Age of blood: Does it matter?

Philip Norris, M.D.

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How does the clinician look at blood?

Fresh Stored

Does the RBC storage lesion exist?

- Retrospective/observational studies suggest older RBC units associated with:
  - Increased risk of pneumonia
  - Longer length of stay
  - Increased mortality
  - Decreased recurrence of colorectal cancer
  - Decreased alloimmunization

Association of mortality with age of blood transfused in septic ICU patients

F. Robert Purdy MSc DVM MD FRCPC,
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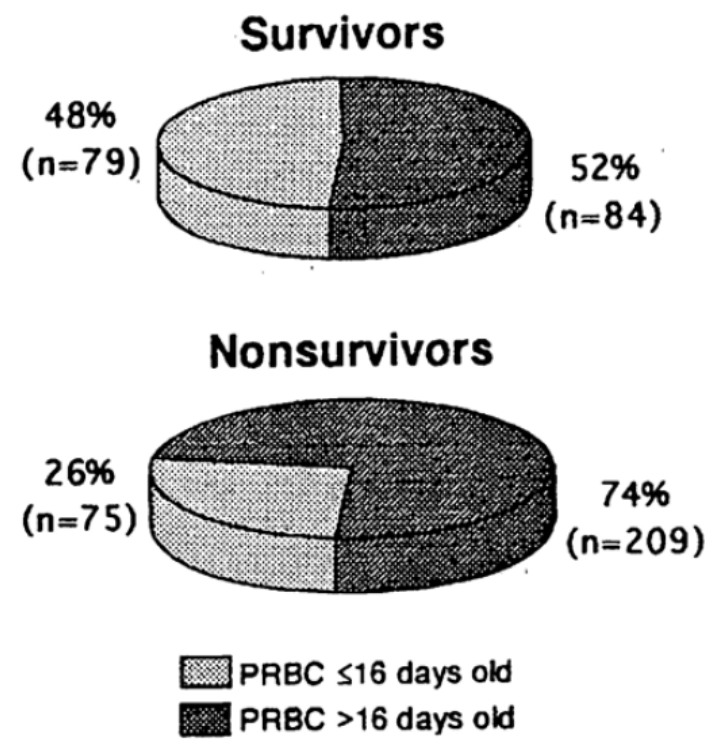
	*APACHE II Score**
Survivors (n = 12)	31(18–45)
Nonsurvivors (n = 19)	33(20–55)
P	0.06

	*During Septic Episode**	
	Number of units transfused/patient	*Age of units (days)*
survivors	5(2–70)	17(5–35)[16–19]
nonsurvivors	8(2–103)	25(9–36)[23–27]
P	0.21	<0.0001



RBC age in cardiac surgery patients

TABLE 6. Length of storage of transfused RBCs in relation to the development of postoperative pneumonia or wound infection among patients receiving allogeneic, poststorage-WBC-reduced allogeneic, or autologous RBC transfusions

		Length of storage of transfused RBCs (days)							
		All RBC units*				Oldest and second-oldest RBC units†			
Infection site	Patient group	Mean (± SE)	Median	Range	p value	Mean (± SE)	Median	Range	p value
Pneumonia or wound infection	Yes (n = 53)	15.2 (± 1.1)	12.2	4 - 34.7	0.0091	21.6 (± 1.5)	21.5	4 - 41	0.0002
	No (n = 214)	12.2 (± 0.5)	10.2	1.2 - 39		15.3 (± 0.8)	13.0	2 - 39	
Pneumonia only	Yes (n = 46)	15.1 (± 1.3)	11.7	4 - 34.7	0.0306	21.3 (± 1.7)	20.8	4 - 41	0.0018
	No (n = 221)	12.3 (± 0.5)	11.0	1.2 - 39		15.6 (± 0.8)	13.0	2 - 39	
Wound infection only	Yes (n = 10)	14.4 (± 1.5)	14.1	8.3 - 22.2	0.1963	20.7 (± 2.7)	17.8	10 - 33	0.1153
	No (n = 257)	12.7 (± 0.5)	11.0	1.2 - 39		16.5 (± 0.7)	14.0	2 - 41	

N = 216 transfused patients

RBC age in cardiac surgery patients

TABLE 2. Postoperative LOS in the hospital, postoperative LOS in the ICU, and number of transfused RBCs stratified by length of storage of the oldest RBC unit administered to each patient

	Length of storage of the oldest RBC unit transfused					
	1-7 days (n = 62)	8-14 days (n = 67)	15-21 days (n = 53)	22-28 days (n = 30)	29-35 days (n = 26)	36-42 days (n = 30)
Postoperative LOS in the hospital (days)						
Mean ± SE	7.3 ± 0.5	9.0 ± 0.7	9.5 ± 1.2	8.9 ± 0.9	10.3 (± 0.9)	11.4 ± 1.9
Median	6.0	6.0	7.0	8.0	8.5	9.0
Range	4-31	4-42	5-42	5-25	5-20	5-63
Postoperative LOS in the ICU (hours)						
Mean ± SE	38.5 ± 5.7	52.1 ± 5.5	65.2 ± 10.0	61.2 ± 13.2	57.4 ± 10.4	100.3 ± 30.7
Median	25.0	41.0	43.0	41.0	42.0	47.5
Range	14-336	16-243	17-447	17-377	18-265	21-912
Number of transfused RBCs						
Mean ± SE	2.4 ± 0.1	3.8 ± 0.4	4.3 ± 0.5	4.0 ± 0.5	5.2 ± 0.7	7.0 ± 0.9
Median	2.0	3.0	3.0	3.0	5.0	5.0
Range	1-6	1-18	1-23	1-12	1-19	2-23

RESULTS: There were no significant associations after adjustment for the effects of confounding factors.
CONCLUSION: This study did not corroborate the previously reported association between transfusion of old RBCs and increased morbidity. However, there is surprisingly little research on the clinical outcomes of the transfusions of old RBCs, and this hypothesis should be investigated further.

N = 268 patients

RBC age in cardiac surgery patients

The Association Between Duration of Storage of Transfused Red Blood Cells and Morbidity and Mortality After Reoperative Cardiac Surgery

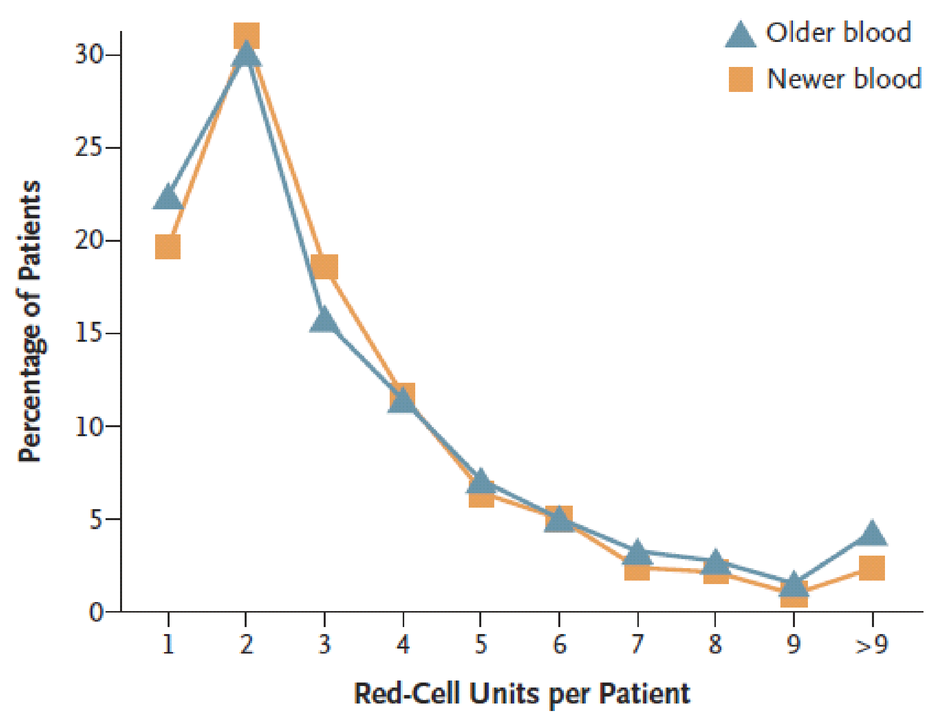
Sukhjeewan Basran, MD
Robert J. Frumento, MS, MPH
Allison Cohen, BS
Samuel Lee, MD
Yuling Du, PhD
Ervant Nishanian, MD, PhD

Red blood cells (RBCs) undergo numerous changes during storage; however, the clinical relevance of these storage "lesions" is unclear. We hypothesized that the duration of storage of transfused RBCs is associated with mortality after repeat sternotomy for cardiac surgery, because these patients are at high risk for both RBC transfusion and adverse outcome. We retrospectively analyzed 434 patients who underwent repeat median sternotomy for coronary artery bypass graft or valve surgery and who received allogeneic RBCs. Three-hundred-twenty-one (74%) patients met the criteria for eligibility. After adjusting for the effects of confounders and the total number of RBC transfusions, the duration of storage of the oldest RBC unit transfused was found to be associated with both in-hospital mortality (Cox proportional hazard ratio (HR) = 1.151; $P < 0.0001$) and out-of-hospital mortality (HR = 1.116; $P < 0.0001$). The mean duration of storage of transfused RBCs was also an independent predictor of in-hospital mortality (HR = 1.036; $P < 0.0001$).

Age of blood and mortality

- Compared cardiac surgery patients who received only blood ≤14 days (“fresh”) vs. only blood stored >14 days.

- Older blood 2.8% mortality vs. 1.7% in “fresh” blood



N = 6002

The Association Between Duration of Storage of Transfused Red Blood Cells and Morbidity and Mortality After Reoperative Cardiac Surgery

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Harold S. Kaplan, MD

Mark Stafford-Smith, FRCPC

Elliott Bennett-Guerrero, MD

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(Anesth Analg 2006;103:15–20)

RETRACTED ARTICLE

More than 12 million units of allogeneic red blood cells (RBCs) are administered in the United States annually, with more than 2 million units alone going to patients undergoing cardiovascular surgery (1). Patients undergoing repeat sternotomy for cardiac surgery are approximately three times more likely to receive a perioperative transfusion than those undergoing primary cardiac surgery (2). The transfusion of allogeneic RBCs has recently been described as a risk factor for decreased long-term survival after coronary artery bypass graft

effects may be caused by storage-related changes, including the depletion of 2, 3 diphosphoglyceric acid and adenosine triphosphate, reduced RBC deformability (6,7), and a significant increase in abnormally shaped RBCs (8). These storage lesions might impair oxygen delivery to tissues by increasing capillary transit time and reducing oxygen unloading from hemoglobin (9). A study in trauma patients demonstrated that the mean duration of storage of RBCs, the number of RBC units stored for longer than 14 days, and the number of RBC

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Basran et al., Anesth Analg 2006

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RBC age in European cardiac surgery patients

TABLE 3. Association of RBC storage time with length of ICU stay and 30-day mortality

	Crude model		Adjusted model	
Characteristic	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
ICU stay ("risk" of ICU discharge)				
Storage time*				
Mean of all RBC units (weeks)	1.01 (0.96-1.06)	0.64	1.01 (0.96-1.06)	0.76
Oldest RBC unit (weeks)	0.95 (0.91-0.99)	0.015	1.01 (0.96-1.05)	0.80
Youngest RBC unit (weeks)	1.05 (1.01-1.10)	0.029	1.00 (0.96-1.05)	0.90
All RBCs > 18 days†	0.97 (0.89-1.06)	0.52	0.98 (0.89-1.09)	0.74
30-day survival				
Storage time*				
Mean of all RBC units (weeks)	1.13 (0.89-1.43)	0.34	0.96 (0.72-1.29)	0.80
Oldest RBC unit (weeks)	0.85 (0.69-1.05)	0.13	0.98 (0.76-1.25)	0.85
Youngest RBC unit (weeks)	1.33 (1.04-1.68)	0.021	0.93 (0.71-1.23)	0.62
All RBCs > 18 days†	0.97 (0.58-1.61)	0.89	0.76 (0.42-1.37)	0.35

* Storage time is analyzed as a continuous variable, expressed in weeks.

† In the analysis "All RBCs > 18 days," the 950 patients receiving all RBCs older than 18 days are compared to the 945 patients receiving all RBCs younger than 18 days. The 837 patients receiving RBCs both younger and older than 18 days or RBCs stored for 18 days were excluded from this analysis.

