Chapter

The Role of Neurohormonal Systems, Inflammatory Mediators and Oxydative Stress in Cardiomyopathy

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Abstract

Cardiomyopathy and more specifically the dilated cardiomyopathy, regardless of severity, is associated with activation of neuro-hormonal, cytokine and oxidative stress signaling pathways that alter the structure and function of cardiac myocytes and non-myocyte cells. These cellular alterations culminate in the morphological changes in cardiac structure termed as cardiac remodeling, a maladaptive process that contributes to further left ventricular dysfunction and heart failure development. This pathological progression is mainly driven by circulating mediators, in particular angiotensin II and norepinephrine. Natriuretic peptides, endothelin-1, vasopressin play also an important role in the progression of the cardiomyopathy. Cardiac inflammation, mediated by cytokines such as tumor necrosis factor-α (TNF-α), interleukins 1 (IL-1) and 6 (IL-6), as well as the oxidative stress were also shown to worsen the cardiac function. Although these pathways have been described separately, they are critically inter-dependent in the response to the development and progression of the dilated cardiomyopathy. This chapter reviews the cellular basis for cardiac remodeling and the mechanisms that contribute to these cellular abnormalities and, more broadly, to the pathophysiology of dilated cardiomyopathy, its progression and its potential treatments.

Keywords: Angiotensin II, Adrenergic signaling, Natriuretic peptides, Vasopressin, Prostaglandin, Endothelin, Nitric Oxide, Cytokines, ROS, Oxidative stress

1. Introduction

Cardiomyopathy is a group of diseases that affect the heart muscle [1]. As the disease worsens, symptoms of heart failure will occur including shortness of breath, fatigue, and fluid retention with pulmonary congestion and peripheral edema.

The majority of patients with heart failure have an underlying cardiomyopathy as the causative etiology. In the US, the most common cause of heart failure (HF) is a primary or secondary dilated cardiomyopathy [1, 2] encompassing approximately 60% of the HF cases.

Whether the etiology of the cardiomyopathy is idiopathic, inflammatory, viral, or ischemic, the pathological processes leading to the clinical syndrome of heart failure begin with myocardial injury. The hemodynamic consequences of the initial

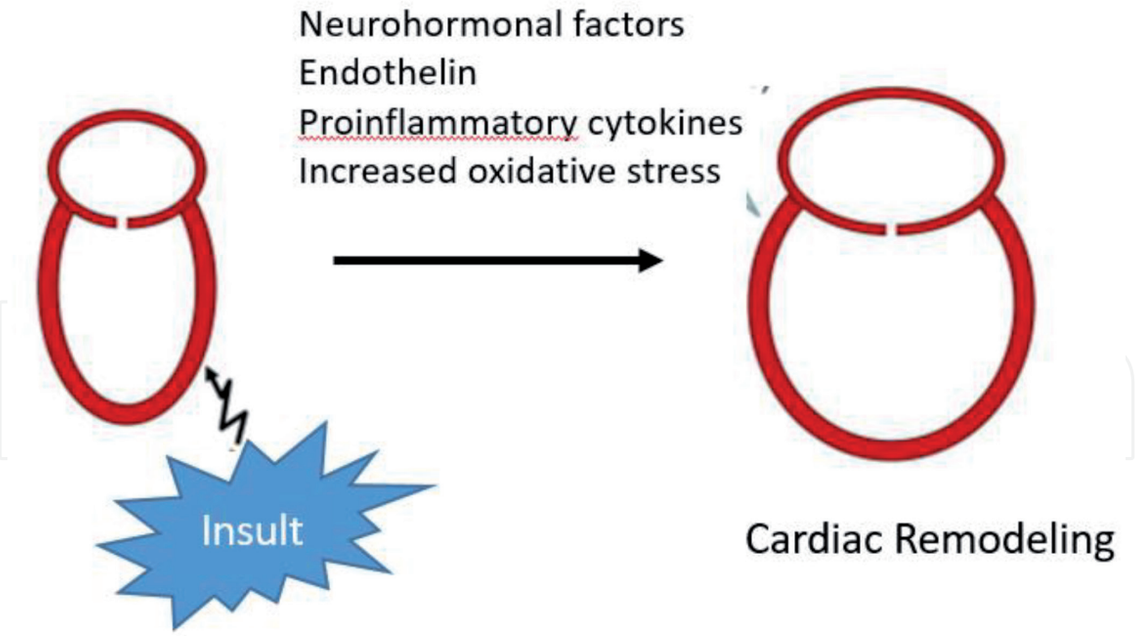

Figure 1.
Schematic representation of cardiac remodeling in dilated cardiomyopathy and HF.

injury will lead to a decline in myocardial contractility. The reduction of cardiac output will elicit a complex humoral and inflammatory response. The humoral response comprises two major components, the renin-angiotensin-aldosterone (RAA) pathway [3] and the sympathetic nervous (SN) system and is referred as neuro-hormonal activation [4]. Additional circulating mediators, such as natriuretic peptides, nitric oxide, endothelin and vasopressin also play a role in the circulatory adaptation to the heart failure state. Furthermore, the initial myocardial injury leading to the development of cardiomyopathy stimulates the production of cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [5]. Finally, oxidative stress, defined as an excess production of reactive oxygen species (ROS) relative to antioxidant defense, is enhanced in HF [6–9].

For neuro-hormonal and cytokine activation, these pathways are initially compensatory in response to acute injury but have ultimately maladaptive consequences on the long term, leading to cardiac remodeling and worsening heart failure.

Cardiac remodeling refers to changes in the size, shape, structure and function of the heart. Ventricular remodeling involves hypertrophy and apoptosis of myocytes, regression to a fetal phenotype, as well as modification of the extracellular matrix (**Figure 1**).

2. Neuro-hormonal activation in cardiomyopathy and heart failure

Heart failure associated with cardiomyopathy is a highly complex syndrome in which the insufficient cardiac output leads to neuro-hormonal activation and subsequent ventricular remodeling [10]. The characteristic hemodynamic abnormalities in patients with HF are a reduction in stroke volume with concomitant increase in systemic vascular resistance. In the early phase of heart failure, neuro-hormonal activation, with the stimulation of the SN and RAA systems, helps maintaining adequate cardiac output and peripheral perfusion. Sustained neuro-hormonal activation, however, will result in increased cardiac wall stress, ventricular dilatation and adverse remodeling effects [11, 12]. A variety of endogenously produced mediators, including norepinephrine, angiotensin II, aldosterone, endothelin and vasopressin

have been implicated as biologically active molecules which will contribute to disease progression of the failing heart.

Stimulation of these neuro-hormones and their receptors influences myocardial contractility, heart rate and conduction, cardiac metabolism, and cellular growth. Therefore, these cardiac neuro-mediator and neuro-receptors play a key role in cardiac physiology and myocyte function in healthy and diseased heart. For example, cardiac hypertrophy is produced by a combination of increased myocyte stretch, neurotransmitter release, and several types of autocrine, paracrine, and hormonal stimulation that mediate myocyte growth. In this context, the α-1 receptor pathway, the angiotensin II AT1 receptor pathway, the endothelin 1 receptor pathway, and the β-adrenergic receptor pathway have all been implicated in the pathogenesis of myocyte hypertrophy.

Activation of the adrenergic nervous system and the renin-angiotensin systems appears to be of primary importance in producing major adaptive cardiac receptor-signal transduction changes in the failing heart.

The most important modulated function mechanisms responsible for the stimulation of cardiac function appears to be the adrenergic signaling pathway. In addition to the adrenergic stimulation, an increase in plasma volume will take place, resulting in an increased ventricular preload as well as an increase in cardiac myocyte hypertrophy, which results in more contractile elements, increased wall thickness with a subsequent decrease in wall tension. The plasma volume increase is associated with stimulation of the RAA system and production of angiotensin II and aldosterone which will enhance sodium and water reabsorption in both the proximal and distal renal tubules [13].

