Basic sciences review

The Oxyhaemoglobin Dissociation Curve in Critical Illness

T. J. MORGAN
Intensive Care Facility, Division of Anaesthesiology and Intensive Care, Royal Brisbane Hospital, Brisbane, QUEENSLAND

ABSTRACT

Objective: To review the status of haemoglobin-oxygen affinity in critical illness and investigate the potential to improve gas exchange, tissue oxygenation and outcome by manipulations of the oxyhaemoglobin dissociation curve.

Data sources: Articles and published peer-review abstracts.

Summary of review: The P50 of a species is determined by natural selection according to animal size, tissue metabolic requirements and ambient oxygen tension. In right to left shunting mathematical modeling indicates that an increased P50 defends capillary oxygenation, the one exception being sustained hypercapnia. Increasing the P50 should also be protective in tissue ischaemia, and this is supported by modeling and experimental evidence. Most studies of critically ill patients have indicated reduced 2,3-DPG concentrations. This is probably due to acidaemia, and the in vivo P50 is likely to be normal despite low 2,3-DPG levels. It may soon be possible to achieve significant P50 elevations without potentially harmful manipulations of acid-base balance or hazardous drug therapy.

Conclusions: Despite encouraging theoretical and experimental data, it is not known whether manipulations of the P50 in critical illness can improve gas exchange and tissue oxygenation or improve outcome. The status of the P50 may warrant more routine quantification and consideration along with the traditional determinants of tissue oxygen availability. (**Critical Care and Resuscitation 1999; 1: 93-100**)

Key words: Critical illness, haemoglobin-oxygen affinity, ischaemia, P50, tissue oxygenation, shunt

In intensive care practice, manipulations to improve tissue oxygenation are generally accomplished by altering the commonly accepted determinants of global tissue oxygen delivery, namely cardiac index, arterial oxygen tension and haemoglobin concentration.[1] It is unusual for haemoglobin-oxygen affinity to be taken into consideration at these times, mainly because the effects of changes in haemoglobin-oxygen affinity on tissue oxygenation are less well understood. The characteristics of oxyhaemoglobin dissociation affect both oxygen uptake in the lungs and oxygen unloading in the tissues. A fall in haemoglobin-oxygen affinity simultaneously reduces transfer of oxygen from pulmonary alveoli to pulmonary capillary blood while facilitating oxygen unloading from blood to tissues, whereas raising haemoglobin-oxygen affinity enhances oxygen uptake in the lungs but inhibits oxygen unloading. Because these are opposing effects at different points in the oxygen delivery pathway, estimating the best haemoglobin-oxygen affinity to defend tissues against a reduction in oxygen supply can be a complex task.

Correspondence to: Dr. T. J. Morgan, Intensive Care Facility, Division of Anaesthesiology and Intensive Care
Royal Brisbane Hospital, Brisbane, Queensland, 4029 (e-mail: morgant@health.qld.gov.au)

