Cardiol Young 1993; 3: 196-200
© World Publishers Limited
ISSN 1047-9511

Editorial

Extracorporeal membrane oxygenation and pediatric cardiology

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DESPITE THE WIDELY PERCEIVED ASSOCIATION OF modern methods of extracorporeal membrane oxygenation[1] with neonatal intensive care, increasing opportunities for its more general application in older children meant that the introduction of the first service for extracorporeal life support in the United Kingdom was within a pediatric cardiothoracic unit.[2] The reasons behind this approach are practical as well as historical. Prolonged extracorporeal life support has a common ancestry with perioperative cardiopulmonary bypass and has evolved in parallel to it. Moreover, there is a major potential benefit in providing a "rescue" therapy for patients undergoing initially successful surgery for repair of congenital cardiac lesions. In this review, therefore, we discuss the advantages to be gained by organizing the service in the setting of centers dealing with the surgical treatment of congenital heart disease. First, however, it is pertinent to review some of the history of the process.

Attempts to provide direct support for circulation and gas exchange started with animal experimentation over 100 years ago. In particular, one man's work[3] anticipated intermittent positive pressure ventilation, cardiac and respiratory pacemakers and variations upon the theme of circulatory assist devices. Benjamin Ward Richardson (Figure) was born in Somerby, Leicestershire in 1828. As a youth, he was apprenticed to Mr. Henry Hudson, a local surgeon, and in 1845 he entered Anderson's College, Glasgow to study medicine. His studies were interrupted in 1847, when he fell victim to "Famine fever." After his recovery, he moved to Essex where he assisted the surgeon Mr. Thomas Brown. He continued practical work, under Mr. Brown and later Edward Dudley Hudson (the brother of his old master), before returning to Glasgow and completing his examinations as a Licentiate of the Faculty of Physicians and Surgeons. In 1865, he published a synthesis of his experiments in reanimation.[4]

In a series of experiments, Richardson had attempted to reanimate animals (usually rabbits) which he had sacrificed using chloroform, carbonic acid or drowning. His first efforts involved providing positive pressure ventilation and inverting the animal so as to bring a current of blood to pass by its mechanical weight into the lungs. In later endeavors, he found that respiratory movements could be restored for as long as seven minutes after death, using electric shocks delivered via a pair of electrodes, one on the diaphragm and one in the larynx. Using a similar apparatus, he also introduced a negative electrode via the inferior caval vein into the right side of the heart. The opposite pole was then connected to the exterior of the heart and similar rhythmic shocks delivered. In this circumstance, he documented restoration of blood flow to the lungs and, when combined with oxygenation (from positive pressure ventilation), he generated brief signs of reanimation.

In his subsequent attempts mechanically to assist the flow of blood through the lungs, he used the intravenous injection of blood and/or a current of gaseous oxygen. This alone resulted in the restoration of brisk rhythmical contraction of the right atrium and right ventricle, but was never sufficient to achieve a cardiac output. Further attempts at circulatory support involved drawing blood from the aorta using a syringe. In isolation this achieved little, but he observed that reinfusing oxygenated fluid into the systemic arterial circulation could restore muscular contraction and "the external phenomena of life." Richardson's most successful experiments, therefore, involved oxygenation, by positive pressure ventilation, combined with mechanical circulatory support. Richardson also observed that his most responsive subjects were those treated immediately after death, but he was confounded by difficulties with the blood itself and the "rapid coalescence of the blood corpuscles as the motion of the blood ceases" (Richardson's work preceded the discovery of heparin). He concluded his thesis with the assertion that "Resuscitation by artificial means is a possible process and it only requires the elements of time, experiment and patience for its development."

It was the subsequent ability to prevent coagulation which allowed the maintenance of an external circulation

https://doi.org/10.1017/S1047951100001542 Published online by Cambridge University Press

Figure. *Benjamin Ward Richardson.*

using simple pumps. The development of cardiopulmonary bypass[5] which followed, initially involved the use of mechanical "bubble" oxygenators which relied upon the apposition of blood and oxygen to achieve gas exchange. This inherently destructive contact precluded prolonged support as it caused extensive hemolysis. Improvements in design resulted in a patient successfully being supported in 1966, using a disc oxygenator for removal of carbon dioxide.[6] It was the development of a silastic membrane[7,8] that could separate gas and blood while, nonetheless, still allowing respiratory exchange that led to the ability for prolonged normothermic extracorporeal membrane oxygenation.[9,10] Two types of support are now offered and the choice is provided by the mode of cannulation. Venoarterial exchange provides cardiopulmonary support while the venovenous route provides support primarily with gas exchange.

