

# Hooray for Hypoxia?

A new study comes to a counter-intuitive conclusion: hypoxia may have its benefits for patients with lung injury

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## The Risks of Hypoxia and Hyperoxia

Hypoxaemia kills. Recently we have shown, in a study of over 50 000 critically ill patients, that mortality rises steadily as the partial pressure of arterial oxygen ( $\text{PaO}_2$ ) falls below about 11 kPa (80 mm Hg) (Figure 1) [1]. Rats exposed to hypoxic conditions develop a mild inflammatory response with increased capillary leak and pro-inflammatory cytokine release [2]. Hypoxia increases leukocyte adhesion, prolongs neutrophil survival, enhances pro-inflammatory responses (in particular, increasing leukocyte IL-8 expression), and reduces lung fluid transport [3,4]. A new study by Thiel et al. in *PLoS Biology* that shows a potential benefit for hypoxia is therefore a challenge to current thinking [5].

To put this finding into context we must acknowledge the equally accepted fact that hyperoxia is toxic. Experiments in primates show that 100% oxygen results in progressive damage to the pulmonary endothelium and epithelium. It causes free radical release, capillary leak, and impaired surfactant function in addition to arteriolar vasoconstriction and maldistribution of microcirculatory perfusion [6,7].

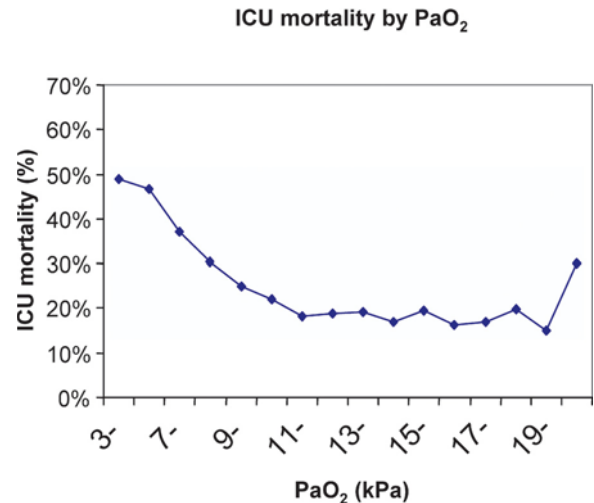
What, then, is the clinical balance we should strike between these extremes? Oxygenation of patients with acutely impaired lung function saves lives, but what is the right amount of oxygen? Many clinicians use the oxygen dissociation curve, aiming for saturations of above 92%. Others highlight the fact that patients with severe respiratory failure can survive despite being mechanically ventilated for days on 100% oxygen. In other words, a high percentage of inspired oxygen itself may not be harmful. (In

animal studies showing harm from giving 100% oxygen, the lungs are usually normal at the beginning of the study, so the arterial oxygen is correspondingly high—typically a  $\text{PaO}_2$  of 40 kPa (300 mm Hg); thus, it may be the high  $\text{PaO}_2$  rather than the high percentage of inspired oxygen that causes lung damage.) Some researchers question the importance of oxygen toxicity at all—for example, Meier et al., using a haemorrhagic shock model, found a significant improvement in outcome from the addition of 100% oxygen to the resuscitation [8].

## The New Study in Mice: Hyperoxia May Enhance Tissue Damage

It is against this background that the study by Thiel et al. is so interesting. Two of the study's authors, Ohta and Sitkovsky, showed recently that adenosine receptors are important in down-regulating inflammation [9]. They argued that a negative feedback loop operates: inflammation causes tissue damage, leading to adenosine release, which acts on G-protein-coupled adenosine  $A_{2A}$  receptors ( $A_{2A}$ Rs) to increase intracellular cyclic AMP, which in turn reduces the activity of NF $\kappa$ B and down-regulates the inflammatory response (Figure 2). Indeed, inflammation was dramatically enhanced in  $A_{2A}$ R-deficient mice compared with wild-type controls. Importantly, no significant compensatory changes in the expression of other adenosine receptors have been demonstrated in these  $A_{2A}$ R-deficient mice.

Sitkovsky and colleagues went on to propose that tissue inflammation induced local hypoxia and that this



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Figure 1. Mortality Rises Steadily as  $\text{PaO}_2$  Falls

hypoxia was important in regulating the adenosine-driven protective response. As a corollary they postulated that hyperoxia interrupts the hypoxia→adenosine→ $A_{2A}$ R lung protection pathway and hence could enhance tissue damage (Figure 2). The current paper by Sitovsky's group in *PLoS Biology* examines this hypothesis [5].

