Review

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Obese phenotype and natriuretic peptides in patients with heart failure with preserved ejection fraction

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Abstract: The results of several recent experimental studies using animal models and clinical trials suggested that obesity is not merely an epiphenomenon or a prominent comorbidity in patients with heart failure (HF). Indeed, recent studies suggest that obesity is intimately involved in the pathogenesis of HF with preserved ejection fraction (HFpEF). The most recent studies indicate that approximately 50% of HF patients have HFpEF. As standard pharmacological treatment usually shows only a weak or even neutral effect on primary outcomes in patients with HFpEF, treatment strategies targeted to specific groups of HFpEF patients, such as those with obesity, may increase the likelihood of reaching substantial clinical benefit. Considering the well-known inverse relationship between body mass index (BMI) values and B-type natriuretic peptide (BNP) levels, it is theoretically conceivable that the measurement of natriuretic peptides, using cutoff values adjusted for age and BMI, should increase diagnostic and prognostic accuracy in HFpEF patients. However, further experimental studies and clinical trials are needed to differentiate and better understand specific mechanisms of the various HFpEF phenotypes, including obese HFpEF.

Keywords: body mass index (BMI); B-type natriuretic peptide (BNP); fat tissue; glycosylation; heart failure; left ventricular ejection fraction; natriuretic peptides; NT-proBNP; obesity.

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Introduction

According to the 2016 European Society of Cardiology (ESC) guidelines [1], heart failure (HF) comprises a wide range of patients, from those with a left ventricular ejection fraction (LVEF) ≥50% (indicated as HFpEF) to those with a reduced (<40%) LVEF [indicated as HF patients with reduced ejection fraction (HFrEF)] (Table 1). Moreover, patients with LVEF values in the range of 40%–49% are defined as patients with HF with mid-range ejection fraction (HFmrEF) [1].

The prevalence of HF reported in epidemiological and clinical studies depends on the definition applied but is approximately 1%–2% of the adult population in developed countries, rising up to ≥10% among people >70 years of age [1, 2]. Among people >65 years of age presenting to primary care with breathlessness on exertion, one in six will have unrecognized HF (mainly HFpEF) [2, 3]. The proportion of patients with HFpEF varies greatly among the studies (from 22% to 73%), depending not only on the definition applied but also on the clinical setting (primary care, hospital clinic or hospital admission), age and sex of the studied population, as well as the year of publication [1]. In accordance with these considerations, even if the prevalence of HFpEF remains at 50% of all HF patients [1, 4, 5], further studies are needed to accurately evaluate the prevalence of HFpEF with regard to clinical setting, gender and age.

Recent data demonstrated that patients with HFpEF or HFrEF have different epidemiological, etiological, clinical and prognostic profiles [1, 2, 4–10]. Compared to patients with HFrEF, patients with HFpEF are older, more often women and more commonly they have a history of hypertension and atrial fibrillation, whereas a history of myocardial infarction is less common [1–5] (Table 2). According to these data, some studies [6–10] have been specifically designed to demonstrate one or more distinct phenotypes in patients with HFpEF with respect to HFrEF.

Table 1: Classification of heart failure according to 2016 ESC guidelines [1].

Criteria	HFrEF	HFmrEF	HFpEF
1	Symptoms ± signs[a]	Symptoms ± signs[a]	Symptoms ± signs[a]
2	LVEF < 40%	LVEF 40%–49%	LVEF ≥ 50%
3		1. Elevated BNP/NT-proBNP 2. At least one additional criterion: a. Relevant structural heart disease (LVH and/or LAE); b. Diastolic dysfunction	1. Elevated BNP/NT-proBNP 2. At least one additional criterion: a. Relevant structural heart disease (LVH and/or LAE); b. Diastolic dysfunction

BNP, B-type natriuretic peptide; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; LAE, left atrial enlargement; LVH, left ventricular hypertrophy. [a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

Table 2: Differences between patients with HFrEF and HFpEF, concerning the demographic and clinical characteristics, as well as the presence of comorbidities and functional and structural cardiac alterations (according to the references [1, 4–9]).