2.1 Activation of the renin-angiotensin system with LV dysfunction

When the heart fails, the RAA system is activated as demonstrated with increased of the renin activity with production of angiotensin II and aldosterone [14–18].

The RAA system consists of a cascade of enzymatic reactions involving three components, angiotensinogen, renin and angiotensin-converting enzyme (ACE), which generate angiotensin (Ang) II as the biologically active product. Ang II binds to two types of specific receptors, angiotensin type-1 (AT1R) and type-2 (AT2R). Both receptor belong to the family of seven transmembrane domain heterotrimeric G protein-coupled receptors (GPCR). The majority of the deleterious mitogenic and hypertrophic actions of Ang II have been attributed to interaction with the AT1 receptor, which is the predominant receptor, while AT2 generally produces beneficial effects.

The deleterious effects of the activation of the RAA system are mediated primarily through increased circulating and tissue levels of the neuro-hormonal angiotensin II (**Figure 2**). Ang II is an extremely potent vasoconstrictor, acting directly on vascular smooth muscles and indirectly by increasing sympathetic tone [19, 20]. In addition, it produces sodium retention (through aldosterone and renal vasoconstriction), as well as fluid retention through anti-diuretic hormone [21, 22]. At the cellular level, Ang II promotes migration, proliferation, and hypertrophy, thus producing numerous adverse effects, including remodeling of the left ventricle, and development of endothelial dysfunction [23, 24].

Ang II promotes cardiac remodeling in several ways. By increasing arterial smooth muscle tone and causing salt and water retention, it increases cardiac preload and afterload. Also, increased wall stress is a potent stimulus for remodeling. In addition, Ang II has direct effects on the myocardium; it causes hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts as well as an increase

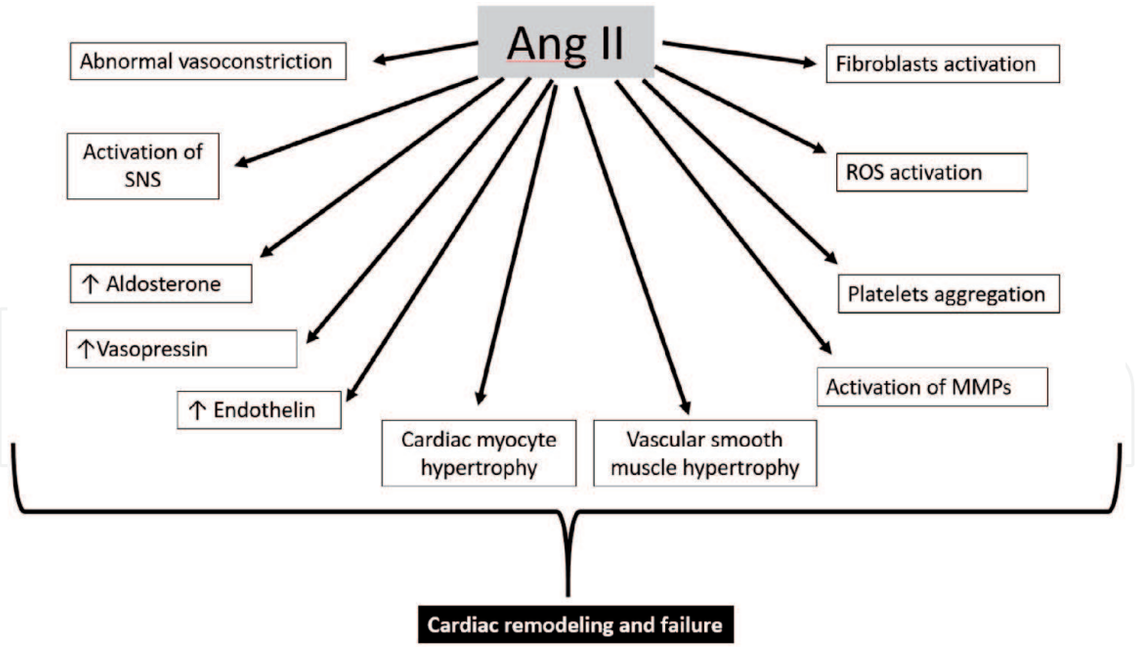

Figure 2.
Deleterious pathophysiologic effects of angiotensin II in dilated cardiomyopathy and heart failure. MMP: Matrix metalloproteinases, ROS: Reactive oxygen species.

in extracellular matrix deposition, [25] and stimulates the release of other growth factors, including norepinephrine and endothelin, which in turn stimulate cardiac remodeling [26]. These actions of Ang II are largely mediated through the angiotensin type 1 (AT1) receptor. Thus RAA system inhibition by ACE inhibitors or by angiotensin receptor blockers, attenuates many of the key hemodynamic, mechanical and functional disturbances crucial to the pathophysiology of cardiac dysfunction. ACE inhibitors are therefore a mainstay of therapy in patients with symptomatic and asymptomatic LV systolic dysfunction.

2.2 Sympathetic nervous system activation with LV dysfunction

Similarly to the RAA system, when the cardiac function fails, the adrenergic nervous system is activated. Numerous studies have documented elevated circulating norepinephrine levels with LV myocardial dysfunction [14–17, 27]. Even in asymptomatic patients with left ventricular dysfunction, an 35% increase in plasma norepinephrine was demonstrated [18]. In the failing heart, the increase of adrenergic activity seems to occur as a consequence of increased central sympathetic release at the pre-synaptic level [28].

Pre-synaptic facilitation of norepinephrine release by angiotensin II may also play an important role in adrenergic activation, [29] thus demonstrating a positive feedback of angiotensin II on cardiac adrenergic activity. Conversely, the adrenergic nervous system provides a major stimulus for activation of the RAA system, as activation of renal nerves by the SN system results in renal renin release [30, 31]. Thus activation of the adrenergic and renin-angiotensin systems appears to be co-regulated with cardiac dysfunction. Activation of one system stimulates the other and maneuvers that decrease the activity of one system may inhibit the other [32]. For example, administration of an ACE inhibitor to patients with heart failure with reduced ejection fraction (HFrEF) results not only in a decrease in plasma angiotensin II levels but also in a fall in circulating norepinephrine [33, 34].

Activation of cardiac β-adrenergic receptor (AR) represents the body's most powerful principle to increase cardiac contractility and heart rate [35] (**Figure 3**).

Adrenergic receptors are a family of G-protein-coupled receptors with nine members, three α1, three α2, and three β: β1, β2 and β3. When the first subdivision of adrenergic receptors was defined on the basis of pharmacological experiments, [36] the α-subtype was defined as the one that causes smooth muscle contraction, whereas the β-subtype mediates smooth muscle relaxation. Twenty years later, the β-receptors were subdivided again, into the β1-subtype, which stimulates cardiac muscle, and the β2-subtype, which relaxes smooth muscle [37].

The mammalian heart expresses all three β-adrenergic receptor subtypes [38–40]. In the healthy heart, the majority (i.e. 60–80%) of receptors are the β1-subtype in most species, while the β2-subtype accounts for a minor fraction of total βARs. A third β-adrenergic receptor subtype, the β3-subtype, was initially thought to be limited to adipose tissue, [40] but was later also detected in the heart [39]. This subtype is generally perceived as less important due to its very low expression level and relatively minor functional effects. There is evidence that the β1-subtype is preferentially located on cardiac myocytes, whereas the β2-subtype is expressed to a significant extent on non-cardiomyocyte cells, including vascular smooth muscle cells and synaptic nerve endings.

