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Intravenous iron loading inhibits the pulmonary vascular response to hypoxia in humans

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ABSTRACT

Aim: To manipulate the hypoxia-inducible factor (HIF) transcription factors pharmacologically and thereby confirm that HIF regulates human pulmonary vascular responses to hypoxia.

Background: HIF controls intracellular responses to hypoxia, and our recent work strongly implicates HIF in regulating human heart/lung physiology (Smith et al. *PLoS Med* 2006; 3: e290[Medline]). Iron is an obligate co-factor in the degradation pathway through which HIF is primarily regulated, and iron supplementation potentiates HIF degradation *in vitro*.

Hypothesis: Supraphysiological levels of iron similarly augment HIF degradation *in vivo* and thus inhibit acclimatisation to hypoxia.

Methods: Six normal subjects were each studied on two days. Day 1 (control) began with an infusion of saline while on Day 2 it was 200 mg iron sucrose. On each day subjects then underwent:

1. a 40-min acute isocapnic hypoxia protocol (end-tidal PO_2 50 mmHg), with pulmonary vascular tone assessed echocardiographically;
2. 8 h of isocapnic hypoxia in a chamber;
3. repeat of the acute hypoxia protocol.

Results: Iron loading prevented the rise in pulmonary arterial pressure normally present after sustained hypoxia and blunted acclimatisation of the acute hypoxic pulmonary vasoconstrictive response ($p < 0.01$; Fig 1).

Conclusions: HIF degradation is limited by physiological levels of iron, and HIF appears to control human pulmonary vascular responses to hypoxia.

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