	HFpEF	HFrEF
Demographic		
Age	Older median age (>75 years)	Younger median age (≤75 years)
Sex	More likely to be females	No sex prevalence
Comorbidities		
Hypertension	High prevalence	Low association
Obesity	High prevalence	Low association
Diabetes mellitus	High prevalence	Low association
Metabolic syndrome	High prevalence	Low association
Renal dysfunction	High prevalence	Low association
COPD	High prevalence	Low association
Anemia	High prevalence	Low association
Structural alterations		
Type of LV remodeling	Concentric	Eccentric
LV chamber dimension	In the normal range	Increased
Wall thickness	Increased	In the normal range
Ventricular mass	Increased	Increased
Mass/volume ratio	Increased	Reduced
CAD	Variable prevalence of CAD related to the presence of comorbidities	High prevalence of CAD
AMI	Low presence of previous AMI	Strong association with previous AMI
LBBB	Low prevalence	High prevalence
Functional alterations		
LVEF	LVEF > 50%	LVEF < 40%
DD	Present	Low presence of DD
EDV	In the normal range	Increased
ESV	In the normal range	Increased
Stroke work	In the normal range	Reduced
ESE	In the normal range	Reduced
EDS	Increased	Reduced
Ultrastructure alterations		
Myocyte diameter	Increased	Normal
Myocyte length	Normal	Increased
Type of myocardial fibrosis	Interstitial and reactive	Focal or replacement

COPD, chronic obstructive pulmonary disease; LV, left ventricular; CAD, coronary artery disease; AMI, acute myocardial infarction; LBBB, left bundle branch block; LVEF, left ventricular ejection function; DD, diastolic dysfunction; EDV, end-diastolic volume; ESV, end-systolic volume; ESE, end-systolic elastance; EDS, end-diastolic stiffness.

Can obesity actually contribute to HFpEF pathophysiology?

The pathophysiology of both HFrEF and HFpEF is complex, and these disorders are actually considered a heterogeneous syndrome that is caused or exacerbated by a variety of comorbidities linked to both cardiac and extracardiac abnormalities [4, 5].

In contrast to HFrEF, HFpEF does not present a well-defined model of progression and exhibits a wide heterogeneity in phenotypic expression [4, 5, 7]. The initial description of this entity was based on the occurrence of HF in a concentrically hypertrophied heart with a normal EF and small cavity size (often in the setting of hypertension) [4]. Because this clinical condition was believed to be primarily related to diastolic dysfunction, it was initially described as "diastolic" HF [5]. More recently, a great number of studies have made clear that several mechanisms, a variety of comorbidities and some cardiac and extracardiac abnormalities are involved in the pathophysiology of HFpEF [4–7]. The differences between patients with HFrEF and HFpEF, with regard to their demographic and clinical characteristics as well as the presence of comorbidities and functional and structural cardiac alterations, are summarized in Table 2.

Obesity has reached epidemic proportions worldwide, and it is also a common comorbidity in HFpEF patients [4, 7]. Obesity has many deleterious effects on the cardiovascular system, mediated by changes in volume status, cardiac load, energy substrate utilization, tissue metabolism and systemic inflammation, which are believed to promote disease progression [11–13]. These data suggest that obesity-related HFpEF actually may represent a clinically relevant, distinct phenotype (i.e. independent of other risk factors including hypertension, diabetes mellitus [DM] and other cardiovascular alterations) within the broad spectrum of HFpEF. However, it is well known that obesity is strongly associated with other common non-cardiac clinical conditions, which can actually contribute to the pathophysiology of HFpEF (i.e. systemic arterial hypertension, DM, metabolic syndrome and obstructive sleep apnea) [6, 7, 14–17]. This observation may indicate that obesity may only be a surrogate of these clinical conditions in the pathogenesis of HFpEF.

