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Optimizing response of the neonate and infant to cardiopulmonary bypass

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THE EVOLUTION OF CARDIAC SURGERY HAS LED TO increasing emphasis on complete repair of congenital heart defects early in life, nowadays increasingly performed in neonates or small infants. Good results have been achieved because of innovative techniques permitting reconstruction of normal anatomy, and restoration of normal physiology, before either the heart or the patient undergo deleterious adaptation to the congenitally abnormal physiology. Despite the ability surgically to correct complex defects in such small patients, limitations in outcome are sometimes encountered related to the systems necessary for repair. In particular, exposure to cardiopulmonary bypass may present the greatest challenge for these tiny patients.

These patients have high metabolic demands, and are exposed to wide ranges of temperature, haematocrit, pH, blood pressure, and flow. The deleterious effects of cardiopulmonary bypass in neonates are often more pronounced than those seen in larger children or adults. This is due to the immature function of their tissues and organs in the first few months of life, and the tremendous disparity between the size of the circuit used for cardiopulmonary bypass as compared to the size of the patient. The volumes of the bypass circuit are often twice or thrice as large as the circulating neonatal blood volume. In addition, it is becoming fairly well appreciated that there is a substantial "inflammatory" reaction that accompanies exposure to the surface area of the circuit used for cardiopulmonary bypass, and the ramifications of this reaction can create significant challenges to the management of fluids and haemodynamics in the postoperative period. Although the solutions to these problems are not completely available, my presentation is intended to provide the clinician with practical interventions that can be currently employed to help rein in these potentially deleterious effects, and to enhance outcome for this important group of patients.[1,2]

There are specific periods when the surgical team has an opportunity to alter the response of the patient to the effects of cardiopulmonary bypass, and these will be addressed in sequence. My overview does not presume to include all the possible interventions that some may find helpful, but rather catalogues those protocols that our group found useful in our practice at Oregon Health and Sciences University.

Prior to cardiopulmonary bypass

Certain patients seem to be at greater risk than others for pump-related morbidity. In particular, patients who have ductal-dependent malformations producing a high flow of blood to the lungs, such as interruption of the aortic arch, hypoplastic left heart syndrome, and double outlet right ventricle with subpulmonary ventricular septal defect and coarctation, or cyanotic lesions with a high flow of pulmonary blood, such as transposition with or without a ventricular septal defect, common arterial trunk, or aortopulmonary window, seem to form a group at high risk for development of oedema and pulmonary dysfunction after bypass. Furthermore, infants who are septic, who have multiple congenital problems in addition to their cardiac defect, or who are small, weighing less than 1800 grams, also present an increased risk for cardiopulmonary bypass. Ironically, many of these

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patients have defects that require surgical intervention in the neonatal period. It may be that neonates, in general, comprise a group of patients at high risk. Recognition that a patient is at such increased risk for pump-related morbidity may help the clinical team initiate protocols appropriately designed to reduce morbidity. It is our policy to consider any patient who requires cardiopulmonary bypass in the first month of life as a patient at increased risk, and to treat them accordingly.

Many of these patients, by virtue of the anatomic nature of their cardiac malformation, their dependence on prostaglandin, or their weight at birth, will be in the hospital, and usually in the intensive care unit. We premedicate all patients who are high risk with 10 milligrams per kilogram of solumedrol (methylprednisolone) given intravenously 8 hours, and again 2 hours, prior to surgery. Recent data from our laboratory demonstrates a significant improvement in the gain of fluid after cardiopulmonary bypass, pulmonary compliance, and pulmonary vascular resistance in animals premedicated with this regime compared to control animals which either did not receive steroids, or which were first exposed to steroids in the pump prime.[3] Results with patients receiving this pre-treatment have also been extremely encouraging, especially with respect to objective factors related to the so-called "post-cardiopulmonary bypass syndrome" and neuroprotection, suggesting that there is an inflammatory component to neurologic injury following bypass in neonates using continuous flow.[4–6] These infants have much less need for additional volume during their pump run, have less oedema subsequent to weaning from the pump, and a generally undergo a more expeditious postoperative convalescence. Pretreatment with steroids, therefore, may play an important role in protecting neonates from the inflammatory component of cardiopulmonary bypass that can lead to serious problems in postoperative management of fluids.

