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## The TRICC trial: A focus on the subgroup analysis

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Red blood cell (RBC) transfusions, administered to improve O<sub>2</sub> delivery to the tissues, are common in critical care practice.<sup>1</sup> However, there are divergent views regarding the risks and benefits of using transfusions to treat anemia in this setting. In particular, critically ill patients may be at greater risk of the immunosuppressive<sup>2,3</sup> and microcirculatory<sup>4,5</sup> complications of RBC transfusions. There is also concern that changes that occur in red cells during storage may decrease their ability to transport, release, or deliver O<sub>2</sub>.<sup>6</sup> For these reasons, optimal transfusion practice has not been definitively determined for the various types of critically ill patients with anemia. Traditionally, RBCs are given when hemoglobin (Hb) concentrations fall below 100 g/L. However, the concerns mentioned above, together with a declining blood supply, have supported a move towards a more conservative approach to blood transfusions.

The Transfusion Requirements In Critical Care (TRICC) trial was designed to determine whether a restrictive transfusion strategy (maintaining Hb concentrations between 70 g/L and 90 g/L) is equivalent to a liberal strategy (where Hb concentrations are maintained between 100 g/L and 120 g/L) in critically ill patients with euolemia after initial treatment. In this issue of *Critical Care Rounds*, two subgroup analyses of patients enrolled in the TRICC trial are presented. These analyses extend the investigation of the effects of transfusions to more specific populations of the critically ill. The first subgroup consists of patients with cardiovascular disease, while the second includes patients who received mechanical ventilation during their time in the intensive care unit (ICU). Patients with cardiovascular disease are considered to be at very high risk for the complications of anemia. Anemia has also been widely identified as a barrier to the process of weaning from mechanical ventilation.<sup>1</sup> These subgroups were explored because transfusions are widely used to treat anemia in these setting and there are a small number of clinical studies addressing their effect in these patients.

### Transfusion and the critically ill

Of the 838 patients enrolled in the TRICC trial, 418 were assigned to the restrictive strategy group, and 420 to the liberal group. Nine patients did not complete the trial (5 from the restrictive group and 4 from the liberal group), and 3 additional patients were



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lost to follow-up after 60 days. No significant differences were found in any of the baseline characteristics between the restrictive and the liberal strategy groups. The mean age was approximately 58 years, average APACHE II score was 21, and >80% of patients received mechanical ventilation.

The rate of 30-day all-cause mortality – the primary outcome for the trial – was lower in the restrictive strategy group than in the liberal strategy group (19% vs 23%,  $P=0.11$ ). The same was true for mortality rates: during hospitalization (22% vs 28%,  $P=0.05$ ); during stay in the ICU (14% vs 16%,  $P=0.29$ ); and after 60 days (23% vs 27%,  $P=0.23$ ).

There was no significant difference between the two groups in the number of patients with multi-organ failure (5% vs 4%,  $P=0.36$ ). These results suggest that the use of a threshold for transfusion as low as 70 g/L, combined with maintenance of Hb concentrations in the range of 70 g/L to 90 g/L, was at least as effective as, and possibly superior to, a liberal transfusion strategy in critically ill patients with normovolemia.

For the total patient group, Kaplan-Meier survival curves were similar. However, significant differences were noted in patients with an APACHE II score <20, and in patients <55 years. Patients in the restrictive strategy group with an APACHE score  $\leq 20$  had clinically and statistically important decreases in 30-day all-cause mortality, compared with the liberal strategy group (9% vs 16%,  $P=0.03$ ). Similarly, patients <55 years of age fared much better in the restrictive transfusion group (30-day mortality rates of 6% vs 13%,  $P=0.02$ ). These two groups further demonstrated that at worst, both transfusion strategies are equivalent. It is much more likely that the restrictive approach is superior to the liberal one.

