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Effects of blood transfusion on oxygen extraction ratio and central venous saturation in children after cardiac surgery

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BACKGROUND: Red blood cell transfusion is common in critically ill children after cardiac surgery. Since the threshold for hemoglobin (Hb) transfusion need is not well defined, the threshold Hb level at which dependent critical oxygen uptake-to-delivery (VO_2-DO_2) status compensation is uncertain.

OBJECTIVES: To assess the effects of blood transfusion on the oxygen extraction ratio (O_2ER) and central venous oxygen saturation ($ScvO_2$) to identify a critical O_2ER value that could help us determine the critical need for blood transfusion.

DESIGN: Prospective, observational cohort study.

SETTING: Cardiac Surgical Intensive Care Unit at Prince Sultan Cardiac Center in Qassim, Saudi Arabia.

PATIENTS AND METHODS: Between January 2013 and December 2015, we included all children with cardiac disease who underwent surgery and needed a blood transfusion. Demographic and laboratory data with physiological parameters before and 1 and 6 hours after transfusion were recorded and O_2ER before and 6 hours after transfusion was computed. Cases were divided into two groups based on O_2ER: Patients with increased O_2ER (O_2ER >40%) and normal patients without increased O_2ER (O_2ER ≤40%) before transfusion.

MAIN OUTCOME MEASURE(S): Changes in O_2ER and $ScvO_2$ following blood transfusion.

RESULTS: Of 103 patients who had blood transfusion, 75 cases had normal O_2ER before transfusion while 28 cases had increased O_2ER before transfusion. Following blood transfusion, O_2ER and $ScvO_2$ improved in the group that had increased O_2ER before transfusion, but not in the group that had normal O_2ER before transfusion.

CONCLUSIONS: The clinical and hemodynamic indicators O_2ER and $ScvO_2$ may be considered as markers that can indicate a need for blood transfusion.

LIMITATIONS: The limitation of this study is the small number of patients that had increased O_2ER before transfusion. There were few available variables to assess oxygen consumption.

Red blood cell transfusion is common in critically ill children after cardiac surgery. Improving oxygen transportation and tissue oxygenation are the main goals of blood transfusion in critically ill patients. Thresholds for red blood transfusions in critically ill pediatric cardiac patient are controversial and not well defined. A higher hemoglobin level is frequently targeted to compensate for hypoxia in children with cyanotic heart lesions.[1] Some experts advocate transfusion thresholds as high as 14 to18 g/dL in critical cyanotic cases.[2] On the other hand, blood transfusion is not without risk. It carries a risk of infection, allergic reaction, morbidity and can lead to transfusion-related acute lung injury.[1-3] The critical level of hemoglobin that will improve oxygen transportation and oxygen delivery (DO_2) in critically ill children is uncertain. Furthermore, it is unclear at which hemoglobin level blood transfusion has substantial effects on tissue oxygenation or the ability of tissue to extract more oxygen.[4] American Heart Association and sepsis campaign guidelines advocate for blood transfusion in critically ill children with hemoglobin less than 10 g/

dL and central venous O$_2$ saturation (ScvO$_2$) <70 percent.[5]

The normal O$_2$ER (oxygen extraction ratio) is around 25% to 30%. When O$_2$ER exceeds 40% to 50%, DO$_2$ starts to be exhausted, leading to tissue dysoxia, a VO$_2$/DO$_2$ dependent status and evidence of O$_2$ debt.[6] O$_2$ER and ScvO$_2$ are clinical tools that can help clinicians estimate DO$_2$ and O$_2$ consumption (VO$_2$) status in the body. When hemoglobin drops, the body compensates by multiple physiological compensatory mechanisms, aiming to increase cardiac output and improving DO$_2$ to meet VO$_2$. These compensatory mechanisms are limited and vary within and between individuals and are influenced by different physiological circumstances.[7] The threshold Hb level where the compensation process reaches a critical VO$_2$/DO$_2$ status, where VO$_2$ is dependent on DO$_2$, is an important target threshold. There are multiple biomarkers that have been suggested as triggers for transfusion need in critically ill children approaching the critical deflection point of VO$_2$/DO$_2$ dependency status. These may include hemoglobin level, mixed venous oxygen saturation (SVO$_2$), ScvO$_2$ and lactate level. Few adult studies suggested using O$_2$ER as an additional marker or trigger to determine transfusion need in critical condition.[8] When O$_2$ER increases in a critically ill patient with low hemoglobin levels, blood transfusion to optimize DO$_2$, the DO$_2$/VO$_2$ balance and O$_2$ER becomes detrimental.[5,9,10] Because many cardiac patients have cyanosis and low systemic saturation to start with, the use of O$_2$ER in addition to ScvO$_2$ may reflect better body oxygenation status, VO$_2$/DO$_2$ balance and a critical need for blood transfusion. New monitoring methods such as near-infrared spectroscopy measure regional rather than global perfusion. The role of O$_2$ER as a trigger for blood transfusion in postoperative cardiac children has not been well evaluated. In this study, we assessed the effects of blood transfusion on O$_2$ER and ScvO$_2$ in postoperative cardiac patients. Our goal was to identify a critical O$_2$ER value that can help us better determine the critical need for blood transfusion and avoid an unnecessary and potentially harmful transfusion.

