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NARRATIVE REVIEW

Importance of assessing biomarkers and physiological parameters of anemia-induced tissue hypoxia in the perioperative period

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Abstract Anemia is associated with increased risk of Acute Kidney Injury (AKI), stroke and mortality in perioperative patients. We sought to understand the mechanism(s) by assessing the integrative physiological responses to anemia (kidney, brain), the degrees of anemia-induced tissue hypoxia, and associated biomarkers and physiological parameters. Experimental measurements demonstrate a linear relationship between blood Oxygen Content (C_aO_2) and renal microvascular PO_2 ($y = 0.30x + 6.9$, $r^2 = 0.75$), demonstrating that renal hypoxia is proportional to the degree of anemia. This defines the kidney as a potential oxygen sensor during anemia. Further evidence of renal oxygen sensing is demonstrated by proportional increase in serum Erythropoietin (EPO) during anemia ($y = 93.806*10^{-0.02}$, $r^2 = 0.82$). This data implicates systemic EPO levels as a biomarker of anemia-induced renal tissue hypoxia. By contrast, cerebral Oxygen Delivery (DO_2) is defended by a profound proportional increase in Cerebral Blood Flow (CBF), minimizing tissue hypoxia in the brain, until more severe levels of anemia occur. We hypothesize that the kidney experiences profound early anemia-induced tissue hypoxia which contributes to adaptive mechanisms to preserve cerebral perfusion. At severe levels of anemia, renal hypoxia intensifies, and cerebral hypoxia occurs, possibly contributing to the mechanism(s) of AKI and stroke when adaptive mechanisms to preserve organ perfusion are overwhelmed. Clinical

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methods to detect renal tissue hypoxia (an early warning signal) and cerebral hypoxia (a later consequence of severe anemia) may inform clinical practice and support the assessment of clinical biomarkers (i.e., EPO) and physiological parameters (i.e., urinary PO_2) of anemia-induced tissue hypoxia. This information may direct targeted treatment strategies to prevent adverse outcomes associated with anemia.

Introduction: evidence that anemia poses a risk to patients

Anemia is prevalent worldwide, and negatively influences diverse patient populations including neonates,[1,2] children,[3] young adults,[4] pregnant women[5,6] and the elderly.[7,8] The risk posed by anemia has been assessed in terms of its global impact[9] and its impact on clinical outcomes in patients undergoing surgical procedures.[10,11] In perioperative patients, acute and chronic anemia are associated with increased brain, heart and kidney injury, and increased mortality by currently undefined mechanisms.[10,12] Assessment of patients with severe acute surgical-induced anemia, particularly those who refuse treatment with blood transfusion, strongly suggest that mortality is proportional to the severity of anemia.[13–18] Thus, assessing the impact of anemia on oxygen delivery to tissues and the physiological adaptation to anemia may provide a clinically relevant understanding of potential mechanisms of anemia-induced organ injury, and additional underlying mechanisms responsible for anemia-induced morbidity and mortality. We propose that careful review of experimental and clinical studies may help to direct the development of novel treatment pathways to improve outcomes for anemic patients.

Anemia is associated with perioperative morbidity and mortality

As previously reviewed,[10,12] preoperative anemia is prevalent and has been associated with severe adverse outcomes, including Acute Kidney Injury (AKI), myocardial injury, stroke and mortality. In a large systematic review and meta-analysis, in which 39.1% (371,594 of 949,445) of patients were anemic, the odds ratios for increased mortality in anemic patients undergoing non-cardiac (OR = 2.87 [2.10, 3.93]) ($p < 0.001$) and cardiac surgery (OR = 2.98 [2.02, 4.38]) ($p < 0.001$) indicate that anemia poses a significant risk to perioperative patients.[19] In addition to increasing the utilization of acute treatments, including RBC transfusions (OR = 5.04 (4.12, 6.17]) ($p < 0.001$), anemia was associated with increased risk of Acute Kidney Injury (AKI) (OR = 3.75 (2.95, 4.76]) ($p < 0.001$) and stroke (OR = 1.28 (1.06, 1.55]) ($p = 0.009$).[19] Given the association between anemia, Acute Kidney Injury (AKI) and stroke, we focused our review and analysis on the potential mechanism of injury for these vital organs.

Evidence of acute anemia-induced kidney injury

Based on analysis of retrospective data, anemia is a predictor of acute kidney injury following both non-cardiac[20] and cardiac surgery.[19,21–23] The incidence and severity are more prominent for patients undergoing cardiac surgery, in which the severity of intraoperative anemia is proportional to the degree of AKI.[24] Experimental studies suggest that the mechanism of anemia-induced AKI may be related to the degree of anemia-induced renal tissue hypoxia.[25,26] The importance of renal tissue hypoxia during heart surgery and Cardiopulmonary Bypass (CPB) has been emphasized by studies which demonstrate an association between low urinary PO_2, which reflects renal medullary PO_2, and AKI post-cardiac surgery.[27,28] The link between anemia and renal hypoxia is strengthened by an experimental study demonstrating that the combination of anemia and CPB resulted in the lowest levels of renal medullary tissue PO_2.[29] Furthermore, in a small prospective study, acute hemodilutional anemia was associated with increased serum Erythropoietin (EPO) levels (hypoxic response), and acute decline in renal function.[30] Further clinical studies utilizing these available techniques are needed to determine if there is a direct link between anemia, renal hypoxia, and AKI, and if treatments (including treatment of preoperative anemia and targeted RBC transfusion) can positively influence outcomes.