## Establishing patients in each subgroup

### Cardiovascular subgroup

For the subgroup analysis of cardiovascular patients, all patients at risk from anemia because of heart disease were identified. The investigators selected all patients with a primary or secondary ICU admission diagnosis of a cardiovascular disease, as well as those with cardiac disease as a significant co-morbid illness defined as New York Heart Association (NYHA) class III or IV. All patients known to have ischemic heart disease were also

examined. The cardiovascular disease category included all diagnoses related to ischemic heart disease (myocardial infarction, angina, congestive heart failure, and cardiogenic shock), rhythm disturbances, cardiac arrest, other forms of shock, uncontrolled hypertension, as well as cardiac and vascular surgical procedures (eg, abdominal aortic aneurysm repair and peripheral vascular surgical procedures).

### Mechanical ventilation subgroup

The subgroup analysis of patients receiving mechanical ventilation was limited to those who required mechanical ventilation through an endotracheal tube or tracheostomy, regardless of the duration of ventilation, subsequent to being enrolled in the TRICC trial. Patients receiving noninvasive ventilation were not analyzed. Because RBC transfusions might have a greater effect on patients requiring a longer course of mechanical ventilation, *a priori*, the investigators also decided to examine the subgroup of patients who were mechanically ventilated for >7 days.

### Transfusion and patients with cardiovascular disease

From the total TRICC trial population of 838 patients, 357 (43%) were identified with cardiovascular disease. Of these, 160 had been in the restrictive RBC transfusion group and 197 in the liberal transfusion strategy group. All patients in this subgroup analysis completed the clinical trial and were followed for 30 days, with 1 patient lost to follow-up at 60 days.

Among the patients with cardiovascular disease, all baseline characteristics except for the use of cardiac medications (75% vs 85%,  $P=0.02$ ) and anesthetic agents (17% vs 7%,  $P<0.01$ ) were balanced equally. The average age was in the mid-60's, average APACHE II score was 23, and >85% were mechanically ventilated. Less frequent diuretic use in the restrictive group (43% vs 58%,  $P<0.01$ ) accounted for the observed difference in cardiac medications between groups, while the use of epidural anaesthetic medications was greater in the restrictive group (8% vs 2%,  $P<0.01$ ).

The 30-day all-cause mortality rate was 23% in the restrictive transfusion group versus 23% in the liberal group (95% CI, -8.4% – 9.1%,  $P=1.00$ ; Table 1). No significant differences between the 2 treatment groups were seen in other mortality rates, including 60-day

**Table 1: Outcomes in the 357 patients with cardiovascular disease**

Characteristics	Restrictive Group (n = 160)	Liberal Group (n = 197)	Difference	95%CI of Difference		P Value
				Lower	Upper	
<b>Mortality rates No. (%)</b>						
30-day	36 (23)	45 (23)	0.3%	-8.4%	9.1%	1
60-day (n=356)	42 (26)	53 (27)	0.8%	-8.4%	10.0%	0.9
ICU	31 (19)	32 (16)	-3.1%	-4.8%	11.1%	0.49
HOSPITAL	43 (27)	56 (28)	1.9%	-6.9%	10.9%	0.81
<b>Organ failure and dysfunction</b>						
MODS (n=351)	8.6 ± 4.9	9.0 ± 4.4	0.4	-0.6	1.4	0.4
Δ MODS (n=351)	0.23 ± 4.2	1.28 ± 4.4	1.1	0.1	2.4	0.023
MODS* (n=357)	11.1 ± 7.6	11.9 ± 7.9	0.7	-0.8	2.4	0.39
Δ MODS* (n=357)	2.7 ± 6.9	4.0 ± 7.3	1.3	-0.2	2.8	0.081
<b>Length of stay, mean ±SD</b>						
ICU (days)	9.2 ± 9.1	11.3 ± 11.6	2	-0.2	4.3	0.11
Hospital (days)	33.0 ± 19.6	35.1 ± 19.5	2.2	-2	6.2	0.27

CI, confidence interval; ICU, intensive care unit; MODS, multiple organ dysfunction score; Δ MODS, change in multiple organ dysfunction score from baseline values.  
\* Non-survivors are considered to have all organs failing on date of death.

