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B-type natriuretic peptide levels and benign adiposity in obese heart failure patients

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Abstract
Obesity is a major risk factor for the development of chronic heart failure (CHF) and does not only pose diagnostic challenges, but also has prognostic implications for these patients. Paradoxically, obese patients with CHF have a better prognosis than thinner individuals. In recent years, it has been demonstrated that the adipose tissue, even in patients with HF, is not always detrimental, and that obesity may coexist with a phenotype of benign adiposity without systemic metabolic abnormalities. Experimental data have shown that natriuretic peptides (NPs), and in particular brain natriuretic peptide (BNP), play a major role in the communication of the heart with the adipose tissue. Body fat distribution and adipose tissue function show a large degree of heterogeneity among depots and may explain the complex relationship between NPs and body fat. NPs can affect both the quality and the behaviour of fatty tissue, promoting a healthy adipocyte phenotype, and can favourably affect body fat metabolism. In this article, we review the existing literature on the bidirectional effects of BNP and adipose tissue in HF and highlight the complexity of this relationship.

Keywords Natriuretic peptides · Obesity · Heart failure · Body mass index

Introduction

Natriuretic peptides (NPs) are produced by the endocrine action of the heart, brain and endothelium when cardiac function is disrupted and the organism attempts to restore normal circulatory conditions [1]. Chronic heart failure (CHF) is a clinical condition that is mainly characterised by a profound activation of NPs. Apart from their significant contribution to the preservation of homeostasis and the organism's hemodynamic load, the release of NPs in CHF has beneficial metabolic effects on adipose tissue metabolism and function [2, 3].

The NP system consists of the following: atrial natriuretic peptide (ANP); brain natriuretic peptide (BNP) and C-type natriuretic peptide. The amino-terminal fragment of the BNP prohormone (NT-pro-BNP) is also one of the NPs, since it derives from the proteolysis of BNP. Since its discovery, BNP has been established as a biomarker for both the diagnosis and prognosis of CHF [2]. Recently, treatment modalities that increase its bioavailability and action have been indicated as an established treatment in HF patients [4, 5].

Obesity is a major risk factor for the development of CHF and complicates its diagnosis [6–8]. Paradoxically, obese patients with CHF appear to have a better prognosis than lean individuals [9, 10]. Interestingly, in recent years, it has been shown that the adipose tissue, even in HF, does not always have a detrimental action and that under certain circumstances, fat depots may exert favourable endocrine effects. The adipose tissue exerts a major impact on the cardiovascular system by release of active adipokines that control nutritional intake, sensitivity to insulin and secretion of anti-inflammatory mediators [11]. Although there is a different response between physiological and pathological conditions, epicardial and perivascular adipose tissue secretomics are critical for cardiovascular system health, via secretion of adipokines which protect the myocardium and vasculature by regulating energy substrate and Ca^{2+} metabolism [12]. In addition, experimental evidence has shown that the presence

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of BNP is a pivotal messenger in the cross-talk between the heart and adipose tissue. Many studies in CHF patients have proved that obese individuals have reduced NP levels [13], suggesting that there is a differential activity of BNP and NT-pro-BNP that is related to body mass index (BMI). No precise interpretation of this relation has been reported so far, nor is it clear what the pathophysiological mechanisms are, or what role the adipose tissue plays in HF. The current concept is that the adipose tissue is a complex organ with different subtypes and depots. Some of these appear to have cardioprotective properties that additionally activate BNP and NT-pro-BNP in a positive manner [14, 15]. However, the pathophysiological interplay between fat and BNP in CHF is complex, depending on several coexistent conditions and factors that we are still unable to interpret. In this article, we review the existing literature on the bidirectional effects of BNP and adipose tissue in HF.