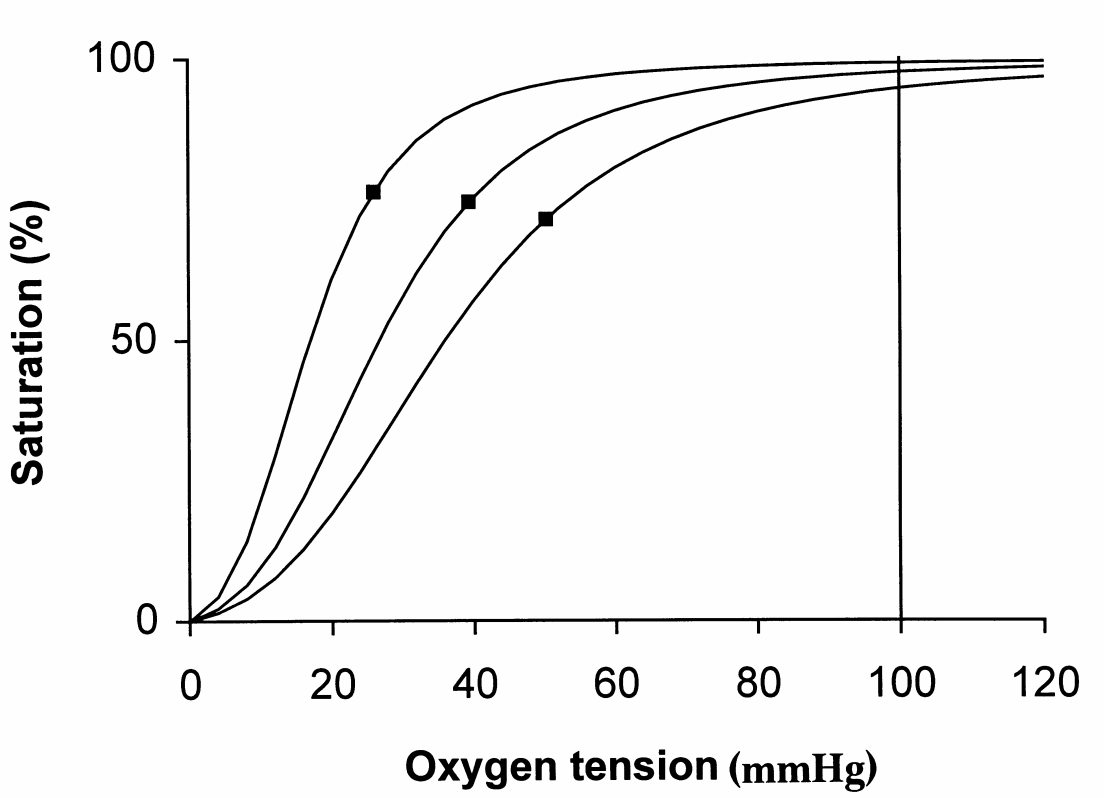

Figure 1. Three oxyhaemoglobin dissociation curves – normal (P50 = 26.7 mmHg), left-shifted (P50 = 17 mmHg) and right-shifted (P50 = 36 mmHg). The vertical line represents normal oxygen loading tension (PO_2 = 100 mmHg). The points on the curves to the left of the line correspond with an oxygen extraction of 5 ml/100 ml blood, assuming a haemoglobin concentration of 15 g/100ml.

The oxyhaemoglobin dissociation curve

The oxyhaemoglobin dissociation curve describes the relationship between the oxygen tension of blood and its oxygen content (Figure 1). Any point on the sigmoid-shaped curve will represent the haemoglobin-oxygen affinity at that point, but the P50 is normally used as a global shorthand quantification of haemoglobin-oxygen affinity.

The P50 is the oxygen tension at 50% saturation of haemoglobin. Factors increasing haemoglobin-oxygen affinity shift the oxyhaemoglobin dissociation curve to the left and decrease the P50, whereas factors decreasing haemoglobin-oxygen affinity shift the curve to the right and increase the P50. These shifts result from allosteric changes in the haemoglobin molecule, which influence the avidity of haemoglobin-oxygen binding. For example, the quaternary conformation of deoxyhaemoglobin (T-tense) differs from that of oxyhaemoglobin (R-relaxed) and is more favourable for binding to 2,3-diphosphoglycerate (2,3-DPG). When 2,3-DPG binds in the central cavity of the deoxyhaemoglobin molecule, it anchors the molecular configuration of haemoglobin in the T-tense form. Haemoglobin-oxygen affinity is thus reduced and the P50 increased.[2-4]

Factors which increase the P50 include acidaemia (the Bohr effect), hypercapnia (which has an additional right-shifting influence independent of its effect on pH), high levels of erythrocytic organic phosphates such as 2,3-DPG and ATP (of which 2,3-DPG is the most important in man[5]) and fever.[6] Conversely, alkalaemia, hypocapnia, low 2,3-DPG levels and hypothermia decrease the P50. Production of 2,3-DPG occurs during erythrocytic glycolysis as an end product of the Rapoport-Luebering phosphoglycerate shuttle.[7]

The Bohr effect

During shifts of the oxyhaemoglobin dissociation curve to the right or left, the most marked alteration is in the middle part of the curve around the P50. The curves converge towards the origin at low oxygen tensions and converge again at higher oxygen tensions (Figure 1). At normal loading oxygen tensions, the arterial points of normal and shifted curves are therefore much closer together than the venous points. This means that the arterial oxygen contents of normal and curve-shifted

blood will be quite similar, but after extraction of the same amount of oxygen, the highest venous oxygen tensions (and by implication end-capillary and tissue oxygen tensions) will be seen in the right-shifted blood (Figure 1).