N = 2732

More European data

TABLE 3. Short- and long-term relative risk of death after blood transfusion in relation to storage age of administered RBCs, among recipients of leukoreduced units only

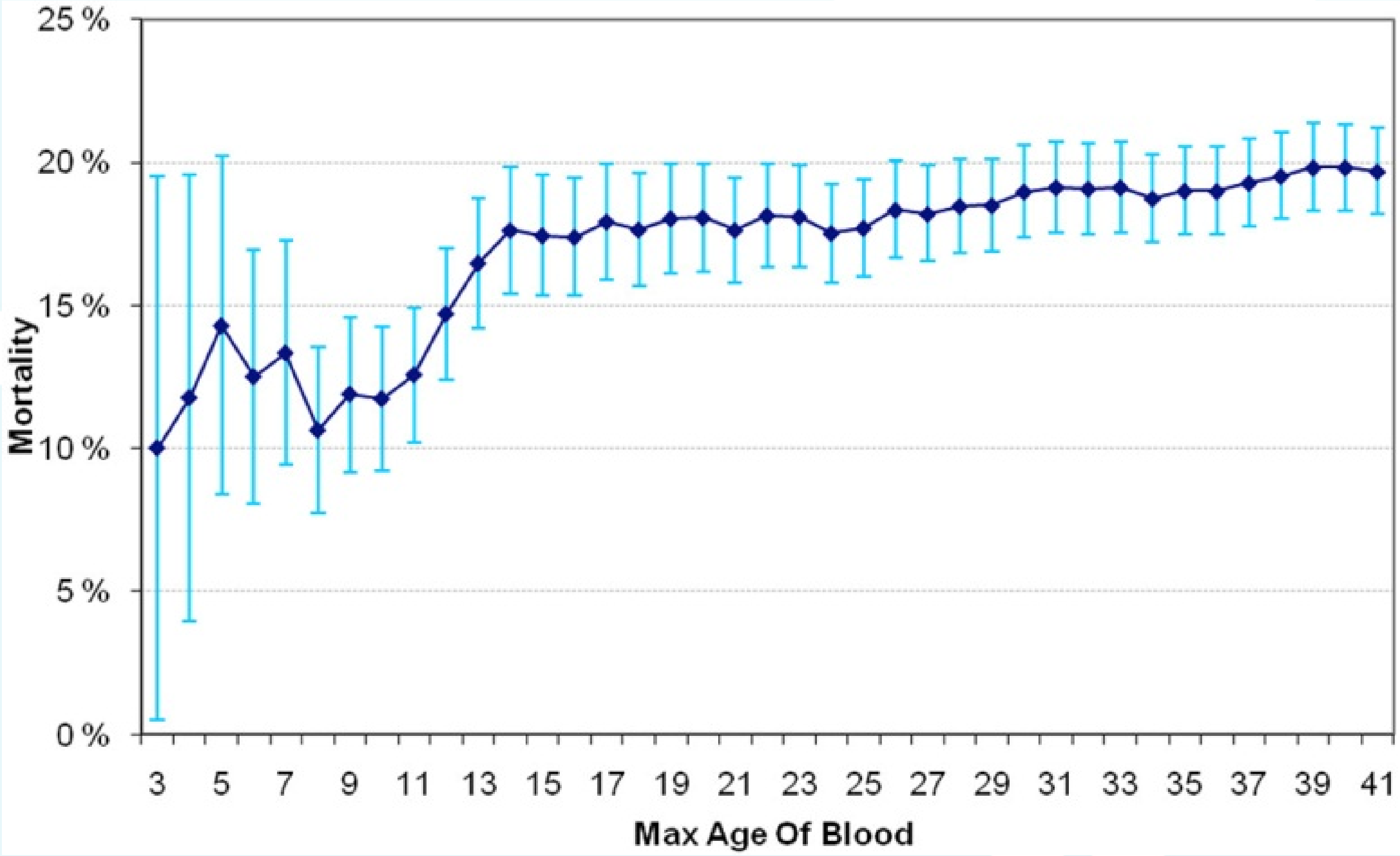
	Day 1 through Day 7		Day 8 through Day 730	
Storage age (days)	Events/person-years	Hazard ratio (95% CI)*	Events/person-years	Hazard ratio (95% CI)*
0-9	768/504	0.88 (0.79-0.97)	2,691/26,778	0.98 (0.94-1.02)
10-19	750/473	1.00 (reference)	2,379/20,152	1.00 (reference)
20-29	280/189	0.94 (0.82-1.08)	847/6,768	0.96 (0.90-1.02)
30-42	182/105	1.10 (0.93-1.31)	481/3,587	1.00 (0.93-1.08)
Mixed age	421/194	0.96 (0.84-1.09)	1,706/17,836	1.00 (0.95-1.04)

* Estimated using Cox proportional hazards regression, adjusted for number of transfusions, age, sex, blood group, calendar period, season, weekday, hospital, and indication.

N = 405,000

Edgren et al., Transfusion 2010

News from the Antipodes: ICU patients



N = 757

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Pettila et al., Crit Care 2011

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Where does this leave us?

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Aubron *et al. Annals of Intensive Care* 2013, **3**:2
http://www.annalsofintensivecare.com/content/3/1/2

Annals of Intensive Care
a SpringerOpen Journal

REVIEW Open Access

Age of red blood cells and transfusion in critically ill patients

Cécile Aubron*, Alistair Nichol, D Jamie Cooper and Rinaldo Bellomo

- Stored RBCs harmful: 18 studies
- Stored RBCs not harmful: 14 studies

How do RBCs change over their shelf-life?

What does that mean to the patient?

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RBC changes with storage

- Decreased 2,3-DPG, pH
- Increased lactate, potassium
- Signs of RBC damage
- Morphological changes
- Increased adhesion to endothelial cells
- Decreased SNO

RBC changes with storage

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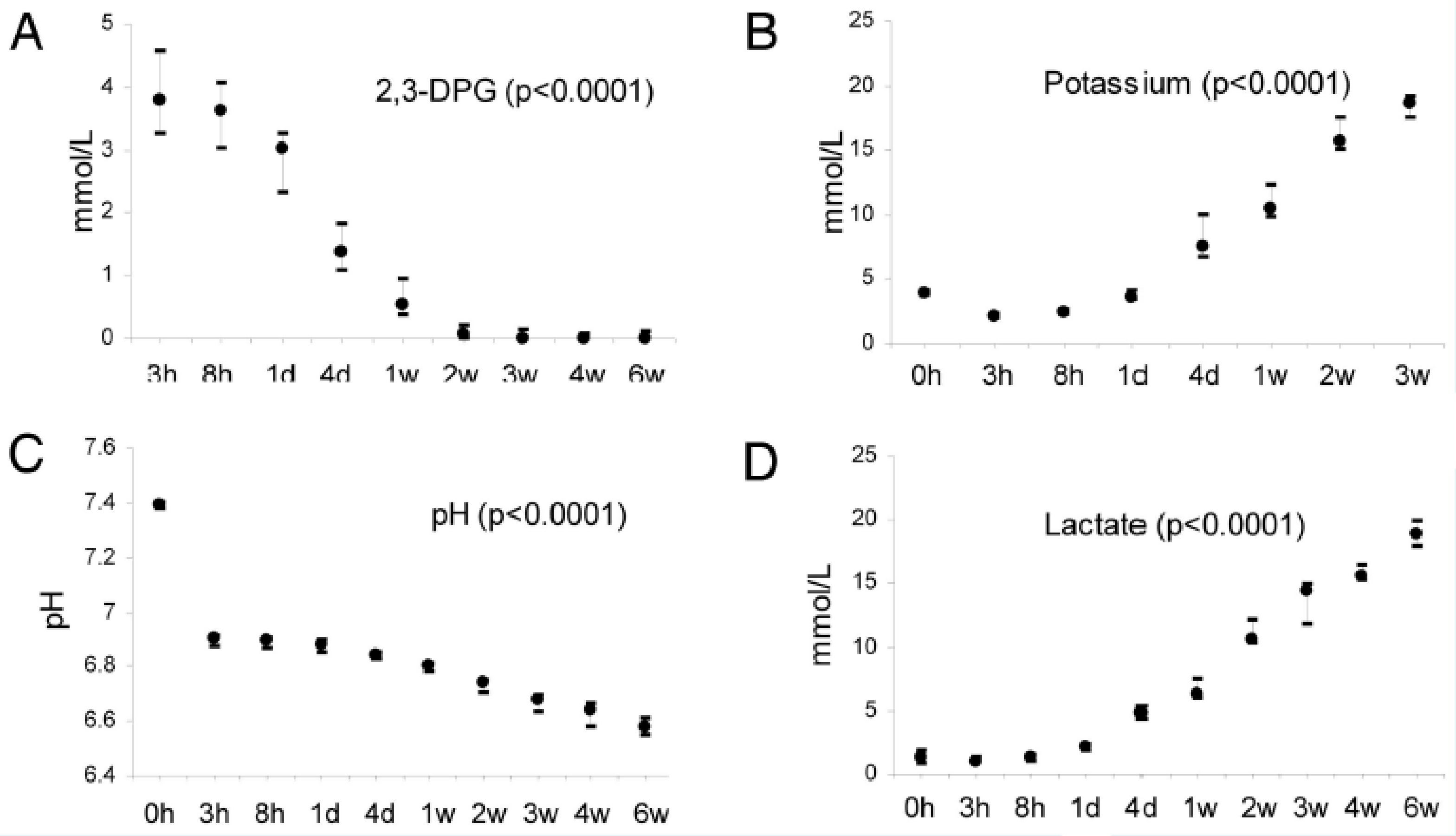
Electrolyte changes with storage



RBC changes with storage

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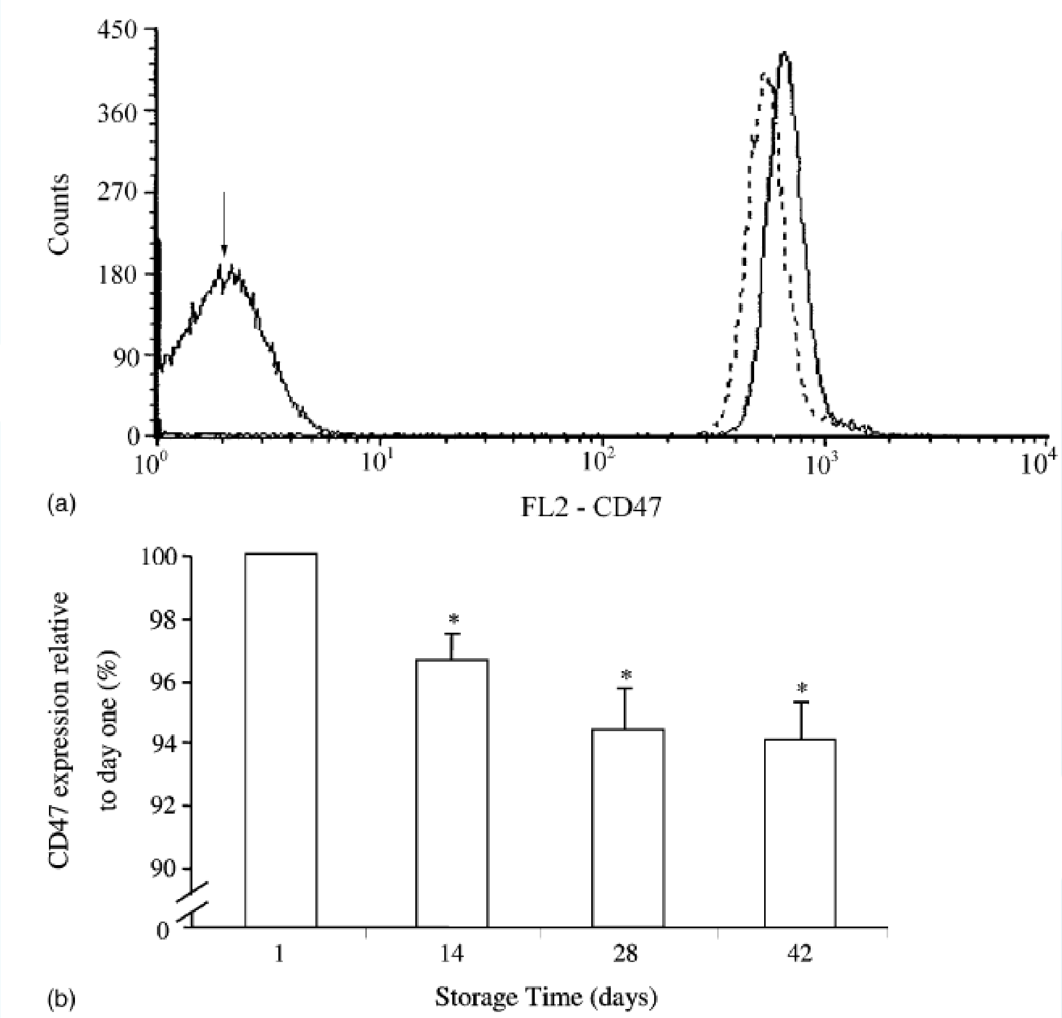
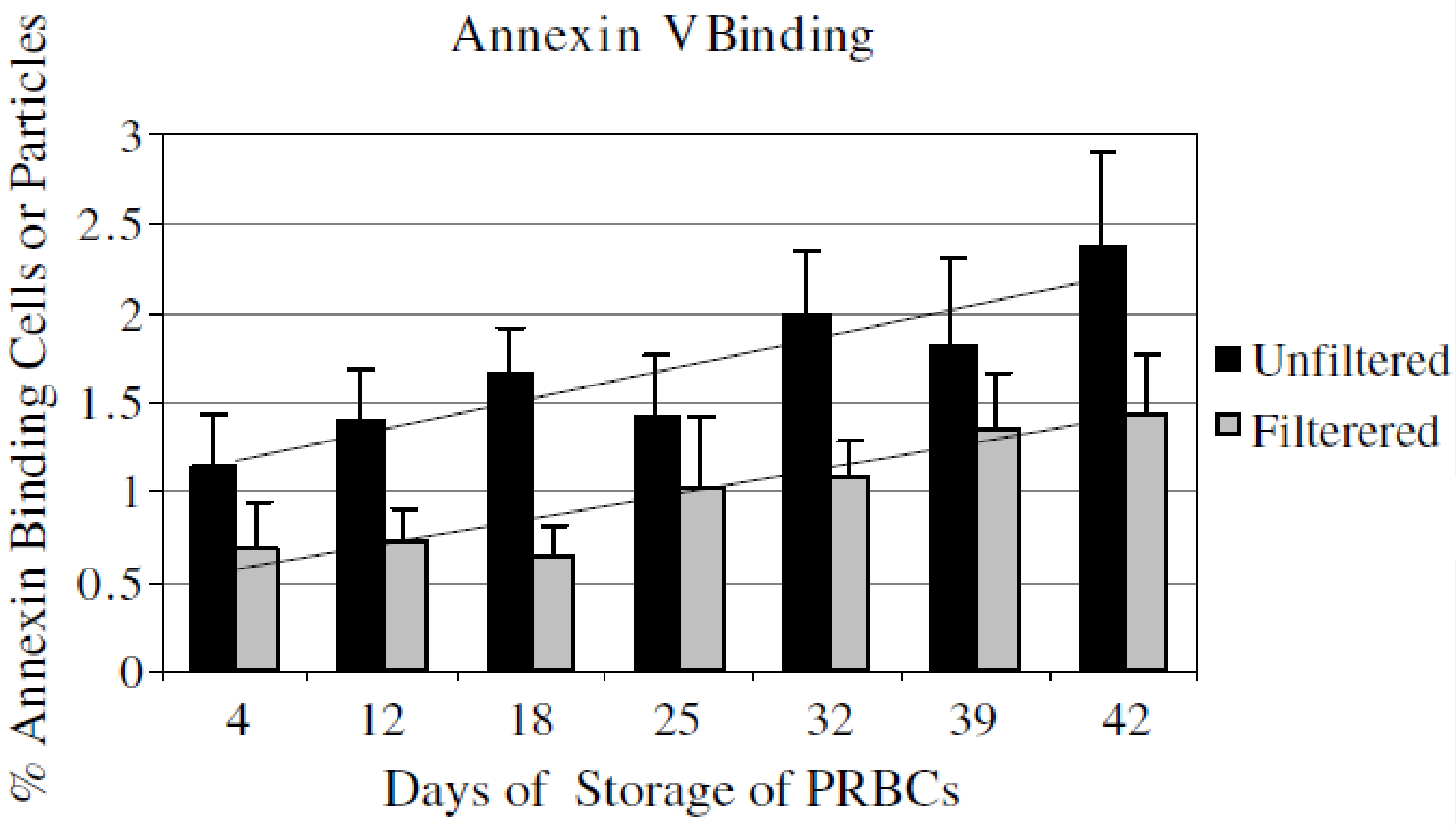
Decreased RBC CD47 at 42 days



