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Review

Energy deficiency in the failing heart: Linking increased reactive oxygen species and disruption of oxidative phosphorylation rate

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Abstract

Heart failure is a complex syndrome of numerous dysfunctional components which converge to cause chronic progressive failure of ventricular contractile function and maintenance of cardiac output demand. The aim of this brief review is to highlight some of the mounting evidence indicating that augmented superoxide, related reactive oxygen species and other free radicals contribute to the oxidative stress evident during the progression of heart failure. While much of the source of increased reactive oxygen species is mitochondrial, there are other intracellular sources, which together are highly reactive with functional and structural cellular lipids and proteins. Bioenergetic defects limiting ATP synthesis in the failing myocardium relate not only to post-translational modification of electron transport respiratory chain proteins but also to perturbation of Krebs Cycle enzyme-dependent synthesis of NADH. Accumulation of pathological levels of lipid peroxides relate to dysfunction in the intrinsic capacity to clear and renew dysfunctional proteins. This review also features key limitations of human heart failure studies and potential clinical therapies that target the elevated oxidative stress that is a hallmark of human heart failure.

Keywords: Heart failure; Reactive oxygen species; Mitochondria; Krebs cycle enzyme; Antioxidant; Cardiolipin; Omega-3 PUFA

1. Introduction

Heart failure, a syndrome resulting in the chronic and progressive loss of ventricular systolic function, is one of the leading causes of death worldwide [1]. Despite significant advances in the treatment of heart failure, morbidity and mortality from heart failure remain high, with the overall one-year mortality estimated at 20–30% for mild to moderate failure and over 50% for severe heart failure. Heart failure may be categorised according to differing underlying etiology, including ischemic heart disease (coronary artery disease, myocardial infarction), cardiomyopathy (dilated, hypertrophic), valvular disease, alcohol/drug-induced heart disease and hypertensive heart disease. In economically advanced nations, ischemic heart disease accounts for almost 75% of heart failure cases [1].

Central to the loss of contractile function in heart failure is the inability of mitochondria to adequately supply the myocardium with ATP, resulting in energy deprivation to the cell and potentially necrotic/apoptotic cell death. It has been approximated that most mitochondrial ATP-derived energy supports myocardial contraction and the maintenance of ion homeostasis, 75% and 25% of cardiomyocyte energy consumption, respectively [2]. However, the underlying molecular causal events leading to metabolic dysfunction are poorly understood. The production of reactive oxygen species (ROS) has been shown to increase in the failing heart, and due to their close proximity to sites of superoxide production, mitochondrial proteins and lipids may be targets of oxidative damage in the failing heart. In this brief review, we describe the evidence linking increased mitochondrial ROS production in the failing myocardium and the potential for oxidative modification of mitochondrial proteins leading to dysfunction in ATP synthesis, and thus highlight potential targets for therapy.

2. Energy metabolism in heart failure: Krebs cycle versus respiratory chain

The heart is the greatest oxygen-consuming organ in the body, consuming around 8–15 ml O_2 min/100 g human heart

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tissue, with the capacity to increase to 70 ml under exercise conditions. [2]. Of this, 90% of available oxygen is consumed by mitochondria, which occupy over 30% of cardiomyocyte volume. Both fatty acid and carbohydrate metabolism converge at the Krebs cycle, with the generation of reduced redox carriers NADH and $FADH_2$ providing substrate for mitochondrial ATP synthesis. The Krebs cycle provides a major point of regulation of energy metabolism at three key enzymes, citrate synthase (CS), isocitrate dehydrogenase (ICDH) and α-ketoglutarate dehydrogenase (α-KGDH) due to their highly negative $\Delta G^{\circ\prime}$ values (standard free energy of ATP hydrolysis) [3]. Notably, the latter two of these three enzymes, along with pyruvate dehydrogenase, are linked to complex I via their supply of NADH, and thus serve NADH oxidation and the regulation of energy flow through the electron transport chain protein complexes, resulting in the reduction of oxygen to water. The proton motive force generated by this process drives ATP synthesis via the F_1Fo–ATP synthase complex (complex V) [3].

