

Oxidative stress and inflammatory markers – the future of heart failure diagnostics?

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Abstract

Heart failure remains one of the most important problems in cardiology despite the progress in its treatment. A number of recent studies have demonstrated the relationship between the intensification of oxidative stress and chronic inflammation and the severity of left ventricular dysfunction, development of heart failure symptoms, and prediction of future cardiac events. Early detection of changes developing in the heart is key in improving the treatment's effectiveness. It appears that determining specific, sensitive biomarkers reflecting the complex pathophysiology of heart failure and using them to detect asymptomatic cardiac alterations may become a crucial screening tool, assisting in the identification of patients requiring further diagnostic examinations. This article presents an overview of the current knowledge of the role of oxidative stress and inflammation in heart failure; it also discusses the potential role of oxidative stress and inflammatory markers as prognostic factors in heart failure that may be used in screening tests.

Key words: heart failure, oxidative stress, inflammatory markers.

Introduction

The morbidity and mortality rates of heart failure (HF) are immense in developed countries. As life expectancy rises, and the population ages, the number of patients with HF grows, which poses a major problem to public health, generating tremendous costs associated with the hospitalization and treatment of patients. Regardless of the enormous progress achieved in research on the pathophysiology of HF and the new diagnostic and therapeutic methods, the prognosis for patients with HF is still poor. Thus, early diagnosis and the implementation of successful treatment in the early stages of HF development are among the major

Streszczenie

Pomimo znacznego postępu w leczeniu niewydolności serca (*heart failure* – HF), pozostaje ona nadal jednym z najważniejszych problemów współczesnej kardiologii. W ostatnich latach wykazano zależność pomiędzy zintensyfikowanym stresem oksydacyjnym i przewlekłym stanem zapalnym a stopniem zaawansowania dysfunkcji lewej komory, nasileniem objawów HF oraz prognozowaniem niekorzystnych zdarzeń sercowych. Zasadniczym czynnikiem prowadzącym do poprawy skuteczności leczenia HF jest wczesne wykrywanie patologicznych zmian w sercu. Wydaje się, że pomiar specyficznych biomarkerów odzwierciedlających złożoną patofizjologię HF może stać się cennym narzędziem w badaniach przesiewowych. Wykrycie bezobjawowej dysfunkcji serca za pomocą czułych markerów może pomóc w wytypowaniu pacjentów, u których należy przeprowadzić dalszą diagnostykę. W artykule przedstawiono przegląd aktualnej wiedzy na temat roli stresu oksydacyjnego i stanu zapalnego w HF. Omówiono także potencjalne markery stresu oksydacyjnego i przewlekłego stanu zapalnego jako czynniki prognostyczne w HF oraz możliwość ich wykorzystania jako narzędzia w badaniach przesiewowych.

Słowa kluczowe: niewydolność serca, stres oksydacyjny, markery zapalenia.

challenges for modern medicine. Such a strategy can bring significant economic and social benefits.

Early diagnosis of HF in patients without clinical symptoms is often difficult due to the lack of universal access to screening echocardiography and the costs associated with it. It seems that the measurement of specific biomarkers that reflect different pathways leading to HF may help identify patients requiring further diagnostics [1-3]. Useful and generally accepted HF markers include B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP); even though these markers have high sensitivity and high negative predictive values to exclude HF, they are not completely specific as their values increase

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in other conditions as well [4, 5]. Numerous studies have shown that combining BNP and NT-proBNP with oxidative stress and inflammatory markers may increase the detection of asymptomatic left ventricular systolic dysfunction and the early stages of HF [5, 6]. Additionally, it is believed that increased oxidative stress and inflammation can be classified as new risk factors for cardiovascular diseases [7]. Oxidative stress and inflammatory biomarkers appear to be a promising diagnostic and prognostic tool in patients with HF. The diagnosis of HF patients with no symptoms is essential for improving the effectiveness of the treatment.