(26% vs 27%,  $P=0.90$ ), ICU (19% vs 16%,  $P=0.49$ ) and hospital mortality (27% vs 28%,  $P=0.81$ ). The multiple organ dysfunction (MOD) scores were not significantly different between groups ( $8.6 \pm 4.9$  vs  $9.0 \pm 4.4$ ,  $P=0.40$ ). However, the change in multiple organ dysfunction (MOD) scores from baseline values was significantly lower in the restrictive group compared to the liberal group ( $0.2 \pm 4.2$  vs  $1.3 \pm 4.4$ ,  $P=0.02$ ). Kaplan-Meier survival curves comparing time to death showed similar trends in the two groups ( $P=0.95$ ; Figure 1).

In the subset of cardiac patients with ischemic heart disease ( $n=257$ ), no discernible differences in 30- and 60-day, as well as ICU mortality rates, were seen. However, there was a nonsignificant ( $P=0.3$ ) decrease in overall survival rate in the restrictive group, for patients with confirmed ischemic heart disease, severe peripheral vascular disease, or severe comorbid cardiac disease.

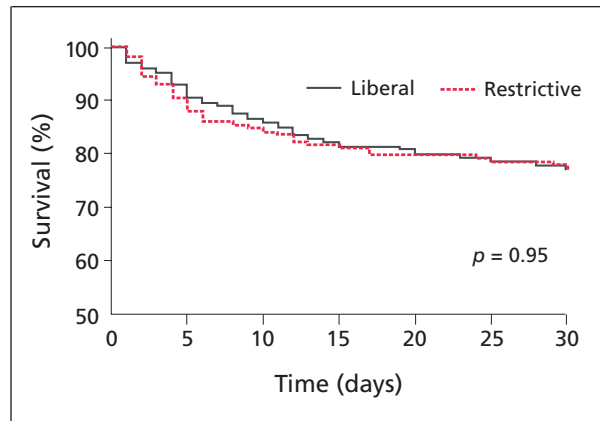
### Transfusion and patients requiring mechanical ventilation

In the TRICC trial, 713 (85%) of the 838 patients were identified as requiring mechanical ventilation. Of these, 357 had been in the restrictive RBC transfusion group and 356 in the liberal group. All patients in this subgroup analysis completed the trial and they were followed for 30 days. Two patients were lost to follow-up at 60 days.

There were no study protocols for mechanical ventilation during the trial. Assist control, assist control with pressure control, and synchronized intermittent mandatory ventilation with pressure support were the primary modes of mechanical ventilation employed in all centres. Assessment of weaning readiness, weaning methods, and extubation decisions were made at the discretion of the ICU team.

In the patients who required mechanical ventilation, all baseline characteristics were equally balanced between the treatment groups ( $P>0.05$ ). The mean

**Figure 1:** Survival in all cardiac patients in the restrictive and liberal allogeneic RBC transfusion groups. This graph illustrates Kaplan-Meier survival curves for all cardiac patients in both study groups. There is no difference in mortality in patients in the restrictive group (dashed line) as compared to the liberal group (solid line) ( $p=0.95$ ).



**Table 2: Outcomes in the 713 patients in the TRICC trial who required mechanical ventilation**

Outcomes	Restrictive (n = 357)	Liberal (n = 356)	P Value
<b>Mechanical ventilation outcomes</b>			
<b>Days of MV (days)<sup>(1)</sup></b>			
Length of ventilation	8.3 ± 8.1	8.8 ± 8.7	0.48
Ventilator-free days <sup>(2)</sup>	17.5 ± 10.9	16.1 ± 11.4	0.09
<b>Off MV for at least 24 hrs</b>			
No. (%)	292 (82)	277 (78)	0.19
Time to wean (days)	7.7 ± 6.6	7.4 ± 6.2	0.55
<b>Off MV for at least 30 days</b>			
No. (%)	283 (79)	261 (73)	0.78
Time to wean (days)	8.8 ± 7.3	8.5 ± 6.9	0.63
<b>Other outcomes</b>			
<b>Mortality No. (%)</b>			
30-day	76 (21.3)	94 (26.4)	0.11
60-day	92 (26)	105 (30)	0.32
ICU	58 (16)	67 (19)	0.38
Hospital	90 (25)	112 (31)	0.07
<b>Organ Dysfunction</b>			
MODS	8.7 ± 4.7	9.3 ± 4.4	0.11
MODS <sup>(3)</sup>	11.4 ± 7.6	12.6 ± 7.7	0.04
Change in MODS	1.1 ± 4.3	1.5 ± 4.2	0.29
Change in MODS <sup>(3)</sup>	3.8 ± 7.2	4.7 ± 7.4	0.09
<b>Length of Stay</b>			
ICU (in days)	12.2 ± 11.1	12.7 ± 11.8	0.54
Hospital (in days)	36.1 ± 19.5	36.5 ± 19.2	0.8

