Membrane oxygenators: current developments in design and application

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ABSTRACT

Cardiopulmonary bypass (CPB) procedures require a blood–gas exchanger (oxygenator) to temporarily replace the respiratory function of the lungs. In the past the majority of CPB procedures have been carried out with bubble oxygenators which effect gas exchange by dispersion of bubbles into the blood. Membrane oxygenators, on the other hand, utilize a hydrophobic gas permeable membrane between the blood and gas phases.

Bubble oxygenators are being superseded by membrane types for CPB due to improvements in membrane technology and mass transfer efficiency. These advances are reviewed in this paper and are illustrated by reference to the gas exchange and operating characteristics of a number of clinical oxygenators designed for adult CPB.

Membrane oxygenators are also being used for long-term support in the treatment of acute respiratory failure. Operated in a partial bypass circuit, the oxygenator may have to function for several days or weeks. In one particular treatment method, the rate of spontaneous breathing is controlled by the partial or total removal of the metabolic CO_2 production by the membrane oxygenator. For this method, known as extracorporeal CO_2 removal ($ECCO_2R$), the oxygenator must be optimized for CO_2 transfer at low blood flow rates. The suitability of clinical oxygenators for $ECCO_2R$ is discussed in terms of gas exchange and functionality over a prolonged operation.

Keywords: Membranes, oxygenators, gas exchange

INTRODUCTION

Oxygenators or, more correctly, blood–gas exchangers are primarily used in cardiopulmonary bypass procedures (CPB) for open-heart surgery. A secondary application is in the long-term respiratory support of patients suffering from acute respiratory failure. It has been estimated[1] that in 1984 worldwide sales of oxygenators exceeded 300 000 units per annum.

The design of oxygenators is influenced by the nature of the application. In CPB the systemic blood flow is diverted from the heart and lungs through an extracorporeal circuit. Venous blood is removed by gravity drainage from the vena cavae and subsequently delivered in an arterialized condition to the aortic arch. Current practice utilizes whole body hypothermia in conjunction with haemodilution for bypass periods of 1–3 hours duration. The extracorporeal circuit must contain, in addition to the blood–gas exchanger and pump, a heat exchanger and a reservoir. The latter serves to dampen out fluctuations in gravity drainage and to provide a safety margin in the event of interruption of blood supply.

The first successful clinical procedure was carried out in 1953 using a film oxygenator[2]. In this device, a thin layer of blood flows over a solid surface which is situated within an oxygen-rich atmosphere. Film oxygenators were extensively used until the late 1960s. Most CPB procedures are presently performed with two basic types of oxygenator. In the bubble oxygenator the ventilating gas is dispersed as bubbles into the venous blood and O_2 and CO_2 exchange occurs across the bubble–blood interface. Before the arterialized blood is returned to the patient it is passed through a defoamer where the bubbles are collapsed and the released gas vented to atmosphere. In the membrane oxygenator gas exchange occurs across a hydrophobic, gas permeable membrane which separates the blood and ventilating gas phases.

Although bubble and membrane oxygenators suitable for clinical CPB were introduced[2] in the mid 1950s the bubble type has been predominant. The performance of early membrane units was limited by the low permeability of the Teflon or polyethylene films used and surface areas of ca. 25 m^2 were required[3]. More compact units with 6–9 m^2 area were made possible with the introduction[4] of highly permeable silicone rubber membranes in 1963. However, bubble units were preferred because they were simpler to use and set-up and, importantly, possessed an integral reservoir and heat exchanger. Also, because of blood trauma due to cardiotomy suction and other components in the CPB circuit, the gentler blood handling characteristics of membrane units could not be fully exploited.

For a variety of reasons, the dominant position held by bubble oxygenators is being challenged[1,5]. Over the last eight years, developments in microporous membrane technology coupled with improvements in efficiency have led to numerous clinical oxygenators with integrated bypass circuit elements. Ease of use and cost approaching those possessed by bubble types is another factor[1]. Kolobow *et al.*[5], in giving reduced hospitalization time as a reason for membrane oxygenator preference, predicted that about 60% of CPB operations in the USA in 1986 would be with this type.

In the application of oxygenators for respiratory support for pulmonary insufficiency the membrane

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type is used exclusively. The oxygenator, operated in normothermic partial bypass via peripheral vessel cannulation, is required to provide gas exchange for several days or more. Use of a bubble oxygenator for such a period would result in unacceptable blood trauma as well as a loss in defoaming capacity.