PATIENTS AND METHODS

This prospective non-interventional observational cohort study was undertaken in the Cardiac Surgical Intensive Care Unit (CSICU) at Prince Sultan Cardiac Center, Qassim, Saudi Arabia, between January 2013 and December 2015, after Institutional Review Board approval. We included all children with cyanotic and noncyanotic cardiac disease who underwent correc-

tive or palliative surgery and needed blood transfusion during the postoperative period. No patients were on ECMO during the time of the study. Children with active bleeding (defined as total surgical drainage more than 4 cc/kg /hour) were excluded from study. Patients were not routinely monitored by near-infrared spectroscopy so it was not included in data collection.

No fixed blood transfusion protocol was followed. During the study period, the attending physician decided whether to transfuse blood. The patient's age, weight, diagnosis of congenital heart disease, RACHS score, and Wernovsky vasoactive score were recorded. The sedation score was not included in the data as some of our patients were extubated at the time of transfusion. Physiological parameters such as heart rate, systolic blood pressure, mean blood pressure, O$_2$ saturation, core temperature, central venous pressure, urine output pre-transfusion and 1 and 6 hours after transfusion were recorded. Laboratory data included complete blood count (CBC), lactate level, arterial blood gas and central venous gas immediately before starting transfusion and then 1 and 6 hours after transfusion. Blood was usually transfused over 2 to 3 hours. No laboratory data were collected during transfusion. The amount of blood transfused was measured as mL/kg. The oxygen extraction ratio was calculated using the formula:

$$O_2ER = VO_2/DO_2 = [(CaO_2 - CvO_2)/CaO_2]$$
$$CaO_2 = (Hb \times 1.39 \times SaO_2) + (PaO_2 \times 0.003)$$
$$CvO_2 = (Hb \times 1.39 \times ScvO_2) + (PvO_2 \times 0.003)$$

Oxygen extraction before and 6 hours after transfusion were subsequently computed after collecting all data. The posttransfusion values reported in the tables are at 6 hour posttransfusion. Attending physicians were unaware of O$_2$ER values when the decision to transfuse was made. Values of O$_2$ER were calculated at the time of study analysis and not considered upon transfusion because critical O$_2$ER is not well defined, differing from one reference to another.[6,16]

A value of 50% to 60% O$_2$ER has been suggested as a critical O$_2$ER value.[6] Nevertheless, we selected an O$_2$ER of 40% because it is an early and safer warning of tissue O$_2$ debt and m ay reflect better an early prediction of inadequate tissue oxygenation. Cases were divided into two groups based on O$_2$ER results: patients with increased O$_2$ER (O$_2$ER >40%) and without increased O$_2$ER (O$_2$ER ≤40%) before transfusion. The groups were then analyzed using 50% O$_2$ER as a cut point.

Physiological and laboratory data, were recorded. O$_2$ER and SvcO$_2$ values were compared pre- and posttransfusion within each group and between the two

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groups. Continuous data were analyzed between the two groups using the unpaired *t* test. Data are presented as mean and standard error or standard deviation where noted and a *P* value below .05 was considered statistically significant. SSPS version 20 was used for the statistical analysis.

