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SPECIAL ARTICLE

Nitric oxide and related factors linked to oxidation and inflammation as possible biomarkers of heart failure☆

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Abstract As a prevalent cardiovascular disease, heart failure is one of the leading causes of morbidity and premature mortality. Therefore, there is a special interest in the study of efficient markers associated with risk and/or prediction of cardiovascular events. Multiple candidates are proposed, especially those involved in oxidative and inflammatory processes typical of cardiovascular disease, such as superoxide anion, nitric oxide, and peroxynitrite. There is a lack of knowledge on the potential usefulness of these systems as biomarkers. This review aims to contribute to a better understanding of these systems, as well as an improved patient profile. Furthermore, a deep knowledge of these complex systems would also allow proposing new lines of research for the development of new therapeutic tools as a promising start for new approaches to this disease.

PALABRAS CLAVE
Biomarcadores;
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Óxido nítrico y factores relacionados a oxidación e inflamación como posibles biomarcadores de insuficiencia cardíaca

Resumen Como enfermedad cardiovascular prevalente, la insuficiencia cardíaca es una de las principales causas de morbimortalidad prematura. Por ello, existe un especial interés sobre el estudio de marcadores eficientes asociados al riesgo y/o predicción de eventos cardiovasculares. En consecuencia se proponen a múltiples candidatos, pero sobresalen especialmente

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aquellos implicados en procesos oxidativos e inflamatorios propios de la enfermedad cardiovascular como el anión superóxido, óxido nítrico y peroxinitrito. En este sentido, existe una falta de conocimiento sobre las potenciales utilidades de estos sistemas como biomarcadores. La presente revisión procura contribuir a la mayor comprensión de estos sistemas para una mejor caracterización de pacientes. Por otra parte, un profundo conocimiento de estos complejos sistemas también permitiría proponer nuevas líneas de investigación para el desarrollo de inéditas herramientas terapéuticas como una auspiciosa frontera para el abordaje de esta patología.

Introduction

With regard to cardiovascular disease (CVD), there is a special interest in the study and development of efficient markers associated with the risk and/or prediction of events, which in turn make timely intervention possible, finally validating their cardiovascular risk prediction potential. This led to the search for new biomarkers, with the proposal of multiple candidates. Nevertheless, those biomarkers involved in oxidative and inflammatory processes typical of CVD are especially noteworthy. In fact, reactive oxygen species (ROS), especially superoxide anion (O^-), and reactive nitrogen species (RNS), such as nitric oxide (NO) and peroxynitrite, show important functions (Fig. 1). In this sense, and with special emphasis on understanding the signalling pathways involved in the pathophysiology of heart failure (HF), there is a lack of knowledge on the potential usefulness of these systems as biomarkers. A better understanding would allow better characterisation of these systems and would also open up new lines of research for the development of novel therapeutic tools, which could mean a promising start for new approaches to this disease.

In particular, various neurohormonal systems have been studied in order to identify biomarkers with good predictive capacity; however, only a few meet all the criteria required to be useful in clinical practice. It is therefore necessary to continue searching for more and better substances that make an improved contribution.

In recent years, CVD has been recognised as a continuum that involves multiple entities, such as primary disease of the heart muscle (cardiomyopathy), hypertension (HTN), left ventricular hypertrophy (LVH), atherosclerotic heart disease, cardiac arrhythmias and diabetes mellitus; and HF is the final common pathway of all these entities with alteration of the signalling pathways involving NO, ROS/RNS, NADPH oxidase (Nox) and superoxide dismutase (SOD).

HF is often tackled from the perspective of the main mechanisms that induce ventricular damage and remodelling as a result of neurohormonal overstimulation by the renin-angiotensin-aldosterone (RAAS) and adrenergic systems. These alterations are classic and mark the progression of the disease. Of particular interest for this review is the fact that increased peripheral vascular resistance and cardiac remodelling constitute the main alterations and are associated with the signalling pathways mentioned above. Therefore, evaluation of HF development from a new perspective for clinical practice is a novel proposal, such as remodelling via the signalling pathways involving NO, Nox and SOD. According to this suggestion, it has recently been reported that damage to the signalling pathways involving NO and related factors may be associated with prognosis and/or mortality during HF.

However, the use of classic biomarkers in HF and drugs for its treatment are expensive and hard to obtain, especially within the field of public health. Consequently, HF is a disease of epidemiological, health and economic importance. This justifies the support offered for major research efforts to ensure a better understanding, treatment and follow-up. The development of new, more accessible and more affordable methodologies for studying its progression/prognosis would therefore allow the natural history of HF to be positively altered. Implementation of these types of biomarker, which are used to improve life expectancy and quality of life, may also help studies on the evaluation of drugs and electrophysiological devices during HF.

Biomarkers in heart failure

In general terms, biomarkers provide useful prognostic information in HF patients and there is currently considerable interest in determining the ability of biomarkers to guide therapy in cases of acute and chronic HF. Under these precepts, Richards and Braunwald listed neurohormonal, inflammatory, oxidative stress, interstitial matrix remodelling, myocyte injury and other newer markers that reflect different pathophysiological aspects of HF.[1,2]

Neurohormonal markers known as B-type natriuretic peptides (BNP, NT-proBNP and proBNP) are currently preferred due to their diagnostic/predictive value. These are secreted in both the left ventricle (LV) and right ventricle (RV) and specifically reflect LV filling pressure and parietal stress. However, they also increase when the patient has RV dysfunction in the absence of LV dysfunction, as is observed, for example, in respiratory diseases with chronic cor pulmonale and in group 1 patients with pulmonary arterial hypertension (Nice). These markers allow HF to be ruled out with reduced inaccuracies and costs and serial BNP testing is a useful tool for identifying the best discharge time and post-discharge progression.

In view of the above, biomarkers are generally useful, but they also have limitations at the time of use. Their clinical usefulness is related to the fact that testing allows for clinical management and improves prognosis for one or more situations and consequently improves diagnostic certainty