The transition from the bubble oxygenator to the microporous membrane oxygenator

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Introduction

The transition from bubble oxygenators to microporous membrane oxygenators is a good example of how industry working with customers and material suppliers can help improve a surgical technique, such as cardiopulmonary bypass. The development is characterized by many individuals who, through their inventiveness and determination, made the transition possible. While the medical personnel involved in the transition may be well known to professionals in the medical field by their other endeavors, many of the key engineers and industry entrepreneurs are mainly unknown. The purpose of this paper is to outline key elements of engineering and material science in the history of the transition, and also to identify some of the key individuals as well (Figure 1).

Early commercial devices

In the early 1960s, the medical device industry, as related to perfusion, was indeed a small endeavor. One of the key people who recognized early the need for some company to actually manufacture devices was William Graham, then president of Baxter Travenol, who approved and nurtured the manufacture of the Kolff twin-coil dialyzer, and a heat-sealed sheet bubble oxygenator based on the DeWall-Lillehei concept. Isolated perfusion was not new, dating from the 1800s, but it took doctors like John Gibbon Jr. to actually determine the details for full body perfusion and use it in the early 1950s. Even membrane oxygenators were not entirely new, as, in the 1960s, men like Clowes and Bramson were doing full body perfusion with primitive devices, built in their own institutions. However, if these devices were ever to be of practical size and priming volume, performance would have to be radically improved.

Several investigators looked into the basic mass transfer problem in membrane oxygenators, with Marx and Snider recognizing the problem in oxygenating tranquil blood films, and Peirce struggling with the limitations of the then available membranes. Both Peirce and Bramson showed that screens in the blood between the membranes could decrease boundary layers and gently improve transfer in the blood, but membranes continued to be limited, both in permeability, especially carbon dioxide, and strength. Walter Robb, then at General Electric, showed that dimethyl silicone rubber could provide good permeability and a good permeability ratio between carbon dioxide and oxygen, given the different partial pressures in normal blood. General Electric advertised this result as a promotion for their research, using a hamster cage, with walls of silicone rubber, submerged in a fish tank, where the hamster could breath comfortably even though his cage was under water, as gases diffused into and from the water. Several developers and manufacturers adopted this new material, the Landé-Edwards, the Travenol Modulung, and the Sci-Med based on the Kolobow spiral coil design. While performance per unit area was still not very high, the devices were clinically useful and provided the basis for exploring how operational they might actually be.

The big opportunity, as identified by various companies’ marketing groups, was in replacing the ventilator, where patients often failed to improve or actually experienced a decline in lung function. Investigators soon learned that putting a patient on an oxygenator long term, as in extracorporeal membrane oxygenation (ECMO), was not an easy task, either in managing the patient or in managing the

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system, and ventilators and ventilator management improved. A key to this was Kolobow’s determination that putting patients on a ventilator at full volume was damaging because areas of fibrous lung refused to stretch, putting a stress on the viable areas, soon damaging them as well. Finally, it was determined in a controlled study, that ECMO was no better than a properly used ventilator in treating these patients. Suddenly manufacturers were stuck with a device with little or no use, that had cost millions of dollars and the time and effort of some very talented people to develop.

Many manufacturers simply gave up, cutting their losses, but some hung on to look for other uses. Newborn ECMO seemed to work, as practiced by Bartlett, when applied in a regimented manner, as the babies seemed to get over their problems in a reasonable time. There was also organ preservation and regional perfusion, but these all were small markets. Some doctors, like Clark in St Louis, Sugg in Alabama, and Baffes in Chicago, started to look at membrane oxygenators as a replacement for the bubble type in pediatric surgery. Often they required multiple units, stacked together to get the desired oxygenation, but they persevered in showing it could be done, and hinting that it might be better. To be a real competition to the other types of oxygenators in use at that time, much improved membranes would be required, and some investigators started looking at different types of membranes other than the solid materials. Wettable porous membranes had been used, but were difficult to control and not very effective, while the use of nonwettable microporous membranes had been proposed by material people like Fatt and LaForce. These were somewhat limited in that they were not really commercially available, and they were composed of various papers or nonwoven material, treated with various agents, such as silicone or Teflon emulsions, that eventually failed in time.