Metabolic effects of BNP on adipose tissue

BNP is a cardiac hormone with cardiovascular and metabolic effects. It has an important role as a beneficial modulator of myocardial remodelling, given its significant antifibrotic, anti-inflammatory and anti-hypertrophic effects on the heart [16]. However, we know that BNP may exert beneficial effects on fat metabolism in humans. Adipocytes express natriuretic receptor-A peptides (NPR-A), which mediate the biological effects of both ANP and BNP [17]. These receptors have an extracellular ligand-binding and membrane-spanning region, an intracellular particulate guanylyl cyclase region and an intracellular cGMP-dependent protein kinase region [18]. NPs have lipolytic and lipomobilising effects on adipose tissue [19]. NPs specifically bind to guanylyl cyclase/NPR-A receptors, which generates the intracellular second messenger cGMP. NPs signal through the NPR-A/cGMP system and are inactivated by a clearance receptor NPR-C and neutral endopeptidases. As an intracellular second messenger, cGMP activates protein kinase and phosphodiesterase to modulate various pathways including ion channels, protein phosphorylation and gene expression, all of which boosts biologic functions such as natriuresis, diuresis, vasodilation, antiproliferation, antihypertrophy, antifibrosis and other cardiometabolic actions [18].

Experimental studies have shown that the activation of brown adipose tissue confers beneficial effects on adiposity and insulin resistance. [20] Apart from the classic human brown adipocytes, there are adipocytes in the white adipose tissue depots that are called beige and can acquire brown adipose tissue-like characteristics in response to environmental cues. The induction of beige adipocytes is called ‘browning’ and might reduce adverse effects of the white adipose tissue and improve metabolic health [21]. NPs may stimulate lipolysis [22], promote browning of adipocytes [14, 15] and enhance the production of adiponectin from adipocytes [23] (Fig. 1). BNP promotes the production of adiponectin from the adipose tissue, not only under healthy conditions but also in CHF [23]. Adiponectin is secreted from the adipose tissue and plays a role in glucose metabolism, insulin resistance and obesity [24–26]. It is an adipokine with well-established beneficial metabolic actions, and it has a protective role against the development of diabetes mellitus and cardiovascular diseases (CVD) [27]. It has been claimed that, in advanced CVD, BNP is elevated as a defence mechanism to protect the cardiovascular system [28]. In healthy individuals, systemic low-grade inflammation suppresses adiponectin levels; researchers have suggested that this may represent a link between inflammation and the development of CVD [2]. The same investigators showed that BNP is a strong stimulus for adiponectin release from all AT depots and regulates the levels and the release of adiponectin [2]. Based on these reports in the literature, part of the beneficial and cardioprotective action of BNP may be mediated by adiponectin and its release by the adipose tissue.

Indeed, the beneficial metabolic effects of BNP have been demonstrated in vitro and in vivo. Experimental studies have shown that animal models that overexpress or are treated with exogenous infusions of NP exhibit reduced fat mass, improved glucose tolerance and enhanced energy expenditure [15]. Neeland et al. [29] demonstrated a significant association between higher levels of NPs and a favourable adiposity profile, including decreased visceral and liver fat and increased lower body fat, independent of age, sex, race and obesity status.

However, the pathophysiology is more puzzling, since in HF and severe atherosclerotic disease the effects of BNP on adiponectin biosynthesis and on adipocyte function are less clear. Starting at the cellular level, the myocardial cells of a failing myocardium are metabolically remodelled. CHF stimulates the release of free fatty acids (FFAs) from the adipose tissue [30]. Although FFAs are the major substrate for cardiac metabolism, the increased FFA influx to the myocardium might have adverse effects on cardiac function, contributing to myocardial lipotoxicity [31, 32]. On the other hand, there may be a marked shift in substrate preference away from fatty acids towards glucose. Nevertheless, the reduction in fatty acid oxidation is not fully counterbalanced by an increase in glucose oxidation, so failing myocardium must make do with a reduced energy supply [33].

The lipolytic and lipomobilising effects of BNP are observed globally in all human adipose tissue depots irrespectively of the underlying clinical condition [19]. The magnitude of lipolysis is lowest in the subcutaneous gluteal–femoral fat and in abdominal subcutaneous fat and is highest in visceral fat [34]. This could be due to the different levels of NPR-A receptor expression between human adipose tissue depots [35, 36].