NB: Intention-to-treat analysis

(1) MV: mechanical ventilation

(2) Patients who died given "0" ventilator-free days

(3) Nonsurvivors are considered to have all organs failing on date of death

All variables described as means ± standard deviation (SD)

APACHE II score was 22, average age was in the late 50s, and >95% of patients in this subgroup were mechanically ventilated at baseline. The mean duration of mechanical ventilation was 8.3 ± 8.1 days in the restrictive group and 8.3 ± 8.1 days in the liberal group ( $P = 0.48$ ; Table 2). Ventilator-free days were 17.5 ± 10.9 and 16.1 ± 11.4 in the restrictive and liberal RBC transfusion groups, respectively ( $P = 0.09$ ). In the patients from the restrictive transfusion group, 82% were considered successfully weaned and extubated for at least 24 hours, compared to 78% for the liberal group ( $P = 0.19$ ).

Among the 219 patients who required mechanical ventilation for >7 days, baseline characteristics were also comparable. The average APACHE II score was >20 and the average age was in the mid-50s. There was no difference in the mean duration of mechanical ventilation or ventilator-free days between the two groups (Table 3). The median time to successful extubation was 17 days (interquartile range 11 to 28) in the restrictive

**Table 3: Outcomes in the 219 patients who required mechanical ventilation more than 1 week**

Outcomes	Restrictive (n = 116)	Liberal (n = 103)	P Value
<b>Days of MV (days)<sup>(1)</sup></b>			
Length of ventilation	16.4 ± 7.9	16.9 ± 8.5	0.7
Ventilator-free days <sup>(2)</sup>	13.6 ± 7.9	13.1 ± 8.5	0.64
<b>Off MV for at least 24 hrs</b>			
Weaned No. (%)	101 (87)	87 (84)	0.7
Time to wean (days)	14.1 ± 6.7	13.3 ± 7.3	0.44
<b>Off MV for at least 30 days</b>			
Weaned No. (%)	97 (84)	82 (80)	0.49
Time to wean (days)	15.8 ± 6.5	15.5 ± 6.7	0.78

NB: Intention - to treat analysis

(1) MV: mechanical ventilation

(2) Patients who died given "0" ventilator-free days

group and 20 days (interquartile range 12 to 30) in the liberal group (Figure 2).

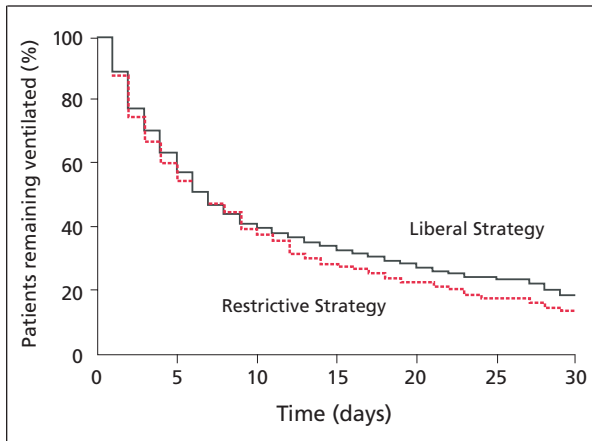
The independent effects of RBC transfusions and Hb concentration were also examined. Each additional transfusion was associated with an increased duration of mechanical ventilation (RR = 1.10; 95% CI, 1.14 – 1.06,  $P < 0.01$ ) adjusting for the effect of age, APACHE II score, and comorbid illnesses. Hemoglobin concentrations did not influence the duration of mechanical ventilation (RR = 0.99; 95% CI, 1.01 – .98,  $P = 0.45$ ). Complications, including pulmonary edema and adult respiratory distress syndrome (ARDS), were increased in patients in the liberal strategy (Table 4).