In the 1970s membrane oxygenators were used in the treatment of patients with adult respiratory distress syndrome (ARDS). The oxygenator provides gas exchange in a veno–arterial circuit processing up to 80% of cardiac output. Clinical results were discouraging. A multi-centre study[6] using this technique, known as extracorporeal membrane oxygenation (ECMO), in conjunction with mechanical ventilation, showed a 90% mortality. An identical mortality rate was obtained with a control group receiving conventional mechanical ventilation only.

Recognizing the barotrauma caused by continuous ventilation at high airway pressures Kolobow *et al*[7] advocated the use of apnoeic oxygenation in combination with extracorporeal removal of metabolically produced CO_2. These conditions are met by an oxygenator operating with a low flow (20–30% cardiac output) veno–venous partial bypass combined with passive diffusion of oxygen in the lungs. Low frequency positive pressure ventilation at a rate of 3–5 'sighs' per minute is provided to maintain lung volume. Clinical results with this technique, known as extracorporeal CO_2 removal ($ECCO_2R$), have been striking. Of 55 patients treated by Gattinoni and colleagues in Milan[8], 26 survived (47%). This is vast improvement over the 10% survival of the earlier ECMO study. ECMO in conjunction with low peak airway pressure ventilation has, however, been successful in neonatal acute respiratory failure. A review[9] of 715 cases from eighteen EMCO centres in the USA reported a survival rate of 81%.

From the above comments, it is clear that membrane oxygenators have a significant role to play in CPB procedures and in the treatment of neonatal and adult respiratory failure. The purpose of this paper is threefold: to review recent advances in oxygenator design; to show how these advances have influenced the efficiency of gas exchange and operation and to outline current developments.

MEMBRANE OXYGENATOR DESIGNS

With the replacement in the 1960s of homogeneous plastic films by silicone rubber membranes, the major resistance to gas transfer no longer resided in the membrane phase but in the blood phase. In designs with laminar rectilinear blood flow (streamlines parallel to the membrane) 90–95% of the resistance to O_2 transfer is due to molecular diffusion in the blood phase. For this flow condition the membrane area is dictated by the required O_2 transfer with CO_2 transfer exceeding that needed for a respiratory quotient of 0.8. If the blood–side resistance is reduced by convective mixing in the blood phase the transfer will revert back to membrane-limited and the area will be determined by the required CO_2 exchange. At this stage, a further reduction in the area may be achieved by introducing more permeable membranes[9]. The oxygenators presently available encompass fluid mechanic and membrane developments over the past 25 years.

Most membrane oxygenators fall into one of the four design configurations shown in *Figures 1* and *2*. The arrangement shown in *Figure 1a* is exclusive to the SciMed Kolobow oxygenators[4]. A screen filled membrane envelope is spirally wound about a central core. Blood passes between adjacent windings and gas is passed tangentially through the envelope. Due to a high flow resistance the membrane deforms into the gas screen creating boundary irregularities which enhance gas transfer in the blood phase. This particular design is one of the few to retain silicone rubber membranes and has been used extensively in long-term respiratory support.

The alternate stacking of screen spacers and sheet membranes (*Figure 1b*) has several advantages in that it provides a support for thin membrane films, creates flow paths for blood and gas and maintains uniform membrane separation distances. Importantly, the screens may induce mixing in the blood phase in order to enhance gas transfer. *Figure 1b* shows the

