

# The Efficacy of Hydrogen Sulfide on Duchenne Cardiomyopathy

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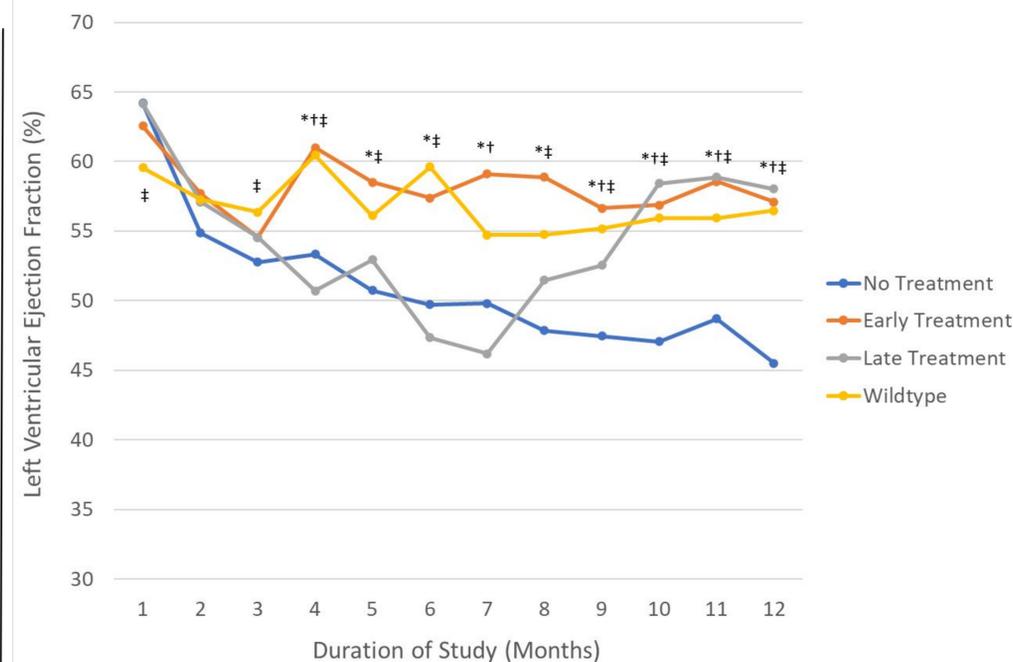
Pauley Heart Center

## Abstract

Duchenne Muscular Dystrophy (DMD) is the most common and severe form of muscular dystrophy. It is a lethal X-linked recessive disease occurring in 1/3,500 male live births. DMD currently has no cure and is caused by a mutation in the dystrophin gene, with diagnosis occurring between 3-5 years of age. This disease causes progressive muscular deterioration, ultimately affecting the skeletal, pulmonary, and cardiac organ systems leading to death in the 2nd or 3rd decades of life. The main cause of death in DMD is dilated cardiomyopathy (DCM). The purpose of this project is to identify the effects of hydrogen sulfide ( $H_2S$ ) on DCM in DMD.  $H_2S$  is mito-protective, anti-inflammatory, anti-apoptotic and anti-fibrotic. We believe  $H_2S$  could serve as a cardioprotective agent for DCM in DMD. Male  $mdx/mTR^{KO}$  mice were fed a diet of SG1002, an orally active  $H_2S$  donor. Mice were separated into early treatment (ET) beginning at the time of weaning, late treatment (LT) beginning at 7 months and no treatment (NT). Mice were followed over a 12-month time course with monthly echocardiography. We were able to determine the NT group showed significant reduction in left ventricular ejection fraction (LVEF) compared to wild type (WT) mice. ET group showed preservation of LVEF. LT group showed LVEF initially declining at a similar rate to NT group. Subsequently, LT mice were treated with  $H_2S$  and showed significant recovery of LVEF. Our results strongly suggest that daily  $H_2S$  therapy is beneficial for preserving cardiac function in DMD.  $H_2S$  could serve to preserve or recover LVEF in a mouse model of DMD.  $H_2S$  could be mediating this cardioprotective effect by suppressing inflammation and decreasing cardiac fibrosis. More studies are needed to further investigate how  $H_2S$  is imparting its beneficial effects.

