From donor biology to donor health protection: Three (very) short stories

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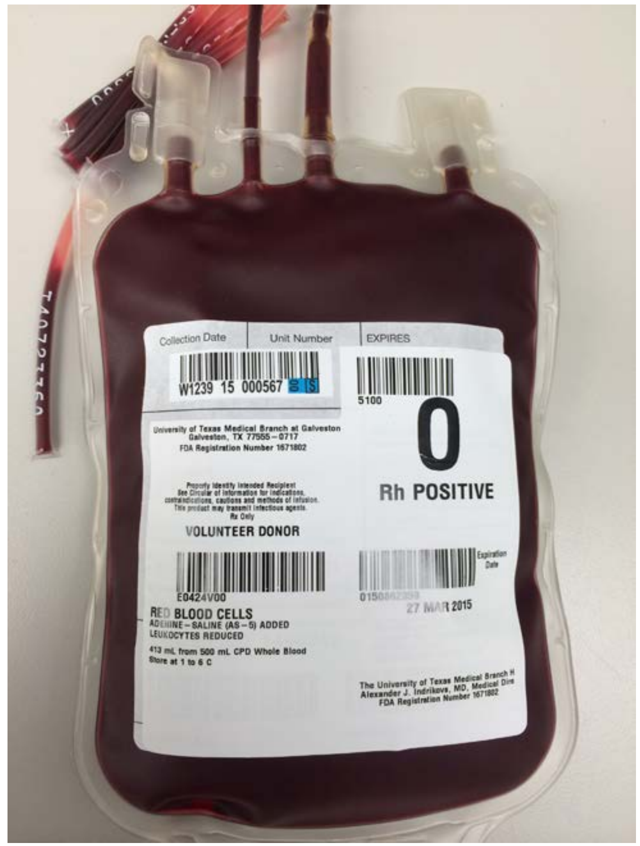
Columbia University
College of Physicians and Surgeons

NewYork-Presbyterian
The University Hospitals of Columbia and Cornell

Potential Conflicts of Interest

Hemanext:	**Advisory Board**
Tioma, Inc:	**Consultant**

This is the focus of our interest



This is the focus of our interest

Are there characteristics of the donor that will “make better products” and affect donor health?

What do we know about refrigerator-stored RBCs?

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As storage time increases (FDA criteria):

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Increasing hemolysis *ex vivo* (<1.0%)

Infuse free hemoglobin, etc.

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As storage time increases (FDA criteria):

Increasing hemolysis *ex vivo* (<1.0%)

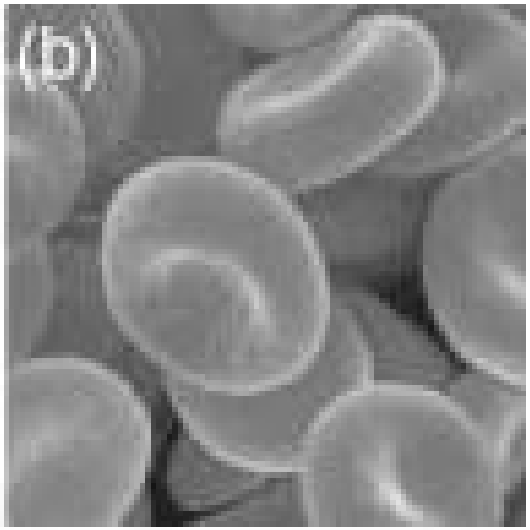
Infuse free hemoglobin, etc.

Decreasing 24-hr post-transfusion recovery *in vivo* (~≥75%)

Less than optimal dose

What happens to the RBCs during refrigerated storage?

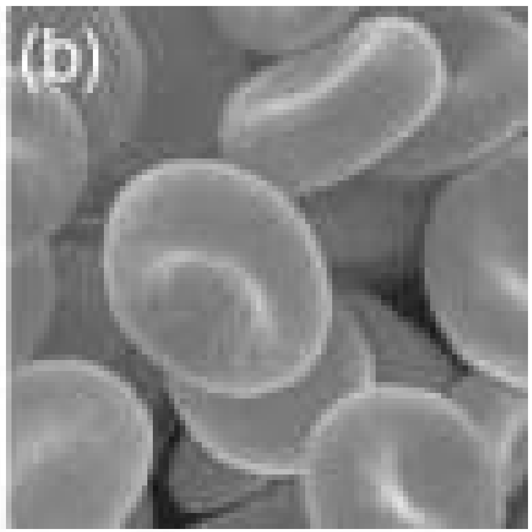
The “RBC storage lesion”



Day 0

Blasi, D’Alessandro, et al. Transfusion Medicine 22:90-96, 2012

The "RBC storage lesion"



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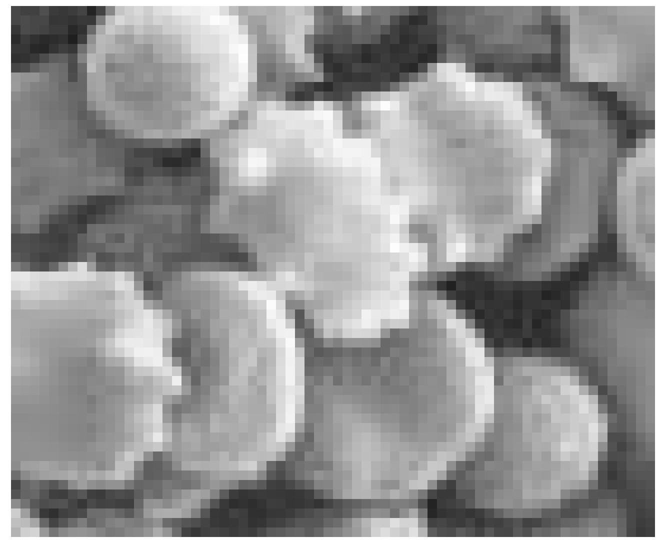

Day 42

Blasi, D'Alessandro, et al. Transfusion Medicine 22:90-96, 2012

The “RBC storage lesion”

- ↓ 2,3-DPG, GSH, ATP
- ↓ Nitric oxide
- ↑ Protein oxidation
- ↑ Membrane- & cytoskeletal-associated hemoglobin
- ↑ Membrane lipid peroxidation
- ↑ Lysophosphatidylcholine species
- ↑ Vesiculation and membrane loss
- ↓ Deformability
- ↑ Phosphatidylserine exposure
- ↓ CD47

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The “RBC storage lesion”
Final common pathway?

Metabolic dysfunction & oxidative stress ➔

↓ Deformability

↑ “Eat me” signals (phosphatidylserine)

↓ “Don’t eat me” signals (CD47)

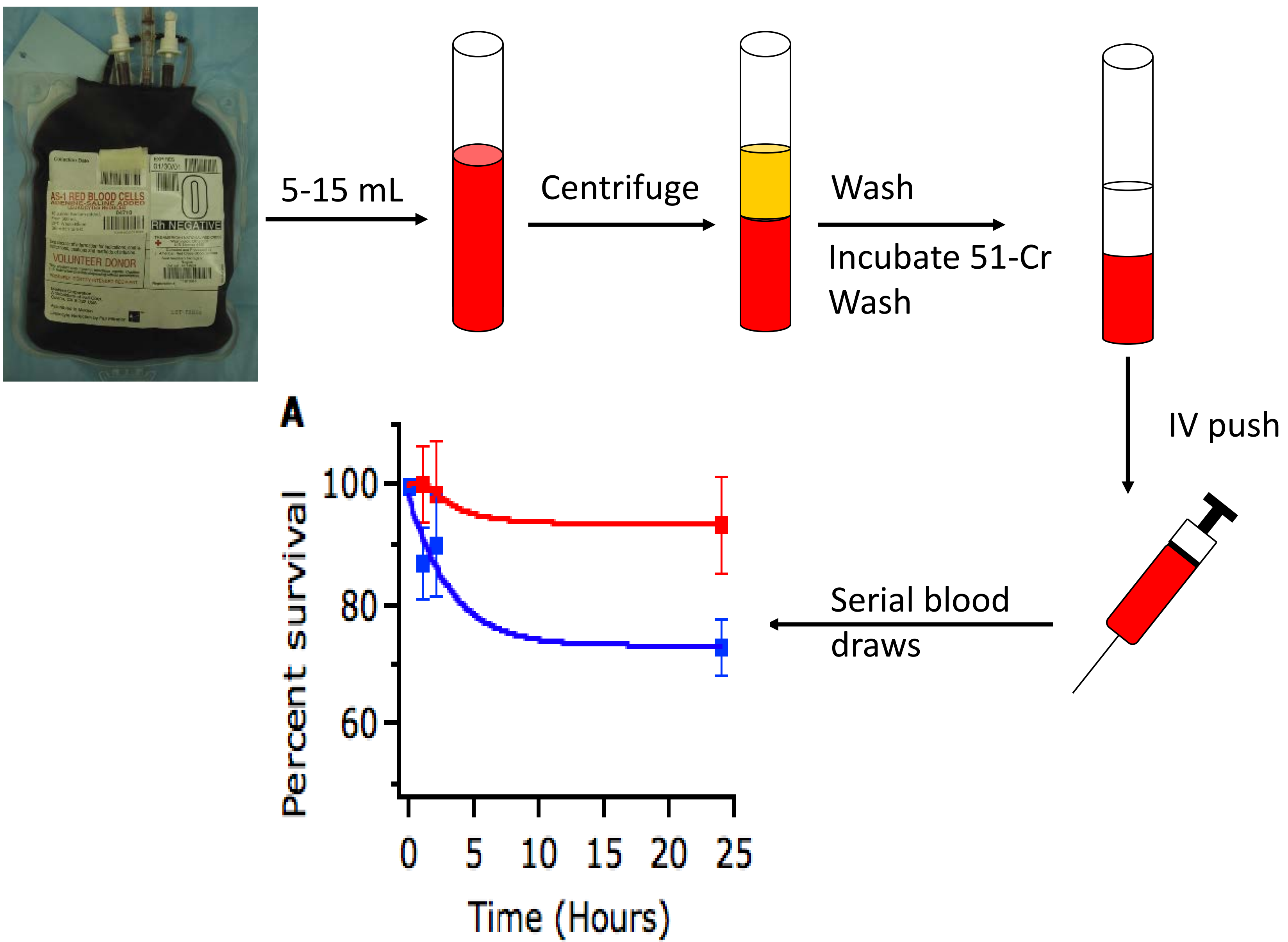
↑ Hemolysis *in vitro*

↑ RBC clearance *in vivo*

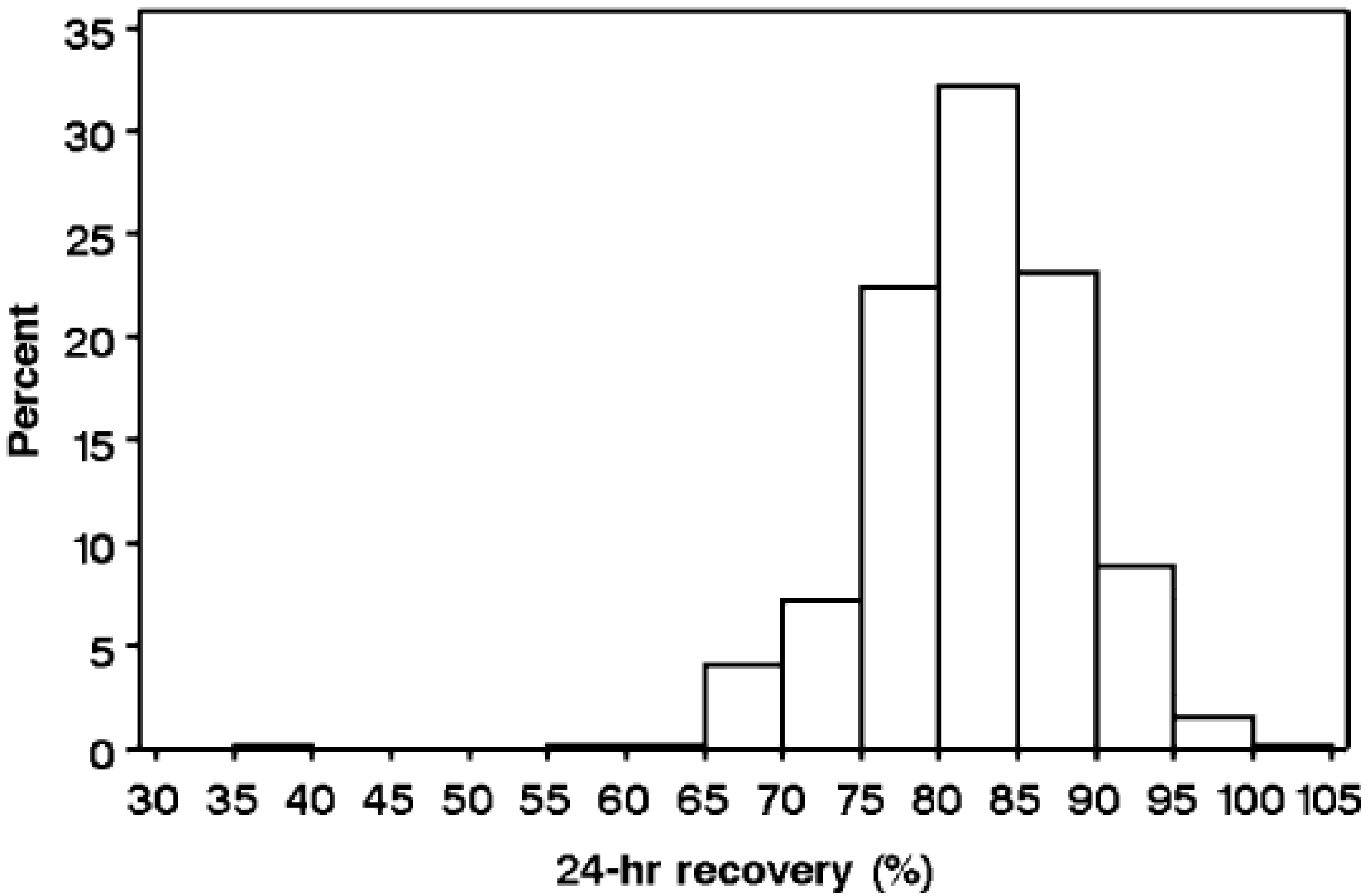
Intravascular and extravascular hemolysis

RBC Clearance Variability

RBC Recovery Study

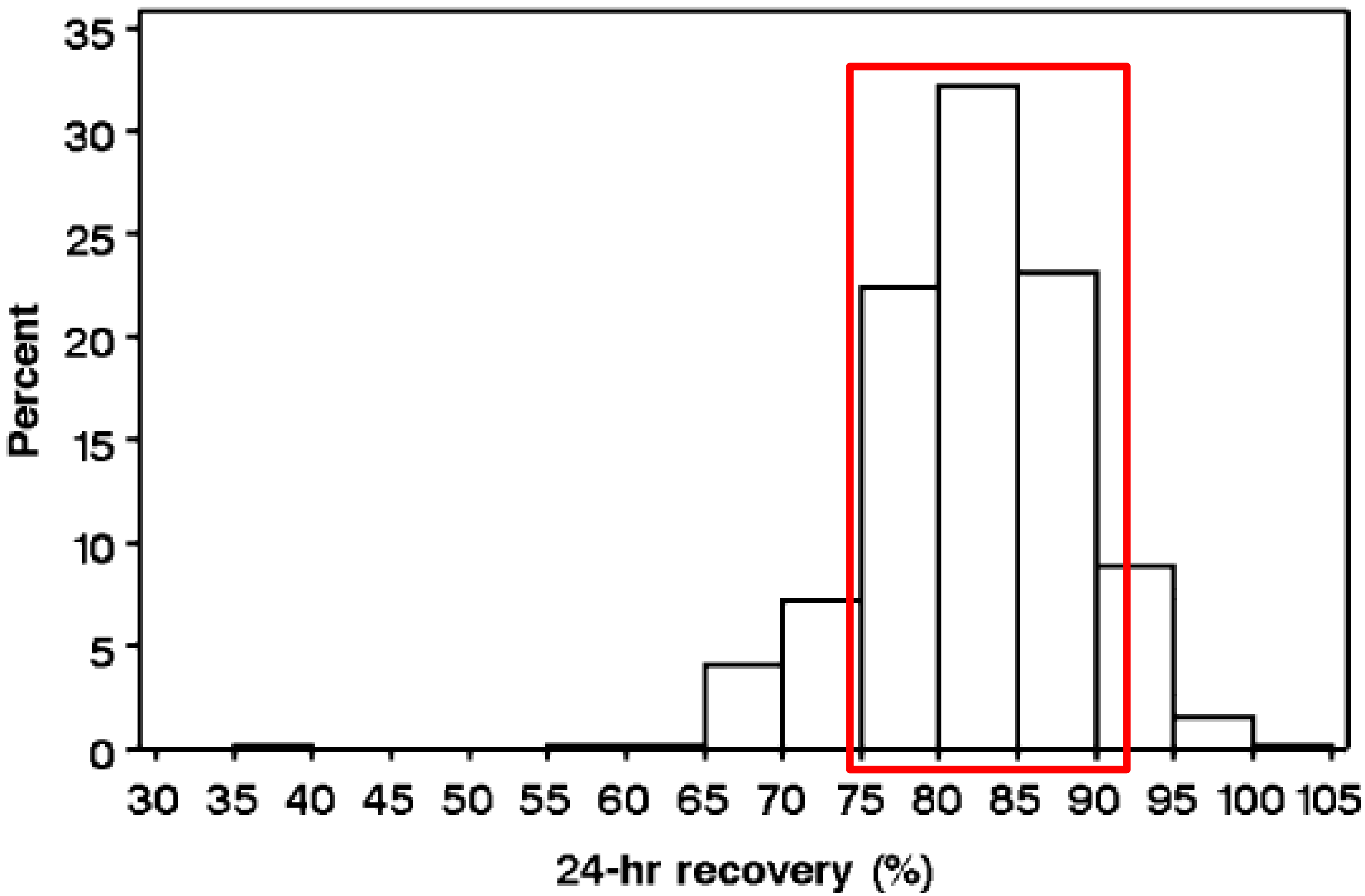


24-hr RBC recovery in 641 healthy volunteers



Dumont et al. Transfusion 48:1053-60, 2008.