RESULTS

One hundred and three children were transfused after cardiac surgery. Some patients received several blood transfusions and were included in both groups. The mean (SD) Hb level pretransfusion was 9.1 (1.1) g/dL. The average increase in Hb after transfusion was 2.7 (0.03) g/dL (*P*=.0001). Seventy-five cases had normal O$_2$ER before transfusion with mean (SD) O$_2$ER of 25 (9.6) percent (normal O$_2$ER group) while 28 cases had increased O$_2$ER before transfusion with a mean (SD) O$_2$ER of 46 (4.7) percent (increased O$_2$ER group) (*P*=.0001).

Mean (SD) Hb levels before transfusion were 9.03 (1.1) and 9.3 (0.1) g/dL for increased and normal O$_2$ER groups, respectively (*P*=.18) (**Table 1**). Patients received a mean of 11.0 (0.2) mL/kg of packed red blood cell that led to an average increase in Hb after transfusion of 2.8 g/dL and 2.7 g/dL in the increased and normal O$_2$ER groups, respectively.

Patients from both groups had a significant improvement in Hb level following transfusion. These changes were statistically significant between pre- and posttransfusion Hb level (**Tables 2 and 3**), but there were no statistical differences in Hb level between the increased and normal O$_2$ER groups during transfusion (**Table 4**).

The increased O$_2$ER group had a lower ScvO$_2$ saturation in comparison to the normal O$_2$ER group, 51.3 (1.8) percent versus 67.5 (1.4) percent (*P*=.0001). Following blood transfusion mean (SD) O$_2$ER improved from 46 (4.7) percent to 36.4 (9.5) percent (*P*=.0001), in the increased O$_2$ER group while in the normal group there were no significant changes in O$_2$ER (25 [9.6] percent to 25.8 [9.8] percent, *P*=.6). Increments of central venous saturation change (ΔScvO$_2$) after transfusion were statistically higher in the increased O$_2$ER group versus the normal O$_2$ER group (*P*=.0001). There were no significant differences in heart rate, systolic blood pressure or mean blood pressure before or after transfusion in either group. There were no statistically significant differences in lactate level.

In a subgroup analysis, in patients with hemoglobin >10 g/dL and increased O$_2$ extraction there was a significant improvement in the change in ScvO$_2$ (increment of ScvO$_2$ posttransfusion) and O$_2$ER after transfusion in comparison with normal ScvO$_2$ and O$_2$ER values in the same subgroup (**Table 5**). Likewise, in patients with

Table 1. Demographic data in patients grouped by oxygen extraction ratio status before transfusion.

Variables	Increased O$_2$ER (>40%) before transfusion (n=28)	Normal O$_2$ER (≤40%) before transfusion (n=75)	P
Age (month)	10.8 (3.0)	14.3 (2.8)	.47
Weight (kg)	6.23 (0.5)	6.7 (0.6)	.63
Hemoglobin (g/dL)	9.03 (1.1)	9.3 (1.1)	.18
Cyanotic/non-cyanotic	8/20 (40%)	33/42 (78%)	.18
RACHS-1 score	2.5 (0.2)	2.7 (0.07)	.13

Values are mean (standard deviation) or n (%). *P* values from unpaired *t* test.

Table 2. Patients with normal oxygen extraction ratio(≤40%) before transfusion (n=75).

Variables	Pretransfusion	Posttransfusion	P
Heart rate (bpm)	138.2 (2.2)	134 (2.3)	.18
Systolic blood pressure (mm Hg)	85 (1.4)	87.2 (1.4)	.26
Mean blood pressure (mm Hg)	65.2 (1.2)	66.7 (1.2)	.37
Diastolic blood pressure (mm Hg)	48.37 (1.2)	49.98 (1)	.3
O$_2$ arterial saturation (%)	91.7 (0.9)	92.5 (0.9)	.5
Central venous pressure (mm Hg)	9.6 (0.36)	10 (0.37)	.44
Urine output (mL/kg)	4.3 (0.3)	4.5 (0.2)	.58
Core temperature °C	36.4 (0.1)	36.5 (0.1)	.48
Hemoglobin (g/dL)	9.3 (1.1)*	12 (1.5)*	.0001
SvcO$_2$ (%)	67.5 (1.4)	67.5 (1.2)	1
Lactic acid (mmol/L)	1.9 (0.2)	1.6 (0.2)	.3
SvcCO$_2$ (%)	5.6 (0.4)	6.02 (0.4)	.45
Vasoactive score	7.5 (0.5)	7.6 (0.5)	.88
O$_2$ER	25.0 (9.6)*	25.8 (9.8)*	.6

Central venous oxygen saturation (ScvO$_2$); Oxygen extraction ratio (O$_2$ER). *P* values from unpaired *t* test. *Standard deviation.

