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Role of Oxidative Stress in Disease Progression in Stage B Heart Failure

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Abstract

Oxidative stress represents a persistent imbalance between the production and the compensation of reactive oxygen species. While predominantly found in advanced heart failure, the majority of “at risk” condition has been associated with underlying oxidative stress. It is therefore conceivable that timely detection and early intervention to reduce oxidative stress processes provide an opportunity to prevent disease progression to overt heart failure. This paper reviews our current understanding of the current evidence of oxidative stress involvement in the pathophysiology of human heart failure and its potential therapeutic interventions in patients with Stage A and B heart failure.

Keywords

Oxidative stress; Progression of heart failure; Stage B heart failure

Oxidative stress represents a persistent imbalance between the production and the compensation of reactive oxygen species (ROS). Multiple animal studies have shown the critical role of ROS (and hence redox balance) in maintaining cellular homeostasis and their role as second messenger systems in various physiological and adaptive mechanisms.^{1–3} However, excessive ROS can lead to the accumulation of peroxides and free radicals that damage proteins, lipids, and genes. The balance between reactive cellular species and natural anti-oxidant systems is therefore key to minimize adverse cellular consequences of ROS, while maintaining their physiological functions. Hence, oxidative stress has been implicated in many disease states, including senescence, malignant diseases⁴ diabetes,^{5,6} ischemia reperfusion injury, neurodegenerative diseases, certain infectious processes, rheumatoid arthritis, atherosclerosis and hypertension.^{7–10} When considering oxidative

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stress as a contributor of chronic heart failure disease progression, it can be broadly divided into two categories: *exogenous* (mediated by inflammatory cells) and *endogenous* (mediated by dysfunctional myocardial tissues). However, these processes are difficult to identify and quantify, and challenging to separate from related processes such as inflammation and neurohormonal upregulation in humans.

Oxidative stress has been linked to heart failure over the past decades, with majority of previous and current studies focused on patient populations with symptomatic or advanced heart failure. These ranged from cytokine-targeted therapy^{11,12}, inhibitors of xanthine oxidase¹³, and to various non-specific immunomodulatory therapy.¹² Clearly, the main objective to include these “relatively ill” patient populations was to allow adequate event rates to demonstrate statistically significant differences. However, most studies identify eligible patients with clinical characteristics since there is a lack of reliable *in vivo* tools that can aid the identification and quantification of ongoing oxidative stress.

Markers of inflammation and/or oxidative stress have been associated with incident heart failure^{14,15} even after controlling for coronary artery disease, suggesting that inflammation has a direct effect (possibly through exogenous oxidative stress) on the myocardium. However, these studies also assumed that oxidative stress was generated as the primary mediator of heart failure disease progression. In reality, such an assumption has never been validated in humans, in part because our contemporary understanding of the role of ROS (particularly in an individual patient) is limited. Nevertheless, it is important to recognize that even if oxidative stress may not directly cause cardiac dysfunction, appropriate modulation of such potential secondary pathologic processes may still yield favorable therapeutic interventions (as in the case of neurohormonal antagonism). This chapter summarizes our current understanding of the role of oxidative stress leading to the development of heart failure in at-risk individuals, and highlights the current diagnostic and therapeutic options under active investigations.

