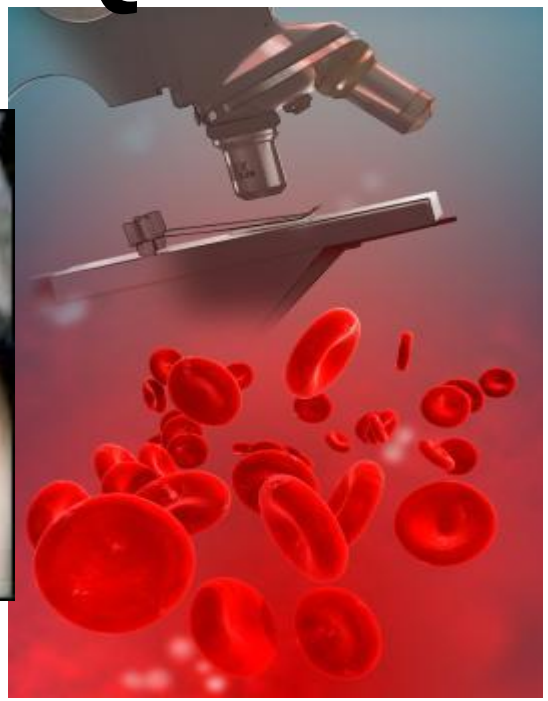
Age of Transfused RBCs in ICU
One or Two Questions?



By
Samia El Azab
MBBch, MSc, PhD, MD
Professor (A) of Anesth. & IC
Al Azhar University

Consultant Intensivist
The Police Hospital Nasr City

Objectives

1. Understanding the nature of storage lesions, the biochemical and structural changes that occur during storage of red blood cells

2. Review the debate concerning the detrimental consequences associated with the transfusion of relatively older red cells.

Review of Some Physiological Consideration

To ensure aerobic metabolism, Oxygen supply has to be adequately matched to tissue oxygen needs

Whole-body oxygen delivery (DO_2) = cardiac output (CO) x arterial oxygen content (CaO_2)

$$CaO_2 = (SaO_2 \times 1.34 \times [Hb]) + (0.23 \times PaO_2)$$

Adequacy of tissue oxygenation is the relationship between (DO2) and (VO2).

DO_2 (800–1200 ml min^{-1}) exceeds VO_2 (200–300 ml min^{-1}) by a factor of up to 4, resulting in an oxygen extraction ratio ($O_2ER = VO_2 / DO_2$) of 20–30%.

(DO2crit),

Oxygen demands are no longer met

→ ⬇ VO_2.

