Hemolysis Contributes to PDE5 Dysregulation and Priapism in Sickle Cell Bone Marrow Transplanted Mice

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I have no actual or potential conflict of interest

to this presentation.

- Priapism is a penile erection that persists without sexual purpose.

Broderick *et al*. JSM, 2010.

- Types of priapism

1. Ischemic priapism (95%)
2. Nonischemic priapism

Recurrent ischemic priapism is called *stuttering priapism*

Burnett & Sharlip. JSM, 2013.

Stuttering Priapism

- Clinical manifestations
  - Typically painful
  - Sleep related
  - Less than 4 hours in duration
  - Generally self-limiting
- Therapeutic dilemma
  - Young patients
  - Risk of erectile dysfunction: 25%
  - Current guidelines remain less than ideal

Morrison & Burnett. Curr Urol Rep, 2012.

Sickle Cell Disease and Priapism

- The most common cause of priapism is sickle cell disease (SCD).
  - 63% of the pediatric cases
  - 23% of the adult cases

Nelson & Winter. J Urol, 1977.

- 72% of the men with SCD have a history of stuttering priapism.

Adeyoju *et al*. BJU Int, 2002.

Preventive Treatment of Stuttering Priapism

- Hormonal therapy
  - Gonadtropin-releasing hormone agonists, antiandrogens, 5α-reductase inhibitors

Shamloul & el Nashaar. JSM, 2005. Yamashita *et al*. Urology, 2004.
Barroso *et al*. Int Braz J Urol, 2012.

- α / β -agonist: etilefrine, turbutaline *etc*.

Morrison & Burnett. Nat Rev Urol, 2011.

- Phosphodiesterase 5 (PDE5) inhibitors

Burnett *et al*. J Urol, 2006.

Pathophysiology of Priapism

- Nitric oxide (NO) imbalance and PDE 5 dysregulation

  Bivalacqua & Burnett. Cur Urol Rep, 2006. Champion *et al*. PNAS, 2005.

- RhoA / Rho-kinase expression changes

  Bivalacqua *et al*. Urology, 2010.

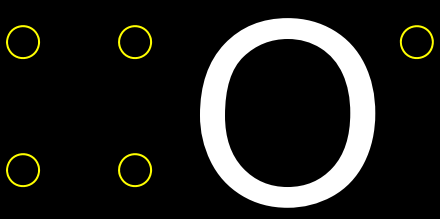
- Opiorphin-associated priapism

  Kanika *et al*. AJP: Cell Physiol, 2009.

- Adenosine overproduction

  Wen *et al*. FASEB J, 2010.

Nitric Oxide



Imbalance

↓

PDE5 Dysregulation

NO Imbalance & PDE5 Dysregulation

- PDE5 dysregulation resulting from altered NO/cGMP/PKG signaling cause priapism.

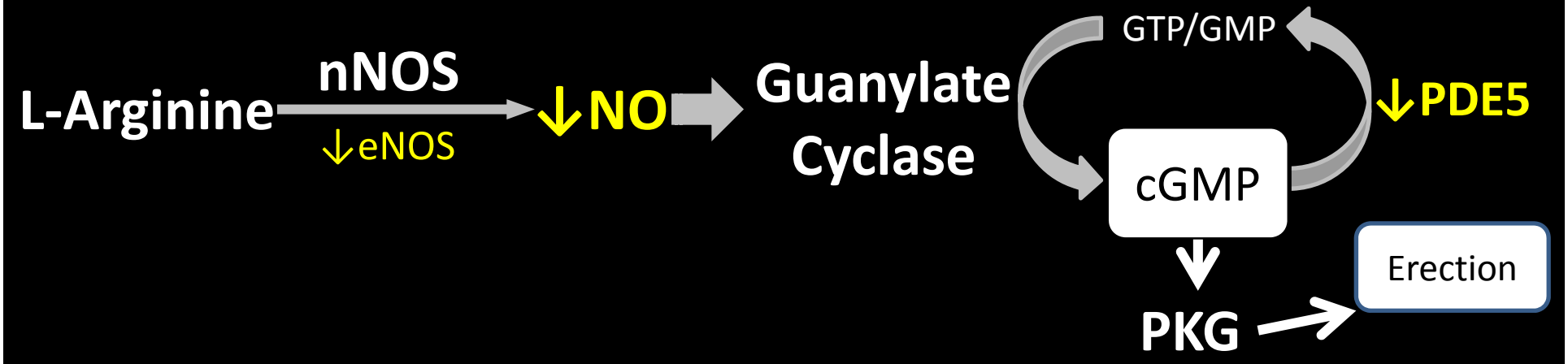
Champion *et al*. PNAS, 2005. Bivalacqua *et al*. PLOS ONE, 2013.