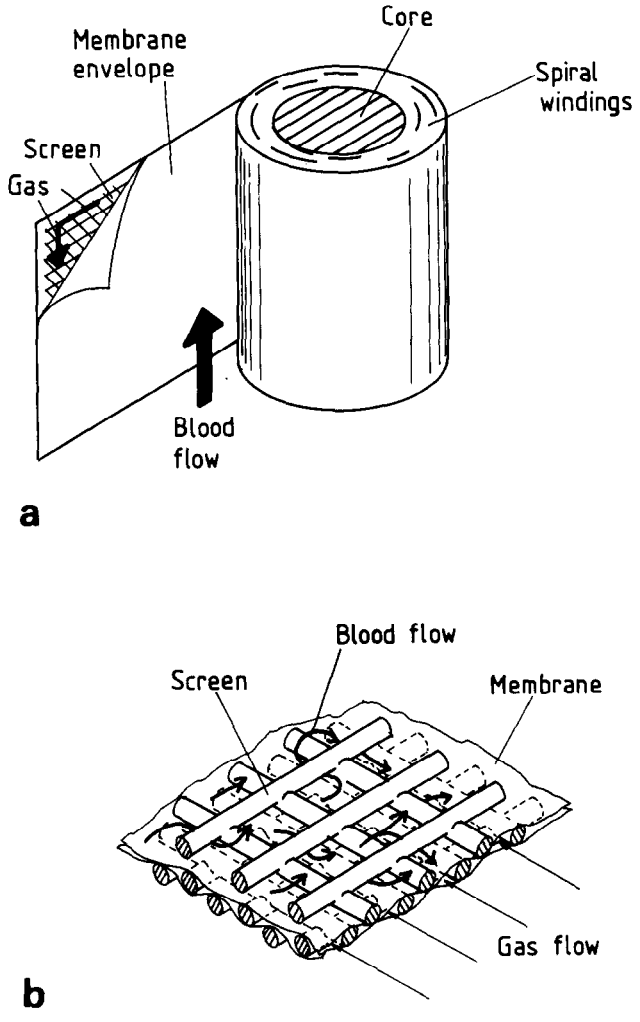

Figure 1 **a**, Spiral coil construction of SciMed Kolobow oxygenator. A plastic screen within the membrane envelope defines the gas flow path. **b**, Plate (membrane) and screen construction of Shiley M-2000 oxygenator. Interdigitation of the screens creates a tortuous blood flow path which induces lateral mixing.

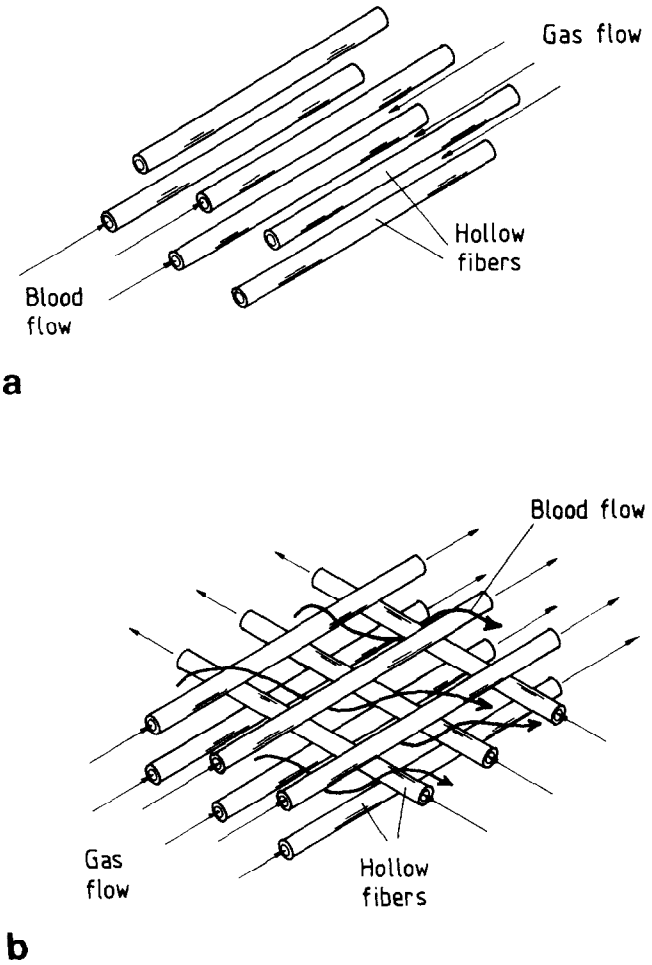

Figure 2 **a**, Shell and tube configuration using hollow fibres (ca. 200 μm bore and 25 μm wall thickness). Spacing between fibers is greatly exaggerated for clarity. **b**, Cross-flow hollow fiber configuration. The strength of mixing is influenced by the tube stacking arrangement

arrangement present in the Shiley M-2000 oxygenator. Non-woven polypropylene screens interdigitate to create the flow patterns shown. A microporous polypropylene membrane is employed.

From artificial kidney experience it is well known that capillary or hollow fiber membrane technology results in compact devices with a high surface area/volume ratio. Initial development of hollow fiber oxygenators was frustrated by extensive thrombus formation at the orifices of the silicone-based polymer fibers then in use[10]. However, this problem has been solved with the introduction of microporous polypropylene[11] or polyethylene fibers which can be encapsulated in polyurethane resins and can be cleanly cut.

