Mitochondrial Oxidative Stress in Heart Failure

“Oxygen Wastage” Revisited

Douglas B. Sawyer, Wilson S. Colucci

There is growing evidence that oxidative stress is increased in myocardial failure and may contribute to the structural and functional changes that lead to disease progression. The report by Ide et al., in this issue of Circulation Research, provides the first direct measurement of increased oxidative stress in the myocardium of an animal model of heart failure. In this same model, the authors previously used electron paramagnetic resonance (EPR) with the O$_2^-$ spin trap 5,5'-dimethyl-1-pyrroline-N-oxide (DMPO) to show that formation of superoxide anion was increased 2.8-fold in submitochondrial particles from failing (vs non-failing) myocardium. The increase in DMPO spin signal was seen with NADH, but not succinate, as a substrate, suggesting that O$_2^-$ was being formed by electron leakage at the level of the NADH-ubiquinone-reductase complex, or complex I. This view was supported by the finding that complex I activity was 50% lower in the failing myocardium, suggesting a functional blockade of the electron transport system. Because the isolation of submitochondrial particles removes competing antioxidant enzymes, the observed increase in DMPO spin signal was indicative of an increase in gross (but not net) O$_2^-$ production and therefore was not necessarily indicative of oxidative stress per se. Oxidative stress was suggested, however, by the finding of increased lipid peroxidation products in the myocardium of the animals with heart failure.

In the present study, Ide et al. extend their earlier observations by showing that the production of reactive oxygen species (ROS) is increased in the failing myocardium. By measuring the production of OH$^-$, a byproduct of other ROS that will only be formed when the production of ROS overwhelms the capacity of antioxidant defenses, they provide evidence of increased oxidative stress. Fenton showed more than 100 years ago that H$_2$O$_2$ becomes a more powerful oxidant in the presence of iron salts. Haber and Weiss later showed that OH$^-$ radicals were the oxidizing species in this reaction. Ide et al. use a combination of experiments with an iron chelator, superoxide anion scavenger, and catalase to demonstrate that the hydroxyl radicals in failing myocardium are derived from O$_2^-$ and H$_2$O$_2$ via Fe$^{2+}$-dependent Haber-Weiss and/or Fenton reactions.

Mitochondria have been recognized as a source of ROS for some time. Although the majority of electrons entering the mitochondrial electron transport chain reduce molecular oxygen to water, there is evidence for “leakage” of single electrons to molecular oxygen to form O$_2^-$ via ubiquinone at the level of complexes I and II. This “oxygen wastage” is minimized by the tight coupling of the components of the electron transport system. Nevertheless, the density of mitochondria in cardiac myocytes and the high rate of oxidative phosphorylation can result in a substantial flux of O$_2^-$. Normally, ROS production is balanced by the antioxidant activity of the mitochondrial enzymes manganese superoxide dismutase (MnSOD) and glutathione peroxidase (GPx). The importance of MnSOD in the regulation of ambient oxidative stress in the myocardium is highlighted by the demonstration that homozygous knockout mice deficient in MnSOD develop normally in utero but die soon after birth with dilated cardiomyopathy. The phenotype of the MnSOD knockout mouse underscores the importance of the mitochondria as a source of O$_2^-$ in the myocardium.

Decreased antioxidant activity could also contribute to the “net” increase in the production of OH$^-$ observed by Ide et al. Dhalla and Singal and Hill and Singal have found that antioxidant capacity is decreased in models of heart failure. For example, late after aortic banding or myocardial infarction there appears to be increased oxidative stress and maladaptive decreases in the activities of SOD, GPx, and catalase, associated with depletion of nonenzymatic antioxidants. Essentially nothing is known about the mechanism that, in the face of increased oxidative stress, leads to downregulation of these antioxidant systems in the failing heart.