- As a result of PDE5 dysregulation, cGMP generated in the erectile tissue cannot be degraded.

Burnett *et al*. Urology, 2006

- Altered erectile homeostasis can be restored by PDE5 inhibitors (PDE5i).

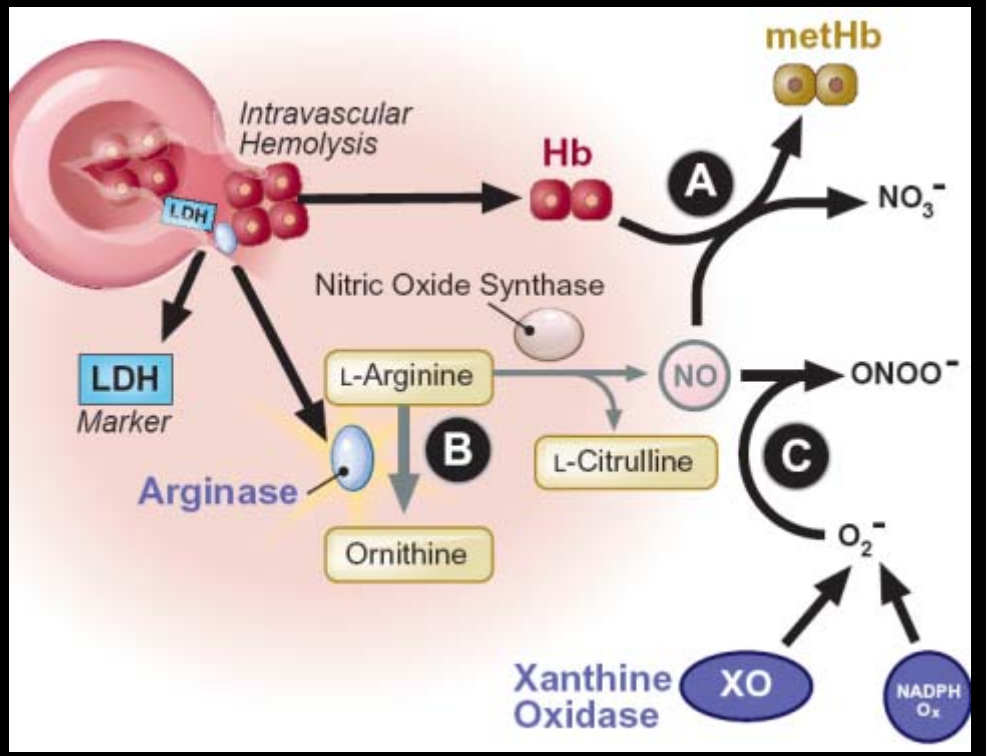
Bivalacqua *et al*. PLOS ONE, 2013.



What causes NO imbalance in SCD?

Hemolysis Decreases NO Bioactivity in SCD

A. Free hemoglobin (Hb) reacts with NO to produce metHb and nitrate.
B. Arginase from erythrocytes converts L-Arginine into Ornithine.
C. Reactive oxygen species (ROS) reduces NO bioavailability.



Kato *et al*. Blood Rev, 2007.

Hemolysis and Priapism

- Chronic hemolysis in transgenic SCD mice induced:
  - NO/cGMP/PDE5 dysregulation
  - Overproduction of ROS
  - Priapism

PDE5i treatment alleviated all of the above.