The Bohr effect is a right shift of the curve in response to acidaemia and is more pronounced in reduced haemoglobin and at high 2,3-DPG concentrations. It is usually quantified at 50% saturation as $\Delta \log P50/\Delta$ pH. The normal value for the CO_2 effect is - 0.48 and for metabolic acid changes - 0.40.[8] The capillary Bohr effect is primarily a CO_2 effect, which acts to reduce the fall in the oxygen diffusion driving pressure during desaturation of arterial blood in the capillaries. As a result there is a decreased likelihood that mitochondrial oxygen tension will fall below the anaerobic threshold (i.e. Pasteur point 1-2 mmHg[9]). With the CO_2 Bohr effect eliminated and tissue perfusion held constant, total oxygen consumption would need to be reduced by 25 ml / minute in the average human to prevent any further fall in end-capillary oxygen tension. In working muscle, local heat, high CO_2 production and high concentrations of reduced haemoglobin increase the influence of the capillary Bohr effect.

Standard versus in vivo P50

The standard P50 is the oxygen tension at which haemoglobin is 50% saturated at pH = 7.4, PCO_2 = 40 mmHg, temperature = 37°C with carboxyhaemoglobin < 2%, whereas the in vivo P50 is the oxygen tension at which haemoglobin is 50% saturated at the pH, PCO_2, temperature and carboxyhaemoglobin concentration of the blood in the subject. The standard P50 is thus a reflection of both red cell organic phosphate levels and haemoglobin structure and is altered by abnormal 2,3-DPG concentrations and haemoglobinopathies. The in vivo P50 reflects the total effect of 2,3-DPG, haemoglobin structure, acid-base balance, temperature, and the influence of carboxyhaemoglobin (which causes a left shift), and is therefore the better description of true haemoglobin-oxygen affinity.

The two P50 values may respond differently to a given perturbation. For example, in acidaemia there is an initial increase in the in vivo P50 because of the Bohr effect. Over approximately 24 hours of acidaemia, the standard P50 steadily decreases due to reduced production of 2,3-DPG, which simultaneously brings the in vivo P50 either partially or completely back to normal. This is because glycolytic production of 2,3-DPG is inhibited by a fall and stimulated by a rise in intra-erythrocytic pH.[10] Unless otherwise specified, when the term P50 is used in this paper it refers to the in vivo P50.

Calculating the P50

Highly accurate determinations of the P50 require construction of the oxyhaemoglobin dissociation curve, or at least a Hill plot.[11] In the intensive care unit, reasonably accurate P50 values can be calculated more simply from a single-point measurement of blood gases and haemoglobin-oxygen saturation.[12-14] The Siggaard-Andersen Oxygen Status Algorithm,[15] incorporating the tanh equation, is the most clinically useful single point method. This is because it remains accurate up to a haemoglobin-oxygen saturation of 97% provided there are no severe perturbations of acid-base balance combined with alterations of the standard P50, which can change the shape of the oxyhaemoglobin dissociation curve.[16]

The normal P50

The normal P50 of each species has been determined by natural selection. Schmidt-Neilsen suggested that the P50 of a species is that which is the most favourable for tissue unloading at the metabolic requirements, organ capillary density and environmental oxygen tension of the animal.[17] The value for man is 26.7 mmHg. In general, smaller animals have higher P50 settings. Schmidt-Neilsen devised the following expression for the relationship between the P50 and the average body weight of mammalian species living at normal ambient oxygen tension:

$$P50 = 50.34\ BW^{0.054}$$

where the P50 is expressed in mmHg and BW (body weight) in grams. In fact the correlation between body weight and the P50 is not always as strong as this formula implies. For example, the normal P50 of a fox is 26.2 mmHg,[18] less than the normal human P50.