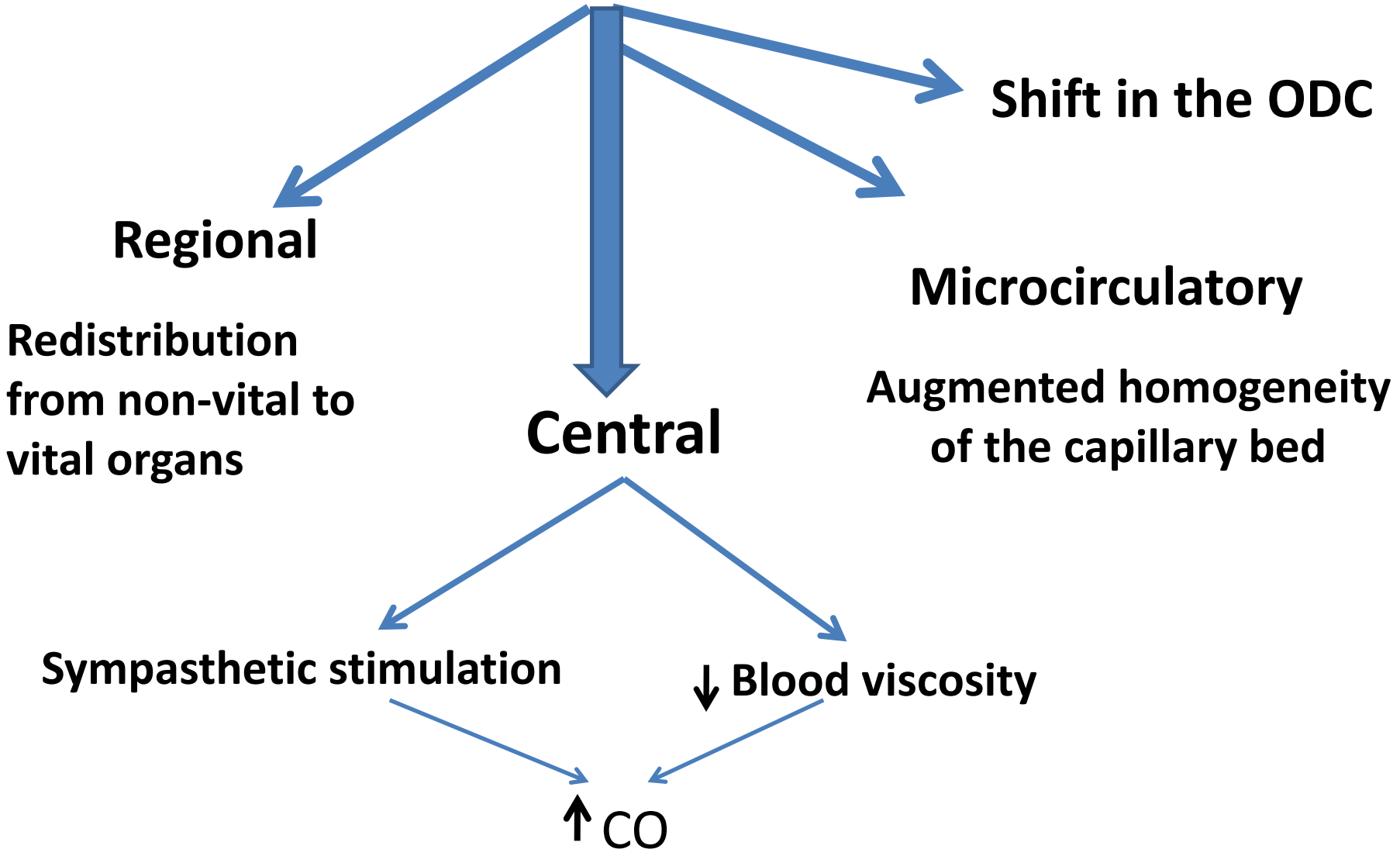
→ 'VO_2 - DO_2'dependency'

→ tissue hypoxia

When metabolic energy production is limited by supply

→ shock.

Physiological adaptation to normovolaemic anaemia



Goal of transfusion

Increase hemoglobin levels.

Increase O2 delivery and consumption.

to decrease morbidity and mortality.

RESULTS of 18 studies examining the effect of RBC transfusions on oxygenation variables.

Hébert PC et al, *Crit Care Clin* 2004; 20

Increase haemoglobin concentration (in all studies)

Increase DO_2 (14 studies)

Increase VO_2 (5 studies) explained by the absence of an oxygen debt prior to infusion.

Conclusion:

There should be oxygen debt and VO_2 - DO_2 dependency prior to transfusion.