Evidence of anemia-induced cerebral injury (stroke)

Case series in severely anemic patients secondary to acute blood loss demonstrated evidence of "watershed" cerebral infarction associated with inadequate cerebral tissue perfusion.[31] Assessment of patients with sickle cell anemia[32] demonstrate evidence of cerebral ischemia and stroke at Hemoglobin (Hb) thresholds below 70 $g.L^{-1}$. In these young patients, a baseline Hb below 70 $g.L^{-1}$ was associated with an increased hazard ratio for silent ischemic infarcts (HR = 2.79 [1.43, 6.17]) ($p = 0.004$).[32] For patients undergoing non-cardiac surgery, coordinated experimental[33–36] and clinical studies[37,38] suggest that the impact of anemia, in combination with β-blockade, accentuates cerebral tissue hypoxia and stroke incidence.[35–37] Anemic patients undergoing cardiac surgery and CPB have an increased risk of stroke.[19,21–23] An experimental study suggests that the mechanism includes global reduction in brain Oxygen Delivery (DO_2).[39] In clinical studies, the severity of acute intraoperative anemia secondary to blood loss and hemodilution during CPB was associated with increased stroke incidence,[24] supporting a possible causal relationship between anemia-induced cerebral hypoxia and stroke.[39,40] Understanding the mechanism(s) associated with anemia-induced cerebral hypoxia is a central goal of experimental studies, which define the hemoglobin threshold for cerebral hypoxia associated with acute anemia.[41]

Summary of the cardiovascular adaptation and renal and cerebral blood flow responses to anemia

In 1807, Halle published one of the earliest descriptions of the physiological responses of severe acute anemia: "We think it proper to give this disease the name of *Anemia* (deficiency of blood)" in which "the heart. . .beat(s) very strongly against the ribs".[42] This clinical observation strongly links the impact of anemia on cardiovascular responses, including Cardiac Output (CO) and cerebral blood flow.[43,44] Experimental and clinical studies demonstrate that CO and CBF increase in proportion to the degree of anemia in animal[25,41,43–46] and human studies.[47,48] These well characterized cardiovascular responses to anemia tightly defend brain perfusion. However, despite these cardiovascular adaptations to maintain cerebral perfusion, at more sever levels of anemia (Hb ~50 $g.L^{-1}$) healthy volunteers demonstrate evidence of cognitive dysfunction and reduced neuronal transmission, suggesting that the compensation to severe anemia is incomplete.[49,50]

In order to explore the potential mechanisms, translational studies in mammals have assessed the impact of acute anemia on cardiovascular responses and characterize different patterns of kidney and brain perfusion.[25,41,43–46] These studies assessed the adaptive responses to anemia, and the point at which these mechanisms are overwhelmed.[25,26,34,41,51–54] Measurement of organ specific hypoxic gene expression has been utilized to demonstrate specific levels of anemia-induced in the kidney and brain. At comparable Hb levels, more severe levels of tissue hypoxia are observed in the kidney, relative to the brain.[41]

In these studies, we have characterized that stabilization of the hypoxic transcription factor Hypoxia Inducible Factor-α (HIF-α) occurs in both kidney and brain during anemia.[41,54] At the cellular level, HIF-α is a hypoxic transcription factor that activates a number of hypoxia responsive genes including Erythropoietin (EPO). In addition, we have demonstrated that the HIF-α response requires upregulation of another hypoxia regulated gene, neuronal Nitric Oxide Synthase (nNOS).[41,51,54] When nNOS is genetically deleted, the HIFα response is greatly attenuated leading to impaired cardiovascular responses to anemia and reduced survival in acutely anemic rodents.[54] These data are consistent with the hypotheses that: 1) Acute anemia leads to organ specific levels of tissue hypoxia, which is most severe in the kidney;[25,26] 2) Renal tissue hypoxia may activate local hypoxic responses (EPO production/secretion in the kidney) and adaptive cardiovascular responses (increased cardiac output, cerebral blood flow) to maintain brain perfusion;[30,41,54] and 3) These cellular and cardiovascular responses can be measured in anemic patients as potential biomarkers of anemic tissue hypoxia.

At severe levels of anemia, renal hypoxia may become a maladaptive mechanism associated with AKI.[25–27,30] Similarly, during mild to moderate anemia, adaptive changes in CO and Cerebral Blood Flow (CBF) may maintain cerebral DO_2 at a level that maintains cerebral function. However, at more severe levels of anemia, cerebral perfusion may become inadequate, resulting in cellular evidence of tissue hypoxia, and possible stroke.[35,36,41,51,54] In order to better understand the adaptive integrative physiological responses to acute anemia, and potential biomarkers of anemia-induced hypoxia, we undertook a re-analysis of the primary data from a number of previously published studies.[25,36,40,41,52–54] A summary of these integrated physiological responses to anemia, and potential means of their clinical assessment are outlined in Figure 1.

Strategy for assessment of the integrative physiological responses to acute anemia in animal models

In order to assess the impact of changes in blood Oxygen Content (C_aO_2) on physiological parameters, including brain and kidney microvascular PO_2, cardiac output, organ blood flow, and Oxygen Delivery (DO_2), we searched for experimental studies using the following search strategy based on outcomes from several previously published studies:[25,36,40,41,52–54] "tissue oxygen or PO_2" and "kidney or brain" and "anemia or hemodilution". We captured 897 studies on our initial search and selected studies that: 1) Provided data for calculation of blood Oxygen Content (C_aO_2) and that also included 2) Assessed physiological responses at more than one level of anemia and/or 3) That provided measurements for both kidney and brain tissue hypoxia (PO_2). Five of 897 searched studies met the inclusion criteria.[25,26,36,41,54] (Table 1). Of the 892 excluded studies, 4 additional experimental studies provided data which support our proposed hypothesis but were excluded due to inadequate data to directly correlate C_aO_2 with measured parameters including kidney and brain microvascular PO_2.[44,53,55,56]

We re-evaluated data from the five selected studies and performed new analysis utilizing blood C_aO_2 as the independent variable. All data are reported as individual data points, scatter plots or box plots, and Analysis of Variance (ANOVA) was performed to compare changes in measured parameters vs. changes in C_aO_2. Appropriate statistical analysis and regressions were performed utilizing SigmaPlot 14.0 with statistical significance being assessed at and alpha value of $p < 0.05$.

