LECTURE

Alpha-Stat versus pH-Stat: Implications for the Brain During Cardiopulmonary Bypass

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Keywords: Cardiopulmonary bypass: hypothermia, pH management

Abstract

During cardiac surgery, systemic hypothermia is often utilized to augment cardioplegic myocardial preservation. The ensuing reduction in metabolic activity is directly related to the decrease in temperature as predicted by Vant Hoff's law. Lowered metabolic-activity decreases oxygen utilization, thus increasing tissue tolerance for reductions in oxygen delivery.

Among numerous other physiologic effects, hypothermia increases the solubility of O₂ and CO₂ in blood, producing a fall in gaseous partial pressures, while total gas content remains unchanged. When this occurs with CO₂, the corresponding rise in pH may be perceived as a "respiratory alkalosis."

pH During Hypothermia

Increasingly, it is recognized that a pH of 7.4 is appropriate only at a temperature of 37°C (1). Rather than representing some fixed, unvarying constant, tissue pH changes inversely with temperature, in concordance with the neutral pH of water (pNH₂O). This maintains the electrochemical neutrality of the intracellular milieu which is necessary for optimal functioning of intracellular organelles. Hypothermia thus increases the solubility of CO₂ so that for a given CO₂ content, the measured tension (PCO₂) is proportionately reduced. Although this leads to an increase in pH, the resulting elevation of pH is appropriate for the lowered temperature since it maintains a normal transcellular pH gradient, thus allowing egress of metabolic byproducts.

Optimal intracellular pH is determined by the neutral pH of water (pNH₂O), since water represents the greatest primary source of intracellular hydrogen ion (H⁺). As dissociation of water is decreased in proportion with reductions in temperature, intracellular pH rises during hypothermia. In order to eliminate acid metabolites and CO₂, a constant H⁺ gradient of 0.6 to 0.8 pH units is maintained across cell membranes such that at all temperatures, blood pH is more alkaline (1). The primary buffering mechanism anchoring intracellular pH to pNH₂O and changing its dissociation constant (pK) with temperature in parallel with pNH₂O was identified by Reeves (2) as a protein buffer, the imidazole group of the amino acid histidine. The degree of imidazole dissociation is expressed by the term alpha.

pH Management: Alpha-stat vs pH-stat

Alpha-stat pH management, by keeping total CO₂ constant and allowing pH to vary with temperature, maintains intracellular electrochemical neutrality by preserving a constant state of imidazole dissociation relative to pNH₂O over all ranges of temperatures. This is accomplished clinically by measuring the arterial blood gas at 37°C and not correcting the measured values to the patient's body temperature; but rather keeping these uncorrected values within the normal range. Alternatively, the addition of sufficient exogenous CO₂ to maintain PaCO₂ (and thus pH) constant despite reductions in temperature, is denoted as pH-stat since it enables a pH of 7.4 to be preserved independent of temperature. It is important to recognize that such a strategy reverses the normal transcellular pH gradient.

Not only is alpha-stat operative in most species, with the exception of hibernating mammals in whom pH-stat appears to be operative during dormancy (perhaps because intracellular acidosis subserves certain adaptive functions) (3), but blood pH in man is similarly governed. In humans, thermal gradients exist between tissues at the core and those of the periphery. At a skin temperature of 27°C, blood perfusing the extremities will change from a core value of pH 7.4 and PaCO₂ 40 mmHg at 37°C to pH 7.56 and PaCO₂ 25 mmHg (4). Arterialized blood thus contains a heterogeneity of pHs depending on the temperature of the tissues being perfused. This observation has been confirmed in patients undergoing hypothermic cardiopulmonary bypass (CPB) (5). A pH value of 7.4 and PaCO₂ of 40 mmHg should thus be viewed as points in a continuum of physiologic acid-base values, appropriate only at 37°C, rather than as representing some universal constant or fixed biological endpoints.

Cerebral Blood Flow and PaCO₂

Certain organs (particularly the brain, kidney, and heart) have the ability to autoregulate their blood supply, maintaining adequate blood flow and a normal oxygen supply/demand ratio over a wide range of perfusion pressures. The brain regulates
cerebral blood flow (CBF) according to local metabolic needs, maintaining tight regional flow/metabolism coupling. In the normothermic individual, CBF is constant over a range of mean arterial pressures (MAP) from approximately 60 to 150 mmHg (6). Failure of cerebral autoregulation occurs with either intracerebral pathology or in the presence of direct cerebral vasodilators, most notably CO₂. Several investigators have shown CO₂ to be a potent cerebral vasodilator during nonpulsatile hypothermic CPB (7, 8). Given an average 10°C reduction in body temperature during hypothermic CPB, differences in PCO₂ between alpha-stat and pH-stat pH management result in a change in pH of 0.16 pH units and in PaCO₂ of 15 mmHg.