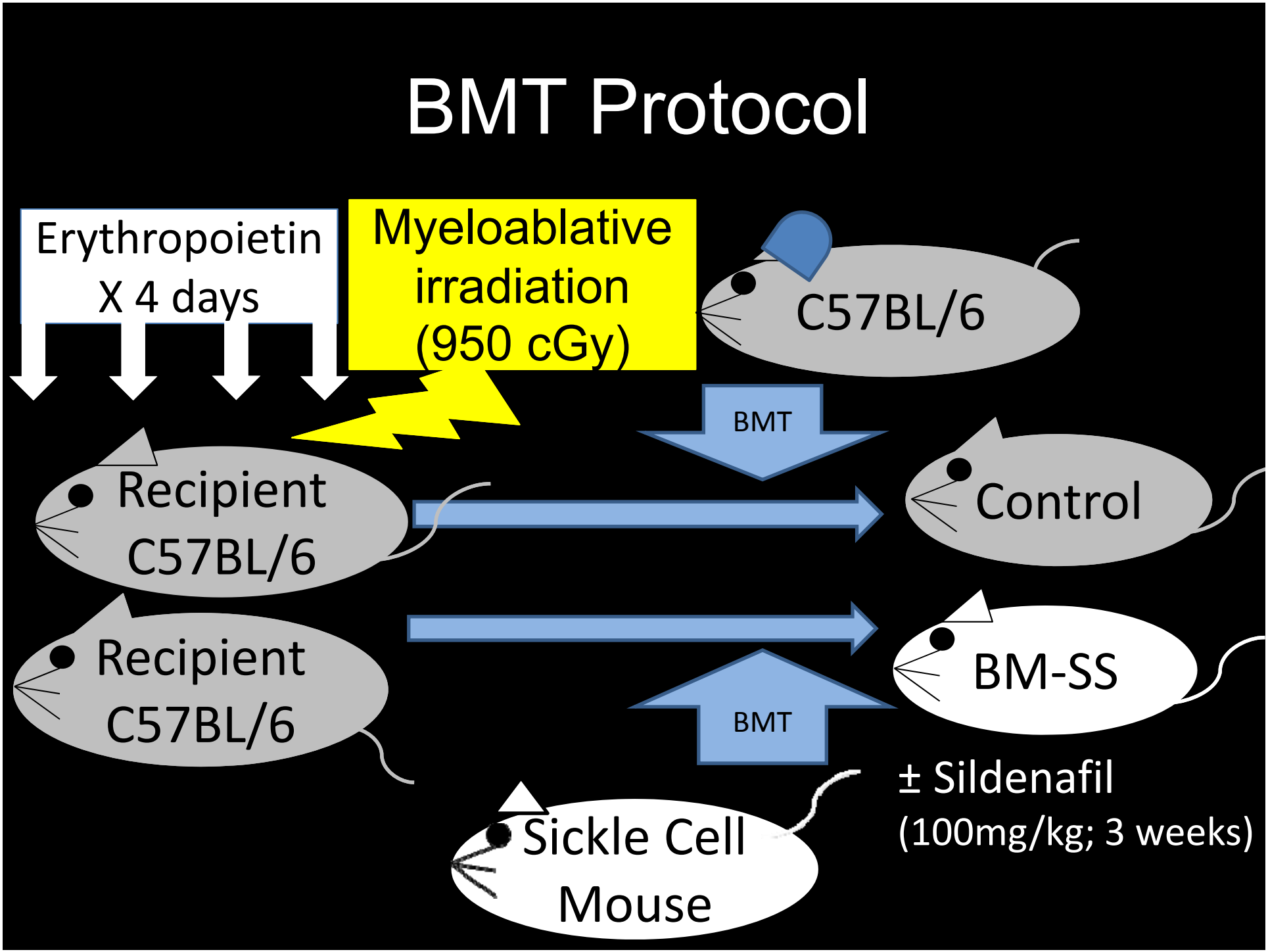
Bivalacqua *et al*. PLOS ONE, 2013.

