Improvement of Patient Outcomes with Hemoglobin Monitoring in the Critical Care and Perioperative Setting

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Hemoglobin and Oxygen Transportation

Of the many functions of blood, oxygen transportation is among the most critical. Blood provides the liquid medium for hemoglobin (Hgb) molecules that chemically bind oxygen and it is circulated by the cardiovascular system. Blood also has a crucial function to maintain hemodynamic stability. Rapid exsanguination can lead to shock, tissue hypoxia, ischemia and ensuing death. Hypovolemia and anemia are harmful medical conditions that should be properly managed.[1]

Hemoglobin molecules significantly increase the blood's capacity to carry oxygen. The total oxygen content of blood (CaO_2) is the sum of two components: Hgb-bound oxygen, calculated by Hgb concentration × Oxygen saturation (SO_2) × Hgb oxygen binding capacity (approximately 1.39 mL/g)) and plasma-dissolved oxygen, calculated by partial oxygen pressure (PO_2) × water oxygen solubility (approximately 0.031 mL per liter for each 1 mmHg of PO_2). Accordingly, each liter of blood with Hgb concentration of 15 g/dL when leaving the lungs where PO_2 is around 100 mmHg and Hgb molecules are nearly fully saturated with oxygen (SO_2 100%) contains over 210 mL oxygen, of which over 98% is bound to Hgb and less than 2% is dissolved in blood.[1-4] As can be seen, under normal conditions, plasma-dissolved oxygen represents a negligible part of the total blood oxygen content versus what is carried by Hgb. This underscores the importance of Hgb concentration measurement for determining the blood oxygen content.[4]

The total amount of oxygen delivered to tissues across the body (total oxygen delivery, DO_2) is a function of CaO_2 and cardiac output (CO), is calculated by CO × CaO_2. The fraction of delivered oxygen (DO_2) that is consumed by the tissues is known as oxygen consumption (VO_2) and it can be calculated by multiplying CO by the difference in oxygen content of systemic arterial (CaO_2) and venous blood (CvO_2).

Eventually, what determines the adequacy of oxygen delivery to tissues is the ratio of VO_2 to DO_2, known as oxygen extraction ratio (O_2ER). Overall whole-body O_2ER is normally around 20-30%, leaving a large reserve in DO_2 that can meet the tissue oxygen demand in face of significant variations in DO_2 that might occur in anemia (a concept known as "supply independency").[4] Nonetheless, O_2ER varies greatly across various tissues and organs. For example cardiac muscle has a much higher O_2ER (around 60% and more with increased activity levels),[4, 5] which results in increased sensitivity of the heart to anemia and other conditions that reduce DO_2. On the other hand, VO_2 can also increase in pathologic conditions such as critical illness and septic shock, leading to increased O_2ER, and eventually resulting in a situation known as "supply dependency" (usually when O_2ER>50% at rest). When supply dependency occurs, even small increases in VO_2 or small drops in DO_2 can result in oxygen demand exceeding supply, leading to tissue ischemia and injury.[6] This explains why critically ill patients might be at increased risk of morbidity when anemic.

Sensory mechanisms at various levels (e.g., kidneys,[7-9] aortic and carotid body chemoreceptors,[10, 11] and cellular level via hypoxia inducible factor (HIF)[12, 13]) continuously monitor oxygen delivery and consumption in the body. In the setting of acute anemia, the body activates a host of compensatory mechanisms to mitigate the harmful effects of anemia and avoid tissue

hypoxia. Examples include such respiratory adaptations as increased respiration and ventilation, improved ventilation-perfusion matching, along with cardiovascular adaptations such as increased CO, reduced systemic vascular resistance, increased O_2ER in specific tissues, and various metabolic adaptations.[1]

While these compensatory mechanisms are able to limit some of the negative effects of anemia, they should largely be viewed as stopgap measures employed by the body to "buy time" and avoid the more life-threatening and urgent consequence of acute anemia, specifically tissue hypoxia and ischemia. In the meantime, the hematopoietic system is activated to produce more blood cells, paving the way for correction of anemia with time.

