Copper Futures

Ceruloplasmin and Heart Failure

Dian J. Cao, Joseph A. Hill

Oxidative stress is a major mechanism contributing to heart failure (HF) pathogenesis. On one hand, oxidative reactions are central to a wide range of signaling cascades, both physiological and pathological. Such redox signaling events participate in the governance of myocyte plasticity, ion homeostasis, excitation–contraction coupling, and metabolism. However, high levels of oxidative stress can damage proteins, membranes, and DNA. There is great interest in understanding mechanisms whereby oxidative events contribute to disease pathogenesis, because clinical trials of antioxidant therapies in HF have disappointed.

One mechanism whereby reactive oxygen species contribute to disease pathophysiology is via post-translational modification of specific proteins. One such modification is tyrosine nitration. Tyrosine nitration is a covalent coupling of protein tyrosine residues with nitric oxide (NO)–derived oxidants. Three major sources of NO–derived reactive species have been identified: (1) peroxynitrite anion, formed as the product of NO metabolism and superoxide radicals; (2) myeloperoxidase-catalyzed nitrogen dioxide radical (NO2), a product of hydrogen peroxide and nitrite; and (3) nitrogen dioxide radical derived from nitric oxide in oxygenated buffers used in vitro experimentation.

Although protein nitration has been recognized for a long time, its functional role in vivo is poorly understood. A wide variety of proteins involved in cardiovascular physiology are targets of tyrosine nitration, and the functional outcome for the targeted protein once modified is diverse, ranging from inactivation, which is most common, to gain of function. The targeted protein once modified is diverse, ranging from inactivation, which is most common, to gain of function. Such redox signaling events participate in the governance of myocyte plasticity, ion homeostasis, excitation–contraction coupling, and metabolism. However, high levels of oxidative stress can damage proteins, membranes, and DNA. There is great interest in understanding mechanisms whereby oxidative events contribute to disease pathogenesis, because clinical trials of antioxidant therapies in HF have disappointed.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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HF group. In fact, patients in the lowest tertile of ferroxidase activity were marked by the most advanced HF, as defined by lower EF and higher B-type natriuretic peptide levels. Patients in the lowest tertile of ferroxidase activity also manifested the greatest mortality at 2 years: 64% (tertile I) versus 29% (tertile III).

The inverse correlation between serum ferroxidase I activity and all-cause mortality in patients with HF is novel and interesting. That said, it tracked with powerful markers of bad outcome, including depressed EF and elevated B-type natriuretic peptide levels; whether ferroxidase I activity will emerge as an independent prognostic factor is unknown.

Given its central role in nitroso-oxidative events, it is not surprising that ceruloplasmin itself is subject to reactive oxygen species modification. Ceruloplasmin has 6 tyrosine residues that can be affected by tyrosine nitration. In the study by Cabassi et al,12 exposure of ceruloplasmin to peroxynitrite triggered ceruloplasmin tyrosine nitration and reduced ferroxidase I activity. However, whether oxidative stress–mediated tyrosine nitration of ceruloplasmin plays a mechanistic role in HF progression is unknown. Whether ferroxidase I activity and nitrated ceruloplasmin could serve as surrogate markers of overall oxidative stress remains to be determined. However, it is intriguing to speculate that these measures could be used to monitor the effectiveness of HF therapy, or even further, to design and tailor targeted interventions.

Whereas this interesting study is suggestive of a novel role of ceruloplasmin/ferroxidase I, it important to note that tertile III, with the highest ferroxidase I activity, highest EF, and a preponderance of female subjects, harbored an over-representation of patients with HF with preserved EF. Are differences in the events reported here confounded by differences in the distribution of patients with HF with preserved EF and reduced EF? Supporting this notion is the authors’ finding that when B-type natriuretic peptide was incorporated in a multivariate model, the predictive value of ferroxidase I activity ceased to be statistically significant. Circulating B-type natriuretic peptide and ventricular EF are among the most powerful prognostic factors in HF, and both of these parameters were significantly different between tertiles I and III.

This study must be interpreted in light of a few caveats. As acknowledged by the authors, the selection criteria were appropriately strict, eliminating patients with conditions that could affect serum ceruloplasmin levels and ferroxidase activity, including diabetes mellitus, myocardial infarction within the past 20 weeks, chronic renal disease, thyroid disorders, and more. Generalizing these data beyond the cohort studied here would be required before envisioning significant real-world clinical impact.

The majority of the subjects had ischemic heart disease (81%). A recent study of 4177 patients undergoing elective coronary angiography reported increased incidence of major cardiovascular events (death, myocardial infarction, stroke) in subjects with higher ceruloplasmin levels.13 Intriguingly, a close association between protein nitration and coronary artery disease has been reported.14–18 Together, these reports raise the possibility that nitrated ceruloplasmin and impaired ferroxidase I activity may reflect global oxidative stress and serve simply as a barometer of overall atherosclerosis burden rather than a true reflection of the severity and progression of HF.

In an isolated heart model, ceruloplasmin was protective of ischemia/reperfusion injury by affording antioxidant activity.19,20 After myocardial infarction, ceruloplasmin levels increase transiently, consistent with an acute-phase response.21 Ceruloplasmin’s nitric oxide oxidase activity raises the possibility that its elevation may diminish nitric oxide bioavailability and promote endovascular dysfunction. The seemingly contradictory functional profile of ceruloplasmin—both oxidant and antioxidant—will continue to complicate delineation of its physiological and pathophysiological roles.

Conclusions and Perspectives

HF, a syndrome in which the myocardium is unable to provide blood supply commensurate with the requirements of the body, continues to explode in incidence and prevalence. Work reported here by Cabassi et al12 draws our attention to ceruloplasmin and its ferroxidase activity as potentially involved. Whether these are markers or mechanisms of HF pathogenesis remains to be determined. Either way, these findings expand the functionality of the already versatile ceruloplasmin molecule, raise the intriguing prospect of gauging redox stress in this syndrome, and point to a rise in (circulating) copper futures.

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References


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