Acute Hemolysis Model

- Bone marrow transplantation (BMT) from sickle mice (BM-SS) is known to:
  - Induce acute hemolysis of blood
  - Make mice have a sickle phenotype

Hsu et a. Blood, 2007.

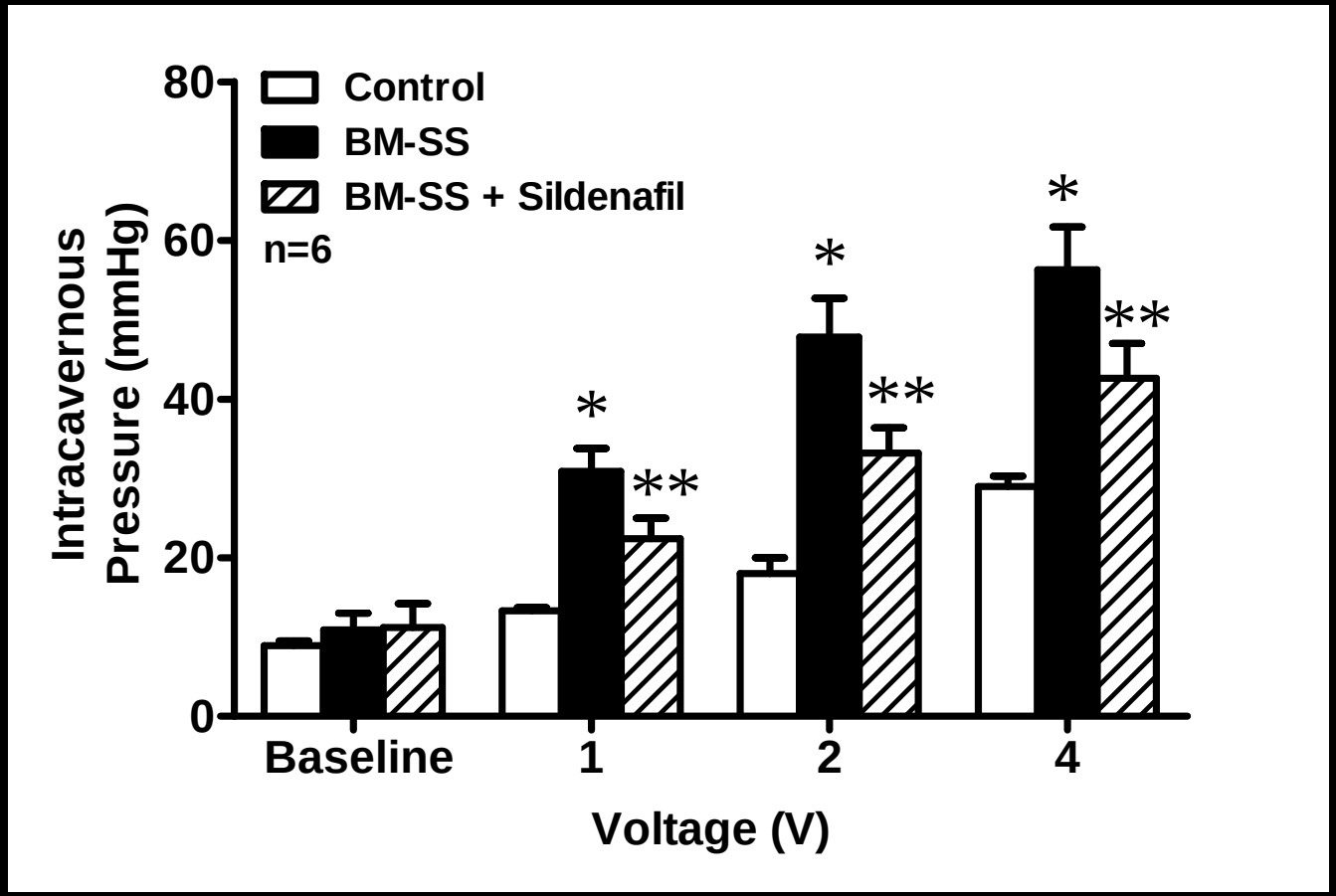
- Using BM-SS, this study examines:
  1. Effect of **acute** hemolysis on the molecular changes in the penis
  2. Role of PDE5i treatment in **acute** setting


