

Targeting oxidative stress in heart failure

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Abstract

Increased oxidative stress is recognized to be important in the pathogenesis of cardiovascular disease, including heart failure. Reactive oxygen species (ROS) can be derived from diverse sources, including mitochondria, NADPH oxidase, and xanthine oxidase. Many agents established in the treatment of heart failure (including angiotensin-converting enzyme inhibitors, statins, β -blockers, hydralazine) may act indirectly by reducing the generation of ROS. In contrast, direct ROS scavengers* (eg, vitamin E) have been less successful in treatment. Newer ROS scavengers are being evaluated, and novel concepts for limiting the damage of ROS, such as the use of poly(ADP-ribose) polymerase 1 inhibitors, remain to be explored in clinical studies.

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Introduction

Heart failure is a leading cause of mortality, and recent advances in therapeutic agents have substantially improved the prognosis for patients, especially with the introduction of angiotensin-converting enzyme (ACE) inhibitors, β -adrenoceptor blockers, and aldosterone antagonists. Recent evidence suggests that oxidative stress is increased in patients with heart failure [1,2], and the heart itself may be the source of these free radicals [3], but no successful large scale trials specifically targeting free radicals in heart failure have been published.

Reactive oxygen species (ROS) can damage cardiac tissue through oxidation of lipids, proteins, and DNA, producing diverse effects such as reduced cardiac contractility, malfunction of ion transporters, and calcium cycling. Their toxic effects are limited by free radical scavengers such as superoxide dismutase (SOD) which catalyzes the formation of H_2O_2 from superoxide ($O_2^{\bullet-}$), glutathione peroxidase, catalase which catalyzes the breakdown of H_2O_2 to water, and

other non enzymatic antioxidants such as vitamins E, C and β -carotene, ubiquinone (coenzyme Q10), lipoic acid, and urate. There is no deficiency of these enzymatic defenses in heart failure [4], although manganese SOD protein may be reduced [5]; hence damage may ensue from excessive production of ROS. In addition, ROS can also act as an intracellular signaling mechanism, affecting transcription factors such as NF κ B and activator protein-1.

Sources of ROS and their effects in the heart

Cellular sources of ROS include neutrophils/monocytes, cardiomyocytes, and endothelial cells, through enzymes such as the NAD(P)H oxidases (phox proteins), xanthine oxidase, cytochrome P-450, nitric oxide synthase, and mitochondria (*Figure 1*). Production of ROS in the heart can be induced by a number of cytokines and growth factors, such as angiotensin II, platelet-derived growth factor, and tumor necrosis factor α through activation of

