Case Report

Efficacy of Measuring Oxygen Extraction Ratio for Determination of Intraoperative Red Blood Cell Transfusion in a Case with Chronic Normovolemic Anemia

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[Abstract] Allogeneic red blood cell transfusion should not be dictated, unless the patient's oxygen-carrying capacity is decompensated, and the signs and symptoms requiring blood transfusion have been observed. In cases with chronic normovolemic anemia, an increase of 2,3-DPG compensates the patient's oxygen delivery capacity by leading the hemoglobin-oxygen dissociation curve shift to right, thereby allowing the unloading of a normal oxygen amount with a lower concentration of hemoglobin, which makes it difficult to assess the appropriate timing for red blood cell transfusion. Here, we describe the efficacy of measuring the oxygen extraction ratio in such a case.

Key Words : Oxygen extraction ratio, Chronic normovolemic anemia, Red blood cell transfusion

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Introduction

Theoretically, the only indication for allogeneic red blood cell transfusion is to increase the oxygen-carrying capacity¹⁾. Red blood cell transfusion should not be dictated unless the patient's oxygen-carrying capacity is otherwise decompensated and the signs and symptoms requiring blood transfusion have been observed²⁾. With respect to the appropriate timing for red blood cell transfusion, absolute hemoglobin or hematocrit values are of limited value in providing the basis for determining

the requirements for red blood cell transfusion, due to the potential for extreme variation in each individual regarding their need for increased oxygen-carrying capacity.

Oxygen transport and unloading at tissue level is regulated by the affinity of hemoglobin for oxygen, and this affinity is altered by several factors such as changes in the carbon dioxide tension (PaCO_2), pH, temperature, and organ phosphates such as 2, 3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate³⁾. The affinity of hemoglobin for oxygen is best described by the PO_2 level at which

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hemoglobin is 50 % saturated (P_{50}) on the oxy-hemoglobin curve. The normal adult P_{50} value is 26.7 mmHg, and a P_{50} higher than 27 mmHg describes a right-shifted oxy-hemoglobin curve, which means that at any given PaO_2 , hemoglobin has a low affinity for oxygen and is less saturated than normal, thus allowing a lower tissue perfusion than normal to produce the normal amount of oxygen unloading. Abnormalities in hemoglobin concentration also result in alteration of 2, 3-DPG metabolism to shift the oxy-hemoglobin curve, thereby allowing the unloading of normal oxygen amount with a lower concentration of hemoglobin. Thus, a patient with chronic normovolemic anemia may easily compensate for low concentrations of hemoglobin. In an attempt to elucidate the appropriate timing for red blood cell transfusion to transport appropriate oxygen to peripheral tissue in such a case, we found that measurement of the oxygen extraction ratio is efficacious in evaluating the requirements for red blood cell transfusion.

I Case Report

A 53-year-old male, previously diagnosed with myasthenia gravis (MG) and who underwent thymo-thymomectomy 10 years ago, was admitted to our hospital because of shortness of breath and dyspnea. He showed no signs of muscle weakness, suggesting that the MG was in remission. His pleural biopsy showed a recurrence of invasive thymoma. On admission, his hemoglobin concentration was 7.9g/dL with an otherwise normal blood cell count profile, and bone marrow aspiration revealed severe erythroid hypoplasia. Accordingly, a diagnosis of pure red cell aplasia (PRCA) was made. Since his thymoma had diffusely disseminated in his left pleural cavity, he was scheduled for intrapleural

perfusion hyperthermo-chemotherapy under video-assisted thoracoscopic surgery (VATS)⁴⁾.

After the induction of general and epidural anesthesia, radial arterial, central venous, and flow-directed pulmonary arterial (via the right internal-jugular vein; Baxter Healthcare) catheters were inserted. Intra-arterial, central venous (CVP), pulmonary arterial (PAP), and pulmonary capillary wedge pressures (PCWP), heart rates, cardiac index (CI), and mixed venous oxygen saturation (SvO_2) were continuously monitored throughout the surgery. Stroke volume index (SVI), systemic vascular resistance index (SVRI), TO_2 , VO_2 , and CaO_2 (TO_2 , VO_2 , and CaO_2 indicate oxygen transport, oxygen consumption, and arterial oxygen content, respectively) were calculated by the standard formula as described in the previous report⁵⁾. The electrocardiogram (ECG; 5-lead) was monitored, and continuous ST-segment trend was analyzed during the surgery. An ischemic episode was defined as a reversible ST-segment shift from baseline of 0.1mV or greater depression at J+60msec, or 0.2mV or greater elevation at the J point lasting for at least 1 minute.