Table 3. Patients with increased oxygen extraction ratio (>40%) before transfusion (n=28).

Variables	Pretrans-fusion	Posttrans-fusion	P
Heart rate (bpm)	138 (3.8)	135.7 (3.6)	.56
Systolic blood pressure (mm Hg)	84.17 (1.8)	84.35 (1.7)	.9
Mean blood pressure (mm Hg)	66.17 (1.5)	64.92 (1.9)	.6
O$_2$ arterial saturation (%)	89.5 (1.6)	89.66 (1.5)	.99
Central venous pressure (mm Hg)	10.14 (0.4)	10.25 (0.38)	.84
Urine output (mL/kg)	3.7 (0.27)	4.2 (0.29)	.21
Core temperature °C	36.45 (0.16)	36.45 (0.11)	.99
Hemoglobin (g/dL)	9.03 (1.1)*	11.8 (1.4)*	.0001
SvcO$_2$ (%)	51.3 (1.8)	58.9 (2)	.0065
Lactic acid (mmol/L)	1.7 (0.2)	1.4 (0.1)	.18
SvcCO$_2$ (%)	8.47 (0.82)	6.6 (0.6)	.07
Vasoactive score	7.9 (0.5)	8 (0.5)	.88
O$_2$ER	11.8 (1.4)*	11.8 (1.4)*	.0001

Central venous oxygen saturation (ScvO$_2$); Oxygen extraction ratio (O$_2$ER). P values from unpaired t test. *Standard deviation.

Table 4. Physiologic and laboratory data in patients grouped by oxygen extraction ratio status before transfusion.

Variables	Increased O$_2$ ER (>40%) before transfusion (n=28)	Normal O$_2$ ER (≤40%) before transfusion (n=75)	P
Pretransfusion heart rate (bpm)	138 (3.8)	138 (2.2)	.99
Systolic blood pressure (mm Hg)	84.17 (1.8)	85 (1.4)	.74
Mean blood pressure (mm Hg)	66.17 (1.5)	65.2 (1.2)	.65
Change in mean blood pressure (mm Hg)	0.02 (0.3)	0.36 (0)	.06
Arterial saturation (%)	89.5 (1.6)	91.7 (0.9)	.21
Core temperature °C	36.45 (0.16)	36.4 (0.1)	.79
Urine output (mL/kg)	3.7 (0.27)	4.3 (0.3)	.25
Change in hemoglobin (g/dL)	2.7 (0.06)	2.7 (0.1)	.99
Vasoactive score	7.9 (0.5)	7.5 (0.5)	.65
Lactic acid (mmol/l)	1.7 (0.2)	1.9 (0.2)	.57
ScvO$_2$ (%)	51.3 (1.8)	67.5 (1.4)	.0001
Change in ScvO$_2$ (%)	7.6 (0.2)	0 (0.2)	.0001
ScvCO$_2$ (%)	8.47 (0.82)	5.6 (0.4)	.0006
O$_2$ER	46 (0.9)	25 (1.1)	.0001
Change in O$_2$ER	9.6 (0.9)	0.8 (0)	.0001

Central venous oxygen saturation (ScvO$_2$); Oxygen extraction ratio (O$_2$ER). P values from unpaired t test.

hemoglobin <10 g/dL there were significant improvements in change in ScvO$_2$ and O$_2$ER after transfusion in comparison with the normal group (**Table 5**). In a subgroup analysis of patients with O$_2$ER >50%, O$_2$ER improved in the increased versus the normal O$_2$ER group (**Table 6**).