Several large clinical trials demonstrated that standard pharmacological treatment, based on drugs effective in HFrEF, usually shows only a weak or even neutral effect on primary outcomes in patients with HFpEF [1, 4, 5, 7, 18–20]. Only in the last 5 years, some studies have addressed the hypothesis that obesity may represent not only a clinically relevant pathophysiological mechanism [6, 12, 13] but also a specific phenotype within the broad spectrum of HFpEF [7, 10, 21]. It is theoretically conceivable that treatment strategies targeted to specific groups of HFpEF patients, such as those with obesity, may increase the likelihood of reaching substantial clinical benefit [22, 23].

It is well known that obesity is associated with structural and functional changes in the heart, such as left ventricular (LV) hypertrophy, left atrial enlargement and subclinical impairment of LV systolic and diastolic function [12]. Many of these abnormalities are considered to be precursors of more overt forms of cardiac dysfunction and HF [6, 12, 23, 24]. In addition, in both HFpEF and HFrEF, there is a large increase in adipose tissue within skeletal muscle, even in non-obese patients, and this is a significant independent contributor to exercise intolerance (specifically in HFpEF) [23, 24]. Increased lipid content in skeletal muscle can impair perfusion and mitochondrial function and reduce capillary density [23, 24]. Accordingly, it is generally assumed that longstanding obesity may lead to HF [12, 23]. However, only more recently, several studies have demonstrated that increased adiposity promotes inflammation, hypertension, insulin resistance and dyslipidemia, leading to impairment of diastolic, systolic, arterial, skeletal muscle and endothelial functions [6–10, 21, 24–28].

Adipose tissues produce not only several proinflammatory cytokines and adipokines [29, 30] but also other cardiovascular active substances, including angiotensin-II and aldosterone [31–33], which promote reverse cardiac remodeling [34]. In particular, obesity is associated with ectopic lipid deposition (even in the heart), which may directly exert a lipotoxic effect on the myocardium by *in loco* secretion of cytokines and adipokines [35]. Increased paracardiac fat is associated with increased cardiac events and adverse changes in myocardial function [36]. These deleterious effects, associated with ectopic deposition of lipids in non-adipose tissues, are currently termed lipotoxicity. Indeed, several experimental studies based on cell culture or animal and human models have clearly shown a close relationship between the accumulation of lipids in cardiac tissues and heart dysfunction [23, 37]. When lipids are largely in excess with respect to body demands, non-metabolized lipids can be stored as triglycerides or, alternatively, shunted into non-oxidative pathways resulting in the accumulation of toxic lipid species [37]. Toxic lipids are able to alter cellular signaling, promote mitochondrial dysfunction and increase apoptosis [37–40]. On the other hand, different classes of lipids, such as sphingolipids can play regulatory roles

in cardiac disease. As an example, ceramide can cause cardiac dysfunction, whereas sphingosine 1-phosphate can prevalently exert cardioprotective effects [41]. These studies, taken as a whole, strongly indicate that obesity is intimately involved in the pathogenesis of HFpEF [6–12, 21, 23–33, 35–41].

Does obesity constitute a distinct phenotype for patients with HFpEF?

Although a considerable number of HFpEF patients are obese, not all patients with HFpEF have an increased body mass index (BMI) [6, 18, 23, 42]. A high BMI value is one of the most important and strongest independent risk factors (together with age, sex and hypertension) for the development of HFpEF [13, 19, 23, 43, 44]. In Western countries, >80% of older patients with HFpEF (more than twice the percentage of the general population) are overweight or obese [13, 23, 43–47]. Thus, obesity is a common, modifiable risk factor for HFpEF, more than twice as common as other risk factors more often cited, such as DM and atrial fibrillation [23]. However, high BMI values are often considered an exclusion criterion in clinical trials regarding patients with HFpEF [18, 23]. As an example, the very recent PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in HF Patients with Preserved Ejection Fraction clinical trial) study excludes patients with BMI ≥ 40 kg/m^2 (ClinicalTrials.gov.https://clinicaltrials.gov/ct2/show/NCT01920711).