Reduced ATP synthesis, as measured by a lowering of state III (ADP-coupled) respiration has been demonstrated in isolated cardiac mitochondria from failing animal [4] and human [5] hearts, relative to non-failing controls. In an attempt to identify possible causes for this decline, many studies have focused on the measurement of the electron transport chain enzymes in a number of human cardiomyopathies. Most notably, complex I [6], complex III [7], and complex IV [8] have been identified as dysfunctional in end-stage human heart failure. A direct causal relationship, however, has proven elusive over the years, with a poor correlation between reduced complex activities and the severity of disease [7]. This may be partly explained by a large reserve capacity for activity of each respiratory protein complex. For example, up to 50% inhibition of complex I or IV activity is required before a significant decline in state III respiration is apparent [9].

In contrast, Krebs cycle enzymes involved in the regulation of substrate metabolism appear to exert more direct control over energy output, with a close correlation between the loss of α-KGDH activity and decreased state III respiration [13]. Due to their close interaction with complex I, a major site of mitochondrial superoxide formation, NADH-linked enzymes such as α-KGDH and ICDH may be susceptible to ROS-dependent perturbation. Reduced ICDH activity (~30%) has been demonstrated as an early marker of hypertrophy before the onset of ventricular dysfunction, in transgenic hypertrophic cardiomyopathic mice [10] and spontaneously hypertensive rats (SHR), [11]. The decline in α-KGDH, PDH and ICDH activity coincides with the formation of protein thiol adducts with 4-hydroxy-2-nonenal (HNE), a lipid peroxidation aldehyde formed via reaction between arachidonic acid and superoxide [12–16]. Reduced α-KGDH activity together with increased HNE-adduct formation has also been described in aged rats [9]. However, the specific role that perturbation of these enzymes may play in contributing to an energy deficit in the failing heart awaits detailed examination. Nevertheless it is apparent that diminished mitochondrial energy metabolism in the failing heart involves dysfunction in Krebs cycle regulation, NADH supply and activity of electron transport chain proteins.

3. Heart failure is a state of augmented oxidative stress

There is a large body of evidence that markers of oxidative stress are augmented in the plasma and tissue of patients with heart failure [17,18]. Due to the short half-life of oxygen free radicals, most studies have relied on the measurement of lipid oxidation products. However, these products (such as malondialdehyde, MDA) are often removed from the source and magnitude of the initial oxidative reaction, as they are intermediates that may undergo further conversion or reaction with proteins, and thus offer limited diagnostic marker specificity. Despite this, the convenience of assay simplicity, low cost and general association with oxidation rate has sustained their continued use. Elevated MDA concentration has been measured in the plasma of patients with moderate symptoms of congestive heart failure (NYHA III, left ventricular ejection fractions less than 40%), compared to age-matched non-failing controls (ejection fractions greater than 40%), which increased with the duration (years) of congestive heart failure [17]. A significantly high concentration of plasma MDA and reduced thiol has also been reported in heart failure patients with underlying coronary artery disease [19]. Mak and coworkers [20] demonstrated that total aldehydes are elevated in the plasma of heart failure patients, with a strong negative correlation between total aldehydes and contractility (+dP/dt) as well as increased time to relaxation (−dP/dt). Keith et al. [18] also reported a correlation between severity of heart failure and elevated lipid peroxides and MDA in both ischemic heart disease and dilated cardiomyopathy patients with end-stage heart failure. Another indirect marker of oxidative stress, 8-*iso*-prostaglandin $F_2\alpha$, derived from the oxidation of arachidonic acid, is increased in the pericardial fluid of patients in proportion to the severity of heart failure of ischemic and/or valvular disease origin [21].

Direct evidence of augmented myocardial superoxide production in the failing heart has been established in studies using electroparamagnetic spin resonance (EPR) spectroscopy ("spin-trapping"). Increased superoxide production has been demonstrated in the myocardium of explanted human heart failure tissue compared to non-failing donor heart muscle [22], confirming the results obtained in a pacing-induced animal model of heart failure [23]. However, in vivo, real time demonstration of increased cardiac superoxide metabolism in human heart failure is yet to be determined. It is also crucial to determine whether there are differences in superoxide metabolism according to the etiology, responsible cell type (smooth muscle, fibroblast, endothelial cell or cardiomyocyte) and progression of human heart failure.

4. Sources of oxygen radicals in the failing myocardium

A significant contribution of oxygen radical generation in the cardiomyocyte originates within mitochondria during oxidative phosphorylation. It is estimated that 1–2% of oxygen is incompletely converted to H_2O during electron transfer, resulting in the formation of ROS such as the superoxide ($-O_2^-$) and hydroxyl (OH^-) anions and hydrogen peroxide (H_2O_2) [24]. The reactivity of oxygen derives from its incomplete pairing of