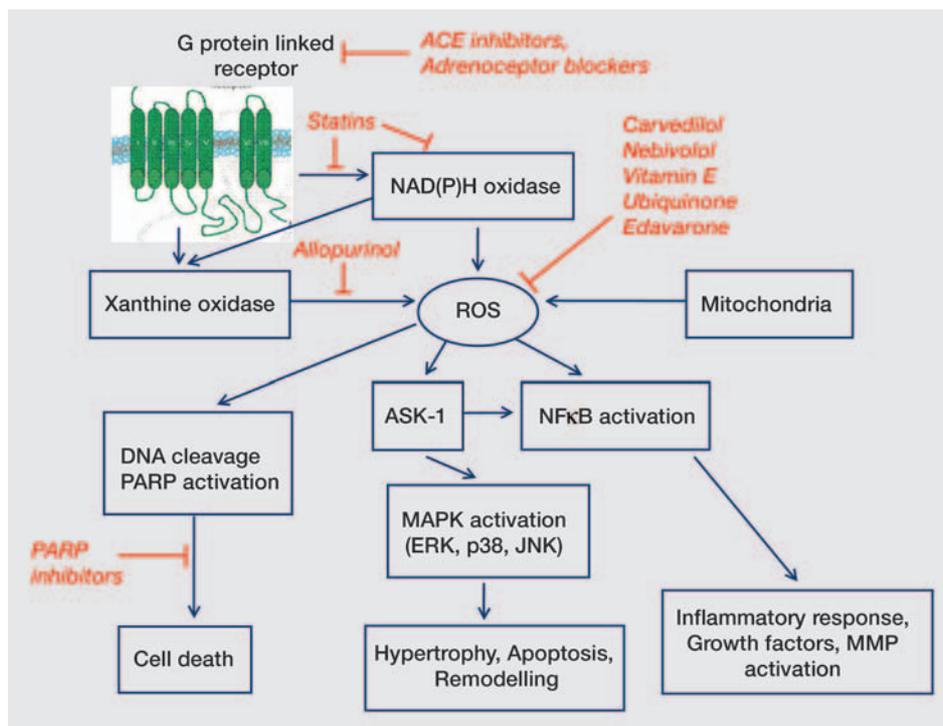


Figure 1. Potential sources of reactive oxygen species (ROS) and their effects on cell pathology. Therapeutic agents and their putative sites of action are illustrated in red. ACE, angiotensin converting enzyme; ASK-1, apoptosis-regulating signal kinase 1; ERK, extracellular-signal regulated kinase; JNK, Jun kinase; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NFκB, nuclear factor κB; PARP, poly(ADP ribose) polymerase 1.

NAD(P)H oxidases. Uncoupled mitochondria could also be a major source of ROS in heart failure [6]. The neutrophil enzyme, myeloperoxidase, is increased in heart failure, suggesting these cells to be another source of ROS [7,8].

Activation of the G protein coupled receptors such as the angiotensin II receptor leads to enhanced production of ROS through the NAD(P)H oxidases (NOX2). Intracellular ROS can activate the redox-sensitive kinase, apoptosis-regulating signal kinase 1 (ASK-1), which leads to activation of other kinases such as mitogen-activated protein kinases (MAPKs), p38MAPKs and Jun kinases, all of which are signaling intermediates in the pathways to cellular hypertrophy and apoptosis [9]. Dominant negative mutant ASK-1 attenuated the agonist-mediated activation of NFκB and inhibited cardiac hypertrophy in response to ROS-generating G protein receptor agonists such as angiotensin and adrenoceptor agonists [10].

ROS can also increase cardiac remodeling through the activation of matrix metalloproteinases (MMPs), which have been implicated in the pathogenesis of heart failure [11–13]. DNA can also be damaged by ROS, and the breaks lead to activation of the DNA base-repair nuclear enzyme, poly(ADP ribose) polymerase 1 (PARP-1), which in turn leads to cell death from depletion of intracellular NAD⁽⁺⁾ and ATP [14].

Existing treatments targeting oxidative stress in heart failure

Drugs that are established for treatment in heart failure may act indirectly to ameliorate the excessive oxidative stress in heart failure. For example, ACE inhibitors and angiotensin receptor blockers may reduce the G protein linked signaling response to NOX2, hence reducing the ROS burden in target tissues. This may also apply to β-adrenoceptor blockers, as β1-adrenoceptor-mediated actions on heart cells may also be mediated through the generation of ROS, activation of Jun kinases, and stimulation of apoptosis [15]. In addition, drugs such as carvedilol [16] and nebivolol [17] may have additional antioxidant properties independent of their β-adrenoceptor blocking effect.

Statins have pleiotropic effects independent of their cholesterol-lowering activity. Mevalonate produced from hydroxymethyl glutaryl coenzyme A reductase is a precursor for the synthesis of ubiquinone and isoprenoids, and isoprenylation of the γ-subunit of G proteins is a prerequisite for their activity. Statin treatment leads to reduced isoprenylation of G protein γ-subunits [18], in addition to the small GTPases, Rho and rac [19]. This may lead to both reduced production of ROS through agonist stimulation and a direct effect on the NOX2s, which require rac as a cofactor. In a recent clinical trial in patients with heart

New therapeutic approaches

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failure (Controlled Rosuvastatin Multinational Trial in Heart Failure [CORONA]), rosuvastatin reduced admissions to hospital significantly, although there was no effect on mortality [20]. Whether depletion of ubiquinone (see below) could have influenced the outcome of the CORONA trial is unknown.

