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Review Article

NADPH oxidase-dependent oxidative stress in the failing heart: From pathogenic roles to therapeutic approach

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ABSTRACT

Heart failure (HF) occurs when the adaptation mechanisms of the heart fail to compensate for stress factors, such as pressure overload, myocardial infarction, inflammation, diabetes, and cardiotoxic drugs, with subsequent ventricular hypertrophy, fibrosis, myocardial dysfunction, and chamber dilatation. Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) generation and the capacity of antioxidant defense systems, has been authenticated as a pivotal player in the cardiopathogenesis of the various HF subtypes. The family of NADPH oxidases has been investigated as a key enzymatic source of ROS in the pathogenesis of HF. In this review, we discuss the importance of NADPH oxidase-dependent ROS generation in the various subtypes of HF and its implications. A better understanding of the pathogenic roles of NADPH oxidases in the failing heart is likely to provide novel therapeutic strategies for the prevention and treatment of HF.

Contents

Introduction

Heart failure (HF) is a major cause of morbidity and mortality in the Western world. It describes a clinical syndrome that results from structural and/or functional cardiac abnormalities impairing the ability of the left ventricle to fill with or eject blood. Approximately 4.9 million Americans are diagnosed with HF [1], and each year 550,000 new cases of HF are reported in the United States [2]. The most common causes of HF are ischemic heart disease, pressure overload resulting from hypertension or valvular heart disease, myocarditis, and drugs such as antineoplastic agents. Structural alterations in the myocardium, for example ventricular remodeling, are not only related to the underlying etiological cardiac pathology leading to HF, but also represent morphological, cellular, and molecular changes that progress over time in response to the initiating event.

Recent research has focused on the hypothesis that oxidative stress is the culprit in the pathogenesis of many cardiac diseases. Oxidative stress occurs when the generation of reactive oxygen species (ROS) overwhelms the capacity of antioxidant-defense systems. Potentially important sources of ROS in HF include the mitochondrial electron transfer chain [3], xanthine oxidase (XO) [4], uncoupled endothelial nitric oxide synthases (eNOS) [5], and NADPH oxidases [6–8]. ROS have been known to demonstrate a variety of effects relevant to the pathophysiology of ventricular remodeling [9]. For example, the superoxide anion (O_2^-) is a potent deactivator of the vasoprotective signaling

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molecule nitric oxide. Further, ROS initiate eNOS uncoupling, resulting in a vicious cycle of O_2^- generation that contributes to myocardial dysfunction [10]. In addition, ROS modulate diverse intracellular signaling pathways—the so-called redox signaling. ROS also affect cellular energetics in the myocardium resulting in an energy deficit, cellular damage, and acceleration of cell death through apoptosis and necrosis [11]. Furthermore, ROS modulate fibroblast proliferation, collagen synthesis, and matrix metalloproteinase (MMP) activation, and their expression in the myocardium causes myocardial hypertrophy, fibrosis, and necrosis, which can lead to endothelial and myocardial dysfunction [12,13].

An important contributor of oxidative stress in the heart is NADPH oxidase-dependent superoxide generation (see Fig. 1). The function of the NADPH oxidase enzymes is to catalyze the one-electron transfer from NADPH to molecular oxygen, thereby generating ROS [14] in a regulated way in response to, e.g., calcium, growth factors, and cytokines [15]. Seven isoforms of the catalytic, membrane-spanning NADPH oxidase subunit NOX exist, each encoded by a separate gene, i.e., NOX1–5 and Duox1 and Duox2. They differ in molecular composition, subcellular localization, tissue distribution, and expression [16]. Endothelial cells mainly express NOX2 and NOX4, and vascular smooth muscle cells mainly express NOX4 [17,18]. In vascular smooth muscle cells of resistance arteries, NOX2 expression is relatively high [19,20], and cardiomyocytes mainly express NOX2 and NOX4 [21].

This review gives an extensive overview of the role of NADPH oxidase-dependent oxidative stress in the pathogenesis of several forms of HF (see Table 1) and discusses the therapeutic possibility of modulating HF-associated myocardial dysfunction by inhibiting the different isoforms of NADPH oxidases.

NADPH oxidases and pressure-overload-induced HF

Pressure overload caused by uncontrolled hypertension or aortic stenosis can lead to compensatory hypertrophy in cardiomyocytes followed by ventricular dilatation, with subsequent decompensated ventricular remodeling. The pathogenesis of pressure-overload-induced ventricular remodeling, including myocardial damage and fibrosis, is a complex interplay of various hemodynamic, structural, neuroendocrine, cellular, and molecular factors [22]. At the cellular level, cardiac function is related to myocardial morphology, and with structural deterioration, the contractility further decreases [23]. At the subcellular level, ROS have been shown to be involved in the pathophysiology of pressure-overload-induced left-ventricular hypertrophy (LVH) and HF [24]. ROS are implicated not only in the process of cellular hypertrophy and remodeling in the decompensated phase, but also in the development of compensated pressure-overload LVH [25].