Evidence that the kidney is a biosensor of blood oxygen content (C_aO_2)

Measurements of microvascular kidney tissue PO_2 (P_kO_2) were made using an intravascular oxygen sensitive phosphorescent dye (Oxyphor G4).[25,26,36] From the available arterial blood gas and co-oximetry measurements, the arterial Oxygen Content (C_aO_2) was calculated from the hemoglobin concentration, pO_2 and SO_2 ($C_aO_2 = 1.34*Hb*SO_2+0.0031*pO_2$). We plotted P_kO_2 vs. C_aO_2 and generated a regression line and r^2 value (Fig. 2). The results demonstrate that there was a direct correlation between changes in C_aO_2 and microvascular renal PO_2, providing a means for the kidney to translate changes in C_aO_2 to local tissue PO_2. Sensing and responding to local changes in PO_2 developed teleologically as a survival mechanism for early aerobic life,[57] and continues to be critical for complex organism (mammalian) survival.[58] There is also evidence of a proportional increase in sympathetic nerve activity with progressive anemia, which supports the hypothesis that "sensed" tissue hypoxia is translated into an autonomic signal during acute anemia.[59] Evidence that the kidney is important in both sensing and transmitting an afferent "warning" signal to the central

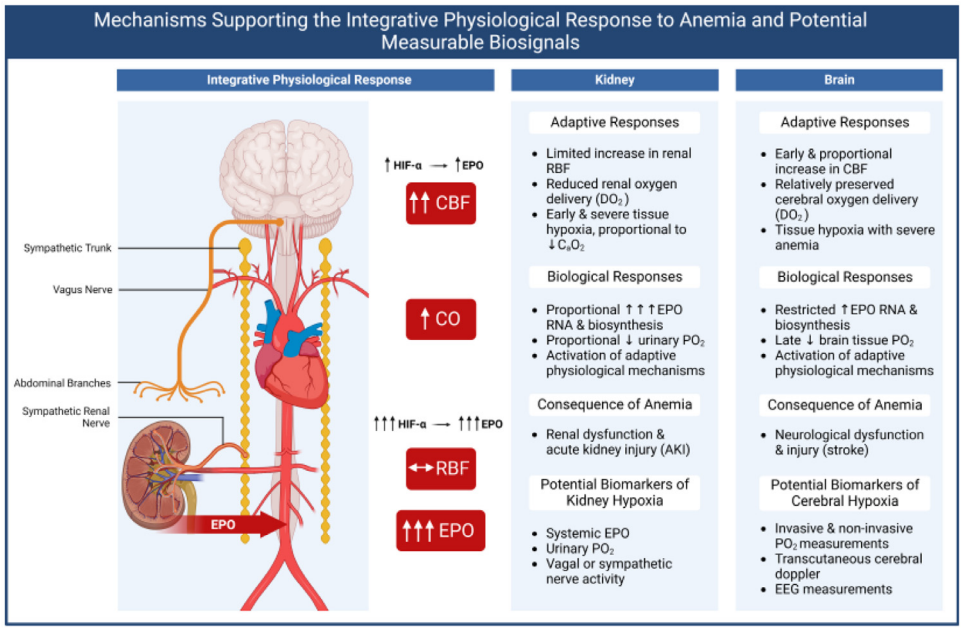

Figure 1 Summary of integrative physiological responses to anemia and potential means of clinical assessment. Under anemic conditions, renal blood flow is maintained but associated oxygen delivery is decreased. This allows the kidney to sense decreases in blood oxygen content. Renal Erythropoietin (EPO) production is greatly stimulated at all levels of anemia in response to stabilization of Hypoxia-Inducible Factor-alpha (HIF-α). The lack of increased Renal Blood Flow (RBF) makes the kidney susceptible to hypoxia and Acute Kidney Injury (AKI). By contrast, the brain is protected to an extent during anemia via an increase in cerebral blood flow, allowing maintenance of oxygen delivery in mild to moderate anemia. Brain tissue hypoxia in response to severe anemia is associated with increased HIFα and EPO expression and may contribute to neurological injury and stroke. Biomarkers to identify renal and brain hypoxia are listed. This figure was created in BioRender.com. CBF, Cerebral Blood Flow; CO, Cardiac Output; DO_2, Oxygen Delivery; C_aO_2, Arterial Oxygen Content.

nervous system is supported by preliminary data demonstrating that removal of the kidneys (bilateral nephrectomy) is associated with profound brain hypoxia in control and anemic animals.[60] Thus, oxygen sensing by the kidney and other cells appears to be a critical starting point which initiates adaptive responses to anemia. Measurements of biomarkers of renal tissue hypoxia may help us to utilize this warning signal to optimally treat acutely anemic patients.[27,30]

Table 1 Inclusion criteria for references that provided adequate data for analysis.