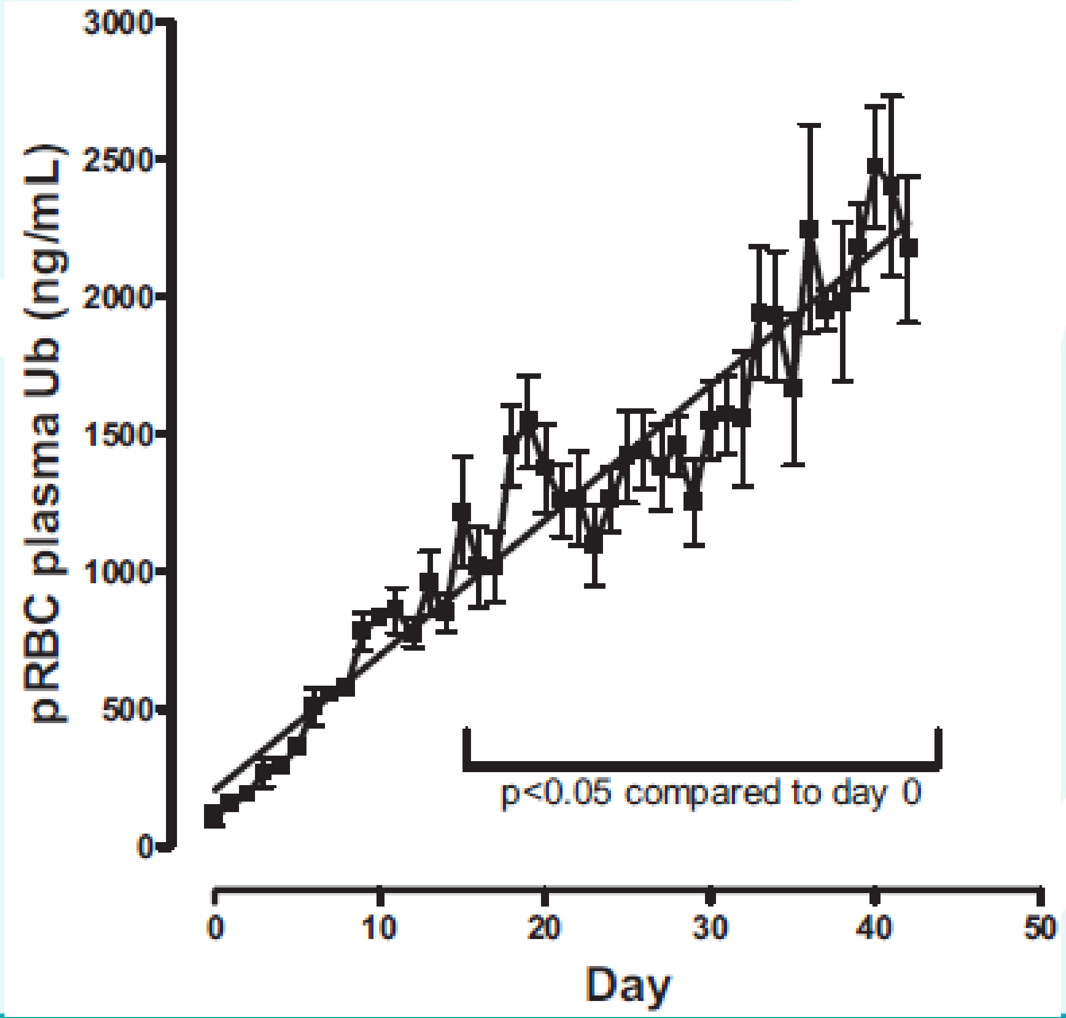
Anniss & Sparrow, Trans Apher Sci 2002

Increased Annexin V Binding

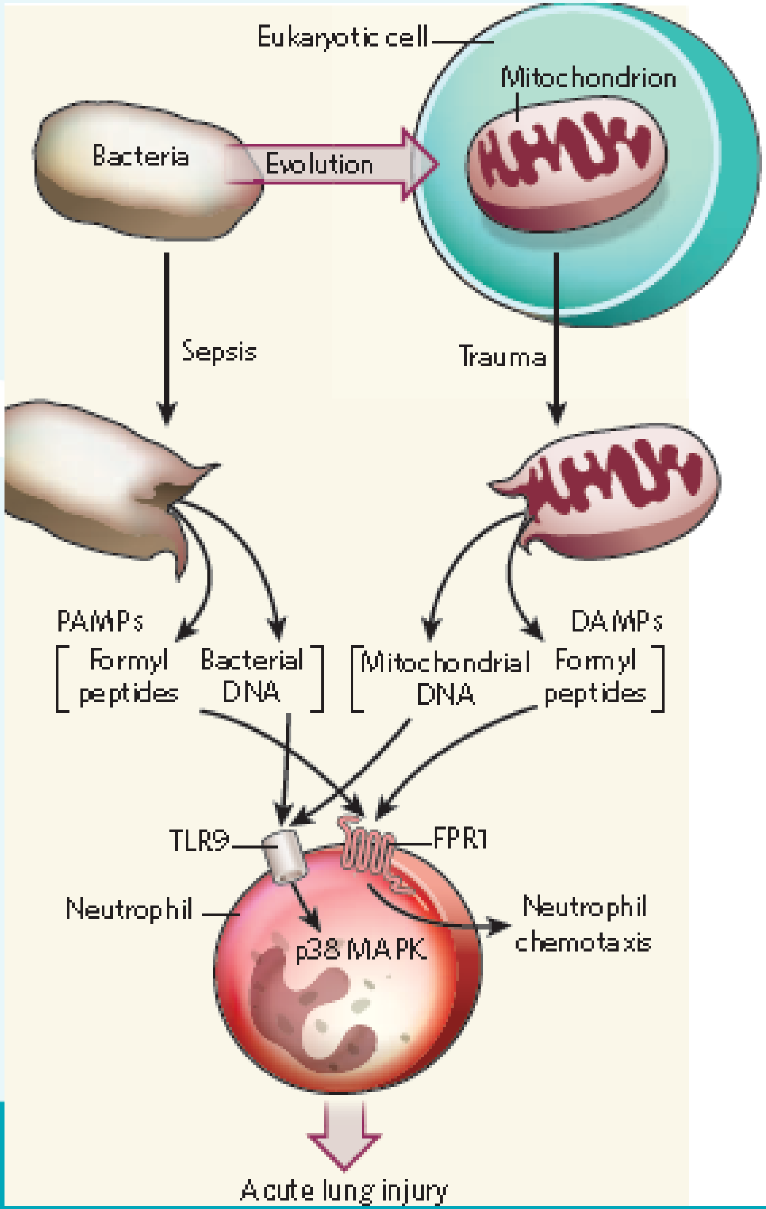


Cardo et al., Transfus Apher Sci 2008

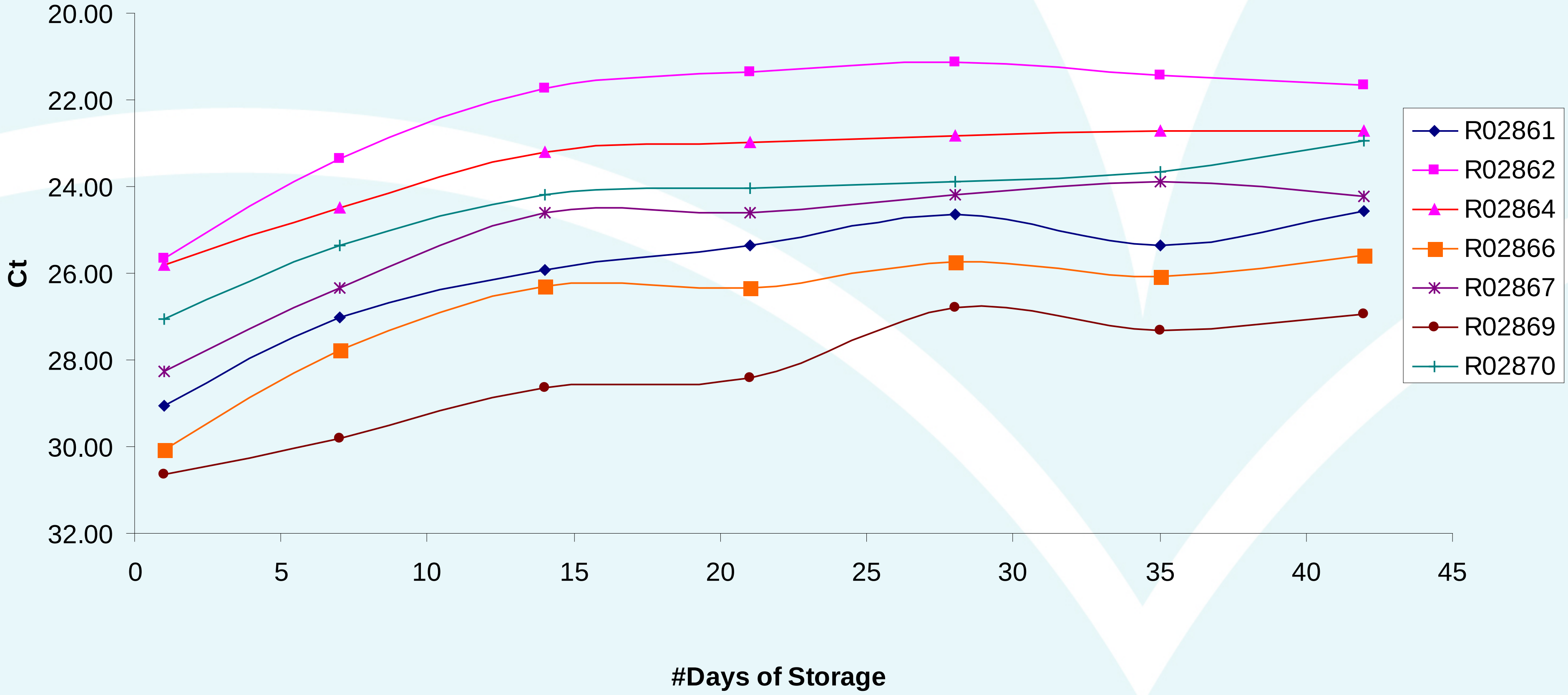
Ubiquitin levels rise in stored RBCs



PAMPs and DAMPs



Mitochondrial DNA release



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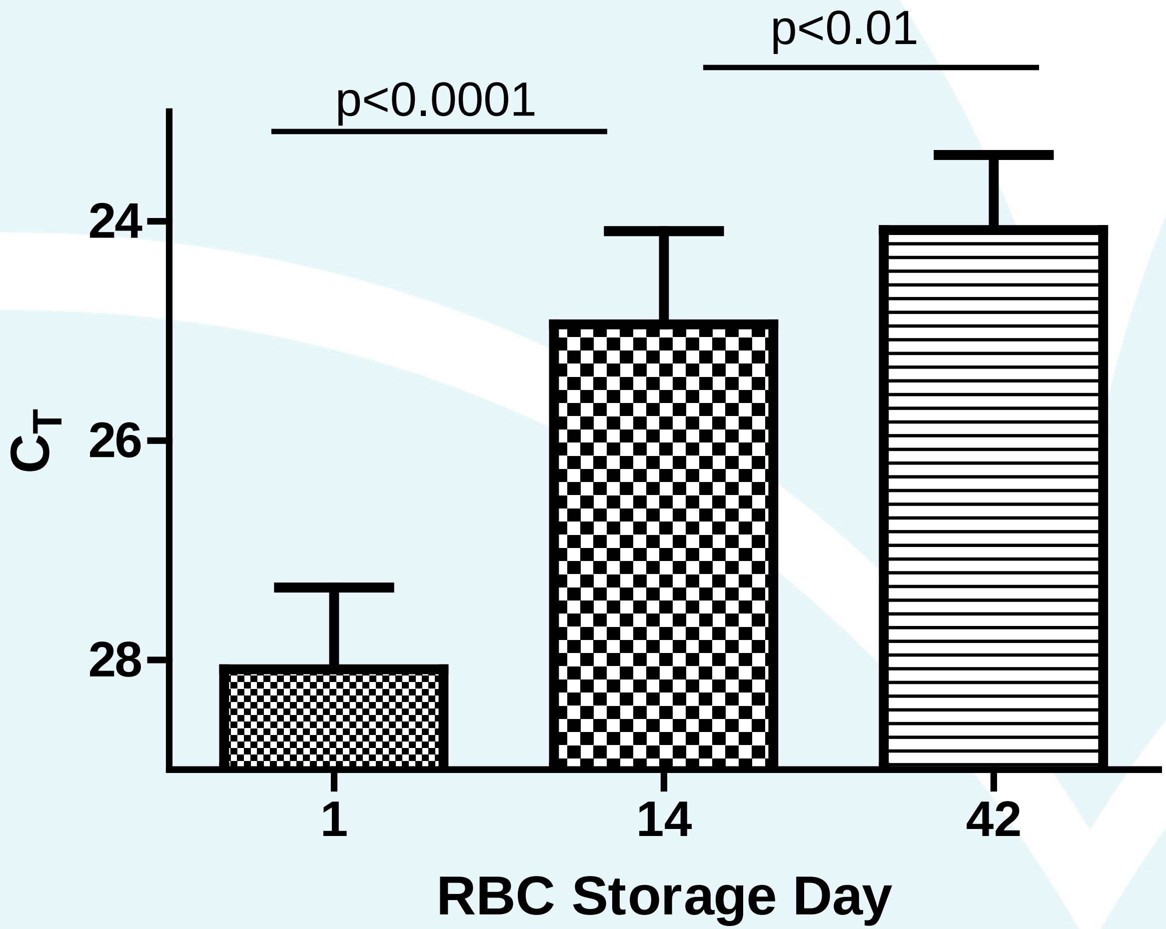
Mitochondrial DNA release