Many centers now also give aprotinin to neonates and infants at the beginning of their exposure to cardiopulmonary bypass. Such use of aprotinin has been shown to reduce the inflammatory response to cardiopulmonary bypass,[7–9] in addition to its effect on postoperative bleeding, and we have begun to use the agent more routinely. As yet, we have not yet generated either experimental or clinical data regarding its efficacy, but our preliminary impression is that its addition has had a beneficial effect on outcome.

Circuitry and strategies for cardiopulmonary bypass

A variety of techniques have been developed to prevent or lessen tissue oedema, which include miniaturization of the circuit and oxygenator, the additions to the prime, such as albumin and steroids, the development of biocompatible circuitry, and variations in strategies of perfusion. The majority of centers use a prime that consists of a balanced saline solution such as Normosol, with blood, albumin and buffer added as necessary. As the volumes of the prime are reduced, the need for blood in the prime becomes arguable, and some centers have reported the use of asanguinous primes in the range of 180 to 250 milliliters. This has been accomplished with tubing having an internal diameter of 3/16 inch, optimization of the orientation of the circuit to reduce the needs for tubes, and elimination of arterial filters and in-line cardioplegia. There is no convincing data, nonetheless, that reducing the volume of the prime will improve the outcome after cardiopulmonary bypass, and the inflammatory component of the response to cardiopulmonary bypass may occur regardless of the volume of the prime. We use tubes of 3/16 inch for the arterial inflow, but have retained 1/4 inch tubing for the venous return, since it is easier to handle air in the venous circuit with the wider tubing. We have more frequently begun to utilize vacuum to assist the venous drainage, and have found it to be very helpful, not experiencing some of the complications reported by others.[10,11] We also use blood cardioplegia in the ratio of four parts blood to one of crystalloid, and have recently be able to reduce substantially the volume of this component of the circuit used in the prime. Our pump is situated close to the side of the patient next to the assistant.

Since reduction of the volume of the prime needed for the circuit may be helpful in the outcome for tiny patients exposed to cardiopulmonary bypass, several investigators, including our own group, are exploring methods to miniaturize the circuit so that asanguinous prime can be used in either animals or patients weighing as little as 2 kilograms. At the current time, we are able to perfuse patients as small as 5 to 6 kilograms without the use of blood prime as long as they begin with an adequate haematocrit, and their postoperative convalescent state will enable them to tolerate anemia. In these patients, we use tubing of 3/16 inch diameter for both the arterial and venous lines, vacuum assistance being essential to ensure adequate venous drainage. With such vacuum assistance, the venous side of the circuit does not require a priming volume. We do not place an arterial filter in-line for these circuits. These patients receive crystalloid cardioplegia, and all of them receive modified ultrafiltration following conclusion of the procedure. We have been successful in avoiding postoperative blood transfusions for patients with normal physiology, such as following closure of ventricular or atrial septal defects, as well as one patient undergoing a

bidirectional cavopulmonary anastomosis who tolerated a postoperative hematocrit in the low 20s, but we have had to transfuse other patients with functionally single ventricles, mixing lesions, and those who have had problems with postoperative pulmonary hypertension. As advances in the design of the circuit enable us routinely to use volumes of prime of less than 200 milliliters, it may be possible to extend asanguinous bypass to even smaller patients. Cardiopulmonary bypass, however, irrespective of the size of the circuit, will provide some degree of hemodilution to any patient. The ability to avoid postoperative transfusion will still relate, in part, to the postoperative haemodynamic requirements of the patient. There is data to show that it is the haemodilution in conjunction with the duration of exposure to cardiopulmonary bypass that creates impairment to myocardial compliance that can lead to patient mortality or morbidity.[12] Miniaturization of the circuit may reduce this problem, and is clearly an ideal issue for laboratory investigation.

Several companies are offering biocompatible coatings on their circuits. These coatings are expensive, and there is no data at the current time to demonstrate their superiority over conventional circuits. They are attractive, nonetheless, from the theoretical perspective,[13,14] and there may be an increasing role for their future use.