### *Is a restrictive transfusion strategy safe in the critically ill?*

A trend toward decreased 30-day all-cause mortality was noted among patients transfused according to the restrictive strategy. This suggests that using a transfusion threshold as low as 70 g hemoglobin/litre, and maintaining Hb concentrations between 70 and 90 g/L, is at least as effective as a more liberal transfusion strategy (threshold at 100 g/L, maintained between 100 g/L and 120 g/L). Further support for this conclusion is drawn from the statistically significant differences observed in mortality rates during hospitalization and in rates of organ dysfunction.

The use of the lower transfusion threshold also resulted in a decrease in the average number of units transfused by 54% and a decreased exposure to any RBCs by 33%. Concern about the risks associated with allogeneic RBC products has increased the use of expensive medications like epoetin alfa and aprotinin that reduce perioperative exposure to transfusions by

**Figure 2:** Time remaining on mechanical ventilation in 713 patients. The time to successful extubation from mechanical ventilation is illustrated using Kaplan-Meier survival curves. Weaning success is defined as remaining off mechanical ventilation, once extubated, during the 30 days of observation. The dashed line refers to the patients in the restrictive transfusion group while the solid line refers to the patients in the liberal transfusion group. Survival curves were not statistically different when compared using a log rank test ( $p=0.21$ ). The median time to extubation was 7 days (interquartile range 2 to 18 days) in the restrictive group and 7 days (interquartile range 3 to 23 days) in the liberal group.



1 to 2 red-cell units. However, the findings of this study indicate that the less costly intervention of using a lower transfusion threshold improved clinical outcomes, while reducing exposure to RBCs.

It has been hypothesized that  $O_2$  delivery should be increased or maintained at high levels to minimize the effects of tissue hypoxia caused by disease processes that

alter the body's ability to extract  $O_2$ . In one meta-analysis,<sup>7</sup> a benefit from augmented  $O_2$  delivery was detected when therapy was initiated preoperatively, but not after patients were admitted to the ICU. In all the published studies, transfusion thresholds exceeded 100 g/L, making it almost impossible to make inferences about optimal RBC transfusion strategies. In this study, allogeneic transfusions, used as a means of augmenting  $O_2$  delivery, did not appear to offer any survival advantage in volume-resuscitated patients when Hb concentrations were  $>70$  g/L.

One plausible explanation is that RBC transfusions did not improve  $O_2$  delivery as expected. Changes in RBC function during storage,<sup>8-10</sup> and/or changes caused by diseases such as sepsis<sup>11,12</sup> may contribute to decreased tissue  $O_2$  delivery in multi-transfused patients compared to similar patients who are transfused more conservatively. Following transfusions, patients may have experienced more acute, life-threatening complications. For instance, a greater number of myocardial infarctions and episodes of pulmonary edema were noted in the liberal group that might have contributed to increased mortality. The greater number of allogeneic red blood cell units transfused in the liberal group may also have significantly depressed host immune responses,<sup>2,3</sup> resulting in increased mortality rates from nosocomial infections and multisystem organ dysfunction. However, this was not detectable in this study since approximately 26% of patients had an infection at baseline.