β1- and β2-adrenergic receptors are potent stimulators of cardiac contraction and relaxation in the human heart [35, 41]. As direct effectors of the sympathetic nervous system, they serve to rapidly adapt cardiac performance to an increased hemodynamic demand. Both β1 and β2 receptors couple to the stimulatory G protein Gs, thereby activating adenylyl cyclase. The formation of the second messenger cAMP then leads to activation of PKA (cAMP protein kinase A), which phosphorylates several key regulators of the cardiac excitation-contraction machinery. This includes phospholamban, [42] the L-type Ca-channel, [42, 43] the

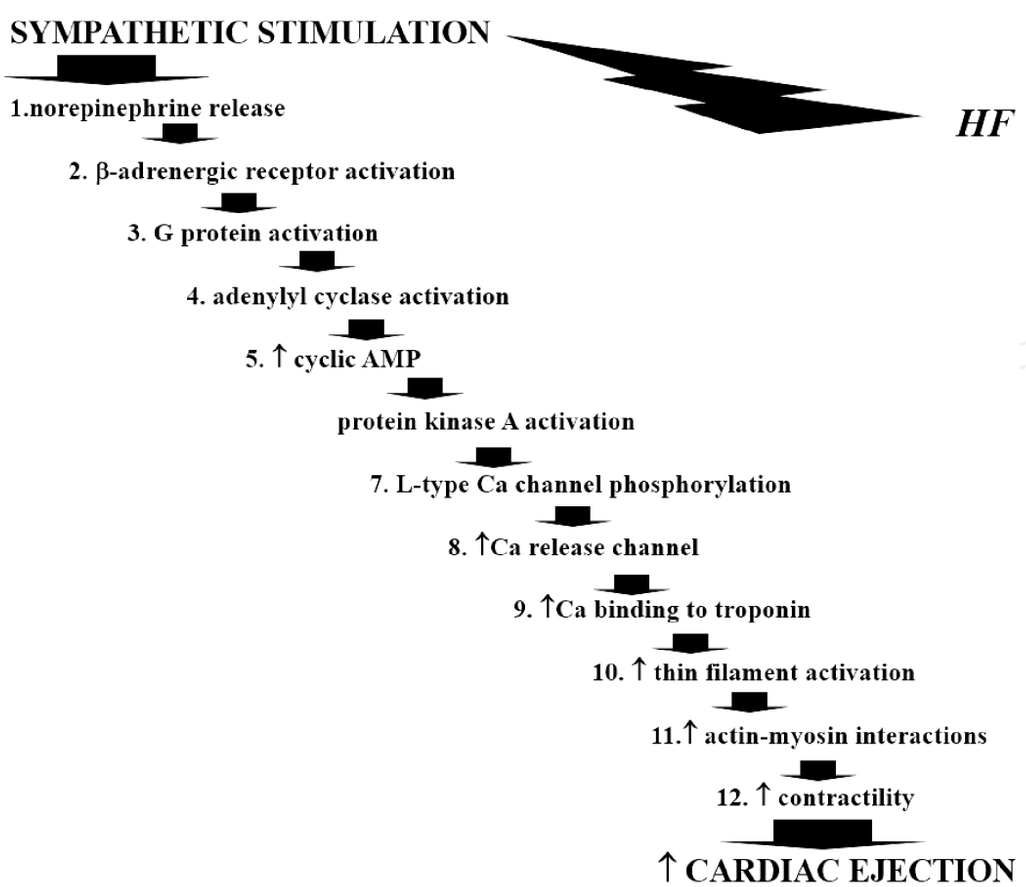

Figure 3.
Shematic representation of the cascade of reactions to increase cardiomyocyte contractility by the sympathetic nervous activation.

ryanodine receptor, [44] troponin T and I, [45] myosin binding protein C [46] and the small protein phosphatase inhibitor-1 [47]. These events lead to rapid changes of the cardiomyocyte calcium transient and enhanced myofilament sensitivity for calcium, resulting in a potent inotropic effect.

Data indicate that sustained stimulation of the β1-receptor system, which is ideally suited to provide short-term increases in cardiac function, causes marked structural and functional damage to the heart on the long term. Thus the chronic activation by the adrenergic system in heart failure represents a maladaptive response.

Also, the β-adrenergic signaling in dilated cardiomyopathy is characterized by the fact that it is desensitized in failing human hearts. In HF, there is a reduction of the density of β1ARs in in failing human myocardium, [48] a decrease of norepinephrine-re-uptake [49] and ultimately an increase in Ginhibitory (Gi) protein expression [50] and in GRK2 (βARK)-activity [51], a receptor kinase that phosphorylates and thereby inactivates βARs. The observed desensitization of βAR receptors represents an adaptation process to the highly increased levels of catecholamines in heart failure. This phenomenon is considered a beneficial readjustment of the signaling cascade to minimize the detrimental effects of chronic stimulation of the myocardium by catecholamines.

β-adrenergic receptor blockade is now regarded as one of the most effective therapeutic principle in dilated cardiomyopathy and heart failure [52].

Several large clinical trials with carvedilol, metoprolol succinate and bisoprolol have demonstrated a significant benefit in large placebo-controlled trial [53–55]. On the contrary, two β-blockers (xamoterol and bucindolol) have failed to significantly reduce mortality or even increased mortality [56, 57]. The most likely explanation for the failure of xamoterol is the pronounced partial agonism exerted by this agent [58]. Bucindolol led to a non-significant reduction of mortality in the BEST trial. Two main reasons might account for this finding. First, the study population differed markedly from the other large heart failure trials. It included a high percentage of African-Americans and of women, and both of these groups are underrepresented in other trials [56]. In the other trials, the beneficial effects of β-blockade were less pronounced compared with the effects in Caucasians [56]. Second bucindolol might display some degree of partial agonism.

2.3 Aldosterone

The pivotal role played by aldosterone in the pathogenesis of dilated cardiomyopathy and HF is well-recognized. Activation of the RAA system leads to marked elevations in plasma aldosterone levels, which have been shown to correlate with increased mortality [59]. Elevated aldosterone levels lead to excessive sodium retention, with expansion of the extracellular volume, worsening hemodynamic conditions, and a fall in cardiac output. Decreased renal blood flow further stimulates the RAA system, causing secondary hyperaldosteronism and further sodium retention. In addition, by contributing to hypokalemia and hypomagnesemia, aldosterone increases the sensitivity of cardiac tissue to arrhythmias, with a resultant increase in sudden death [60, 61].

A growing body of evidence suggests that aldosterone may contribute to endothelial dysfunction, possibly through reduced nitric oxide bioavailability [62]. Since the endothelium plays a critical role in the regulation of vascular tone, platelet aggregation and thrombosis, endothelial dysfunction predicts subsequent cardiovascular events [63]. Furthermore, aldosterone contributes to the development of HF by promoting myocardial fibrosis. In vitro studies have demonstrated that

administration of aldosterone to cardiac fibroblasts significantly enhances collagen synthesis, [64] a finding that has been confirmed in rat models [65]. Another potentially harmful effect of aldosterone is its ability to blunt baroreflex response. Administration of aldosterone to dogs [66] and to healthy human volunteers [67] resulted in an elevation in the threshold for baroreflex activation and a reduction in peak discharge rate. Finally aldosterone has been shown to promote the activation and aggregation of platelets and to enhance arteriolar constriction [68].

The clinical trial Randomized Aldosterone Evaluation Study (RALES) demonstrated the benefits of aldosterone receptor blockade in HF. 1633 patients with NYHA Class III-IV chronic HF, already receiving ACEIs, were randomized to spironolactone versus placebo [69]. The relative risk of death was reduced by 30% over two years (RR 0.7, 95% CI 0.60–0.82; $p < 0.001$) with a 35% reduction in HF hospitalizations and an improvement in functional class.