Role of Oxidative Stress in Disease Progression of Heart Failure

Ischemic Heart Disease

Involvement of oxidative stress in disease progression has been best described in the setting of ischemic heart disease, one of the most common causes of heart failure secondary to structural heart disease (Stage B heart failure). Direct myocardial damage mediated by downstream oxidative stress processes can lead to progressive enlargement and contractile impairment known as “cardiac remodeling.” Adverse myocardial remodeling is the likely basis of unrelenting myocardial dysfunction in ischemic heart disease, with progression of initial myocardial damage from both adaptive and maladaptive changes leading to overt heart failure.¹⁶ Production of ROS occurs during ischemia reperfusion injury¹⁷ while ongoing chronic ischemia can lead to high and sustained levels of ROS caused by dysfunctional electron transport chain systems in the mitochondria. The accumulation of ROS can lead to diverse downstream negative consequences, including cardio-inhibition, hypertrophy, and matrix metalloproteinase stimulation. These intentionally compensatory processes can directly lead to progression of negative myocardial remodeling (Figure 1). The precise mechanisms are complex, but can be in part explained by their role as intracellular second messenger that mediate the remodeling effects of the renin-angiotensin and adrenergic systems.^{18,19} Furthermore, heightened oxidative stress can lead to unwanted modulation of lipids and proteins (e.g. low-density lipoprotein [LDL] cholesterol) and deposition of such oxidized LDL in atherosclerotic plaque, leading to further inflammation and progressive of atherosclerotic coronary artery disease,^{20,21,20} and further ischemic insult.

Anti-oxidant systems are known to be up-regulated in the setting of ischemia, with over-expression of superoxide dismutase (SOD) being associated with reduced infarct size.^{21,22} While such data may imply the harmful effect of ROS, other molecular studies paradoxically show that ROS-mediate adaptive mechanisms vital for cell survival, such as angiogenesis, up-regulation of glucose transport proteins, erythropoiesis, apoptosis, and inflammation during hypoxic episodes.^{23,24} Apart from identification of increased levels of ROS in the peri-infarct area²⁵, up-regulation of these molecules in the remote myocardium suggests more diffuse remodeling and cardio-inhibitory effects of ROS being operational.²⁶ Therefore, it is unclear whether complete suppression of potential adaptive mechanisms can promote or prevent disease progression. Endothelial dysfunction in the non-infarct related artery has also been noted^{27,28}, but the exact mechanisms of this phenomenon have not been elucidated and despite decades of research, treatment to improve endothelial function remains theoretical rather than a practical clinical application.

Hypertensive Heart Disease

Epidemiological studies have shown that hypertension increases the risk of developing heart failure by 2-fold in men and 3-fold in women.²⁹ Hypertension is also one of the most common risk factor for coronary artery disease, hence indirectly contributes to heart failure incidence. Hypertension in the absence of coronary artery disease is best known to cause adaptive left ventricular hypertrophy in response to increased pressure load. Treatment of blood pressure with diuretics, beta-blockers and ACE inhibitors may decrease the incident development of heart failure, and such effects can be in part due to reducing progression of such hypertrophic processes.^{30–32} The role of ROS in progression of direct myocardial changes from hypertrophy to clinical heart failure was suggested first based on experiments in guinea pigs. Vitamin E treated aortic-banded hearts showed more adaptive LV hypertrophy and less clinical signs of heart failure compared to sham animals with no supplementation.³³

Emerging evidence from animal (and now human) studies has implicated a role for neuronal, renal, and vascular endothelial reactive oxygen species for initiation and perpetuation of hypertension.^{34–38} As systemic endothelial oxidative stress can contribute to vascular stiffness, coronary endothelial dysfunction³⁹ may augment myocardial oxidative stress leading to further ischemic insult. Furthermore, poorly controlled blood pressure can also cause increased generation of ROS in the cardiomyocytes that can activate a wide array of intra cellular hypertrophic signaling redox sensitive kinases with or without interactions with neurohormonal systems.^{40–42} In fact, both sympathetic- and renin-mediated hypertension can cause myocardial negative remodeling utilizing oxidative stress as an intermediate. In addition, ROS have also been shown to mediate myocyte hypertrophy secondary to mechanical stress and stimulate mitochondrial permeability protein.⁴³ Such promoter of cell necrosis can create a vicious circle of recruitment of exogenous oxidative stress in the form of inflammation, which in turn worsens endogenous oxidative stress. Hence, hypertension can culminate through multiple pathways to create an oxidative stress load in the myocardium that mediates negative remodeling and ultimately maladaptive changes leading to heart failure.⁴⁴