24-hr RBC recovery in 641 healthy volunteers



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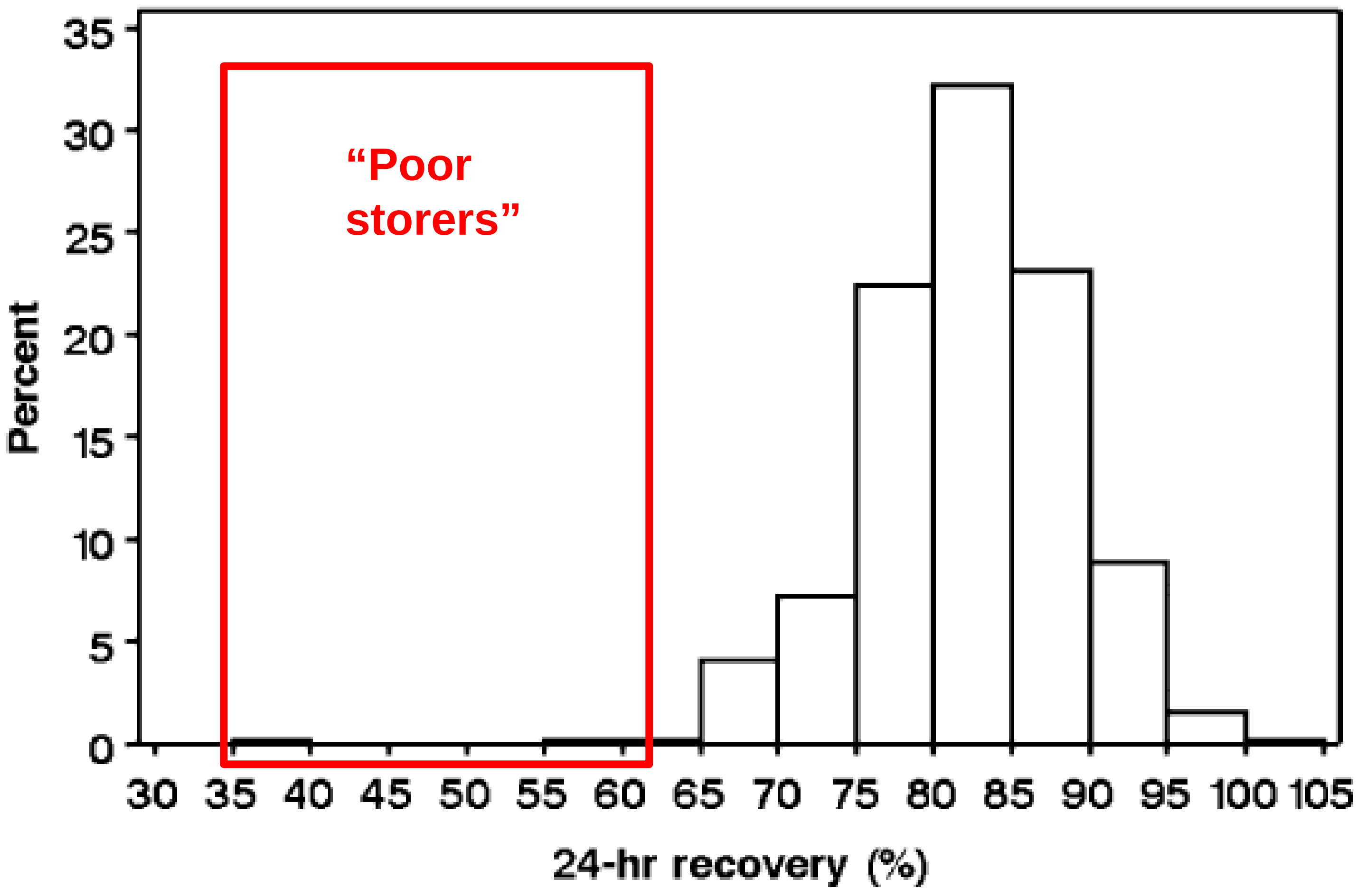

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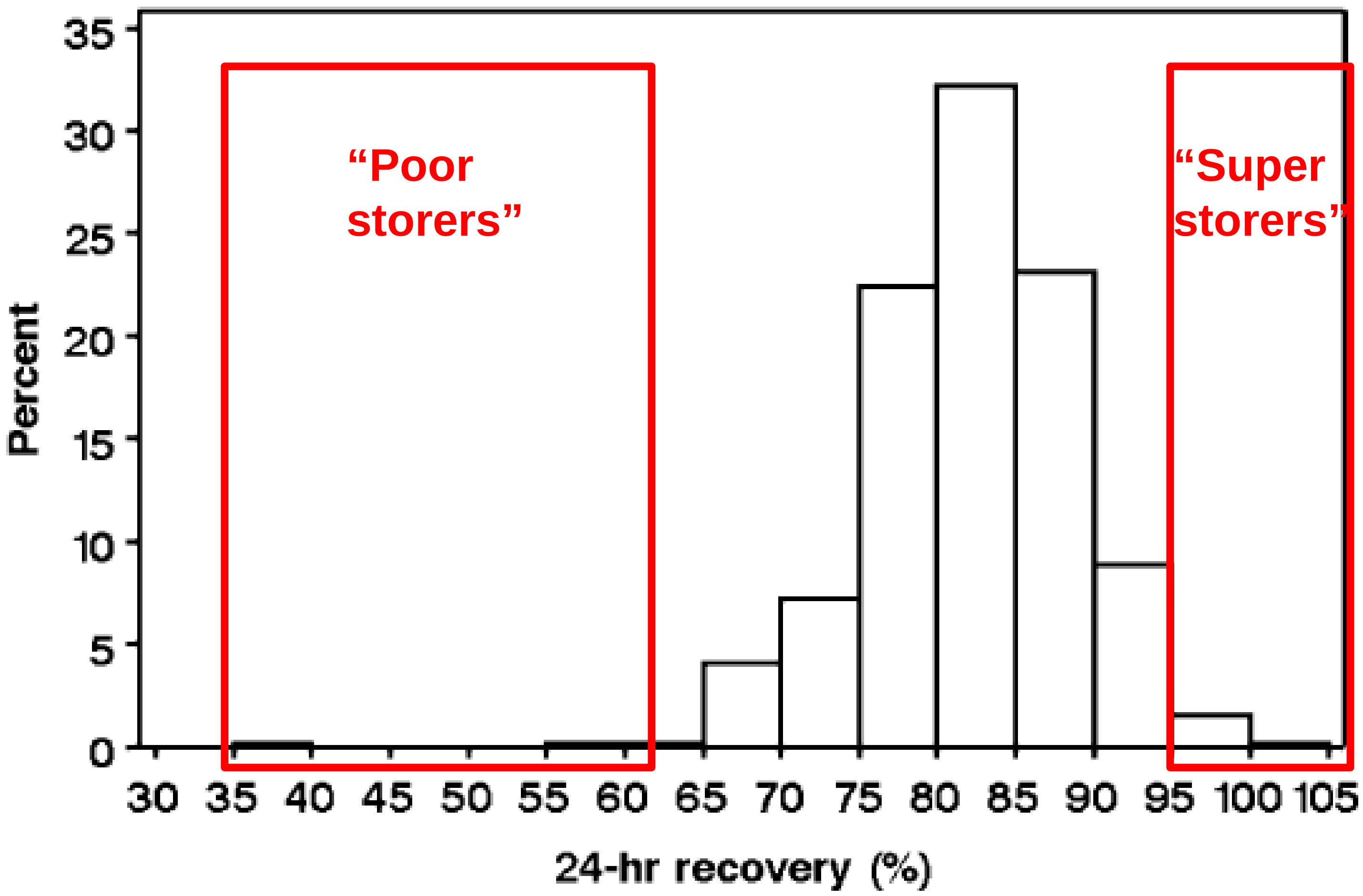

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Is “old” blood bad?

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Infection?
Inflammation?
Thrombosis?
Mortality?

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Not going to talk about these now

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Infection?
Inflammation?
Thrombosis?
Mortality?

Not going to talk about these now
We can discuss these later, if you would like

Is "old" blood bad?

↑ **RBC refrigerated storage time**

↓

↑ **RBC storage lesion *in vitro***

↓

↓ **RBC recovery *in vivo***

Is “old” blood bad?

Why is transfusion of less than a full “dose” OK?

Is “old” blood bad?

Why is transfusion of less than a full “dose” OK?

Transfused RBCs that don’t circulate cannot deliver O_2

When do RBCs “go bad”?

When do RBCs “go bad”?

The Journal of Clinical Investigation CLINICAL MEDICINE

Prolonged red cell storage before transfusion increases extravascular hemolysis

Francesca Rapido,[1,2] Gary M. Brittenham,[3,4] Sheila Bandyopadhyay,[1] Francesca La Carpia,[1] Camilla L'Acqua,[1] Donald J. McMahon,[4] Abdelhadi Rebbaa,[1] Boguslaw S. Wojczyk,[1] Jane Netterwald,[1] Hangli Wang,[1] Joseph Schwartz,[1] Andrew Eisenberger,[4] Mark Soffing,[5] Randy Yeh,[5] Chaitanya Divgi,[5] Yelena Z. Ginzburg,[6] Beth H. Shaz,[6] Sujit Sheth,[7] Richard O. Francis,[1] Steven L. Spitalnik,[1] and Eldad A. Hod[1]

Journal of Clinical Investigation 127:375-382, 2017

60 healthy volunteers enrolled

52 completed study

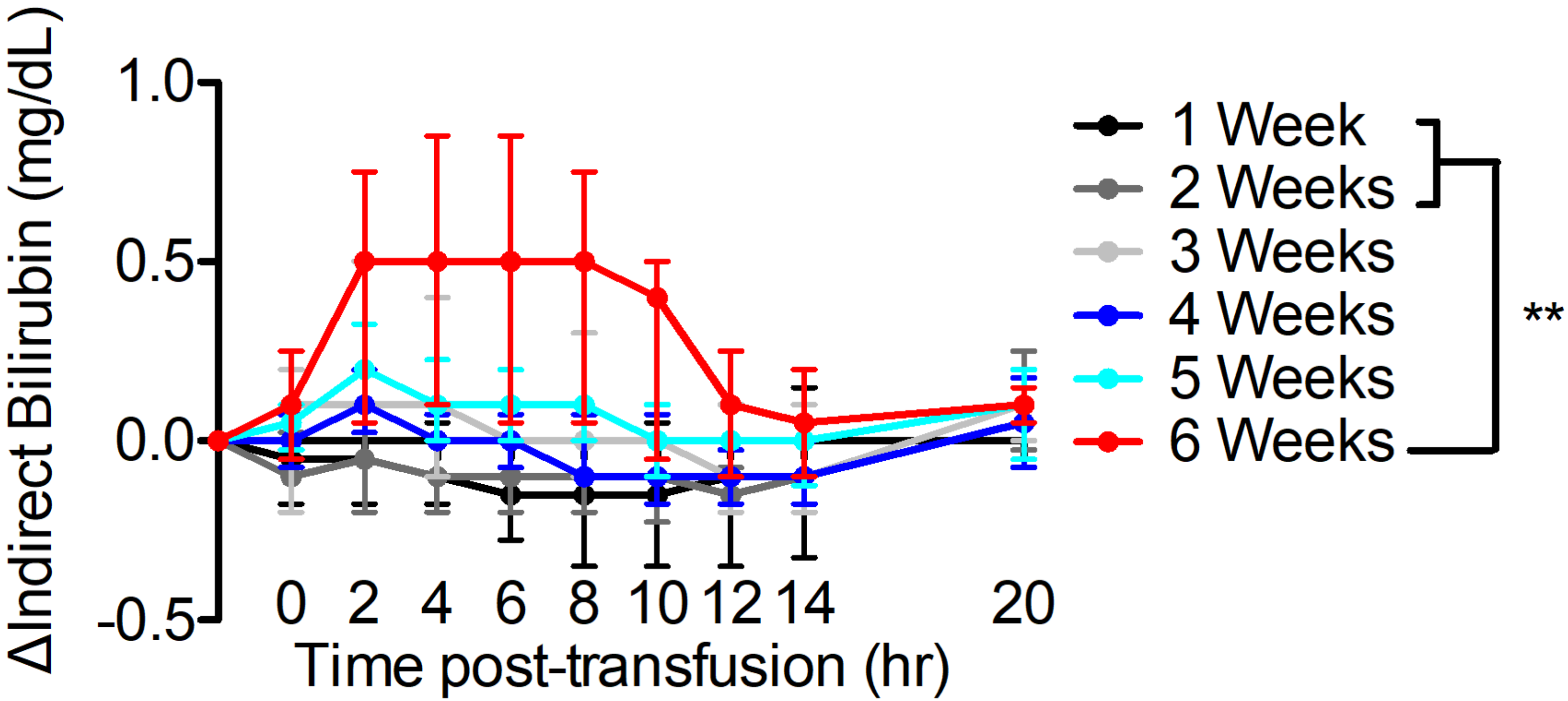
Randomized to 1, 2, 3, 4, 5, 6 weeks of storage

Leukoreduced; AS-3

Transfused entire unit

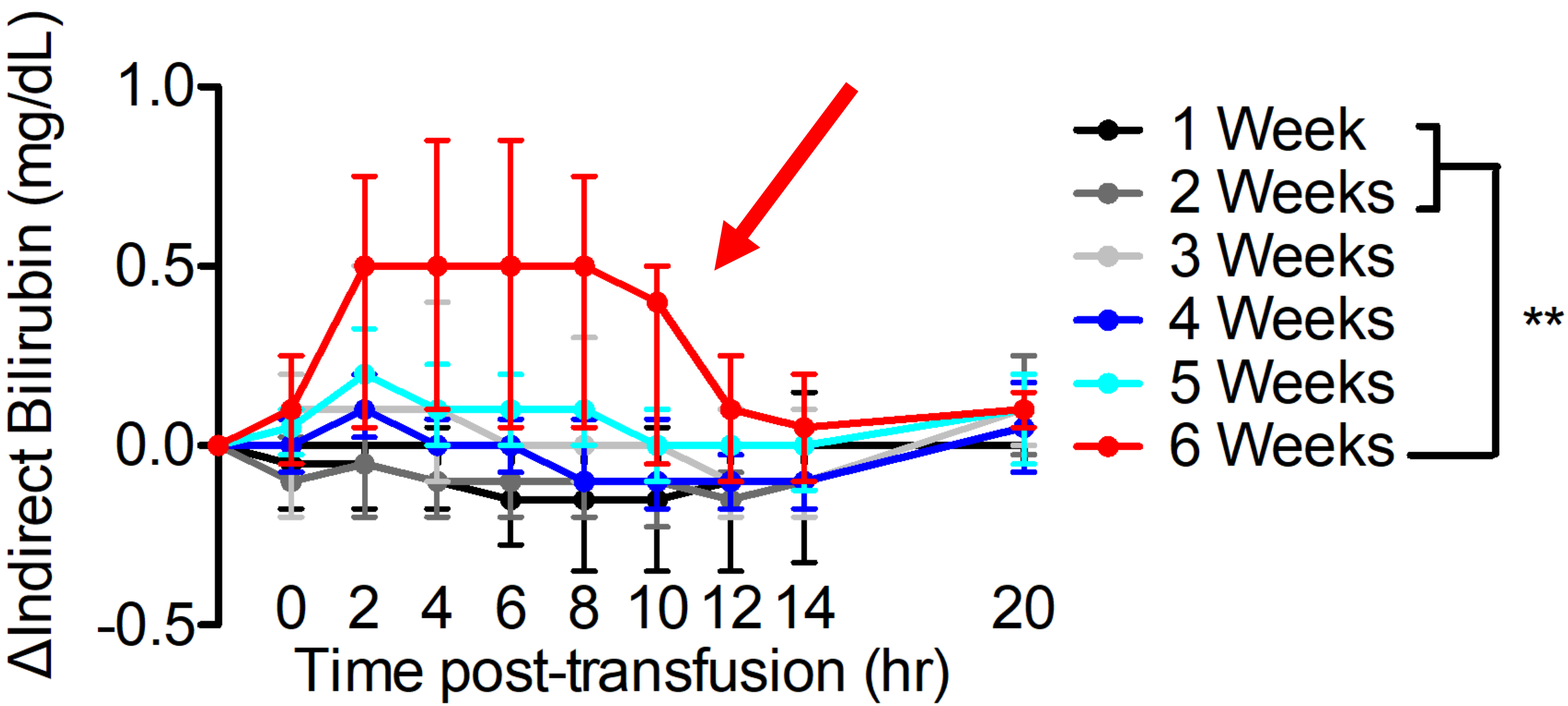
^{51}Cr-labeled post-transfusion recovery

When do RBCs “go bad”?



When do RBCs “go bad”?

6 Weeks



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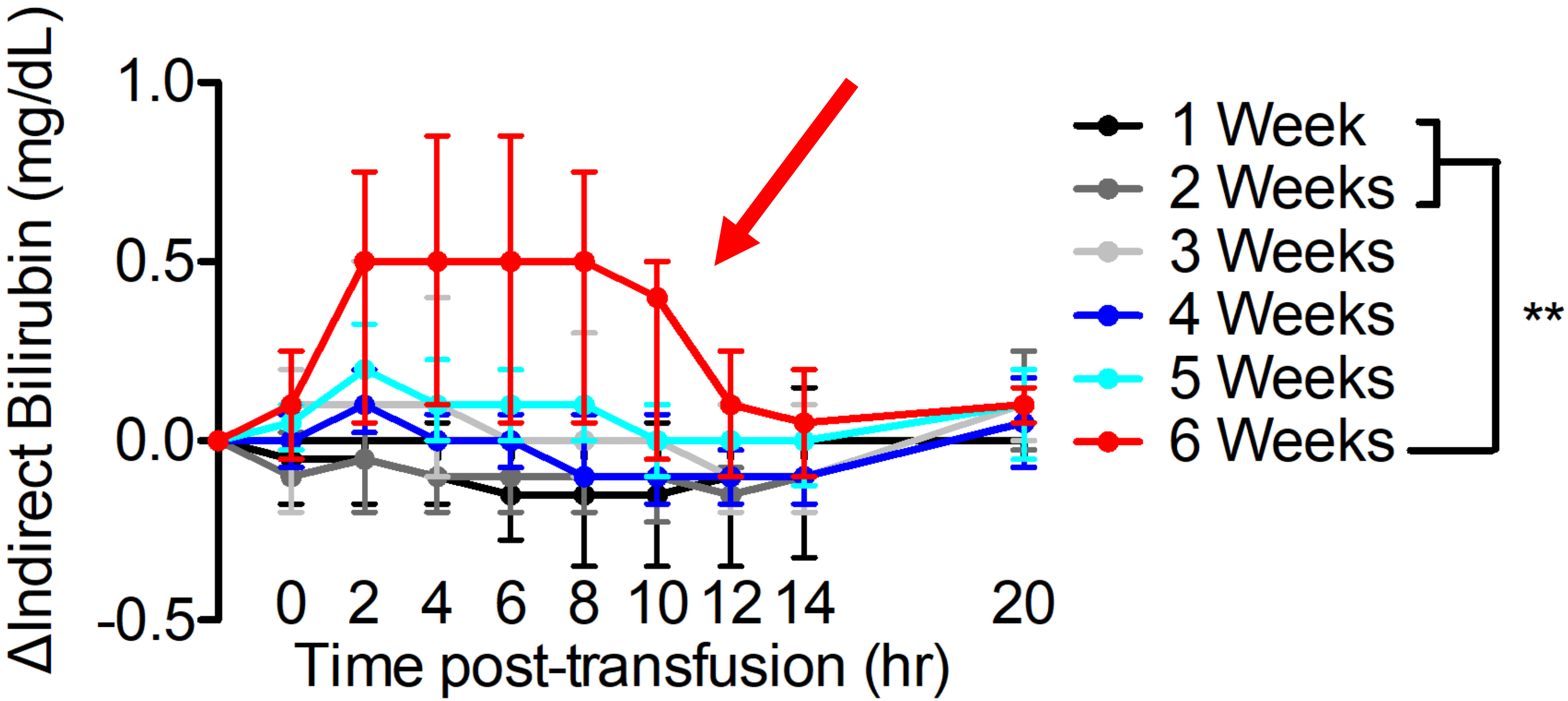

Similar pattern with serum iron, NTBI, etc.