2.4 Endothelin

Endothelin is a potent vasoconstrictor peptide and its synthesis is stimulated by hypoxia, ischemia, neurohormones (norepinephrine, angiotensin II, arginine vasopressin), and inflammatory cytokines [70–72].

Tissue and plasma levels of endothelin-1 and its precursor (big endothelin-1) are elevated in patients with cardiomyopathy and HF [73–78]. These increases are due to increased endothelin synthesis primarily in the pulmonary vascular bed [79] and the myocardium [80]. The vascular distension seen in HF (especially in the pulmonary vascular bed) appears to a stimulus for increased endothelin-1 production [81]. Another potential contributor to the increased endothelin-1 concentration in HF, is the downregulation of endothelin-B receptors, which has been observed in the lung tissue of experimental animals with HF [82, 83]. Endothelin B receptors appear to play a role in the clearance of endothelin-1. Pulmonary vascular tone in HF are largely mediated by endothelin-A receptor [84, 85]. Increased levels of endothelin-1 are associated with increased angiotensin II levels, more advanced HF symptoms, worse hemodynamics, and decreased survival [70, 75, 78, 81, 85–94].

Endothelin-A receptor antagonists prevent remodeling, improve LV function, and prolong survival in rats [95–97].

The Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Study (VERITAS), the largest clinical trial of an endothelin receptor antagonist for ADHF, enrolled 1435 patients. Patients treated with tezosentan experienced significant reduction in pulmonary arterial pressures and pulmonary capillary wedge pressures as well as an increase in cardiac index. Despite these significant improvements in hemodynamics, use of tozosentan did not improve the composite primary end point of dyspnea at 24 hours, worsening HF or death at 7 days [98].

The Resource utilization Among Congestive Heart Failure Study (REACH) was another clinical trial investigating the effects of bosentan in 370 patients with advanced HF and an LVEF <35%. The trial was stopped prematurely due to elevations in liver transaminases. At the time of the study termination, there was no significant differences in outcomes between the bosentan compared to the placebo group. Nevertheless, a post-hoc analysis of 174 patients who completed the 6-month follow up demonstrated significant clinical improvement ($p = 0.045$) [99].

Finally, the Enrasentan Cooperative Randomized Evaluation (ENCOR) trial studied enrasentan, a dual A/B endothelin receptor antagonist in 419 patients with stable NYHA Class II and II with LVEF ≤35%. There was no significant improvement in the primary endpoint of clinical HF score with the active drug [100].

2.5 Vasopressin

Arginine vasopressin (AVP) is a peptide hormone that is elevated in heart failure, and associated with a poor prognosis [18, 101]. AVP contributes to fluid retention and hyponatremia [102, 103]. AVP exerts its cardiao-vascular effects trough two receptors subtypes V1a and V2. V1a is found on vascular smooth muscle cells and cardiac myocytes. Whereas, vasopressin V1A receptors mediate vasoconstriction, positive inotropic and mitogenic effects, the V2 receptors inhibit free water clearance [104–106]. Stimulation of the V1a-receptor, initially leads to increased myocardial protein synthesis resulting in myocardial hypertrophy [107, 108]. V2-receptors are found in the distal tubule of the kidney, and their activation results in water retention via upregulation of aquaporin channels [104, 109].

The control of Vasopressin secretion is complex and involves both osmotic and nonosmotic stimuli [110]. Factors causing vasopressin release include plasma osmolality, intra-cardiac and arterial pressures, as well as Angiotensin II levels [111]. Under most circumstances, Vasopressin is coupled to osmolality levels, making osmo-receptor the major determinant of Vasopressin release.

When the pressure within the heart or arterial vessels decreases, tonic inhibitory restraint of vasopressin is diminished and plasma vasopressin levels rise. Inversely, elevated blood pressure leads to decrease plasma vasopressin level [112–114].

Despite their hypo-osmolar hyponatremia state, patients with HF have inappropriately elevated plasma vasopressin levels [101, 115, 116].

Agents that antagonize V1A receptor reduce vascular tone and the mitogenic myocardial effects of AVP. Because V2 antagonists increase aquaresis, the addition of an AVP V2 antagonist improves free water clearance, and reduces hyponatremia.

Conivaptan is a dual V1a/V2 receptor antagonist that has been investigated in the treatment of HF. One hundred and forty-two patients with NYHA class III or IV HF were randomized to either a single IV dose of conivaptan or placebo and evaluated over 12 hours for changes in hemodynamics. Both capillary wedge pressure and right atrial pressure were significantly reduced in the treatment group compared to placebo. However, cardiac index did not improve [117].

The EVEREST study investigated whether short term and long term blockade of the V2 receptor with Tolvaptan is beneficial in patients with HF. The results confirmed that Tolvapatan when added to standard therapy improved symptoms and signs of HF, however no benefit was observed on all-cause mortality or the combined endpoint of cardiovascular mortality or hospitalization for worsening HF The drug had no significant effect on long term LV remodeling in patient with LVEF <30% [118].

2.6 Natriuretic peptides

While the activation of the RAA and SN system is detrimental in HF, other counter-regulatory pathways are activated in HF, including the natriuretic peptide (NP) system. The NP system consists of atrial (ANP) [119]. B-type (BNP) [120] and C-type (CNP) NPs. These hormones regulate blood pressure and fluid homeostasis [121–123]. ANP is synthesized and secreted in atria. BNP is secreted from the ventricles in response to mechanical stretch and increased intra-cardiac volume and pressure, while CNP mostly originates from endothelial and renal cells and is secreted in response to endothelium-dependent agonists and pro-inflammatory cytokines [121, 122, 124].

NPs activate three transmembrane receptors: natriuretic peptide receptor (NPR)-A, NPR-B and NPR-C.27 The binding of NPs to type A (NPR-A) and type B

(NPR-B) receptors activates guanylate cyclase, increasing levels of the second messenger cyclic guanosine monophosphate (cGMP) and its effector molecule protein kinase G. This induces natriuresis, diuresis, vasodilation and inhibition of the RAA and the SN systems, as well as antifibrotic, antiproliferative and antithrombotic effects [121, 122, 124].

Blockade of NP breakdown by neprilysin inhibitors has, therefore, been investigated [125]. Oral neprilysin inhibitors, such as candoxatril, produced clinical benefit in patients with chronic HF [126, 127]. However, candoxatril has no effect on, or increases, systolic BP (SBP) in normotensives, an effect prevented by enalapril, and does not reduce BP in hypertensive subjects, probably because its vasodilatory effect may be offset by an increased activity of the RAAS and sympathetic nervous system and/or by downregulation of NP receptors [128, 129]. In addition, since neprilysin acts on numerous physiological targets, the effect of candoxatril was broader than anticipated [128].

Neprilysin inhibition results in activation of the RAAS, therefore, in order to be clinically beneficial, neprilysin inhibition requires concomitant inhibition of the RAAS [130]. Vasopeptidase inhibitors are dual inhibitors of ACE and neprilysin and, therefore, emerged as a new therapeutic option in HF and hypertension, but their pharmacological profile is complex [131]. Omapatrilat was more effective than either lisinopril or amlodipine in reducing BP, [131] but in patients with chronic HF it was not more effective than enalapril in reducing the combined risk of death or hospitalization for HF requiring intravenous treatment [132]. However, omapatrilat was discontinued due to the risk of angioedema, possibly due to excessive inhibition of bradykinin degradation (presumably via neprilysin, ACE and aminopeptidase P) [133, 134].

Sacubutril/Valsartan is an oral combination medication consisting of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan. The combination is called angiotensin receptor-neprilysin inhibitor (ARNi). The PARADIGM-HF trial compared sacubitril/valsartan to enalapril [37] in heart failure patients with reduced LVEF. The trial was stopped early after a prespecified interim analysis revealed a significant reduction in the primary endpoint of cardiovascular death or heart failure in the sacubitril/valsartan group compared to enalapril [135].

