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HISTORICAL NOTE

The history of extracorporeal oxygenators*

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Summary

Extracorporeal oxygenators are artificial devices that substitute for anatomical lungs by delivering oxygen to, and extracting carbon dioxide from, blood. They were first conceptualised by the English scientist Robert Hooke (1635–1703) and developed into practical extracorporeal oxygenators by French and German experimental physiologists in the 19th century. Indeed, most of the extracorporeal oxygenators used until the late 1970s were derived from von Schroder's 1882 bubble oxygenator and Frey and Gruber's 1885 film oxygenator. As there is no intervening barrier between blood and oxygen, these are called 'direct contact' oxygenators; they contributed significantly to the development and practice of cardiac surgery till the 1980s. Membrane extracorporeal oxygenators introduce a gas–permeable interface between blood and oxygen. This greatly decreased the blood trauma of direct-contact extracorporeal oxygenators, and enabled extracorporeal oxygenators to be used in longer-term applications such as the intensive therapy of respiratory distress syndrome; this was demonstrably beneficial for neonates but less so for older patients. Much work since the 1960s focused on overcoming the gas exchange handicap of the membrane barrier, leading to the development of high-performance microporous hollow-fibre oxygenators that eventually replaced direct-contact oxygenators in cardiac theatres.

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The distinguished 17th century English scientist and philosopher Robert Hooke (1635–1703) demonstrated experimentally in 1667 that inflation and deflation of the lungs of an animal was not mandatory for the oxygenation of the blood flowing through them. He also speculated as to 'whether suffering the blood to circulate through a vessel, so that it may be openly exposed to the fresh air [might] not suffice for the life of an animal' without using the lungs for oxygenation [1, 2].

The artificial oxygenation and perfusion of individual organs was an objective of early 19th century physiologists. Julien-Jean Cesar le Gallois failed in his attempts to perfuse isolated decapitated rabbits by the injection of arterial blood in 1812 because of coagulation [3] but, following the description of the method of defibrinating blood by Prevost and Dumas in 1821 [4], Lobell [5] successfully perfused an isolated kidney by injecting arterial blood in 1849. In 1858, Brown-Sequard perfused the head of a dog with moderate success by injection, and showed that 5 min of ischaemia of the brain resulted in death of the organ [6, 7].

Early development of extracorporeal oxygenators for isolated organ perfusion

The first 'direct contact' artificial oxygenation of blood in an extracorporeal circulation was achieved in 1869 by Ludwig and Schmidt [8] by shaking together defibrinated blood with air in a balloon. Further development of 'direct-contact', 'three-dimensional' extracorporeal oxygenation of blood was the perfusion of an isolated kidney in 1882 by Schroder of Strasburg, using the first simple

'bubble oxygenator' [2, 6, 9, 10] and, from the same laboratory in 1882, Frey and Gruber described the first 'two-dimensional', direct-contact extracorporeal oxygenator that exposed a thin film of blood to air in an inclined cylinder which was rotated at a frequency of 30 min^{-1} by an electric motor [2, 6, 10, 11].

Several bubble and surface type oxygenators were developed in the first two decades of the 20th century [10]. For example, Hooker described in 1910 a bubble oxygenator [10, 12] and in 1915 a film oxygenator in which blood flowed over a single rotating disc to be oxygenated [10, 13]. Richards and Drinker described an oxygenator in 1915 that incorporated a perforated silk screen through which the blood flowed [10, 14].

Progress towards whole body perfusion: heparin

The problem of reliably preventing coagulation in perfusion was solved by the 1916 discovery of heparin by Jay Maclean. Maclean, a medical student working in the laboratory of W. H. Howell at the John Hopkins University at Baltimore, demonstrated that a phosphatide (cuorin) extracted from canine heart muscle prevented coagulation of the blood [2, 6, 15]. Subsequently, it was discovered that the active substance could also be extracted from dog liver in reasonable quantities and it was given the name 'heparin' [6, 16]. The discovery of the anticoagulant property of heparin paved the way to the development of whole body perfusion in animals and, subsequently, extracorporeal oxygenators for use in human cardiac surgery [2, 6].

Crucial developments in apparatus for extracorporeal oxygenation

The first whole body extracorporeal perfusion with isolation of the heart was, in fact, demonstrated in a canine model by the Russian scientists Brukhonenko and Tchetchuline in 1929 [2, 17–19]. They used the quiescent isolated lung as an oxygenator in a remarkable series of perfusion experiments, first with the isolated head and then using the whole body of the animal.

