Editorial Comment

Studying Systemic Oxidative Stress in Heart Failure: Does It Have Any Role in Clinical Practice?

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Oxidative stress in the cardiovascular system is characterized by the increased bioavailability of reactive oxygen species (ROS) in cardiac and vascular cells, due to an imbalance between their production by the various pro-oxidant enzymatic systems and their elimination by the endogenous antioxidant defenses.[1,2] Increased oxidative stress is involved in the pathogenesis of most cardiovascular pathologies.[3]

In this issue of the HJC, Simeunovic et al[4] report the changes in the redox state of patients with dilated cardiomyopathy (DCM) before and after cardiopulmonary exercise testing, and they link them with changes in catecholamine levels. Catecholamines are hormones that are often dysregulated in the context of cardiovascular disease, acting as failing compensatory mechanisms that ultimately result in a deterioration of cardiovascular function.[5] They have been associated with increased oxidative stress,[6] although the causal links of this relationship remain unclear. In their study, Simeunovic et al[4] measured the activities of antioxidant enzymes superoxide dismutase, catalase, glutathione reductase and glutathione peroxidase in the blood, as well as the circulating levels of noradrenaline, adrenaline and dopamine, in DCM patients and healthy individuals. They documented a significant increase in the activities of catalase, glutathione reductase and glutathione peroxidase, as well as in the circulating levels of all evaluated catecholamines, in the non-diseased group after cardiopulmonary testing; conversely, DCM patients exhibited increased levels of adrenaline and noradrenaline, as well as glutathione reductase activity, post-testing. In addition, patients in NYHA classes III/IV had reduced activity of antioxidant enzymes and increased levels of circulating catecholamines compared to patients in NYHA classes I/II. The authors also demonstrated a negative correlation between catecholamine levels and left ventricular ejection fraction, both pre- and post-testing; left ventricular ejection fraction was correlated positively with glutathione peroxidase before testing and negatively with superoxide dismutase after testing. The authors conclude that DCM is associated with a disruption of redox–hormonal balance.

There is a wide variety of ROS-producing enzymes *in vivo*, which include NADPH oxidases (enzymes exclusively dedicated to ROS production), uncoupled nitric oxide synthases (resulting from oxidation and depletion of their important co-factor tetrahydropterin), xanthine oxidase, mitochondrial oxidases, and others.[1] Although ROS are important signalling

molecules in cardiomyocytes, they also modify various proteins and cause DNA damage, exerting clearly detrimental effects on myocardial biology when in excess.[7,8] ROS also affect a variety of not fully identified redox-sensitive signal transduction pathways, such as the pathway of NF kB and AP1.[1,7] Via these effects, ROS can regulate cell proliferation or apoptosis, tissue inflammation, and overall cellular function. Despite the significant progress in understanding the mechanisms of cardiovascular diseases over the last few years, the field of redox signalling has always been, and remains, controversial. The reasons for that are the wide chemical variety of ROS, the plethora of their potential signalling targets, and the difficulty of understanding when a physiological oxidative stimulus becomes pathophysiological. An additional challenge is to identify appropriate circulating markers of oxidative stress, able to describe the tissue availability of ROS in the cardiovascular system.[1] In this context, measuring the circulating levels of antioxidant enzymes is a questionable way to assess systemic oxidative stress, let alone to speculate about myocardial redox state. Indeed, the relative contribution of the cellular components of blood to the circulating pool of antioxidant enzymes has not been evaluated; thus, it is unclear whether such measurements can accurately reflect true systemic redox state or are influenced by local redox regulation in the blood.[9] Conversely, the most widely used way of monitoring systemic oxidative stress in humans is measuring circulating levels of oxidation products such as malondialdehyde.[1] Such substances are considered to be stable end-products of oxidative reactions that may reflect overall redox state. Of course, this approach is not without disadvantages; indeed, the available methods are not specific and the measurement of circulating oxidation products still reveals little about the individual, tissue-specific sources and actions of ROS.