RBC changes with storage

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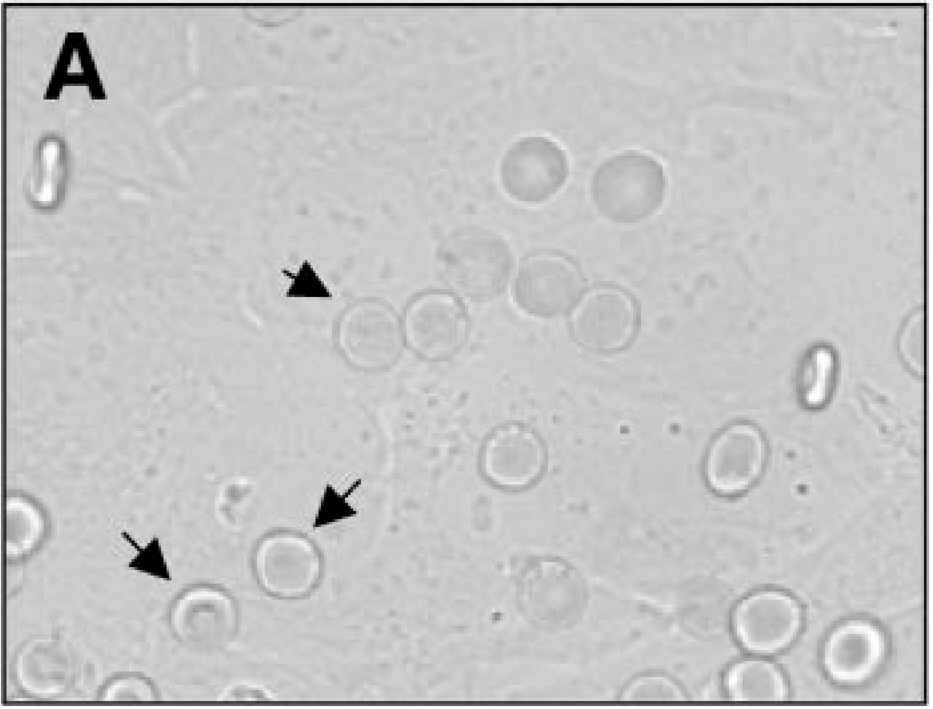
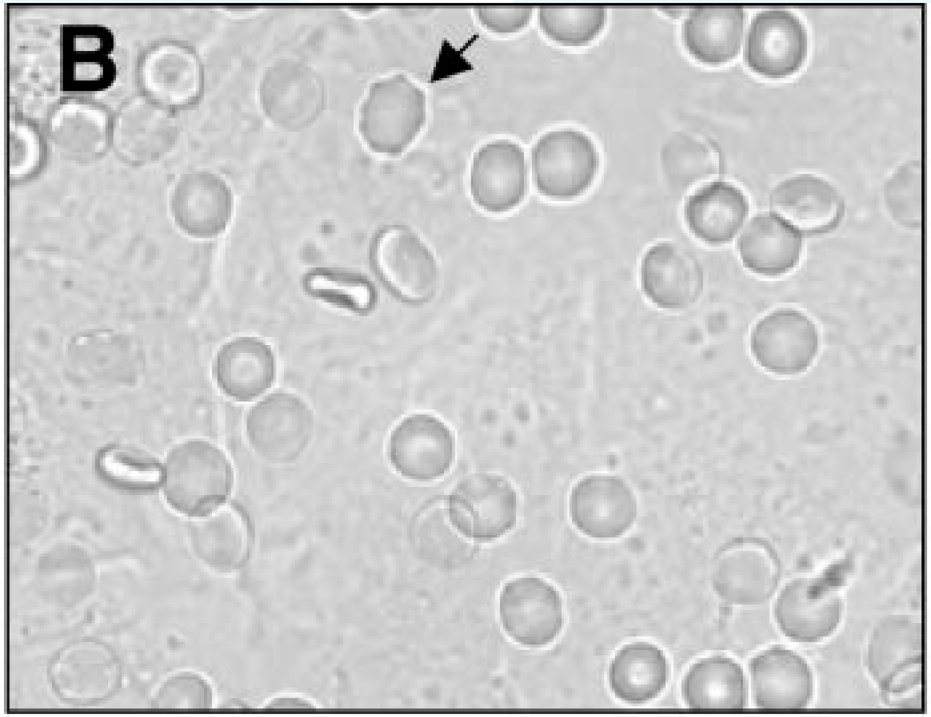
RBC morphology changes with storage time

Day 1



Day 21



Anniss & Sparrow, Transfusion 2006

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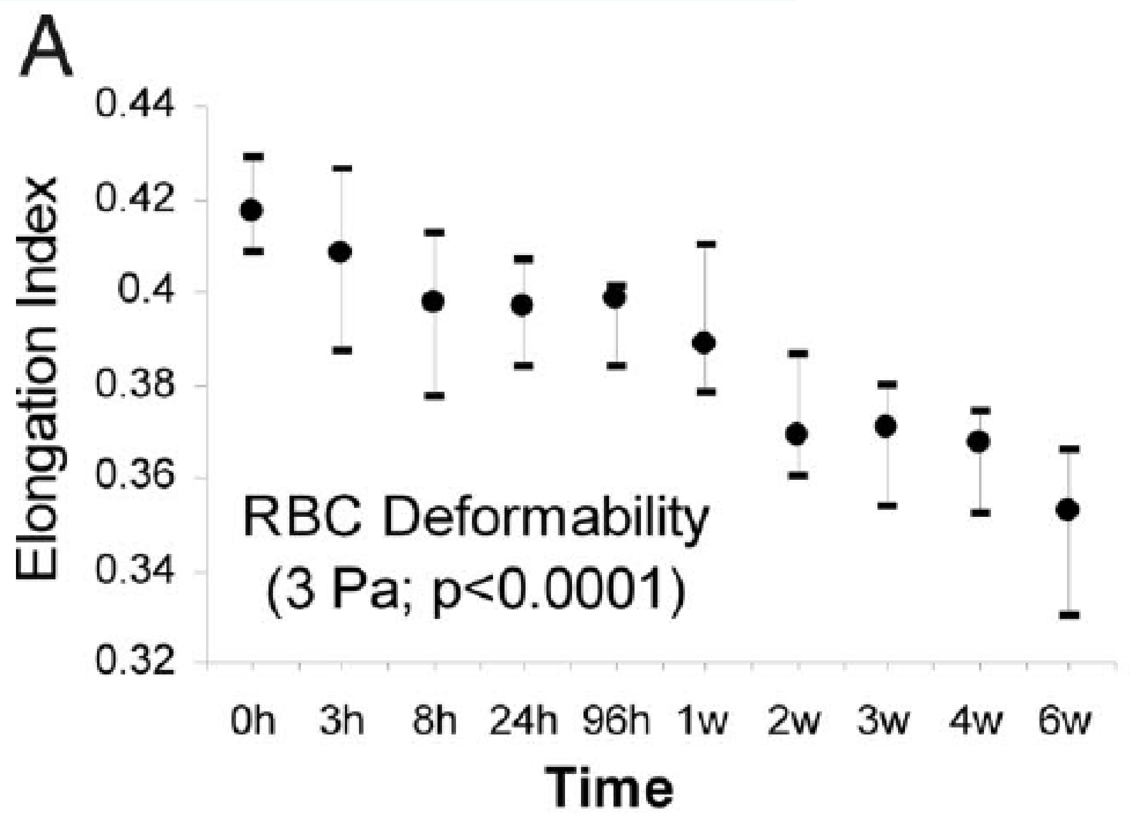
RBC deformability decreases



Bennett-Guerrero et al., PNAS 2007

RBC changes with storage

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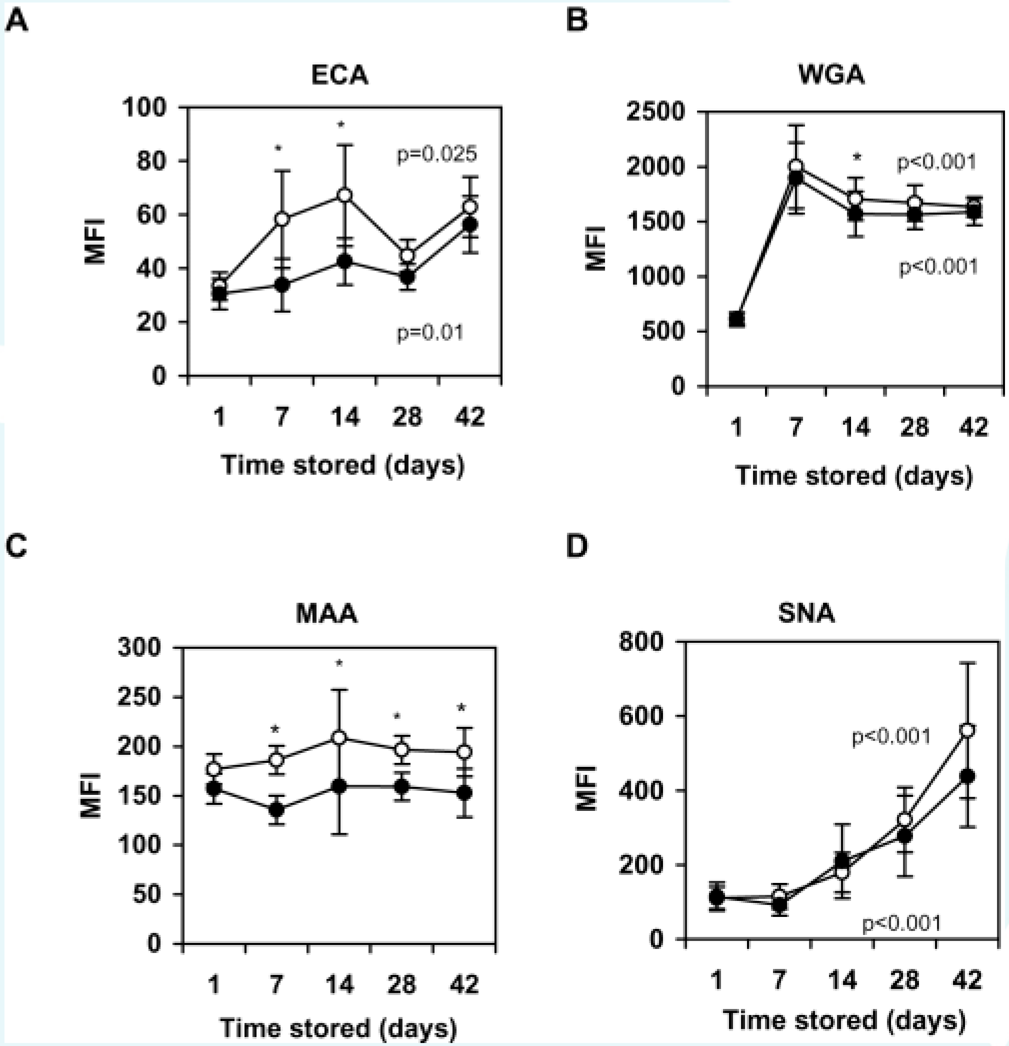
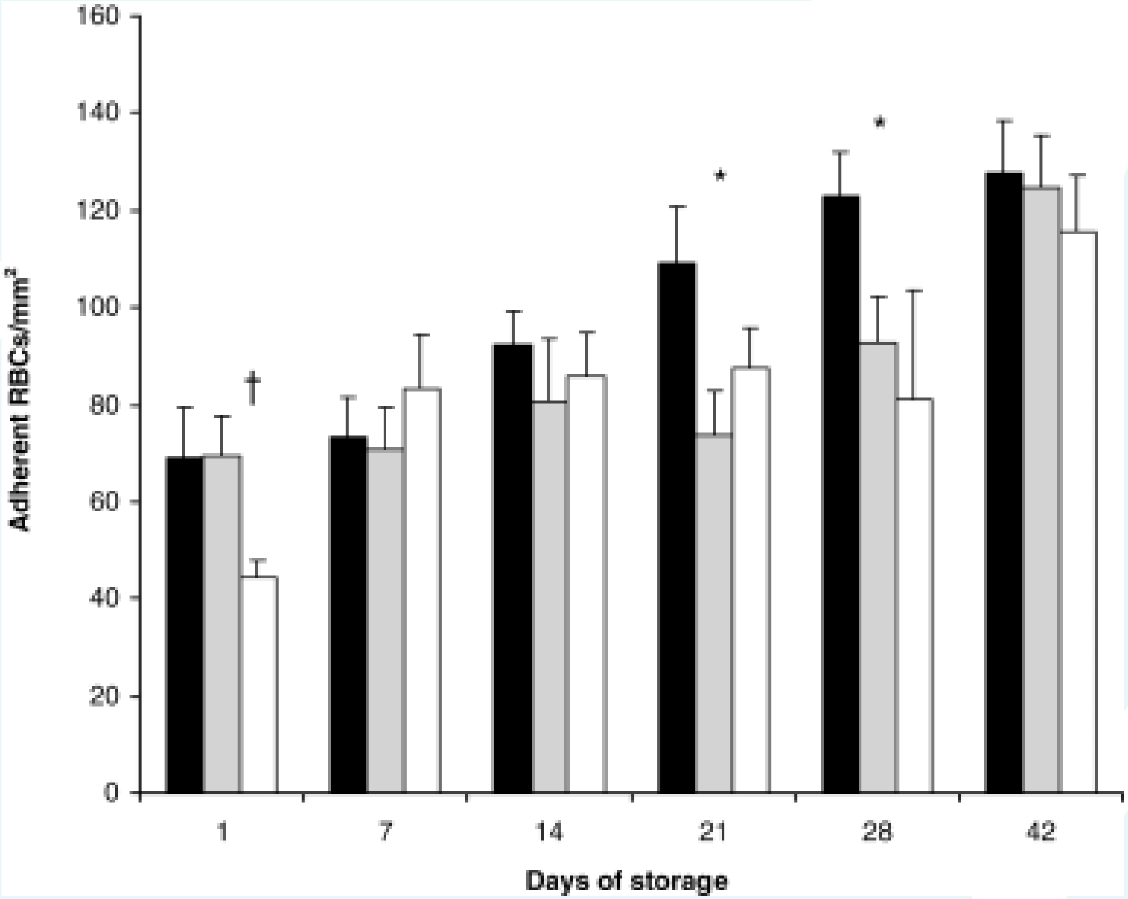
Lectin binding changes with RBC storage