Many workers described ingenious oxygenating systems for isolated organs between 1920 and 1950. Von Schröder of Strasburg, for instance, built the first bubble oxygenator in 1882 [9], in which air was introduced into a venous reservoir and the subsequent increase in pressure in the reservoir forced oxygenated blood into an arterial reservoir, which then perfused an isolated organ. Von Euler and Heymans [20] in 1932 developed the opposite and novel approach of introducing 'atomised' blood into an air/oxygen environment. However, there were three important devices that were to be ultimately developed into apparatus for clinical open heart surgery in man: the film oxygenator developed by Gibbon between 1937 and 1953 [2, 10, 21–25]; the rotating disc oxygenator described in 1948 by Bjork [2, 10, 26]; and the improved all-glass bubble oxygenator described in 1952 by Clarke, Gollan and Gupta [2, 27].

The use of oxygenators during the early years of open-heart surgery

The Mayo-Gibbon pump-oxygenator

The painstaking work of Gibbon in designing experimental film oxygenators that had extended over two decades [21–25] was crowned with success when he carried out the first successful human intracardiac operation under direct vision using a mechanical extracorporeal pump-oxygenator on 18th May 1953 [2, 10, 22, 25]. Gibbon's original objective was to develop an apparatus capable of suspending the natural circulation during Trendelenburg's emergency operation for pulmonary artery embolectomy [21, 22]. However, the first human operation was in fact closure of an atrial septal defect [25]. Gibbon's early experimental oxygenator filmed blood over the inner surface of a rotating cylinder in an oxygen atmosphere [2, 21–23]. However, this could not be enlarged to perfuse animals larger than a cat [28]. Thus, in Gibbon's later animal experiments and the first human operation, he used a stationary screen oxygenator that he had developed [24, 25]. This consisted of a series of six to eight wire mesh screens arranged vertically and in parallel in a plastic container down which the blood flowed, forming a stable film that was exposed to a flow of oxygen [10]. Each of the screens was 60 cm high and had a width of 10 cm.

Kirklin *et al.* [29, 30], at the Mayo Clinic in Rochester Minnesota, further developed the Gibbon-type stationary screen oxygenator into the Mayo-Gibbon pump-oxygenator apparatus after careful animal experimentation. This was a sophisticated commercially available unit [6]. Kirklin *et al.* began their pioneering series of human intracardiac operations in March 1955 using the Mayo-Gibbon pump-oxygenator and were very successful [31]. A number of cardiac surgery units worldwide obtained and used this apparatus [2, 31, 32]. The results were satisfactory but the apparatus was bulky and cumbersome, quite complicated to sterilise and operate, prone to the problem of blood streaming (resulting in diminishing blood surface area for gas exchange), and also required a large blood and saline priming volume [33].

The Kay-Cross disc oxygenator

The Bjork rotating disc film oxygenator (1948) [2, 26] employed in animal studies was modified for clinical use

by Melrose in 1953, by Kay and Cross and their colleagues in 1956 [34, 35], by Osborn, Bramson and Gerbode in 1960 [36] and by other workers. The Melrose model described in 1953 after comprehensive animal studies was used clinically very successfully for open heart surgery for human patients at the Royal Postgraduate Hospital in London and other cardiac units [2, 37]. It was an ingenious drum and disc oxygenator. It gave good service in the early days of clinical cardiopulmonary perfusion, but it was cumbersome and required considerable time and expertise to service and assemble. Later, simpler versions with Teflon®-coated stainless steel discs in a silicone-coated Pyrex® chamber were preferred [6, 10, 22, 34–36]. Some disc oxygenators with presterilised disposable plastic discs became available later [6].

The need for blood conservation required the filming discs to be placed close to their disc enclosure. This led to risks of foaming and haemolysis when the discs spun, which limited their clinical applicability [22, 33]. Nevertheless, rotating disk oxygenators continued to be favoured by many clinicians in the 1960s and 1970s despite the dominance of the practical disposable single-use disposable bubble oxygenators until single-use membrane oxygenators became generally available. This was in part due to their perception that the Kay-Cross oxygenator caused less blood damage than the bubble oxygenator in longer surgical cases [10, 38].