Membranes with holes become commercially available

Sometimes things happen by pure serendipity. Dr Dietrich Birnbaum, a resident working with Eiseman at the University of Colorado with Travenol Modulung oxygenators, met William Gore on the ski slopes in the Rockies. They talked about each other’s careers and thought that the porous Teflon material that Gore had developed at Dupont and was now set up to manufacture might be suitable for oxygenators. The material was strongly nonwetting with well-controlled pore structure of less than one micron, was made of pure Teflon, and, when suitably backed up with a screen or nonwoven, could be handled in production. Plus, it seemed to be more pinhole free, and more reliable than the thin silicone rubber material available at the time. Ron Leonard and Lou Wolf constructed prototypes using the new material and the Modulung design at Travenol Laboratories and found, in in vitro studies, that with just over 2 m² surface area they could handle the blood gas requirements of a well-anesthetized adult patient. In addition, in spite of the blood gas interface at the pores, there seemed to be no difference in blood handling between the microporous material and the usual silicone material by any tests commonly used at the time. Leonard and others had predicted that the stationary interface, unlike the constantly renewed interface in a bubble oxygenator, would be acceptable. Work with the material was published by Travenol and the University of Colorado. William Graham, then Chief Executive Officer of Baxter Travenol, heard about this success and approved moving ahead into commercialization. In just over a year, the first truly operational microporous membrane oxygenator was on the market.

There were concerns for the new device, and these were addressed in the hardware. A blow-off type manometer indicated any increase in gas pressure that might lead to gas emboli and released pressure if the pressure became too high. A heater built into the gas supply was designed to heat the incoming gas to prevent the build-up of water in the gas phase,
then thought to lead to plasma leakage. Finally, a two-pump system with two reservoirs, mimicking the human circulatory system, was used to protect the device from high pressures. All of these turned out to be overkill, but reflected the concern for the new concept in day-to-day use. Oxygenation was controlled by an inflatable shim that modified the blood path thickness for carbon dioxide removal by total gas flow.

The first clinical case was done by Peter Anthony at Rhode Island Hospital and was listed as uneventful, a good outcome for a new device. Several of the early investigators went on to use the device, another good sign, at Houston, Pittsburgh, and Rhode Island, and production was scaled up to actual manufacturing quantities. Microporous membrane oxygenators were on their way.

From the perspective of the company, it was what was called missionary selling at first, trying to convince perfusionists and surgeons to give up the bubble oxygenator for something more expensive, more complex, and more difficult to run. However, many were eager to try it, and once tried, they seemed to stay with it in spite of early growing pains in terms of production and technique. Some early users put a bubble oxygenator, primed and ready to go, in the cardiopulmonary bypass circuit in case this newfangled contraption let them down. Travelnol even built a simulator, which was a feature at trade shows, so potential users could see how easily they could master the use of the device and hardware. Soon, some evidence started to accumulate that concluded it was better than using a conventional bubble oxygenator, especially if suction blood, long known to be a culprit in the biocompatibility area, could be suppressed. Charles Wildevuur even developed a special suction device, which, when used with a membrane oxygenator, showed remarkable improvements in CPB.

New membranes were introduced from Celanese that were made of polypropylene, which were stronger, more controlled, and less apt to creep, further improving the oxygenator. It was not long before the oxygenator passed the eighth of a million case mark, in days when worldwide cases were nowhere near what they were to become. Soon, a worthy competitor appeared in the COBE Laboratories' CML oxygenator, especially if suction blood, long known to be a culprit in the biocompatibility area, could be suppressed. Charles Wildevuur even developed a special suction device, which, when used with a membrane oxygenator, showed remarkable improvements in CPB.