Also of importance in the impact of cardiopulmonary bypass on small patients are the strategies used for perfusion. In recent years, there has been a movement towards avoidance of deep hypothermic circulatory arrest during repair of cardiac defects in infants. Development of improved circuits, along with advances in the design of cannulas and vents, has made it easier and safer to employ bicaval cannulation and continuous perfusion in such tiny patients. Concurrent improvements in myocardial protection have allowed use of prolonged periods of myocardial ischaemia during moderate hypothermia such that surgeons are now able to provide cardioplegia through a combination of antegrade and retrograde techniques. The impact of these advances is that the simple strategy of rapidly cooling a patient to 18 degrees centigrade, using a single venous cannula, turning off the pump for the entire repair, remembering that periods of deep hypothermic circulatory arrest that were occasionally extended beyond 60 minutes, and then rewarming the patient on cardiopulmonary bypass have been replaced with alternative, albeit more complex, methods which avoid the use of any periods of deep hypothermic circulatory arrest. Although it is indeed possible to provide continuous cardiopulmonary bypass to almost any patient, the question of which strategy is best is not yet determined. Initial success with neonatal cardiac repairs was achieved by those who employed the simple strategy of short exposure to cardiopulmonary bypass with use of longer exposure to deep hypothermic circulatory arrest. Neurologic outcomes for these patients, however, were suspect.[15] Despite some prospective information on clinical outcomes showing that these patients had minimal measureable neurobehavioural impairment,[16] there have been numerous laboratory investigations that have clearly demonstrated the reality that the brain is not adequately protected by the methods of deep hypothermic circulatory arrest as they were used in the 1980s, and early 1990s.[17–24] Despite the successful outcomes that were being achieved, patients were probably being injured neurologically by the strategy of deep hypothermic circulatory arrest in the format it was offered. With the advances described above, several prominent surgeons began to develop techniques that made it possible to avoid deep hypothermic circulatory arrest. Their patients, nonetheless, were exposed to prolonged periods of cardiopulmonary bypass. The consequences of such prolonged cardiopulmonary bypass have enormous impact on postoperative convalescence. Furthermore, the complexity of the circuitry required in some cases creates a spectrum for the surgeon that ranges from a nuisance, through one that hinders exposure, thus compromising the ability to achieve an accurate repair, to one that creates complications related to the system itself, such as stenosis of the caval veins at the sites of cannulation, tears in the pulmonary veins at sites of venting, and so on. Although there is clearly an advantage to providing continuous cardiopulmonary bypass using moderate hypothermia, cases should be individualized, and one system will not be the best for all. There is an increasing body of data that continuous hypothermic cardiopulmonary bypass at low rates of flow might lead to excessive post-bypass oedema and diminished pulmonary function.[25,26] In part, this may be due to prolonged exposure to cardiopulmonary bypass. Furthermore, continuous perfusion at low flow leads to substantial cerebral oedema,[5,27] and more severe damage of neuronal golgi apparatus, than exposure to deep hypothermic circulatory arrest.[28] Laboratory data suggests that there is some acute neurologic metabolic injury following prolonged exposure to hypothermic cardiopulmonary bypass at low flow that is not apparent if the brain is exposed to short durations of deep hypothermic circulatory arrest.[27] Substantial research has been performed over the past 15 years showing how more safely to apply the strategy of deep hypothermic circulatory arrest.[1,2] This research has led to several modifications for applying deep hypothermic circulatory arrest such as

- pre-bypass treatment with steroids and aprotinin,[5,9] as well as pre-bypass and pre-deep hypothermic circulatory arrest hyperoxygenation[29]

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- adequate duration of cooling, of more than 20 minutes,[21,30,31] to ensure more uniform and homogeneous cerebral protection, as well as maintenance of higher haematocrits during the phase of cooling phase
- use of pH stat blood gas strategy,[32–34] especially for patients considered at high-risk, such as those with aorto-pulmonary collateral arteries or those with preoperative cyanosis[35,36]
- limiting the duration of exposure to deep hypothermic circulatory arrest by providing intermittent cerebral perfusion for 1 to 2 minutes at 15 to 20 minute intervals.[27] This technique virtually eliminates the detrimental ischaemic effects of deep hypothermic circulatory arrest while avoiding the disadvantages of continuous low-flow perfusion.
- the use of modified ultrafiltration following cardiopulmonary bypass[37] and
- attention to postoperative cerebral energetics, since this is a time at which much cerebral injury can occur.[18,38] This latter area includes techniques such as limiting hyperthermia and providing adequate cardiac output with inotropes, leaving the sternum open, or using extracorporeal life support or ventricular assist devices to ensure adequate cerebral delivery of oxygen, especially for patients who are hypoxemic after surgery, such as those with mixing lesions. The impact of information generated in recent years regarding the safe application of deep hypothermic circulatory arrest may make this an attractive technique for some patients deemed to be at high risk, and can improve the outcomes for these patients.