The DeWall bubble oxygenator

Studies of the function of the version of the bubble oxygenator devised by Clarke, Gollan and Gupta were important for the subsequent design of the DeWall bubble oxygenator [39] that was used by Lillehei and his team in their continuing pioneer work in intracardiac surgery [2, 6, 39–41]. Clarke, Gollan and Gupta [27] reported in 1950 that although small bubbles with their large surface area to volume ratio favoured oxygen uptake, they were less buoyant. This means that smaller bubbles are less likely to rise spontaneously to the surface and are more likely to remain in suspension – air embolism is therefore more likely. An optimum balance has therefore to be obtained. This optimum is believed to exist if the bubbles are between 2 mm and 7 mm in diameter [42]. Alternatively, a mixture of small and big bubbles may be used [41]. Furthermore, since carbon dioxide removal occurs by diffusion, the partial pressure of the gas vented from the oxygenator cannot exceed its partial pressure in blood, which is normally 4.5 kPa, in contrast to the 13.3 kPa of oxygen [33]; increasing the gas exchange area is of limited benefit. Carbon dioxide removal is therefore limited by the rate of fresh gas flow necessary to maintain an optimum carbon dioxide partial pressure differential.

The commercially available DeWall oxygenator [10] had a vertical oxygenating column through which oxygen bubbled upwards at a high gas flow rate. The resulting foamy blood subsequently entered a defoaming chamber, in which silicone-coated surfaces decreased the surface tension of the bubbles, causing the smaller bubbles to coalesce into larger bubbles. These larger bubbles were then eliminated in a helical tubular reservoir in which the bubbles floated upwards while the blood was pumped downwards.

In March 1954, after careful animal research, Lillehei and his team of the University of Minneapolis, Minnesota, began to conduct an interesting and relatively successful series of intracardiac operations for the closure of atrioventricular defects in children using the arterial blood of an adult in a controlled cross-circulation technique [43]. Lillehei *et al.* then began to use the DeWall bubble oxygenator clinically in May 1955 [40, 44]. DeWall type bubble oxygenators gained widespread acceptance, being used in an estimated 90% of open heart operations worldwide in 1976 [44]. This was because of their many advantages: they were highly efficient because of the large cumulative surface area of the oxygen bubbles; they had a simple design without moving parts other than the mechanical pumps that drove the circulation; the components of the circuit were easily sterilised and they were disposable [2, 6, 38, 45]. Their popularity was cemented with the advent of single-use, relatively inexpensive, presterilised and prepacked plastic versions [2, 45–48]. A further advantage was that the priming volume required for these disposable devices was so small that a saline prime would often suffice without the addition of donor blood. Some bubble oxygenators were fitted with integral heat exchangers and had plastic venous reservoirs that allowed direct observation of the changes of blood volume in the circuit [33].

The DeWall oxygenator is a 'sequential bubble oxygenator', i.e. the components (bubbler, defoamer, reservoir and pump) are arranged linearly in series. Other variants have been designed that are 'concentric bubble oxygenators', in which for the sake of compactness the components are arranged concentrically, and also 'foam oxygenators', in which gas exchange is achieved when blood films down a column in a counter-current system [49]. Foam oxygenators consequently share some functional properties with both film and bubble oxygenators.

Limitations of the performance of direct contact extracorporeal oxygenators

The length of time for which either bubble or film direct contact extracorporeal oxygenators could be used without

causing serious complications did not extend much beyond 4 h [6, 45]. The principal limiting factor was damage to blood constituents due to the direct contact of blood with air surfaces and to contact with the plastic and metal constituents of the pump oxygenator circuit. Blood trauma included damage and destruction of red blood cells and platelets, coagulation disorders and protein denaturation. Prolonged extracorporeal perfusion could also result in vascular problems, including diffuse capillary leakage, poor peripheral perfusion, acidosis and progressive organ failure [50].

These disadvantages of direct contact extracorporeal oxygenators could be accepted and usually counteracted for the relatively short duration of intracardiac surgery. Many cardiac surgery units used profound hypothermia, cooling the body with the aid of a heat exchanger to a nasopharyngeal, i.e. brain, temperature of 10–12 °C. This allowed the perfusion to be turned off completely for up to 1 h while prolonged intracardiac surgery was performed [6, 45]. Some units adopted the Drew method of profound hypothermia [51, 52]. This technique eliminated the use of an extracorporeal oxygenator completely. The patient's own lungs were employed as oxygenators during cooling by bypassing both the left and right sides of the heart with separate simultaneous perfusions [6, 45, 51, 52].