DCM is an idiopathic disease that ultimately results in heart failure. As with all forms of heart failure, it is characterized by cardiac remodelling and systolic ventricular dysfunction, processes in which oxidative stress has been implicated.[10] In fact, the apparent association of oxidative stress with heart failure has been well-established by clinical and experimental studies,[11-13] and there are studies in cell culture and animal models demonstrating a pathophysiological role of ROS originating from mitochondria and xanthine oxidase,[14-18] as well as profound mitochondrial dysfunction and DNA damage related to mitochondrial oxidative stress.[19] In addition, the well-known effects of ROS on vascular function seem to indirectly affect the pathophysiology of heart failure. Indeed, endothelium-dependent relaxation of the coronary vasculature is reportedly impaired in DCM-associated heart failure,[20] an effect presumably resulting from depletion of nitric oxide due to oxidative stress. Hydrogen peroxide has also been shown to induce direct injurious effects on rat cardiomyocytes,[21] whereas a plethora of redox-sensitive inflammatory pathways has been implicated in the pathophysiology of heart failure.[22] Angiotensin-converting enzyme inhibitors have been shown to exert some of their cardioprotective effects partially through regulation of the redox state in rats.[23]

We have recently shown that myocardial redox state plays a critical role in myocardial biology, predisposing to arrhythmias such as atrial fibrillation.[24,25] We have also shown that treatments targeting myocardial redox state (e.g. statins) are able to suppress myocardial inflammation controlled by redox-sensitive transcriptional pathways such as NF kB and AP1.[24,26] This effect has been clinically important, since we have demonstrated that myocardial redox state is an independent predictor of clinical outcome in patients with atherosclerosis and can be modified by high-dose statin treatment.[26] Importantly, we have also very recently revealed novel redox-sensitive signalling roles for 4-hydroxynonelal (4HNE) adducts (lipid peroxidation products) in the vasculature,[27] which may also be relevant in heart failure, given that 4HNE adducts are also increased in the hearts of DCM cases.[28] This novel hypothesis suggests that there is a bidirectional paracrine loop amongst cardiomyocytes as well as between myocardium and adjacent tissues, such as epicardial adipose tissue. The presumed mechanisms by which redox signalling interferes with myocardial pathophysiology in disease states such as heart failure are summarised in Figure 1.

The mechanistic link between oxidative stress and heart failure is still poorly understood. There is a growing body of data suggesting that oxidative stress is indeed a key player in heart failure, with roles more complex than previously believed. Rather than their obvious cytotoxic effects, ROS are believed to affect a network of signal transduction pathways, some of which may even be unidentified or poorly understood, and this fact, in combination with a dysregulation of the neurohormonal background and the overall genetic and/or environmental predisposition, creates a complex framework within which the irrevers-

ible remodelling of the failing heart can occur. Therefore, the findings of Simeunovic et al[4] are important, because they link heart failure with dysregulation of myocardial redox state (as well as the neurohormonal background), highlighting oxidative stress as a reasonable potential therapeutic target. However, the key questions still remain unanswered. How biologically and clinically relevant is the measurement of circulating biomarkers of oxidative stress in heart failure? What do these biomarkers describe? How can we target tissue ROS production? Could ROS actually be protective in some types of cardiovascular disease? The study by Simeunovic et al[4] provides a way forward in understanding the role of oxidative stress in heart failure, but many more studies are needed to contribute to a better understanding of the complex relationships between oxidative stress, catecholamines and cardiovascular diseases in advanced disease states such as heart failure.