Sparrow et al., Transfusion 2007

RBC-EC adhesion increases with storage time



Anniss & Sparrow, Transfusion 2006

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RBC changes with storage

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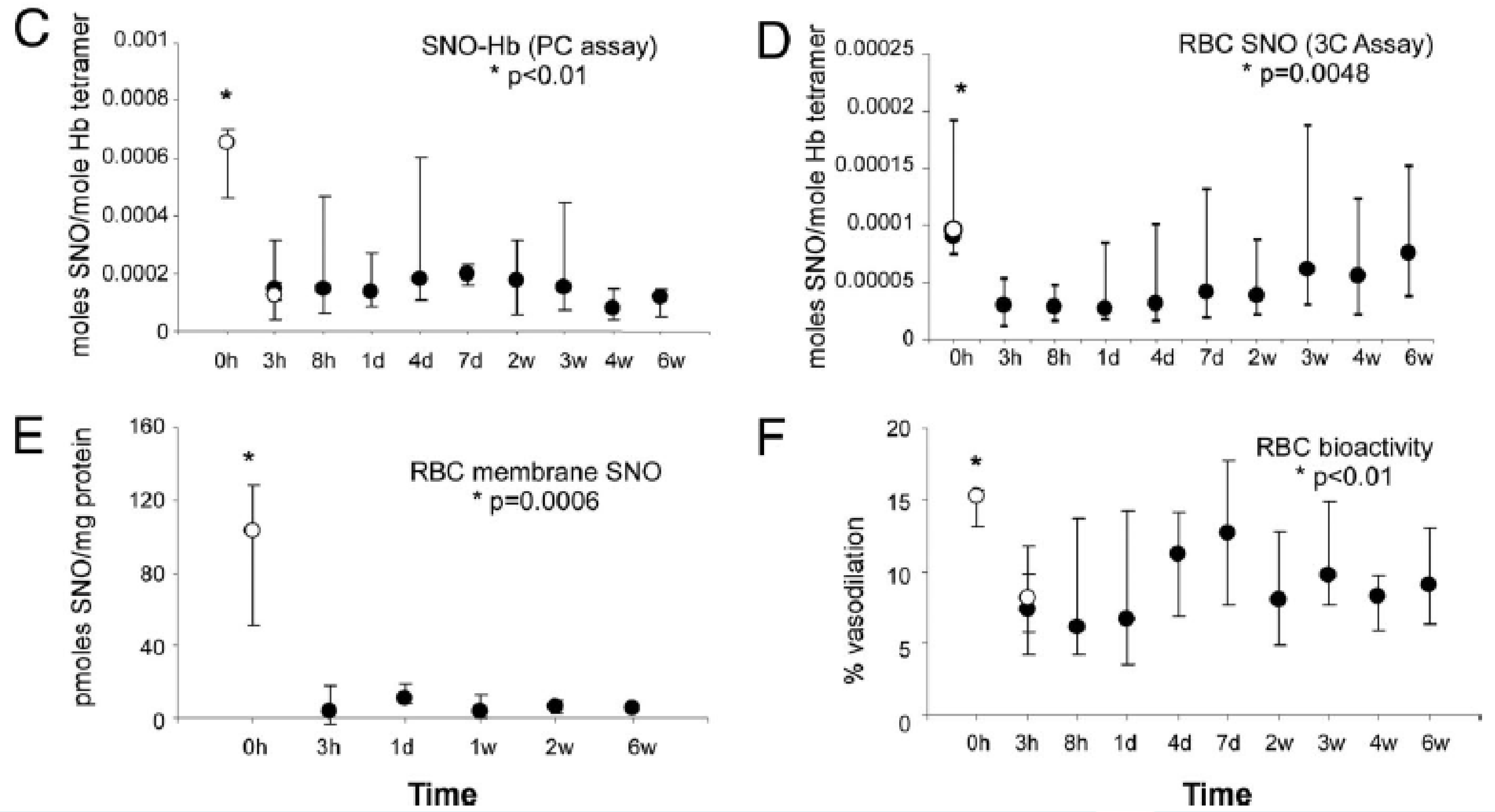
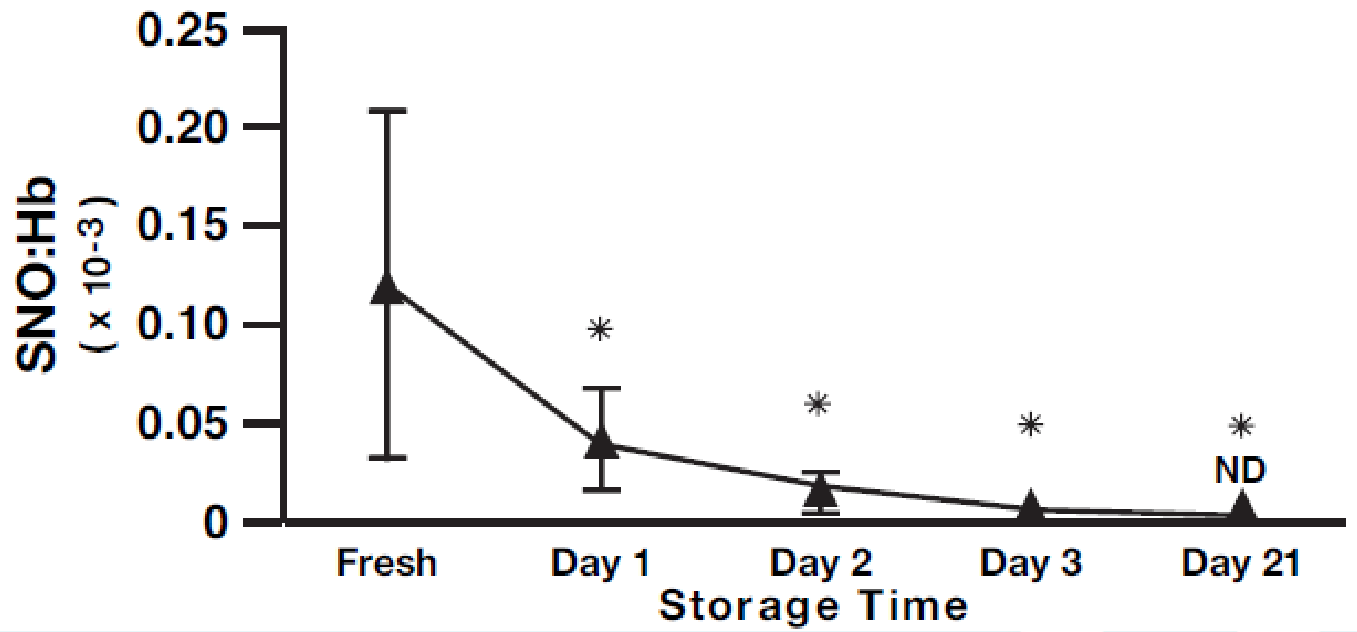
Decreased SNO



Bennett-Guerrero et al., PNAS 2007

Decreased SNO



How do RBCs change over their shelf-life?

What does that mean to the patient?

Recipient effects of RBC storage

- Blood flow in transfused tissues
- Effects on the clotting cascade
- Activation of recipient immune system

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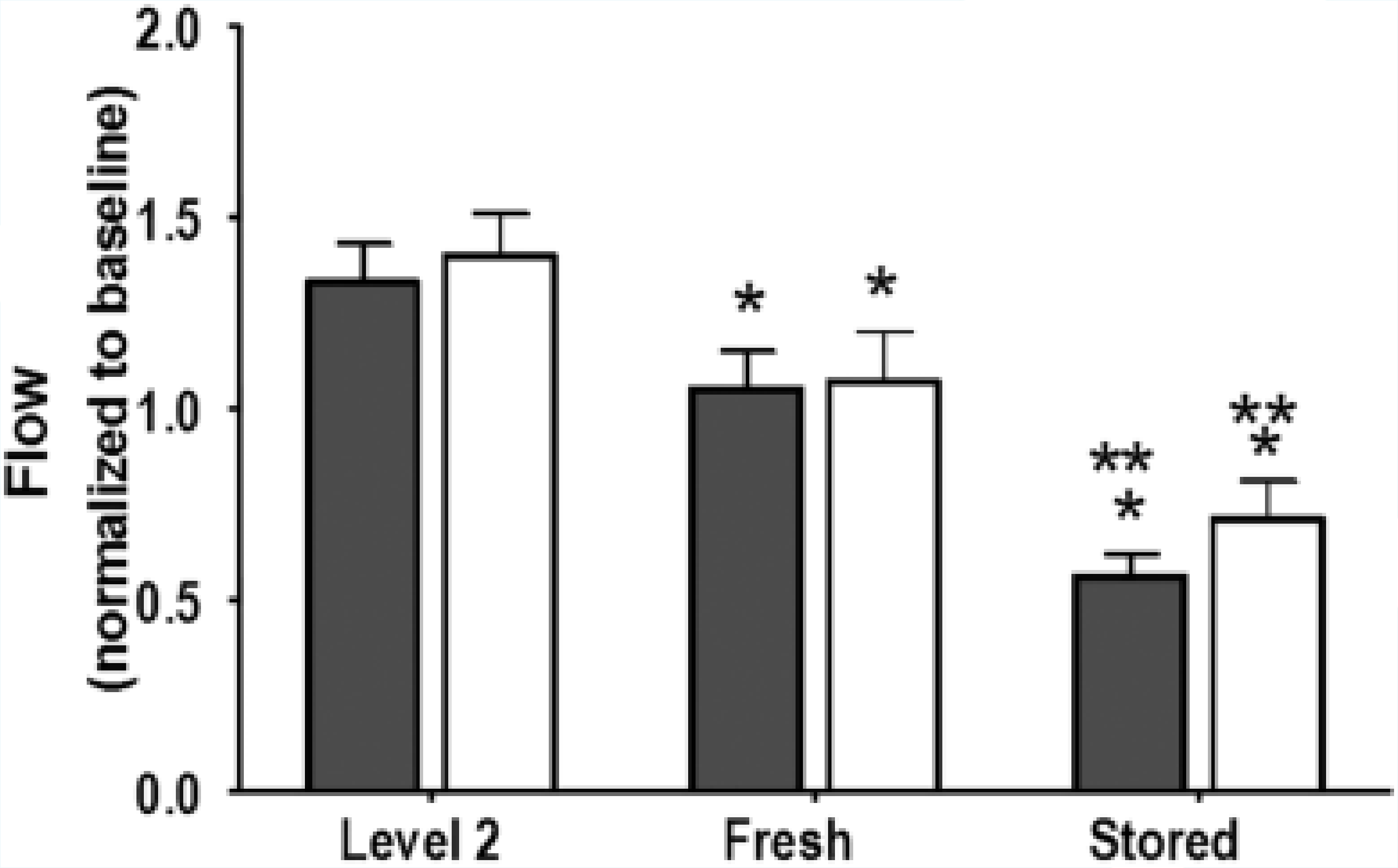
Decreased vascular flow with stored blood transfusion (hamsters)