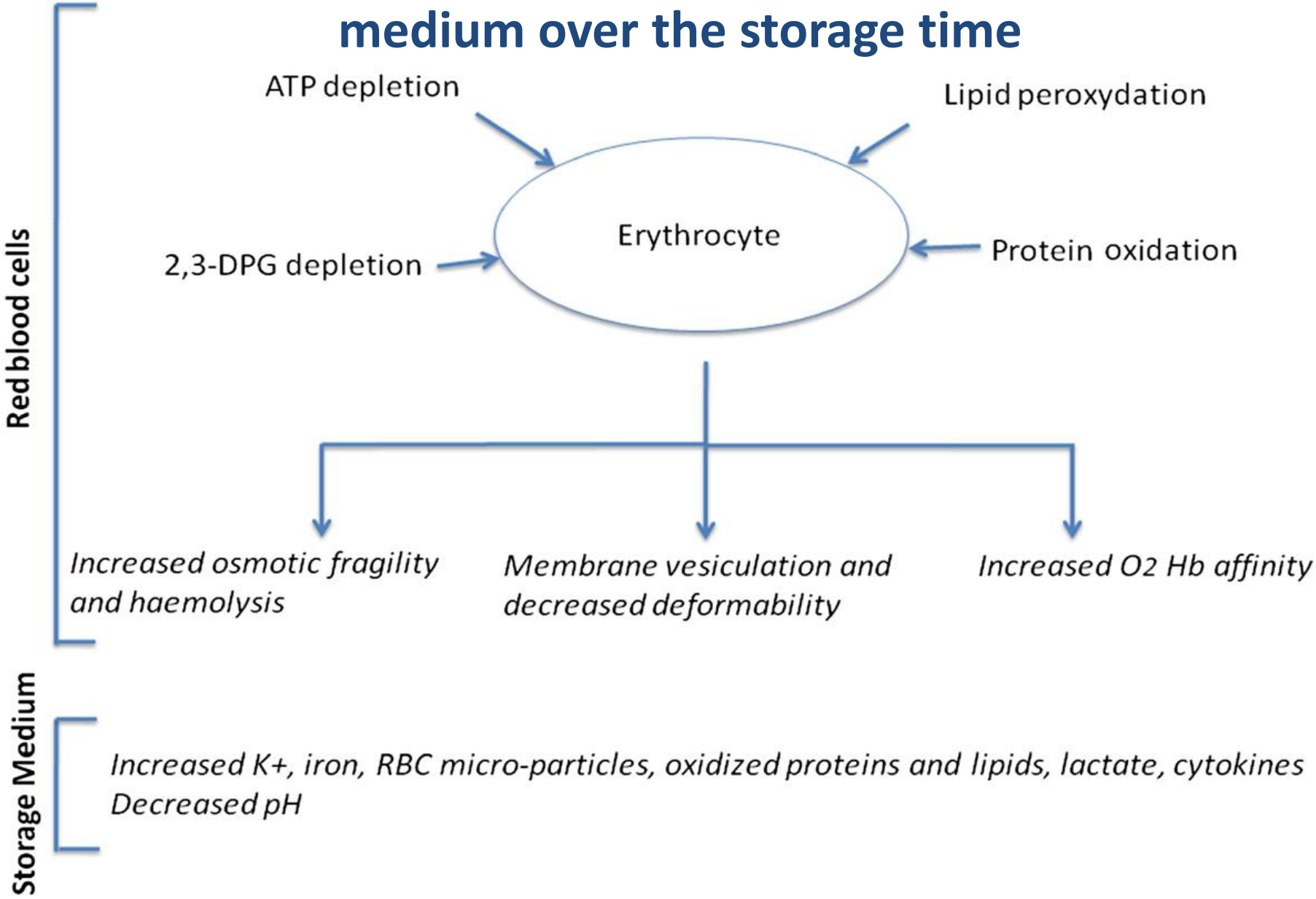
The Storage Lesion

Definition:
The constellation of changes occurring in a unit of packed red cells during storage.

I. ***Changes to red cell structure & function***

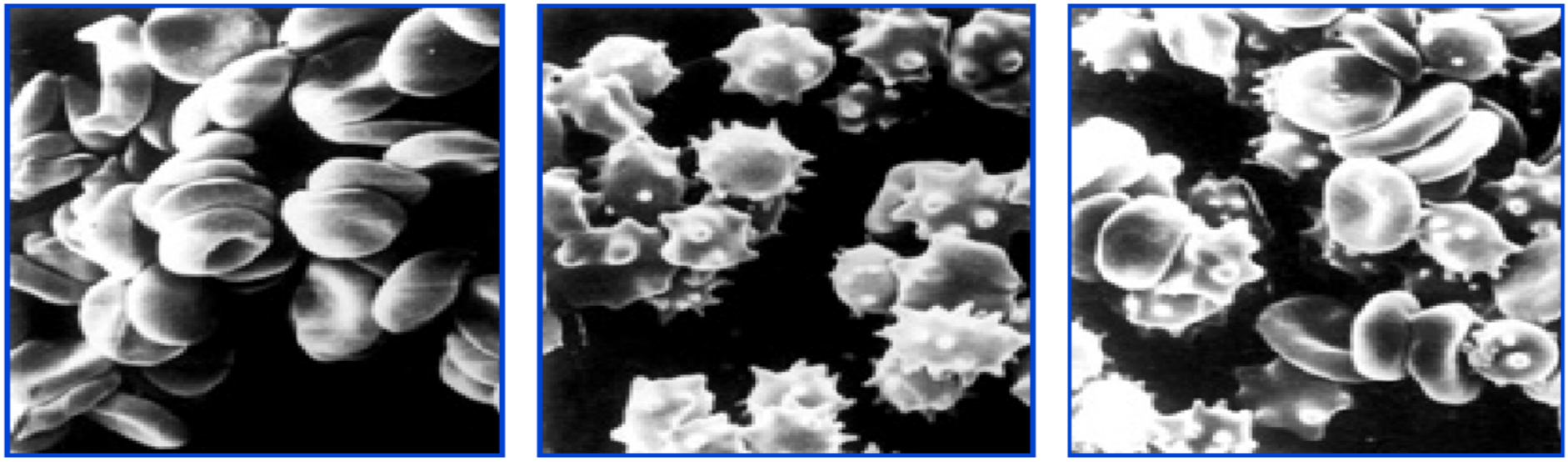
II. ***Changes in red cell storage medium***

