Vascular Effects of Hemolysis

Gregory J. Kato, MD
<table>
<thead>
<tr>
<th>Company name</th>
<th>Research support</th>
<th>Employee</th>
<th>Consultant</th>
<th>Stockholder</th>
<th>Speakers bureau</th>
<th>Advisory board</th>
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<td>Baxalta</td>
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<td>CSL Behring</td>
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### This talk is applicable for:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definite</th>
<th>Probable</th>
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<td>Thalassemia’s</td>
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<td>Sickle cell disease</td>
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<td>Membrane disorders (e.g. spherocytosis)</td>
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<td>Enzyme defects (e.g. PKD, G6PD)</td>
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<tr>
<td>PNH</td>
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<tr>
<td>Other forms of hemolytic disease</td>
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</table>
Hemolysis Promotes Vascular Complications

- Nonhemorrhagic Stroke
- Pulmonary Hypertension
- Decreased NO Bioactivity
- Priapism
- Blood Clots
- Leg Ulceration
What is hemolysis?

- **Normal**
- **Mild Hemolysis**: 15-30 days
- **Severe Hemolysis**: 15-30 days

Days: 0, 30, 60, 90, 120

- 90-120 days
- 60-90 days

6th European Symposium on Rare Anaemias - 1st Dutch-Belgian meeting for patients and health professionals
Categories of Hemolysis

EXTRAVASCULAR HEMOLYSIS
Macrophage takes up damaged red blood cells and digests them
NOT SO BAD

INTRAVASCULAR HEMOLYSIS
Red blood cells break apart in the blood vessels
AFFECTS BLOOD VESSELS
Intravascular Hemolysis

Deficit in Nitric Oxide (NO) and Oxidative stress
Nitric Oxide promotes good blood flow  Its inhibition interferes with blood flow

Plasma Hb

- Vasoconstriction
- Platelet aggregation and attachment
- Release of procoagulant factors
- Inflammatory cell attachment (via VCAM-1)
- Release of growth factors

Nitric Oxide promotes good blood flow  Its inhibition interferes with blood flow
Intravascular Hemolysis and ↓NO

Reactive Oxygen Species

Hemolysis

Marker of hemolysis

LDH

ADMA

NO

NO\(^{-3}\)

Arginase

Nitric Oxide Synthase

L-Arginine → NO

L-Citrulline

Ornithine
Intravascular Hemolysis

Deficit in Nitric Oxide (NO) and

Oxidative stress

VASCULOPATHY

Constricted, adhesive blood vessels

High blood pressure
Pulmonary hypertension
Blood clots
How Does Pulmonary Hypertension Develop?

- Chronic constriction of blood vessels
- Vessel wall thickening
- Blood clots

Hemolysis and Vasculopathy

• Who is affected?

• Most of this research has been done in sickle cell disease.

• Some patients with thalassemia are also affected

• Rare reports also in other hemolytic diseases
Echocardiography Screening for PH

Peak TR velocity 4.1 m/s
Peak gradient 67mm Hg
Est. RVSP 72mmHg
Distribution of TRV in SCD

n = 195

TRV < 2.5
67%

TRV = 2.5 - 2.9
24%

TRV > 2.9
9%

Gladwin et al., NEJM 2003
Thalassemia Intermedia

Pulmonary Hypertension Screening Prevalence of 11%

<table>
<thead>
<tr>
<th>Complication/parameter</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
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<td>Age &gt; 35 y</td>
<td>2.59</td>
<td>1.08-6.19</td>
<td>.032*</td>
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<td>Splenectomy</td>
<td>4.11</td>
<td>1.99-8.47</td>
<td>&lt; .001*</td>
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<td>Transfusion</td>
<td>0.33</td>
<td>0.18-0.58</td>
<td>&lt; .001*</td>
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<tr>
<td>Hydroxyurea</td>
<td>0.42</td>
<td>0.20-0.90</td>
<td>.025*</td>
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<tr>
<td>Iron chelation</td>
<td>0.53</td>
<td>0.29-0.95</td>
<td>.032*</td>
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Paroxysmal Nocturnal Hemoglobinuria

Pulmonary Hypertension Screening Prevalence up to 36%


## Other Hemolytic Anemias

<table>
<thead>
<tr>
<th>Condition</th>
<th>PH</th>
<th>Priapism</th>
<th>Leg Ulcers</th>
</tr>
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<tbody>
<tr>
<td>Thalassemia</td>
<td>*</td>
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<td>Pyruvate Kinase deficiency</td>
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<td>Hereditary spherocytosis</td>
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<tr>
<td>Unstable Hemoglobins</td>
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<td>Paroxysmal Nocturnal Hemoglobinuria</td>
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<td>Autoimmune Hemolytic Anemia</td>
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<td>Congenital Dyserythropoietic Anemia</td>
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Treatment of PH

• Treat the underlying hemolytic disorder
• Endothelin receptor antagonists
  – Bosentan, ambrisentan (macitentan?)
• Prostacyclins
  – Epoprostenol, treprostinil and iloprost
• Soluble Guanylate Cyclase Stimulators
  – Riociguat
• PDE5 Inhibitors?
  – Sildenafil, tadalafil
Summary

• Intravascular hemolysis is an important part of many anemias

• Depending on its severity, hemolysis may contribute to vascular complications
  – Pulmonary hypertension, stroke, blood clots, leg ulcers, priapism

• Screening strategies and treatments have been developed in SCD
Experts

- Who are some clinician-scientist experts in hemolysis and vascular complications?
- US: Kato GJ and Gladwin MT
- Switzerland: Dominik Schaer
- Lebanon: Musallam KM, Taher AT
- Italy: Cappellini MD
- Israel: Rachmilewitz EA

And many others...
References

- Schaer DJ, Buehler PW, Alayash AI, Belcher JD, Vercellotti GM. Hemolysis and free hemoglobin revisited: exploring hemoglobin and hemin scavengers as a novel class of therapeutic proteins. Blood. 2013 Feb 21;121(8):1276-84. PMID: 23264591; PMC3578950.
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