In the **table**, although his hemoglobin concentration was as low as 4.2 g/dL with apparently lower values of TO_2 and VO_2 than normal individuals on the day of surgery, his oxygen delivery capacity was well preserved as demonstrated by the CI value of 2.4L/min/m², heart rate of 76 beats per minute, SvO_2 of 74 %, and 0.2 of VO_2/TO_2 (20 % of oxygen extraction ratio), suggesting that the compensation of oxygen delivery by the shift in the oxygen-hemoglobin dissociation curve had actually taken place. However, soon after intrapleural perfusion hyperthermo-chemotherapy was begun under the one-lung ventilation, SVRI and SvO_2 started to

Table Peri-operative cardiopulmonary variables and oxygen-delivery profiles

Variables	Pre-operative values	Just before the transfusion	Post-operative values
SVRI (dyne/s/cm ⁻⁵ /m ²)	1,736	1,034	1,383
Heart Rate (beats per minute)	76	96	82
SVI (mL/m ²)	31.57	55.2	46.3
PVRI (dyne/s/cm ⁻⁵ /m ²)	177	80	115
CI (L/min/m ²)	2.4	5.3	3.8
TO ₂ (mL O ₂ /kg/min)	5.13	10.8	9.02
SvO ₂ (%)	74	65	83
Arterial Blood pH	7.479	7.454	7.396
Base Excess (mEq/L)	0.4	0.5	-4.3
VO ₂ (mL O ₂ /kg/min)	1.04	3.29	1.31
Hb (g/dL)	4.2	4.4	5.2
Hematocrit (%)	12.3	13	15.9
CVP (mmHg)	12	17 *	13
PAP (mmHg)	18	22 *	16
PCWP (mmHg)	10	20 *	12
CaO ₂ (mL/dL)	7.113	6.83	7.886
VO ₂ /TO ₂	0.2	0.3	0.14

For abbreviations used in this table, refer to the text.

* These variables reflect the intrapleural direct pressure of hyperthermo-chemotherapy.

decrease, and his heart rate, SVI, and CI increased in response to the increase in VO₂/TO₂ ratio (oxygen extraction ratio), thereby compensating for the increased oxygen consumption under the status of decreased arterial oxygen content, which led us to start the 2 units of red blood cell transfusion, with the cutoff value of oxygen extraction ratio at approximately 30 % and with a body temperature of 37.8°C. No ST changes were observed in the monitored ECG. Two units of red blood cell transfusion totally resolved his observed inadequate oxygen delivery, with an SvO₂ value of 83 %, which was even higher than the pre-operative value, and with an oxygen extraction ratio of 14 %, which was even lower than pre-operative value. Thus, we concluded that a hemoglobin concentration of 5.2 g/dL was sufficient for adequate oxygen delivery.

II Discussion

Despite the recommendations for red blood cell transfusion published to date^{6), 7)}, significant variances in transfusion practice persist between institutions. Although the incidence of transmission of diseases such as human immunodeficiency virus (HIV) and human hepatitis C virus (HCV) has become rare these days, serious complications related to red blood cell transfusion may still occur. The three most common causes of transfusion-related deaths were hemolytic transfusion reactions, septic transfusions, and transfusion-related acute lung injury (TRALI)¹⁾. From 1976 to 1985, 328 deaths related to transfusion have been registered with the US FDA (United States Food and Drug Administration), and 159 of these were from hemolytic reactions⁸⁾. Therefore, blood transfusions,

like all the other medical treatments, should be prescribed only after consideration of the risks as well as the benefits of the therapy.