Insulin Resistance: Type 2 Diabetes Mellitus, Metabolic Syndrome, and Obesity

Diabetes and insulin resistance is a significant risk factor for atherosclerotic heart disease and contributes to incident heart failure in the form of macro and microvascular atherosclerosis leading to ischemia. Apart from accelerating atherogenesis, diabetes mellitus can contribute to derangement of myocardial metabolism via intracellular accumulation of fatty acids and triglycerides leading to cellular lipotoxicity. Such derangement can lead to cellular apoptosis, contractile dysfunction, and relaxation abnormalities.^{45–48} Though altered

cardiac metabolism in diabetes mellitus has not been consistently reproduced in humans,^{49–51} epidemiological data shows an 8% increased risk of heart failure for every 1% increase in hemoglobin A1c (even after correcting for underlying coronary artery disease).⁵²

There is accumulating evidence to suggest that diastolic dysfunction may predate onset of systolic dysfunction in diabetic mellitus.^{53,54} The prevalence of pre-clinical diastolic dysfunction varies from 20–60% based on the criteria used. Epidemiologic data from the Olmstead County suggested that the presence of pre-clinical diastolic dysfunction predicts future onset of heart failure independent of age, body mass index, coronary artery disease, hypertension, and echocardiographic cardiac structural and functional abnormalities.⁵⁵ This finding recognizes the importance of identifying patients with underlying diastolic dysfunction as “Stage B heart failure” in the setting of diabetes mellitus.

Metabolic syndrome has been associated with future development of heart failure,⁵⁶ but more recent data have identified the presence of hyperglycemia, abdominal adiposity, and coronary artery disease as confounding factors rather than the syndrome itself.^{57,58} In other patients, metabolic derangements secondary to hyperglycemia and insulin resistance may play a role in what is called diabetic or insulin-resistance cardiomyopathy, but the nebulousness of these ill-defined clinical phenotypes have precluded more rigorous clinical investigations.⁵⁹

Specific mechanism(s) of oxidative stress that are pertinent in patients with diabetes mellitus are complex but may worth some discussion. Oxidative stress in diabetes mellitus can mediate direct downstream consequence like apoptosis, mediated through apoptosis stimulating kinase-1, and increased ceramide accumulation, and direct cellular, genetic and mitochondrial damages.^{60–63} Inflammatory markers like tumor necrosis factor alpha (TNF- α) are elevated in patients with insulin resistance, probably contributing to exogenous oxidative stress.^{64,65} Hyperglycemia-induced overproduction of SOD by the mitochondrial electron transport chain is suggested to be the first and important event that cascades further cellular derangements.⁶⁶ One mouse transgenic model showed protection from developing diabetic cardiomyopathy when the antioxidant protein metallothioneine was over-expressed.⁶⁷ Nitroso-oxidative stress has also been implicated with the finding of increased inducible nitric oxide synthase in streptozocin-induced diabetic rats.⁶⁸ Novel adipokines (proteins secreted from adipocytes) have been associated with the pathophysiology of insulin resistance and obesity. They can possess primary anti-inflammatory (such as adiponectin) and/or pro-inflammatory properties (such as resistin), and has shown to correlate with concentrations of plasma cytokines or cardiac-specific markers of dysfunction.^{69,70} The latter may potentially be perpetuating its deleterious effects through intracellular ROS. Epidemiologic studies have demonstrated that high levels of resistin are associated with increased incident heart failure during long-term follow-up,^{71,72} and even after adjusted for heart failure risk score.⁷³

Valvular Heart Diseases

Geometric changes and physical stretch in volume overload conditions as a result of valvular regurgitation can increase stretch mediated up regulation of intracellular ROS, contributing to oxidative stress in a heart that already is over utilizing the available substrates. Studies using myocardial strips from patients with mitral regurgitation have shown derangement of calcium-handling proteins and increased cytokines which could be attributed to oxidative stress.^{74–76} In patients with severe mitral regurgitation and normal ejection fraction, the total serum oxidant stress was significantly higher when compared to normal controls.⁷⁷ Also, the serum oxidant stress was higher in those with atrial fibrillation when compared to individuals in sinus rhythm while the oxidant stress index correlated with atrial size. Utilizing lateral endocardial biopsy specimens from patients undergoing mitral valve

surgery, protein content of tissue xanthine dehydrogenase and transiently modified xanthine oxidase were increased more than 5-fold in density in patients with mitral regurgitation when compared with that of control subjects⁷⁸.

