Pathophysiology of cardiopulmonary bypass

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Since its development by Dr. John Gibbon and its clinical introduction in 1953, cardiopulmonary bypass (CPB) has seen widespread application as a circulatory support modality, enabling complex surgery of the heart and great vessels to be performed successfully. Various factors inherent in its use can, however, produce organ system dysfunction in the perioperative period. Systemic heparinization, acute haemodilution, core cooling, activation of various blood cascades, generation of microgaseous and blood element emboli, bypass of the pulmonary circulation, and alterations in perfusion pressure characteristics i.e., nonpulsatility, comprise some of the key elements attending CPB and having the potential to influence organ system functioning.

While survival is no longer in question after routine CPB, subtle signs of organ system dysfunction can be detected postoperatively in many otherwise apparently intact patients. This is most evident in the CNS, as transient neurological dysfunction has been observed in over 60 per cent of patients.[1,2] Although persistent neurological deficits are relatively uncommon (0.5–1.5 per cent),[1,2] there is evidence that patients suffering transient postoperative neurological dysfunction may exhibit subtle neurobehavioural deterioration at five-year follow-up.[3] The following discussion will describe some of the physiological responses to CPB, particularly as they relate to the CNS, and examine the rationale for current techniques and management during this procedure.

pH management during hypothermia

It is increasingly recognized that a pH of 7.4 is appropriate only at a temperature of 37° C.[4] Rather than being a fixed, unvarying constant, tissue pH changes inversely with temperature, concordant with the neutral pH of water, in order to maintain electrochemical neutrality of the intracellular milieu.[5] To facilitate the egress of metabolic byproducts and allow the retention of intermediary metabolites, a transcellular pH gradient of 0.6 pH units exists across cellular membranes, intracellular pH being the more acidic. Hypothermia increases the solubility of CO_2 such that for a given content the measured tension is proportionately reduced. This increases pH, giving rise to what may be perceived as a respiratory alkalosis, but is in fact an appropriate pH for lowered temperature, effectively preserving intracellular electrochemical neutrality and the transcellular pH gradient.

During CPB, pH management is carried out primarily by alterations of $PaCO_2$ (i.e., the amount of exogenous CO_2 added to the fresh gas inflow of the oxygenator) and generally falls into two main categories: alpha-stat, whereby the non temperature-corrected $PaCO_2$ is maintained at 40 mmHg, thus allowing pH to vary with temperature; and pH-stat, during which the temperature corrected $PaCO_2$ is maintained at 40 mmHg, thus keeping pH constant at 7.4 independent of temperature.[6] At 37° C both types of pH management produce pH 7.4 but, during hypothermia eg., 27° C, there is a pH difference of 0.15 units and a $PaCO_2$ difference of approximately 15 mmHg between the two.

In addition to influencing the intracellular milieu, differences in $PaCO_2$ profoundly affect autoregulation and flow/metabolism coupling within the brain. Varied and apparently discordant results had been reported for cerebral blood flow (CBF) during CPB, some groups observing cerebral hyperaemia and loss of autoregulation,[7,8] others demonstrating a dramatic reduction in CBF and apparent extension of the limits of cerebral autoregulation.[9,10] It is now evident that most of this discordance resulted from differing modes of pH management during hypothermia. Murkin *et al.*[9] demonstrated that alpha-stat pH management preserves cerebral autoregulation and flow/metabolism coupling whereas pH-stat results in loss of autoregulation and pressure passive CBF. While alpha-stat is evidently more physiological, optimal pH-management remains hotly contested.[11,12] Whether pH management can influence the incidence of postoperative neurological dysfunction is currently under investigation.

Cerebral autoregulation

A potentially surprising result of CBF data obtained during hypothermia using alpha-stat pH management is the apparent extension of the lower limit of cerebral autoregulation. In a clinical population undergoing cardi-

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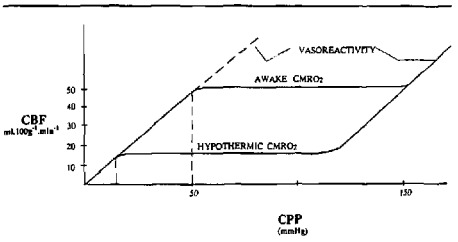

FIGURE 1 Cerebral autoregulatory curves during hypothermia and normothermia. The upper curve demonstrates a higher autoregulatory plateau appropriate for the awake state, versus the much lower plateau during hypothermia. With maximal cerebral vasodilatation, lower perfusion pressure would result in a lower cerebral blood flow, appropriate at a low but not a high level of cerebral metabolic activity. $CMRO_2$ refers to cerebral metabolic rate for oxygen.

ac surgical procedures, Govier *et al.*[10] and Murkin *et al.*[9] observed that CBF was independent of mean arterial pressure (MAP) down to 30 mmHg, or cerebral perfusion pressures (CPP = MAP – jugular venous pressure) of 20 mmHg. Rather than an alteration of the limits of cerebral autoregulation, which would possibly require increased compensatory cerebral vasodilatation, however, this data can be readily interpreted by recognizing that the cerebral metabolic rate ($CMRO_2$) during hypothermia is greatly reduced.[9,13]

While vascular reactivity defines the perfusion pressure range over which CBF is maintained (i.e., cerebral autoregulation), it is the cerebral metabolic rate that determines the particular level of CBF, cerebral flow/metabolism coupling being an expression of that linkage. During hypothermia $CMRO_2$ is lower, thus in the presence of intact flow/metabolism coupling, e.g., alpha-stat pH management, a much lower CBF is required. This effectively moves the autoregulatory plateau to a different curve (Figure 1), which can be readily achieved at a lower perfusion pressure.

