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Editorial

Oxidative stress in heart failure

More than just damage

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Chronic heart failure (CHF) continues to cause substantial morbidity and mortality despite major therapeutic advances, such as the use of angiotensin-converting enzyme (ACE) inhibitors and β-blockers. The main causes of CHF today are ischaemic heart disease (IHD) and hypertension. Extensive experimental and clinical studies over the last 20 years have established that a fundamental process in the progression to CHF (especially in patients with prior myocardial infarction [MI]) is cardiac remodelling—a series of alterations in heart structure and function that involve significant changes in gene expression and protein function, both in the extracellular matrix and in cardiomyocytes. Although ventricular remodelling may initially be adaptive by normalizing wall stress and maintaining contractile function in the face of muscle loss or increased load, with time there is progressive ventricular dilatation, increasing interstitial fibrosis and arrhythmia, and a decline in ejection fraction. At least part of the benefit of ACE inhibitors and β-blockers is believed to involve the amelioration of adverse cardiac remodelling.

The poor prognosis of CHF despite the use of multiple evidence-based therapies has provided an impetus for the elucidation of new pathophysiological pathways that could be therapeutically targeted to improve patient outcome. Two such pathways that have received increasing attention are (a) the activation of matrix metalloproteinases (MMPs), a family of enzymes capable of degrading all the matrix components of the heart, and (b) myocardial oxidative stress. MMPs are critically important in determining the balance between matrix deposition and degradation, which ultimately influences chamber size, shape and function. The inappropriate activation of MMPs and/or an imbalance between their actions and those of tissue inhibitors of MMPs (TIMPs) are implicated in cardiac remodelling, and pharmacological inhibition of MMPs has recently been shown to reduce adverse remodelling in experimental CHF.[1] Oxidative stress has long been implicated in clinical and experimental CHF. The term refers to an imbalance between the production of reactive oxygen species (ROS-including free radicals such as superoxide and non-radicals such as hydrogen peroxide) and endogenous antioxidant defence mechanisms. Markers of oxidative stress are elevated in CHF patients and have been correlated with myocardial dysfunction and overall severity of heart failure. An obvious mechanism through which myocardial oxidative stress might impair cardiac function is through oxidative damage to cellular proteins and membranes, thereby, inducing cellular dysfunction or death through apoptosis and necrosis. However, recent studies in other organ systems indicate that ROS can exert much more subtle effects, depending upon the concentrations produced, the site of production, and the overall redox status of the cell.[2] One example is the potential for ROS to influence extracellular matrix remodelling through the activation of MMPs.[1]

In the current issue of the journal, Kameda et al.[3] provide clinical evidence for a link between oxidative stress, MMP activation and LV dilatation in a study in 47 patients with IHD who were undergoing coronary artery bypass graft surgery. The authors report a significant positive correlation between LV end-diastolic volume index (LVEDVI) and MMP-2 and MMP-9 activities in pericardial fluid obtained at the time of surgery. Furthermore, both LVEDVI and MMP-2/MMP-9 activities were also positively correlated with pericardial levels of 8-iso-prostaglandin F2α, a marker of oxidative stress. While there are a number of limitations to the study (including its correlative nature, potential confounding effects of drug therapy, and the use of angiography to estimate LVEDVI), these results are nevertheless consistent with

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the hypothesis that myocardial oxidative stress is an important regulator of MMP activity and that this contributes to ventricular remodelling and LV dilatation in patients with IHD.