Hollow fiber oxygenators are available in two forms: the classical shell and tube arrangement (*Figure 2a*) and the cross-flow layout (*Figure 2b*). In the former, blood flows within the lumens of a bundle of parallel-connected hollow fibers typically 200 μm internal diameter and 25 μm wall thickness. Gas flows over the fiber exterior countercurrent to the blood. Because of the laminar rectilinear blood flow the blood side transfer resistance is high in this design. This could be reduced with smaller fiber bores in order to decrease the diffusion path length. However, it is impractical to reduce the inner diameter, d, below the present level of 200 μm for several reasons: the hydrostatic pressure drop over the bundle varies as d^{-4}; manufacture is more difficult for $d < 200$ μm and the potential for fiber occlusion by cellular aggregates would increase.

For the cross-flow design shown in *Figure 2b* augmentation of gas transfer is achieved by the creation of mixing in the blood passing over the exterior surfaces of the fibers. Ventilating gas is circulated through the fiber lumens. The generation and strength of the secondary flows is dependent on the blood velocity and viscosity, the fiber external diameter and the inter fiber spacing[12]. For similar O_2 transfer rates, the membrane area required for a cross-flow design is about 2–2.5 times smaller than that for a shell and tube design.

The parallel plate/screen and cross-flow configurations are representative of passive mixing schemes for transfer augmentation. That is, the primary blood flow generates convective mixing in combination with the flow path geometry. Greater enhancement may be obtained with active mixing units in which an additional external energy input is required, e.g. the rotation of a membrane-lined disc[9]. Although many active mixing oxygenators have been tested[9] very few have reached clinical application because of their greater complexity, higher production cost and the need for ancillary drives. The pulsed-vortex design developed by Bellhouse[13] was marketed as the Interpulse membrane oxygenator. In this oxygenator each blood channel is composed of two opposing sheets of microporous membrane supported over plastic plates to form longitudinal furrows perpendicular to the blood flow direction. As the blood is pulsed across the membrane vortices are cyclically formed within, and ejected from, the furrows. This method of mixing is highly effective and reduces by a factor of six the membrane area needed by a shell and tube unit for the same O_2 transfer.

Figure 3 gives some idea of the overall size of membrane oxygenators for adult CPB procedures.

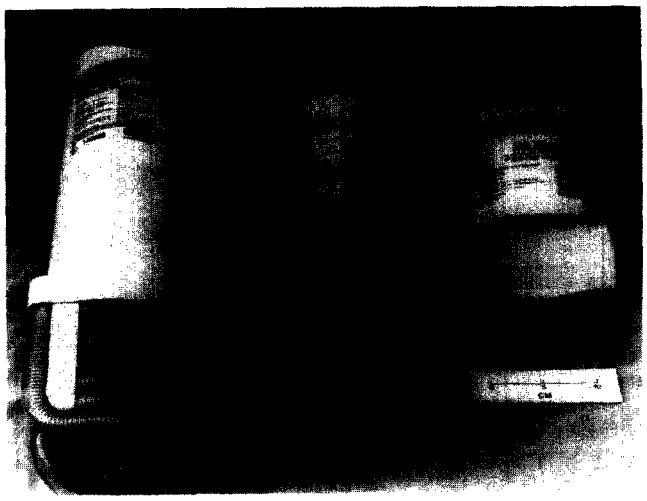

Figure 3 Examples of three membrane oxygenator designs. From left to right: SciMed SM35 spiral coil; Bentley BOS-CM50 shell and tube hollow fiber; Extracorporeal MAXIMA cross-flow hollow fiber

All the devices shown have venous side heat exchangers. A more recent innovation has been the addition of a blood reservoir, thereby matching the integrated concept of the bubble oxygenator.

PERFORMANCE CHARACTERISTICS

CPB application

Theoretical models[9,12,14] of varying complexity have been developed to predict blood gas exchange for the geometries described in the last section. Usually the models relate to transfer within one exchange element of a multi-element design and hence are unable to predict the loss in performance that may occur with scale-up. Recourse to *in vitro* experimentation under standard test conditions greatly facilitates the comparison of clinical oxygenators.