Indeed, the exclusion of patients with higher BMI values from clinical studies enrolling HF patients actually precludes the possibility to test the hypothesis that obesity is a distinct phenotype for HFpEF. To explore this specific hypothesis, Obokata et al. [10] performed a clinical trial based on a detailed characterization of cardiovascular structure, function and reserve capacity in three distinct groups of individuals: obese HFpEF patients (BMI ≥ 35 kg/m^2; n = 99), non-obese HFpEF patients (BMI < 30 kg/m^2; n = 96) and non-obese control subjects without HF (n = 71). Compared to both non-obese HFpEF patients and control subjects, obese HFpEF patients displayed increased plasma volume, more concentric LV remodeling, greater right ventricular (RV) dilatation and dysfunction, increased epicardial fat thickness and greater total heart volume, despite lower NT-pro B-type natriuretic peptide (BNP) levels. Moreover, pulmonary capillary wedge pressure (PCWP) was related to BMI and plasma volume in obese, but not in non-obese HFpEF patients. The increase in heart volumes in obese HFpEF patients was associated with greater pericardial restraint and elevated ventricular interdependence, reflected by increased ratio of right-to-left-sided heart filling pressures, higher pulmonary venous pressure relative to LV transmural pressure and greater LV eccentricity index. Finally, compared with non-obese HFpEF patients and control subjects, obese HFpEF patients displayed worse exercise capacity, higher biventricular filling pressures with exercise and depressed pulmonary artery vasodilator reserve. These data, taken as a whole, strongly suggest that obesity-related HFpEF is a genuine form of cardiac failure based on a clinically relevant phenotype [10, 18].

Cardiac natriuretic peptides in HFpEF

The measurement of cardiac natriuretic peptides (i.e. ANP and B-type natriuretic peptide [BNP]) was proposed for the diagnosis and management of HF in 90th years of the last century [48–51]. The most recent ESC international guidelines [1] propose natriuretic peptides for the diagnosis of exclusion of HF. The proposed cutoff values for BNP/NT-proBNP measurement have a high negative predictive value for HF, in particular for HFrEF [1]. On the other hand, these guidelines suggest that BNP or NT-proBNP levels higher than the suggested cutoff values are required for the diagnosis of HFpEF [1]. It is important to take into consideration the different role of cardiac biomarkers in the diagnosis of HF subtypes (i.e. HFrEF vs. HFpEF). In HFrEF, the measurement of low BNP/NT-proBNP levels is recommended for ruling out HF [1, 52], whereas increased levels of cardiac natriuretic peptides are essential for the diagnosis of HFpEF [1]. In particular, in patients with symptoms and signs of HF and LVEF ≥ 50%, elevated levels of cardiac natriuretic peptides are needed, together with the presence of relevant structural heart disease or diastolic dysfunction, for the diagnosis of HFpEF [1].

From the analytical point of view, it is important to note that the cutoff values, suggested by international guidelines [1] for BNP measurement, should only be considered indicative by clinicians [52], because there are great systematic differences (up to two to three fold) between the BNP values measured with the most popular immunoassay methods, commercially available in both Europe and North America [53–55]. On the contrary, the cutoff values reported by international guidelines for NT-proBNP assays are more reliable, because only one manufacturer distributes the standard and materials for all

immunoassay methods, commercially available in Europe for NT-proBNP measurement [52–55].

From a clinical point of view, BNP/NT-proBNP assays cannot differentiate between HFrEF and HFpEF; however, the BNP/NT-proBNP levels found in HFpEF patients are on average lower than those of HFrEF patients [1, 52, 56]. However, cutoff values of BNP and NT-proBNP, validated for diagnosis of undifferentiated acutely decompensated HF, remain useful in HFpEF patients with minor loss of diagnostic performance [56].

Relationship between cardiac natriuretic peptides and obesity in HFpEF

Stavrakis et al. [57] reported an inverse relationship between BMI and BNP levels in a cohort of 150 patients hospitalized with HFpEF. In this study [57], higher BMI values were associated with lower mortality, whereas higher BNP levels predicted higher mortality in male patients with HFpEF. However, this study has the limitation that studied patients were not accurately investigated with regard to hemodynamics, filling pressures and wall stress.