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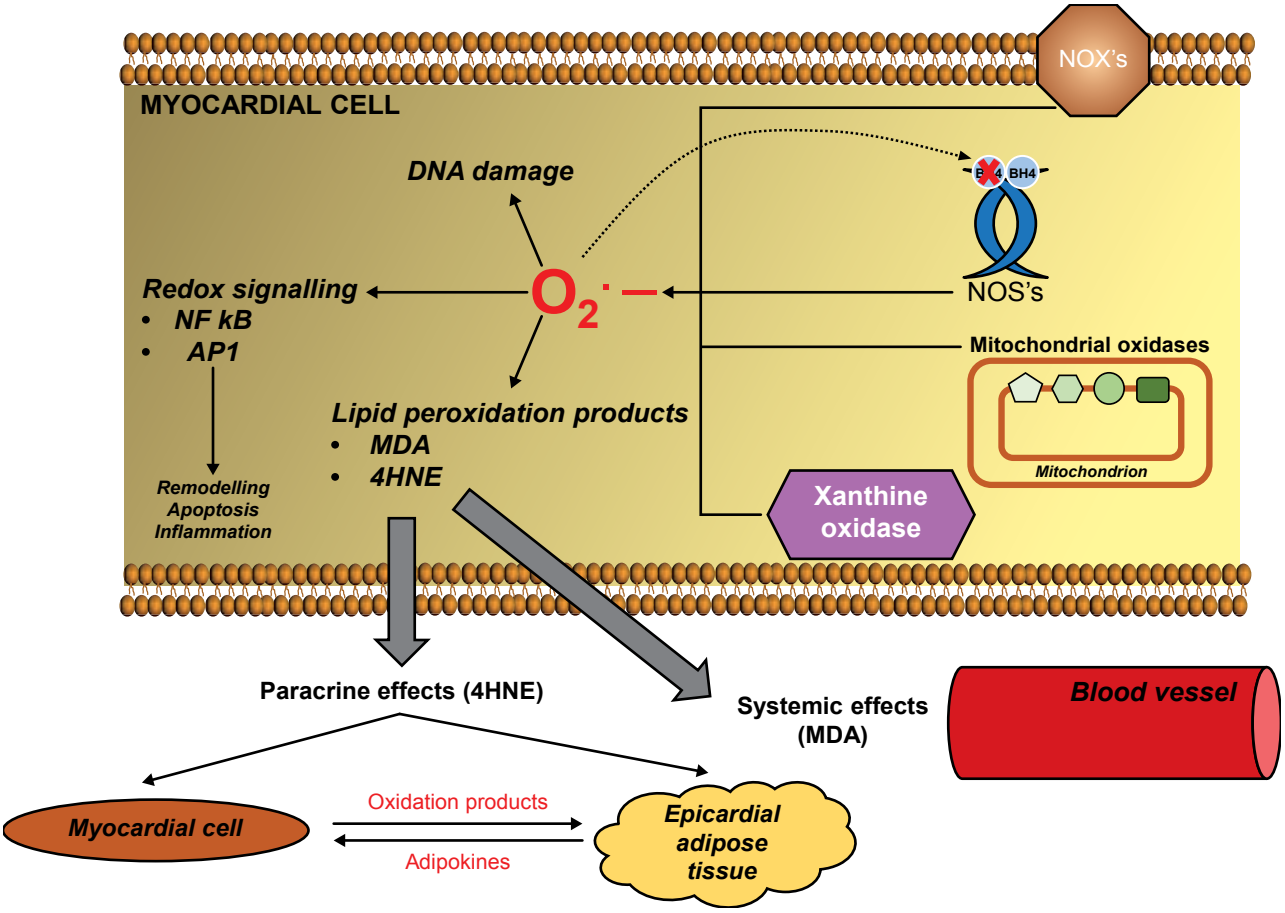

Figure 1. Overview of myocardial redox signalling. Reactive oxygen species (ROS) in the myocardium originate mainly from NADPH oxidases as well as uncoupled nitric oxide synthases (NOSs) resulting from oxidative tetrahydropterin (BH4) depletion; other enzymatic sources such as xanthine oxidase and myocardial oxidases also contribute to ROS production. Once formed in the myocardium, ROS exert various effects, including DNA damage and the initiation of redox signalling cascades, such as the pathway of NF kB and AP1. Through these actions, ROS control important cellular responses, such as apoptosis, hypertrophy, remodelling and inflammation. Importantly, ROS can rapidly oxidise lipids, leading to the formation of lipid peroxidation products that may have paracrine signalling roles in adjacent myocardial cells and epicardial adipose tissue (such as 4HNE), or may enter the circulation, exerting systemic effects and allowing evaluation of systemic oxidative stress (such as MDA). In addition, myocardial tissue may also be the recipient of oxidative signals/effects originating from the epicardial adipose tissue, thus creating a bidirectional paracrine redox-sensitive loop within the heart.

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