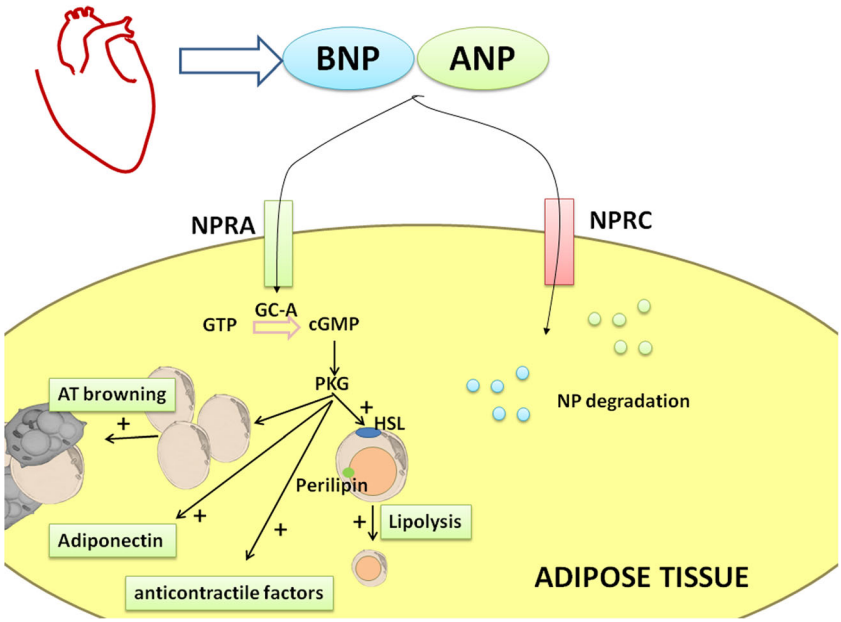

Fig. 1 Effects of natriuretic peptides (NPs) on adipose tissue

BNP in obese individuals with HF

Obesity may lead to the misdiagnosis of HF, and this may adversely affect a patient's prognosis. Obesity may be associated with ectopic lipid deposition, even in the heart, and this may exert a lipotoxic effect on the myocardium by secreted cytokines and pro-inflammatory factors. Visceral adiposity is associated with hyperinsulinemia, which has been shown to suppress NP levels [37, 38]. On the other hand, there is the paradoxical observation that, in acute and chronic HF, obesity is associated with lower all-cause mortality [39]. Although it appears that overweight individuals have a better prognosis when they suffer from HF, this is not associated with the cardioprotection provided by BNP, since these individuals exhibit the lowest levels of plasma NPs. Horwich et al. [40] found that obesity in patients with advanced HF was associated with a greater than sixfold increase in the odds of having low BNP values.

Obesity is associated with lower BNP levels in both healthy individuals and patients with HF, through many and various mechanisms (Fig. 2). NPs stimulate lipolysis, mitochondriogenesis and thermogenesis [15]. However, BNP in HF patients is, in a large proportion, in the form of the prohormone, proBNP1-108, which has little biological activity, suggesting proBNP1-108 may not be processed in HF [41].

Notably, NP deficiency in obesity may trigger metabolic dysfunction and lead to type 2 diabetes. In contrast, increasing circulating NP levels and adipose tissue signalling may help to counter metabolic complications. Notably, human studies with sacubitril-valsartan administration have been shown that pharmacological inhibition of endopeptidase neprilysin that degrades NPs may modulate lipid metabolism and improve insulin secretion and glucose metabolism [42].

A previous study in 204 patients with acute HF has pointed out that overweight and obese patients have lower circulating NT-pro-BNP and BNP levels, suggesting a BMI-related differential NP activity and indicating that both markers may have reduced sensitivity when used as a diagnostic tool to identify CHF in such patients [43].

Obese patients have reduced concentrations of BNP and NT-pro-BNP compared to non-obese patients, despite having elevated left ventricular end-diastolic pressure, and this poor relationship has led some investigators to suggest that their levels should not be considered surrogates for cardiac filling pressures or volumes [44].