More recently, Obokata et al. [10] reported that 99 obese HFpEF patients showed NT-proBNP values (median 213 ng/L, interquartile range 62–838 ng/L) significantly higher than those observed in 71 non-obese control subjects (median 89 ng/L, interquartile range 54–241 ng/L), but greatly lower (about 2/3 less) than those found in 96 non-obese HFpEF patients (633 ng/L, interquartile range 249–1545 ng/L). Furthermore, in this study [10], plasma NT-proBNP levels were correlated with filling pressures in all patients with HFpEF, and the PCWP values were higher in the presence of obesity. Although BMI, estimated plasma volume and PCWP values were significantly higher in obese compared to non-obese HFpEF patients, NT-proBNP circulating levels were significantly lower in obese than in non-obese patients [10].

The data reported by Stavrakis et al. [57] and by Obokata et al. [10] actually confirm that obese patients with HF, including those with HFpEF, usually show lower cardiac natriuretic circulating levels than non-obese patients with HF [58]. Moreover, these data [10, 57] are well in accordance with the hypothesis suggesting that the cardiac natriuretic hormone system is abnormally regulated in obese subjects [58–61]. The cause(s) of lower levels of natriuretic peptides in obese compared to non-obese patients is (are) at present unknown [58–61]. This natriuretic handicap was previously attributed to enhanced natriuretic peptide degradation in fat tissue, presence of substances secreted by adipose tissue with inhibitory effects on cardiac natriuretic peptide production by cardiomyocytes, alterations in sex hormone production/activity or insulin resistance [58–64].

Obokata et al. [10] have recently suggested a new hypothesis to explain the natriuretic handicap in obese patients with HFpEF. Assuming that diastolic wall stress is the primary stimulus for BNP release in obese HFpEF patients and that wall stress is reduced as external pressure applied to the ventricle increases; therefore, in obese patients, increased epicardial fat can induce a pericardial restraint, and in this way (in accordance with the Laplace's law) it can reduce wall stress and, consequently, also the production of BNP by ventricular cardiomyocytes.

Although this hypothesis may have a role in the pathophysiology of HFpEF, there are other important biochemical and methodological aspects to take into account regarding the production and measurement of BNP in obese patients with HFpEF. It is well known that obese patients with HFpEF have an increased prevalence of DM compared to HFrEF patients [1–7]. In the study by Obokata et al. [10], the prevalence of DM in obese HFpEF patients is 33% compared to 15% in non-obese HFpEF patients ($p < 0.001$). Furthermore, it is well known that diabetic patients have increased production of glycosylated peptides and proteins [65] and that glycosylation of peptides and proteins can play an important role in the pathogenesis of complications of DM [66]. Recent studies demonstrated that glycosylation can interfere with the regulation of BNP production [67]. In addition to BNP and the inactive peptide NT-proBNP, a large number of circulating proBNP-derived fragments can be identified by chromatographic procedures in human plasma of HF patients, including the intact and glycosylated forms of the precursor proBNP [68–77]. Several studies have also demonstrated that intact or glycosylated forms of proBNP constitute the predominant portion of immunoreactive B-type-related peptides circulating in the plasma of patients with HF [67–75]. The proBNP is in part O-glycosylated within the Golgi apparatus. If the proBNP is glycosylated at position 71, the propeptide cannot be processed by proteases, and so 71-glycosylated proBNP will be secreted in its intact form into circulation [75]. According to these data [67–75], another possible cause of lower NT-proBNP values in obese HFpEF patients compared to non-obese HFrEF patients may be represented by the increased glycosylation at position 71 of proBNP, which is able to inhibit the conversion of prohormone into BNP and NT-proBNP, and

so in this way to reduce the circulating levels of the biologically active peptide BNP_{1-32}. However, to date, there are no data about increased plasma concentrations of 71-glycosylated proBNP in obese compared to non-obese patients with HFpEF.