The Mayo-Gibbon type screen oxygenators, the disposable versions of the DeWall-type bubble oxygenator, and the Kay-Cross disc oxygenator and its modifications remained in use throughout the 1960s and 1970s. The disposable bubble oxygenators became very popular because of their convenience in use and low prime volume but there was a general view that the rotating disc oxygenators were somewhat better for longer cases [2, 10, 38, 45]. There are very few papers attempting to make direct comparisons of the clinical performance of the various forms of direct contact extracorporeal oxygenators. However, in 1961 Gerbode *et al.* gave their reasons for marginally preferring a rotating disc over a bubble oxygenator [53]. Engell *et al.*, writing in the same year, also gave their reasons for marginally preferring the disposable bubble oxygenator over a stationary screen oxygenator [54].

The limit on the length of time that direct-contact extracorporeal oxygenators could be used made them unsuitable for use in the longer term for the therapeutic support of adults and infants suffering from respiratory distress syndrome (RDS). One thing was certain: clinicians concerned with cardiopulmonary perfusion in the 1950s, 1960s and 1970s followed the lengthy gestation of membrane oxygenators very closely, and looked forward with keen anticipation to the advent of a practical, disposable version.

Introduction of the membrane oxygenator

The idea of a protective membrane between blood and air to decrease the problem of blood trauma inherent in direct-contact extracorporeal oxygenators began with observations by Kolff and Berk in 1944 [55]. They noted that blood in their haemodialysis machine, which contained 20 000 cm^2 of cellophane tubing, became oxygenated when exposed to aerated dialysates; the gas contents of the blood equilibrated with that of the dialysate through the process of passive diffusion. Although the potential advantage of the membrane oxygenator in decreasing the degree of blood trauma associated with direct-contact oxygenators was immediately evident, the problems were also quickly appreciated, namely:

- a dearth of suitable membrane biomaterials, which were judged on their gas permeabilities, mechanical strength, how thinly they can be made without pinhole defects and blood–artificial surface interactions;
- the membrane constituted an additional barrier to gas exchange;
- the problem of optimal distribution of blood and gas flows so that there is efficient gas exchange.

The emphasis in early membrane oxygenator development concentrated on finding suitable biomaterials [56], as early biomaterials had low gas exchange performance and poor mechanical properties, limiting the development of membrane oxygenators. Of the earliest available materials, ethylcellulose and polyethylene were the most permeable to oxygen and carbon dioxide [57]. Polyethylene offered good mechanical strength and was rolled into a coil for the first experimental membrane oxygenator [58, 59]. Clowes, Hopkins and Neville in 1958 used 25 m^2 of the more permeable ethylcellulose [60] (soon replaced by the mechanically stronger polytetrafluoroethylene or Teflon® [61]) in multiple sandwiched layers in their device that constituted the first clinical membrane oxygenator. Membrane support with grooved plates was later added, making an arrangement akin to a manifold of straight capillaries in parallel. This was to stop blood collecting unpredictably in thick rivulets, a problem similar to that of blood streaming in film oxygenators.

One disadvantage of hydrophilic membrane oxygenators is their tendency to leak plasma in a manner akin to tents leaking water when wetted on the inside. This severely shortened the duration of the use of the membrane lung. To prevent this, membranes made of hydrophobic polymers [56] were used. These materials were initially derived from packaging materials used in the capacitor industry, such as polytetrafluoroethylene (Teflon®). With hydrophobic membranes, Melrose [62] realised in 1958 that it is carbon dioxide removal that

was the limitation, as carbon dioxide solubility in hydrophobic solids is much less than its solubility in hydrophilic solids. To emphasise the importance of carbon dioxide transfer, the term 'membrane lung' was coined. This problem was partly solved by the use of silicone as the hydrophobic material in membrane lungs. Although silicone had been discovered in 1947 and had played an important role as a defoaming agent in direct-contact devices, its excellent gas exchange properties [63] were not discovered until 1957. Silicone had a permeability (the product of diffusivity and solubility) of 2600–6500 $\times 10^{10}$ ml oxygen.cm^{-2}.mmHg^{-1}.s^{-1} for oxygen and four to five times higher than this for carbon dioxide, these figures being some 40 times higher than those for Teflon®.