The road to anemia recovery is often hindered by lack of the body's ability to restore the balance which explains why anemia is such a prevalent condition. Examples include deficiency of iron and other nutrients needed to make new red blood cells, ongoing chronic blood loss exceeding the body's capacity to replace it, and inflammation which can negatively affect hematopoiesis at various levels.[14] Anemia and its underlying causes are important medical, conditions that require proper diagnosis and management regardless of compensatory mechanisms.[1, 15]

Anemia is commonly defined based on the Hgb concentration dropping below a specific threshold. The most widely used definition is the World Health Organization (WHO) criteria which is Hgb <12 g/dL in adult non-pregnant women and <13 g/dL in adult men. While convenient and easy to understand, this "one size fits all" definition lacks physiologic justification, is largely arbitrary and rooted in epidemiologic surveys. Accordingly, lower Hgb levels are considered "acceptable" in women, merely because women tend to have lower Hgb levels in studied populations.[16]

Anemia is one of the most common health problems globally with even higher prevalence in hospitalized patients, those undergoing surgery and the critically ill. As many as two-thirds of patients admitted to intensive care units (ICUs) have been found to be anemic at admission, and its prevalence continues to increase during ICU stay, reaching as much as 95% within a few days.[17-23]

An extensive body of evidence indicts even mild or moderate anemia as a significant contributor to worse outcomes across various populations. Studies have shown that anemia is independently associated with increased risk of short and long-term mortality and morbidity, including renal and cardiovascular events, poor functional outcomes and increased risk of hospitalization and readmission among many other unfavorable outcomes.[1]

Hemoglobin Concentration in Clinical Practice

Hgb is only one of the several factors involved in ensuring adequate oxygen delivery to the tissues throughout the body. Nonetheless, Hgb concentration in blood remains the most widely used measure to assess the presence of anemia and its severity to guide management strategies, namely various allogeneic blood transfusion guidelines that rely heavily on Hgb concentrations (Table 1).[4, 24-36]

Throughout a century of clinical use, allogeneic blood transfusion has been known as a "gift of life" and has been credited with saving countless lives from exsanguination especially in military and

trauma settings. However, disadvantages range from transmitting deadly blood infections to unsuspecting recipients to contributing to a growing list of adverse outcomes.[1] No medical treatment is free of risks and the challenge is to balance the benefits versus risks when prescribing a treatment.[37]

The purported benefits of allogeneic red blood cell (RBC) transfusion are primarily related to its ability to rapidly increase the blood Hgb concentration, leading to increased oxygen-carrying capacity, in addition to its hemodynamic properties and rheological characteristics, critical in supporting circulation and microvasculature.[38] Although transfusion of RBCs may not readily lead to improved oxygen transportation as the stored RBCs are often deficient in 2,3-diphosphoglycerate and need time to effectively unload oxygen in the periphery, increased Hgb concentration following transfusion is commonly considered to be a positive endpoint that can be easily measured by the clinicians to monitor treatment response. In practice, a review of several studies in the critical care setting has indicated that while Hgb level invariably increased following transfusion in all studies, increased DO_2 was observed in 14 out of 19 studies, and increased VO_2 was seen in only 3 out of 19 studies, and no study reported any significant decrease in markers of ischemia such as lactate level.[34]

On the other hand, the risks of allogeneic blood transfusions are well established.[1] Transmission of infections remains relatively rare thanks to advancements in transfusion medicine and donor screening and current blood bank techniques. But from time to time, we are reminded that the risk persists with emergence of new infections such as West Nile and Zika, and most recently COVID-19 which has been proposed as a theoretical possibility although no case of COVID-19 transmission through transfusion has been reported to date.[39] More importantly, it is now evident that allogeneic blood transfusions are associated with a long list of non-infectious complications that lead to worsening of clinical patient outcomes, namely increased risk of mortality and morbidity and prolonged hospital stay.[1] Similarly, clinical trials have shown that outcomes of adult patients managed with restrictive transfusion strategies, commonly defined based on transfusing patients at Hgb levels below 6-7 g/dL are comparable to and often better than those who were transfused liberally in various settings.[40]

These revelations underscore the heavy reliance on Hgb measurements in clinical settings, as the single most-widely used, albeit inherently limited parameter to make transfusion decisions. Nonetheless, we should not forget that the endpoint is to treat a patient and not a laboratory number which is often limited to sporadic blood draws, measured by instruments that are prone to measurement errors and inaccuracies.[41] Hgb concentration is just that, a concentration, and it may change irrespective of total Hgb mass (e.g. when plasma is expanded), which is a more meaningful parameter.[42] A similar amount of blood loss can have very different implications in two patients with the same baseline Hgb concentration if one patient has a substantially smaller total blood volume, and hence less total Hgb mass. Red cell mass is an alternative measure that is reflective of the total amount of RBCs in the circulation and more accurately assesses the oxygen delivery capacity of blood, but it is not available for routine clinical use.[43]

From a more fundamental perspective, Hgb concentration is a surrogate parameter to assess oxygen carrying capacity of blood without consideration of the total blood oxygen content.