Animals living in hypoxic environments such as deep burrows or at high altitude tend to have a lower P50 than animals from the same species living at normal ambient oxygen tensions. Similarly, foetal blood (HbF; P50 = 18 mmHg) has a low P50 as an adaptation to the hypoxic conditions in utero. The appropriateness of a low P50 as an adaptation to environmental hypoxia is reviewed elsewhere.[19]

Modeling the effects of P50 changes

Trends in mixed venous oxygen tensions provide some insight into trends in tissue and mitochondrial oxygen tensions, although some organs extract much more oxygen than the total body value of 4.6 ml/100ml blood. For example, the brain and heart extract 6.2 ml/100 ml and 11.0 – 15.0 ml/100 ml respectively,[20, 21] while oxygen extraction in working skeletal muscle can greatly exceed these values.[22] It is also important to

remember that the oxygen content of the venous effluent from any organ is a flow-weighted average of all end-capillary oxygen contents within the organ plus a variable positive offset from A-V diffusive shunting.

It is possible to model the effects of P50 alterations on arterial, mixed venous and capillary oxygen tensions in any combination of environmental hypoxia, lung disease and low perfusion states at differing inspired oxygen concentrations and barometric pressures. For example, in this paper the tanh equation is used in combination with a two compartment lung model (the two compartments comprising ideal alveoli and shunt) plus standard corrections for O_2/CO_2 exchange[23-25] and the increased buffering of reduced haemoglobin[26] (Figures 2-4). A high extraction parameter (oxygen tension after extraction of 15 ml/100 ml blood) can also be calculated as a more representative index of the average capillary driving pressure for diffusion of oxygen to the tissues (Figures 2 and 3). High extraction parameters are more indicative of capillary and tissue oxygen tensions in organs with high oxygen extraction and/or A-V diffusive shunting. A-V diffusive shunting is a widespread phenomenon, particularly in tissues with countercurrent systems such as the kidney and the gut.[27-29]

There are many flaws with this type of modelling, including the fact that no allowances are made for changes in cardiac output or for the presence of any type of ventilation perfusion mismatch other than pure shunt. It nevertheless remains a useful method with which to illustrate basic principles.

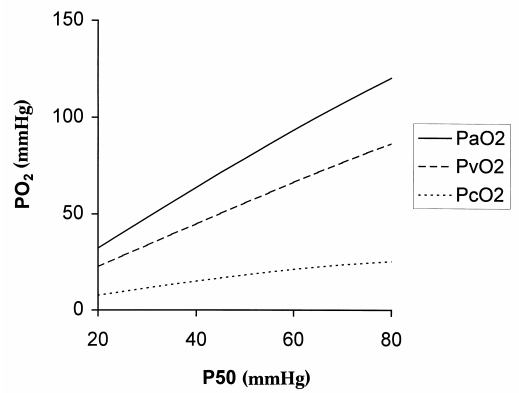

Figure 2. Changes with P50 of oxygen tension in simulated arterial (P_aO_2) mixed venous (P_vO_2) and capillary (P_cO_2) blood in an individual with a 50% right to left shunt breathing 50% oxygen. Barometric pressure = 760 mmHg, haemoglobin concentration = 15 $g.dL^{-1}$, arterial pH = 7.4, arterial PCO_2 = 40 mmHg. Increasing the P50 improves P_aO_2, P_vO_2 and P_cO_2.

The P50 in critical illness

In critical illness many factors which have a potential bearing on haemoglobin-oxygen affinity can operate simultaneously. Acidaemia reduces haemoglobin-oxygen affinity via the Bohr effect and at the same time reduces 2,3-DPG production, which acts to increase haemoglobin-oxygen affinity. Alkalaemia does the opposite. Hypophosphataemia reduces 2,3-DPG production and hyperphosphataemia increases it. Prolonged hypoxaemia increases 2,3-DPG concentrations.[6] Many critically ill patients are also febrile, which shifts the oxyhaemoglobin dissociation curve to the right.