**Table 4: Complications throughout the study in the 713 patients who required mechanical ventilation**

Complications No. (%)	Restrictive Group (n = 357)	Liberal Group (n = 356)	Difference	95% CI		P Value
				Lower	Upper	
Cardiac	51 (14)	80 (22)	8.2	2.3	13.9	<0.01
Angina <sup>(1)</sup>	5 (1)	9 (3)	1.1	—	—	0.28
Myocardial infarct <sup>(1)</sup>	2 (1)	12 (3)	2.8	—	—	<0.01
Cardiac arrest	29 (8)	31(9)	0.6	-3.5	4.7	0.78
Pulmonary edema	18 (5)	38 (11)	5.6	-0.1	7.3	<0.01
Pulmonary	102 (29)	114 (32)	3.5	-3.3	10.2	0.33
ARDS	31 (9)	48 (13)	4.8	0.2	9.4	0.04
Hematologic	9 (3)	9 (3)	0.0	-2.3	2.3	1
Gastrointestinal	13 (4)	17 (5)	1.1	-1.8	4.1	0.46
Infectious	41 (11)	50 (14)	2.6	-2.3	7.5	0.32
Neurologic	24 (7)	32 (9)	2.3	-1.7	6.2	0.27
Shock	65 (18)	51 (14)	-3.9	-1.5	9.3	0.19
Any	193 (54)	210 (59)	4.9	-2.4	12.2	0.19

(1) Unable to calculate 95% CI because of the small number of patients

### *Is a restrictive RBC transfusion strategy safe in patients with cardiovascular disease?*

In the subgroup analysis of cardiovascular patients, mortality was not significantly increased in those randomized to the restrictive RBC transfusion group, and there were no clinically important mortality differences in the subgroup of 257 patients with ischemic heart disease. As a measure of morbidity, the degree of multiple organ dysfunction was comparable between the 2 treatment groups. In this subgroup analysis, the use of a restrictive transfusion strategy appeared to be as safe as the liberal RBC transfusion strategy in volume resuscitated critically ill patients with cardiovascular disease. These findings need to be confirmed in a prospective study.

In an observational study examining the association between transfusion practice and mortality, critically ill patients<sup>13</sup> with cardiovascular disease had higher mortality rates when Hb concentrations fell below 95 g/L (55% versus 42%,  $P=0.09$ ) as compared to anemic patients with other diagnoses. In this same study, patients with anemia, APACHE II score >20, and a cardiovascular diagnosis, had a significantly lower mortality rate when transfused with either 1 to 3, or 4 to 6, RBC units. The ICU mortality rate was 55% if not given any RBCs versus 35% when given 1 to 3 RBC units, or 32% when administered 4 to 6 RBC units, respectively ( $P=0.01$ ).<sup>13</sup> In a study examining Jehovah's Witness patients undergoing surgical interventions,<sup>14</sup> the adjusted odds of death increased from 2.3 (95% CI, 1.4 – 4.0) to 12.3 (95% CI, 2.5 – 62.1) as preoperative Hb concentrations declined from a range of 100–109 g/L to 60–69 g/L in patients with cardiovascular disease. In noncardiovascular patients with comparable levels of anemia, there did not appear to be an impact from anemia on 30-day mortality. Differences between this subgroup analysis and the observational studies mentioned above may be due to biases and confounding factors affecting the observational designs.

The inability to document differences in outcomes for patients with cardiac disease may also be a result of a small sample size, the heterogeneity of patients, or the diversity of therapeutic interventions in this subgroup analysis. Coronary artery disease was documented in only 257 of the 357 patients with cardiovascular diseases and even then, it was not the primary reason for ICU admission in a significant proportion. There may have been a selection bias by physicians who excluded

patients with cardiac disease from participation in the TRICC trial. Patients with cardiac disease represented 26% of patients excluded, compared to 20% of patients enrolled in the trial.<sup>15</sup> This analysis was also conducted on a subgroup of a larger clinical trial and should therefore be considered as an explanatory analysis, given that unknown prognostic variables may not be completely balanced between groups.

### *Does a liberal RBC transfusion strategy improve outcomes related to mechanical ventilation?*

There were no significant differences in the duration of mechanical ventilation, the number of ventilator-free days, or the time to successfully wean and extubate patients from mechanical ventilation among those receiving a restrictive versus liberal transfusion strategy. Therefore, Hb concentrations and RBC transfusions did not influence the duration of mechanical ventilation or other mechanical ventilation outcomes.