As far as the methodological aspects are concerned, a recent study [78] reported that the commercial immunoassays commonly used for NT-proBNP assay use non-glycosylated calibrator materials and mostly antibodies directed against epitopes with potential O-glycosylation site occupancy. It is also well known that there are systematic differences between the different immunoassay systems for BNP and NT-proBNP due to some cross-reactions with glycosylated or non-glycosylated proBNP-related peptides [53–55, 79]. Recent studies indicated that a large part of circulating levels of proBNP and NT-proBNP are glycosylated [73–76]. Considering these data as a whole [73–76], it is conceivable that the commercially available immunoassays measure only a part of the circulating NT-proBNP molecules. Moreover, the intact peptide proBNP (especially if non-glycosylated) can also interfere in the commercially available immunoassays for NT-proBNP [79]. In conclusion, the commercially available immunoassays for NT-proBNP do not allow an accurate measurement of this peptide. Therefore, data dealing with NT-proBNP levels in obese compared to non-obese patients need to be confirmed using more accurate methods for the measurement of BNP [80].

Usefulness of BNP/NT-proBNP monitoring in obese HFpEF patients

The data reported by Obokata et al. [10] clearly suggest that obese HFpEF patients can be separated from non-obese HFpEF patients by taking into account a set of several functional parameters and structural characteristics, including BMI, plasma volume, NT-proBNP, DM, obstructive sleep apnea and renal dysfunction. Therefore, these data could be used to separate the HFpEF patients into two different distinct phenotypes, as also suggested by other authors [7, 14, 23, 81].

New pathophysiological classifications are useful only if they actually improve the clinical management of patients. Several studies indicated that prevention of HFpEF by optimally treating comorbidities (such as hypertension, obesity, DM, coronary artery disease and renal failure) is effective [82]. However, the standard pharmacological treatment recommended by international guidelines for HFrEF patients is less effective in HFpEF patients [1, 7, 22, 83–85]. Potential explanations for these negative results are not only the use of drugs inactive (or poorly active) against the pathophysiological mechanisms of HFpEF but also inadequate diagnostic criteria, enrolment of patients without true HF or at early stages of the syndrome, poor matching of therapeutic mechanisms and primary pathophysiological processes, as well as some limitations in experimental study protocols, such as suboptimal study designs, inadequate statistical power or patient heterogeneity [22]. Matching treatment strategies to a specific patient's phenotype in HFpEF may be a promising approach that warrants testing in clinical trials and may increase the likelihood of demonstrating clinical benefit [7, 18, 22, 23].

In 2013, the Dallas Heart Study [86] investigated the association between NT-proBNP levels and body fat distribution by dual energy x-ray absorptiometry and magnetic resonance imaging in a multiethnic cohort, including a total of 2619 participants without HF. Cross-sectional associations of natriuretic peptides with adiposity phenotypes were examined after adjustment for age, sex, race, comorbidities and BMI. This study demonstrated that higher NT-proBNP levels were independently associated with a more favorable distribution of tissue fat, characterized by decreased visceral and liver fat and increased lower body fat [86]. More recently, some studies reported an increase in NT-proBNP levels after a short time (3 weeks) [87] or longer periods (1 year) [88] of lifestyle intervention in obese patients, suggesting that an appropriate therapeutic intervention is able to correct the natriuretic handicap in obese patients.

In the last years, increasing experimental evidence has supported the hypothesis that natriuretic peptides play an important role in energy balance control (both at rest and during exercise) and glucose homeostasis [89] (Figure 1). Activation of the cardiac natriuretic peptide system by exercise may contribute to increase fatty acid mobilization from adipose tissue and their oxidation by skeletal muscle [90]. The lipolytic activation due to cardiac natriuretic peptides in adipose tissue is reduced in some pathophysiological conditions, including overweight/obesity [91], polycystic ovary syndrome [92] and hypothyroidism [93], whereas it is increased in hyperthyroidism [93], HF [94] and cancer cachexia [95]. Moreover, natriuretic peptides can activate a thermogenic program in brown and white fat in mice [96], increase energy expenditure and inhibit food intake [61, 97].

Taking into account these results [8, 83–97], some authors suggested the usefulness of monitoring BNP/NT-proBNP levels not only in patients with obesity and/or diabetes [61] but also in obese HFpEF patients [23, 98].