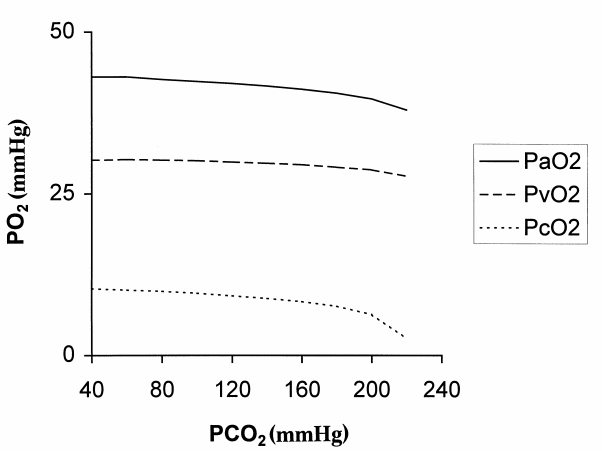

Figure 3. Changes in oxygen tension in simulated arterial (P_aO_2) mixed venous (P_vO_2) and capillary (P_cO_2) blood as P_aCO_2 is increased and the in vivo P50 kept normal in an individual with a 50% right to left shunt breathing 50% oxygen. Barometric pressure = 760 mmHg, haemoglobin concentration = 15 g/100mL, in vivo P50 = 26.7. Simulated capillary oxygen tensions decrease with worsening hypercapnia.

The final result of all these conflicting influences on haemoglobin-oxygen affinity can be difficult to determine, and there have been a number of studies on this subject. In a comparison of patients in whom pulmonary artery catheters had been inserted with healthy controls, the mean standard P50 was reduced in the patient group.[30] Another Australian investigation into patients with acute respiratory distress syndrome also documented a left-shifted curve.[31] In neither study were red cell 2,3-DPG concentrations measured. In contrast, a group of Belgian investigators compared 29 patients suffering from acute respiratory distress syndrome with 29 controls and found a significant rightward shift of the oxyhaemoglobin dissociation curves. These workers measured 2,3-DPG concentrations and found them to be significantly elevated in the patient group.[32] The authors attributed the increased mean 2,3-DPG concentration in these patients to prolonged hypoxaemia.

We recently measured red cell 2,3-DPG concentrations in 20 critically ill patients (APACHE scores > 20 on the preceding day) and 20 healthy

controls.[33] Mean 2,3-DPG concentrations were significantly reduced in the critically ill group – the reduction being almost solely due to acidaemia. Importantly, patients with 2,3-DPG levels below the normal range had virtually the same mean in vivo P50 as the patients with normal 2,3-DPG concentrations, due to the opposing effects of acidaemia and low 2,3-DPG concentrations on the oxyhaemoglobin dissociation curve. In other words overall tissue oxygen availability was not reduced despite low 2,3-DPG levels. Our calculations of the in vivo P50 assumed normothermia, whereas many of the patients were febrile (which would have increased the true in vivo P50 still further).

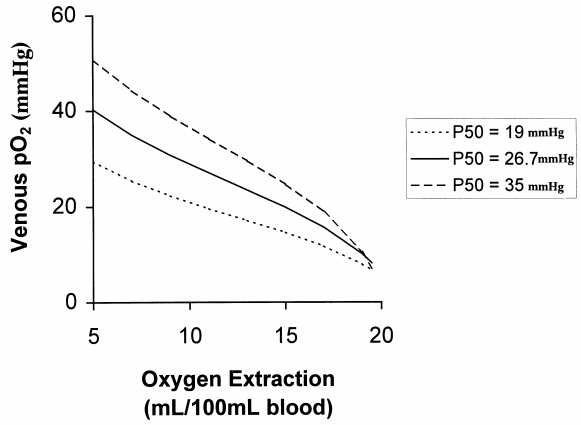

Figure 4. The effect of differing haemoglobin-oxygen affinities on venous oxygen tension with increasing oxygen extraction from arterial blood. Haemoglobin concentration = 15 g g/100mL, arterial pH = 7.4, arterial PCO_2 = 40 mmHg. High P50 improves post–extraction oxygen tensions, although the advantage is reduced by very high oxygen extraction.

