Surplus antioxidants are pathogenic for hearts and skeletal muscle

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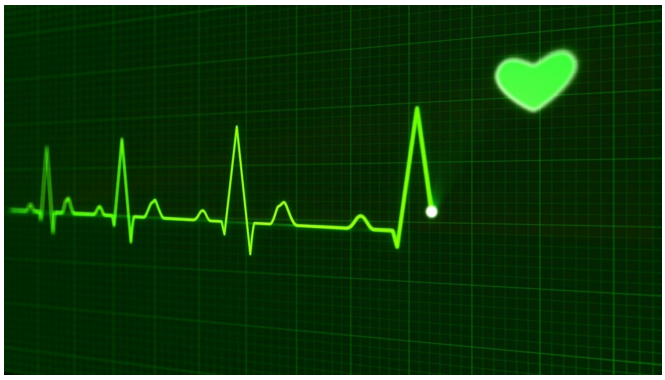

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Many heart diseases are linked to oxidative stress, an overabundance of reactive oxygen species. The body reacts to reduce oxidative stress—where the redox teeter-totter has gone too far up—through production of endogenous antioxidants that reduce the reactive oxygen species. This balancing act is called redox homeostasis.

But what happens if the redox teeter-totter goes too far down, creating antioxidative stress, also known as reductive stress? Rajasekaran Namakkal-Soorappan, Ph.D., associate professor in the University of Alabama at Birmingham Department of Pathology, and colleagues have found that reductive stress, or RS/AS, is also pathological. This discovery, they say, may have clinical importance in management of heart failure.

They report that RS causes pathological heart enlargement and diastolic dysfunction in a mouse model. This study, published in the journal *Antioxidants and Redox Signaling*, was led by Namakkal-Soorappan and Pei Ping, Ph.D., David Geffen School of Medicine at the University of California-Los Angeles.

"Antioxidant-based therapeutic approaches for human heart failure should consider a thorough evaluation of antioxidant levels before the treatment," they said. "Our findings demonstrate that chronic RS is intolerable and adequate to induce heart failure."

The study used transgenic mice that had upregulated genes for antioxidants in the heart, which increased the amounts of antioxidant proteins and reduced glutathione, creating RS. One mouse line had low upregulation, and one had high upregulation, creating chronic low RS and chronic high RS, respectively, in the hearts of the mice.

The mice with high RS showed pathological heart changes called hypertrophic cardiomyopathy, and had an abnormally high heart ejection fraction and diastolic dysfunction at 6 months of age. Sixty percent of the high-RS mice died by 18 months of age.

The mice with low RS had normal survival rates, but they developed the heart changes at about 15 months of age, suggesting that even moderate RS can lead to irreversible damage in the heart over time.

Giving high-RS mice a chemical that blocked biosynthesis of glutathione, beginning at about 6 weeks of age, prevented RS and rescued the mice from pathological heart changes.

Gobinath Shanmugam, Ph.D., postdoctoral fellow in the UAB Department of Pathology, and Namakkal-Soorappan point out that a 2019 survey found about 77 percent of Americans are consuming dietary supplements every day, and within this group, about 58 percent are consuming antioxidants as multivitamins. Thus, a chronic consumption of antioxidant drugs by any individual without knowing their redox state might result in RS, which can induce pathology and slowly damage the heart.

Effect of RS on skeletal muscle

In a related study, published in the journal *Redox Biology*, Namakkal-Soorappan looked at the impact of RS on myosatellite cells, which are also known as muscle stem cells. These cells, located near skeletal muscle fibers, are able to regenerate and differentiate into skeletal muscle after acute or chronic muscle injury. The regulation of myosatellite cells is of interest given the loss of skeletal muscle mass during aging or in chronic conditions like diabetes and AIDS.

Recently, Namakkal-Soorappan reported that tilting the redox teeter-totter to oxidative stress impaired regeneration of skeletal muscle. Now, in the Redox Biology paper, he has shown that tilting the redox to RS also causes significant inhibition of muscle satellite cell differentiation.

Rather than genetic manipulation to induce RS, as was done in the heart study, the researchers used the chemical sulforaphane or direct augmentation of intracellular glutathione to induce RS in cultured mouse myoblast cells. Both treatments inhibited myoblast differentiation. Finally, authors attempted to withdraw antioxidative stress by growing cells in medium without sulforaphane, which removes the RS and accelerates the differentiation. Namakkal-Soorappan and colleagues found that a pro-oxidative milieu, through a mild generation of reactive oxygen species, was required for myoblast differentiation.

The researchers also showed that genetic silencing of a negative regulator of the antioxidant genes also inhibited myoblast differentiation.

More information: Gobinath Shanmugam et al. Reductive Stress Causes Pathological Cardiac Remodeling and Diastolic Dysfunction, *Antioxidants & Redox Signaling* (2020). DOI: 10.1089/ars.2019.7808