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Interpretation of B-type natriuretic peptides in the era of angiotensin receptor-neprilysin inhibitors☆

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Abstract Assessment of serum levels of natriuretic peptides, especially the amino-terminal portion (NT-proBNP) and the carboxy-terminal portion (BNP) of pro-B-type natriuretic peptide, has had a highly significant clinical impact on the diagnosis and prognostic stratification of patients with heart failure (HF). They are now an instrument with recognized value in this context and several studies have demonstrated their value in tailoring therapy for these patients. Following the recent advent of angiotensin receptor-neprilysin inhibitors (ARNIs), there is a need to review how these two biomarkers are interpreted in HF. The use of ARNIs is associated with a reduction in NT-proBNP but an increase in BNP levels. The authors of this concise article review the interpretation of natriuretic peptide levels in the light of the most recent evidence.

PALAVRAS-CHAVE
Insuficiência cardíaca;
Peptídeos natriureticos;
BNP;
NT-proBNP

Interpretação dos peptídeos natriuréticos tipo B na era dos antagonistas da neprilisina/recetores da angiotensina (ARNIs)

Resumo A determinação dos níveis séricos de peptídeos natriuréticos (porção aminoterminal do peptídeo natriurético tipo B–NT-proBNP ou da porção carboxiterminal - BNP) constituiu avanço científico com impacto clínico muito relevante no diagnóstico e na determinação prognóstica de doentes com insuficiência cardíaca (IC). São hoje um instrumento com valor reconhecido nesse contexto e diversos estudos sugerem o seu interesse na titulação da

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terapêutica desses doentes. Recentemente, com o conhecimento do valor terapêutico do uso de inibidores da neprilisina/antagonista dos recetores da angiotensina, o uso desses dois biomarcadores na IC carece de interpretação diversa. O uso desses fármacos associa-se à redução dos níveis de NT-proBNP mas a aumento dos níveis de BNP. Os autores neste artigo conciso reveem a interpretação e valorização dos níveis de peptídios natriuréticos à luz da evidência mais recente.

Since the end of the 20th century there has been an explosion of clinical research on biomarkers in heart failure (HF), particularly B-type natriuretic peptide. The value of this biomarker in the diagnosis of HF, particularly acute HF, is now clear.[1] Assessment of the carboxy-terminal portion (BNP) and the amino-terminal portion (NT-proBNP) of B-type natriuretic peptide enables clinicians to determine the mechanism associated with dyspnea: HF, when elevated or of non-cardiac cause; and pulmonary disease when low.[2,3] The diagnostic value of B-type natriuretic peptide is now recognized to be even greater when there is a high degree of uncertainty concerning the mechanism underlying dyspnea in the acute patient.[4] This instrument is available in most emergency departments in Portugal and it will be a challenge to evaluate its cost-effectiveness in the Portuguese health system. In other health systems, its clinical value, including cost-effectiveness, has been clearly demonstrated.[5,6]

The prognostic value of B-type natriuretic peptide is also recognized across the spectrum of HF severity, in both acute and chronic patients.[7–9] Variations in its levels are significantly associated with prognosis[10,11]: patients with higher levels despite optimization of therapy have a significantly worse prognosis than those with large (>30%) reductions.[10–14] These observations prompted various trials that set out to assess whether B-type natriuretic peptide levels were a valid target for evaluating the efficacy of treatment of HF patients. Another motive for these trials was the observation that therapies associated with prognostic improvement were linked to reductions in B-type natriuretic peptide levels (except for adrenergic blockers, which are associated with medium-term reductions only). The conclusions of these trials (10 to date) have been conflicting,[15,16] and differences in study design, target B-type natriuretic peptide levels and the methods used to achieve them hinder accurate interpretation of the results. However, all these trials have some points in common: therapy aimed at reducing B-type natriuretic peptide levels was not associated with a higher incidence of adverse effects, and natriuretic peptide-guided therapy appears to be of more benefit in patients aged under 75 years. When interpreting these biomarkers, it is also important to identify patients in whom modulation of the natriuretic peptide system will be more difficult due to 'ventricular exhaustion' (pathophysiological inability to synthesize and secrete natriuretic peptides).[17] Although these trials do not show decisively that modulation of natriuretic peptides is the way forward for the individualized treatment of HF patients, it still has considerable potential and hence remains under investigation.

The medical world was recently startled by the results of a study (PARADIGM-HF) that compared sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), and standard chronic HF therapy with enalapril. Sacubitril/valsartan simultaneously modulates the natriuretic peptide system and the renin-angiotensin-aldosterone system, a new approach in the treatment of chronic HF.[18] Sacubitril directly inhibits neprilysin, a neutral endopeptidase that degrades various endogenous vasoactive substances including A, B and C-type natriuretic peptides, angiotensin (hence the concomitant use of valsartan), bradykinin and adrenomedullin. The use of sacubitril/valsartan therefore results in higher BNP levels, although it has different affinities with BNP and NT-proBNP.[19] In vitro, neprilysin cleaves B-type natriuretic peptide at various levels, and the different assays used to determine serum BNP levels detect different epitopes, with the result that serum BNP measurements can vary by 25% depending on which epitopes are identified by the antibodies used in different reagents. Since sacubitril/valsartan affects all BNP assays, it may do so in different proportions, further complicating the interpretation of serum BNP levels.[19,20] Unlike BNP, NT-proBNP is not a substrate for neprilysin, so its levels are not directly affected by the drug's mechanism of action.

In the PARADIGM-HF trial, the use of sacubitril/valsartan resulted in increases of about 10% in BNP and of 90% in urinary cGMP (second messenger of BNP), and a reduction in NT-proBNP, in the short and medium term. Recent data from the trial show that patients in whom NT-proBNP levels were reduced below 1000 pg/ml had lower cardiovascular mortality and HF hospitalization rates regardless of the treatment arm to which they were allocated (with a 59% risk reduction compared to those in whom NT-proBNP levels did not decrease below 1000 pg/dl).[14] Sacubitril/valsartan decreased NT-proBNP to levels below 1000 pg/ml nearly twice as often as enalapril (31% vs. 17% of patients, respectively).[14] These observations have made NT-proBNP the tool of choice for monitoring HF patients in clinical practice in the future. The long-term behavior of BNP in patients under ARNI therapy is as yet unknown, and there

may even be further reductions in BNP levels, but its potential for monitoring these patients will remain compromised. In the authors' opinion, clinicians should be knowledgeable and experienced in the use of one of the forms of B-type natriuretic peptide; current knowledge indicates that NT-proBNP offers the best possibilities to the clinician in terms of clinical utility.

Recently, research into this new drug class has indicated that soluble neprilysin is a potential new biomarker in acute and chronic HF, and preliminary observations suggest it may be a more valuable prognostic marker than NT-proBNP.[20–23] More research will be needed to test this hypothesis and to refine the reagents before this biomarker can be introduced into clinical practice.

Take-home messages

- B-type natriuretic peptide (BNP/NT-proBNP) is an important instrument in the diagnosis of HF.
- B-type natriuretic peptide has prognostic value across the entire spectrum of HF severity.
- The clinical benefit of B-type natriuretic peptide for monitoring patients with HF is not yet proven.
- Clinicians should be familiar with the use of one of the forms of B-type natriuretic peptide, and currently NT-proBNP offers the most possibilities in terms of clinical utility.

Conflicts of interest

The authors have no conflicts of interest to declare.

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