3. Inflammation

Ample evidence exists that dilated cardiomyopathy and HF are associated with the activation of the immune system resulting in elevated levels of pro-inflammatory cytokines. In patients with cardiomyopathy and HF, elevated levels of tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) are found [136–138]. The best characterized inflammatory molecule in DCM and HF is TNF-α.

The importance in understanding the role of inflammation in the pathogenesis of dilated cardiomyopathy arises from the observation that many aspects of the development of dilated cardiomyopathy can be explained by the biological effects of pro-inflammatory cytokines. Cytokines, when expressed at sufficiently high concentrations, can mimic the development of the dilated cardiomyopathy phenotype features, which include left ventricular remodeling and dysfunction with myocyte hypertrophy, changes in fetal gene expression, alteration of the extracellular matrix, and cardiac myocyte apoptosis [139–143]. As it is the case with neuro-hormonal activation, overexpression of cytokines results in cardiac direct toxicity [144, 145].

Clinically, the progressive increase in inflammatory cytokine levels is in direct relation with NYHA functional class deterioration. Also, data from the VEST trial demonstrated a strong correlation between survival and TNF-α levels [146]. Similar findings were observed with levels of IL-6 [146].

One of the marks of pro-inflammatory cytokines is their ability to depress LV function. Preclinical studies in rodents showed that circulating levels of TNF-α that correspond with those observed in patients with HF were sufficient to produce negative inotropic effects [139]. Also, transgenic mice with TNF-α overexpression studies resulted in depressed LV function [140, 147].

The cytokine hypothesis proposes that cardiomyopathy progression is an inflammatory process and that amplification of pro-inflammatory cytokines worsens left ventricular dysfunction and facilitates the development of HF [10, 148].

There is significant cross-talk between the neuro-hormonal and the cytokine systems [144]. Data have shown that these cytokine signaling pathways augment local neuro-hormonal activation, which in turn promotes the enhanced expression of these same cytokines [144]. For instance adrenergic stimulation as seen in HF, induces myocardial TNF-α expression, [149] which in turn attenuates beta-adrenergic responsiveness. Also, Angiotensin II is known to activate nuclear factor-kappa B (NF-kB), a redox-sensitive transcription factor that is important in stimulating the myocardial inflammatory response, [150] including activation of inflammatory cytokines, NO, chemokines and cell adhesion molecules [150, 151].

Clinical studies that have examined the effect of ACE-inhibitors have shown that while ACE inhibitors have mixed results in terms of inhibiting pro-inflammatory cytokines, Angiotensin Receptor Blockers (ARBs) have consistently led to significant decrease in circulating levels of inflammatory mediators such as TNF-α in patients with cardiomyopathy and HF [152, 153]. Similar findings have been reported with the use of beta-blockers in experimental animal models and clinical heart failure studies. Beta-adrenergic blockade with a beta-1-selective adrenergic antagonist has demonstrated partial inhibition of the expression of pro-inflammatory mediators in an experimental model of post-infarct LV heart failure remodeling model [55]. In sub-group analysis of the MERIT-HF, treatment with metoprolol did not lead to a decrease in the level of pro-inflammatory mediators, whereas in a different trial, the use of carvedilol, a non-selective beta-1 and beta-2 adrenergic antagonist with anti-oxidant properties resulted in a significant reduction in the production of TNF-α [154–156]. These data suggest that here are interactions between the renin-angiotensin and adrenergic systems with pro-inflammatory cytokines.

3.1 Tumor necrosis factor-α (TNF-α)

TNF-α is recognized as a cytokine with pleiotropic biologic capacities [157, 158]. TNF affects growth, differentiation and function of every cell type, including cardiomyocytes.

TNF-α binds to a lower affinity the type 1 receptor called TNFR1 and a higher affinity type 2 receptor called TNFR2. Intracellular signaling occurs as a result of TNF-induced cross-linking (oligomerization) of the receptors. Previous studies have identified the presence of both types of TNF receptors in the non-failing and failing heart [159, 160]. Normal myocardium does not contain TNF-α. In the failing heart, with the increased expression of TNF-α, the receptors for TNF-α, TNFR1 and TNFR2, are downregulated, [159] similar to the β1 adrenergic receptor downregulation and the SN system in heart failure.

The majority of the deleterious effects of TNF-α are coupled to activation of TNFR1, whereas activation of TNFR2 appears to exert protective effects. Activation of TNFR1 is responsible for mediating negative inotropic effects, and cardiac myocyte apopotosis [142, 159, 161]. In contrast activation of the type 2 TNF receptor appears to protect the cardiomyocyte against hypoxic stress and ischemic injury [159, 162]. Previous studies have shown that both TNFR1 and TNFR2 exist in the circulation as circulating soluble receptors and are referred as sTNFR1 and sTNFR2. Elevated levels of sTNFR1 and sTNFR2 have been shown to be strong independent predictors of adverse outcomes in hospitalized HF patients [146, 163, 164].

Early in the disease process, much of circulating TNF-α is derived from immune cell line such as activated macrophages. However, late in disease progression much of the TNF-α is produced by the cardiac myocytes themselves [165]. Transgenic mice overexpressing TNF will develop an early inflammatory myocarditis that later progresses to myocyte hypertrophy, left ventricular dilatation, and progressive left ventricular dysfunction [140]. In this model, TNF also activate expression of matrix metalloproteinases, [166] which contribute to LV remodeling and dilatation. Administration of TNF in experimental animal models at concentrations comparable to those observed in clinical heart failure, produces significant declines in myocardial contractility with worsening left ventricular function [139]. In another rat model, the infusion of TNF, caused progressive left ventricular enlargement with significant degradation of the extra-cellular matrix [167].

The negative inotropic effects of TNF-α on cardiac myocytes are mediated through increased expression of iNOS with production of nitric oxide [168, 169] and activation of norepinephrine and angiotensinogen II. TNF-α was shown to increase the expression of the AT1 receptor in cardiac fibroblasts by a mechanism dependent on NF-ĶB, thereby augmenting Ang II effects on cells via an increase in AT1 receptor density [170]. Increase of Ang II stimulates the synthesis of cardiac fibroblasts and the inhibition of MMP2 activity. Ang II activates NF-ĶB, via the AT1 receptor and thus increases the production of pro-inflammatory cytokines [171]. Transgenic mice with TNF-α overexpression demonstrate increased levels of both ACE and Ang II [172]. These different studies support the presence of cross-talk between the RAA and cytokine signaling pathways. TNF-α also augments sympathetic activation. Isoproterenol administration in rodents increases the expression of TNF-α, IL-1β, and IL-6 [163, 173]. These studies support that the sympathetic nervous system regulates positively the cytokine gene expression, while cytokines potentiate the effects of catecholamines on the myocardium.

3.2 Interleukin-1 (IL-1)

There are three members of the interleukin-1 (IL-1) family: IL-1α, IL-β, and IL-1 receptor antagonist (IL-1Ra) [158]. IL-1α and IL-β are agonist and IL-1 Ra is a specific receptor antagonist. Similar to TNF-α, IL-1β appears to be activated in response to stressful environmental stimuli [136, 174].

