

# Cardioprotective effects of lysyl oxidase inhibition

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Heart failure is a progressive condition, where structural and functional alterations of the ventricle limit the ability of the heart to either fill or eject blood. There are approximately 550,000 new cases of heart failure each year with a prevalence of nearly 5 million; most patients die within five years of diagnosis. A prominent characteristic of heart failure is the adverse alteration of the extracellular matrix (ECM). The heart's size, shape, and function are regulated, in part, by the composition of the ECM. The major structural component of the cardiac ECM is collagen, which is produced by fibroblasts. Lysyl oxidase (LOX), also produced by fibroblasts, is a collagen cross-linking enzyme. Cross-linking makes collagen fibrils resistant to degradation and promotes collagen deposition. Although cross-linking is necessary for normal collagen formation, increased LOX expression is associated with fibrosis in the heart. Further, cardiac LOX is elevated in failing human hearts and reduced LOX expression is associated with improved function in heart failure patients, suggesting that excess activation of LOX may play a causative role in the progression of cardiac failure.

In a study reported in the March issue of *Experimental Biology and Medicine* Gardner and colleagues used a rat model of volume-overload (VO)-induced heart failure to evaluate the cardioprotective effects of LOX inhibition in animals with established disease. Volume overload was surgically induced through creation of an abdominal aorto-caval fistula. Prior to LOX inhibition, rats were subjected to 8 weeks of chronic volume overload, a duration previously demonstrated to produce significant cardiac hypertrophy, ventricular dilation, and dysfunction,

and collagenous ECM alterations. After 8 weeks of VO, LOX was inhibited using beta-aminopropionitrile delivered intraperitoneally for 6 weeks, which irreversibly binds to the active site of LOX inhibiting its activity and ability to cross-link [collagen](#). LOX inhibition partially attenuated VO-induced increases in LV hypertrophy and completely reversed VO-induced increases in interstitial myocardial collagen, and protein expression of collagens I and III. Using ultrasound echo and ventricular pressure-volume catheterization, we found that LOX inhibition partially restored both systolic and diastolic function, while having little effect on sham-operated controls. Overall, our data demonstrate the cardioprotective effects of LOX inhibition on the volume overload stressed heart, and its potential to slow or even prevent the transition to heart failure.

J.D. Gardner said "The strong cardioprotective effects and functional restoration provided by LOX inhibition in our model were surprising given that one would expect that a reduction in LOX, and thereby mature collagen, would promote further ventricular dilatation in the volume overloaded heart. However, we found that the opposite was true. Reduced LOX activity reversed cardiac fibrosis and partially restored cardiac function in rats with established cardiac dysfunction. Our findings indicate that over-activation of LOX during cardiac disease promotes progressive cardiac fibrosis and [heart failure](#). If we can determine how excessive LOX is damaging the heart, these mechanisms could be targeted for clinical benefit. "

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said "Gardner et al have provided the intriguing and unexpected result that inhibiting lysyl oxidase (LOX) reversed cardiac fibrosis improving heart function. This suggests that LOX may play a key role in volume overload induced cardiac dysfunction.

**More information:** E. C. El Hajj et al. Featured Article:

Cardioprotective effects of lysyl oxidase inhibition against volume overload-induced extracellular matrix remodeling, *Experimental Biology and Medicine* (2015). [DOI: 10.1177/1535370215616511](https://doi.org/10.1177/1535370215616511)

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