Activation of NADPH oxidases has been suggested as a potential player in pressure-overload-induced HF. Indeed, NADPH oxidases are expressed in both vascular [19,20] and heart tissues [9,21], and the mechanisms leading to cardiac dysfunction have been related to NADPH oxidase in the myocardium and/or fibroblasts. Various roles for individual NOX isoforms have been reported. In $NOX2^{y/-}$ mice in which pressure overload was induced by ascending aortic constriction, there was no difference in LV wall thickness or chamber dimensions compared with wild-type (WT) mice. Interestingly, however, there was a 17-fold increase in $p22^{phox}$ and a 2-fold increase in $p47^{phox}$ mRNA expression 10 weeks after ascending aortic constriction in $NOX2^{y/-}$ mice, whereas in WT mice there was a 6-fold increase in $p22^{phox}$ and no increase in $p47^{phox}$ mRNA expression. In addition, ROS levels in myocardium of $NOX2^{y/-}$ mice were two times higher compared with WT mice [26]. This suggests that there is cross talk between NOX isoforms, in this case that depletion of NOX2 can induce compensation by other NOX isoforms that depend on $p22^{phox}$ and $p47^{phox}$. Unfortunately, the levels of NOX1 were not reported.

In more investigations about the role of NADPH oxidases in the myocardium, Bendall et al. [27] and Byrne et al. [28] reported contrasting roles for NOX isoforms in pressure-overload- versus angiotensin II (AngII)-induced myocardial hypertrophy using $NOX2^{-/-}$ mice in which hypertrophy was induced by transaortic constriction (TAC) or chronic AngII infusion, respectively. Whereas AngII-induced oxidative stress was abrogated in $NOX2^{y/-}$ mice, ROS levels were unchanged after TAC in $NOX2^{y/-}$ compared to WT mice. In addition, in $NOX2^{y/-}$ mice exposed to TAC, NOX4 mRNA and protein levels were increased in the myocardium. These findings, which support Maytin et al. [26], indicate that the function of cardiac NADPH oxidases is isoform-dependent and depends on the specific pathological processes. NADPH-dependent ROS production was significantly increased in LVH caused by chronic abdominal aortic banding in guinea pigs. The protein levels of the NADPH oxidase subunits NOX2, $p22^{phox}$, $p67^{phox}$, and $p47^{phox}$ were increased in the cardiomyocytes of these guinea pigs. These subunits were identified as a major source of ROS in pressure-overload-induced LVH and contributed to pathophysiological change such as the activation of redox-sensitive kinases and progression of HF [8]. Using cardiac-specific $NOX4^{-/-}$ ($cNOX4^{-/-}$) mice it was demonstrated that ROS production under baseline conditions is reduced compared with WT mice, which supports the findings of Kuroda et al. [6] regarding the important role of NOX4. After 4 weeks of TAC, $cNOX4^{-/-}$ mice showed significantly attenuated LVH, interstitial fibrosis, and apoptosis, whereas systolic function was improved compared to WT mice. However, a contrasting finding has been reported from using $NOX4^{-/-}$ mice and a cardiomyocyte-targeted NOX4-transgenic model, with the latter overexpressing NOX4 in the heart. NOX4 mRNA expression was increased in cardiomyocytes after pressure overload and myocardial infarction. However, $NOX4^{-/-}$ mice showed significantly larger cardiac dilatation and contractile deterioration compared with WT mice, and NOX4-transgenic mice developed less hypertrophy and fibrosis compared with WT mice [29]. These data suggest that endogenous NOX4 has an important role in mediating cardiomyocyte hypertrophy, fibrosis, and apoptosis in response to pressure overload. The potential reasons for the opposing effects of NOX4 reported by Kuroda et al. [6] and Zhang et al. [29] are differences in the knockout strategies, mouse models, methods of inducing pressure overload, and/or time of TAC induction. The heart phenotypes are the same in the two groups. In the experiments of the Kuroda group, the baseline expression of NOX4 protein in $NOX4^{-/-}$ mice was reduced by 78% in the heart, and $p22^{phox}$ protein was reduced to about 50%, whereas in the experiments of the Zhang group, NOX4 was completely absent from the heart and kidney, and $p22^{phox}$ was unaffected. The other difference is that Kuroda et al. used aortic constriction and Zhang et al. used suprarenal banding. Thus, further research needs to be done to determine the exact role of NOX4 in pressure-overload-induced HF. In conclusion, possible explanations for these different results can be (i) severity of pressure overload, (ii) acute versus chronic pressure overload, (iii) differences in angiogenesis, and (iv) different knockout results.

NADPH oxidases and myocardial infarction

Myocardial infarction (MI)-induced myocardial dysfunction, i.e., ischemic cardiomyopathy, is the most common etiology of HF. Each year, the estimated incidence of new MI is 610,000 attacks and 325,000 recurrent attacks in the United States. In addition, MI is the cause of approximately 1/6 of all deaths in the United States [30]. Cardiac remodeling post-MI comprises progressive changes in the structure of cardiomyocytes and extracellular matrix and leads to insufficient cardiac function. ROS cause cardiomyocyte hypertrophy, interstitial fibrosis, and activation and expression of MMPs, but how ROS affect cardiac remodeling in post-MI processes remains unclear [12,31]. ROS are likely to promote damage of mitochondrial DNA,