Biomarkers of Oxidative Stress

The ability to measure markers of oxidative stress in various disease states has been challenging due to the non-specific nature of many of the markers. Myeloperoxidase, biopyrrins, F-2 isoprostanes, malondialdehyde and thiobarbituric acid reactive substances, oxidized LDL and uric acid have been studied, while newer markers like allantoin and S-nitrosohemoglobin are emerging as evidence of nitroso-reactive species.

The contribution of systemic oxidative stress in the development of heart failure following acute coronary syndromes can be demonstrated by detectable circulating markers of inflammation and oxidative stress. One of the most widely studied of such markers is myeloperoxidase (MPO), a hemoprotein released from neutrophils and monocytes that has been implicated in progression and destabilizing of atherosclerotic plaque.⁷⁹ *In vivo* magnetic resonance studies⁸⁰ have identified local expression of MPO in areas of plaque rupture in humans. In patients presenting with ACS, high levels of MPO (as a marker of inflammation and probably as a source of exogenous oxidative stress) has been associated with future development of cardiovascular death and ischemic events.^{81,82} Biomarker data from large clinical trials have confirmed the incremental value of MPO in short-term⁸³ as well as long-term risk prediction.⁸² Recent data also identified a MPO level greater than 670 pmol/L on admission, in the setting of non-ST elevation MI has a 1.6-fold increased risk of subsequent development of heart failure over 1-year follow-up.⁸⁴ These findings are indicative of the long term impact of the acute oxidative stress elicited as a response to an acute ischemic event.

Epidemiological and clinical trial data from hypertensive individuals have shown mixed results of association with increased levels of thiobarbituric acid-reactive substances (TBARS), 8-epi-isoprostanes, and biomarkers of lipid peroxidation when compared to normotensive individuals.^{85,86}

Uric acid has been used as a biomarker of oxidative stress due to its generation from xanthine oxidase (during generation of ROS in the Xanthine oxidase system). Hyperuricemia has been associated with worse clinical outcomes and animal studies suggested cardioprotective role of xanthine oxidase inhibitors. Yet, clinical trials have not reproduced the same in established heart failure.¹³ In a propensity matched control study using data from the Cardiovascular health study in 5,461 community dwelling older adults > 65 years, the presence of hyperuricemia was associated with incident heart failure particularly in the subgroups with normal kidney function (HR 1.23, 95% C.I-1.02–1.49, p=0.031), those not receiving thiazide diuretics (HR 1.2, 95% C.I-1.01–1.42, p=0.044), and without hyperinsulinemia (HR 1.35, 95% C.I-1.06–1.72, p=0.013).⁸⁷ The true incidence of structural abnormality in these studies is difficult to assess but the prevalence of risk factors makes it highly likely that most of them would qualify as Stage B heart failure. For example, in the Cardiovascular Health Study, only 7% had left ventricular hypertrophy by EKG criteria despite a high percentage with a diagnosis of hypertension.

