Review

The Role of NtproBNP in Diagnosis and Treatment of Heart Failure with Preserved Ejection Fraction, Its Not Always a Seek and Hide Game

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The Role of NtproBNP in Diagnosis and Treatment of Heart Failure with Preserved Ejection Fraction, Its Not Always a Seek and Hide Game

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Abstract: Although heart failure with preserved ejection fraction (HFpEF) has become the predominant heart failure subtype, it remains clinically under-recognized. This, has been attributed to the complex pathophysiological mechanisms that accompany individuals with several co-morbidities and symptoms and signs of HFpEF. Natriuretic peptides have been recognized to have important role in the diagnosis and monitoring of patients with heart failure with reduced ejection fraction (HFrEF), but their role in HFpEF remains controversial. Its seems that the role of NtproBNP in the diagnosis of HFpEF, is mainly driven by the pathophysiological characteristics of the patients.

Keywords: heart failure; NPs; HFpEF; diet

1. Introduction

Heart Failure with preserved left ventricular ejection fraction (HFpEF) represents a complex pathophysiological condition, diagnosed in almost half of the patients with heart failure symptoms, while sharing the same prognosis with heart failure of reduced ejection fraction (HFrEF). Research in the last decade has substantially advanced our understanding of the pathophysiology of HFpEF [1,2]. However, diagnosis of those patients still remains challenging, especially compared to HFrEF. Natriuretic Peptides (NPs) measurement by General practitioners in high-risk populations such as those with hypertension or type 2 diabetes mellitus, may help in identifying patients with elevated ventricular diastolic pressures in order to strength the initiation of preventive measures, including medicine up-titration or novel therapies and, therefore, prevent or slow the development of heart failure [3,4]. In the case of patients with comorbidities like in the setting of obesity, HFpEF diagnosis may be underestimated due to the limitations of natriuretic peptides and resting echocardiography [5,6]. In this review, we aimed to present the current knowledge on the role of NtproBNP in the diagnosis and monitoring of patients with HFpEF, to illustrate pathophysiologic explanations that justify limitations in their use.

2. Pathophysiology of HFpEF

Heart Failure with preserved left ventricular ejection fraction does not represent a rare clinical condition. Furthermore, it is recognized that dichotomizing function using left ventricular ejection fraction is a major oversimplification, as those with small cavity size (due to hypertrophy), or significantly impaired long axis function may also develop low flow. Thus, heart failure can be presented with normal, increased, or reduced end-diastolic volume, but with reduced stroke volume. HFpEF has been described as a condition resulting from complex pathophysiological procedures, where abnormalities in peripheral blood circulation, coronary microvascular dysfunction, chronotropic incompetence, intrinsic left ventricular systolic dysfunction, pericardial restrain, and vascular stiffening [7,8]. Patients with HFpEF exhibit diastolic dysfunction due to impaired relaxation and/or increase passive stiffness; while imaging reveals left atrial dysfunction accompanied by right

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ventricular systolic impairment and progressive pulmonary hypertension. In a simplified approach of HFpEF, four main phenotypes have been introduced: the stiff artery HFpEF phenotype where decreased aortic compliance with decreased vasorelaxation with exercise and deacresaed blood pressure lability leads to alteration to arterio-ventricular coupling causing impaired left ventricular function; the second phenotype is the obese HFpEF where fat accumulation in epicardial and epicardial space promote systemic inflammation, plasma expansion and insulin resistance leading to bi-ventricular remodeling, volume overload and pericardial restrain; the third phenotype is the left atrial myopathy, where increased left ventricular filling pressures lead to morphologic and functional alterations of left atrial causing alterations to pulmonary circuit and right ventricular dysfunction; the fourth phenotype is the ischemic HFpEF where macrovascular or microvascular ischemia cause alterations in left ventricular systolic and diastolic function [9,10]. In clinical practice most patients with HFpEF show a combination of those phenotypes, where several pathophysiological procedures are overlapping causing a variety in the expression of circulating biomarkers and in cardiac imaging [11].