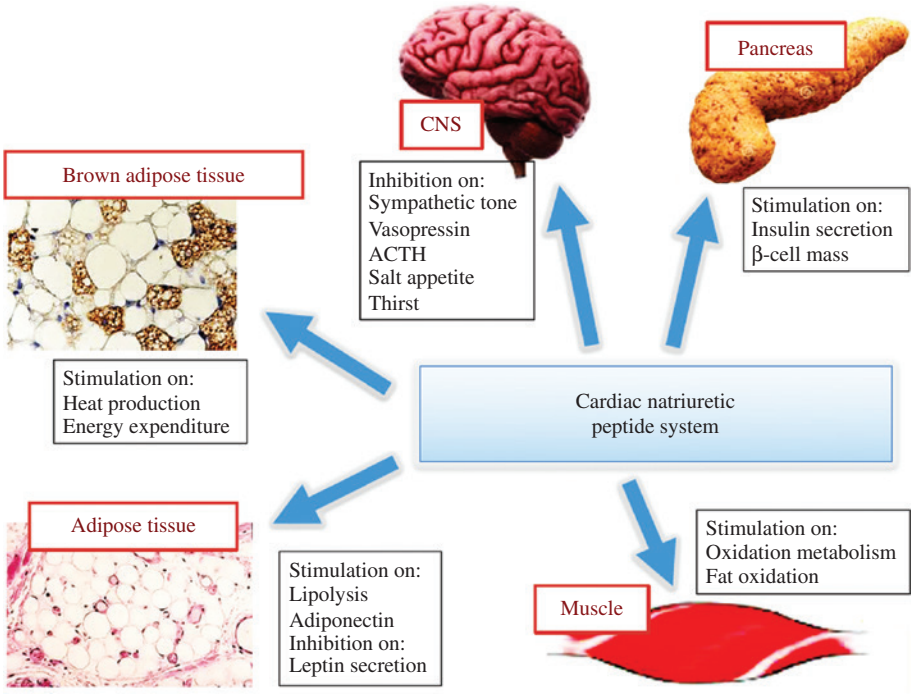

Figure 1: Effects of cardiac natriuretic peptides on energy balance control and glucose homeostasis, according to references [87–92]. CNS, central nervous system.

Considering the well-known inverse relationship between adiposity and BNP/NT-proBNP levels [45, 58, 98], it is theoretically conceivable that BNP/NT-proBNP assays should show reduced diagnostic sensitivity for HF but increased specificity in detecting obese HFpEF patients [23]. Accordingly, an obese patient who crosses a specific threshold for BNP/NT-proBNP is likely to have a true diagnosis of HF and also more severe disease than a patient with a lower BMI and the same cardiac biomarker levels [23, 99]. Furthermore, BNP/NT-proBNP assays may be used to detect the response of obese HFpEF patients to lifestyle interventions, as suggested by results of some recent clinical trials [87, 88, 98].

Conclusions and future perspectives

The results of several recent experimental studies using animal models [12, 31–33] and clinical trials [10, 11, 24–28, 36] strongly indicate that obesity is not merely an epiphenomenon or a prominent comorbidity in HF patients but that it is intimately involved in the pathogenesis of HFpEF [18, 23]. As standard pharmacological treatment usually shows only a weak or even neutral effect on primary outcomes in patients with HFpEF [5, 7, 20, 22], treatment strategies targeted to specific groups of HFpEF patients, such as those with obesity, may actually increase the likelihood of reaching substantial clinical benefit [7, 26–28]. Considering the well-known inverse relationship between BMI values and BNP/NT-proBNP levels in HF patients [58–60, 98, 99], it is theoretically conceivable that the measurement of natriuretic peptides, using cutoff values adjusted for age and BMI, should increase diagnostic and prognostic accuracy in HFpEF patients [18, 23]. Unfortunately, at present time, there is no evidence that the cutoff values adjusted for BMI can improve the diagnosis and prognosis in HFpEF patients. Therefore, further studies are needed to demonstrate the usefulness of BMI-adjusted cutoff values. Furthermore, there is a pressing need of some studies specifically designed to better understand the pathophysiological mechanisms of various HFpEF phenotypes, including obese HFpEF.

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