Reference	Experimental model	Inclusion Criteria (A plus B and/or C)		
		A Individual data for C_aO_2 available	B Assessed > One level of anemia	C Measure PO_2 outcomes in both kidney and brain
Abrahamson JR. Am J Physiol. 2020[25]	Rat hemodilutional anemia	Yes	Yes	No
Chin K. Can J Anesth. 2021[26]	Rat hemodilutional anemia	Yes	Yes	No
Ragoonanan T. Anesthesiology 2009[36]	Rat hemodilutional anemia	Yes	No	Yes
Tsui AKY. Proc Nat Acad Sci. 2011[54]	Mouse hemodilutional anemia	Yes	Yes	Yes
Tsui AKY. Am J Physiol. 2014[41]	Mouse hemodilutional anemia	Yes	Yes	Yes

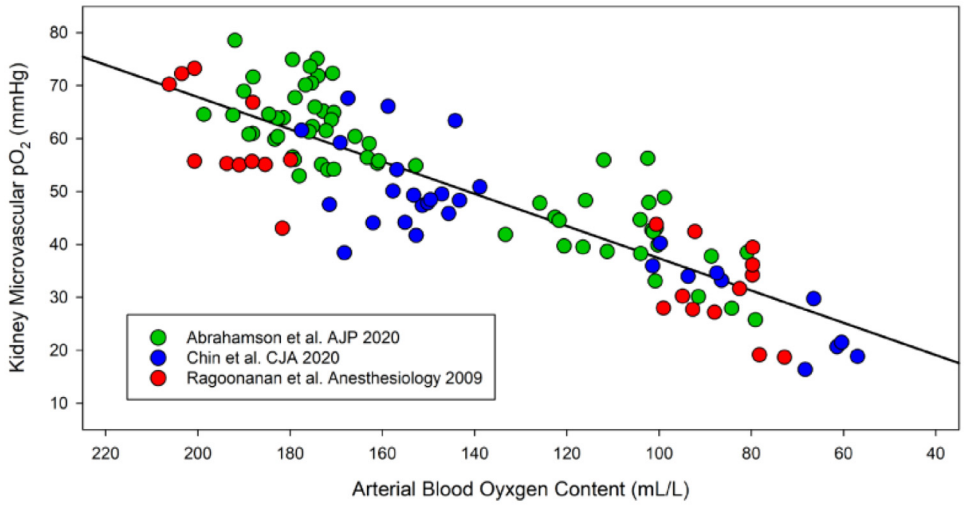

Figure 2 Scatterplot of the relationship between kidney microvascular PO_2 versus arterial blood oxygen content in anesthetized Sprague-Dawley rats exposed to acute hemodilutional anemia. A significant correlation ($y = 0.30x + 6.9$, $r^2 = 0.75$) is observed between microvascular kidney tissue PO_2 and arterial oxygen content. As arterial oxygen content decreases, microvascular kidney tissue PO_2 decreases proportionally in a linear manner. This data demonstrates the ability of the kidney to translate C_aO_2 into a local regional microvascular PO_2 based on organ blood flow and tissue metabolic requirements. Data from Abrahamson et al., AJP 2020[25] (n = 8); Chin et al., CJA 2021 (n = 5);[26] and Ragoonanan et al., Anesthesiology 2009[36] (n = 5).

Adaptive cardiovascular responses to severe anemia result in differential degrees of tissue hypoxia in the kidney and brain

Our dataset reflects the most fundamental finding during acute anemia: that there is an immediate and proportional increase in CO observed with acute anemia (Fig. 3, upper panel). Despite this clear increase in CO, global DO_2 decreases (Fig. 3, lower panel), particularly at more severe levels of anemia. This finding has been reported in mammals and humans,[41,48] however, the subsequent impact on end organ perfusion, tissue hypoxia, and hypoxic gene expression has been lacking. We assessed the impact of different levels of acute anemia on cerebral and renal blood flow and DO_2 in response to mild, moderate, and severe anemia (Hb $\sim$ 90, 70 and 50 $g.L^{-1}$, respectively)[41] (Fig. 4). Comparison of the renal and brain perfusion demonstrate that renal blood flow is not increased during anemia and therefore, renal DO_2 decreases progressively (Fig. 4). This leads to a dramatic increase in hypoxic gene expression including EPO whose RNA expression increased 10,000-fold (Fig. 5, upper panel). By contrast, the brain is relatively protected from tissue hypoxia by a progressive increase in CBF, resulting in a less profound decrease in DO_2 and relatively preserved brain PO_2 as indicated by a relatively small increase in hypoxia EPO RNA expression (10-fold) (Figs. 4 and 5).

A key systemic response to anemia induced renal tissue hypoxia is the secretion of EPO into the blood, the magnitude of which is proportional to the degree of acute anemia (Fig. 5, lower panel). While knowledge of this response is decades old,[61] the clinical utilization of this robust bio signal of tissue hypoxia has been lacking. Our animal studies demonstrate that EPO is amongst the most sensitive HIF responsive molecule in the kidney and brain.[25,41,53,54] Furthermore, in a small prospective study in humans undergoing heart surgery, we have identified that postoperative serum EPO levels correlated to reduce Hb on CPB and systemic lactate levels.[30] In addition, elevated postoperative EPO levels were associated with a trend toward increased creatinine and mild AKI.[30] These data raise the possibility that systemic EPO may be a potential biomarker of anemia induced tissue hypoxia and that a threshold for renal injury may be identified.

Summary of adaptive physiological responses to acute anemia

The key findings of this analysis are as follows: 1) The kidney is capable of detecting changes in blood oxygen content during acute anemia and converting these changes into a local microvascular and tissue PO_2 response providing a mechanism for local hypoxia sensing and increased expression and secretion of EPO during acute anemia;[25,26] 2) Removal of the kidney can severely impair brain perfusion during anemia;[60] 3) The kidney can respond to anemia-induced tissue hypoxia by increasing EPO production in proportion to the degree of anemia,[41] and this response may serve autocrine and paracrine as well as endocrine functions; 4) Adaptive cardiovascular responses to acute anemia may protect vital organs, including the brain, from hypoxic injury;[62] 5) Inhibiting these cardiovascular responses resulted in elevated levels of brain tissue hypoxia, suggesting that they are critical for maintaining cerebral oxygen homeostasis during acute anemia;[34–36] 6) Differences in renal and cerebral hypoxia are reflected by the magnitude of the local EPO mRNA responses, which are directly reflected in EPO transcription and secretion.[41,45]