Therapeutic considerations

As the extent of ROS might cause direct myocardial damage, anti-oxidant therapy appears to be a logical strategy to limit the amount of jeopardized tissue and lower the risk of subsequent development of heart failure in patients experiencing insults to the myocardium. In animal MI models, allopurinol has been shown to reduce infarct size,⁸⁸ limit left

ventricular cavity dilatation and dysfunction, along with a markedly reduced myocardial hypertrophy and interstitial fibrosis.²⁶ Similar findings were noted in an MPO knock-out mice model.⁸⁹ Clinical studies of anti-oxidant supplementation during acute ischemia are lacking in the contemporary era. In fact, small human clinical studies in the setting of coronary artery bypass surgery and MI have shown contradictory findings, and there have been no large scale randomized studies of xanthine oxidase inhibitors in the ACS or post-MI settings.^{90–92}

Statins, with their “anti-oxidant” properties, have been suggested to have a role in reducing reperfusion injury in the setting of an acute MI in the short-term.⁹³ By reducing recurrent ischemic events, statins should result in reduction of heart failure. There is limited clinical trial data in this regard. Moreover, markers of oxidative stress were often not analyzed, and their benefits have focused on those before overt heart failure ensues.⁹⁴ A randomized controlled study done at the University of Michigan in 774 ACS patients >65 years found that statin initiation <24 hours from admission reduced the incidence of in-hospital heart failure.⁹⁵ In another Japanese study comprising of mostly ST-elevation MI patients, similar hypothesis was studied with a 96 hour window showing benefit of statin therapy in the composite end point that was driven primarily by heart failure hospitalization and revascularizations.⁹⁶ Statins have been time tested in many trials to improve mortality and adverse clinical outcomes in patients with coronary artery disease and post myocardial infarction. The pleiotropic effects of statins broadly encompass all beneficial non-cholesterol lowering effects. Statins have been shown to reduce inflammation and oxidative stress through their effects on reducing isoprenylation. NADPH oxidase (NOX) is an important source of oxidative radical synthesis in the cells (more so in endothelial cells). Rac-1 protein acts as a second messenger immediately after NOX stimulation in the reactive oxygen species pathway and statins inhibit Rac1 as isoprenylated proteins are needed for the latter’s activation.⁹⁷ On the contrary, statins are postulated to bind and decrease levels of coenzyme Q and hence possibly increase oxidative stress. Though in patients with established heart failure, statins have shown inconsistent benefits (even in ischemic cardiomyopathy), they have at least not lead to worsening heart failure.⁹⁸ One explanation for the inconsistent benefit is reflected by the variable effects and lipid soluble properties of different statins. In the context of patients with coronary artery disease and post MI patients, data from Pravastatin or Atorvastatin Evaluation and Infection Therapy -- Thrombolysis in Myocardial Infarction 22 (PROVE IT TIMI-22) showed that 80 mg/d of atorvastatin significantly reduced the rate of hospitalization for heart failure (1.6% vs 3.1%; HR, 0.55; 95% CI, 0.35–0.85; $P = 0.008$) compared with pravastatin independent of recurrent MI or prior heart failure.⁹⁹ In the Incremental Decrease in Events through Aggressive Lipid Lowering (IDEAL) study, 80 mg/d of atorvastatin was associated with a 26% decrease in new HF events compared with 20 to 40 mg/d of simvastatin. Atorvastatin was associated with fewer heart failure events even in patients without a history of MI. However, none of these studies specifically analyzed markers of oxidative stress.¹⁰⁰

Omega 3-polyunsaturated fatty acids have antioxidant properties and have been extensively studied for both primary and secondary prevention of ischemic events. Supplementation in post MI patients has been shown to improve survival and sudden cardiac death.^{101–103} Other studies did not show any benefit in reducing adverse cardiovascular events.^{104,105}

Though many trials have not used heart failure as an outcome, data from HOPE (Heart Outcomes Prevention Evaluation) and HOPE TOO (Heart Outcomes Prevention Evaluation -- The Ongoing Outcomes) trials, that studied the impact of Vitamin-E supplementation in high risk for cardiovascular disease population, showed a paradoxical increase in heart failure incidence (RR, 1.13 [95% CI, 1.01–1.26]; $P = 0.03$) and heart failure hospitalizations (RR, 1.21 [95% CI, 1.00–1.47]).¹⁰⁶ Approximately 80% of trial participants had coronary

artery disease and up to 50% had a previous myocardial infarction. Such controversial data makes it difficult to interpret the role of oxidative stress but does emphasize the fact that oxidative stress might have an adaptive role.