Early silicone membranes had a number of problems. They had low mechanical strength and were not free of pinholes when made into a thin film. Solutions were found to these problems. In 1959, Thomas designed the first silicone membrane lung using a thin continuous silicone membrane on a fabric support, which was made by dip-coating a nylon mesh, and the pairing of two sheets of ultrathin membranes together so as to decrease the risk of leakages through random pinhole defects.

The definitive solution belonged to Burns [64] who, in 1959, developed a new process at Hammersmith Hospital in London for the low-cost production of thin films of silicone membranes that were virtually free of pinholes and had greatly increased strength. Modern versions of the silicone membrane oxygenators are still in use and are marketed as long-term extracorporeal oxygenators [65].

Improving the gas exchange efficiency of membrane oxygenators

With sufficiently thin membranes, the gas exchange bottleneck was now recognised as having shifted from the membrane to gas diffusion through blood. This was a result of the thickness of the blood layer. Marx *et al.* [66] determined that oxygen transfer into a blood film is proportional to the square of the thickness of the blood film and the diffusion resistance of the boundary layer.

This latter factor requires elaboration. In alveolar capillaries, the blood channels are one cell thick, resulting in efficient gas exchange. In artificial oxygenators, the blood channels are much thicker. With laminar flow, blood flows in orderly layers through these channels. The boundary layer, i.e. the layer that is adjacent to the gas exchange surface, quickly equilibrates with the venting gas. However, this equilibration is slow to spread through the other layers because of the low diffusivity of gas through blood, which is 1.73×10^{-9} m^2.s^{-1} for oxygen and 1.45×10^{-9} m^2.s^{-1} for carbon dioxide at 37 °C, with consequent deterioration of gas exchange efficiency. Subsequent development therefore concentrated on minimising these two bottlenecks. The first silicone capillary oxygenator, comprising capillaries that were 100–500 μm in diameter, was designed by Bodell *et al.* [67] in 1963. The small diameter of the hollow fibres decreases the distance of the blood layers from the gas exchange surface in two dimensions. Capillary oxygenators also have the additional advantage of being better able to control the volumes of both gas and blood compartments.

Configurations with blood inside the fibres and oxygen outside and the reverse configuration of blood outside the fibres and oxygen inside were tried. Wilson *et al.* [68] showed that the preferred configuration used blood flowing inside the fibres. However, the opposite is the case with current microporous hollow-fibre oxygenators, as is described later. The second problem, i.e. the diffusion resistance of the boundary layer, was addressed by the induction of secondary flows in blood. Secondary flows are fluid flows that are additional to the mainstream. They may be used to disrupt laminar flow and impart convective mass transfer to the mass of the fluid. Mixing and therefore gas exchange performance are thus increased. Passive internal secondary flows are induced by forcing blood to 'eddy' around passive obstacles, e.g. forcing blood to move in curved paths around a helically wound tube [69] or by the insertion of surface elements into blood passages [70]. Active secondary flows are induced by using energetic mechanisms to disrupt laminar flow more effectively, resulting in greater gas exchange efficiency. Mechanisms devised for this include:

- periodic deformation of the membrane through cyclical oxygen pressure to produce microscopic foci of mixing [71];
- a rocking membrane envelope [72];
- pneumatic pulsation of the membrane [72];
- a rotating membrane-bound disk [72];
- moving rod massage [73];
- the toroidal membrane oxygenator [74, 75];
- the annular membrane oxygenator by Gaylor *et al.* [76];
- vortex-shedding designs [77, 78].

The measures employed were very successful in enhancing gas mass transfer. Kolobow's device [71] in fact exceeded 200 ml oxygen.min^{-1}.m^2, the limit for the thickness of the silicone membrane used. This was because the membrane inverted and stretched into the gas side, increasing the surface area when hypobaric pressure was applied. Kolobow's device was mass-manufactured and marketed by SciMed, then AveCor and now MedTronic, becoming the only solid silicone membrane

device consistently available for long-term life support during the past few decades [79].