3. Clinical course of HFpEF

The clinical course of HFpEF across all spectrum of phenotypes is progressive in a long time period. Initially HFpEF: relatively little cardiac remodeling and mild impairment in LV mechanics, with elevation in LV filling pressures exclusively during exercise. With time, progressive deterioration in LA function and remodeling leading to secondary atrial functional MR and development of paroxysmal AF. Mild elevation in LV filling pressures at rest may develop at this stage. With further progression, LA remodeling/dysfunction progress further, with transition to permanent AF, worsening PH, pulmonary vascular remodeling and vasoconstriction, RV and RA dysfunction, severely impaired cardiac output, and increased pericardial restraint, findings of advanced HFpEF [1,2,12–14]. Thus, one of the main challenges is the early recognition of occurrence of HFpEF using a method with high accuracy in discriminating symptoms related to HFpEF from other conditions.

4. The Role of NtproBNP in the Diagnosis of HFpEF

In the diagnostic work up of HFpEF two algorithms have been created by American College of Cardiology and European Society of Cardiology. The first one which is more simplified uses clinical factors like age, obesity, arterial hypertension, atrial fibrillation, pulmonary hypertension and evidence of diastolic dysfunction, while the second one uses functional and morphological indices from echocardiography and levels of NtproBNP. Both scores, according to the points aligned to each characteristic, categorize patients in low- intermediate and high probability of having HFpEF [15,16]. Contrast to the diagnostic algorithm used for HFrEF in HFpEF the measurement of NtproBNP or BNP does not play any sole role, even as a high specificity marker. Interestingly, in HFpEF patients, NT proBNP values do not direct always diagnosis, as a significant proportion (up to 20-25%) show low BNP/proBNP (NPs) levels, even with confirmed increased levels of pulmonary wedge pressures. This situation has been attributed to genetic factors, obesity with mainly pericardial restrain due to adipose tissue but with mild intrinsic myocardial involvement, lack of wall stress, insulin resistance and increased androgens. Nevertheless, even HFpEF patients with mild intrinsic myocardial involvement, show a 3-fold worse outcome compared with patients without HFpEF. [17,18]

What is the main pathophysiological explanation for this controversy?

The prime stimulus for synthesis and release of BNP is myocyte stretch secondary to transmural distending pressure. On cleavage of proBNP 108; NT-proBNP 1–76 is released in a 1:1 ratio with its carboxy-terminal congener BNP 1-32. Plasma levels of NPs are influenced by left ventricle structure and function. In HFpEF, especially in the early stages, there is less increase in left ventricular dimension compared to increase to wall thickness, resulting to different influence of ventricular internal dimension, wall thickness and interventricular pressure on unit wall stress and cardiomyocyte stretch, compared to HFrEF. The primary driver of NP synthesis is the increased wall tension; thus, the diagnostic performance of NPs can be impaired especially in the early stages of

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HFpEF; although in acute setting of advanced symptomatic HFpEF NPs preserve their diagnostic role, but in the setting of incipient or treated HF, may remain in sub-diagnostic values [19,20]. Accordingly, plasma NP in acute decompensated HF (ADHF) are lower in HFpEF compared with HFrEF.

Plasma NT-proBNP (>600 pg/mL) and BNP (>100 pg/mL) are strong, relatively nonspecific, independent predictors of left ventricular restrictive filling. In HF, plasma NT-proBNP correlates with E/e', an echocardiographic index of LV filling pressures, With respect to right heart function, plasma concentrations of B-type NPs are inversely related to right ventricular ejection fraction and directly related to right ventricular dimensions and estimated intraventricular pressures. PARAMOUNT trial of valsartan-sacubitril therapy in HFpEF, demonstrated a significant relationship between plasma NT-proBNP and decreases in LV systolic longitudinal and circumferential strain, independently of age, sex, systolic and diastolic blood pressures, body mass index, left ventricular ejection fraction, left atrial volume index, atrial fibrillation and renal function. [21,22]