Hydralazine used in combination with nitrates has been demonstrated to reduce mortality in heart failure [21]. Hydralazine, an arterial vasodilator, also has additional inhibitory effects on the generation of superoxide and peroxynitrite [22], which may provide a basis for its salutary effect.

In view of the potential importance of xanthine oxidase as a source of ROS, inhibitors of this enzyme may be expected to have an effect in heart failure. In addition, angiotensin II and NAD(P)H oxidases may have a role in upregulating xanthine oxidase activity. The findings of certain small trials tended to suggest that allopurinol may attenuate remodeling after myocardial infarction [23]. However, larger trials with oxypurinol [24], the active metabolite of allopurinol, have not confirmed a clinical benefit on mortality or admissions to hospital because of heart failure. The subgroup of patients in that trial with higher uric acid concentrations may have benefited to some extent, but definitive studies are needed to test this specifically. Uric acid itself is an endogenous free radical scavenger, and could act concurrently as a biomarker surrogate of xanthine oxidase activity, which may explain the disparate results with inhibition of that enzyme.

Free radical scavengers in heart failure

Ubiquinone (coenzyme Q10) is a natural antioxidant, and is essential for mitochondrial electron chain transport activity. There may be evidence of ubiquinone depletion in heart failure, and this may be a theoretical drawback to the use of statins – as, for example, in the CORONA study [20] – which may have limited the positive effects of statins. Many of the trials utilizing ubiquinone have been small and underpowered. A meta-analysis of 11 randomized clinical trials with ubiquinone suggested a small but significant improvement in ejection fraction (3.7%) in those individuals who received ubiquinone – especially those patients who were not receiving ACE inhibitors [25]. A multinational trial of ubiquinone as adjunctive therapy in heart failure (“Q-symbio”) is in progress, and results are eagerly awaited [26].

Large clinical trials of the antioxidant vitamins (A, E) or their precursors have been disappointing, with no evidence of benefit on cardiac mortality or morbidity [27,28]. In general, the vitamin E isomer that is used in trials is predominantly α -tocopherol, and different bioactivity of the various vitamin E isomers (eg,

γ -tocopherol and the tocotrienols) has not been studied extensively.

Other drugs with antioxidant properties, such as probucol, may improve ventricular function in heart failure [29], but larger human studies may be necessary to establish their true place in the therapeutic armamentarium.

Future perspectives

In addition to further studies on the aforementioned agents, there may be further possible avenues for heart failure research. For example, 3-methyl-1-phenyl-2-pyrazolin-5-one (Edaravone), a novel free radical scavenger, has been used in the treatment of diseases in which oxidative stress is implicated (eg, cerebral infarction) [30]. Its antioxidant properties remain to be tested in heart failure. As previously mentioned, ROS may cause DNA strand breaks and activation of the repair enzyme, PARP-1, leading to intracellular depletion of NAD(+) and ATP, resulting in cell death [14]. Novel compounds targeting PARP-1 may be of use in abrogating this ROS-induced damage, and several have been described in the literature:

BGP-15	O-(3-piperidino-2-hydroxy-1-propyl) nicotinic acid-amidoxime
GPI 6150	1,11b-dihydro-[² H]benzopyrano [4,3,2-de]isoquinolin-3-one
PJ-34	[¹ C]2-(dimethylamino)-N-(5,6-dihydro-6-oxophenanthridin-2-yl)acetamide
INO-1001	

Their use in heart failure remains to be investigated.

Conclusion

Heart failure is associated with increased oxidative stress, and many of our therapies proven to be of clinical benefit may have mechanisms of action related to reducing this stress in vivo. However, some exciting new therapies remain to be tested in this challenging clinical condition.

*See glossary for definition of these terms. ■

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