The presence of cerebrovascular disease or untreated hypertension presumably shifts the hypothermic cerebral autoregulatory curve to the right as it does at normothermia, thus higher cerebral perfusion pressures are required in such patients. In determining perfusion pressures during CPB, an important distinction must be made between MAP and CPP, particularly in the presence of a single two-stage venous cannula. Because of malpositioning of the heart during surgery, partial obstruction of cerebral venous drainage can occur. This may give rise to low intracardiac pressures but an elevated jugular venous pressure, with a consequent lowering of CPP despite apparently adequate MAP.[9,14]

Nonpulsatile vs pulsatile perfusion

The physiological importance of pulsatile perfusion is still contested but, in an elegent review of the topic, Hickey *et al.*[15] conclude that variation in perfusion waveform characteristics account for the lack of agreement between clinical investigations. They indicate that there is strong evidence for a salutary effect of pulsatile perfusion on endocrine and catecholamine responses, urinary output and organ perfusion, and autonomic tone, during CPB.

In the majority of centres, nonpulsatile perfusion is still employed during CPB. Until recently, producing a pulsatile waveform required a pneumatic device, greatly increasing the size, complexity and potential for failure, of the CPB circuit. The last decade has seen the successful introduction of a pulsatile flow device (Cobe Stockert®) that intermittently retards the nonocclusive roller pump heads to produce a pulsatile flow pattern. The resulting waveform (Figure 2B) is influenced by several factors including aortic inflow cannula size, oxygenator characteristics, and perfusion flow rates, independent of patient physiology.

During hypothermic nonpulsatile CPB, spontaneous arterial pressure oscillations are frequently observed (Figure 2A). In some instances, these vasomotor waves may reflect resonance between the roller pump and the patient's arterial vasculature. Others have speculated that

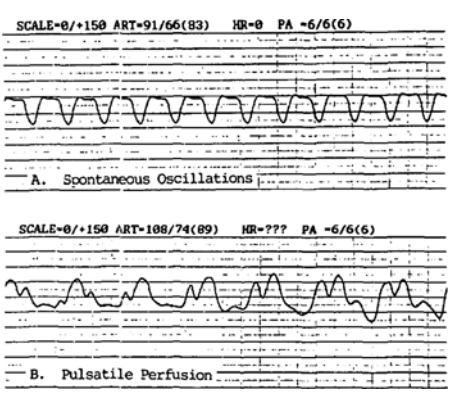

FIGURE 2 Arterial waveforms recorded sequentially from one patient during hypothermic cardiopulmonary bypass. A demonstrates vasomotor oscillations; these did not register on a pulse oximeter and cerebral blood flow at this time was 16.4 $ml \cdot 100\ g^{-1} \cdot min^{-1}$. B demonstrates pulsatile perfusion produced by a flow interruptor. Despite similar mean arterial pressure, during pulsatile perfusion the pulse oximeter was registering and cerebral blood flow increased to 20.9 $ml \cdot 100\ g^{-1} \cdot min^{-1}$.

they may reflect some form of vascular autorhythmicity or the presence of an independent autonomic oscillator.[16] Coupled with the observation that in both animals[13] and man[9,17] nonpulsatile CPB reduces CBF and cerebral metabolism, this phenomenon may also be a manifestation of what Guyton termed CNS ischaemic reflex oscillations.[16,18] There is evidence that the observed reduction in CBF is a result of functional capillary closure,[19] returning to normal after separation from CPB.[17] In nonischaemic dogs, pulsatile CPB increases CBF 20 per cent over nonpulsatile controls[20] and there are preliminary indications of a similar effect in man.*

Membrane versus bubble oxygenators

Gas exchange technology used during CPB has evolved considerably over the preceding three and a half decades. The early disc oxygenators utilized rotation of a convoluted disc to produce a thin blood film that was exposed to the fresh gas flow to achieve oxygenation, but in so doing produced significant rates of red cell haemolysis. The development of disposable bubble oxygenators was a considerable improvement, reducing haemolysis and producing efficient gas exchange. The last decade has seen the refinement and clinical introduction of a new generation of membrane oxygenators. By utilizing a semi-permeable membrane, direct blood/gas contact is minimized, further reducing haemolysis. In clinical practice, however, it is the use of cardiotomy suckers at the surgical site that produces the bulk of red cell damage. No significant difference in the rate of haemolysis is observed between bubble and membrane oxygenators during CPB of less than several hours duration.

One major, clinically important benefit of membrane oxygenators is their much lower incidence of microgaseous bubble formation. Compared with a membrane oxygenator, even the newest generations of bubble oxygenators produce clinically significant amounts of gaseous emboli[21] that may not be completely removed with 40 micron arterial line filtration. Since these microgaseous bubbles may be transfused directly into the arterial circulation, their delivery into the cerebral circulation is in direct proportion to CBF, a potential hazard of cerebral hyperaemia such as can be produced during pH-stat pH management.[7,10]

In summary, although CPB remains an effective circulatory support modality, the occurrence of even subtle morbidity is reason for concern, given that over 200,000 procedures employing CPB are performed yearly in North America. Careful outcome studies, critically evaluating the various techniques currently employed, are essential to determine optimal clinical management.

*Murkin *et al.* unpublished observations.

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