Oxidant byproducts, such as superoxide anion (O$_2^-$) and hydrogen peroxide, are produced as a consequence of normal aerobic metabolism. These molecules, which are highly reactive with other biological molecules, are referred to as reactive oxygen species (ROS). Under normal physiological conditions, ROS production is balanced by an efficient system of antioxidants, molecules that are capable of scavenging ROS and thereby preventing oxidant damage. At the cellular level, naturally occurring enzymatic antioxidants such as superoxide dismutase, glutathione peroxidase, and catalase play an important role in the conversion of ROS to oxygen and water. Several nonenzymatic antioxidants, including the lipid-soluble antioxidants vitamin E and β-carotene and the water-soluble antioxidants vitamin C and glutathione, are also important in scavenging free radicals. Vitamin C in particular protects plasma lipids from peroxidation, scavenges O$_2^-$, and plays a role in recycling vitamin E.

In pathological states, ROS may be present in relative excess. This shift of the balance in favor of oxidation, termed “oxidative stress,” may have detrimental effects on cellular and tissue function. Oxidative stress is thought to contribute to the pathogenesis of a wide variety of disease states, including atherosclerosis and cancer, as well as to the normal process of aging. There is increasing evidence that myocardial oxidative stress may contribute to disease progression in heart failure. 2 Although the effects of oxidative stress on the myocardium have been investigated in pathological states, very little is known about the role of ROS in the regulation of normal cardiac function. Recently, Ekelund et al. 3 tested the role of the pro-oxidant enzyme xanthine oxidase in regulating contractile function in normal dogs. Their finding that the xanthine oxidase inhibitor allopurinol exerted a positive inotropic effect suggested that ROS participate in the control of normal myocardial function. In this issue of Circulation, Mak and Newton 4 provide the first direct evidence that ROS contribute to the regulation of normal contractile function in humans. In patients with normal left ventricular function undergoing cardiac catheterization for evaluation of a chest pain syndrome, the contractile response to intravenous dobutamine was assessed before and during the intracoronary infusion of vitamin C. The infusion rate of vitamin C was chosen to achieve an intracoronary concentration between 1 and 10 mmol/L, a level that improves endothelial function in vivo. 5 Vitamin C had no effect on basal contractile function, but it potentiated the positive inotropic response to dobutamine by 22%. In a group of control patients, there were no differences in the inotropic responses to sequential dobutamine infusions, suggesting that the augmentation of the inotropic response to dobutamine was due to vitamin C rather than repetitive dobutamine infusions.

There are several possible mechanisms by which vitamin C may have augmented the response to dobutamine. Vitamin C corrects coronary vasomotor regulation and increases coronary blood flow in patients with hypertension and vasospastic angina. 6,7 Although the patients studied by Mak and Newton 4 had normal left ventricular systolic function, the majority had coronary artery disease and/or coronary risk factors (eg, hypertension and diabetes) that are associated with oxidative stress. 1 Thus, it is possible that vitamin C acted by improving the coronary blood flow response to β-adrenergic stimulation. Another possibility is that myocardial ROS can directly regulate the function of cardiac myocytes. It is now apparent that nontoxic quantities of ROS can mediate biological processes in a variety of cell types. 8 For example, Griendling and colleagues 9 showed that ROS play a critical role in mediating angiotensin-stimulated growth in vascular smooth muscle cells. The finding that vitamin C increases the contractile response to an exogenous β-adrenergic agonist raises the possibility that ROS modulate β-adrenergic signaling. Such an action could occur at one or more points between the receptor and contractile elements. Potential mechanisms include redox-dependent alterations in the expression or function of β-adrenergic receptors, related G-proteins, adenylyl cyclase, cAMP metabolism, calcium handling proteins, or proteins in the contractile apparatus. There is evidence that ROS can regulate β-adrenergic receptors, G-proteins, and adenylyl cyclase function in rat myocardium. 10 Likewise, it has been demonstrated that the function of several calcium handling proteins, including the calcium-release channel, the voltage-dependent calcium channel, and the sodium/calcium exchanger, undergo redox-sensitive alterations in activity. 11-13 Understanding the molecular mechanism by which ROS regulate myocardial contractile function may provide new insights regarding both normal myocardial function and the potential role of deranged ROS in disease states.

These data have other, somewhat less obvious implications. The β-adrenergic system plays an important role in determining the myocardial responses to exercise and other
short-term demands for an increase in myocardial contractile function. At the same time, it now seems likely that the β-adrenergic system contributes to the pathophysiology of myocardial failure.14 When viewed in this latter context, the finding that vitamin C increases the inotropic response of normal human heart to dobutamine raises an interesting conundrum. If blocking β-adrenergic responses is beneficial in the failing myocardium, then ROS should play a protective role by attenuating this pathway. Because vitamin C increases β-adrenergic “throughput,” it could be argued that antioxidants, although improving short-term function, exert a deleterious effect on the myocardium.

However, another hypothesis is also possible in which ROS represent the “dark side” of long-term β-adrenergic receptor stimulation. According to this thesis, β-adrenergic receptor activation leads to increased production of ROS, perhaps as a necessary consequence of increased myocardial oxygen consumption.15 There might be multiple consequences of a β-adrenergically-mediated increase in ROS formation. As already suggested, the data from Mak and Newton4 provide evidence that ROS production could act as a counter-regulatory mechanism to control the intensity of β-adrenergic responses. In vitro studies have also shown that tonic exposure to ROS can exert deleterious effects on myocardial structure and function. In isolated cardiac myocytes, we and others found that ROS cause myocyte apoptosis.16,17 Likewise, peroxynitrite, the product of O2− and nitric oxide, may mediate myocyte apoptosis in response to interleukin-1.18 Evidence that ROS are involved in pathological myocardial remodeling comes from studies in which strategies to reduce ROS, including the use of antioxidant vitamins, have exerted beneficial effects in animal models of pressure overload or myocardial infarction.19,20

Thus, although ROS might serve in the short-term to reduce the intensity of β-adrenergic signaling, in the long run, a β-adrenergically-mediated increase in ROS formation could be detrimental to myocardial health. In this scenario, treatment with antioxidants would not only augment the short-term inotropic response to β-adrenergic stimulation, but also prevent the direct ROS-mediated adverse effects of long-term β-adrenergic stimulation on the myocyte. The findings of Mak and Newton4 thus raise the intriguing possibility that ROS contribute to the dark side of long-term β-adrenergic stimulation of the myocardium and offer a mechanism by which interruption of β-adrenergic signaling could exert a beneficial effect on the myocardium.

References

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