## Background

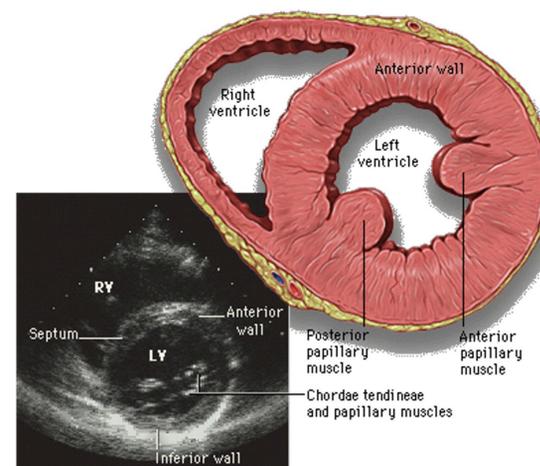
Duchenne Muscular dystrophy (DMD) is the most commonly inherited form of human myopathy and has very detrimental impacts to those affected by it. DMD affects young males, while females can be carriers for this disease. Young boys often display symptoms of DMD around the ages of 3-5, primarily affecting the skeletal muscles at first. Due to progressive muscular deterioration, a limited ability to exercise masks many of the early signs of cardiomyopathy (DMD-CM). Initially, respiratory failure was the leading cause of death in most patients with DMD, however with the progression of various forms of respiratory therapy the lifespan of patients with DMD has increased. Now, most patients with DMD can live until their 20s or 30s, before, unfortunately, suffering from the effects of DMD-CM. As the cardiac muscle continues to deteriorate as patients get older, the dystrophin deficiency in cardiac tissue can lead to many more serious issues. Dystrophin is a protein which is responsible for strengthening muscle fiber and preventing degradation and injury. However, in a patient with DMD this dystrophin in the cardiac tissue is defected leading to loss of membrane integrity, extracellular calcium influx, and eventually cardiomyocyte death.



Graphical representation of left ventricular ejection fraction (LVEF) assessed by echocardiography in  $mdx^{4ex}/mTR^{G2}$  mice (n = 10-70). Mice with no treatment (NT) showed significant reduction in LVEF compared to wildtype (WT) mice. Early treatment (ET) with  $H_2S$  starting at the time of weaning showed LVEF remained similar to WT mice ( $P > 0.05$ ) and significantly higher than NT mice. The late treatment (LT) mice showed LVEF initially declining at a similar rate to NT mice ( $P < 0.05$  vs. ET and WT). Subsequently, LT mice were treated with  $H_2S$  starting at the 7-month time point, resulting in significant recovery of LVEF.

\* =  $p < 0.05$  ET vs NT, † =  $p < 0.05$  LT vs NT, ‡ =  $p < 0.05$  WT vs NT.

## Parasternal Short Axis



Lynah P. Focused Cardiac  
Ultrasound for the Nephrologist:  
The Parasternal Short Axis  
View. 2019

The parasternal short axis view in echocardiography was used to determine LVEF and overall cardiac function in Male  $mdx/mTR^{KO}$  mice.

## Purpose

Hydrogen Sulfide, ( $H_2S$ ), has been shown to be anti-fibrotic, mito-protective, anti-inflammatory, and anti-apoptotic in several models of cardiac diseases making it a suitable candidate to prevent cardiomyopathy in DMD and potentially reverse some of the effects of this disease in heart tissue.  $H_2S$  can prevent the scarring of heart tissue and prevent the death of cells in the heart. With the development of  $H_2S$  as treatment, the lifespan of those suffering from DMD could increase.

## Results

Results showed that  $H_2S$  can play an important role in preventing the development of DMD-CM if used as a method of early treatment. Similarly, if a patient is already diagnosed with DMD, our study demonstrates that late treatment with  $H_2S$  can cause a reversal of some of the effects of DMD-CM. Even with late treatment, LVEF was preserved to values similar to early treatment and wild type mice. Our data suggest that  $H_2S$  can play a powerful role in not only cardio-protection, but also improving the quality of life of those suffering from DMD.

## Future Directions

Further research is needed to determine how exactly  $H_2S$  is able to preserve cardiac function and reverse the effects of DMD-CM. We are still unsure what route is used by  $H_2S$  to cause recovery and prevention in patients with DMD, although we suspect that improving mitochondrial function and suppressing inflammation with  $H_2S$  are important pathways.

## References

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