Use of membrane oxygenators for treating respiratory distress syndromes

Adult respiratory distress syndrome

Right from the early stages of membrane oxygenator development it was evident that membrane oxygenators had significant advantages over bubble oxygenators. Besides inflicting less blood damage, they are more suitable for infants and children as they have a closed non-distensible circuit, giving better control of blood volume. They (and in particular the hydrophobic continuous membrane devices) were therefore used in longer-term applications such as in intensive care. The conventional treatment of respiratory distress in premature babies and in injured adults is by mechanical ventilation. This is beneficial in the short term, but long-term forcible distension resulting in barotrauma or volutrauma can cause significant pulmonary damage. This damage may be further complicated by associated oxygen toxicity to lung tissues. Theoretically, extracorporeal membrane oxygenation (ECMO) allows the lungs to rest, by taking over the gas exchange functions of oxygenation and carbon dioxide removal of the lungs. This may allow the lungs of premature infants to mature into the vital life-sustaining organs they should be, and should allow the damaged lungs of adults to recover their function.

In support of this hypothesis, there were numerous reports [80–83] of favourable outcomes with ECMO as a treatment for adult respiratory failure. This led to the important ECMO trial of 1975–77 [84]. However, the results were disappointing. In a nine-centre prospective, randomised trial involving 92 patients, patient survival rate was <10% regardless of whether they were treated with ECMO or on mechanical ventilation. All autopsies showed extensive lung fibrosis, although a significant number of patients died from technical complications. Subsequent critiques identified the following confounding factors [50]:

- a selection bias that excluded both best-risk and worst-risk patients;
- failure of ensuring lung rest in some ECMO patients;
- absence of prior ECMO experience in some centres;
- a patient pool biased by an epidemic of influenza pneumonitis in 1976.

After these disappointing results, Kolobow and Gattinoni [85] introduced a modified extracorporeal gas exchange technique, called extracorporeal carbon dioxide removal ($ECCO_2R$), in 1978. Extracorporeal membrane oxygenation required a high membrane surface area and extracorporeal blood flows to carry out its dual function of oxygenating and decarbonating the blood. In contrast, $ECCO_2R$ uses the large surface area of the natural lungs to effect efficient oxygenation and delivers high gas flows to the extracorporeal membrane lung for efficient extraction of carbon dioxide. As the lungs no longer need to extract carbon dioxide, low-minute volume ventilation can be employed, resulting in minimal risks of barotrauma and volutrauma. At the same time, alveoli are recruited, avoiding the pitfall of poor lung perfusion with ECMO [86]. Because the membrane lung is no longer responsible for oxygenation, smaller membrane areas and lower extracorporeal blood flows are needed compared to ECMO, minimising the risk of blood trauma. Again, while there were numerous favourable anecdotal accounts, a randomised trial [87] failed to show any statistically significant benefit for patients who were treated by $ECCO_2R$, compared to patients who were treated by individualised mechanical ventilation regimes.

Not surprisingly, these disappointingly negative studies dampened enthusiasm for extracorporeal gas exchange as being a useful treatment for adult respiratory distress syndrome.

Neonatal respiratory distress syndrome

In contrast to the results in adults, prospective, randomised, clinical trials investigating the efficacy of extracorporeal gas exchange in patients with neonatal respiratory distress syndrome consistently showed favourable results for ECMO therapy. The first study by Bartlett *et al.* [88] looked at 12 infants and used the randomisation technique of 'play the winner', i.e. the first patient was afforded a 50 : 50 randomisation but all subsequent patients were allocated odds favouring the previous effective therapy. This avoids the ethical issue of unbiased randomisation. In this study, the only patient allocated mechanical ventilation died, whereas 11 patients allocated ECMO survived, and the results were statistically significant. Criticism of this study having a control population of one led to a second prospective randomised study with a more even treatment distribution. Nevertheless, ethical concerns prevented unbiased randomisation. In a later study [89], 39 infants with an expected 85% mortality from severe persistent pulmonary hypertension and respiratory failure were allocated conventional medical therapy or ECMO patients. Randomisation ceased, as planned, after the fourth conventional medical therapy death. The ECMO arm had a 97% survival (28 of 29) and the conventional medical therapy arm had a 60% survival (6 of 10); the results were statistically significant.