When do RBCs "go bad"?

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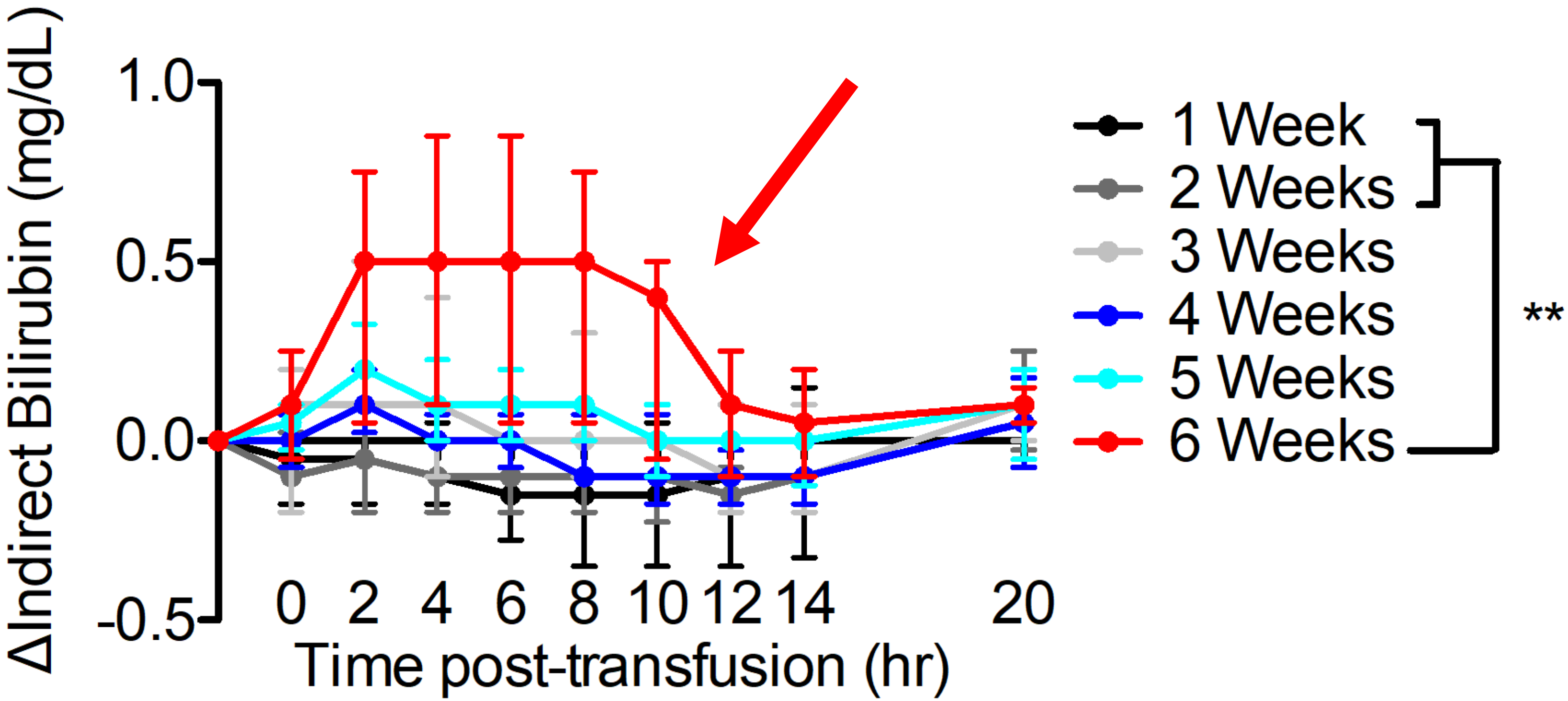
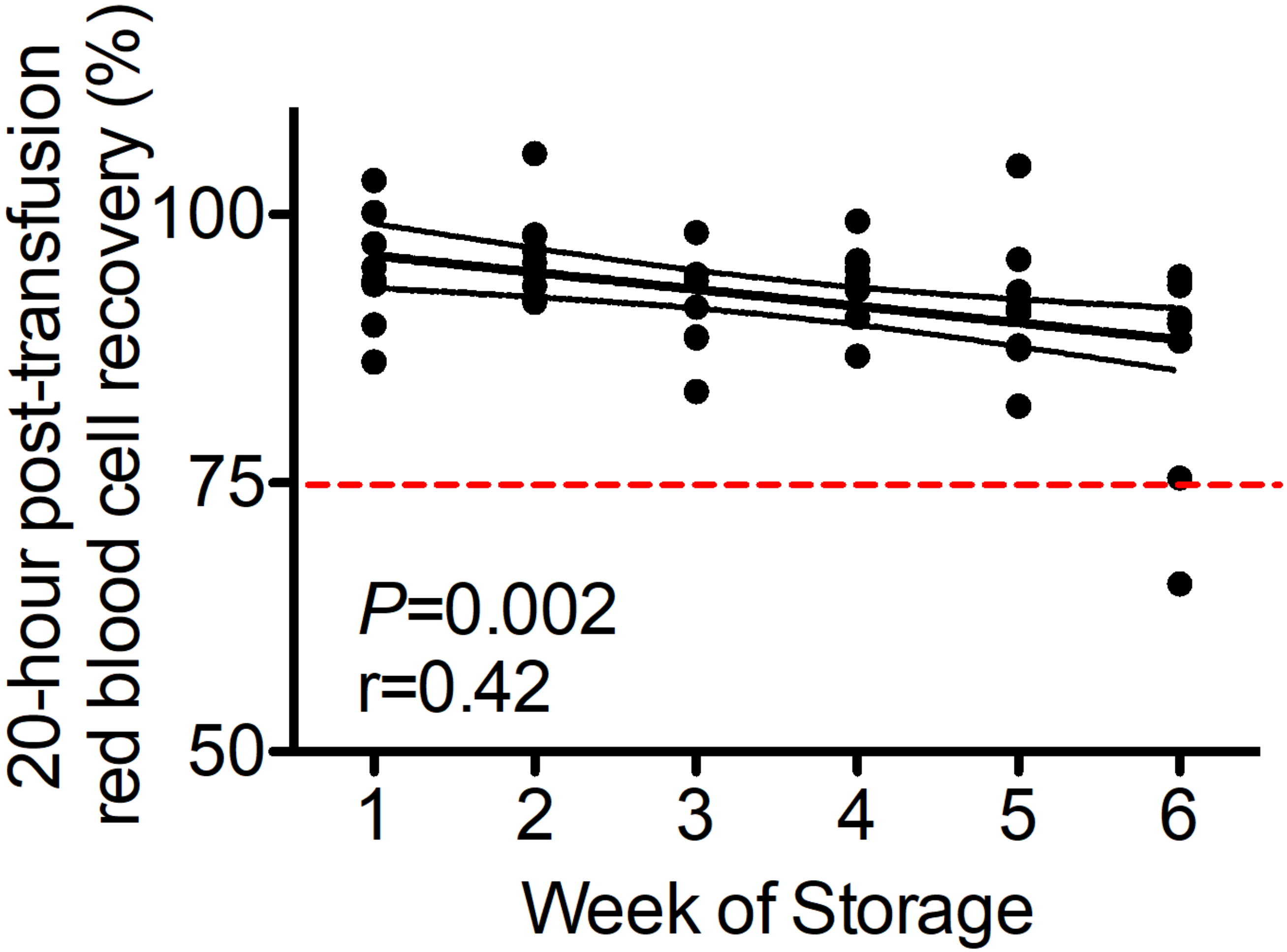


Similar pattern with serum iron, NTBI, etc.

No evidence of intravascular hemolysis

When do RBCs "go bad"?



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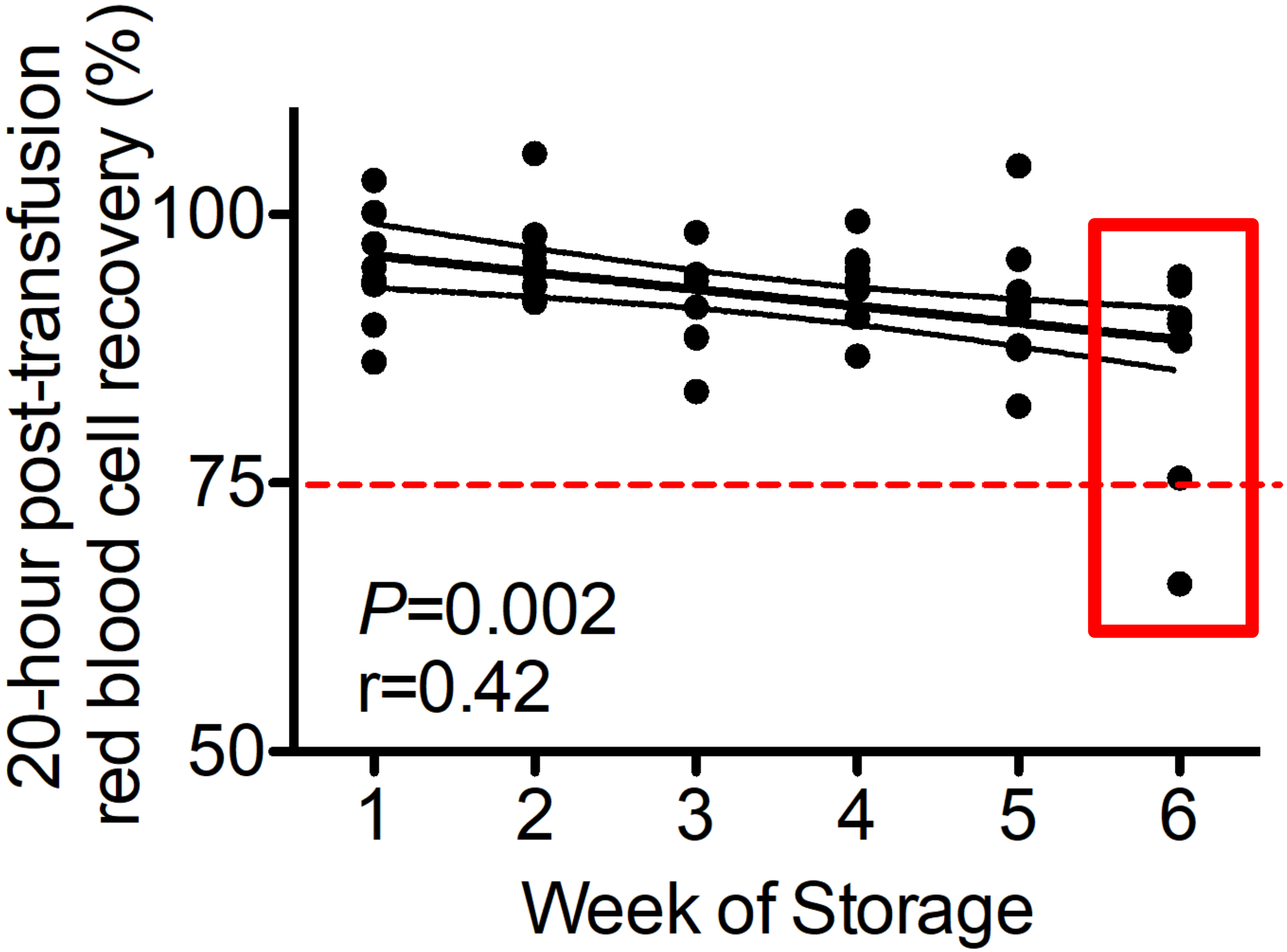

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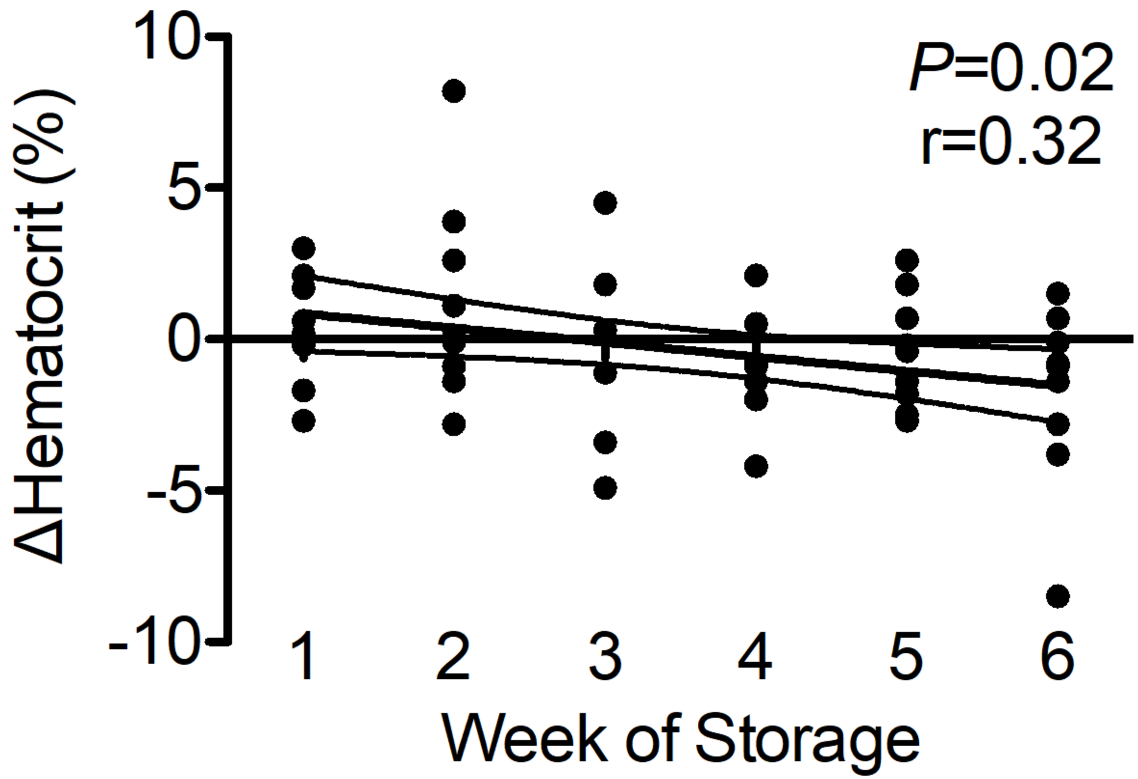

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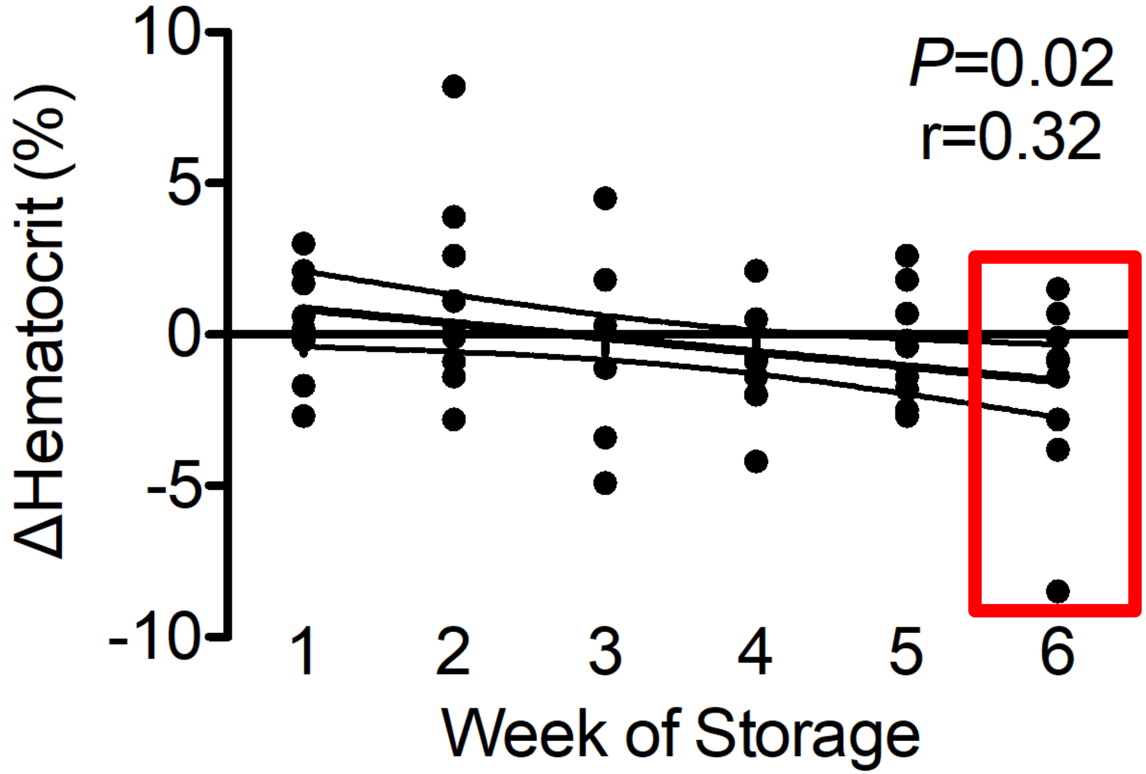


What donor characteristics influence variation in post-transfusion recovery?

Story #1:

Genetics:
G6PD deficiency

Richard O. Francis, M.D., Ph.D.

The "RBC storage lesion"
Final common pathway?

Metabolic dysfunction & oxidative stress ➔

↓ Deformability

↑ "Eat me" signals

↓ "Don't eat me" signals

- ↑ Hemolysis *in vitro*
- ↑ RBC clearance *in vivo*
  - Intravascular and extravascular hemolysis

Inherited Hemolytic Anemias

Final common pathway

Metabolic dysfunction & oxidative stress ➔

↓ Deformability

↑ “Eat me” signals

↓ “Don’t eat me” signals

↑ Hemolysis *in vitro*

↑ RBC clearance *in vivo*

Intravascular and extravascular hemolysis

What are the consequences of the clearance of stored RBCs?