IL-1β expression is elevated in the myocardium of failing hearts and is present at high circulating concentrations in patients with dilated cardiomyopathy. The primary sources of IL-1β within the myocardium are macrophages and cardiac fibroblasts [175, 176]. Similar to TNF-α and IL-6, IL-1β inhibits fibroblast-mediated production of collagen and suppresses proliferation of fibroblasts [177, 178]. IL-1β also increases the expression and activity of MMP's which cause destruction of the fibrillary collagen network. Moreover, IL-1β induces the expression of nitric oxide synthase. Furthermore, IL-1β causes cardiac myocytes hypertrophy and inhibits the expression of the fetal genes, β-MHC and skeletal α-actin. In summary, IL-1β alters

the phenotype and genotype of cardiac myocytes, [177, 178] while also disrupting the composition of the extracellular matrix.

3.3 Interleukin IL-6

Similar to TNF-α and IL-1β, levels of IL-6 are elevated in patients with dilated cardiomyopathy and HF. The degree of IL-6 elevation correlates to heart failure severity and prognosis [179]. IL-6 signals through its receptor, IL-6R, associates with the gp130 cytokine receptor, and forms a membrane complex that activates downstream signaling pathways. The source of IL-6 production are cardiac myocytes, fibroblasts and mononuclear inflammatory cells [175]. IL-6 stimulation of fibroblasts decreases collagen synthesis and increases MMP activity, contributing to disintegration of extracellular matrix [175]. Transgenic mice expressing both IL-6 and IL-6R develop LV hypertrophy, resulting from activation of the gp130 receptor. Other cytokines within the IL-6 family, including cardiotropin 1 and leukemia inhibitor factor, induce cardiomyocyte hypertrophy [180–182]. Thus IL-6 participates to the alterations of the extracellular matrix and cardiomyocyte hypertrophy.

3.4 Nitric oxide synthases

While the contributions of neuro-hormonal and cytokine signaling pathways to ventricular remodeling are well-established, cytokine-mediated increase in inducible nitric oxide synthase may be an important downstream pathway that contributes significantly to the cardiac remodeling [183, 184]. There are three known members of the nitric oxide synthase (NOS) family, [183] neuronal NOS (nNOS or NOS 1), inducible NOS (iNOS or NOS II) and endothelial NOS (eNOS or NOS III). Cardiac myocytes in the normal heart express mainly eNOS [185]. However, studies have shown that iNOS is expressed at high levels in the myocardium of failing hearts [186–188].

Evidence from in vivo studies supports a detrimental effect of iNOS in the failing heart. Cardiac specific over-expression of iNOS in transgenic mice leads to cardiac fibrosis, dilatation and premature death, [189] although Heger et all reported no demonstrable phenotype accompanying iNOS overexpression in the mouse heart [190]. Sam et al. demonstrated that 6 months after an MI, the extent of LV dysfunction and myo-cardiac apoptosis was significantly diminished in iNOS knockout mice, supporting a detrimental role of iNOS in this ischemic cardiomyopathy model [191]. These data suggest that iNOS may play an important role in ventricular remodeling and cardiac myocyte apoptosis. Supporting this concept, iNOS expression in end-stage failing heart normalized after placement of ventricular assist device [188].

3.5 Anti-inflammation treatment in cardiomyopathy and heart failure

Despite an abundance of evidence implicating the inflammatory pathway in HF and cardiomyopathy, and numerous examples of anti-inflammatory therapies improving HF in experimental animal models, these agents have been largely unsuccessful in treating human cardiomyopathy and HF.

3.5.1 Prednisone

Prednisone was shown to suppress TN-Fα biosynthesis at the translational and transcriptional levels. Parrillo et al. randomized 102 patients to prednisone versus placebo to 102 patient with dilated cardiomyopathy. Following three months of therapy, an increase in LVEF of >5% was observed in 53% of patients receiving prednisone. All patients were categorized prospectively in two separately

randomized subgroups. "Reactive" patients (n = 60) were those who had fibroblastic (n = 36) or lymphocytic (n = 2) infiltration or immunoglobulin deposition (n = 16) on endomyocardial biopsy, a positive gallium scan (n = 7), or an elevated erythrocyte sedimentation rate (n = 18). Nonreactive patients (n = 42) had none of these features. At three months, 67 percent of the reactive patients who received prednisone had LVEF improvement, as compared with 28 percent of the reactive controls (P = 0.004) [192]. The data of this study suggested that patients with idiopathic dilated cardiomyopathy may have some improvement when given a high dose of prednisone. However, the increase in the ejection fraction was overall small with limited duration, and the side effects were important. In conclusion, prednisone was judged to have only a marginal clinical benefit, and should not be administered as standard therapy for dilated cardiomyopathy.

3.5.2 Etarnecept

TNF-α inhibitors are immunomodulators that are used in a wide variety of rheumatological/autoimmune diseases including RA, [193, 194], inflammatory bowel disease, [195] and psoriasis/psoriatic arthritis [196].

Etanercept is a human recombinant TNF-α receptor that binds and inactivates circulating TNF-α molecules.

Preclinical experimental studies have demonstrated that etanercept reversed the deleterious negative inotropic effect of TNF-α [139, 197].

A series of phase I clinical studies in patients with moderate to advanced HF showed improvements in 6 –minute walk distance, quality of life and LV cardiac function following treatment with etanercept for up to 3 months [198, 199]. Subsequently, two large multicenter quality of life clinical trials RENAISSANCE (Randomized Etanercept North American Strategy to Study Antogonism of Cytokines) and RECOVER (Research into Etanercept Cytokine Antagonism in Ventricular Dysfunction) were conducted in HF patients with NYHA class II-IV and demonstrated no clinical benefit [200]. The RENEWAL (Randomized Etanercept World-wide EvALuation) clinical trial with all cause mortality and hospitalization for HF as primary end-point, did not reveal any benefit either with etarnecept [201].

3.5.3 Infliximab

Infliximab is a chimeric monoclonal antibody that binds and inactivates circulating TNF-α that has been shown to be effective in the treatment of Crohn disease and rheumatoid arthritis. The ATTACH clinical trial (Anti-TNF-α Therapy Against CHF), a phase II study enrolled 150 patients with NYHA class III-IV HF. The results of this trial revealed no beneficial effects on clinical status with infliximab. There was even a dose related increase in mortality and HF hospitalizations with infliximab when compared to placebo at 14 and 28 weeks, resulting in early termination of the trial [202].

3.5.4 Intravenous immunoglobulin

Although the exact mechanism of intravenous immunoglobulin (IVIg) therapy is not known, IVig therapy is being used in a wide range of immune-mediated disorders, such as dermatomyosis, Kawasaki and multiple sclerosis [203, 204]. Based on an initial report that IVIg was beneficial in acute cardiomyopathy, [205] Gullestad et al. conducted a double-blind clinical trial with IVIg for 26 weeks in 47 patients with Class II-III HF, who were receiving standard HF therapy including ACE inhibitors and β-blockers. In this study, IVIg induced a marked rise in plasma

levels of the anti-inflammatory mediators (IL-10, IL-1 receptor antagonist and soluble TNF receptors) and was associated with a significant increase in LVEF [206]. Thus in this small study, therapy with IVIg was potentially effective in patients with cardiomyopathy and HF, but these results should be confirmed in a larger subset of patients and also needs to examine the effect on morbidity and mortality of this therapy.

4. Oxydative Stress

Oxidative stress, defined as an excess production of reactive oxygen species (ROS) relative to antioxidant defense (**Figure 4**), has been shown to play an important role in the pathophysiology of cardiac remodeling in HF, [6–9, 207]. Specifically, ROS activate a broad variety of hypertrophy signaling kinases and transcription factors and mediate apoptosis. They also stimulate cardiac fibroblast proliferation and activate the matrix metalloproteinases (MMPs), leading to the extracellular matrix remodeling. Moreover, ROS can directly impair the cardiac contractile function by modifying proteins involved in excitation-contraction coupling. These cellular events are involved in the development and progression of maladaptive myocardial remodeling and failure.