Following initial proposals by Galletti *et al.*[15] in 1972, the Association for the Advancement of Medical Instrumentation (AAMI) have produced a draft standard for oxygenator evaluation. The standard covers aspects such as mechanical integrity, cleanliness, biological compatability as well as gas exchange testing. It relates primarily to CPB application of oxygenators and defines suitable reference blood flow rates for oxygen and carbon dioxide transfer. Specifically these are:

O_2 reference flow rate: that blood flow rate which produces an increase in blood O_2 content of 45 ml (STPD) per litre after direct passage through the device. Blood inlet conditions should conform to those given in *Table 1.*

CO_2 reference flow rate: that blood flow rate which produces a reduction in blood CO_2 content of 38 ml (STPD) per litre after direct passage through the device. Blood inlet conditions are again given in *Table 1.*

For gas exchange the standard stipulates *in vitro* testing with bovine blood at a minimum of three blood flow rates spanning the manufacturer's recommended operating range. However, it does not recommend specific ventilation ratios (gas flow rate/blood flow rate), Q_G/Q_B nor the oxygen fraction, FiO_2 in the gas phase. Most manufacturers however supply data for Q_G/Q_B ratios of 1.0 and 2.0 with an FiO_2 of 1.0 (100% oxygen).

Table 1 AAMI Standard blood inlet conditions

Oxyhaemoglobin saturation	$65 \pm 5\%$
Haemoglobin content	120 ± 10 kg m^{-3}
Base excess	0 ± 5 mmol l^{-1}
P_{CO_2}	6 ± 0.67 kPa
Temperature	37 ± 2°C

Comparative O_2 and CO_2 transfer data taken from the literature are presented in *Table 2* for nine oxygenators used in adult CPB. The transfer is given in terms of O_2 content increase and CO_2 content decrease per litre of blood at a blood flow rate of 6.0 l min^{-1} (5.5 l min^{-1} for SciMed SM-35). All the units listed in *Table 2* possess heat exchangers but, with the exception of the Harvey HF-4000 and Terumo CAPIOX-E, lack an integral reservoir. The priming volume is that contained within the heat exchanger and gas exchanger sections at the above blood flow rate. The flow resistance of the units is reflected in the pressure drop measured at the same blood flow rate. Microporous polypropylene membranes are employed in all the oxygenators with the exception of the SciMed SM-35 (silicone rubber) and the Harvey HF-4000 (microporous polyethylene).

It is clear from the data shown that, with one exception, the O_2 reference flow rates for the oxygenators are in excess of 6.0 l min^{-1}. Indeed, some units are capable of O_2 reference flow rates as high as 7.5 l min^{-1}. An O_2 transfer of approximately 57 ml (STPD) l^{-1} results in full saturation of the blood under the stated input conditions. Hence, most manufacturers recommend the use of oxygen/air blenders to control the arterial (outlet) P_{O_2} particularly if the oxygenator is operated at low blood flows. In addition, carbon dioxide transfer may be significantly increased from the values given in *Table 2* using ventilation ratios greater than 1.0. Raising the ratio to 2.0 will typically result in a 20–40% increase in CO_2 removal.

Table 2 Physical and operating characteristics of clinical membrane oxygenators. Gas transfer measured at 6 l min^{-1} blood flow rate and 6 l min^{-1} gas (100% O_2) flow rate with AAMI standard input conditions. Design configurations are: S, sheet; PS, plate and screen; ST, shell and tube hollow fibre; XT, crossflow hollow fibre; PV, pulsed vortex

Oxygenator	Design	Number of channels/tubes	Area (m^2)	O_2 transfer (ml (STPD) l^{-1})	CO_2 transfer (ml (STPD) l^{-1})	Pressure drop (kPa)	Priming volume (ml)	Maximum blood flow rate (l min^{-1})
SciMed SM-35	S	1	3.5	45*	–	32.0*	930*	5.5
Shiley M-2000	PS	60	2.3	48	48	21.7	660	6.0
Terumo CAPIOX II-54	ST	6×10^4	5.4	50	50	23.3	700	6.5
Bentley BOS-CM50	ST	5.3×10^4	5.3	56	57	35.2	730	7.0
Harvey HF-4000†	XF	1.5×10^4	4.5	59	41	6.7	—	7.5
Terumo CAPIOX-E†	XF	–	3.0	51	–	6.7	500	6.5
Extracorporeal MAXIMA	XF	2.8×10^3	2.0	53	38	10.7	480	7.0
Sarns HFO	XF	1.1×10^4	1.8	55	46	30.6	320	7.0
Extracorporeal Interpulse	PV	7	0.8	50‡	35‡	2.7	920	6.5

*At 5.5 l min^{-1} blood flow rate
†Integral reservoir
‡At 250 pulses/min operation

As expected, the transfer rate per unit area increases in the order: no mixing (shell and tube) → passive mixing (cross-flow) → active mixing (pulsed vortex). Conversely, the priming volume generally decreases with higher transfer efficiencies. The exception is the Interpulse oxygenator in which relatively large membrane separation distances are required for vortex generation as well as the need for pump chambers producing the oscillatory flow.

