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The effect of hydralazine on cardiorespiratory responses to hypoxia may not involve activation of the HIF pathway

Chun Liu , George M Balanos , Thomas G Smith , Keith L Dorrington and Peter A Robbins

Department of Physiology, Anatomy and Genetics, University of Oxford, Sherrington Building, Parks Road, Oxford, OX1 3PT, United Kingdom

ABSTRACT

Hypoxia-inducible factor 1(HIF-1) regulates the expression of many genes involved in cellular oxygen homeostasis. In mice, partial HIF-1 deficiency is associated with impaired pulmonary vascular and ventilatory responses to hypoxia. Hydralazine, a vasodilator and respiratory stimulant, has recently been found in vitro to stabilise HIF-1 and in mice to increase plasma vascular endothelial growth factor (VEGF) concentration. To examine whether this occurs in humans, we studied changes in VEGF and erythropoietin (EPO) together with cardiorespiratory responses following hydralazine administration. Ten volunteers participated in two 2-day protocols. Hydralazine or placebo was administered at 1 pm and 11 pm on the first day, and at 1 pm on the second day. In the mornings and afternoons of both days we measured plasma VEGF and EPO concentrations, systemic arterial blood pressure, and changes in heart rate (HR), cardiac output (CO), maximum systolic pressure difference across the tricuspid valve ($\overset{\Delta}{}$ Pmax) and ventilation (VE) in response to 20 min of isocapnic hypoxia (end-tidal PO_2=50 torr). Hydralazine had no significant effect on plasma VEGF and EPO concentrations at any time point, but did affect cardiorespiratory responses:

1. recent hydralazine decreased diastolic blood pressure (P<0.05);
2. hydralazine increased HR and CO in both euoxia and hypoxia (P<0.05) whilst having no effect on $\overset{\Delta}{}$ Pmax;
3. Recent hydralazine increased both VE in euoxia and the sensitivity of the ventilatory response to hypoxia (P<0.05). The human cardiorespiratory responses to hydralazine may not involve activation of the HIF pathway.

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