Manipulating the P50 in critical illness

In critical illness, tissue oxygenation can be under threat from any combination of lung disease and global or regional circulatory dysfunction. It is not known whether manipulating the P50 to improve tissue oxygen availability under these circumstances can improve outcome, but theoretical and experimental data support the proposition.

Shunt

Shunt is a common contributor to poor gas exchange in the critically ill patient. The raised A-a gradients of acute respiratory distress syndrome,[34] cardiogenic pulmonary oedema[35], lobar pneumonia,[36] massive pulmonary embolism[37] and post cardiopulmonary bypass[38] are all primarily due to intra-pulmonary right to left shunting. As early as 1980 it was realised that mixed venous oxygenation is likely to improve in right to left shunting if the P50 is elevated.[39] This is well demonstrated in Figure 2, where a subject breathing 50% oxygen with 50% right to left shunt is modeled using the tanh equation and a two-compartment lung model. The improvement in simulated venous and capillary oxygen tensions with an increasing P50 continues up to very high P50 values (e.g. > 80 mmHg).

Paradoxically, hypercapnic P50 elevation is less likely to improve tissue oxygenation in right to left shunting, and may even have adverse effects, despite some claims to the contrary.[40] This is an important distinction, as permissive hypercapnia is practiced widely in intensive care to limit inspiratory pressure and tidal volume during the mechanical ventilation of patients with ARDS in order to prevent barotrauma and other adverse consequences of alveolar overdistension.[41] Hypercapnia elevates the P50 via the CO_2 Bohr effect but there are important differences between hypercapnia and other means of increasing the P50. The first is that according to the alveolar gas equation hypercapnia reduces the alveolar oxygen tension at a given inspired oxygen tension. Secondly, sustained hypercapnia causes compensatory renal bicarbonate retention, which in the presence of normal renal function will nearly correct the pH in 24 - 48 hours.[42] Finally the associated acidaemia suppresses 2,3-DPG production, so that even without metabolic compensation the in vivo P50 is likely to return to normal within 24 hours. If progressive hypercapnia is modeled with a normal in vivo P50, no improvement in simulated arterial, mixed venous or capillary oxygenation is seen. In fact there is a steady reduction in simulated capillary oxygen tensions which accelerates to zero above PCO_2 = 200 mmHg (Figure 3).

Despite impressive modeling data and with the above- mentioned caveat concerning hypercapnia, there have been no clinical or laboratory investigations to date into the benefits of elevating the P50 in severe lung disease and only one in the case of cardiac right to left shunting.[43]

Tissue hypoperfusion

Low perfusion threats to organ and tissue function are commonplace in critical illness – whether globally in cardiogenic and hypovolaemic shock or regionally in myocardial ischaemia and infarction, cerebral ischaemia and stroke, vascular obstruction to kidneys, bowel or limbs and following organ transplantation or free and pedicle grafts. In the absence of hyperbaric oxygen therapy, oxygen consumption in tissues subjected to fixed reductions in blood flow can only be maintained at the expense of an increased extraction fraction.

Oxygen extraction modeling clearly shows that at normal arterial oxygen tensions an increased P50 should improve venous and therefore tissue oxygenation at all levels of oxygen extraction (Figure 4). Because all oxyhaemoglobin dissociation curves converge towards

the origin at low oxygen tensions the advantage afforded by an increased P50 decreases progressively as the extraction fraction is increased, and at extreme levels of oxygen extraction will virtually disappear. This is well illustrated in Figure 4. The reduced advantage of a high P50 at extreme levels of oxygen extraction was well demonstrated in a recent perfused dog hindlimb experiment.[44] During normal oxygen extraction, a pharmacologically induced elevation in the P50 increased muscle surface oxygen tensions above controls. However as blood flow to the limb was reduced to increase oxygen extraction, muscle oxygen tensions in treated and control dogs began to converge. At critical oxygen delivery the oxygen extraction ratio in treated and control dogs was identical. The authors attributed the loss of a high P50 advantage during escalating extraction at least in part to the convergence of the oxyhaemoglobin dissociation curves at low oxygen tensions.