A recent secondary analysis of the RELAX trial, evaluated the role of biomarkers corresponding with echocardiographic phenotypes in HFpEF. In this analysis 216 patients with HFpEF were classified in 3 categories: Those with phenotype A, who were characterized by moderate (grade I—II) diastolic dysfunction, low values of left atrial enlargement and the least right ventricular dysfunction, and the highest left ventricular ejection fraction; phenotype B, which was the most common one, with the highest rate of grade III diastolic dysfunction, the high enlargement of left atrial, elevated E/e', and right ventricular dysfunction; and phenotype C with little to no diastolic dysfunction the second highest rate of left atrial enlargement, and normal E/e' in transmitral velocity and issue Doppler imaging. Interestingly, NT-proBNP, was associated with increasing left atrial enlargement and increased ratio E/e', so it was evident in groups A and C, but it was elevated in those patients with mainly presented myocardial fibrosis [23].

The interpretation of the results of every test is important, as in the clinical setting of HFpEF with many comorbidities, NT-proBNP level should be considered in concert with the clinical history, examination findings, and data from other tests, including a standard laboratory workup and cardiac imaging. Antropometric indices and clinical parameters, like age, obesity, preserved ejection fraction, renal dysfunction, and atrial fibrillation may affect the diagnostic performance of NTproBNP.

Table Causes of Nt-proBNP elevation and Echocardiographic correlations.

Cardiac	**Echocardiographic correlations**
_ Heart failure, acute and chronic _ Acute coronary syndromes _ Atrial fibrillation _ Valvular heart disease _ Cardiomyopathies _ Myocarditis _ Cardioversion _ Left ventricular hypertrophy	-left atrial enlargement -increased ratio E/e' -left ventricular longitudinal and circumferential strain
Noncardiac _ Age _ Renal impairment _ Pulmonary embolism _ Pneumonia (severe) _ Obstructive sleep apnea _ Critical Illness _ Bacterial sepsis _ Severe burns _ Cancer chemotherapy - Toxic and metabolic insults - excess sodium intake	**Pathophysiologic etiology for NTproBNP elevation** -increased wall tension -elevated filling pressures -cardiomyocyte stretch -

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5. The Role of NTproBNP in Risk Stratification of HFpEF

In the prognosis of Hf patients left atrial pressures and mitral valve filling and right ventricle function play the most important role [24]. Previous studies have revealed that in patients with exertional dyspnea and preserved left ventricular ejection fraction, NtproBNP levels at rest correlated with mean wedge pressures at peak of exercise [25,26]. In the context of STRONG HF study, 15% of the patients had HFpEF. In the whole study group intensified therapy, driven by NtproBNP levels demonstrated good tolerance and safety and reduction 180-days rehospitalization, illustrating the need for personalized medicine and shared decision-making [27].

6. Preventing Heart Failure Occurrence in Stage A

In primary prevention of HF occurrence, evidence for the role of biomarkers in diabetic patients come from the PONTIAC II (NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease). In patients with NT-proBNP >125 pg/ml without cardiac disease randomized in "control" group and intensified" group (receiving up-titration of RAS antagonists and betablockers), a significant reduction of the primary endpoint (composite CV death and CV hospitalization) (HR: 0.351, p = 0.044) was visible in the intensified group [28,29].

Since in diabetic cardiomyopathy an increased strain is imposed on the left ventricle and these peptides have been shown to correlate with transvalvular gradients and left ventricular hypertrophy, it would be reasonable to examine the possible use of natriuretic peptides for improving prognosis of the time of symptoms onset [30,31].