RBC storage lesion *in vitro*

↓

Decreased RBC recovery *in vivo*

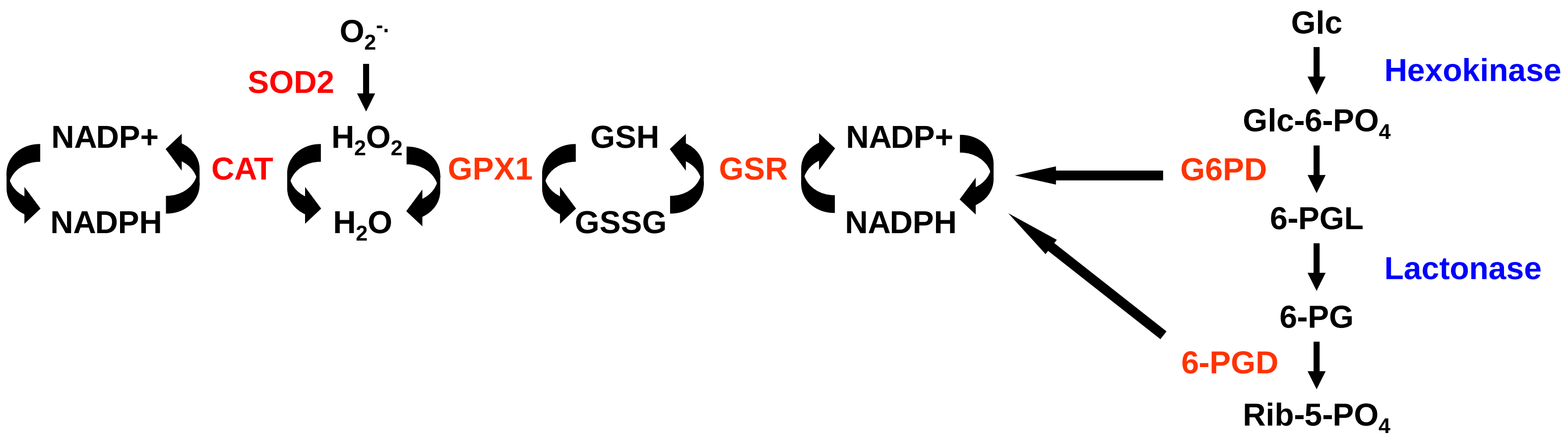
What are the consequences of the clearance of stored RBCs?

Insufficient protection against oxidative stress *in vitro*

↓

Decreased RBC recovery *in vivo*

The case for G6PD: Homeostasis



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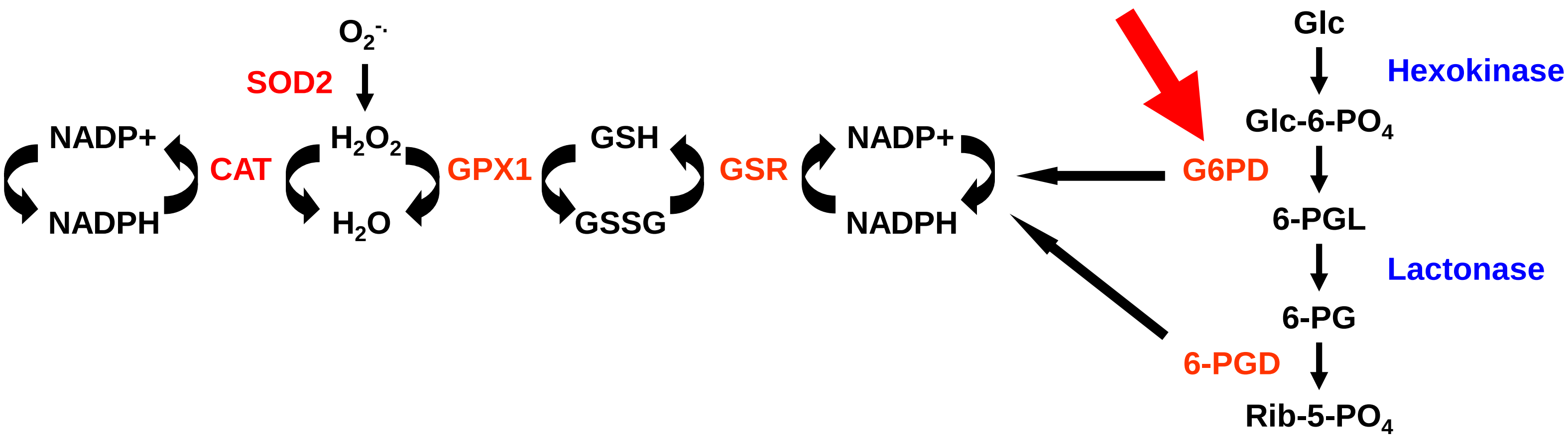

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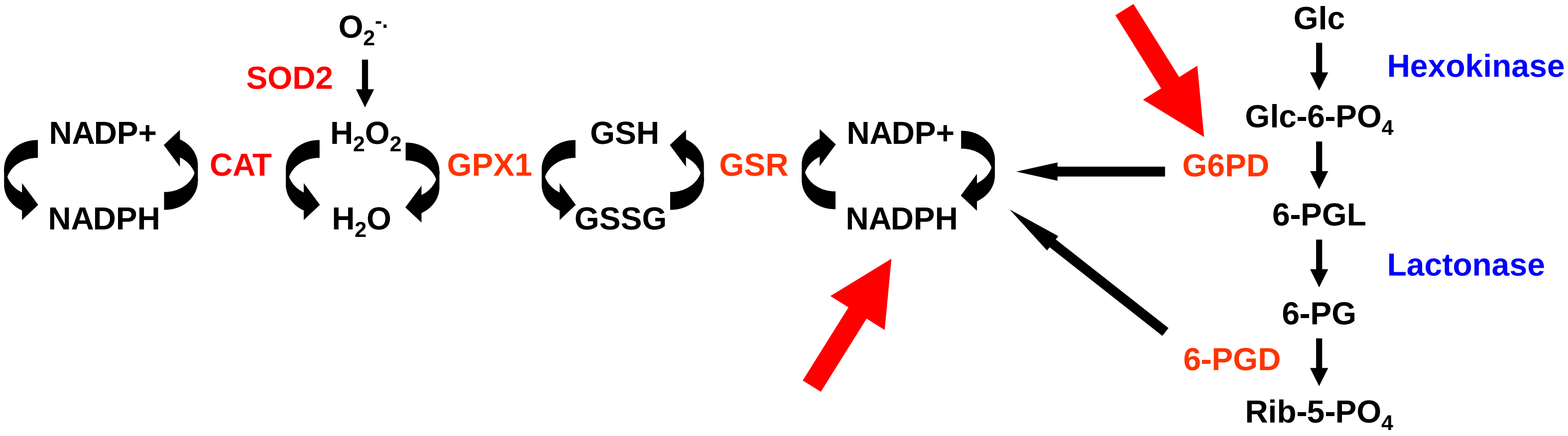

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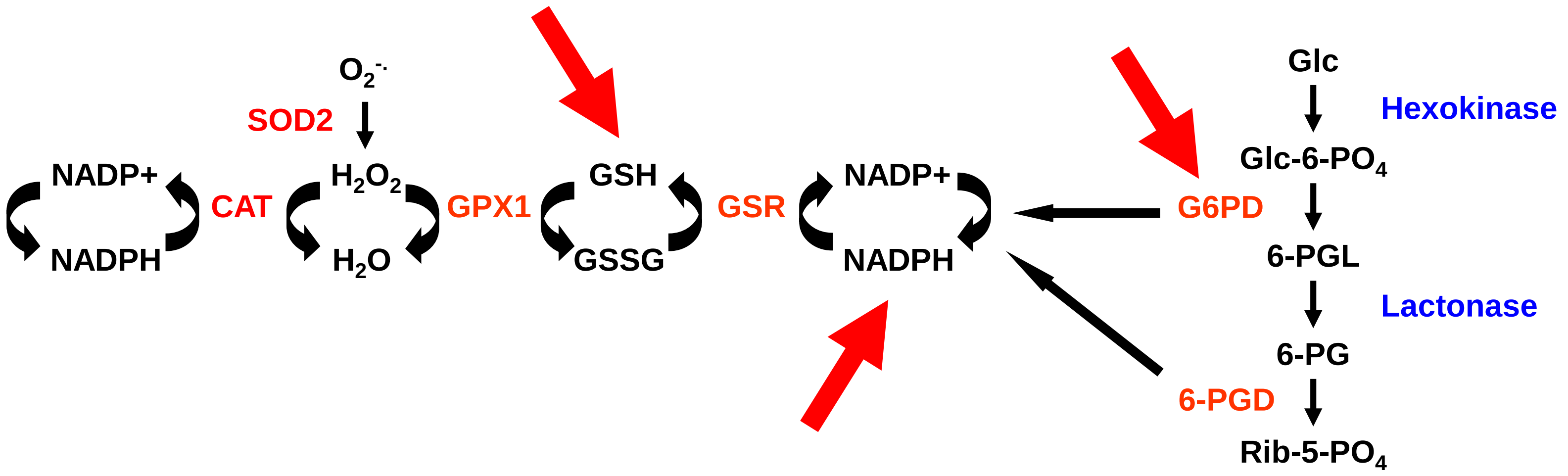

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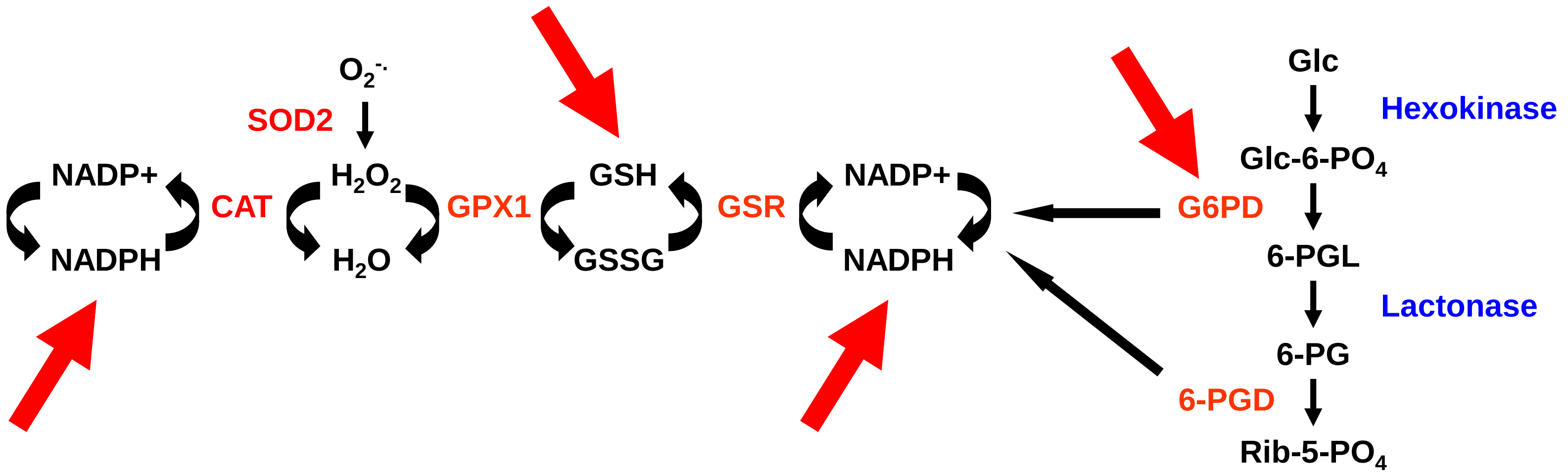

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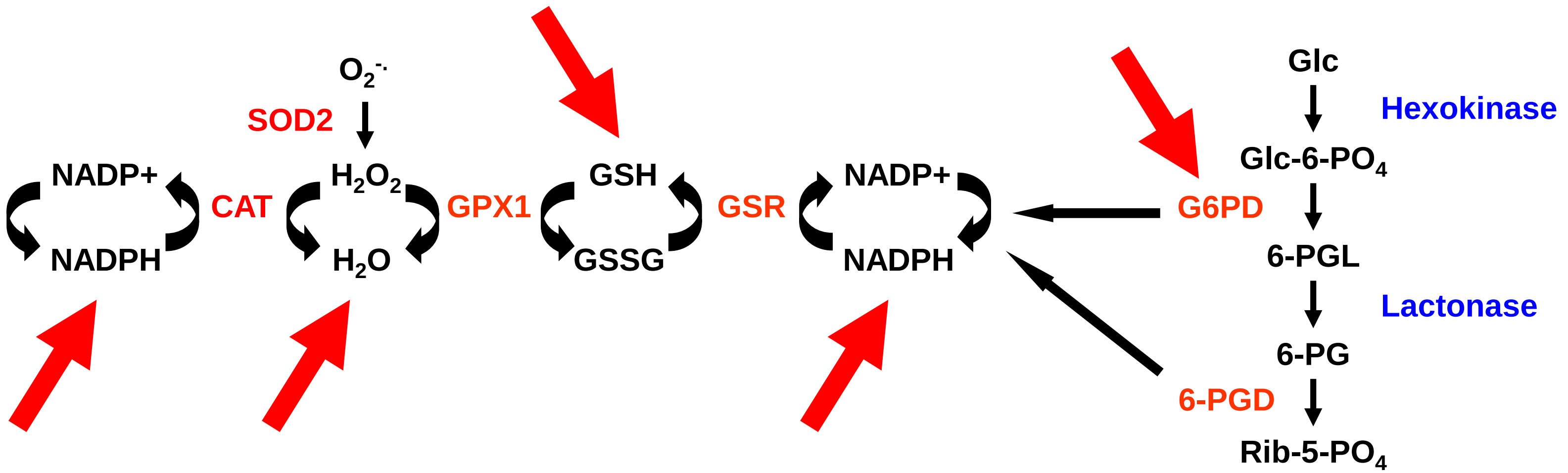
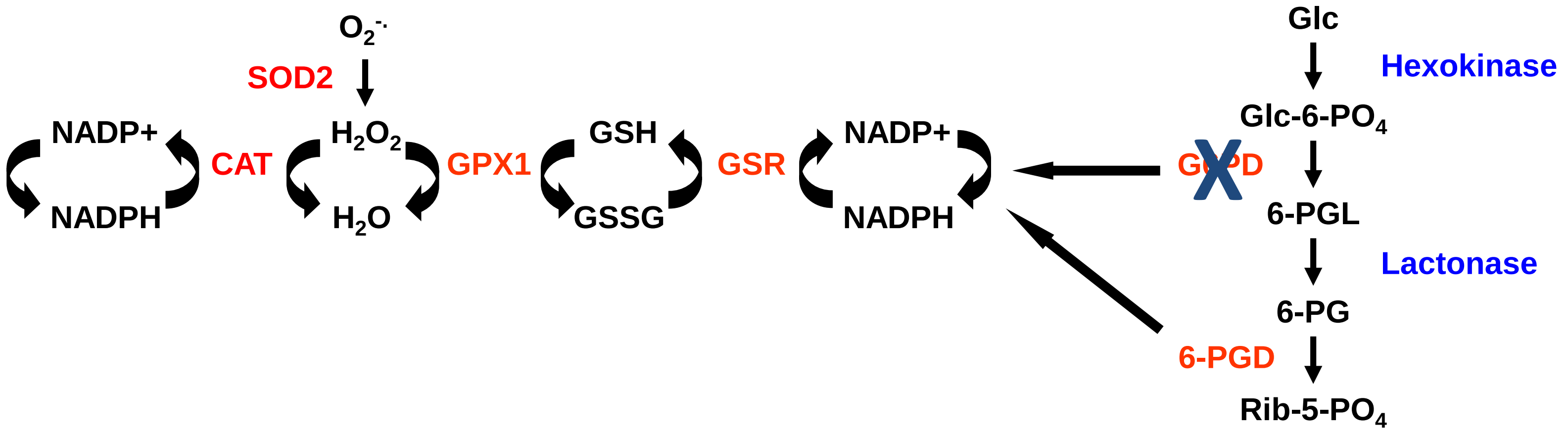


The case for G6PD: G6PD-deficiency



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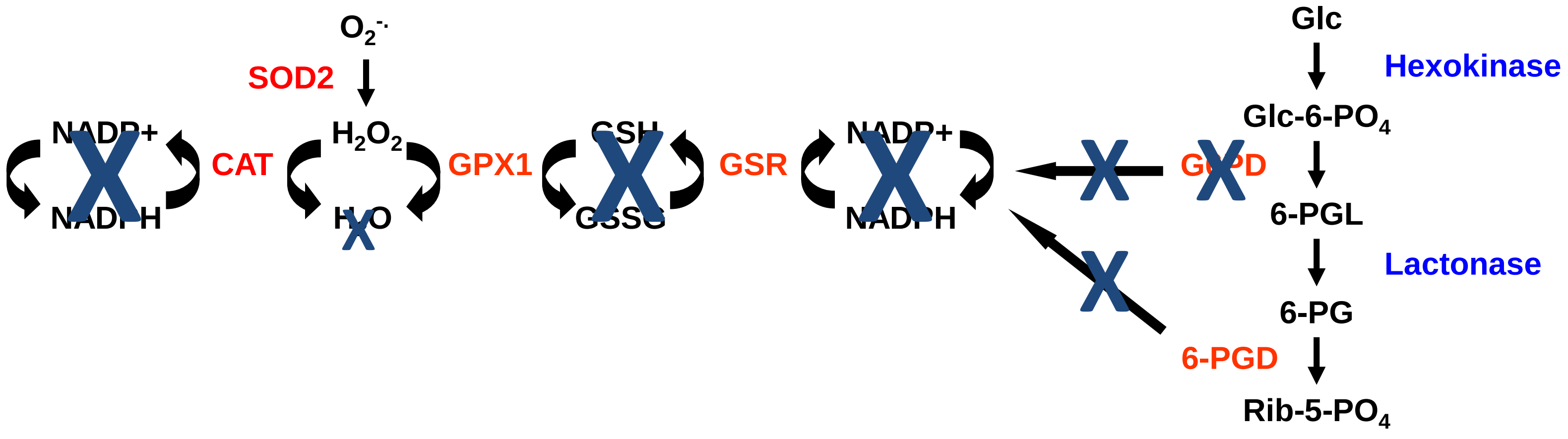