BMT Protocol
Erythropoietin
X 4 days
Myeloablative
irradiation
(950 cGy)
C57BL/6
BMT
Recipient
C57BL/6
Control
Recipient
C57BL/6
BM-SS
BMT
± Sildenafil
(100mg/kg; 3 weeks)
Sickle Cell
Mouse

Methods

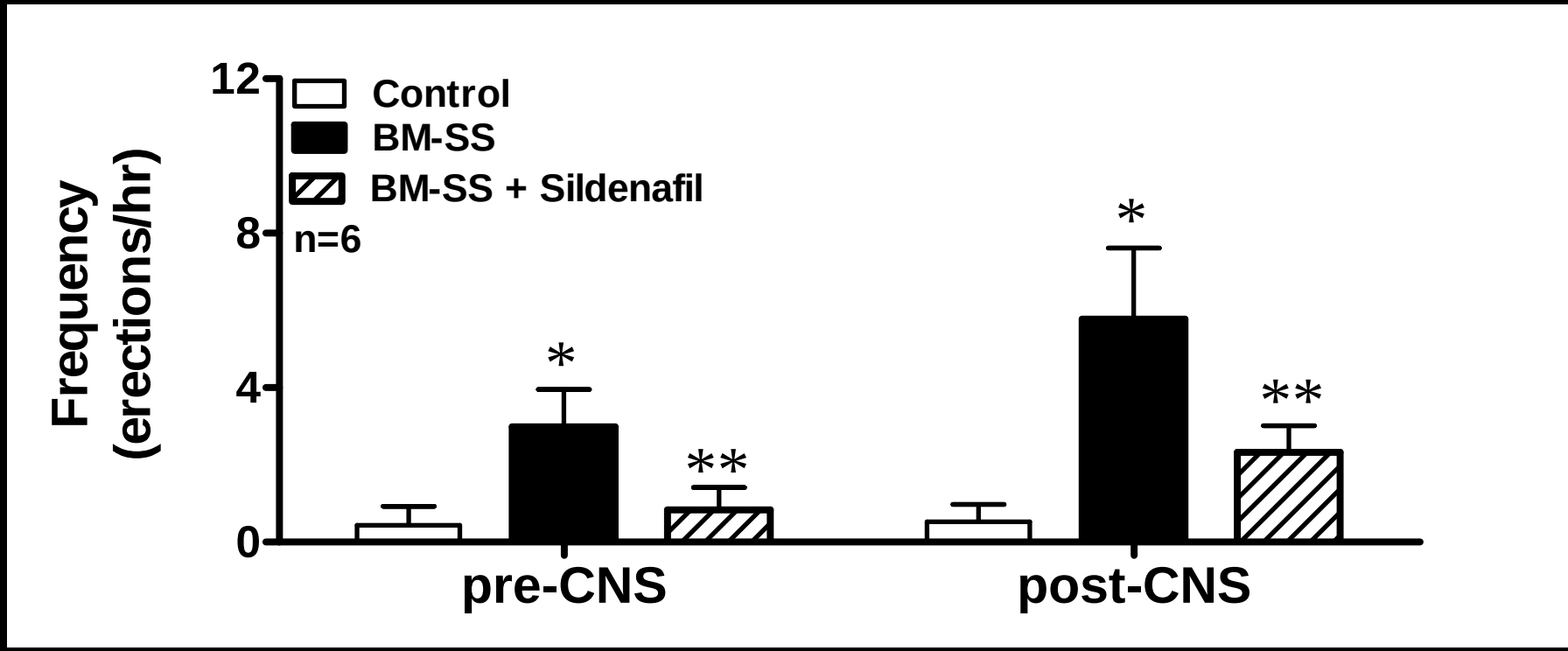
- Erectile function assessment:
  - Intracavernous pressure (ICP) measurement by cavernous nerve stimulation (CNS)
  - Frequency of spontaneous erectile response
    - Pre and post CNS
- Biochemical assessment of the penes:
  - Nitric oxide synthase (NOS) activities
  - Protein kinase G (PKG) activities
  - PDE5 activities
  - ROS generation