Human studies reflect the physiological adaptations defined by animal models

The constellations of adaptive responses to acute anemia in animal models is reflected by a number of published clinical

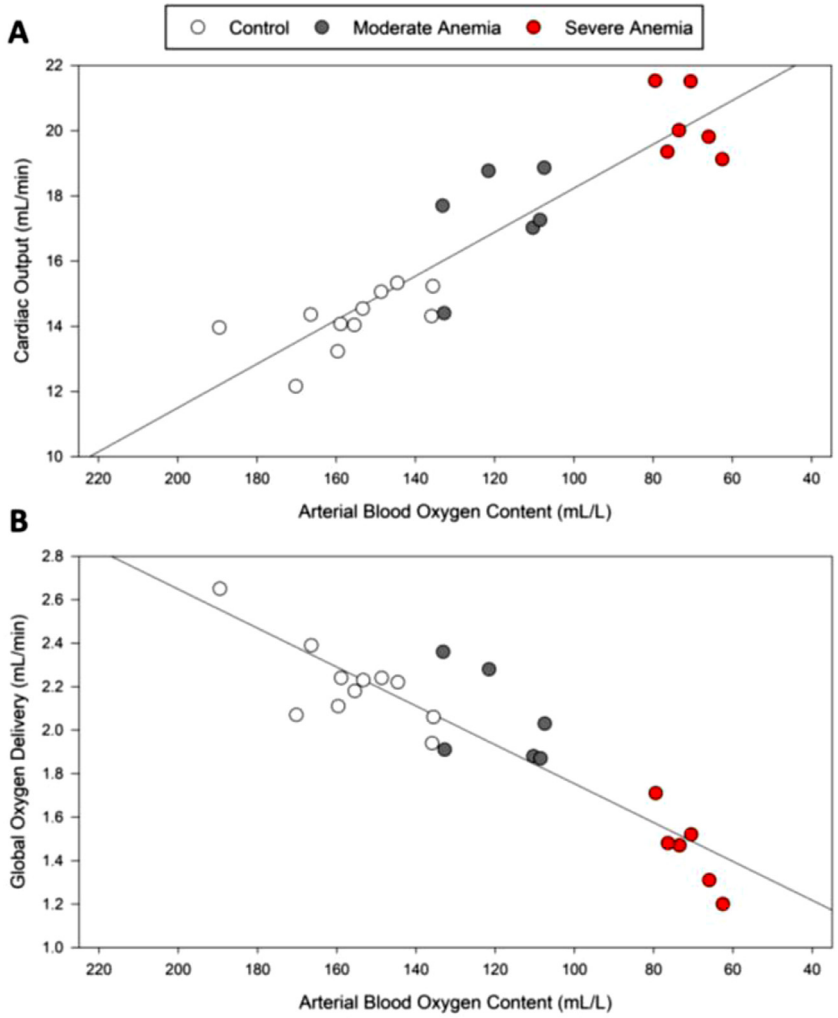

Figure 3 Cardiac output and global oxygen delivery in rats at varying levels of anemia. (A) A strong inverse relationship ($y = -0.07x + 24.9$, $r^2 = 0.83$) is observed between cardiac output and arterial blood oxygen content. Decreasing arterial oxygen content and increasing severity of anemia results in a proportional increase in cardiac output. (B) A strong positive relationship ($y = 0.01x + 0.86$, $r^2 = 0.82$) is observed between global oxygen delivery and arterial oxygen content. Reduced arterial oxygen content results in decreased global oxygen delivery, especially under severe anemic conditions. Data from Tsui et al. 2014.[41]

studies, suggesting that they represent highly conserved mechanism of mammalian adaptation to acute blood loss and anemia.[40,45] In an elegant series of studies in human volunteers, Weiskopf and colleagues, have clearly defined the human cardiovascular responses to acute anemia. They have demonstrated that: 1) The increased cardiac output (heart rate and stroke volume) is directly proportional to the degree of acute anemia;[48] 2) The heart rate response to acute anemia follows a tight linear relationship, suggesting that a sensitive mechanism for anemia detection and proportional responses to acute reduction in C_aO_2 occur;[63] 3) Despite a robust cardiovascular response to acute anemia, evidence of cognitive impairment suggest an inadequacy of cerebral perfusion, and impaired oxygen homeostasis, at severe levels of anemia;[49,50] and 4) Despite these adaptive changes there is a relationship between severe anemia, cardiac injury and mortality. The inability for complete compensation for acute reductions in blood C_aO_2 and subsequent tissue DO_2 are reflected by studies which demonstrate an incidence of vital organ injury (kidney and brain) that is proportional to the degree of anemia following surgery.[22–24] Finally, treatment of anemia with iron, EPO, or blood transfusion improves clinical outcomes and survival in critically ill patients,[64–68] providing proof of concept that treatment of anemia may change the injurious mechanism responsible for organ injury and mortality associated with anemia.[67]

Can measurement of kidney and urinary PO_2 predict hypoxic kidney injury?

Acute kidney injury is prevalent in anemic patients undergoing non-cardiac and cardiac surgery with an estimated 3–4-fold increased risk of AKI in anemic patients (OR = 3.75, 95% CI 2.95–4.76) ($p < 0.001$).[19] Reduced urinary PO_2 is a surrogate of renal medullary hypoxia, and has been associated with an increased risk for AKI.[27,28,69] Measured of urinary PO_2 has been performed during cardiac surgery with the aid of modified urinary catheters placed in the bladder, which contain a real-time PO_2 probe. Two different studies have identified that low levels of urinary PO_2, predominantly at