Oxidation products of several organic molecules including lipids, proteins, and nucleic acids have been implicated in the pathogenesis of dilated cardiomyopathy and their levels are found to be increased in heart failure. The severity of heart failure and levels of oxidative stress increase concurrently, which suggests that oxidative stress could be utilized as a biomarker for dilated cardiomyopathy progression.

Oxidative stress is associated with increased production of ROS and reactive nitrogen species (RNS), diminished nitric oxide (NO) bioavaibility and reduced superoxide dismutase (SOD), glutathione peroxidase and catalase activity. ROS are formed as products of oxidation–reduction reactions and include free radical molecules such as superoxide (O2−), hydroxyl radical (OH−), lipid peroxyl and non-free radical species like hydrogen peroxide (H2O2). RNS like (ONOO−) are

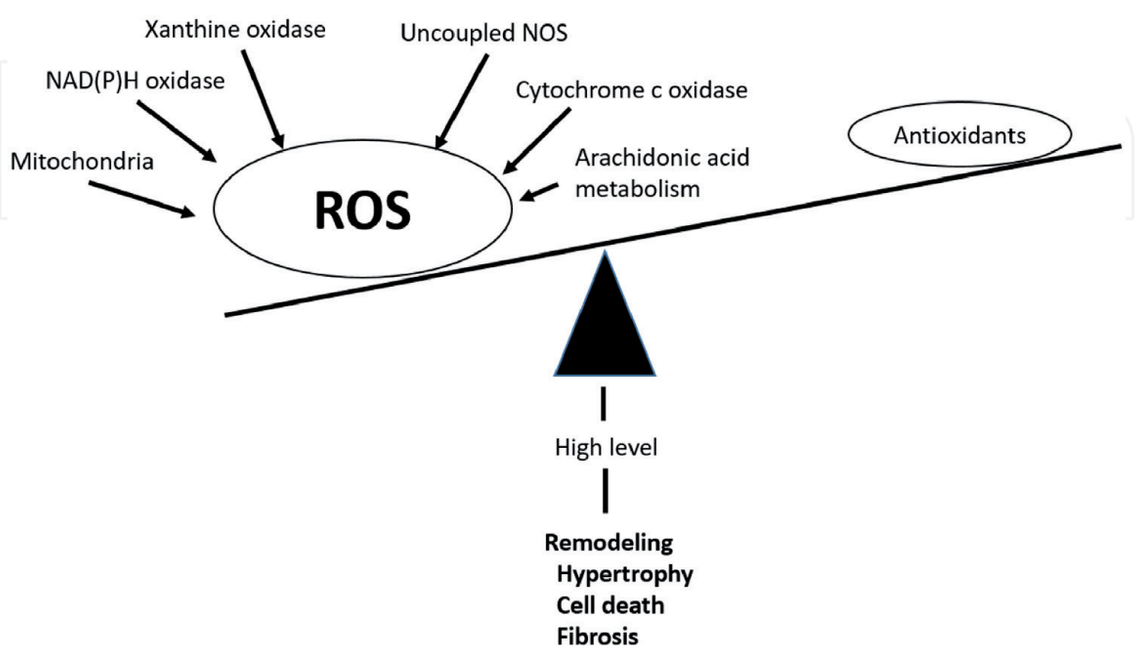

Figure 4.
Source of reactive oxygen species (ROS) and their pathophysiological role in heart failure. NOS: Nitric oxide synthase.

formed by the reaction between nitric oxide (NO) and O2– [208]. Cellular ROS are generated predominantly as by-products of mitochondrial respiration, NADPH oxidase, endothelial nitric oxide synthase (eNOS) [209] and xanthine oxidase activity [210].

Clinically, oxydative stress markers have prognostic values as they correlate with worsening NYHA functional class and cardiac dysfunction [211, 212]. Several studies have demonstrated that the lipid peroxidation products such as malondialdehyde [MDA] [211] and 4-hydroxynonenal [213] are increased in patients with dilated cardiomyopathies compared to normal controls. Myeloperoxidase, a peroxidase enzyme present in granulocytes is increased in the serum of patients with dilated cardiomyopathy. Increased myeloperidase levels correlate with HF severity. Finally, plasma myeloperidase appears also to be an independent predictor of mortality and HF hospitalization [212]. Uric acid, produced by the ubiquitous ROS-generating xanthine oxidase, is considered as a marker for oxidative stress in the cardiovascular system. It is released from the failing human heart, with an inverse correlation between the level of uric acid and left ventricular ejection fraction [214]. Increased serum uric acid levels are associated with increased filling pressures, reduced cardiac index and plasma NT-proBNP [215]. Uric acid is also a strong independent predictor of mortality in patients with dilated cardiomyopathy [216].

One consequence of myocardial oxidative stress is myocardial remodeling, including myocyte hypertrophy, myocyte apoptosis and alteration of the extracellular matrix.

Oxidative stress has direct effects on cellular structure and function and activates integral signaling molecules leading to myocardial remodeling and failure (**Figure 5**). Oxidative stress stimulates myocardial growth, matrix remodeling, and cellular dysfunction, which involve the activation of several downstream signaling pathways. First, ROS activate a broad variety of hypertrophy signaling kinases and

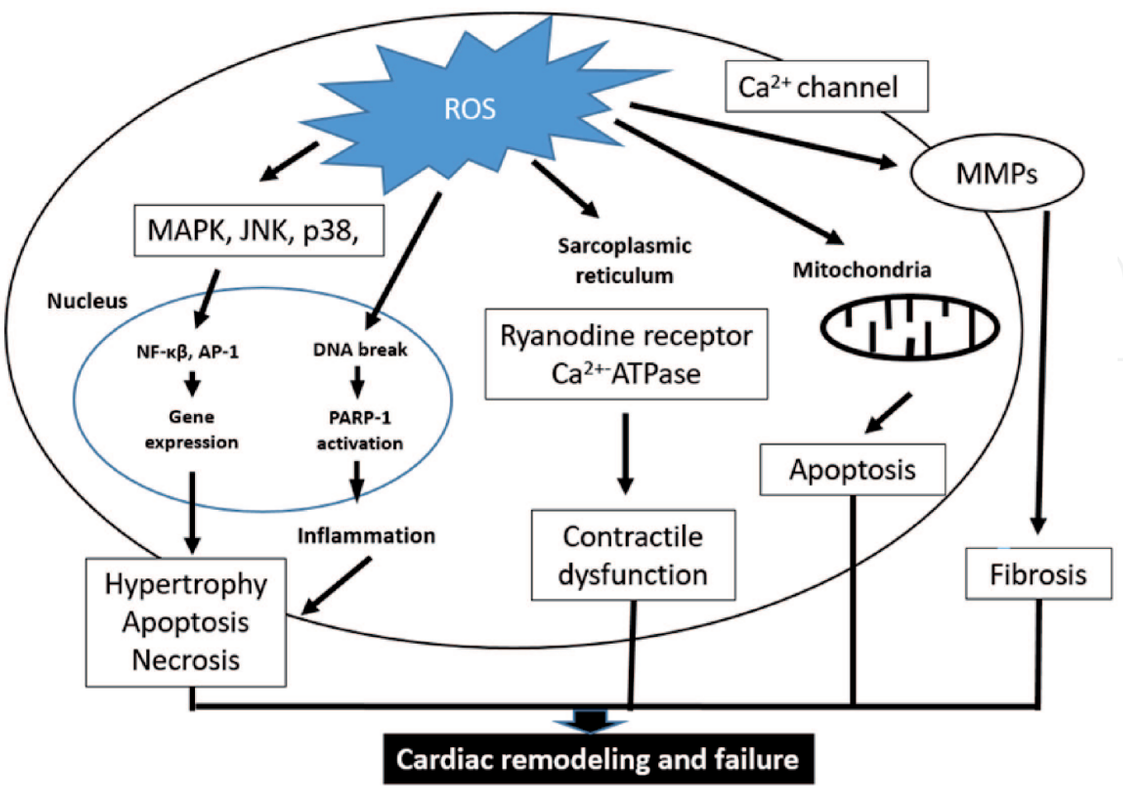

Figure 5.
Oxidative stress and heart failure. MAPK: Mitogen-activated protein kinases; JNK: Jun-nuclear kinase; PARP-1: Poly(ADP-ribose) polymerase-1; MMP: Matrix metalloproteinases; AP-1: Activator protein-1.