Transfusion decisions should ideally be driven by physiologic indicators of end organ tissue oxygenation and ischemia, the so-called physiologic transfusion triggers.[3] While these physiologic indicators are still far from reaching routine clinical use or being incorporated into available transfusion guidelines, we find no option but to use Hgb concentrations to make routine clinical decisions.

Hemoglobin Monitoring in Clinical Setting

The gold standard laboratory method for Hgb measurement is the Hgb cyanide (HiCN) method but it is not commonly used in clinical setting due to its complexity.[44] Instead, hematology analyzers in central laboratories and point-of-care testing devices are routinely used. These methods are "invasive", as they require collection of blood speciments.[45] Dependency on blood sampling poses a number of problems. Diagnostic blood draws are being recognized as an important cause for iatrogenic blood loss and hospital or healthcare-acquired anemia.[46] Furthermore, there is often some delay in the availability of the results and each measurement can only reflect the status at the time the blood draw took place, unable to capture the possible fluctuations that could happen during scenarios of rapid blood loss and blood and volume replacement. Obtaining more measurements to more accurately capture the fluctuations may subject the patient to more blood draws and blood loss.[41]

Non-invasive Hgb monitoring methods can address these issues as they do not require invasive venipuncture and they monitor the Hgb concentration in shorter, immediately available intervals or even continuously in real-time (Figure 1). The underlying technology of current clinically available noninvasive Hgb monitoring devices is rooted in pulse oximetry. It is noteworthy that pulse oximetry revolutionized anesthesia care by providing a continuous and readily available measure of oxygen saturation at bedside.[47, 48] Noninvasive Hgb measurement devices rely on spectrophotometry and analysis of absorption and reflection patterns of light emitted from sensors placed on the skin to calculate the Hgb concentration and other indices.[47] An alternative method utilizes photoplethysmography, analyzing volume changes during cardiac cycles to determine the Hgb content of blood.[49] Another device combines spectroscopy with temporary pressure-induced occlusion of blood flow to create a specific pattern of optical signals that is used to measure Hgb among other parameters.[50]

Having continuous access to Hgb levels in real-time offers a clear advantage over the traditional measurement methods as it enables the clinicians to detect changes in Hgb levels quickly and adjust the clinical management strategies accordingly (Figure 1). A decreasing trend in Hgb levels, even mild,, can alert clinicians to a potential occult source of bleeding or coagulation issues that can be controlled before blood loss becomes life threatening or warrants transfusion.[41, 47]

One major concern with noninvasive Hgb monitoring is the accuracy.[51] In a study of surgical patients admitted to the ICU, noninvasive Hgb measurements were on average 1±1.7 g/dL higher than laboratory measurements (limits of agreement -2.5 to 4.6 g/dL). Best accuracy was observed in the ranges of 10.5-14.5 g/dL, while accuracy was lowest in Hgb ranges of 6.5-8 g/dL.[52] This has been viewed as a major limitation and an area of particular concern by some, since most transfusion decisions are made at Hgb levels below 8 g/dL and

overestimation of Hgb level by noninvasive method in this range can potentially lead to under-transfusion.[52-55] On the other hand, other studies have reported smaller differences and better agreement between noninvasive Hgb monitoring and laboratory measurements. In a study of 80 critically ill pediatric patients at risk of bleeding, mean difference of laboratory Hgb and SpHb values was 0.07±1.46g/dL, but the difference increased in patients with poor peripheral perfusion or higher temperature.[56] In a meta-analysis covering clinical studies published between 1990 and 2018, the overall difference between non-invasive Hgb monitoring values and laboratory Hgb values was not statistically significant and it amounted to 0.23 g/dL (95% CI -0.16 to 0.62) although high levels of inconsistency between different studies was noted.[57] Another recently published meta-analysis of 28 studies involving 2000 subjects reported an overall difference of -0.27 g/dL (95% limit of agreement -0.10 to 0.44) compared with standard central laboratory Hgb measurement. Accordingly, the authors concluded that noninvasive Hgb monitoring had acceptable accuracy compared with laboratory Hgb measurements.[58] Expectedly, incremental technological advancements and fine-tuning of software and sensors over the years have resulted in improved accuracy of non-invasive Hgb monitoring.[59]