Changes occurring in red blood cells and storage medium over the storage time



(Aubron et al. Annals of Intensive Care 2013, 3:2)

Effect of storage on tissue oxygenation



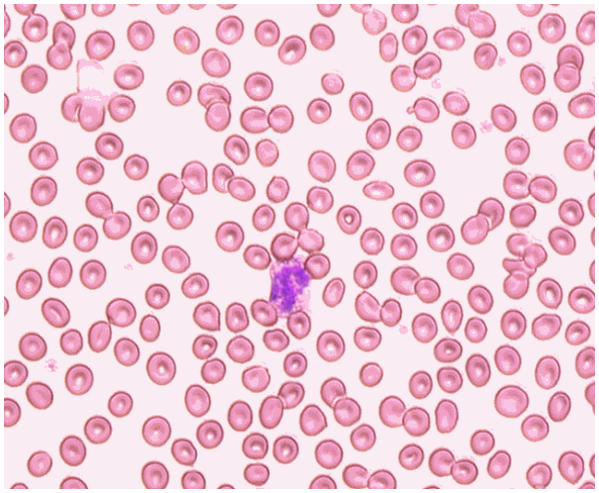
Scanning electron micrographs of red blood cells isolated from stored blood on Day 1, Day 21, and Day 35. During storage, the shape of RBCs changed gradually from normal discoid to echinocytes (dented or shriveled red cells).
Reproduced with permission from: Hovav et al. *Transfusion*. 1999;39:277-281.

After 14 days, the red cells become less pliable and therefore unable to traverse small vessels of the microcirculation, ultimately resulting in decreased oxygen delivery because the oxygenated red cells cannot traverse the end-organ capillary beds.

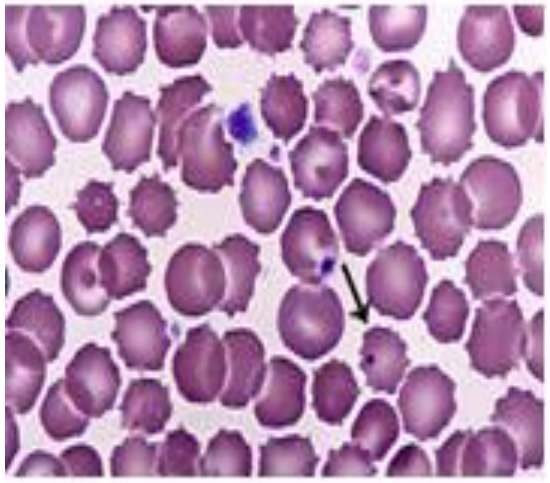
Effect of storage on tissue oxygenation (continue)

