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Title: Modulation of respiration by tissue oxygen: A study in the mutant mouse with presbyterian hemoglobinopathy

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Body: Modulation of respiratory responses by tissue oxygen, as opposed to arterial blood gas content, has not yet been convincingly documented. In the present study we used genetically engineered Presbyterian mice that carry a low affinity variant of Hb (Hb-Presb), which is characterized by a rightward shift in the oxygen dissociation curve and innately increased tissue oxygenation. The study seeks to determine the influence of tissue oxygenation on ventilation by comparing the chemosensory responses in the Hb-Presb and wild-type mice. The animals were anesthetized with urethane and spontaneously breathing. Ventilation and its responses to changes in inspired oxygen, from hyperoxia to hypoxia, and to hyperoxic hypercapnia were measured breath by breath in a whole body plethysmograph before and after carotid body denervation. We found that all the chemosensory responses were significantly downregulated in Hb-Presb. Furthermore, Hb-Presb mice with intact carotid body innervation were more vulnerable to hypoxia, showing a more intense hypoxic ventilatory falloff than the wild type mice. Bilateral carotid body denervation in Hb-Presb mice, performed in normoxia, invariably led to respiratory arrest. The study brought out an interaction between the HB-oxygen dissociation curve and respiration. We conclude that there is a metabolic component of respiratory regulation, linked to tissue oxygenation. The hypoxic vulnerability of respiration and its reliance on carotid body input in Hb-Presb might be of importance in human cases of this hemoglobinopathy.