To better put these ranges of error in perspective, many laboratory blood analyzers commonly used in hospitals also face limitations and while their Hgb measurements are generally more accurate, their error can be as much as 1 g/dL or more, with point-of-care blood analyzer having even less accuracy. Often, there might be very limited agreement between Hgb measurements reported by other methods and devices (Figure 1).[47]

Several other studies have looked into the agreement between Hgb measurements using various methods and noninvasive continuous Hgb monitoring in various patient populations. A systematic review and meta-analysis identified 39 studies comparing noninvasive continuous Hgb monitoring values (SpHb, Rad-7™ and Pronto-7™, Masimo, Irvine, CA) or point-of-care Hgb measurements (HemoCue® 201+ or B-Hemoglobin, HemoCure, Brea, CA) versus laboratory Hgb measurements.[60] SpHb levels had an overall difference (mean ± standard deviation) of -0.03±1.42 g/dL (95% prediction interval -0.30 to 0.23, 95% limits of agreement -3.0 to 2.9 g/dL) while HemoCue measurements had an overall difference of 0.08±0.64 g/dL (95% prediction interval -0.04 to 0.20, 95% limits of agreement -1.3 to 1.4 g/dL) compared with reference laboratory measurements.[60]

Another limitation is lack of precision which is represented by the standard deviation of the bias. The overall range has been reported to be as wide as ±1.35 g/dL with limits of agreement ranging between -1.74 to 3.54 g/dL. Finally noninvasive Hgb monitoring requires adequate perfusion, as quantified by perfusion index (PI) which can be a source of error in a hypotensive bleeding patient.

Nonetheless, it should be emphasized that current noninvasive Hgb monitoring devices are not intended to provide direct replacement for laboratory-measured Hgb. Instead, they are highly useful for trend analysis and to monitor temporal changes in Hgb levels as a supplement to laboratory-measured Hgb during the intervals between individual invasive blood sampling and Hgb measurements. While an ideal measurement device offers both high accuracy and high precision, as real-time monitors, trend accuracy (precision) is the more critical

aspect of Hgb monitoring devides.[47] In other words, while the Hgb concentration measured by the noninvasive method at any given time might not be as accurate as the Hgb measured using a laboratory analyzer from a blood specimen obtained at that time, the continued data feed provided by the noninvasive monitoring devices can provide a highly valuable and useful picture of changes in Hgb concentration in real-time and act as an early-warning system. Indeed the word "monitor" comes from *monere* in Latin which means "to warn".[41, 47]

Examples of how such trend analysis can assist clinicians in making better-informed and timelier decisions are provided here: A clinician spotting a downward trend on an Hgb monitoring device can be alerted to order a laboratory Hgb measurement sooner than they would have otherwise done, or if other warning signs are present, accelerate the decision-making process. On the other hand, seeing a stable or increasing trend in noninvasive Hgb levels in ranges well above the common transfusion thresholds and in absence of other potential warning signs can be considered enough reason for a clinician to rely on laboratory Hgb measurements obtained earlier and avoid repeating the measurements, hence reducing iatrogenic blood loss and possibly avoiding an unnecessary transfusion. Finally, in a scenario involving rapidly changing Hgb levels such as rapid loss of blood, volume replacement and transfusion, it is not difficult to envision how laboratory Hgb levels alone may not fully represent the current status of the patient and real-time monitoring can become almost indispensable (Figure 1).[47]

Applegate et al. conducted a multicenter comparison of three methods of Hgb trend monitoring in adults patients undergoing elective arterial catheterization.[61] The methods included pulse CO-oximetry Hgb (SpHb), arterial blood gas CO-oximetry (ABGHb), and a point-of-care analyzer (aHQHb), compared with arterial blood Hgb measured by laboratory (tHb). Changes of more than 0.5 g/dL agreed with changes of more than 0.25 g/dL in tHb in 94.2% of SpHb, 98.9% of ABGHb, and 99.0% of aHQHb cases. The authors concluded that direction of changes in SpHb, ABGHb and aHQHb trends exceeding 0.5 g/dL agreed closely with changes in tHb, although magnitude of changes were in less agreement. They suggested that a drop of >0.5 g/dL in noninvasive continuous Hgb trending can be considered a good indicator for the need to measure tHb.[61]