The change in shape from

biconcave disks

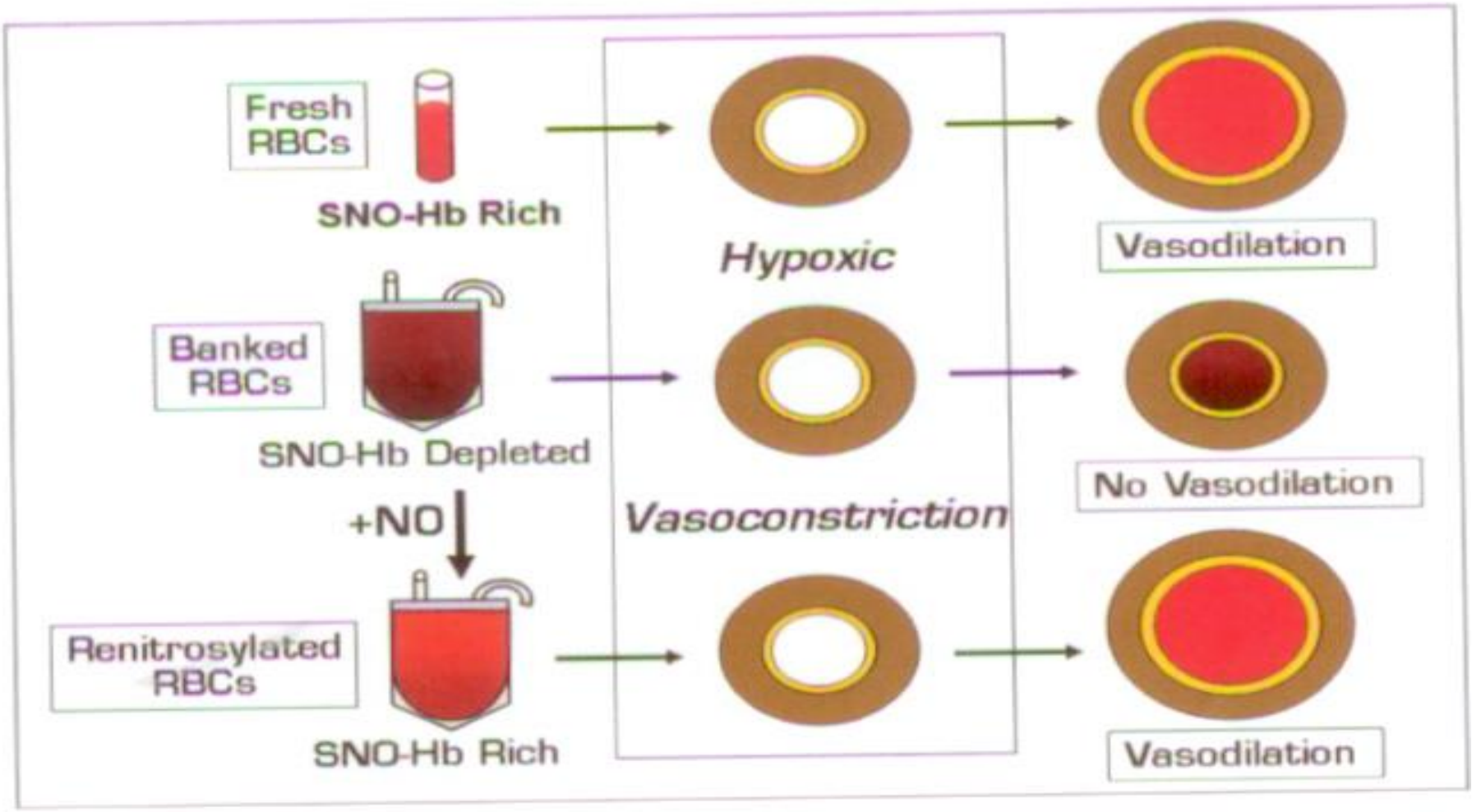


spiculated echinocytic



makes the cells more aggregable, increasing the likelihood of occluding the microcirculation, leading to tissue ischemia

Storage Depletes RBC Nitric Oxide Bioactivity



Main biochemical changes in RBC storage medium and in loss of RBC deformability over the storage period

