Commentary

Physiologic transfusion thresholds, better than using Hb-based thresholds?

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INTRODUCTION

Transfusion of allogeneic packed red blood cells (pRBCs) is one of the therapeutic cornerstones in clinical medicine, aiming to increase oxygen carrying capacity and consecutively oxygen delivery (DO_2) to adequately meet systemic tissue oxygen and metabolic demands. The question of both the right timing as well as the most suitable indicator for pRBC transfusion to avoid both unnecessary transfusion and transfusion-related side effects, as well as anemia-related morbidity and mortality, remains heavily debated. Hemoglobin (Hb)-based transfusion thresholds are still regarded as the gold standard to guide transfusion practice. However, since isolated Hb values do not adequately reflect the relationship between DO_2 and tissue oxygen consumption (VO_2), there is a need for alternative transfusion triggers that might better indicate the limits of acute anemia and the associated risk for tissue hypoxia[1]. This commentary outlines the fundamental physiologic transfusion triggers, discusses the current body of evidence, and contextualizes the role of physiologic transfusion triggers within the complex field of individualized transfusion practice.

HB-BASED THRESHOLDS - THE CURRENT STANDARD

Current transfusion guidelines rely on Hb-based threshold values to inform clinicians when to transfuse pRBCs[2-5]. The most recent guideline from the Association for Advancement of Blood and Biotherapies (AABB) recommends performing pRBC transfusion at a Hb level of 7 g/dL for both adult and pediatric patients who are considered cardio-pulmonary "healthy", whereas in adult cardiac or orthopaedic surgery, as well as in case of cardiovascular comorbidities with limited physiologic reserve, higher transfusion thresholds are recommended (7.5 g/dL and 8 g/dL respectively)[2]. Similar recommendations to use Hb threshold levels between 7 and 9 g/dL as transfusion triggers have been defined by other societies[3-5].

Guidelines tend to differ substantially in their recommendations regarding the use of physiologic transfusion triggers[2-5]. The current AABB guideline does not mention physiologic transfusion triggers, while the European Society of Intensive Care Medicine (ESICM) suggests using Hb-based transfusion thresholds rather than physiologic transfusion triggers[2,3]. On the other hand, the most recent update of the European Society of Anaesthesiology and Intensive Care (ESAIC) guideline for the management of severe peri-operative bleeding recommends specific physiologic

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Blood Transfus. 2025; 23(1): 96-100 doi: 10.2450/BloodTransfus.901
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transfusion triggers (central venous oxygen saturation [$ScvO_2$] or arterial-venous oxygen difference [A-V O_{2diff}]) as a personalized approach to identify patients who might benefit from transfusion[4]. Similarly, the German transfusion guideline explicitly advocates consideration of specific physiologic transfusion triggers (e.g., tachycardia, hypotension, new ECG changes, changes in $ScvO_2$ or lactic acidosis, etc.) as potential indicators of anemic tissue hypoxia to guide transfusion practice[5].

PHYSIOLOGIC PRINCIPLES AND RATIONALE OF PHYSIOLOGIC TRANSFUSION TRIGGERS

According to the physiologic balance between DO_2 and VO_2, VO_2 remains independent of DO_2 under physiological circumstances, since DO_2 remains constant over a wide range, exceeding VO_2 by about 4-fold under resting conditions[6]. Pathologic reductions in cardiac output (CO), impaired arterial oxygenation or a significant drop of Hb levels can cause DO_2 to consecutively fall below VO_2 at rest ("critical DO_2 threshold"), causing VO_2 to become dependent on DO_2, resulting in tissue hypoxia[7]. In case of hemorrhagic anemia causing the DO_2 to fall below the critical threshold, an increase in CO could compensate for the lack of oxygen-carrying capacity and restore DO_2. However, most critically ill patients suffer from impaired cardiac or respiratory function or receive medication (e.g., sedative agents, ß-blockers) which limits the degree of compensation in these patients[1].

The physiological point of cardio-vascular decompensation in anemia is difficult to answer since different organs tend to vary in their individual susceptivity to anemia. Animal data found that the kidney, followed by the intestines, is the first organ whose microvascular oxygen partial pressure declines and becomes dependent on hematocrit, while the myocardium displays a better anemia tolerance[8]. Other animal studies demonstrated that Hb values close to 3 g/dL were associated with a severe reduction in tissue oxygenation, likely representing the lower limit of compensatory mechanisms in acute anemia ("critical Hb value")[9,10]. Nevertheless, pRBC transfusion in daily clinical practice typically occurs at Hb thresholds far higher than the theoretical limits suggested by these animal data[11].

TYPES OF PHYSIOLOGIC TRANSFUSION TRIGGERS

Electrocardiogram changes

Rosenthal *et al.* were one of the first to describe electrocardiogram (ECG) changes due to both bleeding and transfusion[12]. They reported an increased ECG vector during bleeding and a decreased ECG vector after pRBC transfusion, implying that changes in Hb seem to be hidden in the ECG trace. Additionally, animal models displayed significant changes in heart rate variability during hemodilution (Hb <5 g/dL)[13]. A prospective, observational study in neurosurgical patients found a significant correlation between ST-segment changes and changes in Hb values in patients with acute anemia undergoing craniotomy[14]. Nevertheless, no clinical trial so far has investigated the use of ECG changes as a trigger for pRBC transfusion. The main limitations for the use of an ECG as a physiologic transfusion trigger are its low sensitivity and specificity, and the fact that ECG changes are only late indicators of critical anemia.