Tsai et al., Transfusion 2004

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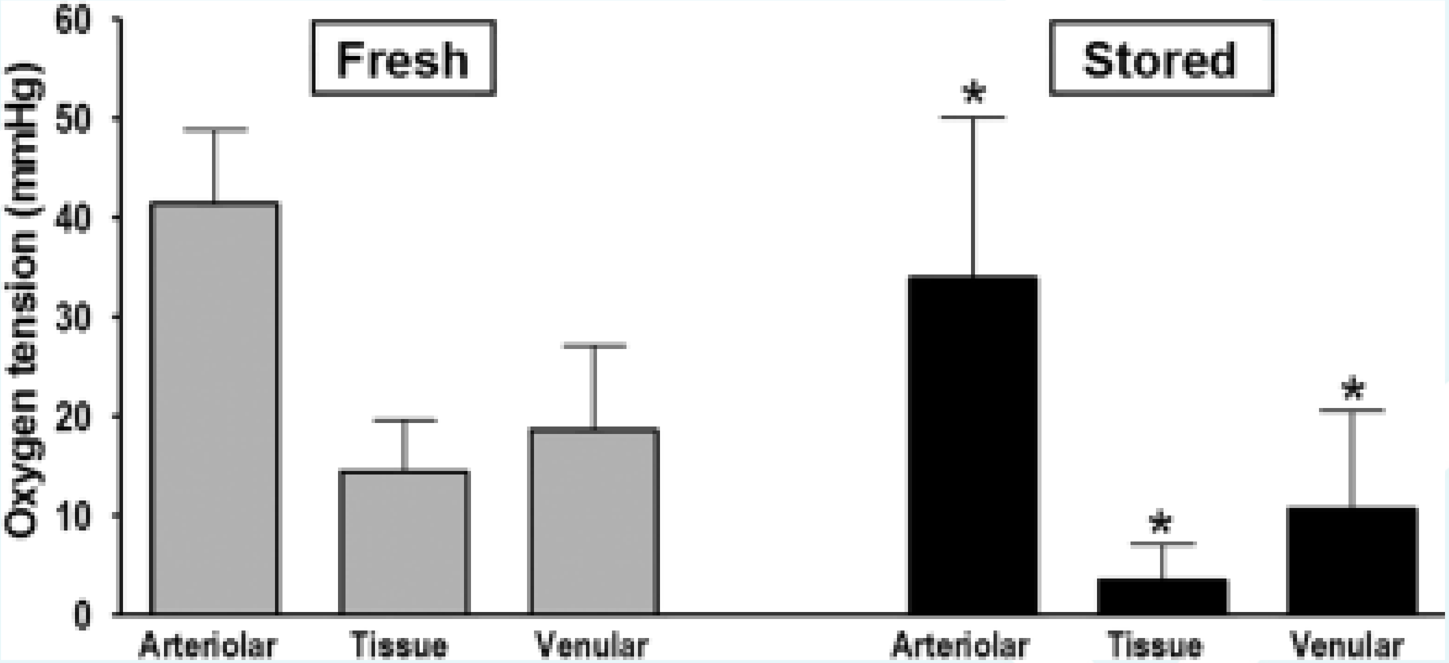
Lower tissue oxygenation with stored blood (hamster model)



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Tsai et al., Transfusion 2004

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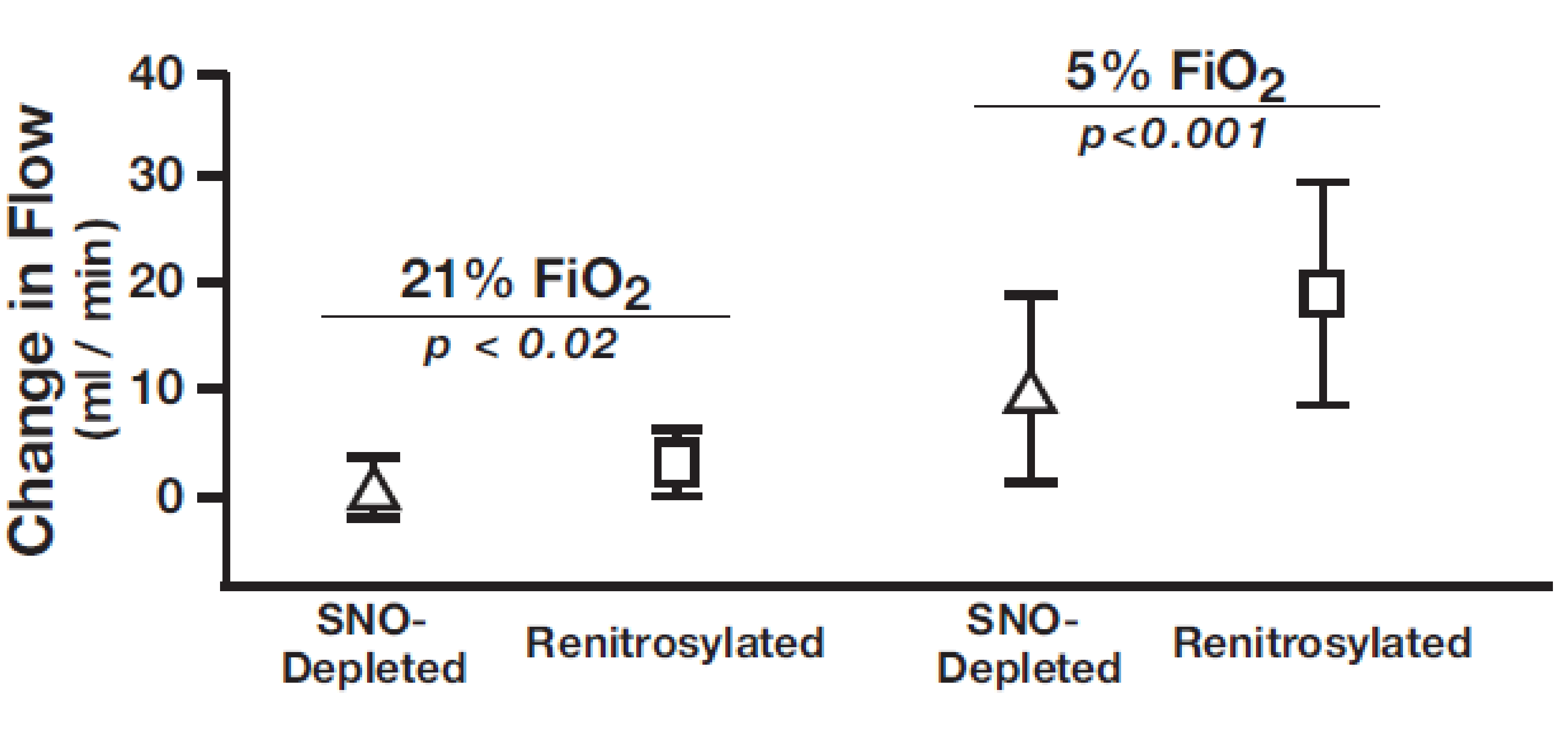
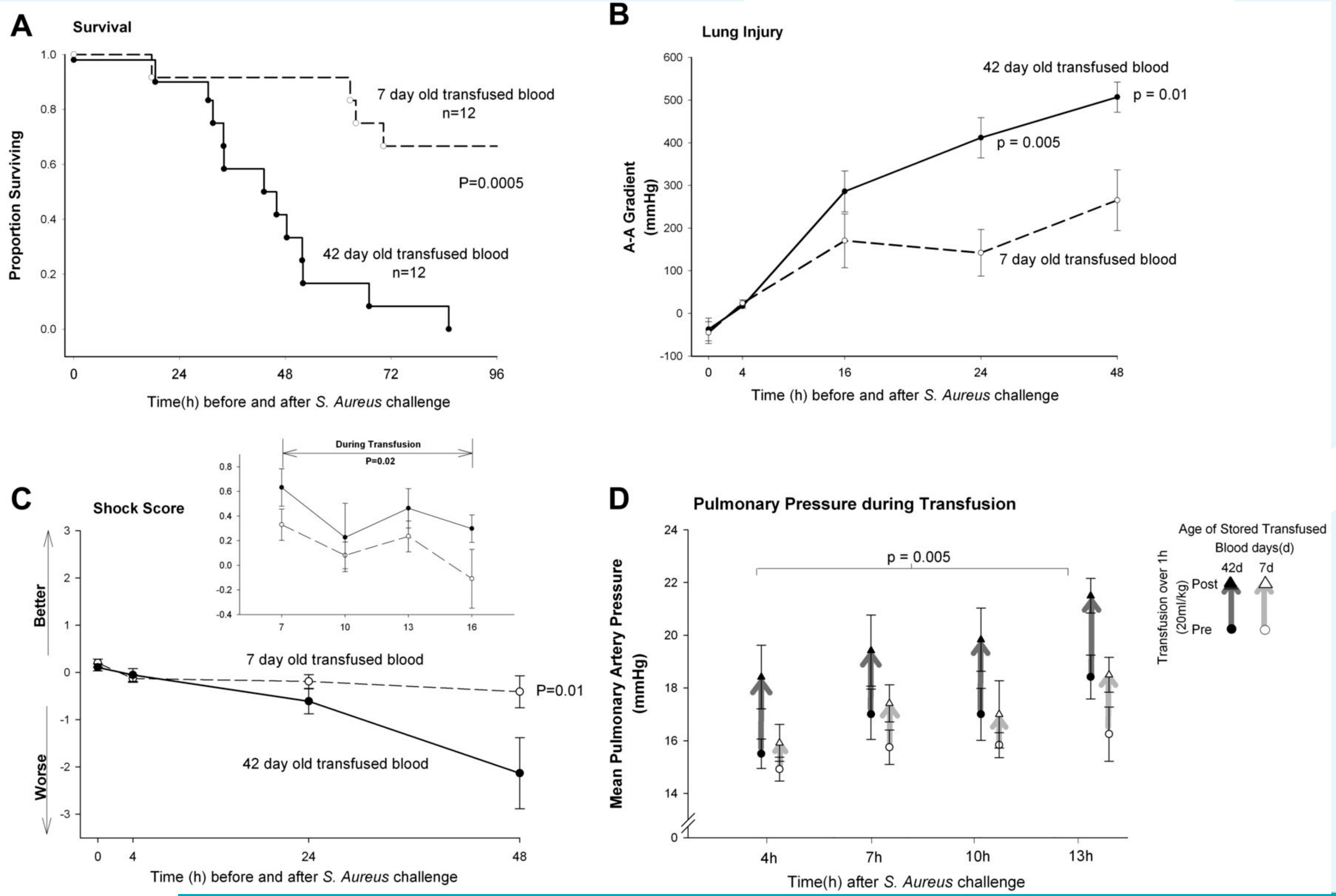
Vasodilation rescued by SNO repletion (canine coronary artery)



Dog pneumonia model



Natanson et al., Blood 2013

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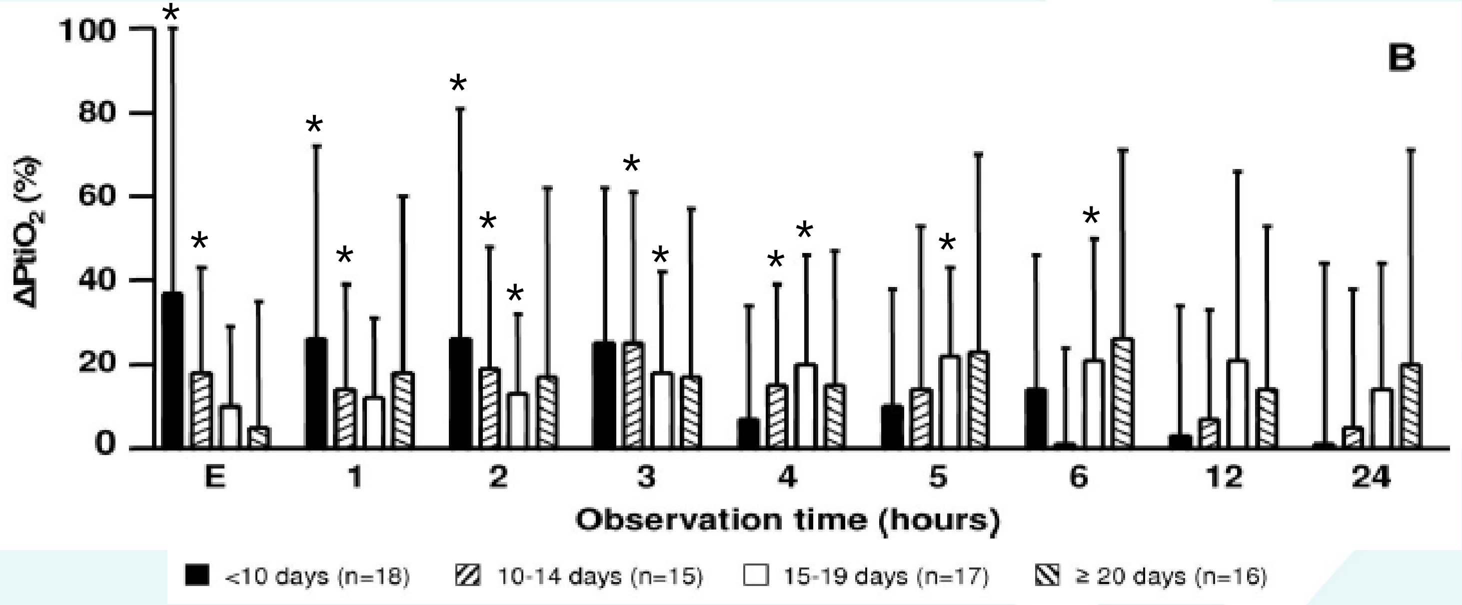
Cerebral oxygenation in men with traumatic brain injury



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Leal-Noval et al., Crit Care Med 2008