Oxidative stress and its role in heart failure

Oxidative stress is defined as a state of imbalance between the production of free radicals and the capacity to neutralize them by the antioxidant mechanisms of the body. Oxidative stress may be the result of excessive reactive oxygen species (ROS) production or the depletion of endogenous antioxidant reserves [8]. Reactive oxygen species can bind to proteins, lipids, or nuclear and mitochondrial genetic material, causing the destruction of their cellular structure and integrity disorders of biological tissue. It has also been discovered that free radicals impair the damage of genetic material remedial systems, increasing the probability of duplication of the ensuing lesions [9].

Free radicals can be produced by all tissues through a variety of mechanisms. Some of the important sources of ROS showing a potential for damaging the structure of the heart include processes of electron transport in the respiratory chain, purine metabolism catalyzed by xanthine oxidase, endothelial nitric oxide synthase (eNOS), and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase. ROS formation can also be induced by pro-inflammatory cytokines, growth factors, and angiotensin II [8, 10, 11]. Two subtypes of NADPH oxidase occur in the heart: NOX-2 and NOX-4, which have opposite consequences for HF. NOX-2 seems to be involved in pathological cardiac remodeling, and NOX-4 may protect the heart muscle by stimulating angiogenesis, thus maintaining the density of capillaries. However, the associated data are ambiguous [8, 12]. The reaction catalyzed by eNOS produces nitric oxide (NO), which has a dual nature. On the one hand, it has a beneficial effect on the heart muscle, regulates blood flow and blood pressure, inhibits smooth muscle cell proliferation, and suppresses the activation and aggregation of platelets. On the other hand, a relationship between NO and heart failure has been proved. NO inactivation, accelerated by the increased production of ROS, in particular by the superoxide anion (O_2^-), results in the creation of highly reactive peroxynitrites ($ONOO^-$), which can damage the protein-lipid structures of cell membranes and inactivate various enzymes. At the same time, in conditions of increased conversion of NO to $ONOO^-$, the beneficial influence of NO on the heart muscle becomes deactivated, which contributes to HF progression [9, 13]. Over the past few years, a significant part of the research has been focused on the role played by free radicals in HF. It

appears that ROS are involved in the processes leading to endothelial dysfunction, apoptosis, interstitial fibrosis, cardiomyocyte hypertrophy, and extracellular matrix remodeling (i.e. processes closely associated with HF) although the molecular mechanisms of ROS effects on these processes have not been fully explained [10, 12, 14, 15]. ROS are an important factor involved in the signaling pathways leading to cardiomyocyte hypertrophy [11]. In the early stages of heart failure, increased activity of antioxidant enzymes accompanies the primary compensatory mechanisms, with the primary objective of maintaining adequate blood flow and tissue perfusion. Heart failure development leads to the depletion of antioxidant enzymes in addition to the increased production of free radicals, which contributes to further progression of the disease [15, 16].

Oxidative stress markers in heart failure

Numerous clinical studies have shown that high levels of oxidative stress markers may reflect the severity of HF [12, 14, 17, 18]. Studies by Díaz-Vélez *et al.* demonstrated that patients with HF had significantly higher levels of malondialdehyde (MDA) concentration in blood plasma when compared to the control group. Additionally, a significant correlation has been found between the level of MDA and the duration of heart failure [14]. Malondialdehyde is a marker of lipid peroxidation and is formed as the final product of oxidation of polyunsaturated fatty acids undergoing ROS attack. The intermediate products resulting from the ongoing oxidation cascade of polyunsaturated fatty acids can react with other lipids, proteins, or nucleic acid bases, contributing to a further cascade of adverse changes in the heart [17, 19]. Studies by Castro *et al.* also confirm the relationship between the severity of HF and increasing oxidative stress, as expressed by the increase of MDA and a decrease of glutathione peroxidase activity in patients with HF in comparison to the control group [17]. Amir *et al.* proved that oxidative stress markers correlate positively with clinical parameters of heart failure and that their high levels are a poor prognostic factor in HF patients. Furthermore, the authors of the studies mentioned above have demonstrated the relationship between the severity of oxidative stress and New York Heart Association (NYHA) functional class, renal function, and levels of hs-CRP and pro-BNP in patients with HF [18]. Similar observations have been made by Karabacak *et al.*, who evaluated the relationship between the oxidative stress index (OSI) and the severity of HF. The OSI was expressed as the ratio of total antioxidant capacity (TAC) to total oxidative status (TOS); it is a useful marker reflecting the overall redox balance between the oxidative and antioxidant components. In the study, the OSI was significantly higher in patients with HF in comparison to the control group; it correlated positively with left ventricular end-systolic volume, uric acid, and the level of TOS, while being negatively correlated with the level of TAC and ejection fraction [20]. Moreover, the research by Kono *et al.* showed that the level of 8-hydroxy-2-deoxyguanosine (8-OHdG) in the serum and myocardium