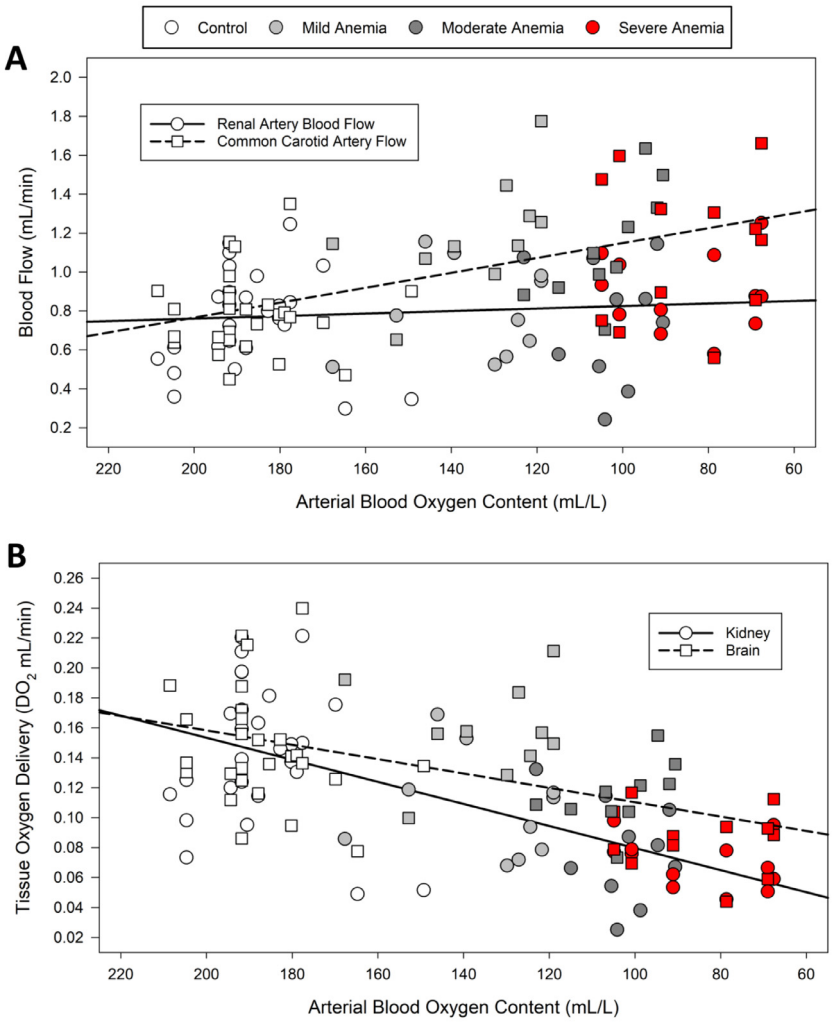

Figure 4 Blood flow and tissue oxygen delivery to the brain and kidney of rats at varying levels of anemia. (A) Renal artery blood flow does not change significantly regardless of anemic status ($y = -0.0006x + 0.89$, $r^2 = 0.14$). Common carotid artery flow increases proportionally as arterial blood oxygen content decreases and anemic status increases in severity ($y = -0.004x + 1.53$, $r^2 = 0.29$) (n = 5). (B) Both kidney and brain DO_2 decrease proportionally as arterial blood oxygen content decreases and anemic status increases in severity. Brain DO_2 ($y = 0.0005x + 0.06$, $r^2 = 0.28$) decreases less profoundly as compared to kidney DO_2 at lower arterial blood oxygen content ($y = 0.0007x + 0.006$, $r^2 = 0.48$) (n = 15). Data from Tsui et al. 2014.[41]

the time of CPB, are associated with impaired renal function.[27,28] In one study, a urinary PO_2 of $\leq$ 15 mmHg for greater than 4.8 minutes per hour, increased the odds ratio for AKI by about 5 fold (OR = 4.9, 95% CI 1.6–14.4) (p = 0.004).[27] In another study, the unadjusted risk of AKI increased by 50% if the mean urinary PO_2 was below 25 mmHg (RR = 1.51 [1.08–2.10]) (p = 0.015).[28] A multivariate analysis identified mean urinary PO_2 to be an independent predictor of AKI (RR = 0.82, 95% CI 0.71–0.950, p = 0.009) for every 10 mmHg decrease in urinary PO_2.[28] Despite experimental evidence that low Hb on CPB worsens renal medullary PO_2,[29] low Hb or Hct was not a risk factor for AKI in these studies.[27,28] Utilizing methods to measure urinary PO_2 may also help to elucidate the impact of fluid management for patients in the ICU and operating room. For example, the negative impact of utilizing intravascular starch for fluid resuscitation on AKI and mortality may be reflected by changes in renal PO_2.[70,71] Experimental evidence suggests that the mechanism of starch induced renal dysfunction may lower kidney PO_2.[25] Further clinical studies would be required to test this hypothesis and assess whether or not assessing the impact of anemia on renal hypoxia, and its treatment, can improve renal outcomes in anemic patients undergoing surgery and critical care.

Can cerebral monitoring predicate the risk of stroke and cerebral dysfunction in anemia surgical patients?

The risk of stroke associated with anemia (OR = 1.28, 95% CI 1.06–1.55) (p = 0.009)[19] may be of a lower magnitude than that of AKI, in part due to the strong adaptive increase in CBF to maintain cerebral DO_2. However, the profound negative impact of stroke in perioperative patients,[38] particularly in patients undergoing cardiac surgery,[24] warrants continued re-assessment. Novel monitoring approaches to minimizing stroke risk include: 1) Near Infrared Spectroscopy (NIRS);[72,73] 2) Direct cerebral oximetry;[74] 3)