Enhanced ICP in BM-SS, Lowered by Sildenafil



* p<0.05 vs control, ** p<0.05 vs BM-SS

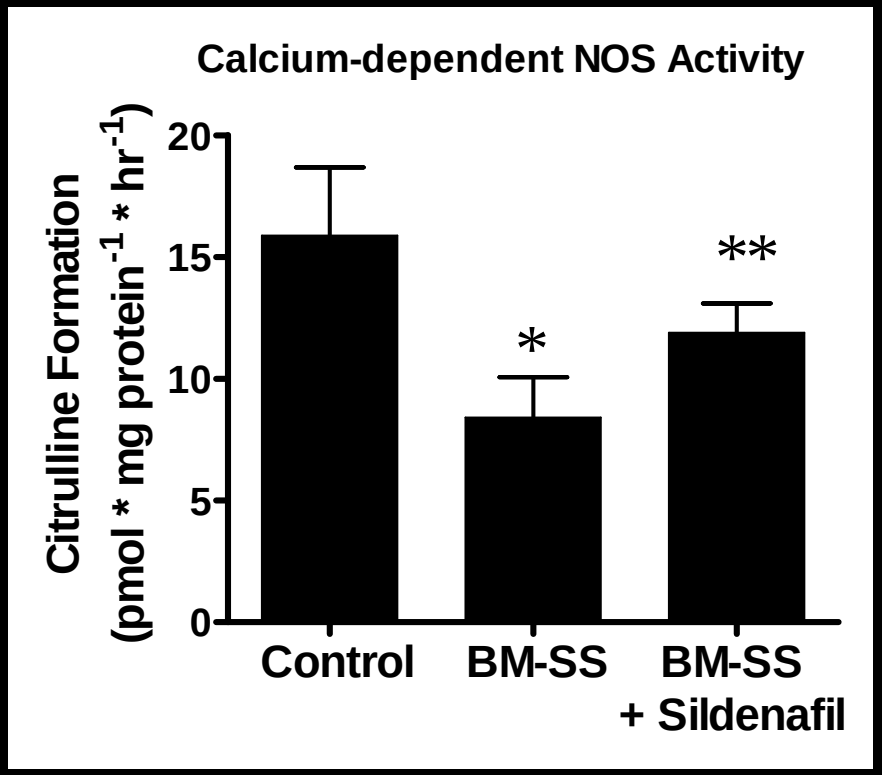
Sildenafil Decreased Priapic Activity in BM-SS Mice

