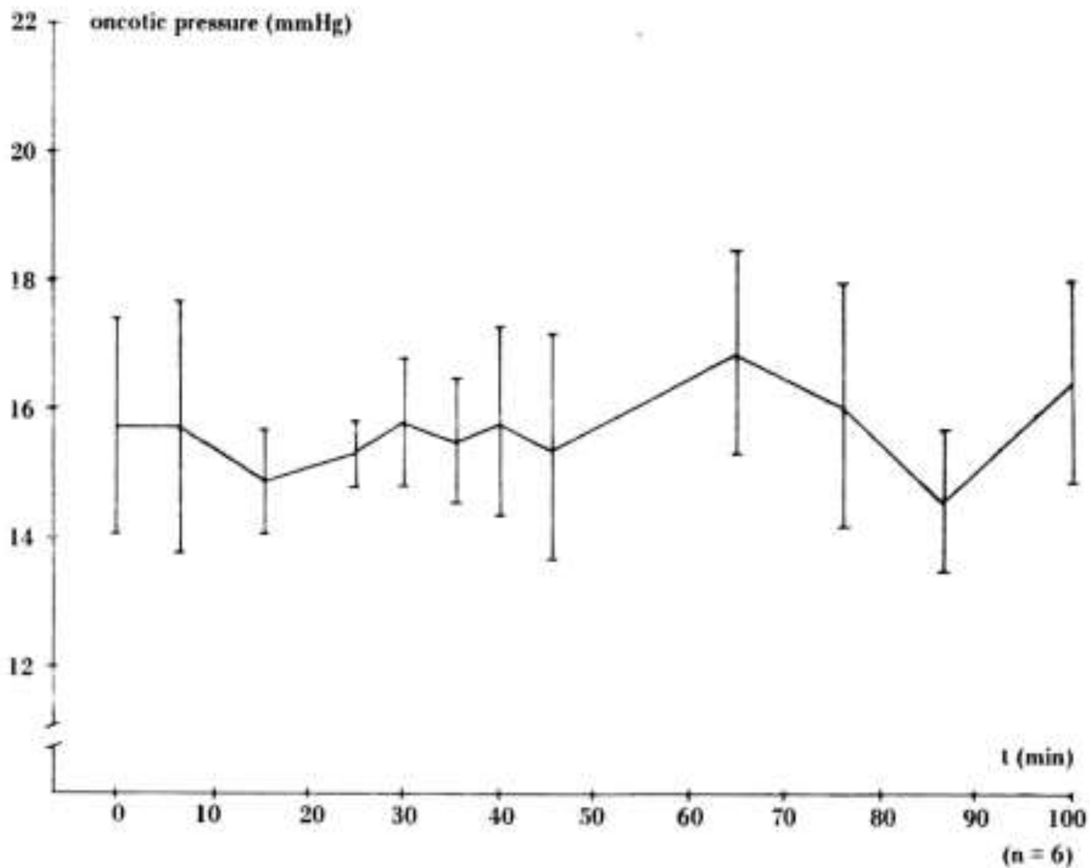
A plasma exchange of 5L can be done in 60 minutes with a blood flow of 225 ml/min and a transmembrane pressure (TMP) of about 150mmHg. This corresponds to a plasma filtrate flow of about 83ml/min. Under these conditions no haemolysis is observed, as shown by plasma haemoglobin determinations.

In contrast to haemofiltration, plasma filtration has to be performed with lower TMP, as higher TMP induces secondary membranes (proteins and platelet layers on the membrane), which lowers filtrate flow.

Lower filtrate flows also result from higher heparinisation, probably because of decreasing separation of plasma and blood cells on the capillary wall with increasing deposition of platelets [4]. With TMP's higher than 200mmHg red blood cells will be deposited on the surface of the filter with consecutive haemolysis.

To calculate the TMP exactly, the resistance on the blood side and the AV difference of the filter, has to be determined in addition to the negative pressure on the filtrate side. Measurement at different blood flow rates showed a linear

increase of the resistance from 40–85mmHg with blood flow rate from 150–300 ml/min. The AV-pressure difference is therefore in the same range as that of the hollow fibre filters used for haemodialysis.