These studies were followed by the first multicentre randomised clinical trial [90] applying unbiased randomisation. In this study, 185 mature newborns with severe respiratory failure were randomly allocated treatment by

either ECMO or conventional management. This allocation was performed by a computerised protocol that used the key prognostic variables of primary diagnosis, disease severity, referral centre and ECMO centre. Of the 93 subjects given ECMO support, 28 died before discharge and another two died before their first birthday. Of the 92 subjects given conventional support, 54 died before discharge with no further deaths by their first birthday. Of the rest, 17 from the ECMO group had various levels of disabilities compared with 11 from the conventional management group. The chance of survival was therefore almost doubled with ECMO. These survival figures were not clouded by high 1-year morbidity rates or outcome measures in a later review at four years [91]. Subsequently, 'recruitment to the trial was stopped early (November 1995) by the trial steering committee on the advice of the independent data-monitoring committee, because the data accumulated showed a clear advantage with ECMO'. However, it must be noted that the patient population of this trial was restricted for methodological reasons. It may not therefore be representative. In addition, although this report shows that ECMO is better than conventional ventilatory therapy in neonates, it does not show that ECMO is better than other alternatives to conventional therapy. The results of this ECMO trial therefore fall short of being conclusive. Important though this trial may be, there is a need for additional studies on a wider variety of patient populations and therapies before we can be confident in judging the efficacy of ECMO at present, and its viability as a therapy in the future.

As a postscript, the Extracorporeal Life Support Organisation (ELSO) Registry has collected data on ECMO patients internationally since 1989 [92]. There are records on over 30 000 patients, with a current average of 800 ECMO patients a year. Sixty-six per cent of these are neonatal patients, with a 77% survival to discharge. Paediatric and, to a lesser extent, adult patients, form the remainder, both with > 50% survival to discharge. Increasingly, extracorporeal support is being applied to cardiac failure and cardiac arrest patients, with survival to discharge about the 40% mark.

Development of high-performance membrane oxygenators for cardiac surgery

Despite the success of silicone membrane oxygenators for long-term clinical applications, direct-contact oxygenators remained dominant for short-term clinical applications such as cardiac surgery in the 1970s. This was due to membrane oxygenators being less efficient than direct-contact oxygenators, cumbersome, prone to plasma leakages and thrombotic occlusions, and time-consuming to assemble [10, 93]. The focus of much research effort in the last 50 years has been to remove these remaining disadvantages.

With the use of secondary flows in membrane lungs, the membrane once again became the bottleneck for gas exchange. The need to retain mechanical strength meant there was limited scope for making the membrane even thinner. An alternative approach was to use microporous membranes, as first suggested by McCaughan *et al.* [94]. These membranes have pores running through them that allow some direct contact between blood and air, allowing for more efficient gas exchange. The first prototypes were made of microporous polyethylene, sintered nickel or hydrophobic cellulose acetate polymers. However, the pore size of these membranes exceeded 1–10 μm in diameter, the limit at which plasma leakage occurs freely [56]. Air embolism is also more likely to occur when the gas pressure exceeded that of the blood side. With the advent of hydrophobic membranes with good distribution of sufficiently small median pore size, e.g. 0.02 μm in the case of Celgard® – a microporous polypropylene membrane, blood penetration of the micropores was prevented by surface tension forces. Microporous membrane lungs have operated for several days without plasma leakage. Polypropylene was the material used for hollow fibre construction as it is reliably fabricated without defects at acceptable cost. Although there is a direct blood–gas interface within the pores, blood trauma is limited. This is thought to be because the processes of protein deposition and water vapour condensation at the blood–air interface cause the microporous membranes to behave like continuous membranes [56]. As with the earlier solid membrane lungs, further development of the microporous membrane lungs involved improving the gas exchange performance of microporous membranes by applying secondary flow and hollow-fibre technologies.

With the advent of microporous hollow fibre technology, oxygenators were made from bundles of microporous hollow fibres 200–300 μm in diameter in a hard shell [56, 93]. With their large surface area to volume ratio, they proved to be efficient gas exchange devices. Other advantages are that these oxygenators are simple to fabricate, can be made into different sizes for different patient needs, and have non-compliant blood and gas compartments more suited to paediatric use. With these advantages, membrane oxygenators began to be widely accepted even in cardiac theatres.

