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Update: Acute Heart Failure (IV)

Biomarkers in Acute Heart Failure

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ABSTRACT

The care of patients with acutely decompensated heart failure is being reshaped by the availability and understanding of several novel and emerging heart failure biomarkers. The gold standard biomarkers in heart failure are B–type natriuretic peptide and N-terminal pro-B-type natriuretic peptide, which play an important role in the diagnosis, prognosis, and management of acute decompensated heart failure. Novel biomarkers that are increasingly involved in the processes of myocardial injury, neurohormonal activation, and ventricular remodeling are showing promise in improving diagnosis and prognosis among patients with acute decompensated heart failure. These include midregional proatrial natriuretic peptide, soluble ST2, galectin–3, highly–sensitive troponin, and midregional proadrenomedullin. There has also been an emergence of biomarkers for evaluation of acute decompensated heart failure that assist in the differential diagnosis of dyspnea, such as procalcitonin (for identification of acute pneumonia), as well as markers that predict complications of acute decompensated heart failure, such as renal injury markers. In this article, we will review the pathophysiology and usefulness of established and emerging biomarkers for the clinical diagnosis, prognosis, and management of acute decompensated heart failure.

Biomarcadores en la insuficiencia cardiaca aguda

Palabras clave:
Insuficiencia cardiaca aguda descompensada
Biomarcadores

RESUMEN

La asistencia de los pacientes con descompensación aguda de la insuficiencia cardiaca está cambiando gracias a la disponibilidad y el conocimiento de varios nuevos biomarcadores de la insuficiencia y otros que están apareciendo. Los patrones de referencia como biomarcadores en la insuficiencia cardiaca son el péptido natriurético tipo B y la fracción aminoterminal del propéptido natriurético tipo B, que desempeñan un papel importante en el diagnóstico, el pronóstico y el tratamiento de la insuficiencia cardiaca aguda descompensada. Los nuevos biomarcadores que se relacionan de manera creciente con los procesos de lesión miocárdica, activación neurohormonal y remodelado ventricular son prometedores para mejorar el diagnóstico y el pronóstico de los pacientes con insuficiencia cardiaca aguda descompensada. Entre ellos se encuentran la región media del propéptido natriurético auricular, la ST2 soluble, la galectina-3, la troponina de alta sensibilidad y la región media de proadrenomedulina. También se ha asistido a la aparición de biomarcadores para la evaluación de la insuficiencia cardiaca aguda descompensada que facilitan el diagnóstico diferencial de la disnea, como la procalcitonina (para la identificación de la neumonía aguda), así como de marcadores que predicen las complicaciones de la insuficiencia cardiaca aguda descompensada, como son los marcadores de la lesión renal. En este artículo se examina la fisiopatología y la utilidad de los biomarcadores establecidos y los nuevos biomarcadores surgidos para el diagnóstico clínico, el pronóstico y el tratamiento de la insuficiencia cardiaca aguda descompensada.

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Abbreviations

ADHF: acute decompensated heart failure
ANP: atrial natriuretic peptide
BNP: B–type natriuretic peptide
MR–proANP: midregional proatrial natriuretic peptide
MR–proADM: midregional proadrenomedullin

INTRODUCTION

Acutely decompensated heart failure (ADHF) is a common and heterogeneous condition that is difficult to diagnose and treat. Evaluation and correct recognition of ADHF in patients with dyspnea (the cardinal symptom of affected patients) may be challenging[1]; when there are doubts about the diagnosis, higher risk is observed. Additionally, delay in diagnosis of ADHF is associated with higher mortality.[2] As a consequence, ADHF is not only morbid but is associated with significant health care expenditures. Improvement in the evaluation and management of the diagnosis is imperative, particularly with the rising incidence and prevalence of heart failure (HF) in the community.

While the basis of assessment for ADHF is (and always should be) standard history and physical examination, adjunctive testing to support clinical judgment has been shown to improve the accuracy of diagnosis and to aid prognostication and management. To be useful, such adjunctive testing should be rapidly available, easily interpretable, add to clinical variables and other objective tests, and should be cost–effective.[3] In this regard, over the last decade, several biomarkers have emerged to aid in the diagnosis, risk stratification, and management of ADHF.