of HF patients was significantly higher than in the control group. 8-OHdG is a marker of oxidative stress to DNA; therefore, the results of this study indicate that ROS can damage genetic material [21]. It has also been claimed that the level of 8-OHdG might be a useful marker for assessing the severity of HF and intensity of oxidative stress in heart failure [22].

Inflammation and its relationship to oxidative stress in heart failure

Chronic inflammation is an important element underlying the pathophysiology of HF, contributing to myocardial remodeling, endothelial dysfunction, and peripheral vascular damage. Higher levels of inflammatory mediators, including IL-1, IL-6, IL-18, high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor α (TNF- α), and FAS ligand, are observed in patients with HF regardless of disease etiology [23, 24]. Pro-inflammatory cytokines are involved in the processes remodeling the heart muscle, including cardiomyocyte hypertrophy, myocyte apoptosis inhibition, endothelial dysfunction, and ventricular fibrosis. It has been proved that TNF- α overexpression exerts a negative inotropic effect on the heart, which is mediated by activation of the sphingomyelinase pathway and inhibition of β -adrenergic signaling. On the other hand, although their involvement in the pathophysiology of HF has been confirmed, the ways in which IL-1 and IL-6 interact are not fully elucidated [25, 26]. Besides cytokines, the important mediators of inflammation include galectin-3 and pentraxin-3, released by activated macrophages as a result of tissue damage. The role of pentraxin-3 in HF has not yet been determined, but it is known that its level increases in HF. On the other hand, galectin-3 is involved in myocardial fibrosis through excessive fibroblast activation. It is suggested that identifying the level of galectin-3 may be useful in predicting and stratifying mortality risk in patients with HF [27, 28]. Increased levels of proinflammatory cytokines, in response to myocardial damage, are important prognostic factors correlating with increased mortality rates in HF patients [25]. In addition, increased oxidative stress may impair the release of anti-inflammatory cytokines such as IL-10, thus contributing to the development of inflammatory processes in the heart [9]. Excessive ROS production, induced by various stimuli, is closely associated with the severity of inflammation [18]. Free radicals stimulate metabolic pathways leading to activation of the transcription factor κ B (NF- κ B), which, in turn, increases the expression of proinflammatory cytokines, capable of further activation causing a vicious circle of self-propelling systems [29]. NF- κ B activity seems to be involved in the signaling cascade of ROS, which may lead to myocardial remodeling. Thus, by modulating the signaling pathways, ROS may play a significant role in modulation of the inflammatory process [11].