In a study of 69 patients undergoing spine or cytoreductive surgery, patients were randomly assigned to SpHb monitoring with diagnostic blood draws performed when SpHb decreased by at least 1 g/dL, or standard care with diagnostic blood draws performed at discretion of clinicians. Diagnostic blood draws ordered in SpHb patients were timed better and led to more accurate and timelier diagnosis of anemia in these patients, although no significant difference in transfusion volumes or prevalence of postoperative anemia was observed between the study arms, findings that should be viewed in light of small sample size of the study.[62] Other studies have indicated that use of noninvasive continuous Hgb mentoring is associated with reduced transfusion rates and volume and significantly shorter interval between the time transfusion becomes indicated and the time blood is transfused.[47]

Discussions on the differences between Hgb levels measured by different methods and concerns over accuracy of noninvasive continuous Hgb monitoring should not make us forget the important notion that relying on a single laboratory measure to make clinical decisions is an inherently flawed and

questionable approach. A decision involving allogeneic blood transfusions should ideally not be made solely based on a single Hgb value regardless of the method used to obtain it. Transfusion decisions should be made with adequate consideration of several factors, including the rate and amount of bleeding and if present, signs and symptoms of anemia and hypoxia, and other existing conditions and comorbidities that might make the patient more susceptible to anemia, in addition to Hgb levels and trends (Table 1).[4, 47] Lastly, the response to any drop in Hgb level does not have to result in reflexive transfusion. There are other strategies that can be utilized safely and effectively to reduce the risk of anemia and the need to transfusion. These strategies are formulated collectively under the concept of Patient Blood Management and are intended to pave the way toward improved patient outcomes.[63, 64]

The data provided by noninvasive monitoring devices are often not limited to Hgb values and these devices can provide other parameters that can further assist clinicians. An example is Pleth Variability Index (PVI), which is reflective of respiratory variations in the pulse oximetry plethysmographic waveform amplitude and can be used to monitor fluid responsiveness and volume status.[65] PVI tends to increase as intravascular volume decreases and vice versa. Combining such a measure with noninvasive Hgb monitoring can yield a more comprehensive picture of the hemodynamic and circulatory status of the patients (Figure 2).

While the focus here has been mostly on adult patients, noninvasive Hgb monitoring devices have been studied in pediatric populations as well. Some reports are suggestive of accuracy levels generally comparable to those reported in adult patients,[66] while others indicate somewhat different performance.[56, 67, 68]

The conclusions from most pediatric studies are similar to adult studies, pointing out to the value of noninvasive Hgb mainly in trend monitoring as opposed to being used as the sole criterion for making transfusion decisions.[56, 66-68] It should be noted that Patient Blood Management strategies – including use of noninvasive Hgb monitoring - are applicable to adult and pediatric patients alike.[69]

Conclusions

Continuous Hgb monitoring devices provide highly valuable real-time trending data that can assist clinicians in making timelier decisions. While the accuracy of these devices is often debated and put forward as a case against their use in clinical setting to guide decisions, the limited accuracy of comparators, other than the gold standard HiCN method, should not be overlooked. Studies support the usefulness of these devices, not necessarily as replacement for laboratory Hgb measurements but for trend analysis to supplement other Hgb measurements and improve transfusion utilization and timelier and more appropriate transfusion decisions. Future technological advancements are expected to further improve the accuracy of these devices. Nonetheless, it should be remembered that no single device or measurement can take the place of the clinical judgment of an astute clinician who considers the totality of signs and symptoms of the patient as well as various measurements and monitoring signals to guide the course of management. The ultimate goal is not to treat a number, but to improve the outcomes of the patient, using a host of strategies described under Patient Blood Management to prevent and reduce the risk of anemia and manage it properly. Noninvasive Hgb monitoring devices can greatly contribute to this goal.

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FIGURES & TABLES

Table 1 – Transfusion guidelines and Hgb levels.