NATRIURETIC PEPTIDES

Among the biomarkers in ADHF, natriuretic peptides are the best studied and validated, representing the gold standard biomarker that serves as a comparison for all other markers. The utility of B–type natriuretic peptide (BNP) and its inactive form, N-terminal pro-B-type natriuretic peptide (NT-proBNP), is reflected in their incorporation into clinical practice guidelines for the diagnosis of HF, as published by the American College of Cardiology, the American Heart Association,[4] the Heart Failure Society of America,[5] and the European Society of Cardiology.[6]

Both atrial natriuretic peptide (ANP) and BNP are primarily produced in the myocytes of the atria and ventricles, respectively,[7] and are produced in response to myocyte stretch from volume or pressure overload.[8] While ANP is premade and stored in cytosolic granules within the cardiomyocyte, BNP is synthesized *de novo* when the need arises. Following a series of processing steps during synthesis, in both cases, a propeptide is produced as the penultimate form of ANP and BNP; following the effects of proteolytic enzymes, corin and furin, the propeptides (pro–ANP and NT–proBNP) are cleaved from mature ANP and BNP, and are released at the same time as the biologically active C–terminal hormonal natriuretic peptides. As will be discussed, amino–terminal propeptides are substantially equivalent to the measurement of the mature, biologically–active natriuretic peptides from which they were cleaved for diagnostic/prognostic application.

While ANP, BNP, and their amino–terminal propeptide equivalents are cleared passively by several organs, including the kidneys, following their release, ANP and BNP also bind to natriuretic peptide receptors, which results in the generation of cyclic guanosine monophosphate, and leads to a cascade of favorable biological responses that teleologically reflect a "response" to the deranged physiology of HF: due to activation of guanylate cyclase, both ANP and BNP trigger vasodilation, natriuresis, and diuresis. Additionally, both lead to a reduction in the effects of the renin–angiotensin–aldosterone system, reduce myocardial stiffness, and improve lusitropy. Beyond passive removal and receptor clearance, both ANP and BNP are also rapidly degraded by catalytic enzymes in circulation, notably including the enzyme neprilysin.

Advances in the understanding of natriuretic peptide biology have led to the recognition of high complexity in their biology. For reasons that are not entirely clear, as HF worsens, it is now known that a greater percentage of circulating "BNP" and "NT–proBNP" is actually uncleaved precursor peptide (proBNP); assays for BNP and NT–proBNP cannot resolve whether they are measuring free peptide or the precursor, because the peptide contains both regions recognized by the assays. Notably, proBNP does not have the same ability as BNP to trigger cyclic guanosine monophosphate; thus, patients with high levels of proBNP show an effect, called the "natriuretic peptide handicap", in which, despite high levels of "BNP" they do not exhibit the effects of the mature, biologically active peptide.[9] Additionally, through the effects of neprilysin and other enzymes, BNP circulates as a mixture of variably degraded fragments, with relatively little mature 32 amino acid BNP.[10]

Diagnostic Evaluation

Natriuretic peptides are objective and reproducible, making them a potentially valuable tool in the evaluation of patients with suspected or proven HF. Several important studies have demonstrated the usefulness of BNP and NT–proBNP in conjunction with clinical judgment to diagnose or exclude ADHF.[11–13] Moreover, both of these natriuretic peptides have been shown to be useful for diagnostic evaluation of ADHF in both HFrEF (HF with reduced ejection fraction) and HF with preserved ejection fraction (HFpEF),[14] albeit with slightly reduced sensitivity in patients with HFpEF due to generally lower BNP and NT–proBNP levels among these patients.[15]

Suggested cutoffs for diagnostic use of BNP and NT–proBNP are depicted in Table 1. In the Breathing Not Properly study,[15] BNP concentrations were higher in patients judged to have ADHF compared with those who did not (110 ± 225 pg/mL vs 675 ± 450 pg/mL) and differed significantly as a function of New York Heart Association HF severity ($P < .001$). A BNP concentration above 100 pg/mL had a sensitivity of 90%, specificity 76%, and accuracy 83% for differentiating HF from other causes of dyspnea, and when compared with history, physical examination, laboratory values, and chest X–ray findings, BNP was the single best predictor of a final diagnosis of HF (area under the curve [AUC] = 0.91; 95% confidence interval [95%CI], 0.90-0.93; $P < .001$).[11]

NT–proBNP has also been shown to have similarly powerful clinical properties. In the PRIDE study,[12] NT–proBNP at age–specific cutpoints was highly sensitive and specific for the diagnosis of ADHF. Not only was NT–proBNP the strongest independent predictor of a final diagnosis of ADHF (odds ratio [OR] = 44; $P < .001$), its diagnostic usefulness when combined with clinical judgment was superior to those of both NT–proBNP testing and clinical judgment alone. Subsequent analysis in the International Collaborative of NT–proBNP study showed that