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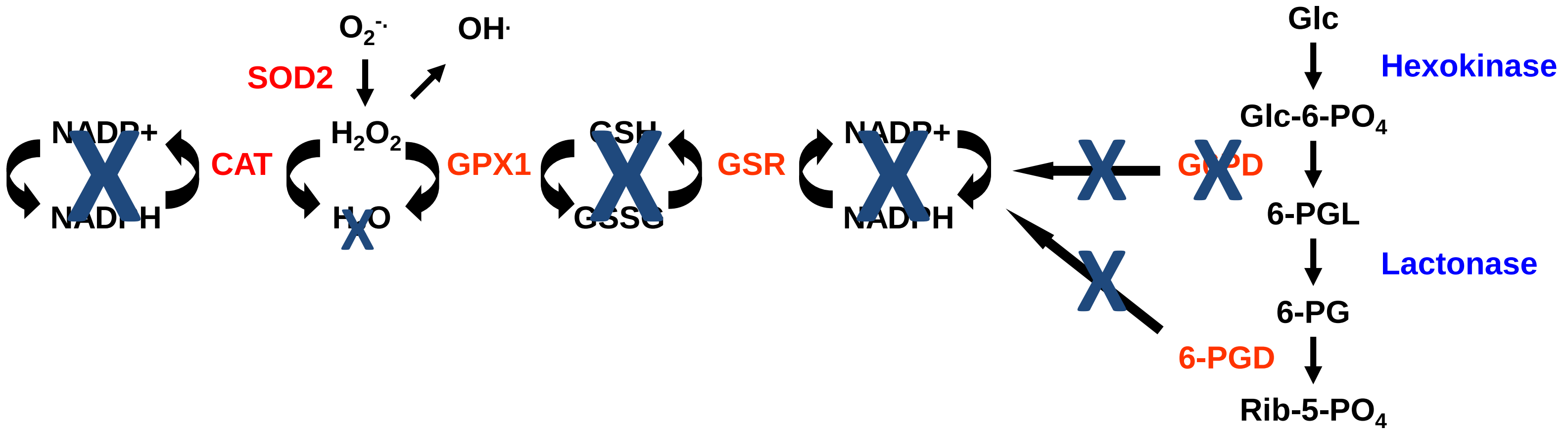

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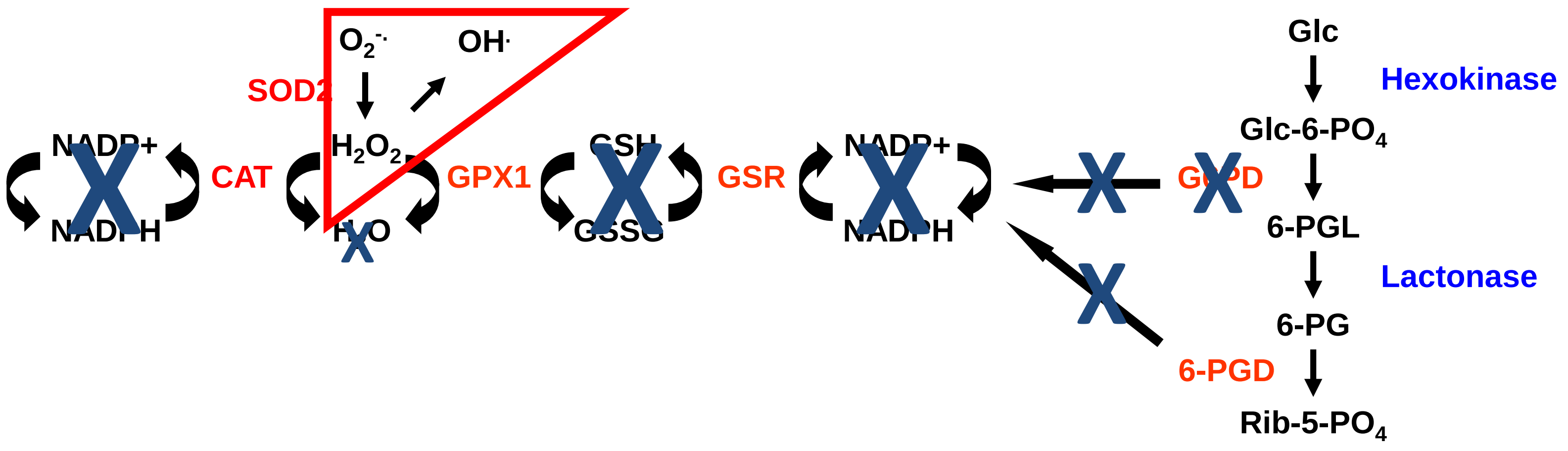

The case for G6PD: G6PD-deficiency

Unreliever oxidative stress:

- **RBC structural damage →**
  - **Intravascular hemolysis (hemoglobinemia)**
  - **Extravascular hemolysis (Bilirubin, serum iron)**

The case for G6PD: G6PD-deficiency

Most common human enzymopathy

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Most common human enzymopathy

~400 million affected individuals

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Genetically-induced enzyme variation:

- **Severely decreased activity**
- **Normal activity**
- **Increased activity**

The case for G6PD: G6PD-deficiency

Most common human enzymopathy

~400 million affected individuals

Genetically-induced enzyme variation:

- Severely decreased activity: poor storers?
- Normal activity
- Increased activity

The case for G6PD: G6PD-deficiency

Most common human enzymopathy

~400 million affected individuals

Genetically-induced enzyme variation:

- **Severely decreased activity: poor storers?**
- **Normal activity**
- **Increased activity: super storers?**

The case for G6PD: G6PD-deficiency

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Prevalence of G6PD-deficiency in normal donors at our hospital:

Random donors: 0.3%

Francis et al. Transfusion 53:606-611, 2013

The case for G6PD: G6PD-deficiency

Prevalence of G6PD-deficiency in normal donors at our hospital:

Random donors:	0.3%
R_0R_0/R_0r donors:	12.3%

Francis et al. Transfusion 53:606-611, 2013

The case for G6PD:
G6PD-deficiency

Prevalence of G6PD-deficiency in normal donors at our hospital:

Random donors:	**0.3%**
R_0R_0/R_0r donors:	**12.3%**

Exchange Transfusions for Sickle Cell Disease

Francis et al. Transfusion 53:606-611, 2013

Study Design

Volunteers:
- **G6PD-deficient**
- **Matched controls**

Donate 1 unit:
- **Pre-storage leukoreduced**
- **Store for 40-42 days in AS-3**

24h 51-Cr post-transfusion recovery

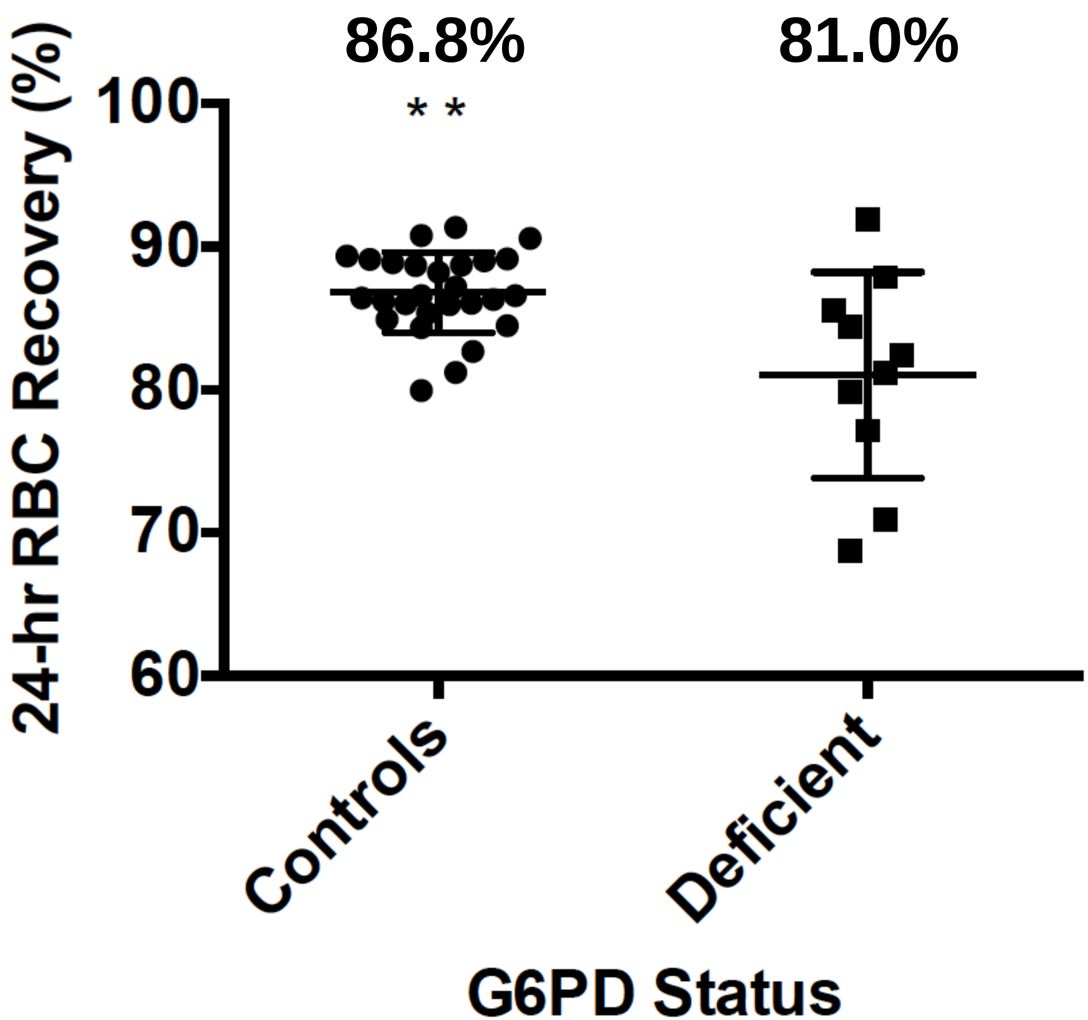
Study Design

Enroll: 10 G6PD-deficient + 30 controls

G6PD-deficient variants: 9 African, 1 Mediterranean

None with hemoglobin variant or thalassemia trait

The case for G6PD: G6PD-deficiency



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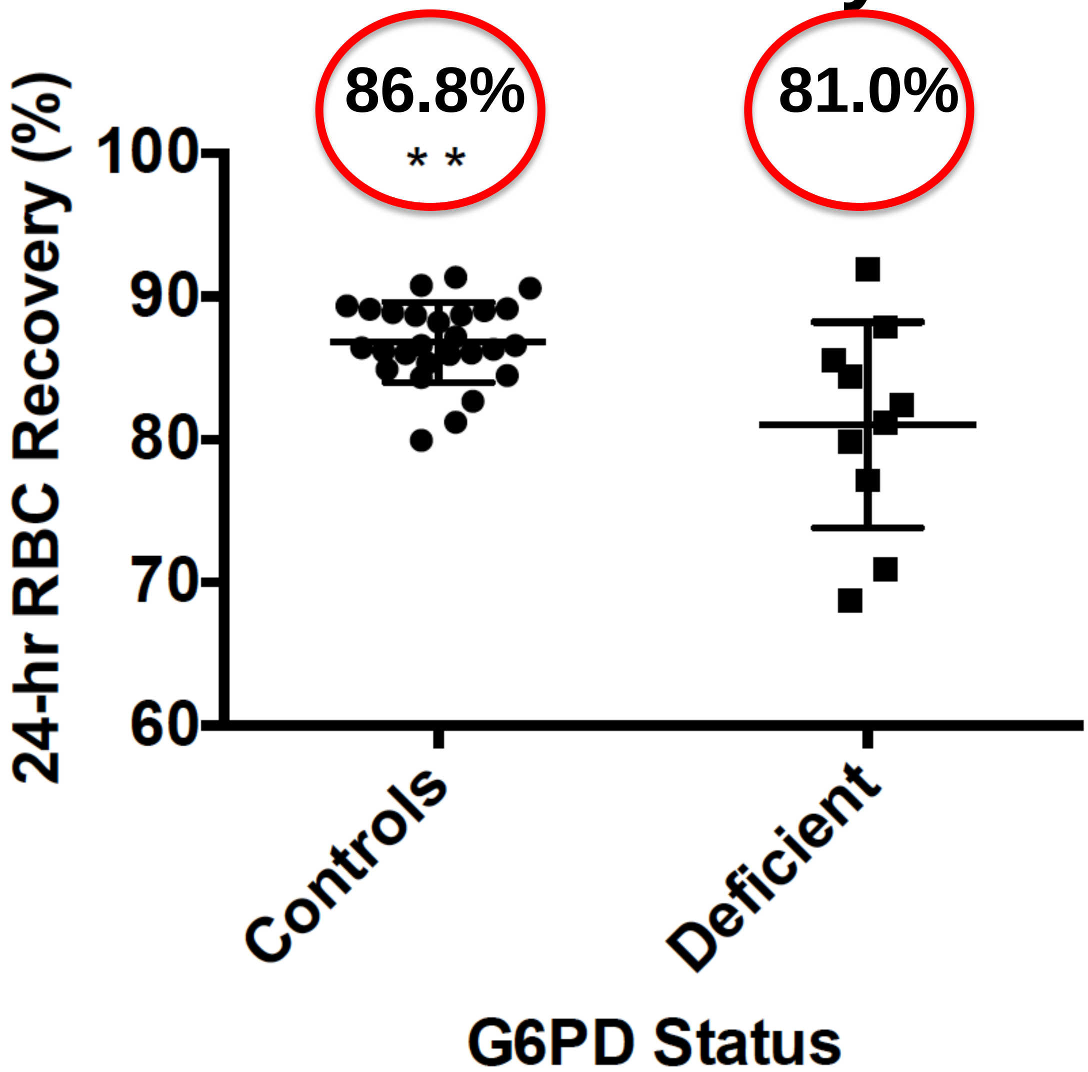

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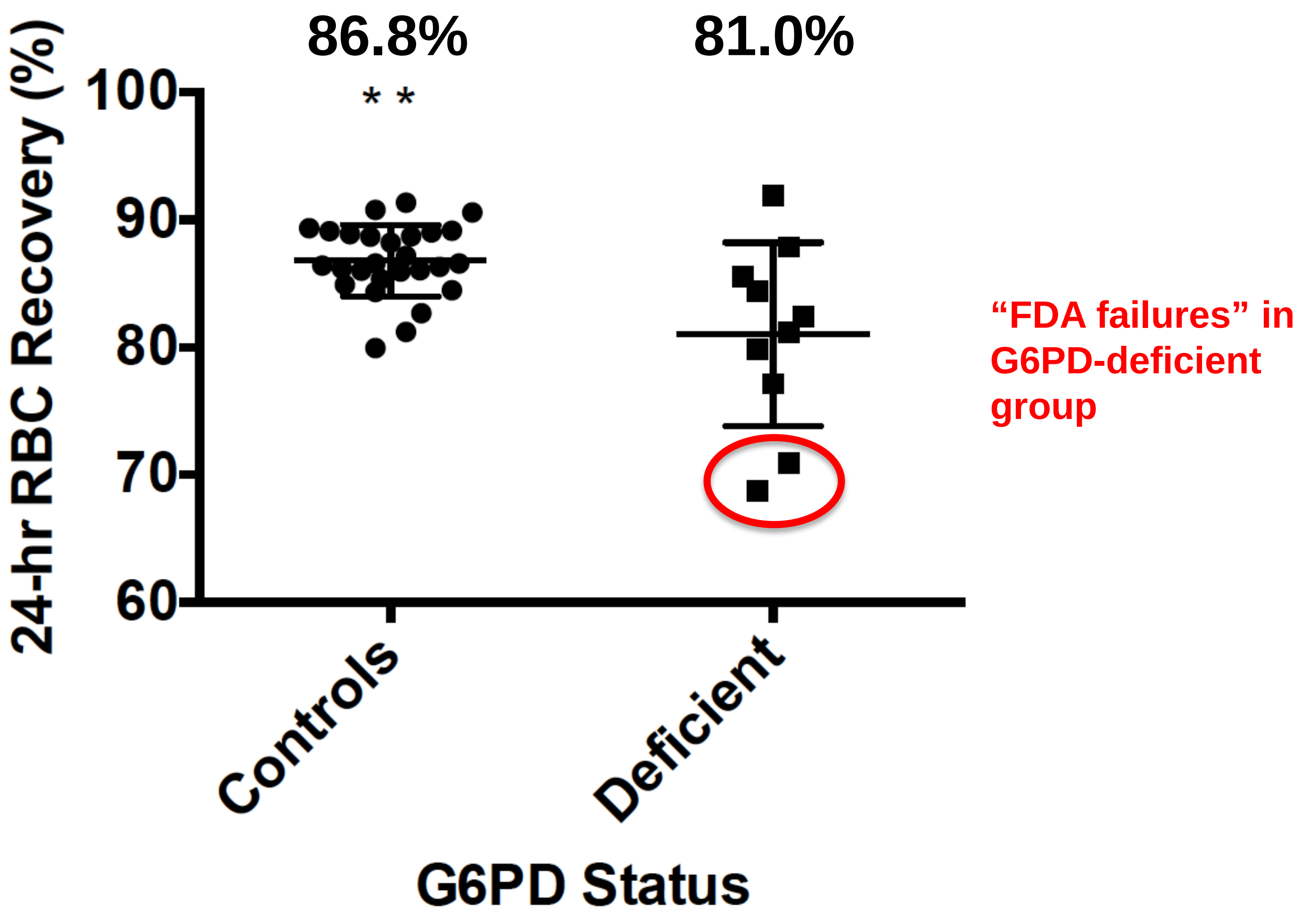