It is difficult to define the appropriate timing for red blood cell transfusion in a patient with chronic normovolemic anemia, because compensation for low hemoglobin concentration may occur. The problem of using an arbitrary hematocrit value for the initiation of red blood cell transfusion in such a case is that it does not take into account the individual patient's ability to compensate for anemia. For instance, young healthy individuals with normal cardio-respiratory function have been shown to easily compensate for acute isovolemic anemia with a hemoglobin value of 5.0 g/dL⁵⁾. On the contrary, a patient with a history of cardiovascular disease may easily reach his limits of compensation at a hemoglobin value of 5.0 g/dL.

In response to acute isovolemic anemia, which is often seen in the surgical setting, the cardiac output increases significantly, which involves both elevation of the heart rate and stroke volume accompanied by a decrease in systemic vascular resistance. All these responses compensate for the decreased arterial oxygen content, maintaining oxygen transport as hemoglobin concentration decreases⁵⁾. However, the magnitude of these responses may be substantially different depending on the individual patient's ability to compensate for anemia. On the contrary, the oxygen extraction ratio, which is the ratio of whole-body oxygen consumption to oxygen delivery, has been validated as an index of appropriate transfusion together with mixed venous oxygen tension⁹⁾. For instance, a previously healthy patient with postpartum bleeding has been reported to be stable at a hemoglobin concentration of as low as 1.7g/dL at an oxygen

extraction ratio of approximately 40 %, while a 40-year-old traffic accident victim was hemodynamically unstable at a hemoglobin concentration of 3.0g/dL on nasal oxygen (FiO₂ 0.4) with an oxygen extraction ratio of nearly 50 %⁹⁾.

In the anesthetic management of the present case, we also found that the oxygen extraction ratio was quite efficacious in defining the appropriate timing for red blood cell transfusion. The cutoff value of the oxygen extraction ratio we utilized to start red blood cell transfusion in the present case was substantially lower than those described previously^{9),10)}. We utilized a lower value in the present case, considering the effects of one-lung ventilation on arterial oxygenation. During one-lung ventilation, the non-dependent lung is not ventilated and any blood flow to the non-ventilated lung becomes shunt flow, in addition to whatever shunt flow might exist in the dependent lung. Thus, one-lung ventilation creates an obligatory right-to-left trans-pulmonary shunt through the non-ventilated non-dependent lung which is not present during dual-lung ventilation. Consequently, given the same inspired oxygen concentration (FiO₂) and hemodynamic and metabolic status, one-lung ventilation results in a much larger P_AO₂-PaO₂ gradient and a lower PaO₂ than dual-lung ventilation does.

One major drawback in utilizing this variable is the use of a pulmonary artery catheter. In view of the outcome of patients who were critically ill, pulmonary artery catheterization has evoked some controversy. The first and most provocative argument arose from the article written by Connors et al.¹¹⁾, followed by the randomized controlled trial of the use of a pulmonary artery catheter in high-risk surgical patients, which concluded that there

had been no benefit to pulmonary artery catheterization over standard care in the elderly and/or high-risk surgical patients¹²⁾. Accordingly, practice guidelines that indicate the appropriate use of pulmonary artery catheters have been published^{13), 14)}. As the guidelines indicate, apparently the routine use of pulmonary artery catheter in any surgical, or non-surgical setting should be avoided due to the potential risks. However, in certain cases and settings, the benefits may outweigh those risks. Aside from its pressure-monitoring capabilities, the most important feature of the pulmonary artery catheter is its ability to measure cardiac output by the thermodilution method, which virtually enables evaluation, in any given circumstance, of the oxygen supply-and-demand balance in the body including the oxygen extraction ratio.

To the extent that arterial hemoglobin saturation, cardiac output, and oxygen consumption remain stable, mixed venous oxygen tension may also be used as an indicator of the adequacy of hemoglobin concentration and may provide comprehensive information on the adequacy of the oxygen delivery and consumption balance in the body. However, although the normal value of mixed venous oxygen tension is well known, the appropriate therapeutic target value for each individual patient remains uncertain to date. By contrast, recent reports suggest that a 40–45 % oxygen extraction ratio is a feasible value for when to start red blood cell transfusion, and 50 % as close to the critical level where oxygen delivery fails to satisfy the oxygen demand in peripheral tissue in a case with acute isovolemic anemia⁹⁾.

