What is \( p_{50} \)?

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\( p_{50} \) is a shorthand representation of hemoglobin-oxygen affinity. A lower \( p_{50} \) is protective in ambient hypoxemia, whereas increasing the \( p_{50} \) should be beneficial in hypoxia due to lung disease, anemia, and tissue ischemia.

Despite encouraging theoretical and experimental data, it is not yet established that manipulations of \( p_{50} \) in critical illness can improve gas exchange, tissue oxygenation, or outcome.

Most practitioners try to improve tissue oxygenation by increasing cardiac index, arterial oxygen tension, or hemoglobin concentrations. It is unusual for hemoglobin-oxygen affinity to be considered at these times.

This is because hemoglobin-oxygen affinity has complex effects on tissue oxygenation. In fact, changes in the oxyhemoglobin dissociation curve can have simultaneously opposing actions through oxygen uptake in the lungs versus oxygen unloading in the tissues.

The oxyhemoglobin dissociation curve

The oxyhemoglobin dissociation curve displays the relationship between the oxygen tension of blood and the oxygen saturation (Figure 1). Although the whole curve is the best representation of hemoglobin-oxygen affinity, \( p_{50} \) is often used as the sole descriptor. \( p_{50} \) is the oxygen tension when hemoglobin is 50% saturated with oxygen. When hemoglobin-oxygen affinity increases, the oxyhemoglobin dissociation curve shifts to the left and decreases \( p_{50} \).

When hemoglobin-oxygen affinity decreases, the oxyhemoglobin dissociation curve shifts to the right and increases \( p_{50} \) (Figure 1). Shifts in the curve happen because of changes in the quaternary shape of the hemoglobin molecule which affect oxygen binding.
Factors which increase \( p_50 \) include a fall in pH (which is the Bohr effect), high levels of erythrocytic 2,3-diphosphoglycerate (2,3-DPG), and fever. Conversely, raised pH, low 2,3-DPG levels, and hypothermia decrease \( p_50 \) (Figure 1).

The importance of \( p_50 \) changes

The oxyhemoglobin dissociation curve is sigmoid shaped. When the curve shifts, the effect is most prominent in the middle around \( p_50 \). The shift is much less at low and high oxygen tensions (Figure 1).

As a result, extracting the same amount of oxygen from arterial blood with low, normal and high \( p_50 \) values at sea level will leave the highest venous oxygen tensions (and therefore tissue oxygen tensions) in the blood with the high \( p_50 \) (Figure 2). However if the same extraction occurs on the top of Mt. Everest, the best result is achieved with the low \( p_50 \) blood (Figure 2).

The Bohr effect comes into action every time arterial blood traverses the capillaries. While oxygen is being unloaded, \( pCO_2 \) rises, pH falls, and the curve shifts to the right. The resultant \( p50 \) increase maintains a better oxygen diffusion driving pressure, increasing oxygen availability in the average human by about 25 mL/min. In working muscle where there is heat and high \( CO_2 \) production, this boost to oxygen availability is especially strong.

Standard versus \( \text{in vivo} \) \( p_50 \)

The standard \( p50 \) is the oxygen tension at which hemoglobin is 50 % saturated at \( pH = 7.4, pCO_2 = 40 \text{ mmHg (5.3 kPa)} \), temperature = 37 °C with carboxyhemoglobin < 2 %, whereas the \( \text{in vivo} \) \( p50 \) is the oxygen tension at which hemoglobin is 50 % saturated at the \( pH, pCO_2, \) temperature, and carboxyhemoglobin concentration of the blood in the subject. The standard \( p50 \) thus depends primarily on red-cell 2,3-DPG concentrations and hemoglobin structure. The \( \text{in vivo} \) \( p50 \) reflects the total effect of 2,3-DPG, hemoglobin structure, acid-base balance, temperature, and the dyshemoglobins. From the perspective of oxygen loading and unloading, \( \text{in vivo} \) \( p50 \) is what matters. Unless otherwise specified, the term \( p50 \) in this paper means \( \text{in vivo} \) \( p50 \).

Calculating the \( p50 \)

For highly accurate \( p50 \) determinations it is necessary to construct the full oxyhemoglobin dissociation curve in the laboratory. However, for clinical purposes, \( p50 \) values can be calculated much more simply from a single-point measurement of blood gases and hemoglobin-oxygen saturation. The Siggaard-Andersen Oxygen Status Algorithm is the most useful single-point method [1]. This is because it remains accurate up to a hemoglobin-oxygen saturation of 97 % provided the oxyhemoglobin dissociation curve maintains its shape.

The normal \( p50 \)

The \( p50 \) of each animal species has evolved over the millennia through environmental selection pressures,
and presumably is optimal for the tissue oxygen consumption, organ capillary density, and environmental oxygen tension of the animal. The value for humans is 26.7 kPa (3.5 kPa). In general, smaller animals have higher \( p_{50} \) settings (Figure 3).

