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**Hemopexin counteracts systolic dysfunction induced by heme-driven oxidative stress**

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**Abstract**

Heart failure is a leading cause of morbidity and mortality in patients affected by different disorders associated to intravascular hemolysis. The leading factor is the presence of pathologic amount of pro-oxidant free heme in the bloodstream, due to the exhaustion of the natural heme scavenger Hemopexin (Hx). Here, we evaluated whether free heme directly affects cardiac function, and tested the therapeutic potential of replenishing serum Hx for increasing serum heme buffering capacity.

The effect of heme on cardiac function was assessed *in vitro*, on primary cardiomyocytes and H9c2 myoblast cell line, and *in vivo*, in Hx<sup>-/-</sup> mice and in genetic and acquired mouse models of intravascular hemolysis. Purified Hx or anti-oxidants N-Acetyl-L-cysteine and  $\alpha$ -tocopherol were used to counteract heme cardiotoxicity.

In mice, Hx loss/depletion resulted in heme accumulation and enhanced reactive oxygen species (ROS) production in the heart, which ultimately led to severe systolic dysfunction. Similarly, high ROS reduced systolic Ca<sup>2+</sup> transient amplitudes and fractional shortening in primary cardiomyocytes exposed to free heme. In keeping with these Ca<sup>2+</sup> handling alterations, oxidation

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