“Oxygen wastage” has previously been viewed as a mechanism for reduced myocardial efficiency. However, the single electron reduction of O$_2$ to form O$_2^-$ in the mitochondria of failing myocardium, perhaps better referred to as “oxygen misappropriation,” has implications beyond any effect on myocardial efficiency. ROS have direct effects on cellular structure and function and may be integral signaling intermediates in many pathways, including myocardial remodeling. In isolated cardiac myocytes, a subtle increase in ROS caused by partial inhibition of SOD results in a phenotype characterized by hypertrophy and apoptosis. Higher levels of ROS are known to cause direct damage to proteins, lipids, and nucleic acids, leading to myocyte death by necrosis or apoptosis. This may, in part, occur through the production of peroxynitrite, particularly if there is substantial nitric oxide present. ROS of mitochondrial origin may be particularly prone to trigger apoptosis through activation of...
the mitochondrial permeability pore transition, release of cytochrome c, and activation of effector enzymes in apoptosis signaling.\(^{13}\)

What is driving oxidative stress in the failing heart? It appears that many recognized remodeling stimuli such as mechanical strain\(^{14}\) and tumor necrosis factor-\(\alpha\)\(^{15}\) can increase the formation of ROS in the myocardium. If mitochondria are the principle source of ROS in response to these or other remodeling stimuli, the results of Ide et al\(^{1}\) suggest that such stimuli may regulate electron transport activity and “oxygen wastage” directly. This thesis would further imply that chronic remodeling stimuli control, in part, the activity of the mitochondrial electron transport system, and according to the work of Ide et al, may thereby alter the level of myocardial oxidative stress. This speculation is supported by the finding that mechanical unloading with a left ventricular assist device in patients with severe heart failure resulted in an increase in mitochondrial complex I activity.\(^{16}\)

Opie et al\(^{17}\) showed years ago that catecholamine stimulation in the intact heart results in “oxygen wastage” and myocardial damage,\(^{17}\) and that both effects could be prevented by \(\beta\)-adrenergic receptor (\(\beta\)-AR) blockade. We now know that catecholamine-induced myocardial damage is due, at least in part, to \(\beta\)-AR–mediated myocyte apoptosis.\(^{18}\) It is therefore possible that a direct effect of \(\beta\)-AR stimulation to depress mitochondrial complex I activity is the basis for an increase in mitochondrial ROS formation that contributes to the cardiotoxic effect of \(\beta\)-AR stimulation. In support of this hypothesis, \(\beta\)-AR antagonists lower not only myocardial oxygen consumption but also “oxygen wastage.”\(^{19}\) This latter effect may be through restoring the activity of complex I and reducing “oxygen wastage” in the form of ROS, thus explaining the apparent antioxidant effect of \(\beta\)-AR blockade.\(^{19}\)

Xanthine oxidase may be another source of oxidative stress and “oxygen wastage” in the failing heart. In the rapid pacing–induced canine model of heart failure, there is a 4-fold increase in myocardial xanthine oxidase activity that is associated with a decrease in myocardial efficiency.\(^{20}\) Treatment with the xanthine oxidase inhibitor allopurinol improved mechanical efficiency and increased myocardial contractile function. How these observations relate to the current work by Ide et al\(^{1}\) remains to be seen, but it is possible that activation of xanthine oxidase in the failing heart is a downstream effect of the increase in mitochondrial ROS.

The direct demonstration of oxidative stress in a model of myocardial failure should help to focus attention on the potential therapeutic value of antioxidants. However, many questions remain. Are these observations applicable to other models of myocardial failure? What is the mechanism by which mitochondrial complex I activity and the “leakage” of oxygen to form ROS is controlled? To what extent does the downregulation of antioxidant enzymes contribute to oxidative stress in failing myocardium, and what is the mechanism for the apparently inappropriate decrease in antioxidant capacity? The answers to these, and other, important questions will be valuable in mapping out therapeutic antioxidant strategies in the new age of molecular therapy.

References


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