	STS (2007)[35, 36]	SCCM (2009)[34]	SIMTI (2011)[31-33]	BCSH (2013)[30]	ATS/AACC/ACCP/SCCM (2014)[29]	ASA (2006, 2015)[27, 28]	NICE (2015)[26]	AAGBI (2016)[25]	AABB (2016)[24]
Target population	Cardiac surgery	Critically ill	Preioperative (general)	Critically ill	Critically ill	Perioperative	General	Hospitalized	Hospitalized, hemodynamically stable
RBC usually indicated	Hgb <6 g/dL (Hgb <7 g/dL in postop and higher if risk of end-organ ischemia)	Hgb <7 g/dL in ventilated, trauma, or stable cardiac disease (Hgb <8 g/dL in acute coronary syndrome)	Hgb <6 g/dL (Hgb 6-8 g/dL if risk factors present; Hgb 6-10 g/dL if symptoms of hypoxia present)	Hgb ≤7 g/dL unless specific co-morbidities or acute illness-related factors modify clinical decision-making; Higher in patients with sepsis, ischemic heart disease or in neuro-critical care (TBI, SAH)	Hgb ≤7 g/dL	Hgb ≤8g/dL may be safely used in general	Hgb ≤7 g/dL as long as patient does not have major hemorrhage or acute coronary syndrome or need transfusion on regular basis for chronic anemia; Hgb ≤8 g/dL for patients with acute coronary syndrome	Hgb ≤7 g/dL in general (same for critically ill unless patient has cardiac disease); Hgb ≤ 7–8 g/dL for patients admitted to ICU with hematological malignancies Hgb ≤8 g/dL in Patients with ischemic heart disease, after cardiac surgery	Hgb ≤7 g/dL in most adults, including critical care patients; Hgb ≤8 g/dL in patients undergoing orthopedic surgery and cardiac surgery and those with existing cardiovascular disease (threshold of 7 g/dL likely comparable to 8 g/dL but more evidence needed)
RBC rarely indicated	Hgb >10 g/dL	Hgb >10 g/dL	Hgb > 10 g/dL	Hgb >9 g/dL	Hgb >7 g/dL in hemodynamically stable, non-bleeding ICU patients	Hgb > 10 g/dL			
Equivocal						Hgb 6-10 g/dL			Insufficient evidence for any recommendations in acute coronary syndrome, severe thrombocytopenia in hematology/oncology patients at risk of bleeding and chronic transfusion-dependent anemia
Factors to consider in making the decision	Age, severity of illness, cardiac function, ischemia, extent/rate of blood loss, Hgb, SVO_2	Volume status, shock, duration/extent of anemia, cardiopulmonary parameters	Rate of blood loss, Hgb level, risk factors, symptoms of hypoxia/ischemia			Rate and magnitude of ongoing bleeding, intravascular volume status, signs of organ ischemia, adequacy of cardiopulmonary reserve.			Hgb levels as well as symptoms (chest pain, orthostatic hypotension, unresponsive tachycardia, heart failure)

Figure 1 - Plot shows real-world data obtained using a non-invasive continuous Hgb monitoring device (Total Hgb [SpHb], Masimo, Irvine, CA) in addition to individual Hgb levels measured using 2 methods (a CO-oximeter and a hematology analyzer) in a patient experiencing rapid changes in Hgb levels. Four points of particular interest are highlighted by letters A-D: At time point A, Hgb levels reported by two other methods vary by almost 2 g/dL, pointing out the fact that other methods used to measure Hgb are not free of error. Time points B and C show how SpHb values can change in a very short period of time (likely reflecting the underlying rapid changes in Hgb concentration), which can significantly inflate the apparent difference between single SpHb values and Hgb levels measured by other methods. Time point D shows how the difference in Hgb readings from other methods can be highly variable (compared with differences at time points A, B and C for example). Actual patient trend plot courtesy of Masimo.[47]