DISCUSSION

Transfusion of red blood cells during and after cardiac surgery is a common practice. When the degree of anemia compromises oxygen delivery and leads to organ hypoxia, the need for blood cell transfusion becomes vital.[4] Although the evidence is poor, most RBC transfusions are given because the hemoglobin concentration has fallen below a static predefined threshold that is perceived to be associated with insufficient arterial oxygen, but this hemoglobin concentration varies between and even within institutions. Hemoglobin level is not sufficient as the only trigger for blood transfusion. The hemoglobin level may vary not only on the basis of cardiac lesion and systemic saturation, but also on the

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Table 5. Changes in oxygen extraction ratio and central venous saturation after blood transfusion in patients with HB ≥10 or <10 in patients grouped by increased and normal oxygen extraction ratio.

| Variable | Low HB HB <10 (n=75) | | | | High Hb HB ≥10 (n=28) | | | |
	Increased group Pretransfusion O$_2$ER >40% (n=20)	Normal group Pretransfusion O$_2$ER <40% (n=55)	P	95% CI	Increased group Pretransfusion O$_2$ER >40% (n=8)	Normal group Pretransfusion O$_2$ER <40% (n=20)	P	CI
Change in ScvO$_2$ Posttransfusion	7.3 (0.4)	0.6 (0.1)	.0001	(6.1,7.3)	9.2 (0.56)	2.8 (0.7)	.0001	(3.9,8.8)
Change in O$_2$ER Posttransfusion	8.5 (0.9)	1.4 (0)	.0001	(6.03,8.16)	13.07 (2.6)	0.3 (0.1)	.0001	(9.6,15.9)

Central venous oxygen saturation (ScvO$_2$); Oxygen extraction ratio (O$_2$ER). P values from unpaired t test for changes in values from the pretransfusion state.

basis of cardiac function and adaption of the circulation to changes in loading conditions imposed by the operative correction. These factors may not only change from heart lesion to lesion, but on the hearts adaption to changes in cardiac loading conditions. Lots of studies have examined other potential triggers to the decision to transfuse blood. In TRIPICU study[11] the authors showed clearly that blood transfusion did not improve the outcome in a restricted or liberal group even in Fontan and Glenn patients. Goal-directed therapy is probably the solution for this dilemma. From the clinical perspective, it is desirable to find more reliable and measurable predictors for adequate organ oxygenation and to replace the static hemoglobin transfusion trigger with a physiologic trigger. Mixed venous oxygen saturation (MVO$_2$) sampled from the pulmonary artery is ideal for measurements of DO$_2$ and VO$_2$. Because of the difficulty in obtaining MVO$_2$ in critically ill children, ScvO$_2$ was suggested as a surrogate for MVO$_2$.[12] In clinical practice ScvO$_2$ taken from the superior vena cava may be the most practical physiological marker of oxygen demand because it reflects the DO$_2$/VO$_2$ balance.[4]

The targeted recommended ScvO$_2$ is 70% in critical children with a normal structural heart,[5] but in children with cardiac disease and cyanotic heart disease the critical ScvO$_2$ is not clearly defined. Interpreting and defining a critical ScvO$_2$ value in children with cyanotic heart lesion is more difficult since many of them have arterial O$_2$ saturation (SaO$_2$) ranging between 75% and 85%. Examining O$_2$ER in those patients is of interest and has clinical relevance. In 1982 Jamieson[13] found that MVO$_2$ saturation changes take place before any changes in mean arterial pressure or heart rate and it is well correlated with the cardiac index. Staphen et al[12] found that increased oxygen extraction is associated with increased length of stay and multiorgan failure in the ICU.

To what extent an increase in hemoglobin concentration will enhance tissue and organ oxygenation is unclear and still under investigation. Herbet et al[14] reviewed 18 clinical studies investigating the effects of RBC transfusions on DO$_2$/VO$_2$ relationship in critically ill patients. They reported that improved VO$_2$ was documented in only five studies. O'Farrell conducted a pilot study in 2006 that measured the relationship between O$_2$ER and postoperative RBC transfusions in cardiac surgery and concluded that elevated O$_2$ER may be a more appropriate transfusion trigger than low hemoglobin concentration and its use may reduce inappropriate transfusions.[9] David et al[10] found a significant improvement in O$_2$ER

Table 6. Comparison of patients with increased (n=6)and normal oxygen extraction ratio (n=97) by oxygen extraction ratio greater than 50%.