Variables	Length of storage			
	Day 1	Days 7	Days 15	Day 42
K (mmol/L)	3.9 ± 0.6	13.6 ± 1.7	24.5 ± 2.1	46.6 ± 4.1
pH	6.8 ± 0.03	6.74 ± 0.03	6.64 ± 0.02	6.37 ± 0.04
Lactate (mmol/L)	3.6 ± 0.4	7.8 ± 0.7	17.2 ± 2.5	34.5 ± 4.4
Iron (µmol/L)	3.8 ± 0.9	6.8 ± 2.9	7.6 ± 1.6	14.2 ± 2.9
Free Hb (g/L)	1.3 ± 0.5	1.5 ± 0.8	1.7 ± 0.5	3.0 ± 2.1
% of irreversible deformed RBCs	-	8.4 ± 1.6	14.7 ± 2.6	29.9 ± 4.0

Lelubre C, et al. Transfusion 2009, 49:1384–1394.
Aubron C, et al. Transfusion 2012, 52:1196–1202.

Accumulation of various soluble bioactive substances (cytokines, histamines, lipids, enzymes) , primarily but not exclusively derived from passenger leukocytes contained in the donor unit.

- **Immunosupression** (increased association with nosocomial and post-operative infections and increased cancer recurrence.

- **Immune overactivation** (HTR, TAGVH, TRALI, and possible autoimmune diseases)

Stored blood and transfusion-related acute lung injury (TRALI)

Acute-onset lung injury within 6 h of receiving any allogeneic blood components, particularly plasma or plasma-containing products

pathogenesis

- **Antibody mediated;** with donor's antibodies against the recipient's human leukocyte antigens → activation and sequestration of granulocytes in lung and endothelial damage

- **“Two-hit” or “Two-event” hypothesis**

TRALI results from two events:

one event is patient-derived; and results in endothelial activation and granulocyte priming (*e.g.*, surgery or sepsis)

other event is delivered by transfused blood; and results in activation of granulocytes (*e.g.*, presence of donor’s antibodies against the recipient’s leukocytes or presence of proinflammatory agents as a result of extended storage of blood)

Controversy on Impact of Aged Stored RBCs

Effect of storage time of RBCs on length of ICU & hospital stay

In 698 ICU patients the transfusion of RBCs stored >14d was associated with ↑ length of ICU stay

Martin et al, Clin Invest Med 1994; **17**

In trauma patients reported that the dose of aged blood was significantly correlated with longer ICU stay

Murrell et al, Am.Surg. 2005 Sep; **71**

Reported in cardiac surgery patients an association of both ICU and hospital LOS

Basran et al, Anesth.Analg. 2006 Jul; **103**

Pettila et al. prospective multicenter , 757 patients increase LOS and mortality

Pettila et al. Crit Care 2011, 15:R116.

Effect of storage time of RBCs on length of ICU & hospital stay (Continue)

Leal-Noval et al, reported in cardiac surgery patients no associated between long storage time of RBCs and ICU-LOS. **Anesthesiology 2003 Apr; 98**

Gajic et al stratified his population of mechanically ventilated patients on mean RBC storage "<15d", "15-20d", ">20d" and found no association of these strata with ICU-LOS. **Transfusion 2004 Oct; 44**

Mckenny et al. in Post-cardiac surgery 1153 Retrospective single center, no effect on Early post-operative mortality, **Br J Anaesth 2011, 106:643–649**

The association between age of transfused RBCs and mortality

Basran et al. reported increase mortality with the mean storage time and the maximum storage time of the transfused RBCs, in transfused cardiac surgery patients. **Anesth.Analg. 2006 Jul; 103**

Koch et al. 6002 pt. Retrospective single-center Post-CABG or valve surgery Mixed Old blood >14 days was associated with increase mortality. **N Engl J Med 2008, 358:1229–1239.**

Van Straten et al. in Post-CABG, 3475 Retrospective single center not increased Mortality. **J Thorac Cardiovasc Surg 2011, 141:231–237.**

The association between age of transfused RBCs and mortality (Continue)

In 2008, Koch et al reported on 6002 cardiac surgery patients, A significant association between mortality and storage time of transfused RBCs

N.Engl.J.Med. 2008 Mar 20

Weinberg et al also analysed mortality with the amount of young (<14 d) and old (≥14 d) RBC transfused in 430 less severely injured trauma patients .The amount of old RBC was associated with mortality, the amount of young RBC was not.