transcription factors [217]. Oxidative stress stimulates the tyrosine kinase Src, GTP-binding protein Ras, protein kinase C, mitogen-activated protein kinases (MAPK), Jun-nuclear kinase (JNK) and p38. Second, Oxidative stress induces apoptosis, another important contributor to remodeling and dysfunction, which is induced by ROS-mediated DNA and mitochondrial damage and activation of pro-apoptotic signaling kinases [218]. Third, Oxidative stress causes DNA strand breaks, activating the nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP-1). PARP-1 regulates the expression of a variety of inflammatory mediators, which facilitate the progression of cardiac remodeling [219]. Fourth, oxidative stress can activate matrix metalloproteinases (MMPs), a family of proteolytic enzymes [220]. MMPs play a pivotal role in normal tissue remodeling processes, such as cell migration, invasion, proliferation, and apoptosis. MMP activity has been shown to be increased in the failing hearts [220, 221]. MMPs are generally produced in an inactive form and are activated by reactive oxygen species (ROS). Because MMP can be activated by ROS, one mechanism of LV remodeling is the activation of MMPs secondary to increased ROS [222]. Sustained MMP activation will lead to extracellular matrix remodeling. Fifth, ROS mediate growth responses in ventricular myocytes by stimulating the activity of several growth factors including transforming growth factor-β1 (TGF-β1), [223, 224] VEGF, [225] fibroblast growth factor-2 (FGF-2), [226], and PDGF [227]. Sixth, oxidative stress promotes vasoconstriction by increasing the production of endothelin-1 [228] and angiotensin II by increased production of 02- via the NADPH oxidase [229]. Seventh, oxidative stress upregulates the transcription of the factors HIF-1α and HIF-2α expression, [230] factors that are also implicated in the development of cardiomyopathy and HF. Eighth, increased oxidative stress leads to inflammation and cell injuries due to oxidation of proteins, lipids and DNA [209]. Finally, ROS directly influence myocyte contractile function by modifying proteins involved in excitation-contraction coupling. Zima and Blatter [231] including the ryanodine receptor, the L-type calcium channel, and the Ca2 + ATPase.

4.1 Oxidative stress and mitochondrial DNA damage

In addition to the role of mitochondria as a source of reactive oxygene species (ROS), the mitochondria themselves can be damaged by ROS. Increased generation of ROS in the failing hearts was associated with mitochondrial damage and dysfunction, characterized by an increased lipid peroxidation in the mitochondria, a reduction in the number of the mitochondrial DNA copy, a decrease in the number of mitochondrial RNA transcripts and a reduced oxidative capacity due to low complex enzyme activities [232]. They thus can lead to a catastrophic cycle of mitochondrial functional decline, further ROS generation, and cellular injury.

4.2 Therapies targeting oxidative stress

To date, there are no positive large-scale clinical trials of antioxidant therapy in cardiomyopathy and heart failure.

4.2.1 Coenzyme Q

Coenzyme Q (CoQ) is an antioxidant via the redox cycle. CoQ inhibits both the initiation and the propagation of lipid and protein oxidation.

Preclinical data has provided information across a variety of models supporting the pathophysiological role of CoQ10 depletion in HF and the concept of improved outcomes with CoQ10 supplementation [233].

There have been a large number of trials examining the effect of CoQ10 in HF. Two meta-analyses have examined the potential benefit of CoQ10. Fotino et al. [234] analysis from 13 trials and 395 patients demonstrated an improvement in LVEF of 3.67% (95% CI, 1.6%–5.74%) in those receiving CoQ10 versus placebo. The majority of benefit of LVEF improvement was in trials published before 1993. The other meta-analysis by Madmani et al. [235] looked at 7 studies data with 914 patients and did not show any significant improvement in LVEF or exercise capacity. Given the significant heterogeneity of the data, it was not possible to make any significant conclusion.

The most recent clinical trial with CoQ10l, Q-SYMBIO (Coenzyme Q10 as Adjunctive Treatment of Chronic Heart Failure: A Randomized, Double-blind, Multicenter Trial With Focus on Symptoms, Biomarker Status) enrolled 420 patients and demonstrated that compared with placebo, CoQ10 reduced the primary 2-year end point of cardiovascular death, hospital stays for HF, or mechanical support or cardiac transplant (P = 0.005; hazard ratio, 0.5; 95% CI, 0.32–0.80) [236]. Although having limitations, this study has renewed interest in evaluating CoQ10 supplementation in patients with HF. The results of the trial warrants future adequately powered randomized controlled trials of CoQ10 supplementation in patients with HF.

4.2.2 Allopurinol

Under normal conditions, the enzyme xanthine oxidase (XO) exists primarily in its dehydrogenase form, serving as the rate-limiting step in purine degradation to uric acid. Xanthine oxidase catalyzes the transformation of hypoxanthine to xanthine and then to uric acid with the associated production of four superoxide anions [237]. Xanthine oxidase is therefore a potential major regulator of cellular oxidative stress [238].

A large body of experimental and clinical data suggests that oxidative stress contributes to ventricular and vascular remodeling and disease progression in HF. XO is a potent source of oxidative stress, and therefore an obvious target for therapy.

Significant hyperuricemia is present in ≈25% of patients with HF with reduced ejection fraction, [215, 216] and it is associated with worsening symptoms, exercise intolerance, and reduced survival [239–241].

Under conditions of tissue hypoxia similar to HF in an experimental model, [242] the breakdown of ATP to AMP to hypoxanthine provides substrate to XO. Subsequently, XO uses oxygen rather than NAD as an oxidant. As a result, XO produces superoxide and hydrogen peroxide (H2O2) rather than NADH [243, 244]. Increased vascular O2• − production has been attributed in major part to XO, which has been found to adversely impact endothelial function by impairing nitric oxide (NO) signaling [245] and to directly contribute to experimental cardiac remodeling.

The Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) Study, a randomized trial with 243 HF patients with reduced ejection fraction and elevated uric acid levels, xanthine oxidase inhibition with allopurinol compared to placebo failed to improve clinical status, exercise capacity, quality of life, or left ventricular ejection fraction after 24 weeks.of treatment [246].

In summary, oxidative stress appears to play an important role in the pathophysiology of cardiac remodeling and cardiomyopathy. Thus therapeutic strategies to modulate this maladaptive oxidative stress response as seen in cardiomyopathy and HF should become a target for future extensive investigation.

5. Conclusions

Cardiac remodeling represents the culmination of complex interactions between neuro-hormonal, stress activated cytokine and oxidative stress signaling pathways. These different signaling pathways feedback positively on one another and act in concert to initiate and propagate the cellular changes taking place within the remodeling ventricle. These pathways stimulate myocyte hypertrophy, increase the rate at which myocytes undergo hypertrophy, apoptotic cell death as well as proliferation of fibroblasts, some of which may differentiate into contractile myofibroblasts.

This constellation of cellular changes ultimately leads to gross morphological features of cardiac dilatation, progressive cardiac dysfunction and worsening heart failure. In this manner, these complex series of signaling events that lead to cardiac remodeling may very well represent the central pathophysiological mechanisms underlying cardiomyopathy progression.

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