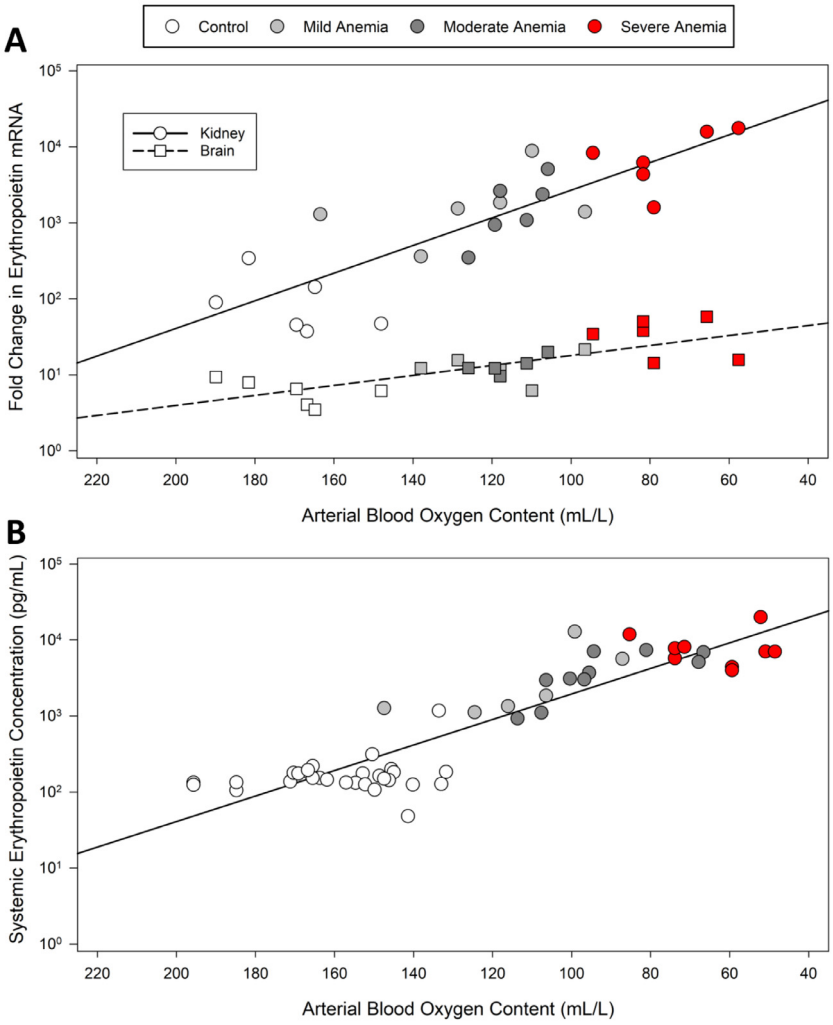

Figure 5 Organ-specific Erythropoietin (EPO) mRNA and systemic EPO versus arterial blood oxygen content in anemic rats. (A) EPO mRNA expression increases exponentially in both kidney tissue and brain tissue as arterial oxygen content decreases (n = 6). Kidney EPO mRNA expression ($y = 178590*10^{-0.018}$, $r^2 = 0.71$) increases more dramatically than brain EPO mRNA expression ($y = 81.72*10^{-0.007}$, $r^2 = 0.57$) in severely anemic conditions. (B) Systemic EPO protein concentration increases exponentially ($y = 93806*10^{-0.02}$, $r^2 = 0.82$) as arterial oxygen content decreases and the severity of anemic status increases (n = 10). Data from Tsui et al. 2011 and 2014.[41,54]

Transcranial Doppler;[75,76] and 4) Processed EEG measurements.[77] In cardiac surgery, NIRS methodology is routinely utilized to assess levels of cerebral perfusion in many centers performing cardiac surgery.[72] These methods effectively detect severe reduction in cerebral perfusion associated with interruption of CPB bypass circuits and during prolonged circulatory arrest.[78] Utilization of NIRS has been proposed for standard monitoring of cerebral perfusion during CPB. Established protocols for optimizing cerebral perfusion have been performed in a few small RCTs. While the clinical demonstration of benefits remains uncertain, the demonstration of feasibility supports the ongoing development of this approach.[72,73] More recently, decline in cerebral oxygen saturation has been associated with increased incidence of delirium and stroke in patients undergoing percutaneous valve replacement, supporting the value of monitoring and treating cerebral oxygen desaturation.[79]

Few clinical settings warrant the placement of direct cerebral oximetry probes in the brain. However, invasive Clarke-type electrodes have been used to assess cerebral perfusion in patients with severe closed head injury and following craniotomy.[74] The hopeful results of the BOOST 2 trial suggest that active treatment of low brain oxygen tension can significantly improve patient outcomes.[74] These data may be confirmed in the ongoing BOOST 3 trial, and may provide evidence that measuring and treating low brain PO_2 may improve outcomes in other type of patients, including those undergoing heart surgeries who have a higher risk of stroke associated with acute anemia.[24]

The well-characterized proportional increase in CBF, associated with anemia, has been assessed by transcranial Doppler in several clinical settings. In the case of anemia, dilation of resistance arterioles results in an increased flow velocity associated with physiological mechanisms to optimize cerebral DO_2. This signal has been used to assess the degree of fetal anemia in utero[76,80] as well as the risk of stroke in young adults with sickle cell anemia.[32,75] The approach in both cases is to use the increased blood flow

velocity signal as a biomarker of adaptive changes in blood flow during anemia, the magnitude of which reflects the degree of anemia. Correlation of the CBF with severity of anemia is used to determine a threshold after which potential cerebral injury and stroke may occur. Once this predefined threshold is reached, the clinical decision to transfuse RBCs has been shown to reduce stroke associated with severe anemia.[32,75] As the physiological mechanism (increased CBF) is shared between differing types of anemia, this approach may be used in surgical patients facing severe acute blood loss. Finally, new advances in assessing changes in evoked EEG patterns may provide means of assessing outcomes including level of sedation, postoperative cognitive decline, and stroke.[77]