It is essential for surgeons to understand the risks and benefits of the various strategies available, and to learn how to use them all in the most appropriate manner. Our experience with deep hypothermic circulatory arrest applied in a manner that takes advantage of the significant research in this area is that the patients have no difference in long-term neurobehavioral outcomes compared to patients whose surgery is performed with techniques that avoid the use of deep hypothermic circulatory arrest.

This experience has been corroborated by the recently reported data following 8 years of follow-up from the Boston Circulatory Arrest Study.[39–41] This essentially indicates no significant differences in neurodevelopmental outcome between patients who underwent an arterial switch using a strategy of deep hypothermic circulatory arrest versus those whose operation was performed using predominantly continuous bypass at low rates of flow. In respect to their intelligence quotient, both groups of patients were significantly worse compared to their peers, although there were no true control patients, such as those with congenital cardiac disease who were not exposed to cardiopulmonary bypass, or those undergoing cardiopulmonary bypass without hypothermia. The group undergoing circulatory arrest manifested more problems with motor skills, while those undergoing surgery with continuous low flow showed more problems with behavior, such as attention disorders. Of importance is that the strategies used for circulatory arrest for the patients randomized to this study in 1992 did not reflect the numerous advances from research that I have discussed. The data from these patients suggests that periods of deep hypothermic circulatory arrest exceeding 41 minutes are more likely to have a harmful effect.[40]

We usually find it helpful to use deep hypothermic circulatory arrest for infants weighing less than 1800 grams because of the simplicity of the system, coupled with our confidence that deep hypothermic circulatory arrest with intermittent perfusion is as safe, and perhaps even safer, than cardiopulmonary bypass achieved with continuous low flow. Infants with excessive pulmonary collateral arterial flow and small pulmonary arteries, such as those with tetralogy of Fallot with small pulmonary arteries, or those with pulmonary atresia, are more easily repaired with short periods of interruption of the flow of blood. On the other hand, simple intracardiac defects, such as atrioventricular or ventricular septal defects, can be easily repaired using moderate hypothermia with cardioplegia and left ventricular venting to enhance exposure. In such patients, deep hypothermic circulatory arrest is rarely necessary. We have also shifted from using single cannulation and deep hypothermic circulatory arrest during repair of the atrial septal defect repair in patients with transposition to the use of bicaval cannulation and retrograde cardioplegia with moderate hypothermia. We find our newer technique to be very satisfying. Each surgeon can find his or her own methods. It is important to recognize that both strategies are safe, and that each can be useful in certain circumstances. Surgeons should pay attention to the advantages and disadvantages of each strategy, and develop comfort applying either in a way that can enable them to provide the best surgical repair for their patient.

It also appears that the lungs are particularly at risk for injury from prolonged cardiopulmonary bypass, and this may be related to both inflammatory as well as ischaemic effects of cardiopulmonary bypass on the lungs.[42,43] This can result in substantial accumulation of fluid in the lungs during cardiopulmonary bypass, which leads to decreased pulmonary compliance at the end of cardiopulmonary bypass, coupled with increased pulmonary vascular resistance. Prevention or diminishment of pulmonary ischaemia during cardiopulmonary bypass may limit this pulmonary injury, and protect the lungs from excess accumulation

of fluid. Although there is no current single strategy for cardiopulmonary bypass that will prevent excess accumulation of fluid by neonates, there is ongoing research that is generating several practical clinical suggestions that are useful for selected patients. At the current time, the best practical options available to the surgeon are pretreatment with steroids, and ultrafiltration after bypass. For patients who require extracorporeal membrane oxygenation following cardiac surgery, it is essential that some form of antegrade flow of blood be maintained to the lungs. This is best ensured by leaving open the shunt open in patients in situations such as the first stage of the Norwood sequence for hypoplasia of the left heart,[44,45] or by making certain that the pulmonary arteries are not obstructed, as for example by extrinsic compression from blood in the chest, in those patients receiving anatomic repairs. Lack of antegrade flow of blood will result in pulmonary ischaemia, and irrecoverable pulmonary dysfunction.[42]