Because anemia may result in limited O<sub>2</sub> delivery, the left ventricle may not be able to increase cardiac output during the weaning process, and O<sub>2</sub> delivery to the respiratory muscles may not keep up with the increased O<sub>2</sub> requirements. The weaning process may precipitate myocardial ischemia because of the increased strain on left ventricular function. In this heterogeneous group of mechanically ventilated patients, no adverse effects of low Hb values were identified; however, no systematic screening for adverse effects was conducted (eg, electrocardiographic evidence of myocardial ischemia).

In a study by Srivastava and colleagues,<sup>16</sup> among 83 patients with coronary artery disease who were ventilated for a mean of 4.6 days, 8 patients had electrocardiographic ischemia during weaning and 7 failed to be liberated on the first day; ischemia was associated with a risk ratio of weaning failure of 2.1 (95% CI, 1.4 – 3.1). A significant increase in the rates of pulmonary edema was observed in patients transfused according to a liberal strategy. The increase in effective circulating volume and subsequent pulmonary edema seen in many liberally transfused patients may have offset any potential benefit from increased O<sub>2</sub> delivery.

This subgroup analysis has a number of limitations.

- First, since the TRICC trial was designed to assess the overall effects of transfusion practices in the critically ill, and not to evaluate the effects of RBC

transfusions on outcomes from mechanical ventilation, decision algorithms for weaning and extubation were not used. However, different approaches to weaning from mechanical ventilation have not definitively determined consistently superior approaches,<sup>17</sup> making it difficult to estimate the effect of this potentially confounding variable. If such protocols had been shown to impact on the duration of ventilation and if they were differentially applied in these two groups, the conclusions would be different. Some randomized trials of different approaches to achieve safe and rapid extubation, including respiratory therapy driven protocols<sup>18,19</sup> and noninvasive ventilation,<sup>20,21</sup> were not used in this study. Nevertheless, the lack of a standard approach to weaning may increase the variability in this trial and may have decreased the ability to detect meaningful differences between the two groups.

- Second, most mechanically ventilated patients can be rapidly and safely extubated,<sup>17,22</sup> and may easily tolerate low hemoglobin values during a relatively rapid process of liberation from mechanical ventilation. Therefore, the potential benefit or harm associated with transfusion may have been attenuated because all ventilated patients were enrolled regardless of the duration of their mechanical support; however, no benefit from a liberal transfusion strategy was observed among the subgroup of patients mechanically ventilated for >7 days.

As with the cardiovascular subgroup analysis, this analysis was based on a subgroup of patients from a larger randomized trial and all inferences should be interpreted cautiously as unknown prognostic variables may not be completely balanced between the groups. The sample size may have been too small to detect clinically important differences in mechanical ventilation outcomes. A *post hoc* power calculation revealed that this analysis would have been able to detect relative differences of 25% in duration of mechanical ventilation, 20% in ventilator-free days, and 10% for extubation success.

### Conclusions and future research directions

Based on the results of the TRICC trial, it is recommended that critically ill patients receive RBC

transfusions when Hb concentrations fall below 70 g/L, and that Hb concentrations be maintained between 70 g/L and 90 g/L. The diversity of patients enrolled in the trial and the consistency of the results suggest that the conclusions may be generalized to most critical care patients, with the possible exception of those with active coronary ischemic syndromes. This conclusion is further supported by the subgroup analyses conducted on the TRICC patients with cardiovascular disease and those requiring mechanical ventilation. For the latter subgroup, careful observational studies will advance the understanding of the relationship between myocardial and respiratory muscle function and hemoglobin values. Additional research should determine the RBC transfusion strategy that should be advocated for patients who are difficult to liberate from mechanical ventilation,<sup>23</sup> whether Hb concentrations influence the success of unassisted breathing trials of different duration,<sup>24,25</sup> and whether a liberal RBC transfusion strategy is advantageous for mechanically ventilated patients with acute coronary syndromes.