ROS may in fact exert multiple effects relevant to CHF pathophysiology. The superoxide anion is a potent inactivator of the signalling molecule nitric oxide (NO); the resulting reduction in NO bioavailability contributes to vascular endothelial dysfunction and the loss of other physiological effects of NO. Furthermore, the reaction between NO and superoxide generates peroxynitrite, which is itself a potent ROS. Secondly, ROS can modulate the activity of diverse intracellular signalling pathways and molecules (a mechanism commonly termed 'redox signalling'), with the potential to induce specific acute and chronic effects.[2] For example, key proteins involved in myocardial excitation-contraction coupling, such as ion channels, sarcoplasmic reticulum calcium release channels and myofilament proteins, can undergo redox-sensitive alterations in activity.[4] ROS may also exert important effects on cellular energetics. An increasing number of recent studies suggest an important role for ROS-mediated chronic changes in cellular phenotype in the pathophysiology of CHF.[4] ROS modulate fibroblast proliferation and collagen synthesis, and are involved not only in MMP activation but also increased MMP expression.[1] Indeed, chronic treatment with ROS scavengers attenuates adverse cardiac remodelling in animal models of CHF, such as those induced by coronary artery ligation.[5] Activation of redox-sensitive signalling pathways (e.g., mitogen-activated protein kinases) and transcription factors (e.g., NF-κB) is also implicated in the development of cardiomyocyte hypertrophy, and some experimental studies suggest that the development and progression of cardiac hypertrophy can be attenuated by antioxidant therapies.[4]

An important area for investigation is to determine the sources of ROS generation in the diseased heart and the factors responsible for their regulation, particularly in relation to redox-signalling events. Potential sources of ROS include infiltrating inflammatory cells, mitochondria, xanthine oxidase and NADPH oxidases. Excessive mitochondrial-derived cardiomyocyte ROS generation has been demonstrated in experimental models of CHF, and may be especially important for contractile dysfunction in advanced CHF. An elevation of xanthine oxidase expression and activity has also been reported in both human end-stage CHF and canine rapid pacing-induced CHF, with the suggestion that this contributes to contractile dysfunction. Indeed, in the study by Kameda et al.[3] in the current issue of the journal, the authors report that patients presenting with acute MI who were treated with a xanthine oxidase inhibitor, allopurinol, had lower plasma MMP activity and urinary 8-iso-prostaglandin F2α levels than those not treated with allopurinol. However, few conclusions can be drawn from this very small non-randomized component of their study, undertaken in patients with acute MI. Furthermore, it is important to note that allopurinol can exert non-specific antioxidant actions and cannot therefore be necessarily regarded as a specific probe for xanthine oxidase activity in such studies.[6]

Recent reports suggest that an especially important source of ROS as far as redox signalling is concerned is a family of complex enzymes termed NADPH oxidases, which were first characterized in neutrophils but are now known to be very widely expressed. Several pathophysiological stimuli involved in CHF, such as angiotensin II, α-adrenergic agonists, endothelin-1, tumor necrosis factor-α and cyclic stretch, can stimulate ROS production by NADPH oxidases.[7] Evidence for an increased expression and activity of myocardial NADPH oxidases has recently been provided in both experimental and human CHF.[8–10] Furthermore, studies from our laboratory using gene-modified mice with defective NADPH oxidase activity demonstrated a pivotal role for NADPH oxidase in signalling angiotensin II-induced cardiac hypertrophy and interstitial fibrosis.[11] These studies also indicate that ROS may play important roles in both adaptive and maladaptive processes (e.g., the early development of hypertrophy and adverse remodelling respectively). While these studies point to the relevance of NADPH oxidase-derived ROS in cardiac hypertrophy and failure, it should also be noted that ROS production by one enzymatic source can modulate or trigger the activity of other ROS sources (e.g., NADPH oxidase can drive ROS production by NO synthase), so that the overall situation may in fact be quite complex in specific disease settings.

Oxidative stress has had a bad press over the years, being generally considered to be uniformly deleterious in the heart. However, recent studies in other organ systems and also the heart teach us that tightly regulated ROS production may in fact exert considerably more subtle modulatory effects, especially through the targetting of redox-sensitive proteins and enzymes.[2] The study by Kameda et al.[3] provides supportive clinical data for the growing experimental evidence that ROS have a pivotal role in cardiac remodelling, through modulation of the processes that govern extracellular matrix deposition and degradation. Elucidation of the precise sources of ROS production and their regulation could provide the basis for devising novel therapeutic strategies for human CHF.

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