We have previously shown that patients in whom pH-stat management (temperature corrected PaCO₂ of 40 mmHg) was followed, demonstrated elevated CBF that was pressure dependent, but independent of cerebral metabolic rate for oxygen (CMRO₂) or arterial oxygen content (CaO₂) (9). Similar results have also been reported by other investigators. Henriksen, et al. (10) also utilized pH-stat management and measured an average CBF of 64 ml 100 g⁻¹ min⁻¹. They found CBF to be independent of PaCO₂ but varied with MAP below 55 mmHg, and concluded that cerebral autoregulation was lost below that level. Another recent study using pH-stat regulation measured flow velocity through the middle cerebral artery using a transcranial Doppler method (11). These authors similarly observed pressure-passive cerebral perfusion and concluded that cerebral autoregulation is impaired during nonpulsatile CPB. These studies are all consistent with the known potent vasodilatory properties of CO₂. It is apparent that the exogenous CO₂ that is added during pH-stat blood gas regulation produces passive cerebral vasodilation, thus confounding cerebral autoregulation by overriding the cerebral vascular responses to pressure changes.

In patients in whom alpha-stat (non-temperature corrected PaCO₂ of 40 mmHg) is maintained, we have shown that CBF is markedly reduced, and that it correlates significantly with CMRO₂ and CaO₂, but not with cerebral perfusion pressure (CPP) over the range from 20 to 100 mmHg (9). This is similar to the results obtained by others, who have reported CBF ranging from 9 to 13 ml 100 g⁻¹ min⁻¹ during hypothermic CPB (7, 12). Govier, et al. found no correlation of CBF with mean arterial pressure (MAP), and demonstrated that the lower limit of cerebral autoregulation appeared to be below a MAP of 30 mmHg (12). Alpha-stat pH management can thus be seen to preserve both cerebral autoregulation and importantly, cerebral flow/metabolism coupling (9).

Cerebral Autoregulation

The seeming extension of the lower limit of cerebral autoregulation is a potentially surprising result of CBF data obtained during alpha-stat pH management. In a clinical population undergoing cardiac surgical procedures, Govier, et al. (12) and ourselves, (9) have observed that CBF was independent of MAP down to 30 mmHg, or cerebral perfusion pressures (CPP = MAP - jugular venous pressure) of 20 mmHg. Rather than being seen as an alteration of the limits of cerebral autoregulation however, this data can be readily interpreted by recognizing that the cerebral metabolic rate (CMRO₂) during hypothermia is greatly reduced (9, 13).

While the reactivity of the cerebrovascular bed 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, i.e. the plateau of the cerebral autoregulatory curve, cerebral flow/metabolism coupling being an expression of that linkage. During hypothermia, CMRO₂ is decreased; thus, in the presence of intact flow/metabolism coupling i.e., alpha-stat pH management, a much lower CBF is required. This effectively moves the autoregulatory plateau to a lower level of CBF, which can be readily achieved at a lower perfusion pressure, without invoking additional cerebral vasodilatation.

The presence of cerebrovascular disease, or untreated hypertension, may shift the hypothermic cerebral autoregulatory curve to the right, as it does at normothermia, thus relatively higher cerebral perfusion pressures may be 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 rotation of the heart during surgery, partial obstruction of cerebral venous drainage can occur. This may give rise to low intracardiac pressures (CVP) but can paradoxically increase jugular venous pressure, thus lowering CPP despite an apparently adequate MAP (9, 14). Monitoring of JVP, or measuring CVP proximally in the superior vena cava would allow more accurate determination of CPP.

Clinical Implications

CO₂ is a potent cerebral vasodilator and directly increases CBF. This is often cited as a primary benefit of pH-stat, but it should be recognized that this cerebral hyperemia may not be beneficial. Although elevations of PaCO₂ can increase global CBF in theory, it may paradoxically increase regional ischemia by diverting blood away from maximally dilated, collateral-dependent regions. CO₂-induced cerebrodilatation can also reduce driving pressure, jeopardizing areas of brain dependent on flow through critically stenosed vessels (15). In addition, because cerebral emboli are believed to account for a majority of neurologic deficits following CPB (16), unnecessary elevations of CBF have the potential to increase delivery of emboli directly into the cerebral circulation. Unqualified cerebral vasodilatation, rather than guarding against cerebral ischemia, may thus increase the potential for neurologic deficits through both an aggravation of regional blood flow inhomogeneities, and a potential increase in cerebral embolization.

The preponderance of evidence demonstrates that there is a sound physiological rationale for the use of alpha-stat pH management, but, as yet, no outcome studies examining neurological sequelae in patients specifically randomized to alpha-stat versus pH-stat management have been reported.
Bashein, et al. (17) reported significant decreases in neuropsychometric test performance after elective coronary bypass surgery, but these were unrelated to the mode of pH-management i.e. alpha-stat or pH-stat. One possible explanation for this inability to discriminate between pH management groups lies in the observation that the difference in PaCO₂ between their groups was only 7 mmHg, less than half the PCO₂ difference that would be anticipated at such temperatures (18). The clinical impact, if any, of variations in pH management during CPB thus still remains unclear.

References


This paper was peer reviewed (in original form) for publication in the Journal of Extra-Corporeal Technology.