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(Abstract)

Contents

Understanding the Integrative Physiology of Acute Anemia: Linking Renal Tissue O2 Sensing with Adaptive Cardiovascular Responses to Preserve Tissue Oxygen Delivery

Hannah Joo[1], Kyle Chin[1,2], Iryna Savinova[3], Helen Jiang[1], Chloe Lin[1], Melina Cazorla-Bak[1,2], Jeremy A Simpson[3], Andrew J. Baker[1,4,5], C. David Mazer[1,2,4,5], Gregory M.T. Hare[1,2,5], William Darrah[1]

1 Department of Anesthesia, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.
2 Department of Physiology, University of Toronto, Toronto, Ontario, Canada.
3 Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada.
4 Institute of Medical Science, University of Toronto, Ontario, Canada.
5 Keenan Research Centre for Biomedical Science in the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada.

Introduction: The integrative physiological response to anemia is complex and incompletely understood. We utilized data from studies of acute anemia in rodents to determine the relationship between changes in blood oxygen content (C_aO_2) and the heterogenous response of the kidney, heart and brain. We hypothesize that renal hypoxia sensing mechanisms contribute to adaptive physiological responses to maintain cerebral oxygen delivery (DO_2) during acute anemia.

Methods: With animal care committee approval, we synthesized novel and published data from 5 previously published studies (REF). Outcomes included: assessment of the relationship between C_aO_2 and microvascular renal and brain PO_2 (phosphorescence quenching of oxyphor G4); cardiac output (CO) and renal and cerebral blood flow (ultrasound Doppler); hypoxia induced cellular responses (brain and kidney erythropoietin (EPO) mRNA and serum protein levels (ELISA)). Statistical analysis (SigmaPlot 14) was performed by ANOVA, Holm-Sidak and Mann-Whitney rank sum test when appropriate. Significance was assigned at $p<0.05$.

Results: In two models of anemia (hemodilution and RBC antibody mediated), acute reductions in blood C_aO_2 were associated with larger decreases in renal microvascular PO_2, relative to brain microvascular PO_2 ($p<0.05$). After acute hemodilution, there was a strong relationship between C_aO_2 and renal microvascular PO_2 ($r^2=0.75$). The magnitude of reduction in renal microvascular PO_2 correlated with the degree of renal EPO mRNA expression and serum EPO protein levels. The magnitude of the increase in EPO mRNA was much larger in the kidney than in the brain ($p<0.03$). While no change in renal blood flow was observed in either model, a significant increase in common carotid and internal carotid blood flow was observed in both models ($p<0.012$). When DO_2 was assessed, the kidney DO_2 was reduced at all levels of anemia ($p<0.01$) whereas brain tissue DO_2 was maintained in mild and moderate (Hb 90 and 70 g/L) ($p=0.44$) anemia but reduced in severe anemia (Hb 50 g/L) ($p<0.02$). The role of active cardiovascular increases in brain blood flow and maintained DO_2 during anemia was impaired by systemic beta blockade, suggesting that active cardiovascular mechanisms are required to maintain optimal brain DO_2 during anemia.

Discussion: Our analysis demonstrated: evidence of quantitative renal PO_2 sensing of changes in C_aO_2; the clamping of renal blood flow (reduced DO_2) during anemia may be a central

mechanism allowing for sensing of changes in C_aO_2; reduced arterial C_aO_2 resulted in a local renal hypoxia response (increased serum EPO) and may have initiated the cardiovascular response to increase cerebral blood flow and maintain cerebral DO_2. Inhibition of the adrenergic system impaired these responses and resulted in reduced brain DO_2. Understanding the heterogeneous adaptive responses to acute anemia may inform clinical practice and optimize management of acutely anemia patients.

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