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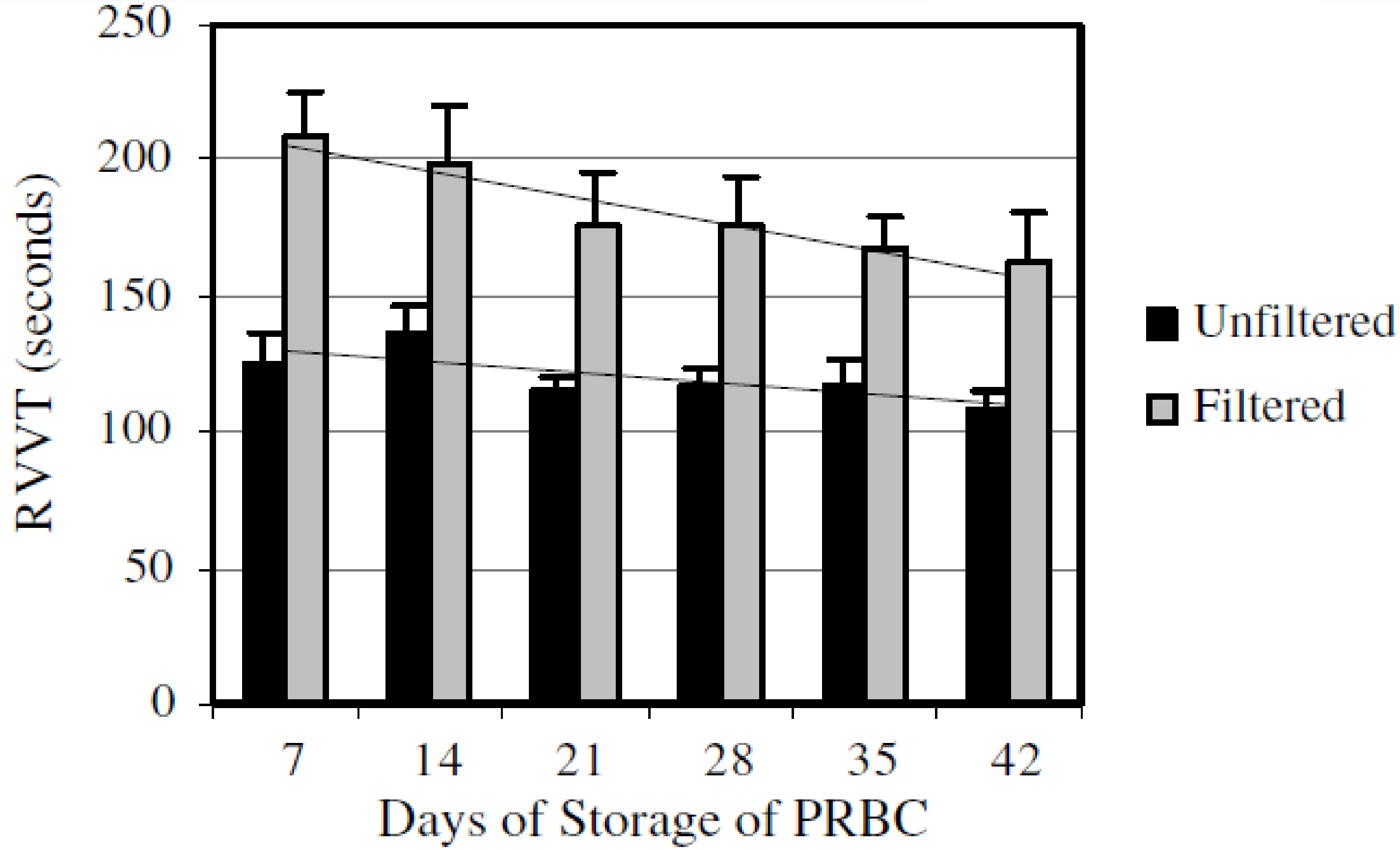
Recipient effects of RBC storage

- Blood flow in transfused tissues
- Effects on the clotting cascade
- Activation of recipient immune system

Russel's viper venom time decreases



Recipient effects of RBC storage

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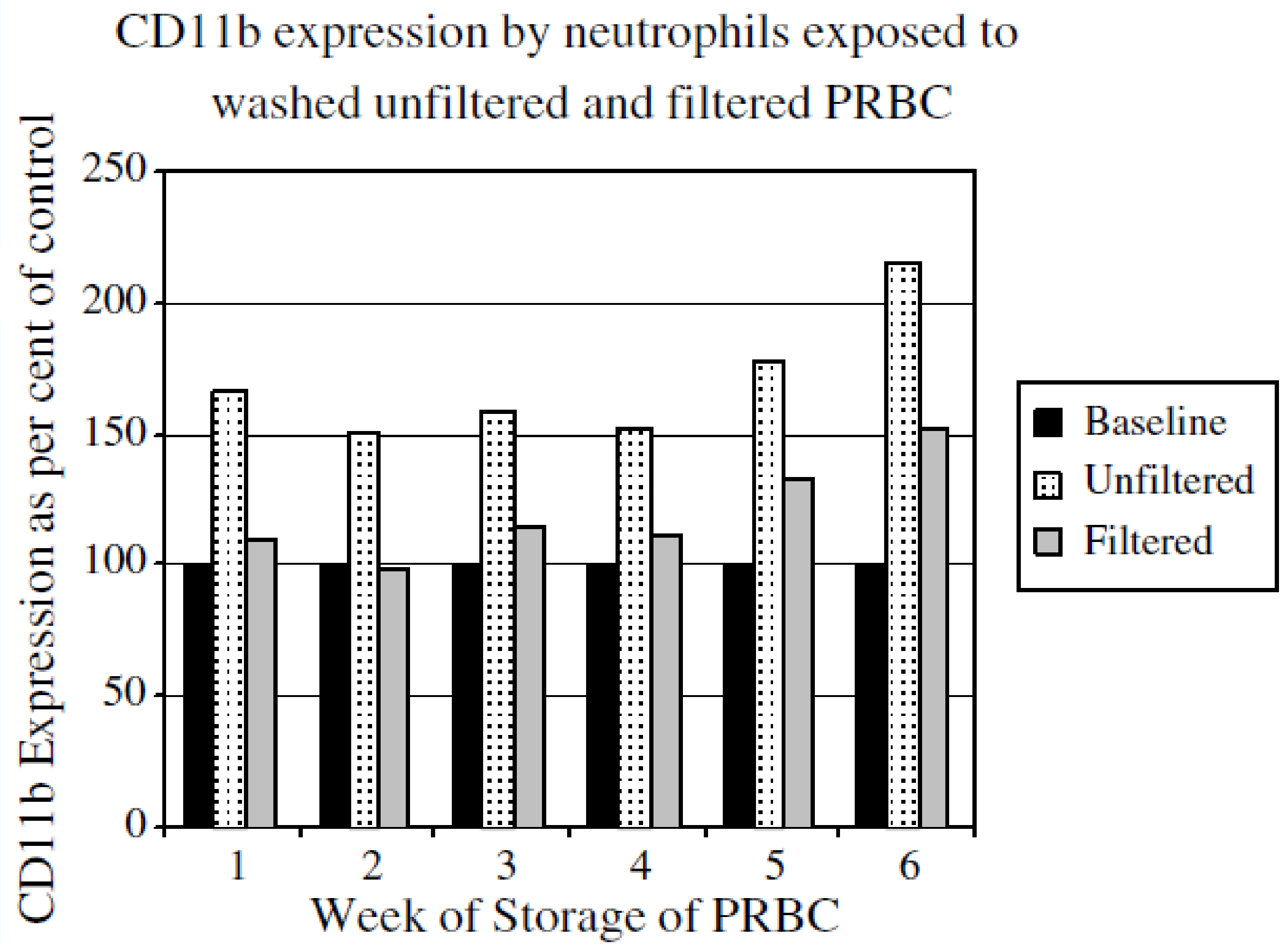
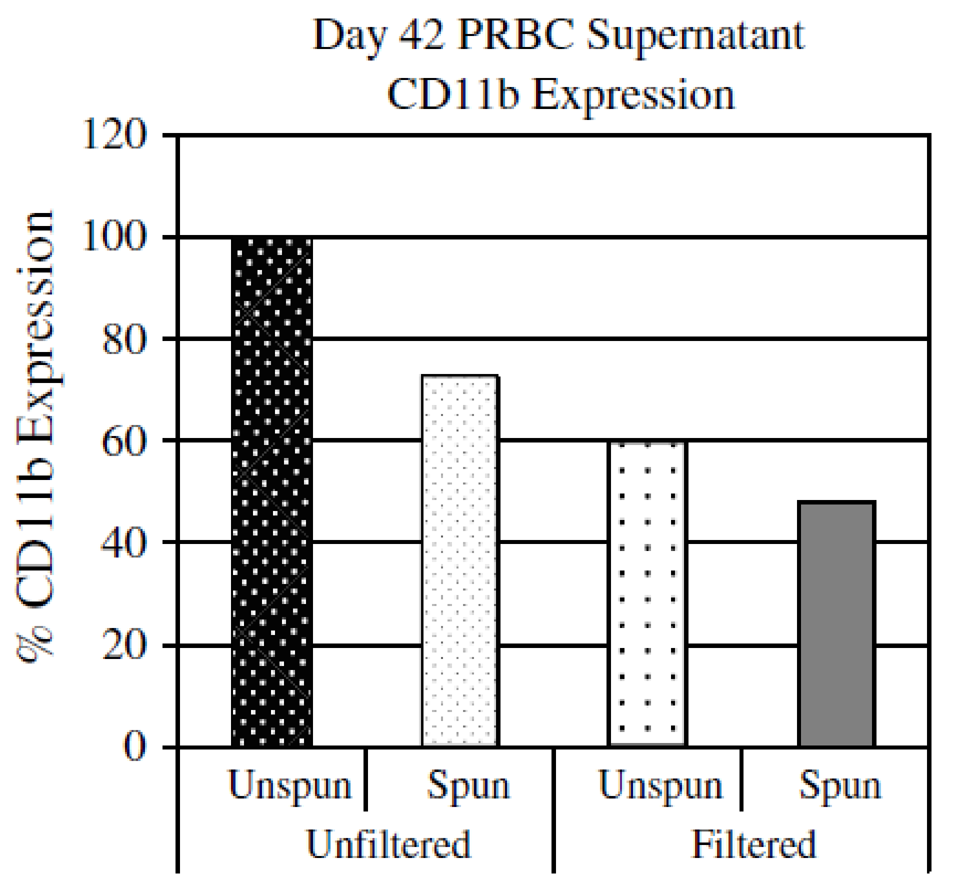
Neutrophil priming increases



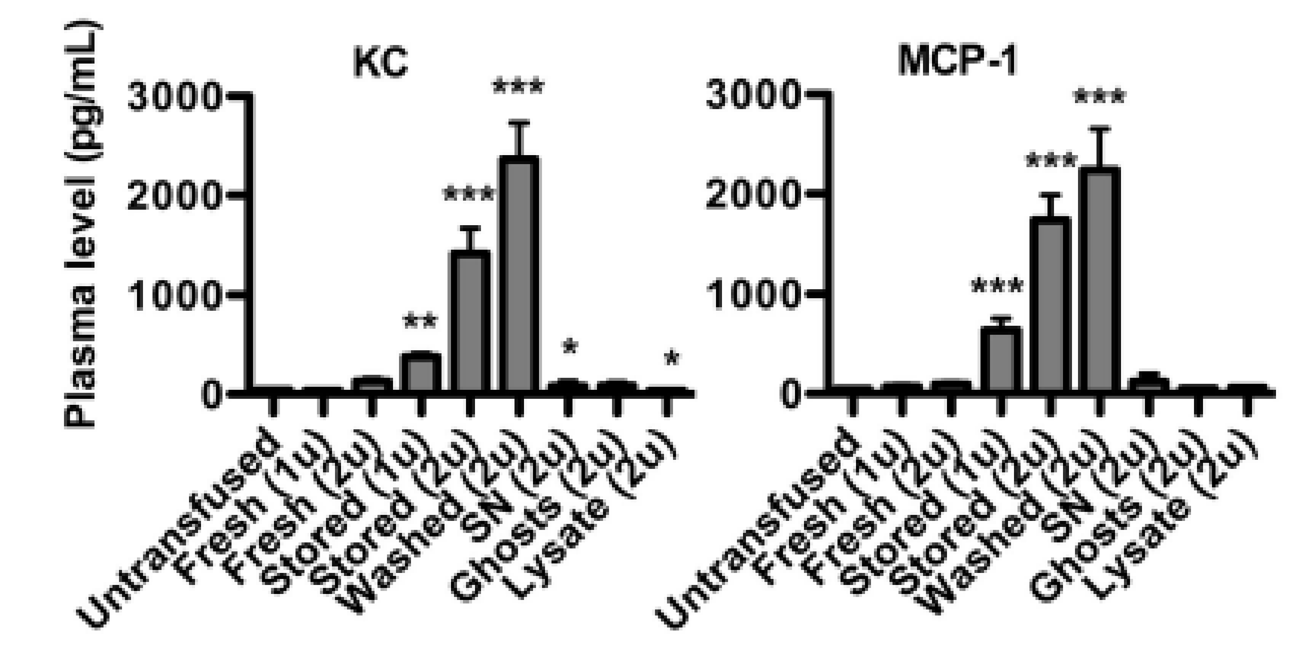
Cardo et al., Transfus Apher Sci 2008

Priming activity in RBC supernatant



Cardo et al., Transfus Apher Sci 2008

Activation of the recipient immune system



Hod et al., Blood 2010

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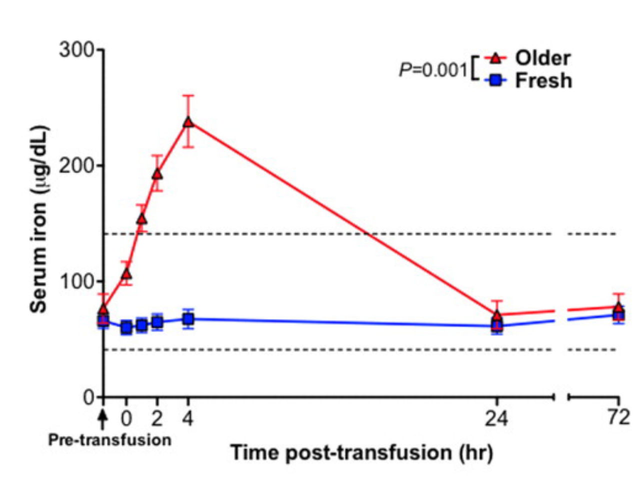
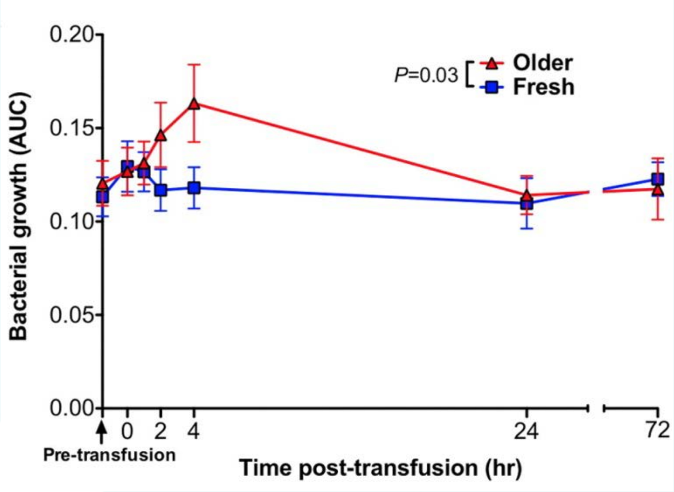
Do humans act like mice?