The convergence phenomenon may help to explain the fact that until recently, experimental evidence in high extraction scenarios for a protective effect afforded by a high P50 or for a detrimental effect from a low P50 have been inconclusive.[45] One other difficulty of experimentation in this field has been that if P50 manipulations also reduce red cell deformability due to disturbances in ATP and other metabolite concentrations, tissue perfusion and tissue oxygen availability can be adversely affected.[46]

Until recently the most encouraging studies in this area were two which seemed to show a protective benefit when the P50 was raised prior to experimental myocardial infarction.[47,48] However, recent work has been more promising. In acutely anaemic dogs, transfusion with high P50 blood compared with control blood resulted in increased oxygen consumption.[49] RSR-13, a synthetic allosteric modifier of haemoglobin-oxygen affinity which causes a major P50 elevation, enhanced recovery when given prior to myocardial stunning by repeated episodes of ischaemia and reperfusion. The same agent used in a dog hind limb preparation increased maximal oxygen uptake during maximal exercise[50]. In another study, RSR-13 reduced the volume of cerebral infarction and improved intra-infarct oxygen tension in a feline stroke model.[51]

A further intriguing possibility is that raising the P50 might afford some protection from the effects of covert splanchnic ischaemia, which may drive some cases of multiple organ dysfunction syndrome.[52] However, all these considerations will remain pure speculation until safe and reliable means of decreasing haemoglobin-oxygen affinity in critical illness are developed and submitted to trial. Any responses to the small P50 elevations achievable by administering drugs such as corticosteroids, beta-blockers and others[6] would be obscured by other more powerful and often potentially detrimental effects.

Methods of safely elevating the P50 are on the horizon. These include the administration of allosteric effectors by direct intravenous injection of agents such as RSR-13.[53, 54] Alternatively, blood can be reinfused after drug incorporation by electroporation, which is a novel technique whereby an electrical pulse creates temporary pores in the lipid bilayer of the erythrocytic membrane. This enables the introduction of charged long-acting allosteric effectors such as inositol hexaphosphate, resulting in stable increases in the P50 of 50 - 100% with minimal alteration to haematological indices or haemolytic wastage.[55,56] Finally, supra-normal P50 values are possible in acellular oxygen carriers such as artificial haemoglobin solutions. For example the P50 of diaspirin cross-linked haemoglobin is 29 mmHg.[57] The potential for high P50 benefits in these solutions is currently overshadowed by their propensity to elevate systemic and pulmonary vascular resistance, particularly in septic shock, a property which has been attributed to nitric oxide scavenging.[58]

In summary, it is probable that the P50 is precisely set in response to animal size, tissue metabolic requirements and ambient oxygen tension. Mathematical modelling indicates that an increased P50 defends mitochondrial oxygenation in right to left shunting, the one exception being sustained hypercapnia. Increasing the P50 should also be protective in high extraction states such as ischaemia, and this is supported by modelling and experimental evidence. Most studies of critically ill patients have pointed to a tendency for reduced 2,3-DPG concentrations. This is probably due to acidaemia, and the in vivo P50 is likely to be normal in most patients despite low 2,3-DPG levels. The time is drawing closer when significant P50 elevations will be achievable in critical illness without potentially harmful manipulations of acid-base balance or hazardous drug therapy. It will then be possible to determine whether manipulations of the P50 can improve tissue oxygenation, reduce the incidence of ventilator associated lung injury and perhaps improve outcome. In the meantime, the status of the P50 may warrant more routine quantification and consideration along with the traditional determinants of tissue oxygen availability.

Received: 14 January 1999
Accepted: 12 February 1999

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