There are a few other significant subgroups under examination comparing the use of a restrictive transfusion strategy versus a liberal one. Specific considerations exist in multiple trauma victims admitted to the ICU. Despite the importance of transfusions as a supportive measure in this population, there are few studies focused on clinical outcomes. Trauma victims also have different risks related to the use of a restrictive transfusion strategy. In particular, there is an ever-present risk of significant hemorrhage, and there are the specialized needs of patients with severe head injury. Finally, patients who are supply dependent may also have improved outcomes with administered RBC transfusions.

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### References

1. Corwin HL, Parsonnet KC, Gettinger A. RBC transfusion in the ICU. Is there a reason? *Chest* 1995;108:767-771.
2. Bordin JO, Heddle NM, Blajchman MA. Biologic effects of leukocytes present in transfused cellular blood products. *Blood* 1994; 84:1703-1721.

3. van de Watering LMG, Hermans J, Houbiers JGA, et al. Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery. A randomized clinical trial. *Circulation* 1998;97:562-568.
4. Langenfeld JE, Livingston DH, Machiedo GW. Red cell deformability is an early indicator of infection. *Surgery* 1991;110:398-404.
5. Baker CH, Wilmoth FR, Sutton ET. Reduced RBC versus plasma microvascular flow due to endotoxin. *Circ Shock* 1986;20:127-139.
6. Messmer KFW. Acceptable hematocrit levels in surgical patients. *World J Surg* 1987;11:41-46.
7. Heyland DK, Cook DJ, King D, Kernerman P, Brun-Buisson C. Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence. *Crit Care Med* 1996;24:517-524.
8. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993;269:3024-3029.
9. Longster GH, Buckley T, Sikorski J, Tovey LAD. Scanning electron microscope studies of red cell morphology. Changes occurring in red cell shape during storage and post transfusion. *Vox Sang* 1972;22:161-170.
10. LaCelle PL. Alteration of deformability of the erythrocyte membrane in stored blood. *Transfusion* 1969;9:238-245.
11. Sielenkamper AW, Chin-Yee IH, Martin CM, Sibbald WJ. Diaspirin crosslinked hemoglobin improves systemic oxygen uptake in oxygen supply-dependent septic rats. *Am J Respir Crit Care Med* 1997;156: 1066-1072.
12. Martin CM, Iwao Y, Potter R, Yee IC, Sibbald WJ. Decreased mucosal capillary perfusion following transfusion of stored blood in control and septic rats. *Am J Respir Crit Care Med* 1996;153: A464.
13. Hebert PC, Wells G, Tweeddale M, et al. Does transfusion practice affect mortality in critically ill patients? *Am J Respir Crit Care Med* 1997; 155:1618-1623.
14. Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; 348:1055-1060.
15. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;340:409-417.
16. Srivastava S, Chatila W, Amoaeng-Adjepong Y, et al. Myocardial ischemia and weaning failure in patients with coronary artery disease: an update. *Crit Care Med* 1999;27:2109-2112.
17. Brochard L, Rauss A, Benito S, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1994; 150:896-903.
18. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996;335:1864-1869.
19. Kollef MH, Shapiro SD, Silver P, et al. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. *Crit Care Med* 1997;25:567-574.
20. Nava S, Ambrosino N, Clini E, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med* 1998;128:721-728.
21. Girault C, Daudenthun I, Chevron V, Tamion F, Leroy J, Bonmarchand G. Noninvasive ventilation as a systematic extubation and weaning technique in acute-on-chronic respiratory failure: A prospective, randomized controlled study. *Am J Respir Crit Care Med* 1999;160:86-92.
22. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med* 1995;332: 345-350.
23. Manthous CA, Schmidt GA, Hall JB. Liberation from mechanical ventilation: A decade of progress. *Chest* 1998;114:886-901.
24. Esteban A, Alia I, Gordo F, et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. Spanish Lung Failure Collaborative Group. *Am J Respir Crit Care Med* 1999;156:459-464.
25. Esteban A, Alia I, Tobin MJ, et al. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. *Am J Respir Crit Care Med* 1999;159:512-518.

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