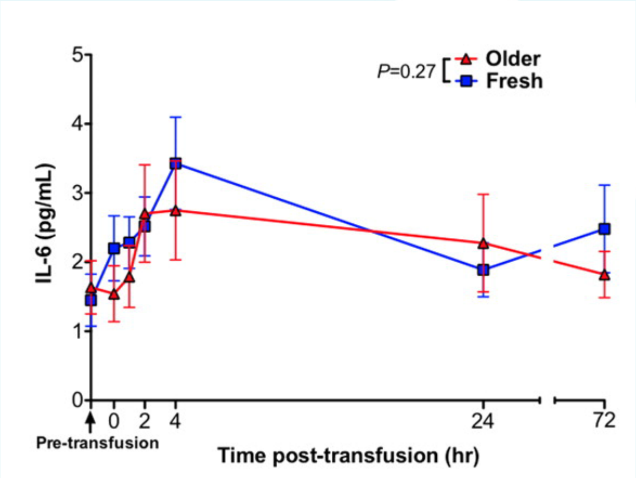
Yes!



Yes!



No!



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Hod et al., Blood 2011

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Prospective studies

Table 4 Multicenter, randomized, clinical trials about blood storage in critically ill adults

Authors or study name	Population	Sample size	Case criteria	Controlled criteria	Outcome	Status
Hebert et al. [51]	ICU	57	<8 days	Standard practices	Composite outcome* (pilot study)	Achieved
Aubron et al. [67]	ICU	51	Freshest compatible available RBC	Standard practices	Feasibility (pilot study)	Achieved
**RECESS (NCT00991341)	Post cardiac surgery	1434	≤10 days	≥21 days	Change in MODS	In progress
**ABLE (ISRCTN44878718)	ICU	2510	<8 days	Standard practices	90-day mortality	In progress
**TRANSFUSE (ACTRN12612000453886)	ICU excluding postcardiac surgery	5000	Freshest compatible available RBC	Standard practices	90-day mortality	In progress

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ABLE pilot study

Table 2. Clinical Outcomes in the 57 Patients Receiving Age-Appropriate Red Blood Cells (RBC)

	Experimental $n = 26$	Standard $n = 31$	Risk difference	95% CI
Interventions, n (%)				
Repeat surgery	3 (12)	2 (6)	0.05	−0.10–0.20
Dialysis	2 (8)	2 (6)	0.01	−0.12–0.15
Swan Ganz catheter	19 (73)	22 (71)	0.02	−0.21–0.25
Urinary catheter	24 (92)	29 (94)	−0.01	−0.15–0.12
Mechanical ventilation	22 (85)	19 (61)	0.23	0.01–0.45
Cardiovascular support	15 (58)	16 (52)	0.06	−0.20–0.32
Composite outcomes—all patients, n (%)				
Any outcome (excluding hospital death)	4 (15)	1 (3)	0.12	−0.04–0.31
Any outcome including hospital death	7 (27)	4 (13)	0.14	−0.07–0.35
Mortality rates, n (%)				
Intensive care unit	4 (15)	2 (6)	0.09	−0.08–0.29
Hospital	5 (19)	3 (10)	0.10	−0.09–0.29
30-day follow-up ($n = 53$)	5 (21)	3 (10)	0.10	−0.09–0.30
90-day follow-up ($n = 49$)	5 (25)	4 (14)	0.11	−0.12–0.34
Vital organ support, n (%)				
Prolonged invasive MV[a]	7 (27)	5 (16)	0.11	−0.10–0.32
Prolonged MV[b]	9 (35)	8 (26)	0.09	−0.14–0.31
Prolonged low cardiac output[c]	5 (20)	4 (13)	0.07	−0.12–0.28
All patients dialyzed once randomized	0	2 (6.45)	0.06	−0.05–0.24

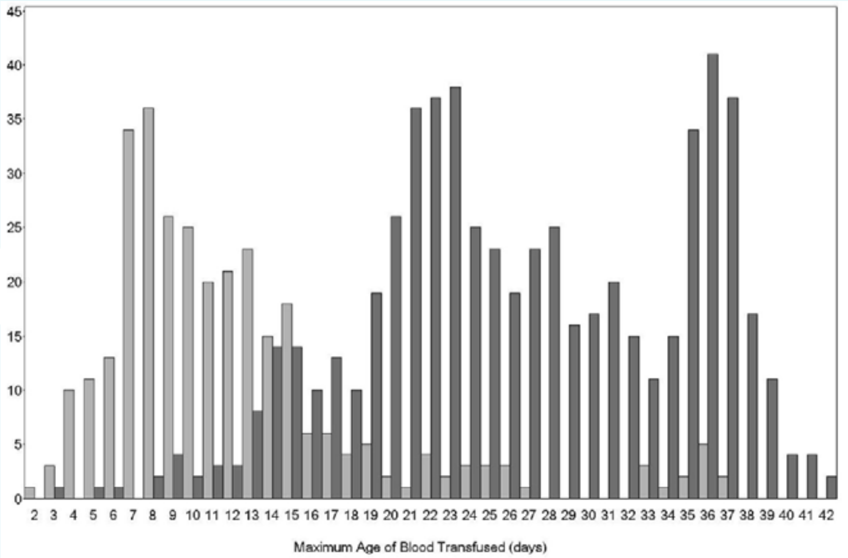
Pilot randomized trial in ICU, Australia

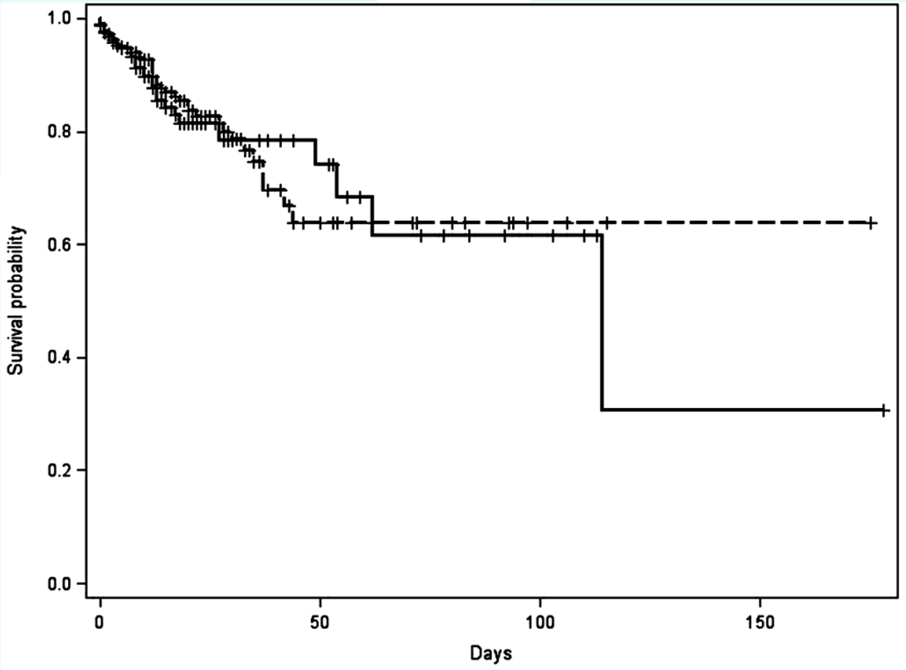
TABLE 1. Baseline characteristics of patients*

Characteristics	Fresher blood group (n = 25)	Standard care group (n = 26)	p value
Age (years)	62 ± 19	66 ± 19	0.4
Male, n (%)	20 (80%)	12 (46%)	0.01
Type of patients, n (%)			
Postoperative	11 (44)	13 (50)	0.88
Cardiovascular	8 (73)	10 (77)	0.85
Medical	14 (56)	13 (50)	0.88
APACHE III score	67.1 ± 30.1	55.3 ± 18.3	0.10
Mechanical ventilation			
Requirement	23 (92%)	19 (73%)	0.16
Duration (days), median (IQR)	156 (6.1-253)	9.85 (0-198)	0.13
Blood group, n (%)			0.33
A	13 (52%)	10 (38%)	0.70
B	4 (16%)	3 (12%)	0.45
AB	0 (0%)	2 (8%)	0.49
O	8 (32%)	11 (42%)	0.24
Positive rhesus status, n (%)	23 (92%)	21 (81%)	0.24
Length of stay			
ICU (days), median (IQR)	11 (5-15)	7 (3-17)	0.59
Hospital (days), median (IQR)	21 (12-38)	17 (8-27)	0.18
Hospital death, n (%)	5 (20)	2 (8)	0.20

* Data are reported as mean ± SD for normally distributed variables and as medians (IQR) for nonnormally distributed variables. Percentages are shown as appropriate.

All hospitalized patients: Canada INFORM-P

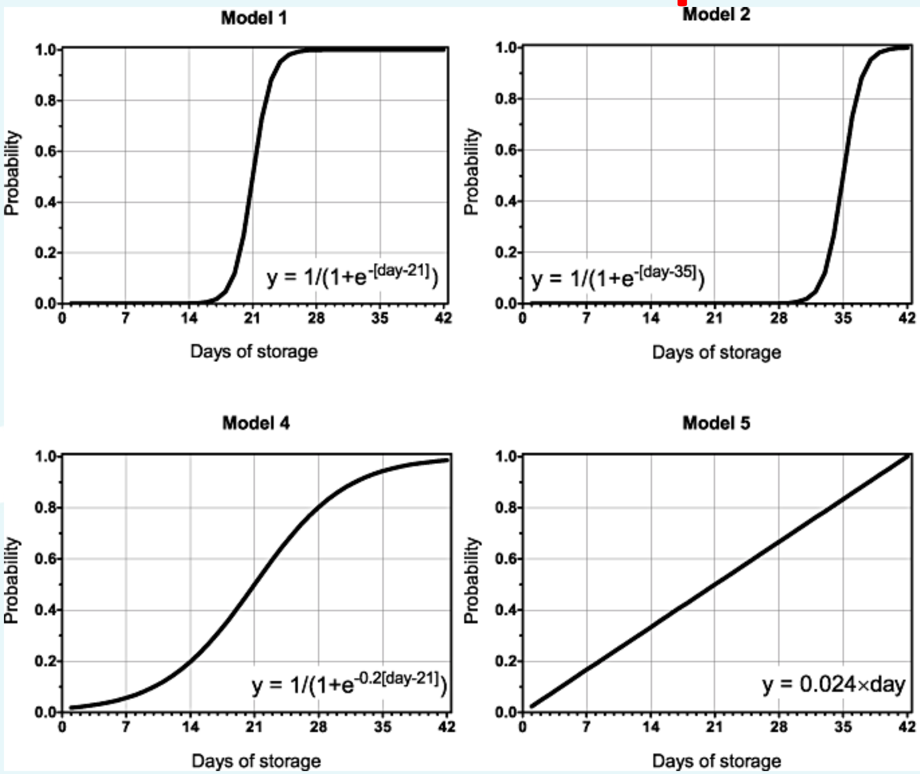


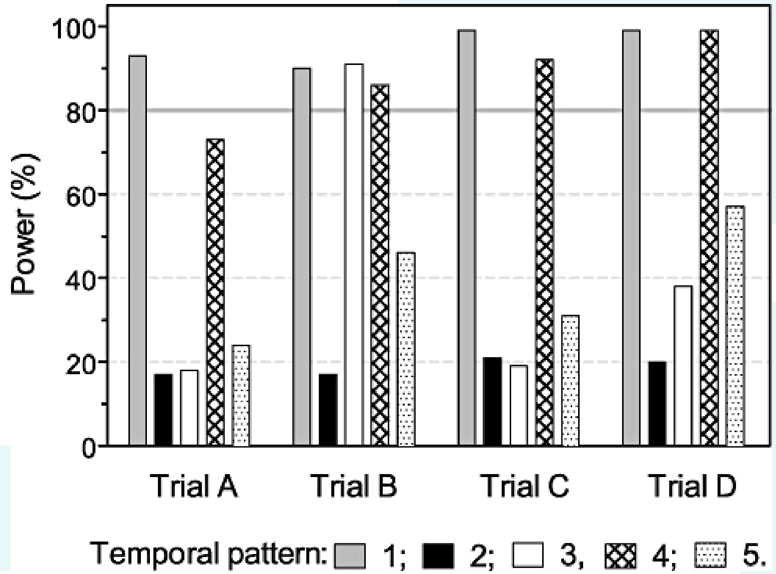


<u>Excluded</u>
sickle cell
massive transfusion
outpatients

N = 910

Are the trials powered appropriately?





	RBC storage time (days)		
Trial	Control arm	Experimental arm	Study inspiring the design
A	>14	≤14	Koch et al.[11]
B	Standard issue (2 to 42)	≤8	The Age of Blood Evaluation Study[12,13]
C	>20	<14	Red Cell Storage and Outcome in Cardiac Surgery[14]
D	≥21	≤10	The NHLBI TMH Network Red Cell Storage Duration Study[15]

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Conclusions

- Retrospective studies of the age of blood have mixed results
- Prospective studies of age of blood and clinical outcome are ongoing
- It's possible that aged blood may have patient population-dependent effects