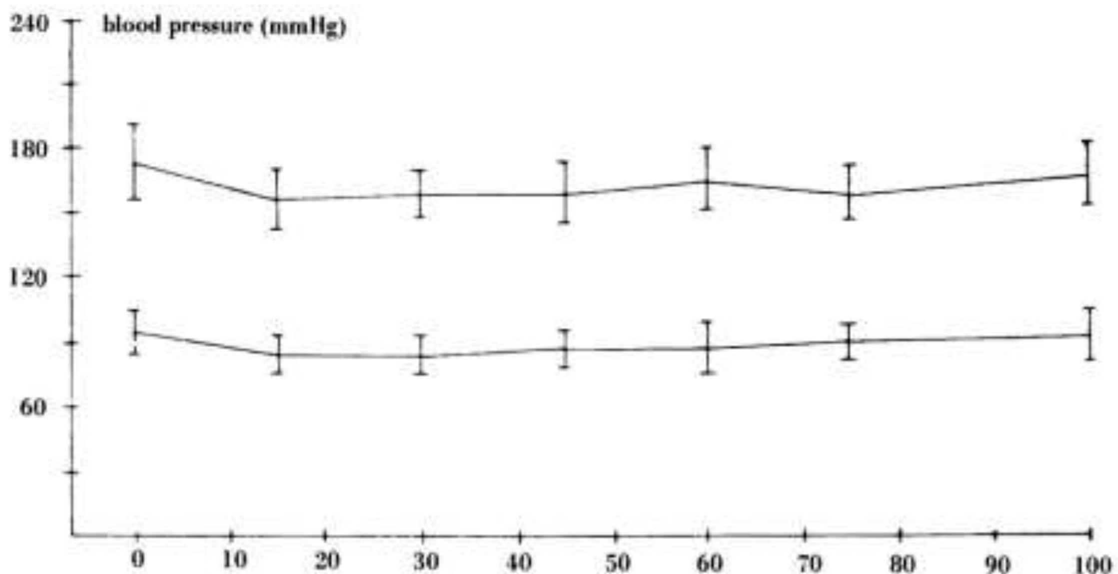


Figure 1. Mean values for oncotic pressure and blood pressure during six plasma separations with 3% albumin-electrolyte substitution.

Oncotic pressure

To prevent hyper- or hypovolaemia with the possible danger of lung oedema by having the wrong HSA concentration, it is highly desirable to measure the oncotic pressure before the start of treatment. The albumin concentration in the substitution fluid should be chosen, so that the solution has about the same oncotic pressure as that of the patient.

As up to 50% of the albumin can leave the vascular space, deviations of oncotic pressure are still possible. This makes repeated determination of the oncotic pressure necessary.

In Figure 1 the values for oncotic pressure during six plasma separations are shown. With a starting oncotic pressure of 14–17mmHg and using a 3% HSA-electrolyte solution, parameters are nearly stable throughout the procedure.

Only once was a 2% HSA solution used. Signs of increasing hypovolaemia, like falling blood pressure and increasing pulse rate, made it necessary to increase the HSA concentration. These side effects are due to the unphysiological low oncotic pressure of this solution, which should not be used. This is in contrast to other authors [5–7] who have used 2% or 2.5% HSA solution without measuring the oncotic pressure.

With HSA concentrations of 3–5% corresponding to the oncotic pressure of the patient, no side effects were observed.

A 5L plasma exchange reduces fibrinogen, IgM, IgA, IgG, complement factor C_3 to 50–60% of the initial value.

Blood count is not altered substantially during the procedure. There was a reduction in leucocytes of 11 ± 4%, haematocrit (initial value = 100%) of 6 ± 2% and platelets of 13 ± 4%.

Measuring of the sieving coefficients (IgG, IgA, C_3 and IgM) shows a falling permeability with increasing molecular weight and duration of treatment.