External fiber flow designs dominate the industry

Hollow fibers arrive

Dow had pioneered hollow fiber oxygenators, using silicone tubes, early in the oxygenator development history, but they failed to meet their expectations due to their size, and the problem with clotting over the large tube header. However, in the late 1970s, Mitsubishi Rayon, using their fiber-spinning experience, developed microporous hollow fiber capillaries. Terumo Medical fashioned these into an oxygenator, using their dialyzer experience, with blood flow inside the capillaries. It was thought that capillary devices, which ruled the dialyzer industry, might do the same in the oxygenator industry. The devices required a large surface area due to the languid blood film inside the constrictive geometry of the tube, but they did not need the screening, which added to the surface area of the flat membrane devices. Soon others were following Terumo's lead, such as Bentley Laboratories with the BOS series, containing as much as 7 m² of microporous capillaries from Celanese Ltd. who also had learned the art of spinning and stretching polypropylene.
devices, with Membrana now entering as a source of capillaries based on a phase separation process that promised finer pore distribution and size control. Membrane oxygenators, mostly microporous, dominated the perfusion market. There were key engineers involved in these efforts, generating many of the patents of the time, including Don Raible at Bentley Laboratories, Roger Elgas from COBE Laboratories, and Bob Curtis at Shiley. The Extracorporeal design passed on to J & J, and then Medtronic, indicating the industry interest in perfusion at the time.

Continued advances and the future

Ulrich Baurmeister, from Membrana, made the next real advance in capillary art by devising and patenting a process whereby capillaries were woven into a mat, angled, and then crossed to make an ideal fluid bed due to the precise control of fiber placement. At first, it was tried in dialyzers, where it failed, since it added cost to an already cost-constrained product without adding much performance. When it was tried with microporous capillaries for oxygenators, it was recognized as a success and incorporated in oxygenators from Sarns in the USA and Dideco in Italy. Not only was the performance of the oxygenator improved, but the manufacturing process could be simplified and made easier to control, thus improving both quality and reliability. Several other manufacturers joined in the use of this technological improvement, and Membrana became the market share leader in oxygenator capillaries.

Oxygenator design today is vastly different from the ‘cut and try’ of the early days. Lyle Mockros and others have developed design equations that describe the performance and pressure drop of even complex blood paths. Newer work even looks at defining such things as shear, which may be damaging to blood, and making sure it is in a safe zone, just as Perry Blackshear had tried to do many years before. Other computer-based techniques, such as computational fluid dynamics (CFD), allow the examination of flow and flow effects before the device is even made. However, oxygenator history seems to have arrived at a crossroads. Years of steady improvement in such aspects as performance per unit area and shear control (Figure 1) are being challenged by cost and the revival of older techniques. Many coronary bypass procedures are now done ‘off pump’, and there are those in third world countries who advocate a return to bubble oxygenators as a lower cost alternative that they can manufacture themselves. Other groups believe that the microporous oxygenator needs to change, incorporating other elements of the CPB circuit, such as the pump and arterial line filter, with the device in a supportive role, such as the CardioVention COR® device. There is even a renewed look at augmented diffusion, with a rotating fiber bundle also acting as a pump. Advanced capillaries have also appeared, such as the PMP (polymethyl-pentene) material from Membrana, which combines a microporous core with a solid material skin, and improved silicone fibers more suited to long-term use.

The oxygenator development history has been a relatively short and interesting series of technological advances, brought about by inventive, determined, and courageous individuals. Not often recognized is the tremendous contribution of perfusionists, who were willing to work with manufacturers on the details and suitability of the devices, and then had the courage and faith to actually use them clinically in their institution, without risking patients, of course, but certainly risking their reputations. On behalf of the industry, I would like to thank these pioneers once more, and thank all of you for sharing this brief but brilliant history with me.

References