At the outset, using an inflammatory challenge that significantly impaired gas exchange, the authors confirmed

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**Abbreviations:** A2AR, adenosine A2A receptor;  $\text{PaO}_2$ , partial pressure of arterial oxygen

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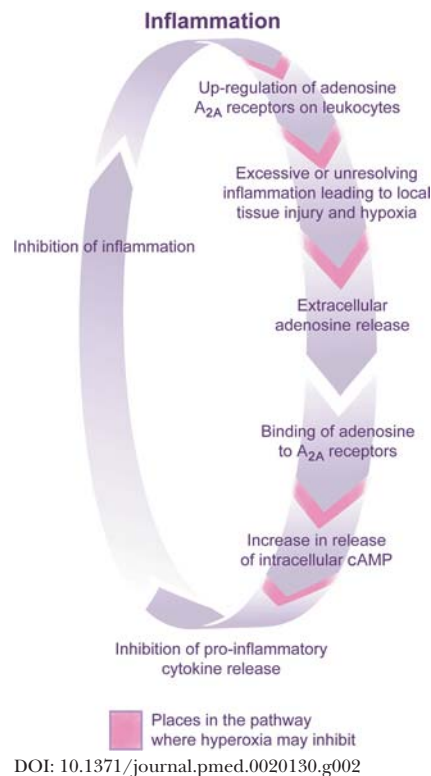
that when mice were additionally exposed to 100% oxygen, the toxicity of the challenge was dramatically increased compared to the inflammatory challenge in normoxic conditions (21% oxygen). (Over the time frame of the experiments high concentrations of oxygen alone were found to be only mildly inflammatory.) Inflammatory neutrophils from the challenged mice expressed the  $A_{2A}R$ , and exposure to high concentrations of oxygen reduced this expression. Moreover, an adenosine agonist could block pro-inflammatory responses.

Mice lacking the  $A_{2A}R$  had increased neutrophil infiltration in the lungs after endotoxin challenge and poorer gas exchange. The same was seen in wild-type mice treated with an  $A_{2A}R$  blocker. Endotoxin-challenged mice breathing 10% oxygen (hypoxia) had a low mortality and, in the survivors, lung inflammation was less severe than in mice breathing room air. Hypoxia also significantly reduced pulmonary neutrophil accumulation and improved gas exchange compared with normoxia, suggesting that hypoxia acted to protect the lung from additional inflammatory damage. Importantly, hypoxia was also associated with elevated adenosine concentrations.

In contrast to the 20% mortality of hypoxic, endotoxin-challenged wild-type mice, hypoxic, endotoxin-challenged  $A_{2A}R$ -deficient mice had elevated local and systemic accumulation of pro-inflammatory cytokines, and all died. As hypoxia per se did not affect the  $A_{2A}R$ -deficient mice, this suggests that both hypoxia and  $A_{2A}R$  functionality are required to induce the anti-inflammatory response. Finally, the authors showed that an adenosine agonist also inhibited lung injury in endotoxin-treated mice, reducing leukocyte influx and capillary leak. Importantly, this agonist could dramatically improve mortality even with a severe two-hit inflammatory challenge under hyperoxic conditions.

### Implications of the Study

These are exciting and provocative results. They are, however, hard to reconcile with many studies showing pro-inflammatory effects from hypoxia. Sitkovsky and colleagues attempt to reconcile this difference by saying that their study had a long time course



**Figure 2.** Adenosine Receptors Down-Regulate Inflammation through a Negative Feedback Loop

Sitkovsky and colleagues postulate that inflammation causes tissue damage leading to adenosine release, which acts on adenosine  $A_{2A}R$ s to increase intracellular cyclic AMP. The rise in cyclic AMP down-regulates the inflammatory response. Tissue inflammation induces local hypoxia, which regulates the adenosine-driven protective response. The figure shows the steps in the pathway where hyperoxia might act (having an inhibitory effect).

(Illustration: Giovanni Maki)

(over 48 hours), whereas studies showing that hypoxia is harmful usually had much shorter study periods.

The authors' explanation is probably too simplistic, and many issues and questions remain. (1) Different challenges—for example, pulmonary versus extrapulmonary—might give different results. (2) There is emerging evidence that more prolonged hypoxia can affect many processes, for example, mitochondrial function, and such complicated metabolic changes may be important and need to be examined [10]. (3) We don't know the mechanism of increased extracellular adenosine. (4) Lung injury may relate to tachypnoea and tidal volume, and these have not been measured. (5) In sampling arterial oxygen 15 minutes after removal

from the hyperoxia, we do not know whether the animals were exposed to excessive  $PaO_2$  levels or whether the degree of lung injury prevented the animals from having excessive  $PaO_2$  levels. In other words, although the animals were given 100% oxygen, they may not have had an elevated  $PaO_2$  (the lung injury may have prevented oxygenation of the blood). This issue is critically important, as the use of high-percentage inspired oxygen simply to achieve a normal  $PaO_2$  is much more akin to clinical practice.

Refreshingly, though, this is a study that invites us to re-evaluate our perspectives. We know hypoxia can be bad, but is it as bad as hyperoxia? The scenario is all too familiar—the patient's lung injury has rendered the patient hypoxaemic, and the paramedics have started high-flow oxygen. In the emergency room the team are heartened to see the patient “pink up” and to hear the ominous sound of the saturation monitor abate. But, beware, is the team *really* in a comfort zone? Is the saturation monitor really now chirping happily with 100% oxygen saturations, or is this the harbinger of future problems as the  $PaO_2$  increases unnoticed? Should we have an additional set of alarm limits, hitherto unrecognised: those of high oxygen tensions? Should the monitors be alarming not only when arterial saturation is below 90% but also when it's above 98%? The study by Thiel et al. suggests that we urgently need to find out. ■

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