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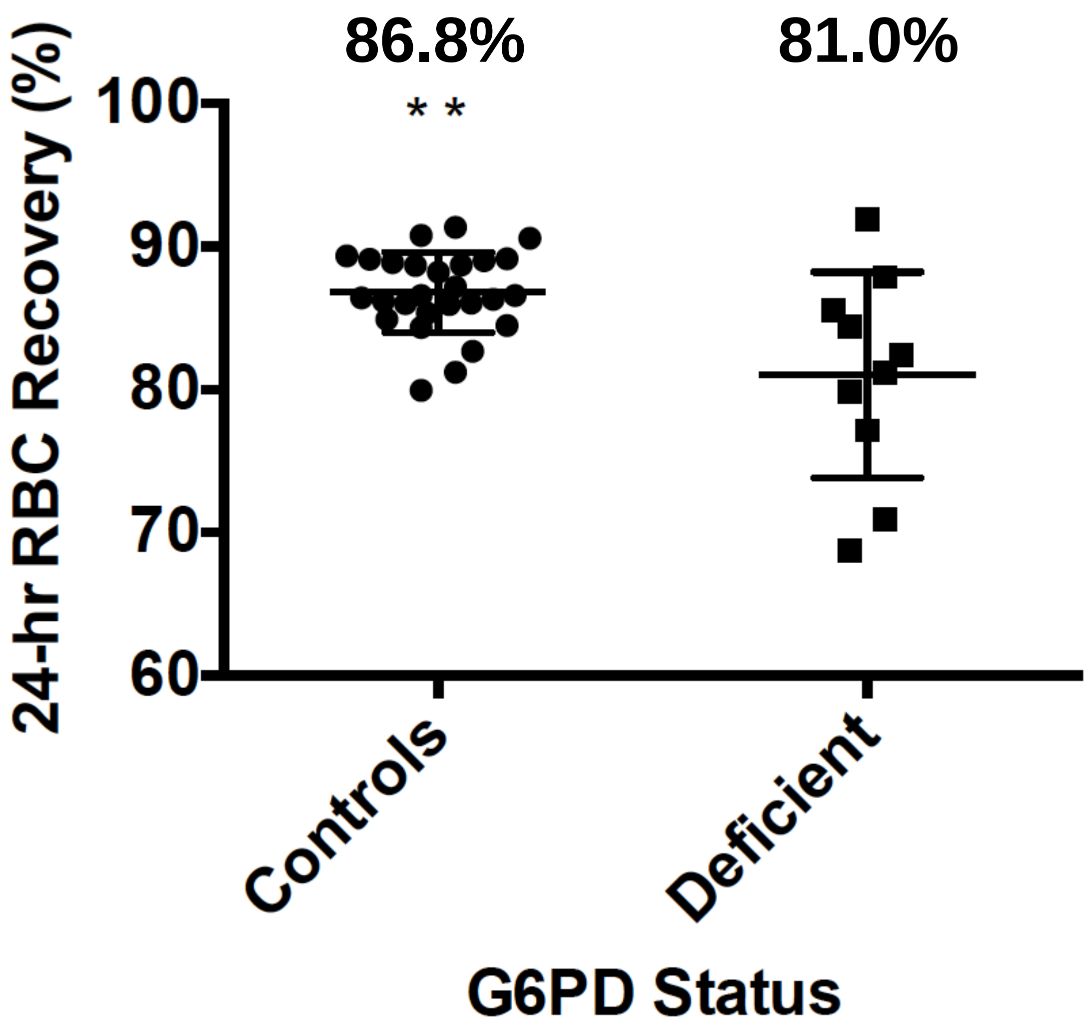
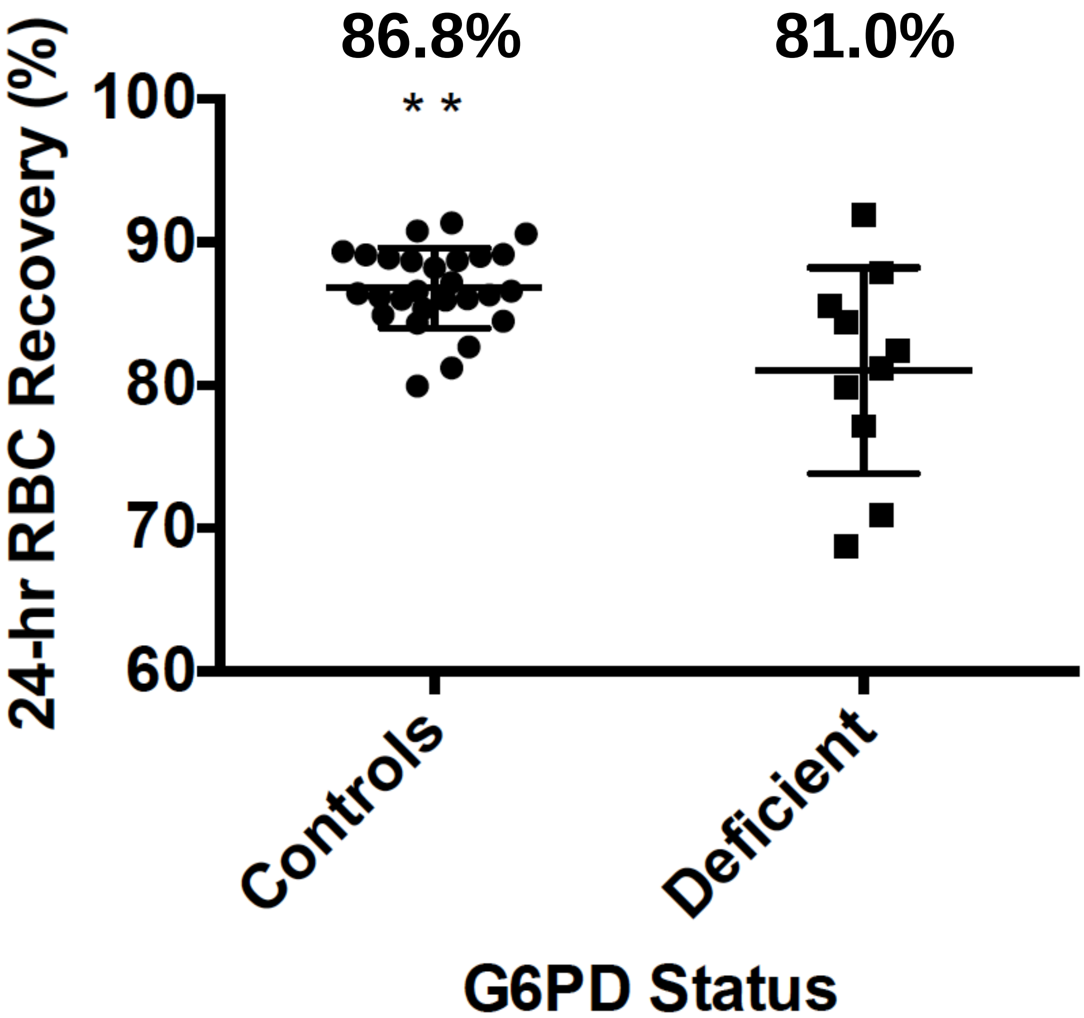


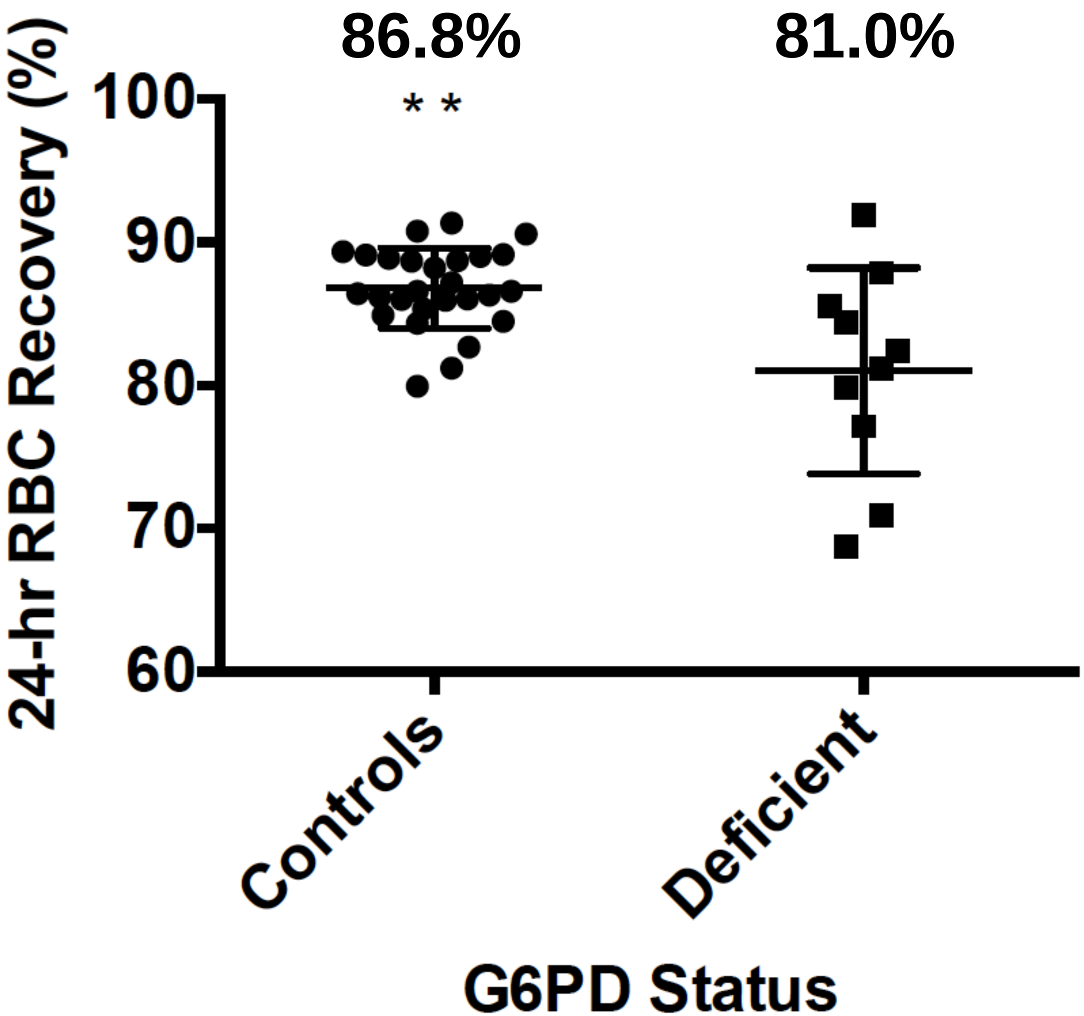
No correlation between PTR and G6PD enzyme activity within groups

The case for G6PD: G6PD-deficiency



No difference in hemolysis "in the bag" at outdate

The case for G6PD: G6PD-deficiency



Would 24-hour post-transfusion recoveries be worse in ill recipients?

Conclusions (G6PD)

RBCs from G6PD-deficient volunteers have inferior storage quality: ↓5.8% ($p=0.001$)

The intrinsic ability of RBCs to resist oxidative stress affects storage quality

Should we test donors to provide better products?

Should we counsel G6PD-deficient donors?

Blood Donor Selection

Guidelines on Assessing Donor Suitability for Blood Donation

World Health Organization

Recommendations

- Policies for the assessment of prospective donors should be developed by BTS in regions where there is a high incidence of enzymopathies and inherited red cell membrane defects

Accept

- Individuals with G6PD deficiency or other inherited red cell membrane defects, without a history of haemolysis; however, their blood is not suitable for intrauterine transfusion, neonatal exchange transfusion or for patients with G6PD deficiency

Defer permanently

- Individuals with G6PD deficiency or inherited red cell membrane defects, with a history of haemolysis

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Defer permanently

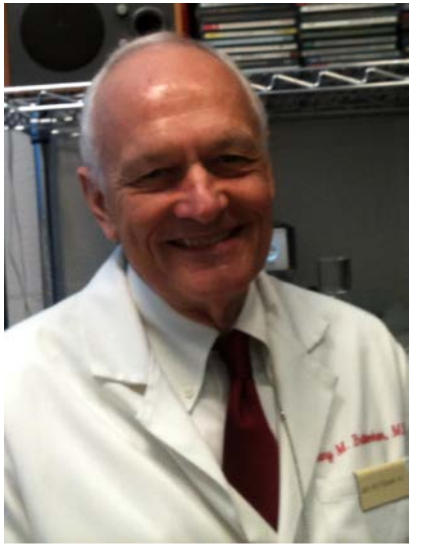
- Individuals with G6PD deficiency or inherited red cell membrane defects, with a history of haemolysis

Should we counsel G6PD-deficient donors regarding their condition?

Story #2:

Diet:
Iron deficiency

Eldad Hod, M.D.



Gary Brittenham, M.D.

The “RBC storage lesion”
Final common pathway?

Metabolic dysfunction & oxidative stress ➔

↓ Deformability

↑ “Eat me” signals

↓ “Don’t eat me” signals

- ↑ Hemolysis *in vitro*
- ↑ RBC clearance *in vivo*
    - Intravascular and extravascular hemolysis

Iron deficiency (without anemia) is very common in blood donors

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Iron-deficient erythropoiesis (IDE)

Iron deficiency anemia affects RBC lifespan & transfusion recovery

- ↓ Resistance to oxidative stress
- ↑ Oxidative damage
- ↓ Resistance to low pH
- ↑ Phosphatidylserine exposure
- ↓ Deformability
- ↑ Splenic clearance

Iron deficiency anemia affects RBC lifespan & transfusion recovery

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Is this relevant in IDE?

Mouse model

Weanling, male C57BL/6 mice:

1. **Control diet: 45 ppm of iron** **(normal)**
2. **Iron-deficient diet: 0-4 ppm of iron** **(IDE)**
3. **Iron-deficient diet + weekly phlebotomy** **(IDA)**

Mouse model

Weanling, male C57BL/6 mice:

1. Control diet: 45 ppm of iron (normal)
2. Iron-deficient diet: 0-4 ppm of iron (IDE)
3. Iron-deficient diet + weekly phlebotomy (IDA)

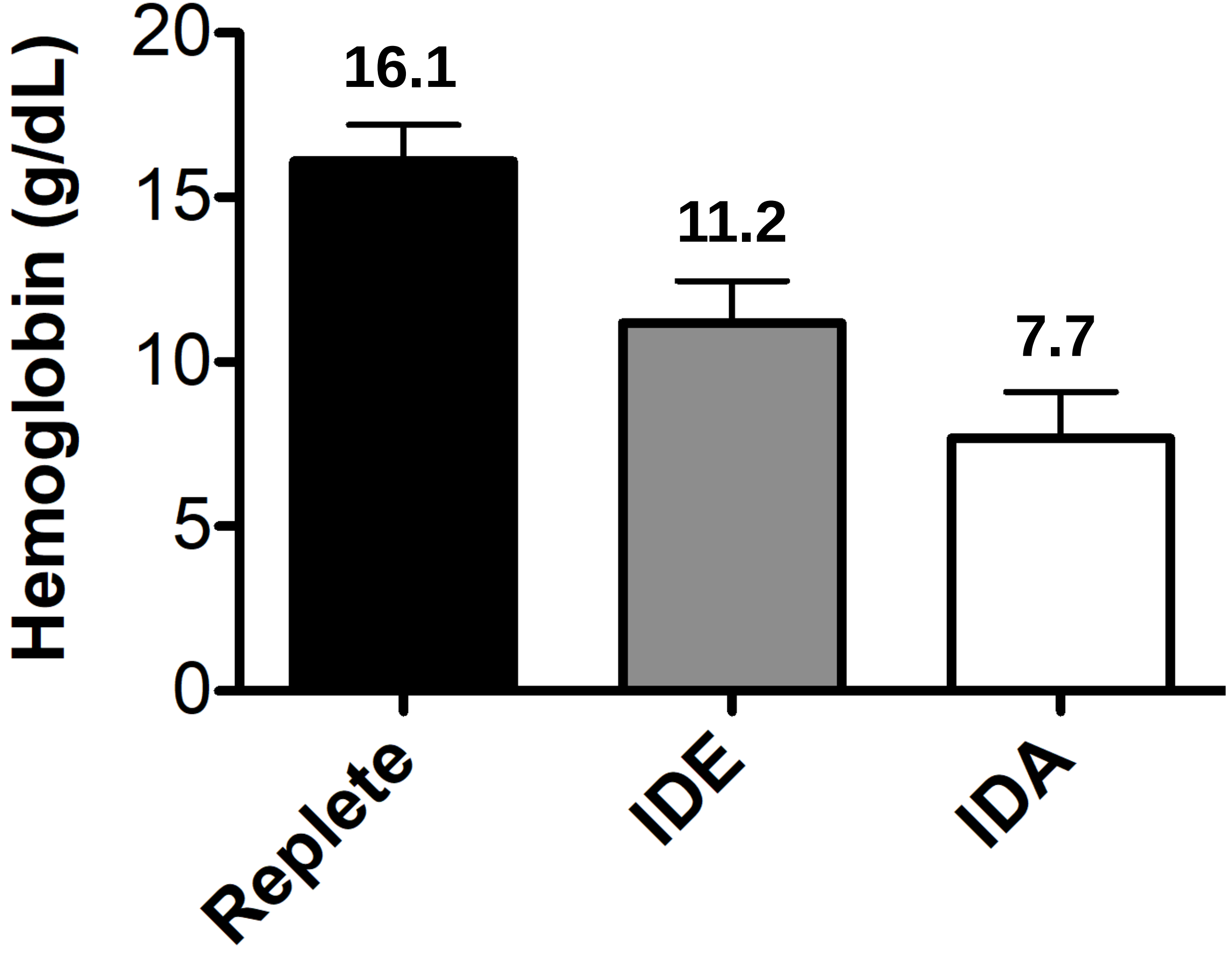
At 10 weeks of age:

Exsanguinated, pooled, leukoreduced, packed, stored in CPDA-1 for 12 days

Transfused into GFP-transgenic recipients

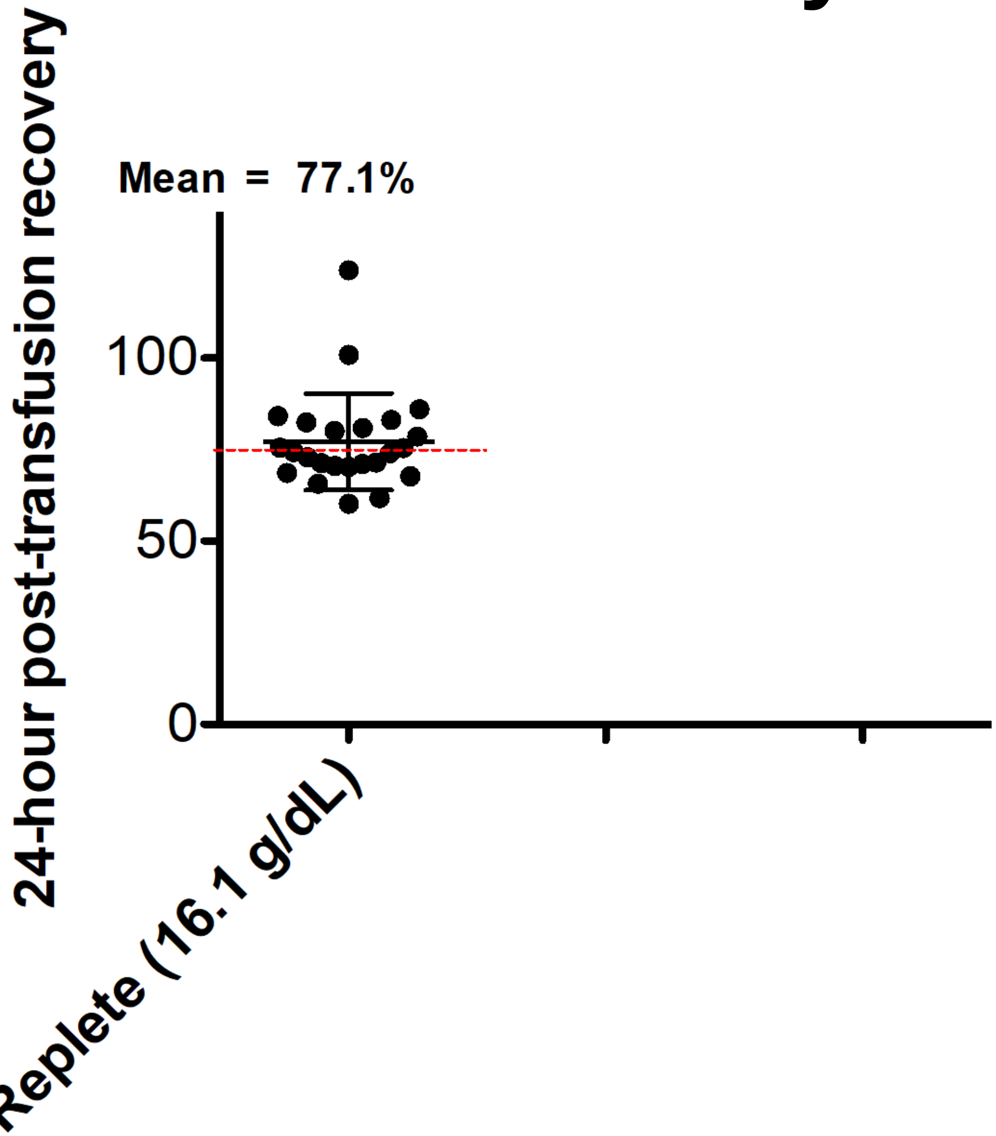
24-hour post-transfusion recovery by flow cytometry