Natriuretic peptides have proven their value in the diagnosis of patients presenting with shortness of breath and in the clinical management of patients with heart failure. However, the long-term prognostic role of natriuretic peptides is being studied especially in subjects with risk factors for HF development (ACC stage A) and not clinically overt HF. In a meta-analysis of primary data from 40 studies including 95,617 individuals without a history of CV disease, NT-proBNP strongly predicted first-onset HF and augmented CHD and stroke prediction. The incremental predictive ability of NT-proBNP for CHD and stroke was greater than HDL cholesterol or CRP and NT-proBNP could serve as a multipurpose biomarker in new approaches that integrate HF into CVD primary prevention [32]. Additionally, in 16,492 patients with T2DM and a history of or at risk of CV events, there was a stepwise increased risk of hospitalization for heart failure with higher quartiles of baseline NT-proBNP. There was a significant increased risk of hospitalization for heart failure with use of established dichotomous cut point 125 pg/mL (for age <75 years). Beyond absolute increase in NT-proBNP by 400 pg/mL is associated with significantly heightened risk of CV events, dynamic changes of NT-proBNP over 6 months follow up, has shown a clear discrimination of risk and may be most practical for clinical practice in high and low categories including subjects with NTproBNP concentrations ≥400 pg/mL and <400 pg/mL, respectively [33,34].

7. Medication and Dietary Factors and NPs Levels

Medication therapy in HFpEF patients has not shown significant impact on NPs levels. In the TOPCAT study, higher NTproBNP levels were associated with a worse prognosis but the treatment benefit was greatest in the lowest risk tertile(<682ng/L) of NtproBNP, where probably fibrosis was predominant [35]. Additionally, Irbesartan in HFmrEF/HFpEF (I-PRESERVE) showed a progressive increase in morbidity and mortality with increasing plasma concentrations of NT-proBNP, but the medication did not improve overall prognosis [36]. In the case of empagliflozin in HFpEF, there was a borderline statistical difference on the impact of therapy on NtproBNP levels, although the impact on clinical outcomes was more significant [37]. The PARALLAX study, in 2572 patients with HFpEF, sacubitril/ valsartan versus standard medical therapy showed no effect on plasma NtproBNP levels and 6-minutes walking test [38]. Recently, Semaglutide treatment led to significant improvements in exercise capacity, as measured by the 6-min walk distance, and weight balance compared to the placebo group, but with no significant effects on NtproBNP levels. [39]

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The role of diet has been extensively investigated on general health [40]. Recent studies have also explored the role of diet on hemodynamic conditions of the heart, including biomarkers related with inflammation and elevated filling pressures. In 9,782 adults from NHANES 1999-2004 without self-reported cardiovascular disease, higher diet quality, and specifically lower dietary intake of sodium and added sugar, was associated with lower serum levels of NT-proBNP [41]. Several clinical trials have demonstrated that higher adherence to Mediterranean or DASH diet is related with lower blood levels of NT-proBNP. In the Prevenzion con Dieta Mediterranea (PREDIMED) trial, which enrolled individuals at a high-risk of cardiovascular disease, those following a traditional Mediterranean diet had lower NT-proBNP levels compared to those assigned to a low-fat diet. In the DASH trial, individuals who were randomly assigned to the DASH diet intervention for 8 weeks had lower levels of NT-proBNP than those who followed a control diet, similar to a typical American diet, mainly attributed to beneficial effect on oxidative stress and inflammation. Excessive salt intake induces inflammation, seems to produce reactive oxygen species, activate transcription of mineralocorticoid receptor-dependent genes, which can raise circulating BNP levels [42,43]. Excess sodium intake also activates the renin-angiotensin-aldosterone system, leading to increased fluid retention and volume expansion, which can place a strain on the heart and blood vessels and thus elevate NT-proBNP [44]. Thus, in patients with HF, type of diet consumed may have modifying effects on plasma levels of NPs.

8. Conclusion

Developing a standardized strategy to screen and intervene in patients at risk of HF can be difficult because of different definitions of HF risk, heterogeneity of prevalence in different populations, variable duration until clinical HF or LVD develops and variable interventions for risk factor modification or treatment. Nowadays, it becomes more obvious that the diagnosis of HF cannot be based only on clinical signs and symptoms, and markers reflecting hemodynamic condition as elevated NP levels can determine HF diagnosis. Special consideration should be taken concerning HFmildy reduced EF and HFpEF, where their diagnostic role is more limited compared to HFrEF.

Conflicts of Interest: The authors declare no conflict of interest.

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