![Horse and mouse](image)

<table>
<thead>
<tr>
<th>Value</th>
<th>Description</th>
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<tbody>
<tr>
<td>( p_{50} = 24 \text{ mmHg} )</td>
<td>VO(_2) 1.72 ( \mu \text{L/g/min} ), Capillaries 1350/mm(^2)</td>
</tr>
<tr>
<td>( p_{50} = 49 \text{ mmHg} )</td>
<td>VO(_2) 28.2 ( \mu \text{L/g/min} ), Capillaries 4200/mm(^2)</td>
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**FIG. 3. Comparison of \( p_{50} \) values, tissue oxygen consumption (VO\(_2\)), and tissue capillary density in the horse and mouse. Note that the four-fold increase in capillary density in the mouse is insufficient to compensate for the sixteen-fold increase in VO\(_2\). An increase in \( p_{50} \) is a necessary adaptation.**

**The \( p_{50} \) in critical illness**

In critical illness, many factors affecting \( p_{50} \) can be operating, at times simultaneously. Acidemia increases \( p_{50} \) via the Bohr effect, but at the same time reduces 2,3-DPG production, decreasing \( p_{50} \). Alkalemia does the opposite. Hypophosphatemia reduces 2,3-DPG production and hyperphosphatemia increases it. Prolonged hypoxemia increases 2,3-DPG concentrations and thus \( p_{50} \). Fever increases \( p_{50} \).

The final result is difficult to predict. Recently, a group of Australian critically ill patients were shown to have a normal mean *in vivo* \( p_{50} \) [2], despite reduced mean 2,3-DPG concentrations (and thus standard \( p_{50} \)). This 2,3-DPG reduction was due almost solely to acidemia. Two other studies of critically ill patients also revealed a reduced standard \( p_{50} \), implying low 2,3-DPG concentrations [3, 4]. The one exception comes from Belgium, where patients with acute respiratory distress syndrome and marked hypoxemia were found to have elevated 2,3-DPG concentrations [5].

**The desirable \( p_{50} \) response to hypoxia**

Investigational drugs and hemoglobin substitutes which can reliably alter \( p_{50} \) are now in existence. As a result, much attention is being given to the best way to manipulate \( p_{50} \) (if at all) when tissue oxygen delivery is under threat. In simple terms, the \( p_{50} \) which best preserves mixed venous oxygen tensions is the appropriate defense of mitochondrial oxygenation.

**Low ambient oxygen tensions (normal A-a gradient)**

Mathematical modeling predicts that a reduced \( p_{50} \) will defend mitochondria against severe environmental hypoxia, and animal and human data support this idea [6]. For example, animals adapted to hypoxic environments such as deep burrows or high altitude have a lower \( p_{50} \) than similar species breathing normal ambient oxygen tensions. Similarly, fetal blood (HbF; \( p_{50} = 19.4 \text{ mmHg (2.6 kPa)} \)) has a low \( p_{50} \) as an adaptation to the hypoxic conditions in utero.

**Critical illness**

In contrast, when inadequate tissue oxygen delivery occurs in critical illness, it is virtually never due to ambient hypoxia. With the exception of severe hypoventilation, arterial hypoxemia is normally associated with a raised A-a gradient, usually from lung pathology or (rarely) from intra-cardiac shunting. Critically ill patients also suffer reduced tissue oxygen delivery from varying combinations of low output states and anemia.

Major vascular obstruction can cause severe regional ischemia. In all these scenarios, increasing the \( p_{50} \) should improve venous oxygen tensions for a given oxygen extraction. However, as oxygen delivery continues to fall and the extraction fraction increases, the advantage afforded by increasing \( p_{50} \) will decrease progressively. In extreme hypoperfusion it virtually disappears.

Clinical and experimental data largely support these concepts and are well illustrated by the findings concerning the investigational agent RSR13. RSR13
increases $p_\text{50}$ by altering hemoglobin shape and has been shown to increase tissue $pO_2$. Benefits have been seen in experimental tumor irradiation [7], strokes [8], and myocardial ischemia [9].

However, in very high extraction scenarios it loses efficacy [10], and it may even damage organs such as the kidney, where arterio-venous shunting already causes very low tissue oxygen tensions [11, 12].

**Conclusion**

It may soon be possible to achieve significant $p_\text{50}$ elevations using artificial hemoglobin solutions or drugs which affect hemoglobin molecular shape. However, despite encouraging theoretical and experimental data, it remains to be established that manipulations of $p_\text{50}$ in critical illness can improve gas exchange, tissue oxygenation, or outcome. When we have better evidence that this is true, the status of $p_\text{50}$ will warrant routine quantification and consideration.

**References**