More widespread application of the technique, nonetheless, was delayed by a study of its use in adults with acquired respiratory distress syndrome[11] which showed no improvement in a condition with a universally poor prognosis. It was proved successful in the treatment of neonatal cardiopulmonary failure,[12] pioneered over the last two decades by Bartlett,[1] which led to more widespread proliferation of this technique in the United States of America for support of mature neonates. During this time, attempts at objective comparison between extracorporeal membrane oxygenation and more conventional treatment of neonates[13,14] were confounded by the ethical difficulties experienced by its protagonists in designing randomizing controlled trials. Following the successful introduction of this same service to the United Kingdom, these issues still remain to be solved.[15,16] Despite these reservations, modern refined methods of extracorporeal support are now being reevaluated. It is already apparent that, with appropriate case selection, extracorporeal life support can be far more successful than was previously envisaged in the treatment of older children and adults.[17-20]

Does extracorporeal membrane oxygenation need pediatric cardiology?

Even when used primarily to assist gas exchange, extracorporeal life support is provided using equipment and techniques for perfusion. The patients treated become largely independent of their own pulmonary (or cardiac) dysfunction and this allows additional time for treatment of the underlying condition. This is naturally a collaborative effort between appropriate specialists, but the life support process itself is an exercise in hemodynamics.

The spread of facilities for extracorporeal life support has important implications for pediatric cardiologists. The majority of patients to whom it is applied are still neonates. Their effective management relies heavily on experienced cardiological advice and monitoring. The main considerations are the screening of candidates for evidence of cyanotic heart disease and the necessity for close monitoring of cardiac function[21] and hemodynamics during perfusion.

Screening

The majority of neonates who are candidates for extracorporeal membrane oxygenation have not been seen by a cardiologist prior to referral, but have frequently been hypoxic from birth. The onus is on the tertiary referral center to determine the precise cause of hypoxia, since the prospect of active treatment increases the importance of excluding a diagnosis of concurrent congenital heart disease. As many as 2% of neonatal patients thought to have a primary pulmonary diagnosis turn out to have congenital heart disease (9% in those patients referred with what is thought to be isolated persistent pulmonary hypertension of the newborn). Of these cases, the largest single group are patients with totally anomalous pulmonary venous connection.[22,23] Invasive and active treatment is currently reserved for situations in which conventional treatment has failed. As a result, patients usually arrive in poor condition, on high settings of their ventilatory support. They may also have suffered pneumothoraces. They are poor subjects for cross-sectional echocardiography and appearances of the chest radiograph are frequently disrupted by the extent of pulmonary disease. Successful distinction of cardiac lesions, particularly totally anomalous pulmonary venous connection, from persistent pulmonary hypertension of the newborn may be complicated by low flow of blood into the lungs together with problems in the extent of the echo window and imaging equipment.[24] Following recognition, appropriate treatment (which may still involve prolonged extracorporeal life support[23,25,26]) will be instigated.

https://doi.org/10.1017/S1047951100001542 Published online by Cambridge University Press

Hemodynamic considerations

Despite sharing a common ancestry, prolonged extracorporeal life support differs significantly from conventional cardiopulmonary bypass. The extracorporeal flow interacts with, rather than replaces, the native circulation.[1] Whether pulmonary or cardiopulmonary support is being offered, monitoring of alterations in hemodynamics (inferred from echocardiography) is essential to management. Any degree of venoarterial bypass alters conditions of cardiac loading proportionately. Right ventricular assist is provided and the flow of pulmonary blood decreases (in the absence of an anatomic left-to-right shunt). Under such circumstances, left ventricular preload is also decreased, but the left ventricle has to pump into the systemic arteries against increased afterload, generated by the return of blood from the extracorporeal circuit.[27-29] A decline in cardiac output can be demonstrated during venoarterial support,[30] although echocardiographic observations of myocardial function during perfusion[31] must be carefully interpreted. Those techniques that do not take full account of loading forces, such as isolated ejection phase indices, are unlikely to be accurate.[32,33] The apparently non- (or poorly) contracting left ventricle, may be displaying isovolumetric contraction in the face of total venoarterial cardiopulmonary bypass.[34,35] This must be distinguished from the recognized syndrome of prolonged cardiac stasis with associated electrical asystole or electromechanical dissociation.[36] This phenomenon has not been observed in the United Kingdom but is, reputedly, not a universally poor prognostic indicator.[34]

Significance of the arterial duct

In the presence of a left-to-right shunt, left ventricular preload may be paradoxically increased. Of particular relevance for neonates is the persistence of the arterial duct.[35,37] In neonatal patients with persistent pulmonary hypertension, a variety of characteristics may be exhibited in shunting across a duct.[38] During venoarterial perfusion, as pulmonary vascular resistance falls in response to treatment, a left-to-right shunt may develop. The resultant combination of raised left ventricular afterload and preload may lead to distension of the left heart, functional mitral regurgitation, and a risk of fatal pulmonary hemorrhage.[35] In the context of a venoarterial cannulation, conventional methods of assessing ductal shunts using Doppler techniques, are unreliable. In addition to systolic pulsatile shunting in either direction, a high volume, non-pulsatile, diastolic, left-to-right shunt from the extracorporeal circuit may still be present and its effects demonstrated by assessment of the ratio of left atrial and aortic dimensions. The consequences of any delay in spontaneous ductal closure must be closely monitored. Experience suggests that the need for ductal ligation under these circumstances is more frequent in patients with congenital diaphragmatic hernia.[39,40] These patients have pulmonary hypoplasia, and so the need to avoid pulmonary edema and further lung damage is increased.