J.Trauma 2008 Oct; 65

The association between age of transfused RBCs and mortality (Continue)

Edna et al could not see any independent association between mean storage time and survival in patients of colorectal surgery. **Dis.Colon Rectum 1998; 41**

Murrell et al, in 2005, did not find an association between the dose of aged blood and mortality in major trauma patients. **Am.Surg. 2005 Sep; 71**

Hebert et al,on a randomised pilot study in 57 transfused cardiac/ICU patients did not find difference between patients receiving either RBCs stored >19d) or RBC stored <8d . **Anesth.Analg. 2005 May; 100**

The association between age of RBCs and infectious complications

In rectal cancer patients the postoperative infections were higher in those who received stored RBCs for >20 days

Mynster et al, Scand.J.Gastroenterol. 2000; 35

In trauma patients there was association between infection and the number of RBCs stored >14 days

Offner et al Arch.Surg. 2002; 137

Andreasen et al. Post-CABG or valve surgery 1748 Retrospective multicenter Place of surgery increase incidence of postoperative infections. **Eur J Cardiothorac Surg 2011, 39:329–334.**

Juffermans et al. 196 Trauma patient. Retrospective single-center PRBCs > 14 days increased infections. **Blood Transfus 2012, 10:290–295.**

The association between age of RBCs and infectious complications (Continue)

In 181 mechanically ventilated patients, there was no association between the age of stored RBCs and the occurrence of sepsis. **Gajic et al Transfusion 2004 Oct; 44**

Yap et al found no association between postoperative pneumonia and the RBC storage time >30 days
Ann.Thorac.Surg. 2008 Aug; 86

Mckenny et al. in Post-cardiac surgery 1153 Retrospective single center, no increase in post-operative infection rate,
Br J Anaesth 2011, 106:643–649

Effect of age of transfused RBCs on patient outcomes after cardiac surgery

2872 patients received 8802 units of blood that had been stored for 14 days or less, and 3130 patients received 10,782 units of blood that had been stored for more than 14 days

Results

Patients who were given older units had higher rates of Intubation >72 hours, renal failure, sepsis, in-hospital mortality and 1 year, mortality

Koch CG, et al.N Engl J Med. 2008 Mar 20

Effect of age of transfused RBCs on patient outcomes after cardiac surgery (Continue)

670 patients who had nonemergency CABG or Valve surgery and had at least 2 RBC units transfused.

Results

The storage age of RBC was not independently associated with increased ventilation hours postoperative early mortality, renal failure, pneumonia, intensive care unit stay.

Yap CH, et al Ann Thorac Surg. 2008 Aug;86

Impact of age of transfused blood on Less Severely Injured Trauma Patients

In a mild to moderately injured intensive care unit patient cohort, the receipt of RBCs stored beyond 2 weeks was independently associated with increase mortality, renal failure, and pneumonia.

Weinberg J A, et al, Journal of Trauma-Injury Infection & Critical Care: October 2008

Impact of age of transfused blood on cerebral oxygenation in severe TBI

The effects of transfusion of erythrocytes with four different storage periods on brain tissue oxygen tension (PtiO2) (Prospective, observational study on NICU 66 male, nonbleeding, HD stable anemic patients (hemoglobin <95 g/L) GCS <9.)

Results

Transfusion of erythrocytes increased cerebral oxygenation in patients with severe traumatic brain injury, except in those transfused with erythrocytes stored >19 days.

Leal-Noval SR, et al, Crit Care Med. 2008 Apr;36

Summary

- RBCs undergo significant changes during storage Which may affect ability of stored RBCs to deliver O2
- There is no consensus in the literature on possible adverse effects of "older" blood.
- Prospective trials needed to evaluate the effects of transfusion of aged stored RBCs
- While waiting for the results of these trials on the age of blood, the word “prioritize” may be the key
- We should identify the patients who benefit most from transfusions and especially those who are likely to benefit most from the newer units of blood.

The age of transfused RBCs in ICU patients: one or two questions?

Is old blood harmful?

Is fresh blood beneficial?

Conclusion

Is old blood harmful?

Unclear if transfusion of older stored RBCs associated with increased morbidity and mortality

Is fresh blood beneficial?

Clear that the storage lesions accumulating over 42 days are unlikely to be beneficial to recipients

"Specially the critical one"


Thank
You