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Invited critical review

Cardiac biomarker testing in the clinical laboratory: Where do we stand? General overview of the methodology with special emphasis on natriuretic peptides

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ABSTRACT

Diagnosis of heart failure (HF) is not based on a single test, but on a combination of history, physical examination and appropriate investigations. For these reasons, the accuracy of diagnosis by clinical means alone is often inadequate, especially in the early, asymptomatic stages of the HF. Thus, there is an increasing interest in the development of new cardiovascular biomarkers and, consequently, a great number of laboratory tests have recently been proposed for their assay. The aim of this article is to provide a general overview on the biomarkers, recommended by international guidelines, for the diagnosis, risk stratification, and follow-up of patients with HF. Cardiac natriuretic peptides and in particular the B-type related peptides, which are considered to be the first line biomarker for HF by international guidelines, will be discussed with special emphasis.

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1. Introduction

Estimates on the prevalence of symptomatic heart failure (HF) in the general European and North American population range from 0.4% to 2% [1–5]; with age, HF incidence and prevalence increase steeply, approaching 1 in 1000 among people over the age of 65 [1–5]. From an economic point of view, compared to other diagnoses and treatments, HF is the primary expenditure in Medicare in the US [4], and in healthcare setting across European countries [1–3].

Despite the remarkable advances made during the past 50 years in understanding and treating the disease [6,7], HF continues to have a poor prognosis: approximately up to 40% of patients diagnosed with severe heart failure (NYHA class III–IV or ACC/AHA stage D) in the European and North American population die within one year, with survival rates similar to those of colon cancer, and worse than those of breast or prostate cancer [1–5].

About 20 years ago, Braunwald and Bristow [8] suggested the intriguing hypothesis that it may be possible to reverse the process of HF, which had long been considered to be irreversible and amenable only to palliative therapy. According to this hypothesis, the intrinsic defects in myocardial contraction featured by some patients with chronic HF could be partially reversed by connecting the patient to a ventricular

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assist device for several months [9] and/or using an appropriate pharmacological treatment [8]. In particular, it is now well documented that patients with chronic HF, treated with β-adrenergic blocking agents, added to background therapy with ACE inhibitors, improve the systolic function and may reverse cardiac remodeling, leading a better clinical outcomes, including prolonged survival and reduced hospitalizations [1–5]. Thus, the view of chronic HF as an irreversible, end-stage process is being replaced by the concept that intrinsic defects of function and structure afflicting the chronically failing heart can be addressed through appropriate therapy [6]. From a theoretical point of view, we can indeed assume that it is easier to arrest – or even reverse – a progressive process such as HF if action is taken in the earliest phase of the cardiac alteration.

In order to emphasize both the development and progression of the disease, the ACC/AHA guidelines for the diagnosis and management of chronic HF in the adult recommend a classification of HF based on 4 stages from A to D (Fig. 1) [4]. The first two stages (A and B) do not include symptomatic patients in an attempt to underscore to healthcare providers the importance of an early identification of patients who are at risk for developing HF. In particular, patients in stage A have only risk factors without structural or functional alterations of ventricular myocardial, while those in stage B show cardiac structural (such as hypertrophy) and/or functional (such as impaired left ventricular dysfunction) alterations. The last two stages C and D identify instead symptomatic patients. Since early identification of individuals and risk stratification and diagnosis can be achieved today through the measurement of specific disease or risk markers, an increasing number of new cardiovascular biomarkers have been proposed, as previously reviewed in detail [9–17].

The aim of this review article is to provide a general outline on the methodology of the biomarkers recommended by international guidelines for the diagnosis, risk stratification, and follow-up of patients with HF, with special emphasis on natriuretic peptides, which are considered to be the most useful biomarker for HF.

2. The clinical relevance of biochemical biomarkers in heart failure

HF is defined as a syndrome, resulting from any structural or functional cardiac disorder that impairs the ability of the heart to function as a pump to support a physiological circulation [1–5]. The diagnosis of HF is not based on one single test [1,2]. Positive history and some physical signs (such as orthopnea, rales, third heart sound or jugular vein distension) share a good diagnostic specificity, but also a poor sensitivity in diagnosing acute congestive HF (Table 1) [16,17]. Therefore, the diagnosis of both acute and chronic HF relies on clinical judgment based on a combination of history, physical examination and