A variant of the conventional hollow-fibre oxygenator is the inverse-flow or 'blood outside' design [93]. These devices have blood flowing in the external chamber originally designed for gas, while gas flows within the

hollow-fibres. The advantages of this design are as follows [22, 93]:

- passive mixing is induced as blood weaves past the hollow-fibres – the improvement in gas exchange performance is such that membrane area is 2–2.5 times smaller than conventional hollow-fibre oxygenators;
- lower pressures are generated, as high-viscosity blood flows in a larger chamber while low-viscosity gas flows in the narrower hollow-fibres;
- the gas exchange area is the outer surface of the hollow fibres, which was larger than the inner gas exchange surface of classical hollow fibre oxygenators.

The disadvantages are:

- fibre arrangements need to be optimised through complex fluid dynamics studies so that efficient distribution and movement of blood and oxygen may be achieved;
- biocompatible shell materials and suitable blood ports are needed.

The combined advantages of high gas exchange efficiency, low blood trauma, compactness, simplicity and low cost meant that microporous membrane lung devices began to replace the efficient bubble oxygenators in cardiac operating theatres [45, 93] in the 1980s. However, for longer-term use, plasma leakage remained a problem with microporous membrane lungs. Thus, membrane lungs have separated into two major classes: microporous hollow-fibre oxygenators for short-term surgical use and non-microporous membrane lungs for long-term intensive care use.

Recent advances

Device innovations

Extracorporeal gas exchange has come a long way since its first conception by Hooke, both in terms of device development and clinical application. Even today, research and development to improve extracorporeal oxygenators continues apace. The success of the hollow-fibre oxygenators led to the innovative concept of an intracorporeal oxygenator called the intravascular oxygenator, or IVOX [95]. In IVOX, a bundle of silicone elastomer-coated hollow fibres forming a non-microporous surface is inserted into the inferior vena cava of a patient and oxygen is pumped through these fibres. Secondary flows are achieved when venous blood weaves its way through these fibres in the inferior vena cava. This device is therefore the intracorporeal equivalent of inverse-flow hollow-fibre oxygenators. Enhancements to these devices include incorporation of balloon pumping within the fibres further to generate secondary flows and improve gas exchange performance – this was named the Intravascular Membrane Oxygenator (IMO). Even then, the gas exchange performance of IVOX/IMO devices (196.8 ml oxygen.min^{-1}.m^{-2} and 78 ml carbon dioxide.min^{-1}.m^{-2}) was inadequate for total respiratory support, although it sufficed for partial respiratory support. These devices are potentially revolutionary, as they do not require complex cannulations and tubing to convey blood extracorporeally for oxygenation. Indeed, the blood-carrying tubes are natural and internal. Thus, by performing a procedure a little more complex and expensive than a vascular catheter insertion, intensivists can quickly institute 'extracorporeal' oxygenation without the risks associated with extracorporeal circulation. Thus IVOX/IMO promises a simple and low-cost method of delivering a form of 'extracorporeal' oxygenation for intensive care use. However, this promise is not being realised, as IVOX/IMO devices have failed to gain widespread acceptance because initial studies failed to demonstrate clinical benefit [96]. Nevertheless, research and development work continues on this fascinating concept.

The recent advent of efficient non-microporous hollow fibres made of new biomaterials such as poly 4-methyl-1-pentene (PMP) [97–100] is also promising, as it has resulted in non-microporous oxygenators that are almost as efficient as microporous hollow-fibre oxygenators. At the same time, non-microporous oxygenators are highly resistant to plasma breakthrough and have a long operating life, enabling long-term extracorporeal applications. The dual advantages of operational efficiency and longevity may herald the future dominance of non-microporous oxygenators.

Conclusions

As with many historical studies, this paper is more than a retrospective glance. There are lessons within this history that are relevant today. The outstanding lesson from this paper is that medical devices need to be effective in what they aim to do, be proven to be clinically effective and, finally, be simple and inexpensive to manufacture to achieve widespread clinical acceptance and therefore market success. These characteristics are very much in evidence in the successful extracorporeal oxygenator designs such as the DeWall bubble oxygenator, the Kolobow silicone membrane oxygenator and the hollow-fibre oxygenator. Where clinical applications are concerned, the main lesson is that technology alone is not enough. Physiologists and clinicians designed the early extracorporeal devices based on their basic scientific knowledge. Clinical perseverance and innovation pushed clinical extracorporeal oxygenation past the many obstacles it encountered along the way. We are not passive consumers in an increasing medical technological age.

Our medical knowledge, clinical skills and professional dedication make us partners with technologists and patients in the ongoing search for improved patient safety.

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