Systemic biomarkers of tissue hypoxia may predict risk of organ injury

Traditional biomarker of kidney injury, including creatinine, Neutrophil Gelatinase-Associated Lipocalin (NGAL), and cystatin C may predict renal injury following CPB.[69] More recently, there was evidence that the hypoxia-induced molecule EPO may also provide an indicator of AKI.[30] EPO is an erythrocyte-stimulating hormone best characterized by its molecular response to acute anemia.[81] Data supports this physiological response but, with more severe anemia, a strong serum erythropoietic response is associated with hypoxic kidney injury,[30] suggesting that at extremes of anemic stress, the adaptive physiological responses may not be adequate to preserve end-organ function.[30]

While systemic EPO levels are thought to be primarily of renal origin, new evidence has emerged that non-renal sources of EPO may contribute to both local tissue levels and systemic EPO levels.[82] As such, EPO may provide a cytoprotective role via autocrine, paracrine, and endocrine mechanisms. Studies have explored the pleiotropic effects of EPO and provided evidence for potential neuroprotective effects.[83] EPO receptors found on brain tissue modulate anti-apoptotic, antioxidant and other neuroprotective functions particularly in the context of ischemia-reperfusion injury.[83]

Clinical trials have demonstrated a number of interesting findings: critically ill patients with anemia, both acute and chronic, do exhibit a relative increase in serum EPO levels compared to non-anemic patients.[84] In a series of clinical trials, treatment of anemic, critically ill patients with EPO resulted in improved outcomes, including improved survival.[65,66] However, a meta-analysis by Mesgarpour et al. (34 randomized controlled trials and 14 observational studies including 944,856 patients from clinical studies conducted up to 2012) demonstrated no benefit and a possible increased risk of thrombotic events, tempering the use of EPO in this patient population.[85] By contrast, other analyses in patients undergoing elective cardiac and non-cardiac surgery demonstrated efficacy of EPO in avoiding RBC transfusion without any adverse thrombotic events.[86,87] Finally, recent work during the Coronavirus-2019 (COVID-19) pandemic has shown the potential for EPO therapy in patients with COVID-19 ARDS.[88] Thus, systemic EPO levels may serve as a biomarker of anemia-induced tissue hypoxia and organ injury.[30] In addition, exogenous EPO may be effective in treating anemia and subsequent anemia-related organ injury and mortality.

Evidence that targeted treatments of anemia improve outcomes

While the summary assessment of several meta-analysis and systematic reviews suggests that, overall, restrictive transfusion strategies are non-inferior to more liberal strategies,[89,90] a number of patient-specific factors must be considered. In the FOCUS trail, in which the restrictive group was randomized to a Hb threshold of 80 $g.L^{-1}$, about 10% of this group were transfused more liberally due to cardiovascular symptoms and signs of hypoperfusion, including hypotension and tachycardia, indicating that a restrictive transfusion threshold may not be tolerated by all patients.[91] Evidence supports that patients with cardiovascular disease may not benefit from a more restrictive transfusion strategy.[92,93] A sub-analysis of the TRICS 3 study demonstrated that when stratified by age, younger patients had a more favorable composite outcome with more liberal transfusion.[94,95] Finally, the positive outcomes from liberal transfusion, including improved survival in surgical patients undergoing extensive abdominal surgery,[64] support the continuation trials to assess evidence of end-organ hypo-perfusion and injury in specific patients during acute anemia. These positive outcomes also support the concept that appropriate targeting of RBC transfusion may improve patient outcome and survival.

Can iron therapy improve outcomes for anemic patients?

While few studies have assessed the impact of intravenous iron therapy on both hemoglobin levels and patient outcomes, two recent studies warrant mention. The PREVENTT trial assessed the impact of preoperative iron infusion on anemic patients undergoing abdominal procedures. While no difference in mortality, or major morbidity, were observed, the authors did report that iron increased perioperative Hb and significantly reduced hospital readmission in the iron intervention group.[68] Another small but important clinical trial demonstrated that treatment of severely iron-deficient patients in the ICU, with biomarker evidence of tissue hypoxia (reduced hepcidin), resulted in improved survival in these patients.[67] These two studies demonstrate the potential for treatment of anemia to improve important clinical outcomes in perioperative patients. Completion of larger RCTS will be needed to provide evidence which support, or refute, that targeted therapies to treat anemia may benefit patients in terms of improved event free survival.

Limitations

There are limitations to our review. It reanalyzes previous experimental data and thus carries the limitations of the previous work which may limit the generalizability of the reported outcomes. As no long-term chronic assessments of the impact of anemia were analyzed, we lack further research into the chronic effects of anemia. In addition, as the analysis was limited by measurements that focused on

the brain and kidney, the effect of anemia on other organs was not investigated.

Conclusions

Comprehensive analysis of experimental studies characterizes the integrated physiological responses to acute anemia and demonstrates differential responses in the kidney and brain. During acute anemia, kidney perfusion is relatively restricted, and Oxygen Delivery (DO_2) is attenuated, thereby contributing to the kidneys' ability to detect acute changes in blood oxygen content, enabling the kidney to function as an oxygen sensor during acute anemia. At more severe levels of anemia, this mechanism may place the kidney at risk of hypoxic injury. Conversely, cardiovascular adaptation to acute anemia, including a proportional increase in cardiac output and cerebral blood flow, ensures preservation of cerebral DO_2 and brain tissue PO_2. These mechanisms defend against hypoxic cerebral injury, until severe levels of anemia occur. Assessing functional biomarkers and physiological parameters of acute anemia-induced tissue hypoxia (i.e., urinary hypoxia, serum EPO, CBF, cerebral oximetry) may help to detect anemia-induced tissue hypoxia and direct the development of effective treatment strategies, including treatment of anemia and targeted RBC transfusion[30,40] to optimize the management of anemic patients and improve clinical outcomes.

Conflicts of interest

The authors declare no conflicts of interest.

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