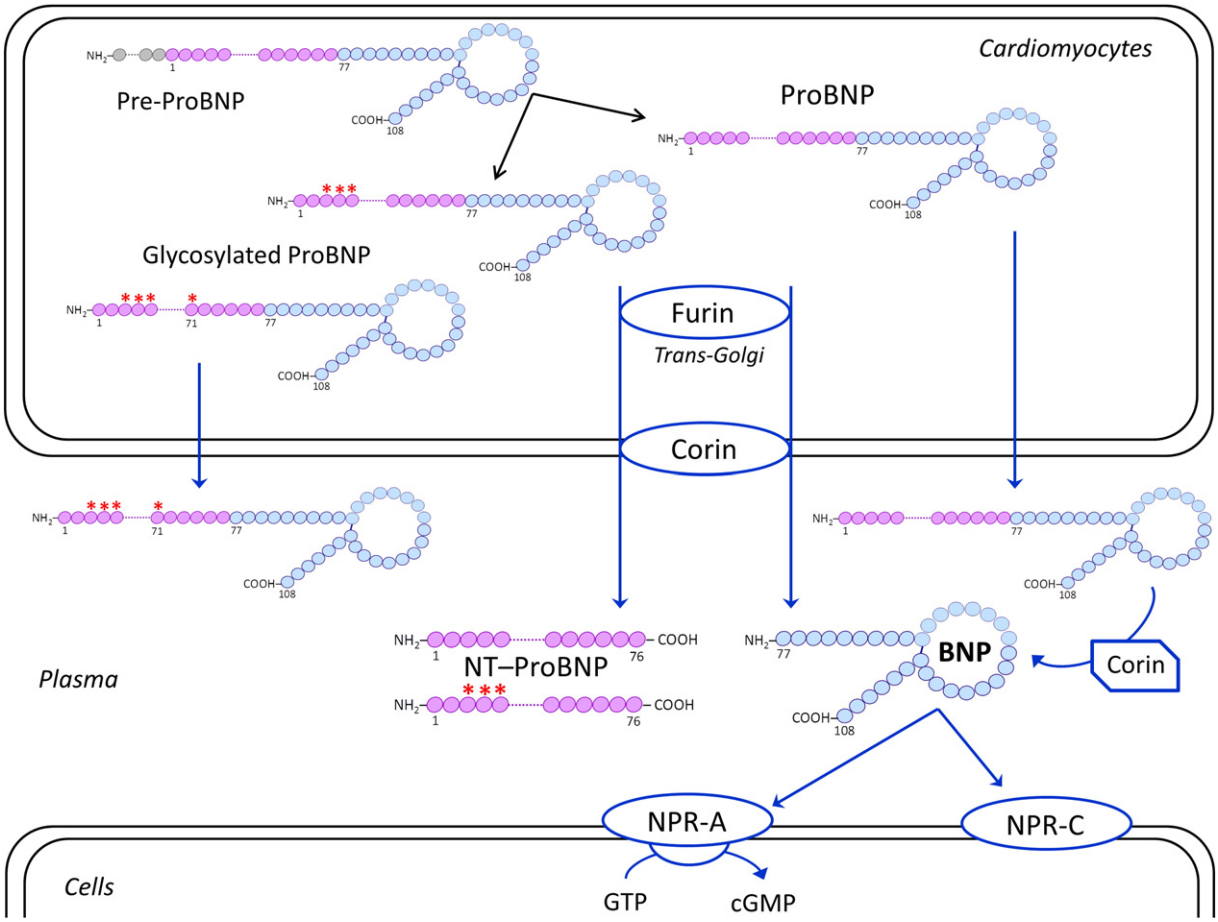

Fig. 1. Schematic representation of biosynthesis, secretion and distribution of B-type related natriuretic peptides. Human BNP is synthesized as a 134-amino acid (aa) precursor protein (pre-proBNP), including a signal peptide of 26 amino acids (grey), and is subsequently processed to form a 108-aa pro-peptide, named proBNP. The proBNP can be enzymatically cleaved by pro-protein convertases produced in the cardiomyocytes, such as corin and furin, mainly located in the trans-Golgi network and on the plasma membrane, respectively [116]. ProBNP is thus processed to form the 76-aa N-terminal peptide (NT-proBNP, violet) and the biologically active 32-aa C-terminal peptide (BNP, light blue), which are both secreted into plasma. Some of the proBNP is O-glycosylated within the Golgi apparatus. Proteolytic cleavage occurs either on or not O-glycosylated proBNP. But, if O-glycans bind to the threonine at position 71 the proBNP will not be processed by furin and corin, thus glycosylated proBNP will be secreted into circulation. Finally, also not glycosylated proBNP can be released as unprocessed peptide. However, the latter can be cleaved into NT-proBNP and BNP by plasmatic corin [117–120]. Only BNP_{1-32}, which is the active hormone, is able to bind the specific receptors, NPR-A and NPR-C. NPR-A is a guanylate cyclase-coupled receptor, which mediates the biological effects of cardiac natriuretic peptides. NPR-C, not coupled to a guanylate cyclase, has essentially a clearance function for all natriuretic peptides.