Although gas transfer efficiency is a desirable goal in the design of an oxygenator, the clinical acceptability of the device involves other considerations. As stated by Drinker and Lehr[16], '... the design involves an iterative process of trade off, or compromise, between the following criteria: gas exchange capacity, minimization of blood trauma and thrombosis, reliability, simplicity of use and cost'. Detailed discussion of these criteria is beyond the scope of this paper and the reader is referred to several relevant reviews[1,5,16].

Respiratory support application

The gas transfer rates to be provided by the oxygenator differ between ECMO and $ECCO_2R$ techniques in the treatment of respiratory failure. Requirements for O_2 and CO_2 exchange in ECMO are similar to those in CPB because extracorporeal flow rates can be as high as 80% of the cardiac output. ECMO has been carried out mainly with silicone rubber membrane oxygenators (SciMed), which are available in a range of membrane areas to suit adult or neonatal patients.

In extracorporeal CO_2 removal with apnoeic oxygenation, ($ECCO_2R$), the oxygenator should be optimized for CO_2 removal at low blood flow rates because it is, in theory, possible to remove the adult metabolic CO_2 production from a blood volume of only 400 ml. Operation at low blood flow rates causes less haemodynamic disturbance, simplifies cannulation techniques and facilitates haemostasis.

In the clinical setting, blood flow rates are typically 20–30% of cardiac output with the oxygenators providing about 10% of the O_2 requirement of the patient. The balance of the patient's O_2 consumption is met by passive diffusion of oxygen in the lungs. In the adult $ECCO_2R$ study[8] described at the beginning of this paper, extracorporeal flow rates ranged from 1.5–2 l min^{-1}. Carbon dioxide transfer rates of 150–300 ml (STPD) min^{-1} were achieved using two SciMed oxygenators in series (total area 7–9 m^2) ventilated with humidifed oxygen/air mixtures at rates approaching 40 l min^{-1}.

Gas exchange criteria for $ECCO_2R$ relating to oxygenator design have yet to be specified. Dorrington *et al*[17] have proposed, on the basis of the clinical experience of Gattinoni and colleagues, an interim definition for a CO_2 reference blood flow rate applicable to $ECCO_2R$. This is the blood flow rate through the device giving a CO_2 elimination of 200 ml per litre of blood. Utilizing this definition it is possible to examine the potential of microporous membrane oxygenators for $ECCO_2R$, bearing in mind the reservations that exist as to their suitability for long-term operation.

The influence of membrane permeability on CO_2 transfer may be predicted theoretically for simple geometries. The author has used Voorhees' model[18] to analyse the performance of microporous membrane oxygenators based on the shell and tube configuration. For laminar blood flow in tubes the model may be solved[19] to give the fractional CO_2 removal, $\Delta C_T/C_{Ti}$ as a function of tube dimensionless length, $\pi D_1 NL/(2Q_B)$ for a range of dimensionless wall resistances, γ. The change in blood CO_2 content over a tube of length, L is C_T and the total content at tube inlet is C_{Ti}. D_1 is the diffusivity of dissolved CO_2 in blood, Q_B is the total blood flow rate through a number, N of parallel-connected tubes. The wall parameter γ represents the ratio of the membrane mass transfer resistance to the blood phase resistance. Assuming ventilation rates high enough to prevent CO_2 build up in the gas phase (gas phase P_{CO_2} = 0 kPa), predictions for CO_2 transfer are given in *Figure 4* for AAMI inlet conditions. *Figure 4* illustrates the well known fact that CO_2 transfer is highly sensitive to changes in the value of γ. If the tube internal diameter, d is fixed, γ is inversely proportional to the membrane permeability.