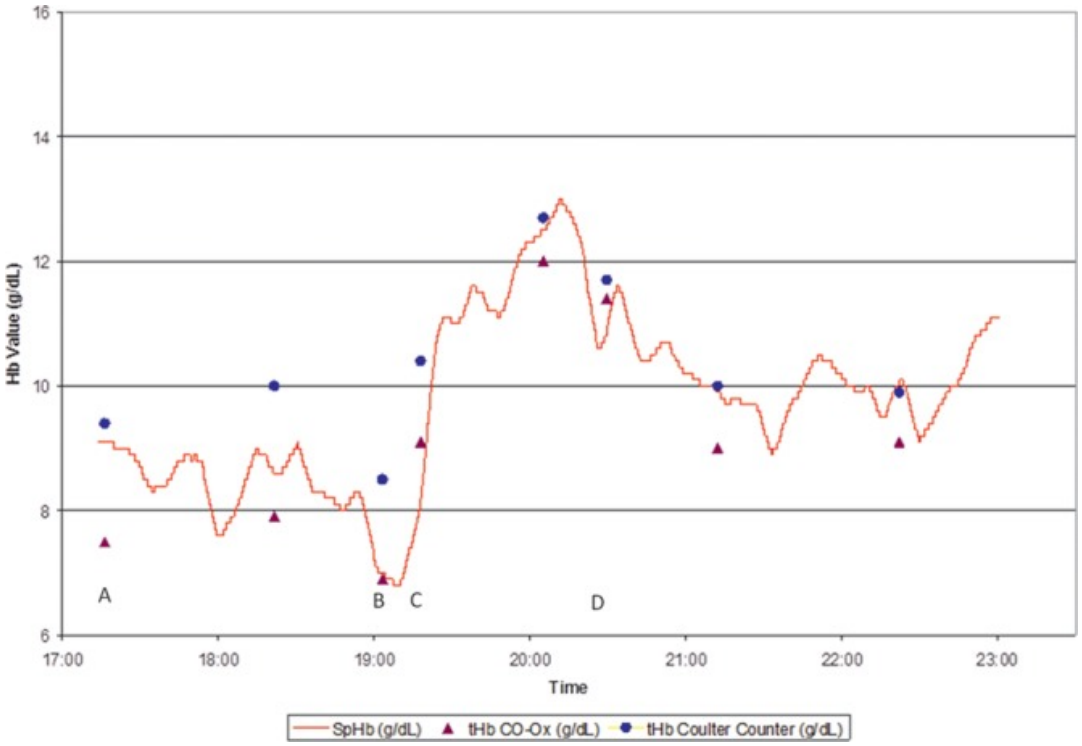
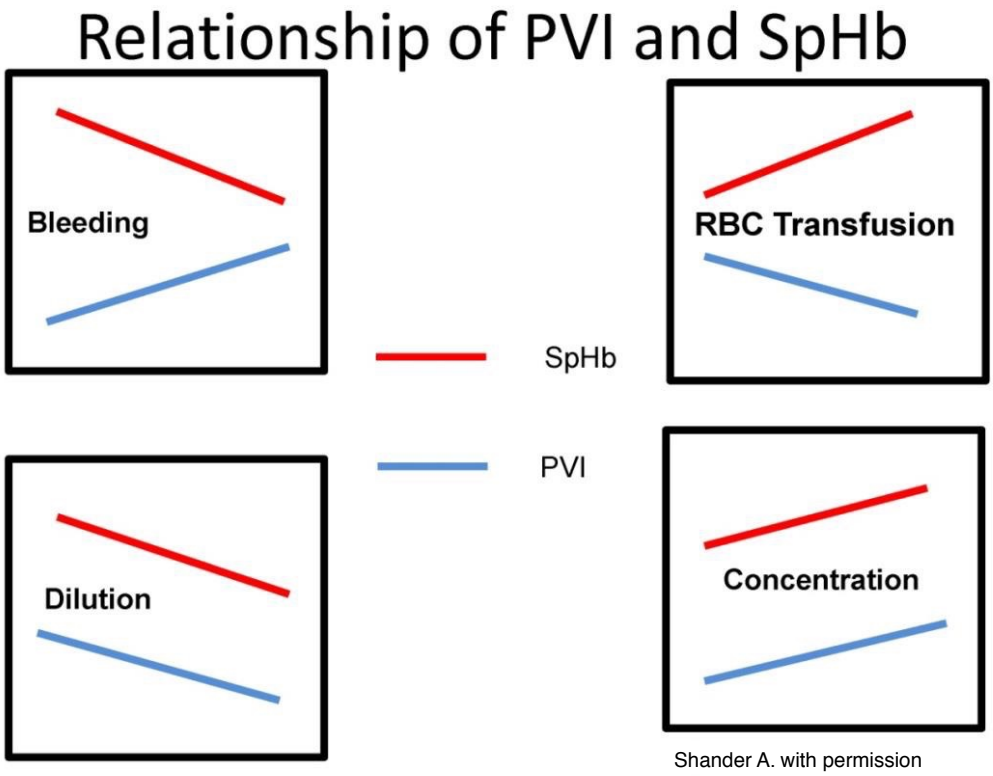


Figure 2 - Relationship of changes in pleth variability index (PVI) and noninvasive total Hgb monitoring (SpHb) in various hemodynamic scenarios.



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