	Increased O$_2$ER	Normal O$_2$ER	P
Pretransfusion			
Heart rate (bpm)	137.4 (1.9)	147.3 (7.9)	.13
Mean blood pressure (mm Hg)	59.16 (3.6)	66 (0.9)	.09
Urine output (mL/kg)	3.5 (0.36)	4.48 (0.19)	.2
Hemoglobin (g/dL)	8.9 (0.49)	9.6 (0.29)	.55
Lactic acid (mmol/l)	2.13 (0.6)	1.8 (0.17)	.63
ScvO$_2$ (%)	44.7 (2.2)	64.22 (1.3)	.0004
O$_2$ER (%)	53 (0.6) (98)	29.31 (1.19) (97)	.0026
Posttransfusion O$_2$ER (%)	43.0 (2.9)	27.7 (1.0)	.0001

Central venous oxygen saturation (ScvO$_2$); Oxygen extraction ratio (O$_2$ER). P values from unpaired t test.

values at 15 and 120 minutes after transfusion and suggested including O$_2$ER into transfusion decision triggers assuming that it would reduce postcardiac surgery RBC transfusions.[10] On the other hand, in 2014 Fiser et al[17] investigated the effect of RBC transfusion in 45 pediatric patients with ECMO and found that transfusion did not significantly alter global tissue oxygenation. In 2013 Mungayi et al[8] studied the direct effect of blood transfusion on oxygen extraction in a general adult intensive care unit and found no statistically significant difference in oxygen extraction pre- and posttransfusion. In these two previous studies, most transfusions were given when the patient did not appear to be oxygen delivery dependent. Thus, Mungayi et al recommended other studies to investigate the effects of blood transfusion in increasing pretransfusion O$_2$ extraction. Whether RBC transfusion may increase DO$_2$ and the VO$_2$/DO$_2$ balance depends on how severely tissue oxygenation is increased.[7] In critically ill patients suffering from acute respiratory syndrome with oxygen supply dependency status and metabolic acidosis, Kruse et al[15] demonstrated that blood transfusions contributed to the augmentation of DO$_2$ thereby providing a significant increase in VO$_2$. Marino[16] pointed out that an O$_2$ER more than 50% is an indirect marker of tissue dysoxia or impending dysoxia and suggested that this number could be used as an indicator for transfusion trigger.

We found statistically significant differences between O$_2$ER and ScvO$_2$ pre- and posttransfusion in the increased O$_2$ER group (both 40% or 50% O$_2$ER) but not the normal O$_2$ER group. Both groups had similar in hemoglobin levels pretransfusion, but there may have been differences in cardiac output but still increase O$_2$ER had benefit from blood transfusion even if increase O$_2$ER

is not because of low hemoglobin. These changes were observed even when hemoglobin was more than 10 g/dL when O$_2$ER was increased, which suggested that hemoglobin concentration is not enough as a sole marker to guide blood transfusion. Furthermore, we observed no changes in urine output or lactate level, which is consistent with the opinion of Jamieson[13] who stated that decreased MVO$_2$ and increased O$_2$ER are early signs of dysoxia which can be picked up earlier than hypotension and acidemia. We found that neither a hemoglobin value nor clinical assessment alone was enough to decide whether to do a blood transfusion. One advantage of using O$_2$ER in guiding transfusion is that in patients with a cyanotic heart lesion as it reflects ratio rather than absolute number where many patients may have systemic O$_2$ saturation ranging between 70%-85% and ScvO$_2$ below 70%.

The unique value of this study is the reliance on measures of oxygen delivery independent of actual hemoglobin level. However, the limitation of this study is the small number of patients in the increased O$_2$ER group and the lack of few variables to assess oxygen consumption rather than core temperature. Large randomized prospective trials are needed to support our findings and to establish a goal-directed blood transfusion protocol. Furthermore, the decision to undertake a blood transfusion is a clinical decision that incorporates many elements such as patient stability, level of hemoglobin, patient preference, the presence of a cyanotic heart lesion and many others. Postoperatively, in children undergoing cardiac surgery with an O$_2$ER more than 40%, blood transfusion improves O$_2$ER and ScvO$_2$. O$_2$ER and ScvO$_2$ might be useful as additional blood transfusion triggers.

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