Studies carried out by Khoo[20] and Wong[21] on microporous polypropylene hollow fibers ($d = 200$ μm) of the type used in the Terumo CAPIOX oxygenator have indicated that a value of $\gamma = 0.2$ is appropriate for this fiber. For $\gamma = 0.2$ a dimensionless length of 0.79 is predicted for a fractional removal of 0.385 which corresponds to the reference CO_2 transfer of 200 ml/l (9 mmol/l) with $C_{Ti} = 23.33$ mmol l^{-1}. If the oxygenator is to be operated at a blood flow rate of 1.0 l min^{-1} then the required membrane

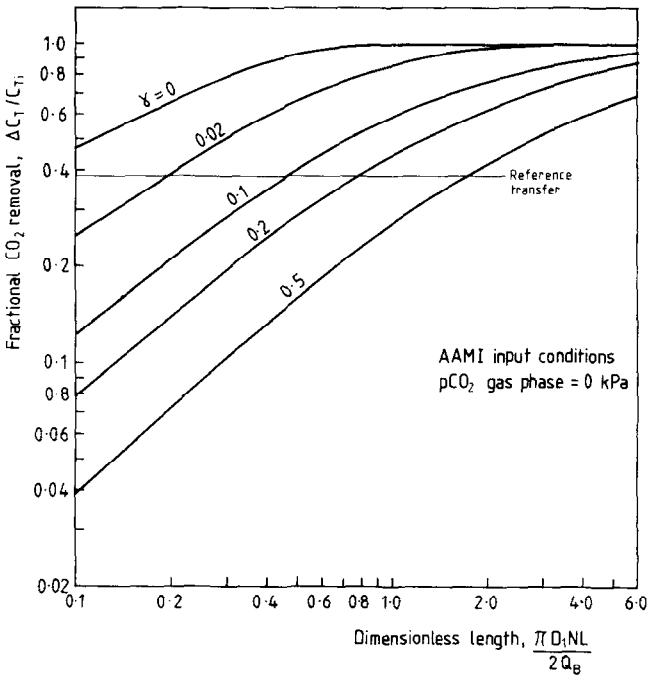

Figure 4 Variation in fractional CO_2 removal $\Delta C_T/C_{Ti}$ with dimensionless tube length, $\pi D_1 NL/(2Q_B)$ for different wall parameter values. Symbols are defined in text. Predictions based on AAMI input conditions (*Table 1*) with $C_{Ti} = 23.33$ mmol l^{-1} and gas phase $P_{CO_2} = 0$ kPa. The plot for $\gamma = 0$ represents a tube with infinite membrane permeability.

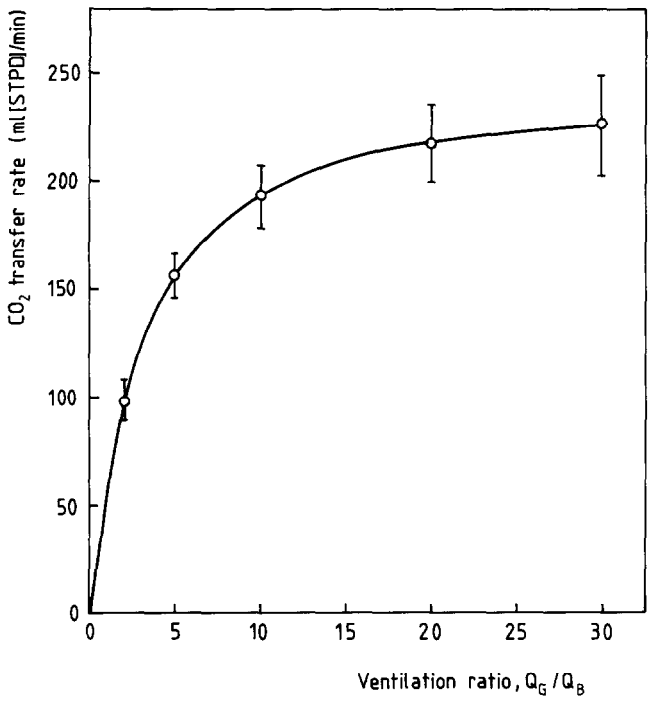

Figure 5 Effect of ventilation ratio, Q_G/Q_B on CO_2 transfer in Bentley BOS-CM50 oxygenators. *In vitro* bovine blood studies under AAMI conditions with heated (37°C) dry air ventilation and 1.0 l min^{-1} blood flow rate. Points are the mean of 2 or more measurements on each of 3 units. Bars are ±1 s.d.