State of the myocardium

Myocardial stun is a recognized effect of myocardial ischemia[41] and may be a feature of the early stages of extracorporeal perfusion.[42] The etiology is thought to be a global hypoxic or ischemic insult to the myocardium prior to the instigation of extracorporeal support. This is supported by evidence of raised myocardial enzymes in patients demonstrating stun.[43] More focal evidence of myocardial ischaemia may also be observed such as infarction of papillary muscles. The occurrence of severe left ventricular dysfunction during perfusion may necessitate left atrial venting and drainage to the circuit.

The quality of myocardial perfusion during support differs between the two styles of vascular access.[44] After venoarterial cannulation, retrograde flow in the ascending aorta contributes little to the oxygen content of coronary arterial blood, which is still largely derived from pulmonary venous return, ejected from the left ventricle. In the face of negligible native pulmonary function, this will be the most desaturated blood in the patient. The improvement in myocardial function that can be observed in association with venovenous cannulation is probably secondary to improved myocardial oxygenation.

Venoarterial support may frustrate attempts at cardiac diagnosis as a consequence of the changes in loading conditions and subsequent changes in the electrocardiogram. On occasion, however, the cannulation can illuminate the diagnosis.[22] Our experience includes a case of preductal aortic coarctation in a patient with congenital diaphragmatic hernia. This discrete lesion, representing a previously unreported association, evolved during bypass and presented with left-to-right steal into the pulmonary circulation and dependent hypoperfusion.

Does pediatric cardiology need extracorporeal membrane oxygenation?

The availability of mechanical cardiopulmonary support, suitable for use over prolonged periods, provides a facility for "rescue" therapy on the cardiothoracic intensive care unit.[45,46] Almost all candidates have pump failure, hence they require venoarterial cannulation and are more likely to need left atrial venting. Restoration of perfusion contributes to the resolution of secondary failure of all organs. It also facilitates the use of simultaneous renal support with hemofiltration or dialysis. The eventual outcome depends primarily on whether the indication for support is a

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reversible problem.

With modern surgical techniques and methods of myocardial protection, low cardiac output states unresponsive to inotropic support are uncommon. Such a presentation is more likely to indicate an undiagnosed, or uncorrected, anatomic problem. A careful appraisal of the cardiac repair is essential before embarking on extracorporeal support. This involves a combination of echocardiography and measurements of intracardiac pressures and saturations (either at operation or at cardiac catheterization). The focus should be upon the recognition of unrelieved obstructions within the outflow tracts and/or residual shunts. The increasing sophistication of both hand-held and transesophageal echo/Doppler techniques will allow more accurate assessment of ventricular function and the quality of surgical repair.

The appropriate application of selection criterions in this environment is essential in order to avoid prolonging an inevitable death in certain patients. The accurate prediction of eventual outcome before or after cardiac surgery is difficult. The time to consider these issues is prior to cannulation rather than after. It is inevitable that, with hindsight, cannulation will in some cases prove to have been inappropriate. This is reflected in documented survival rates.

Current experience in so called "cardiac" support exceeds the data in the registry of the Extracorporeal Life Support Organisation. The registry contains details of 760 cases (the vast majority (87%) of them treated in association with cardiac surgery) with an overall survival rate of 46%. Part of those data is our own experience in which, after appropriate investigation, cannulation has been indicated in 10 patients over 3 years. Over this period of time approximately 500 pediatric open heart procedures were performed and 110 non-cardiac cases were supported with prolonged extracorporeal life support. A successful outcome was achieved in four of the "cardiac" cases. In each of these cases, an element of pulmonary hypertension was complicating the postoperative course. The worst survival figures in the category of "cardiac" support are those which relate to patients who fail to wean from perioperative bypass or who are cannulated during cardiac arrest. Improving results in the former group reflect a fall in the threshold for treatment as much as improvements in technique. The quality of survival, in neurodevelopmental terms, deserves the same scrutiny that has been applied to neonatal patients generally.

Conclusions

The extracorporeal membrane oxygenation program in Leicester, which has currently treated 120 patients, relies heavily on pediatric cardiology. The number of occasions when it can specifically benefit cardiac patients is, however, limited as these patients present infrequently. The success of prolonged extracorporeal life support in salvaging any of these patients was likely to have been helped by the fact that the technique was routine on the cardiothoracic intensive care unit. Rather than treating these patients as they arise, the best approach would seem to be for them to be treated as part of an active, comprehensive, program by an experienced team who then encounters minimal disruption to its normal working practice.

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