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS), a non-invasive method to measure and quantify regional tissue oxygenation that allows detecting organ-specific tissue hypoxia, has been widely adopted in perioperative and critical care medicine throughout the past years. However, a recent systematic review found conflicting results regarding its use as a physiologic transfusion trigger[15]. NIRS displayed only a low sensitivity when used to predict the need for transfusion in bleeding trauma patients. However, a reduction in the number of pRBCs transfused was observed in other patient populations, such as those undergoing cardiac or neurosurgery as well as neonatal patients, when NIRS was used to guide transfusion[15].

Since brain tissue partial oxygen pressure ($PtiO_2$) values

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<15 mmHg were found to correlate with a sustained increase in cerebral tissue oxygenation post pRBC transfusion in patients with severe traumatic brain injury (TBI), impaired brain tissue oxygenation, preferably monitored by non-invasive techniques (e.g., NIRS), could support individualized transfusion management in neurocritical patients[16,17]. Despite significant correlations between invasively inserted brain tissue oxygen tension catheters, and NIRS-provided regional oxygen saturation (rSO_2) measurements, the diagnostic accuracy of NIRS to detect episodes of intracerebral hypoxia in severe TBI patients was found to be low and insufficient in predicting brain oxygenation[18].

Due to a lack of validated data in acute anemia and standardization regarding its use, there are currently no recommendations supporting the application of NIRS to guide transfusion practice.

Central venous oxygen saturation and mixed venous oxygen saturation

Central venous oxygen saturation ($ScvO_2$) and mixed venous oxygen saturation (SvO_2) reflect the relationship between DO_2 and VO_2. This allows for monitoring the degree of tissue oxygen extraction and, therefore, the competence of cardio-vascular compensation mechanisms. Pappachan *et al.* demonstrated a significant correlation between changes in Hb and $ScvO_2$ concentrations in patients experiencing acute blood loss during craniotomy[14]. Two recently published randomized controlled trials (RCTs) investigated the use of $ScvO_2$ to guide transfusion in adult cardiac surgery patients[19,20]. $ScvO_2$-guided transfusion (Hb <9 g/dL + $ScvO_2$ levels ≤65%) resulted in a 32% reduction of pRBC transfusions in the ICU compared to a Hb-based transfusion policy[19]. Similarly, Fisher *et al.* demonstrated that an individualized transfusion strategy based on a $ScvO_2$ threshold of 70% allowed for a more restrictive RBC transfusion strategy without negative impact on postoperative morbidity or 6-month mortality[20].

Despite these promising results, data are still limited regarding the complex interaction between Hb, $ScvO_2$, and SvO_2. A decline in both $ScvO_2$ and SvO_2 does not necessarily mean that tissue oxygenation is compromised. Further, the value of both parameters is questionable in clinical situations where tissue oxygen extraction and utilization are impaired (e.g., septic shock). Additionally, other conditions (e.g., impaired arterial oxygenation, low CO, etc.) can modulate both $ScvO_2$ and SvO_2, thus limiting their applicability as transfusion triggers.

Arterial lactate levels

Plasma lactate levels are recognized as potential indicators of tissue hypoxia and anaerobic metabolism. In bleeding trauma patients, elevated lactate levels can identify patients at risk for requiring massive transfusion, and/or endovascular or surgical hemorrhage control[21]. However, data regarding other patient populations are missing. Pappachan *et al.* failed to show a correlation between lactate levels and Hb or $ScvO_2$ changes in neurosurgical patients experiencing acute blood loss[14]. Animal and human studies on severe isovolemic anemia have indicated that elevated arterial lactate levels are a late sign of acute anemia, since they do not tend to rise until Hb levels fall below a critical level of 5 g/dL[10,22]. Furthermore, lactate is not specific for tissue hypoxia, given that several other clinical conditions can induce hyperlactatemia (e.g., liver failure, ß-receptor agonists, metabolic stress, drugs, etc.).

Arterial-venous oxygen difference

Arterial-venous oxygen difference (A-V O_{2diff}) is the difference between the oxygen content in arterial and venous blood, and can act as a surrogate parameter for the ratio between DO_2 and VO_2. A prospective, observational study demonstrated that A-V O_{2diff} could identify critically ill patients who benefit from pRBC transfusion[23]. The transfusion of pRBCs in case of an elevated A-V O_{2diff} >3.7 mL, while withholding pRBC transfusion in normal A-V O_{2diff}, was associated with a lower 90-day mortality and more rapid organ recovery. The A-V O_{2diff} may represent a good marker of the patient's oxygen reserve[23]. Additional data is needed to externally validate these promising findings.

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Blood Transfus. 2025; 23(1): 96-100 doi: 10.2450/BloodTransfus.901

CONCLUSIONS

The concept of physiologic transfusion triggers might offer a more individualized, patient-centred approach, integrating both patient-specific physiologic compensatory mechanisms and organ-specific anemia tolerance capacities, as opposed to the pragmatic, "one-size fits all" approach of traditional Hb-based transfusion thresholds. However, most data on physiologic transfusion triggers stem from animal models and basic research. Only limited data regarding the use of physiologic transfusion triggers in daily clinical practice are available, in contrast to a magnitude of RCTs and meta-analyses investigating Hb-based transfusion strategies. Future research is needed to evaluate the potential benefit of a physiologic transfusion trigger-based transfusion policy.

ETHICAL CONSIDERATION

This study did not involve human or animal subjects or records of human patients. No ethical approval was required. The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

AUTHORS' CONTRIBUTIONS

All Authors have contributed equally to the work. All Authors have read and reviewed the final version of the article and approve it for publication.

CONFLICTS OF INTEREST

JM is the current chairman of NATA (Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis), and is a member of the Research Committee and the Forum Chair for Intensive Care of Forum 4 (Therapies) of the ESAIC (European Society of Anaesthesiology and Intensive Care). JM serves as the Guest Editor of the monographic issue on "State of the Art and Controversies in Patient Blood Management". All other Authors declare that they have no conflicts of interest.

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