Ultrafiltration

Despite advantageous changes to the circuitry, development of optimal strategies for cardiopulmonary bypass, and efforts to premedicate patients who may be at high risk for morbidity related to cardiopulmonary bypass, neonates and infants constitute a group who may accumulate fluid during their exposure to cardiopulmonary bypass. In light of this, efforts have been directed at removal of such fluid from these patients during or immediately following cardiopulmonary bypass. Conventional ultrafiltration is difficult in neonates, because removal of any fluid from a miniaturized circuit requires replacement to maintain an adequate level in the reservoir. Hence, the results with conventional ultrafiltration are oftentimes inconsistent.[46–49] Others have described removal of small amounts of fluid while on cardiopulmonary bypass,[50] hoping conceptually to remove inflammatory mediators that exacerbate accumulation of fluid, but the most effective method of ultrafiltration seems to be that described by Elliott and Naik.[49,51] This is described as modified ultrafiltration, since it is performed following separation of the patient from the circuit used for cardiopulmonary bypass. Using variations of this technique, it is possible to remove from between 500 and 750 milliliters of fluid from the patient and circuit that is rich in inflammatory mediators. This leads to immediate improvements in pulmonary, cardiac, and cerebral function.[37,46,50,52–54] Although some authorities claim that this reduces postoperative oedema, and shortens the period of time during which mechanical ventilation is required, it has been our experience that preoperative steroids have been associated with a more marked improvement in these parameters. Modified ultrafiltration, nonetheless, appears to be very beneficial for the neonate and tiny infant, elevates the haematocrit without the need for blood transfusion,[46] and produces a generalized acute improvement in pulmonary and cardiac function.[46,49,50,52]

Postoperative management

Once the neonate has been removed from cardiopulmonary bypass, they may continue to accumulate fluid in their third-space fluid for a period of 24 to 36 hours. The extent of this change may relate to hemodynamic factors, such as the underlying defect and type of repair, as well as their cardiac function. Factors that favour continued accumulation are elevation of the central venous pressures, as is sometimes seen following neonatal repair of tetralogy of Fallot, reduced cardiac output with consequent reduced renal blood flow, or the need for high ventilatory pressures, which will raise the central venous pressures and reduce the venous return to the heart. There are several things that the surgeon can do to help reduce accumulation of fluid in this acute convalescent phase which include:

- leaving open an oval foramen in patients who may have decreased right ventricular compliance so that they can shunt from right-to-left, and maintain cardiac output and normal central venous pressure at the expense of mild systemic oxygen desaturation
- judicious use of inotropes in place of continual and excessive replacement of volume during the first 24 to 36 hours after the operative procedure
- leaving open the sternum to prevent excessive increases in pulmonary pressures in selected patients.

If steroids were given preoperatively, it is not known whether it is helpful to continue them in the immediate period after cardiopulmonary bypass. Some groups recommend that catheters for peritoneal dialysis be placed routinely in their patients at the time of surgery, but we have not done this, and have no experience with its effectiveness. In unusual circumstances, infants with extremely elevated central venous pressures, and persistent accumulation of fluid, may benefit from a short period of extracorporeal membrane oxygenation. This will lower the central venous pressure, and help mobilize sequestered fluid while the cardiac compliance and function recovers.

Conclusions

In general, cardiac surgeons in the twenty-first century are now able to use far more sophisticated strategies

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for cardiopulmonary bypass than those to which they may have been exposed during their training. The field has been driven by research, with many techniques developed from a large body of evidence. Despite the huge amount of information available compared to the mid 1980s regarding cardiopulmonary bypass in infants, there is still much room for improvement. Surgical techniques have undergone evolution to the stage where we are capable of providing anatomic repair or optimal palliation to most infants. The next horizon for significant improvement in outcomes will be reached as we learn how better to optimize the response of the infant to the systems we use when repairing its cardiac lesions.

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