There are no clinical trials data suggesting beneficial effects of antioxidants in hypertensive patients in preventing heart failure. Of note, 47% of the study population in HOPE TOO trial, which showed an increased heart failure incidence, had hypertension. Hypertension was also prevalent in the statin trials but incident heart failure as an outcome was never analyzed.

Multiple cardiovascular medications like ACE inhibitors, statins and angiotensin receptor blockers are postulated to have antioxidant properties and hence beneficial in diabetics, but there is no data from the clinical trials of these studies on incident heart failure in at risk individuals. The potent antioxidant vitamin E has been shown in diabetic rat model to improve ventricular function and attenuate myocardial accumulation of markers of oxidative stress (8-iso-prostaglandin $F_{2\alpha}$ and oxidized glutathione).⁶³ In a similar rat model, Vitamin E supplementation showed a significant reduction in lipid peroxidation, protein oxidation, increase in the antioxidant defense systems and apoptosis in the myocardium.¹⁰⁷ The adverse finding from the HOPE TOO study as detailed above remains puzzling and concerning. Approximately 40% were diabetic in this study.

Thiazolidinediones (TZDs) are insulin sensitizers that have come under recent scrutiny for adverse cardiac events. Yet, animal studies have shown that this class of drugs through their action on PPAR improve cardiac function in parallel with reduction of oxidative stress.¹⁰⁸ In a small human clinical trial, Von Bibra et al studied the effect of Rosiglitazone in comparison to a sulphonyl urea on a background of metformin therapy. Though both groups had similar HbA1c reductions, the glitazone group of patients at the end of 16 weeks had significantly lower levels of malonaldehyde and c-reactive protein.¹⁰⁹ They also showed improvement of tissue velocity from baseline. The future of glitazones to be used to reduce incident heart failure in diabetic patients might be limited due to their effects on fluid retention.

Conclusions

There is a common theme in our contemporary understanding of the contribution of oxidative stress in as contributors to the progression of “Stage B” heart failure. First, the large majority of our understanding of this topic is based on experimental findings from animal heart failure models, many of which are crude and simplistic. In humans, the process of oxidative stress is complex in humans, and largely dependent on the nature and extent of the insult, the underlying substrate vulnerability (i.e. host defenses in the form of “anti-oxidant” systems), as well as the contributing of co-existing conditions. In other words, what we learn from experimental models may not directly translate into human pathophysiology. Second, alterations in the overall “nitroso-redox system” can be appreciated as a disruption of the fine balance between oxidative and anti-oxidative processes at various stages of disease processes, but our ability to identify what and where the precise pathways to target is lacking (in part because many of these processes are sub-cellular and localized). In fact, even the best “markers” may only provide a “snap-shot” of oxidative destruction rather than an appreciation or identification of the underlying process of oxidative damage that is targetable for intervention. For example, whether lowering MPO or uric acid can lead to reduction in the future development of heart failure is still unproven. Third, our understanding of how different therapeutic interventions can affect different pathways of oxidative stress is seriously lacking, as they are rarely translatable from animal studies. Such disconnect can be best illustrated by the example of alpha-tocopherol, in which despite

being an “anti-oxidant” alpha-tocopherol may attenuate the anti-inflammatory effects of statins¹¹⁰ while being a pro-oxidant in the setting of an oxidative milieu.¹¹¹ The dosing of alpha-tocopherol used as supplements are often far lower than those tested in animal studies. Newer agents that selectively block NADPH oxidase enzymes NOX2 and NOX4 are being developed. As we unravel the specifics and identify the molecular pathways of maladaptive vs adaptive effects of reactive oxygen species, the future holds promise to make breakthroughs in manipulating oxidative stress in the heart.

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Figure 1.
Role of oxidative stress in progression of heart failure in ischemic heart disease.