Theoretically, tragic deaths may be easily avoided by continuous monitoring of the oxygen extraction ratio, and by alerting surgeons to the status of

the oxygen delivery-demand balance in the body before reaching that critical level where oxygen delivery fails to satisfy its demand in peripheral tissue, for instance, in the surgical setting with patients who refuse blood transfusion for religious reasons or with those who suffer from hemolysis due to unexpected antibodies.

In summary, we report here the efficacy of measuring the oxygen extraction ratio in the anesthetic management of a case with chronic normovolemic anemia. Measurement of the oxygen extraction ratio is beneficial to patients undergoing elective surgery who refuse blood transfusion for religious reasons or to those who suffer from a shortage of donor blood. It also may ultimately help to reduce blood transfusions, thereby reducing the incidence of the transmission of blood-borne diseases and blood transfusion-related deaths.

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慢性貧血患者での術中の赤血球輸血開始の指標としての 酸素摂取率測定の有用性

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赤芽球瘍を合併した播種性再発胸腺腫の麻酔管理を通じ oxygen extraction ratio (OER; 酸素摂取率) が赤血球輸血開始の有用な指標となると思われた手術麻酔症例を経験したので報告する。症例は53歳、男性。再発胸腺腫胸腔内播種に対し胸腔内温熱化学療法が施行された。患者は赤芽球瘍を合併しており、手術室入室時のHbは4.2g/dLであったが、同時に測定された心係数は2.4L/min/m²、混合静脈血酸素飽和度は74%、酸素摂取率は20%であり、慢性貧血による代償機転が働いていると判断されたため赤血球輸血は施行せず手術開始となった。手術進行とともに心係数は5.3L/min/m²に上昇、混合静脈血酸素飽和度は65%に低下、酸素摂取率は30%に上昇した。代謝が低下している全身麻酔中でのこれらの値の変化は覚醒させた際に代謝が上昇すると耐容能を超える可能性が予測されたため、2単位の赤血球輸血を行ったところ、Hbは5.2g/dLであったが、心係数は3.8L/min/m²に低下し、混合静脈血酸素飽和度は83%に改善、酸素摂取率は14%まで低下し、それ以上の赤血球輸血を必要とすることなく手術終了とともに手術室にて抜管することが可能であった。赤血球輸血の厳密な適応は障害された酸素運搬能の改善にあり、失われた循環血液量の補正のために赤血球輸血が施行されることは容認されない。酸素運搬能の障害の度合いに対しての耐容能が個々の患者により大きく異なるため、HbやHtのみで赤血球輸血の適応は規定されない。慢性貧血患者においては、2, 3-DPGの代謝の変化により酸素解離曲線の右方シフトが生じ、通常の急性貧血よりも貧血に対する耐容能が高くなることが予測されるが、このような症例における赤血球輸血開始の指標は現在まで明確に示されていない。過去の急性貧血における報告ではOERとして40～45%が輸血開始として適正な指標となり、50%が耐容能の限界に近いとの報告もある。待機手術でのエホバの証人の手術麻酔時や、不規則抗体を多くもつために輸血血液の供給に問題がある症例などにOERをモニタリングすることによりOERが40%を超えた場合、手術を一時中断してもらうことなどにより生命に危機的な状況を回避できる可能性がある。今後さらにその有用性を積極的に評価、検討していくべきであると思われた。

Key Words : Oxygen extraction ratio, 慢性貧血, 赤血球輸血

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本症例報告は、読みやすく、教育的価値の高い論文であるが、読者であるわれわれに以下のような問題を提起している。

1. Oxygen extraction ratioを指標として赤血球輸血を開始することの是非。
2. 赤芽球瘍を合併しているとはいえ、Hb 4.2g/dLで手術を開始することの是非。

本症例報告を読んで、上記の点に関しなんらかのご意見(当然、賛成意見も歓迎です)をお持ちの先生方は、本誌「コラム」欄にご意見をお寄せください。

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