Results

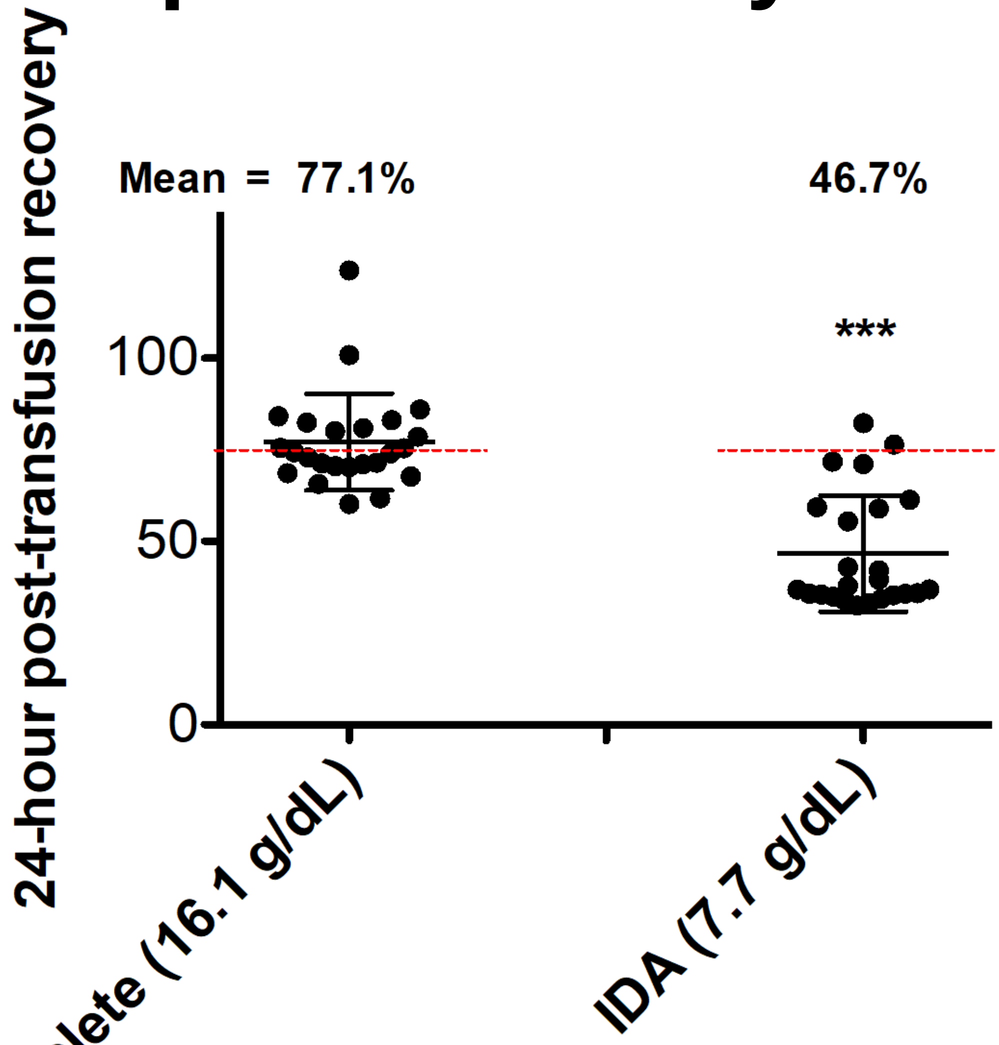


All comparisons: $p<0.001$

RBCs from normal donors had normal recovery

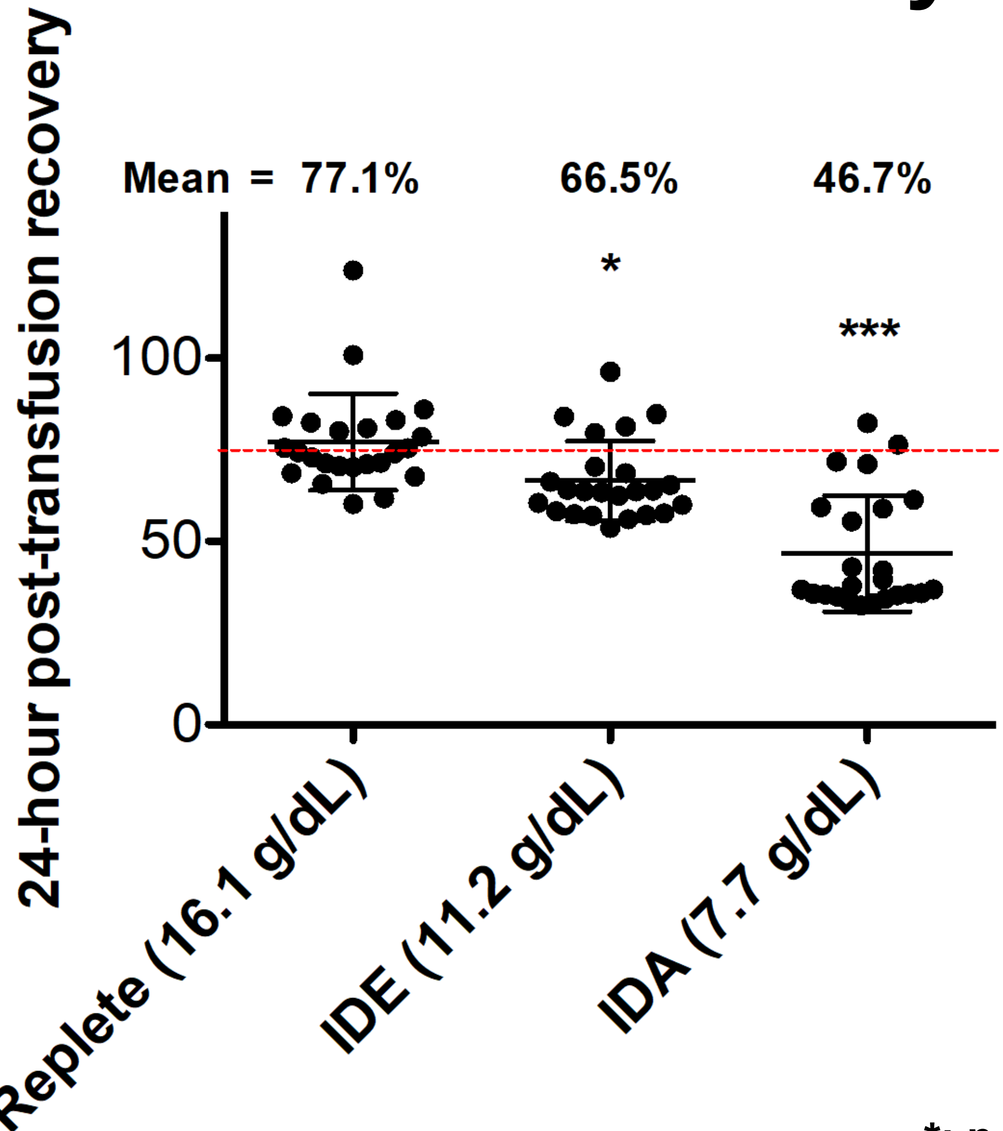


RBCs from donors with IDA had poor recovery



***: p<0.001

RBCs from donors with IDE had sub-normal recovery



*: p<0.05

Would this be true for human recipients of RBC transfusions from donors with IDE?

Would this be true for human recipients of RBC transfusions from donors with IDE?

ClinicalTrials.gov

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Trial record **3 of 5** for: eldad hod

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Donor Iron Deficiency Study - Red Blood Cells From Iron-deficient Donors: Recovery and Storage Quality (DIDS)

This study is enrolling participants by invitation only.

Sponsor:
Columbia University

Collaborators:
New York Blood Center
National Heart, Lung, and Blood Institute (NHLBI)

Information provided by (Responsible Party):
Eldad Arie Hod, Columbia University

ClinicalTrials.gov Identifier:
NCT02889133

First received: August 25, 2016
Last updated: March 20, 2017
Last verified: March 2017
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

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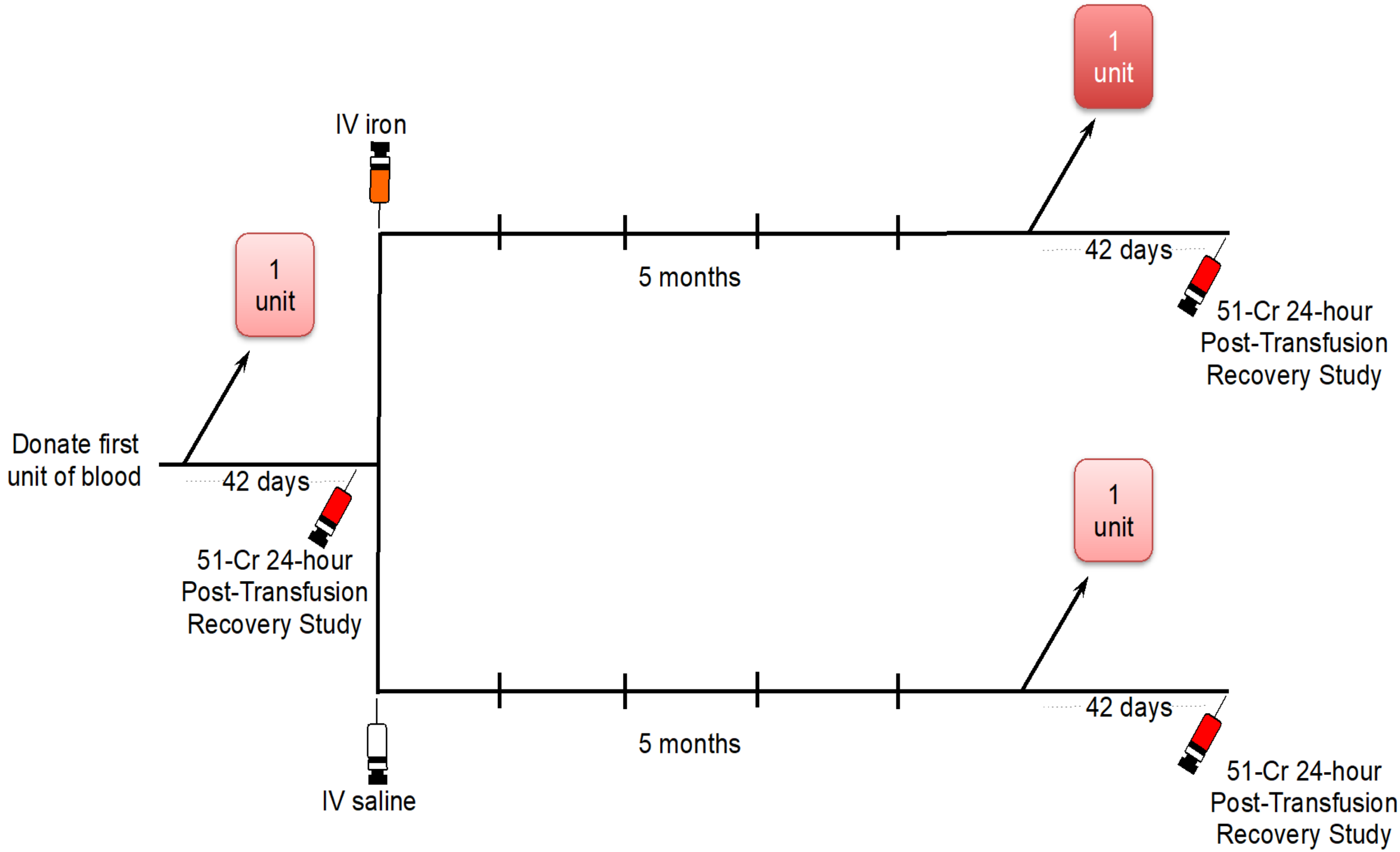
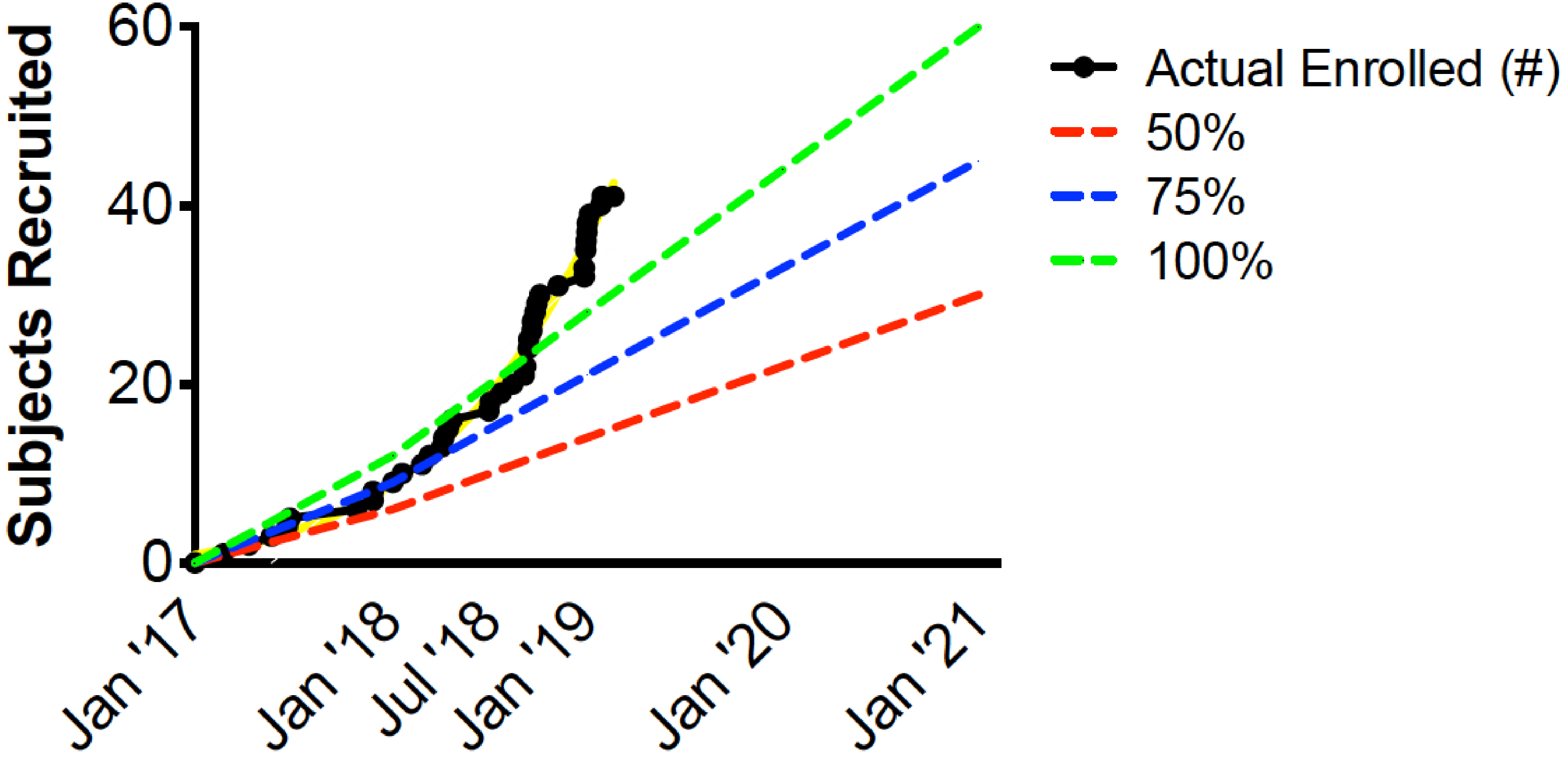


Would this be true for human recipients of RBC transfusions from donors with IDE?



Conclusions (Iron)

Should we screen donors for iron-deficient erythropoiesis?

Should we collect & transfuse RBCs from such donors?

Should we counsel & treat iron-deficient donors?

Story #3:

"Environment": Lead

Tiffany Thomas, Ph.D.

Lead

Lead

Neurotoxicant (synapses, myelin, etc.)

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No threshold effect

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Young children particularly vulnerable

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↑ blood lead level: >5 µg/dL (0.2415 µmol/L)

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No threshold effect

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↑ blood lead level: >5 µg/dL (0.2415 µmol/L)

In whole blood, 75% of lead is in RBCs

Lead

Do donor pRBC units contain high lead levels?

Lead

Do donor pRBC units contain high lead levels?

If so, who cares?