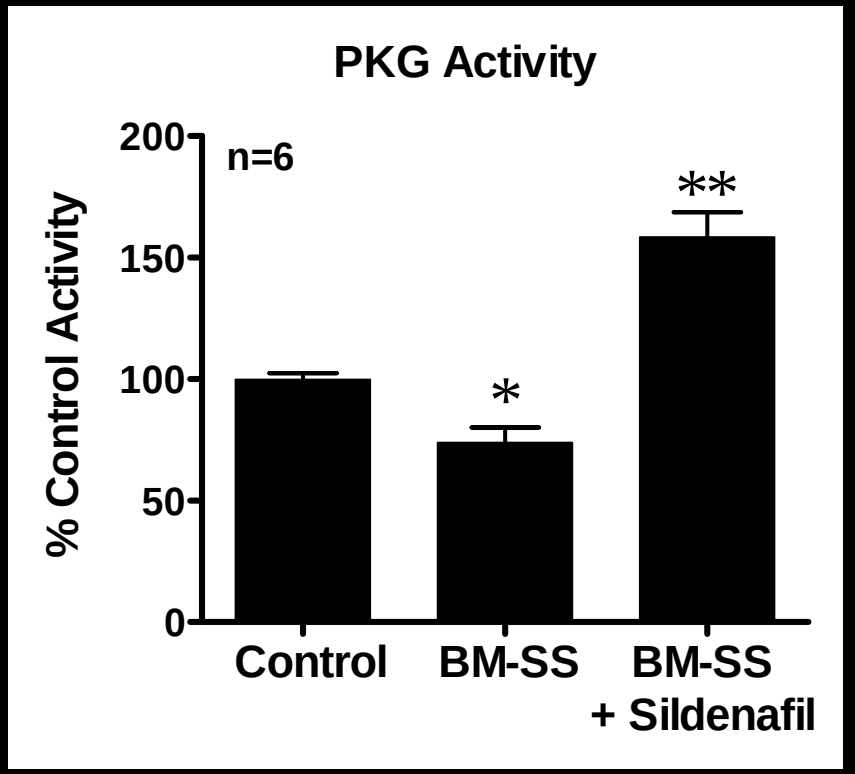


* p<0.05 vs control

** p<0.05 vs BM-SS

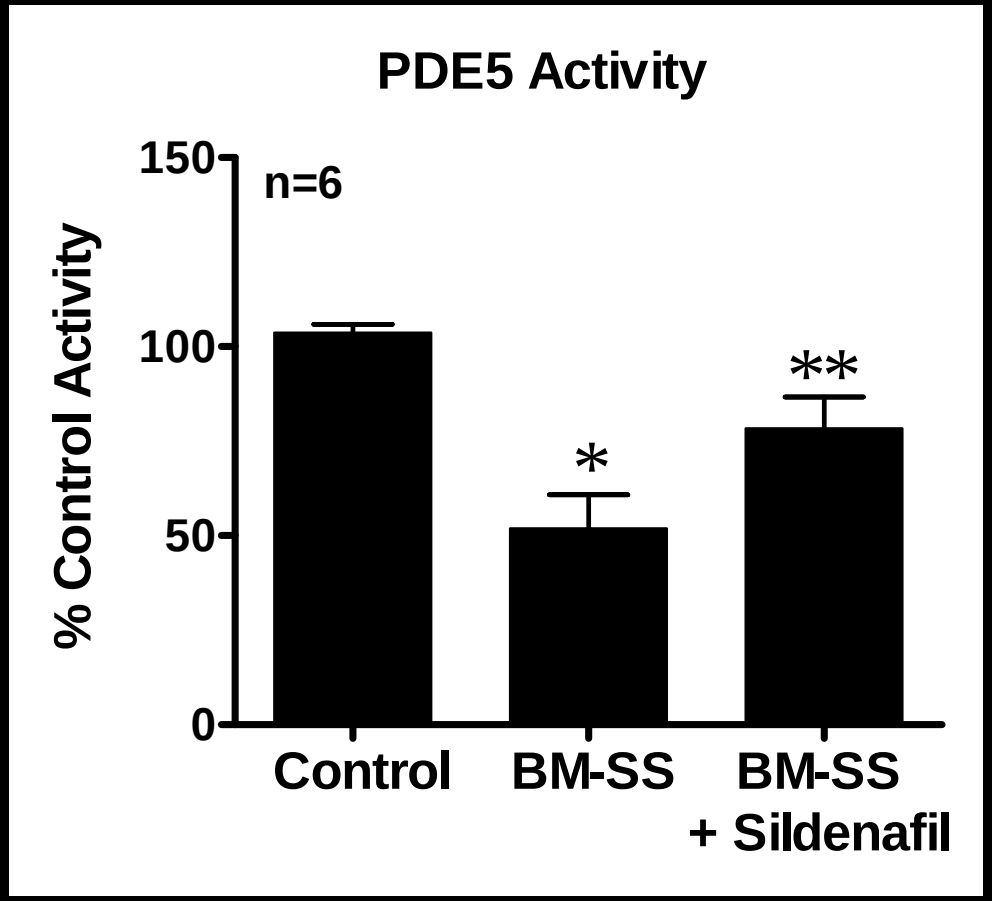
Sildenafil Corrected Downregulated NOS/PKG Activities in BM-SS