area ($\equiv \pi dNL$) is 4.05 m^2. For this calculation D_1 has been taken as 1.3×10^{-9} m^2 s^{-1}. Predicted transfer rates compare quite favourably with *in vitro* experimental data obtained in the author's laboratory (Dr A. Kawak, personal communication) for Bentley BOS-CM50 oxygenators of 5.3 m^2 area. The comparison is made at a high ventilation ratio of 30 which corresponds to the plateau of CO_2 transfer as shown in *Figure 5*. At $Q_G/Q_B = 30$ the measured exchange rate is 226 ml (STPD) min^{-1} for $Q_B = 1.0$ l min^{-1}. The predicted transfer rate is 230 ml (STPD) min^{-1}.

The importance of high ventilation ratios in maximizing CO_2 transfer for $ECCO_2R$ applications is evident from *Figure 5*. The ratios required are far greater than those used in CPB operations because the fractional CO_2 removal must be large to compensate for low blood flow rate operation. Garred *et al.*[22] have presented a useful theoretical model which analyses these effects in detail.

CURRENT RESEARCH AND DEVELOPMENT

Relevant to the theme of this paper are research activities in the following areas: thrombo-resistant membranes; long-term use of microporous membrane oxygenators and high efficiency CO_2 removal.

The risk of major bleeding resulting from systemic heparinization is a problem in CPB and particularly so in ECMO or $ECCO_2R$ procedures. Thrombo-resistant coatings for the extracorporeal circuit are being developed in order to achieve better haemostasis and lower heparin requirements. Bindslev *et al.*[23] studied covalently bound active heparin in $ECCO_2R$ circuits which contained Bentley BOS-CM40 or Terumo CAPIOX II-43 oxygenators. Canine perfusions without additional systemic heparization were possible for periods of 30 hours. Using Bentley BOS-CM40 oxygenators with a heparin-complex coating, Toomasian *et al.*[24] found that additional heparin was not needed over four days partial bypass of sheep. In both studies minor thrombus formation occured in stagnant flow regions of the oxygenators but did not impair function. Modifications in fluid dynamic design of oxygenators to eliminate stagnation zones would appear desirable if heparinized surfaces are to be used.

Reservations have been voiced as to the suitability of microporous membrane oxygenators for long-term respiratory support. It is thought that extended operation will lead to wetting of the pore structure with subsequent plasma leakage. Occurence of this phenomenon appears to be random and few systematic studies have been carried out. There is, however, increasing evidence, on the basis of animal trials, that microporous devices can be functional for many days without significant plasma leakage. In addition to the heparinized surface study of Toomasian *et al.*[24], Mottaghy *et al.*[25] and Palder *et al.*[26] have demonstrated continuous operation with hollow fiber oxygenators for 7 and 4 days respectively. It is interesting to note that these studies were conducted with sheep and with shell and tube, microporous polypropylene oxygenators. This commonality raises several issues. Firstly, is loss of hydrophobicity influenced by blood species? Secondly, is the choice of oxygenator important? From an operational viewpoint, the linear gas flow paths of shell and tube oxygenators assist the gravity drainage of condensed water vapour in the gas phase. This is important in $ECCO_2R$ because CO_2 transfer is sensitive to the formation of additional diffusion resistances in the gas path. Elucidation of other factors (e.g. gas humidity and temperature, ventilation flow rate) which might influence the time course of plasma leakage is necessary.

Why persist with microporous membranes in long-term applications? For the reason that reduced surface areas are possible, especially for CO_2 removal compared with areas needed for silicone ruber membranes. However, to fully realize the potential of microporous membranes, oxygenators with active mixing schemes are necessary. Dorrington *et al.*[17] working with an improved pulsed-vortex design found that CO_2 reference blood flow rates ($ECCO_2R$ definition) per unit membrane area could be as high as 1.2 l min^{-1} m^{-2}. For shell and tube units the corresponding figure is about 0.25 l min^{-1} m^{-2}).

Other developments which may be of interest to the reader but which are not discussed in this paper are:

1. Homogeneous polymer coatings on microporous membrane substrates to prevent plasma leakage but not compromise permeability[27].
2. Automatic control of oxygenator gas exchange[28].
3. Implantable lungs for chronic respiratory failure[29].

In conclusion, from its conception some 33 years ago, the membrane oxygenator has come of age.

Progress continues apace in device design and membrane technology, stimulated by increasing application in cardiopulmonary bypass and treatment of respiratory failure.

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