Normal cellular functions essentially depend on a balanced redox environment. Free radicals and nonradical oxidants can shift the redox balance toward a more “oxidized” state, which is countered by the intracellular antioxidant defense systems. These include the enzymes superoxide dismutase and catalase, as well as the thiol-reducing systems (glutathione, glutaredoxin, and thioredoxin). Glutathione is the most abundant intracellular low molecular weight thiol existing predominantly in the thiol-reduced form (GSH), whereas the disulfide-oxidized form (GSSG) represents <2%. Glutathione regulates numerous cellular functions; GSH as an antioxidant reduces hydrogen peroxide and peroxynitrite directly and indirectly with the help of glutathione peroxidase, detoxifies electrophiles, modulates the reversible oxidation and reduction of protein thiols, and is critically involved in the regulation of enzymes, transcription factors, and signal transduction.1 Loss of glutathione or disturbance of the GSH/GSSG redox potential causes cellular dysfunction. Multiple diseases, including cardiovascular diseases, are associated with the depletion of glutathione and a shift toward more oxidized GSH/GSSG redox potential. Restoring the GSH levels by substituting the glutathione precursor N-acetylcysteine or overexpressing glutathione peroxidase prevents cardiac dysfunction.²,³

However, little is known about the consequences of a more reductive redox state for cardiac function. Rajasekaran et al⁴ first reported about “reductive stress” in mice expressing the human mutant β-crystallin protein. These mice developed enhanced activity of glucose-6-phosphate dehydrogenase with increased production of NADPH and higher levels of GSH resulting in protein aggregation and cardiomyopathy. The human mutant β-crystallin protein further induced expression of heat shock proteins (Hsps), in particular, Hsp25, and glutathione peroxidase, and decreased myocardial levels of reactive oxygen species. Hsps are upregulated under oxidative stress and protect against reactive oxygen species; they have also been implicated to influence glutathione metabolism.⁵,⁶

In the present issue of Hypertension, Zhang et al⁷ report that cardiomyocyte-specific overexpression of Hsp27 induces reductive stress in the heart. In particular, mice expressing high levels of Hsp27 displayed increased myocardial glutathione peroxidase expression and activity, GSH, and GSH/GSSG ratio, and glutathione peroxidase activity, reducing ROS levels. High GSH levels could potentially alter several cardiomyocyte functions by influencing S-glutathionylation of a variety of proteins, S-nitrosylation, or being a substrate for glutathione transferase and its coenzyme function. ROS indicates reactive oxygen species.

Figure. Transgenic mice overexpressing Hsp27 at high levels in cardiomyocytes display cardiomyopathy related to reductive stress. Hsp27 overexpression increases GSH levels, GSH/GSSG ratio, and glutathione peroxidase activity, reducing ROS levels. High GSH levels could potentially alter several cardiomyocyte functions by influencing S-glutathionylation of a variety of proteins, S-nitrosylation, or being a substrate for glutathione transferase and its coenzyme function. ROS indicates reactive oxygen species.
one peroxidase activity to the level of wild-type animals, Zhang et al\(^7\) were able to prevent cardiomyopathy in Hsp27-overexpressing animals, suggesting that Hsp27-induced cardiomyopathy is at least in part mediated by elevated glutathione peroxidase activity. Cardiac structure and function were neither altered in transgenic mice with lower levels of Hsp27 overexpression in the present study nor in mice with overexpression of glutathione peroxidase, which may be explained by the fact that glutathione peroxidase activity was only mildly increased.\(^3\) Whether normalizing GSH levels by partly inhibiting its synthesis prevents cardiomyopathy in Hsp27 overexpressing mice remains open; interestingly, permanently elevated tissue GSH levels do neither influence viability or vascular function in mice.\(^5,9\)

Hsp27 overexpression increased GSH, whereas GSSG levels were not altered. It remains open whether GSH levels are increased because of de novo GSH synthesis or increased activity of GSSG-reductase. Because GSSG levels were unaltered by Hsp27 overexpression despite increased glutathione peroxidase activity, it is likely that GSSG-reductase activity is increased and reduces GSSG back to GSH, contributing to high GSH levels; alternatively, GSSG might be transported out of the cell.\(^10\) Nevertheless, the exact mechanisms linking Hsp27 overexpression to the increase in glutathione peroxidase activity and GSH remain unclear.

In contrast to the current concept of Hsp induction as a protective mechanism against oxidative stress, Zhang et al\(^7\) demonstrate for the first time that high levels of Hsp27 by increasing GSH and GSH-peroxidase induce cardiomyopathy, suggesting that also in this case too much of a good thing may be bad. These data further strengthen the novel concept of reductive stress in the heart as a potential contributor to heart failure development and progression.

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None.

**References**

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