Lead

BLOOD DONORS AND BLOOD COLLECTION

A population-based study on blood lead levels in blood donors

Gilles Delage,[1] Suzanne Gingras,[2] and Marc Rhainds[2,3]

TRANSFUSION 2015;55;2633–2640

Lead

BLOOD DONORS AND BLOOD COLLECTION

A population-based study on blood lead levels in blood donors

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TRANSFUSION 2015;55;2633–2640

“Toxic” levels in ~10% of their donor population

Lead

Lead exposure in preterm infants receiving red blood cell transfusions

Hijab Zubairi[1], Paul Visintainer[2,3], Jennie Fleming[1], Matthew Richardson[1,3] and Rachana Singh[1,3]

Pediatric RESEARCH Volume 77 | Number 6 | June 2015

Lead

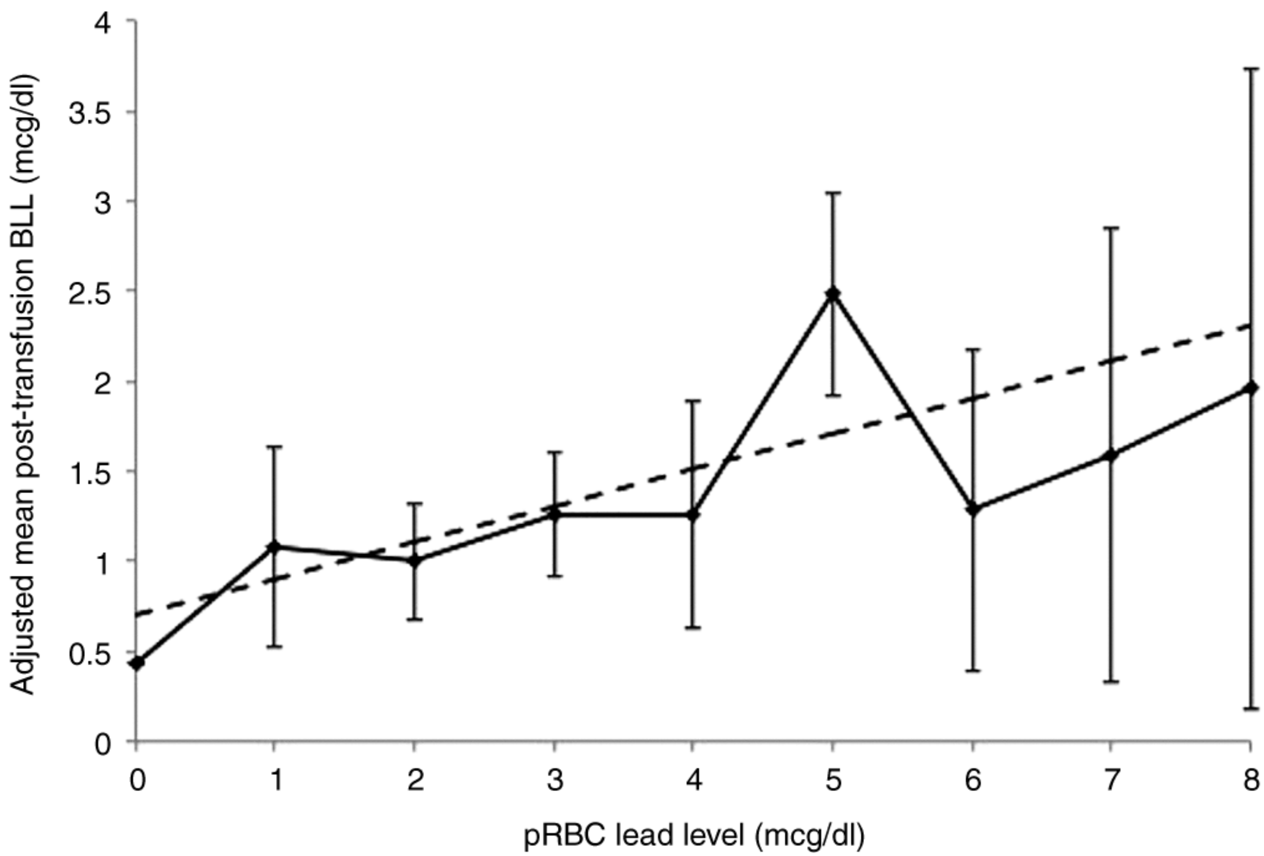
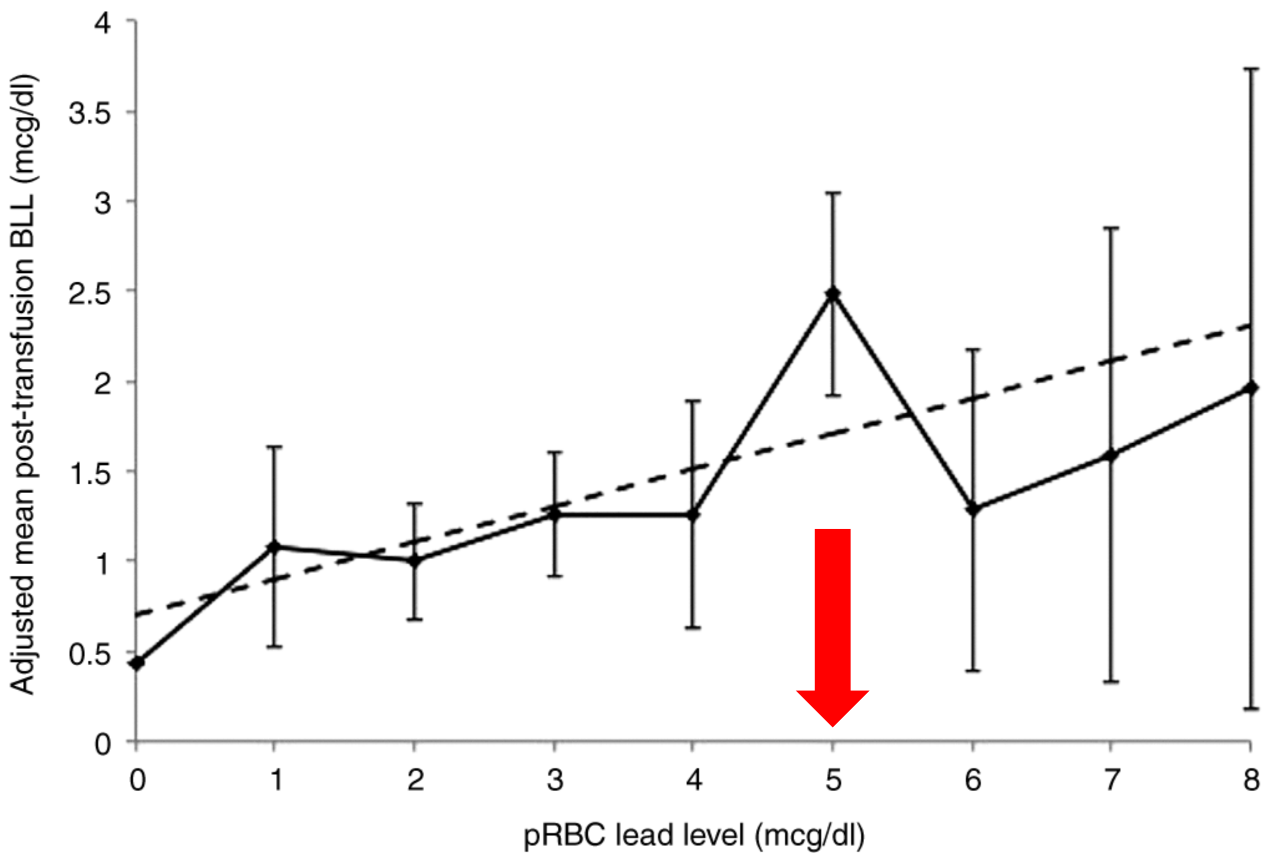


Figure 1. Adjusted mean (and 95% CI) post-transfusion BLL by pRBC lead level. For each 1 mcg/dl increase in transfused pRBC lead level, infant post-transfusion BLL increased by 0.20 mcg/dl (95% CI: 0.07 mcg/dl, 0.33 mcg/dl; test of linear trend: $P = 0.002$). The means are adjusted for gestational age, birth weight, and pretransfusion blood lead level.

Lead



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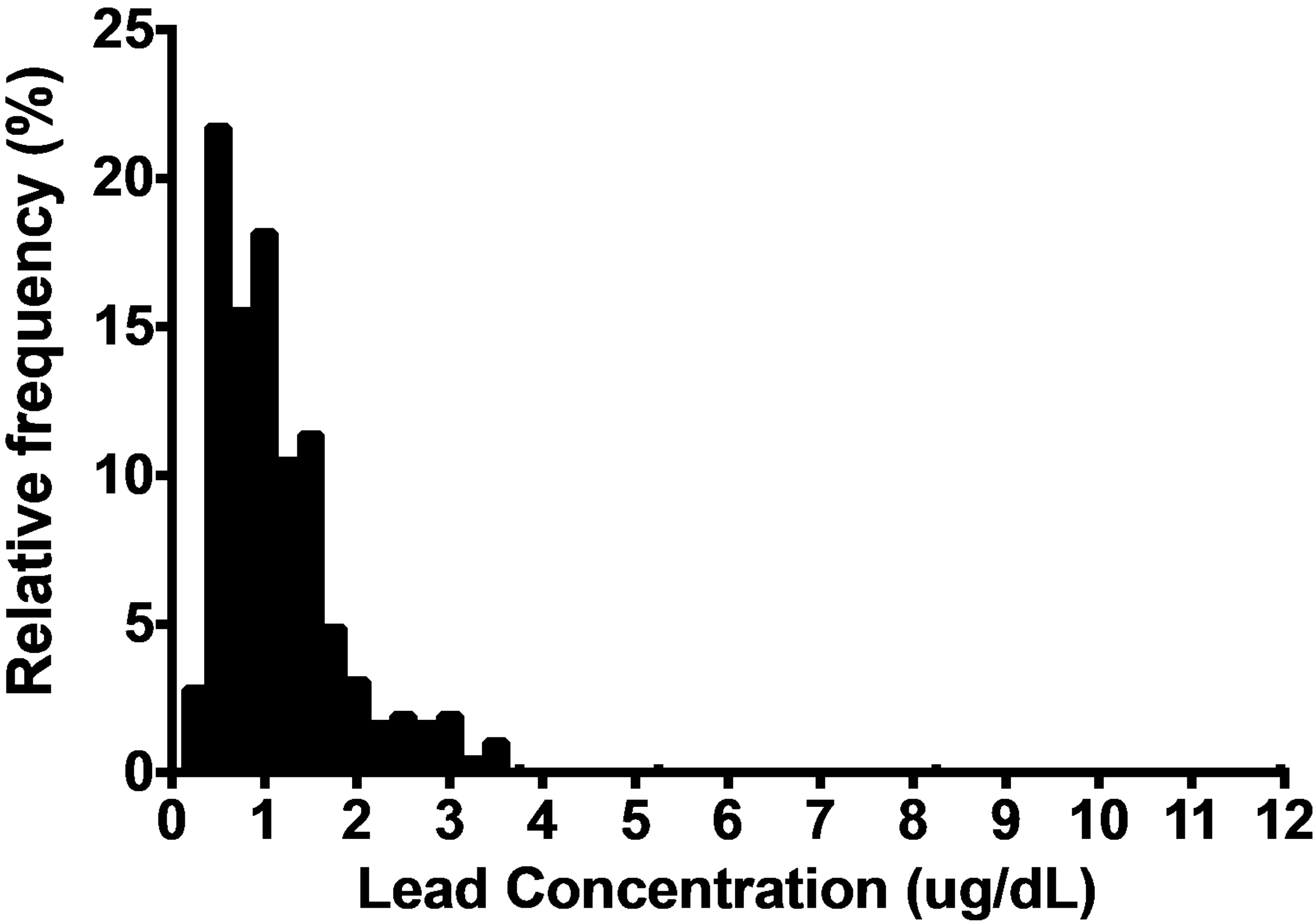
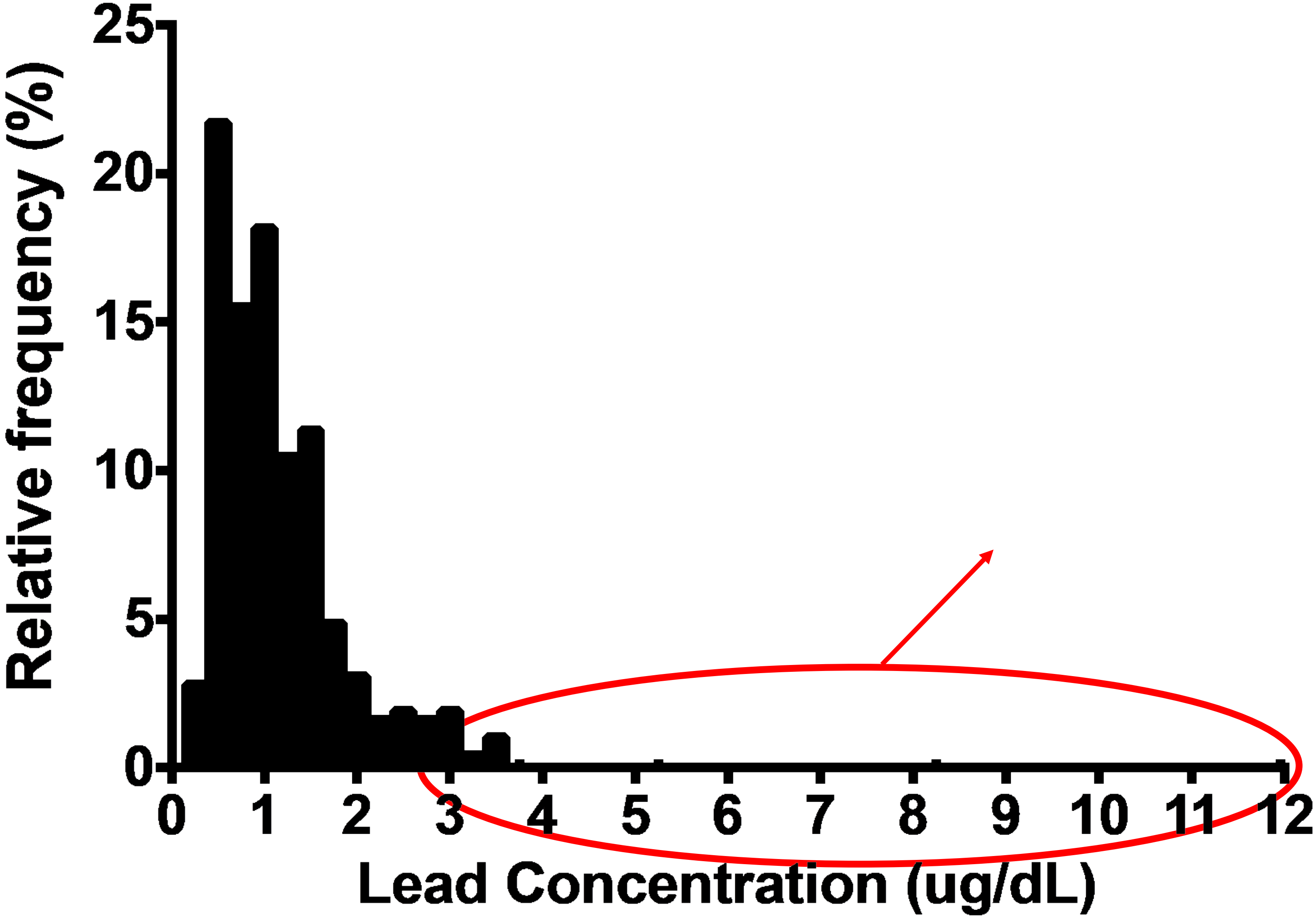
Our data



25
20
15
10
5
0
Relative frequency (%)
0 1 2 3 4 5 6 7 8 9 10 11 12
Lead Concentration (ug/dL)

Our data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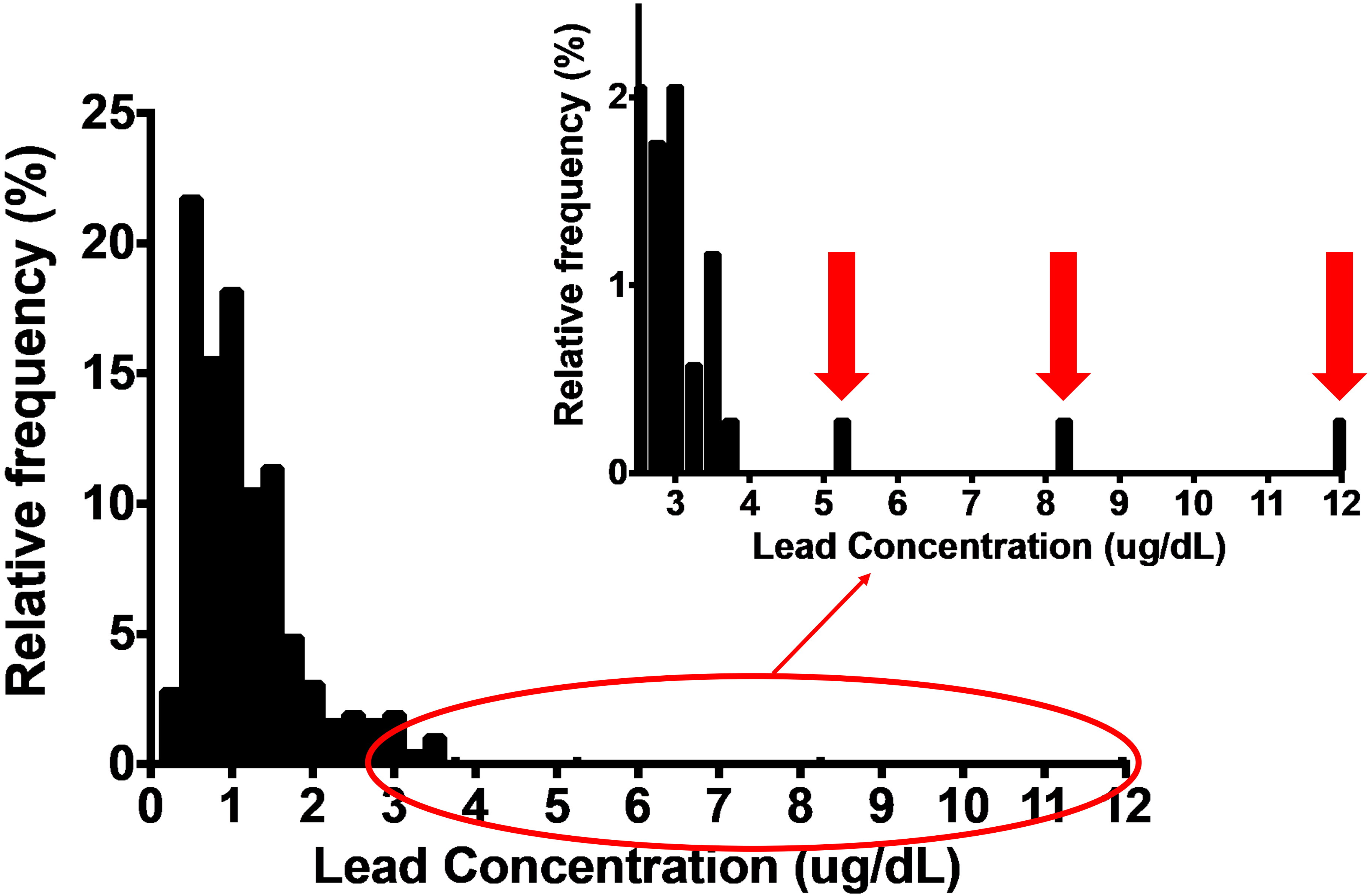
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0 1 2 3 4 5 6 7 8 9 10 11 12
Lead Concentration (ug/dL)
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2
1
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3 4 5 6 7 8 9 10 11 12
Lead Concentration (ug/dL)

Conclusions: Lead

Should we screen units destined for premature infants?

Should we inform donors of their lead “toxicity”?

Future Directions

Making better products: Ideal RBC unit

Future Directions

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Optimal post-transfusion recovery & lifespan

“Equivalent to fresh”

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  "Equivalent to fresh"

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  Avoid febrile NHTRs, HLA alloimmunization, TA-GVHD

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No plasma
Avoid allergic NHTRs, anaphylactic NHTRs, and TRALI

Future Directions

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Lacking clinically-significant RBC blood group antigens
Avoid RBC alloimmunization and HTRs

Future Directions

But, should we "create" better donors?

Future Directions

But, should we "create" better donors?

If so, what ethical obligations do we have to protect and inform our donors?

Thank you