Heart failure multimarkers in screening

The pathophysiology of heart failure is determined by many factors, including inflammation, neuroendocrine ac-

tivation, oxidative stress, severe angiogenesis, apoptosis pathway changes, and vascular remodeling. The evaluation of biomarkers of different signaling pathways appears to reflect the pathophysiology of HF conditioned by many factors [1, 2, 30]. It has been suggested that the assessment of markers associated with the different pathways of HF pathogenesis may facilitate diagnosis and the prediction of mortality risk in patients with HF based on 5 years of observation [1]. Ky *et al.* analyzed the diagnostic and prognostic usefulness of the biomarker panel in patients with chronic heart failure. The group of biomarkers included: hs-CRP, uric acid, myeloperoxidase (MPO), BNP, soluble fms-like tyrosine kinase receptor-1 (sFLT-1), troponin I (TnI), soluble toll-like receptor-2 (ST2), and creatinine levels. The study showed that the evaluation of multiple markers associated with HF pathways is a useful method for the assessment of prognosis and the prediction of risk in patients with heart failure [3]. Research conducted by Richter *et al.* also suggests that the results obtained by measuring the panel of HF biomarkers are more sensitive in predicting the risk of future adverse events in comparison to the conventional clinical risk assessment algorithm (Seattle Heart Failure Model – SHFM) [1]. The combination of the multimarker results and SHFM significantly improves the ability to identify and classify patients with higher risk of symptomatic HF development [3]. The main problem of the widespread use of biomarkers in heart failure is the lack of a specific threshold of these markers qualifying them to identify heart failure.

Notwithstanding, BNP and NT-proBNP concentrations undoubtedly constitute an important diagnostic tool in HF. Among the variables affecting the level of BNP and NT-proBNP, the most important include age, sex, obesity, and comorbidities [4]. It should be noted, however, that these markers are not specific to heart failure and also increase in other diseases. Studies by Ng *et al.* indicate that the measurement of C-reactive protein and myeloperoxidase levels enhances the specificity of NT-proBNP screening measurements in the detection of left ventricular systolic dysfunction (LVSD) [5]. Asymptomatic ventricular dysfunction often precedes the occurrence of HF, and the measurement of specific biomarkers that reflect the ongoing pathological processes may reveal the group of patients in need of undergoing further diagnostics [6]. Thus, the detection of anomalies at this stage can be an important factor in increasing the effectiveness of HF treatment [31]. This may be of particular value in the population of high-risk patients. The accuracy of this screening method, consisting of CRP, MPO, and NT-proBNP measurements, appears to be comparable with the already well-known screening tests used in detecting breast cancer or prostate cancer [32]. Myeloperoxidase is an enzyme released by leukocytes during inflammation, which participates in sustaining the process and catalyzes the oxidation of many organic substances, leading to the formation of reactive oxidants, which may ultimately lead to myocardial remodeling. Myeloperoxidase is, therefore, a marker which combines components of oxi-

oxidative stress and inflammation [31]. Tang *et al.* reported that MPO levels were significantly higher in the plasma of patients with chronic heart failure compared to the control group. They also pointed out a positive correlation between MPO levels and the severity of myocardial dysfunction and HF development [33, 34]. Additionally, a high level of MPO in the plasma of patients with HF appears to be a predictor of future adverse clinical events [34]. It seems that higher values of markers reflecting the pathogenesis of different HF pathways can provide good diagnostic value in screening. Nonetheless, further studies are required to confirm the effectiveness of the simultaneous measurement of CRP, MPO, BNP, and NT-proBNP in plasma as a means to detect left ventricular systolic dysfunction.

Conclusions

To sum up, recent studies on the role of inflammatory and oxidative stress markers bring new insights into some elements of the complex pathogenesis of heart failure. It seems that the simultaneous measurement of several HF biomarkers, with proper clinical assessment of the patient, can be of help in estimating the risk of HF as well as in predicting the probability of future cardiovascular events. Some researchers also suggest that high values of inflammatory and oxidative stress markers in screening correlate with asymptomatic ventricular dysfunction of the heart and may thus be helpful in identifying the patients at risk of developing full-blown HF. Further studies are necessary, however, to fully determine the effectiveness of HF markers in the early diagnosis of HF. On account of the still not fully satisfactory results of the current treatment of heart failure, any attempt at finding a new method for the detection and treatment of this disease is worthy of attention.

Disclosure

Authors report no conflict of interest.

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