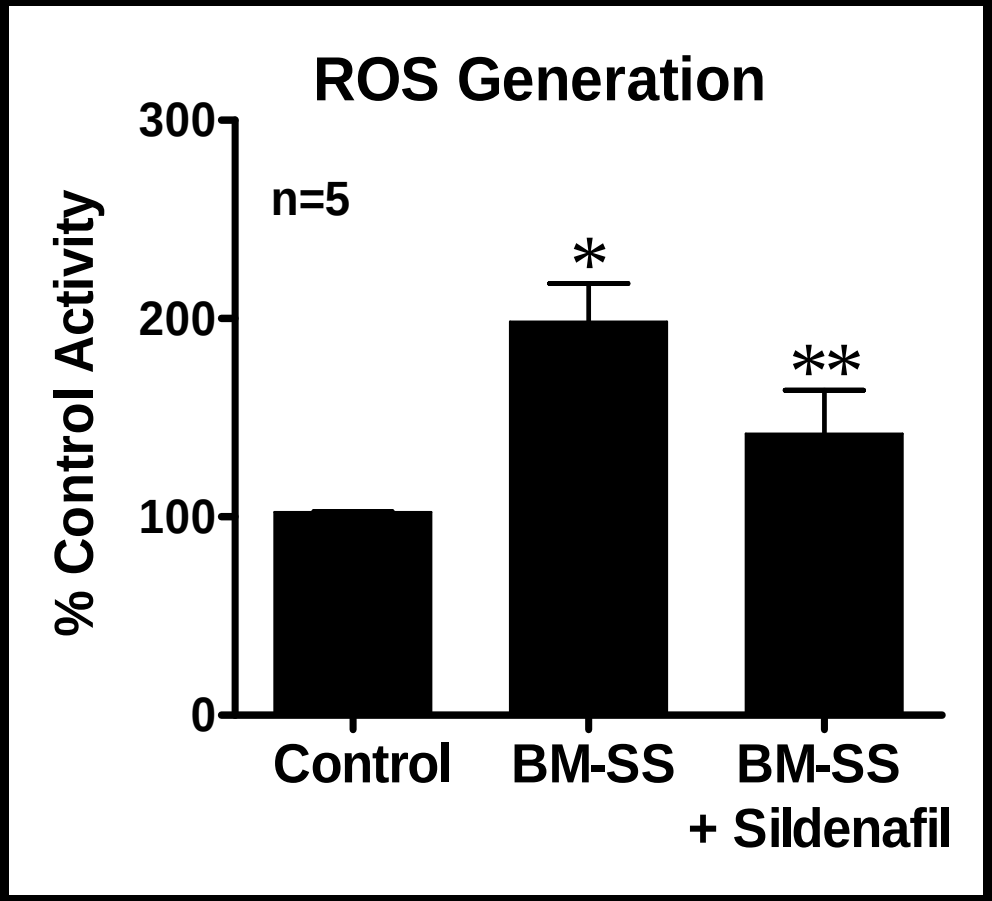
* p<0.05 vs control, ** p<0.05 vs BM-SS

Sildenafil Increased PDE5 Activity in BM-SS



* p<0.05 vs control, ** p<0.05 vs BM-SS

Higher ROS Generation in BM-SS Mice Reduced with Sildenafil



* p<0.05 vs control, ** p<0.05 vs BM-SS

Conclusion

- Priapic activity in BMT sickle mice can be attributed to NO/PDE5 dysregulation.
- Sildenafil treatment ameliorates priapism due to:
  - Restored NO balance
  - Decreased ROS generation
  - Increased PDE5 activity

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NIH National Institutes of Health

Urology Care FOUNDATION The Official Foundation of the American Urological Association