In contrast to the above, another important study has indicated that BNP retains its prognostic capacity in obesity and is not only able to predict ventricular filling pressures and functional class, but also correlates with mortality at each level of

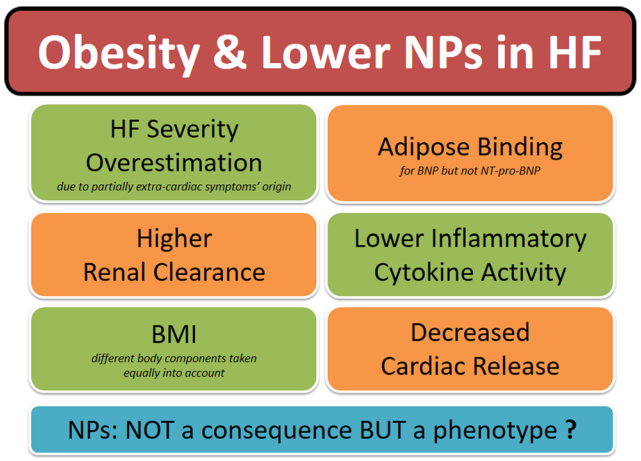

Fig. 2 Possible explanatory mechanisms of the lower natriuretic peptide (NP) levels in obese patients with heart failure (HF)

BMI [40]. The interplay between the heart and fat has been demonstrated by the Malmo Diet and Cancer study [45], where higher NPs levels were associated with a lower incidence of diabetes.

It has been reported that subjects with high plasma levels of NT-pro-BNP are at greater risk of developing systolic HF whether they are obese or non-obese. However, whereas the non-obese exhibit a direct linear association, the relation between NT-pro-BNP and HF in the obese population is U-shaped. Those who have the lowest plasma levels are at the same high risk of developing systolic heart as those with the highest plasma levels [46]. Overall, there is a plethora of data to support the inverse relationship between NP levels and obesity [47, 48]. It has been demonstrated that hypertensive patients with metabolic syndrome also have lower NT-pro-BNP levels, higher cardiac mass and a higher prevalence of left ventricular hypertrophy compared to hypertensive subjects without metabolic syndrome [49]. However, the strong metabolic effects of BNP are apparent in many studies, since lower BNP levels are strongly related to high glucose and insulin levels, regardless of body composition and adipose distribution [50].

Given that BNP contributes in a positive way to several aspects of cardiac remodelling, finding an explanation of the above data is difficult and remains a challenge. It has been argued that the obesity paradox may be partly due to an overestimation of the severity of HF in patients with obesity, because of the multifactorial nature of their dyspnoea. However, there are ample data to suggest that this explanation is simplistic and not entirely satisfactory.

The adipose tissue contains an abundance of NP binding sites. This could be a supplementary mechanism leading to reduced concentrations of BNP in obese patients [17, 22]. However, this alone is not a satisfactory explanation. In any case, it concerns only BNP, because the structure of NT-pro-BNP is such that it would not bind to these receptors [51, 52]. There are also some reports suggesting that inflammatory cytokines, such as tumour necrosis factor-alpha, which may increase the secretion of BNP from cardiomyocytes [53], are less active in obesity. Additionally, renal function and glomerular filtration rate are increased in obese population and as a consequence the reduced BNP levels may be associated with a substantially higher clearance [54]. Even though the prevalent impression is that obese individuals show increased clearance of NPs by the adipose tissue, it appears that the main factor involved is the reduction in their release from the heart in individuals with high BMI [55, 56]. Mizuno et al. recently observed that differences between BNP levels measured in the aortic root and BNP levels in the coronary sinus are negatively correlated with BMI, strongly supporting the hypothesis of an impaired myocardial NP release in obese individuals [57].

From another perspective, one could argue that the decreased circulating BNP levels may not be a consequence of obesity, but are rather involved in the genotype of its manifestation, since they participate in the pathophysiology of metabolic disorders [58]. Body weight loss and cardiac cachexia are linked with a particularly poor outcome in CHF [59]. On the other hand, high levels of BNP could, through their lipolytic effect, exaggerate weight loss in these patients, which implies that a reduced BNP level in obese HF patients may be related to a decreased progression to cardiac cachexia. But the question still pending is whether everyone with BMI > 30 kg/m^2 is 'truly obese'. BMI is an oversimplified easy-to-use parameter for the classification of obesity, but it may be misleading in some clinical conditions, e.g. by overestimating fat in very muscular individuals. In addition, it is not able to assess the distribution of components of body weight or of body fluid content [60, 61].

All of the above highlight the complexity of the relationships and information we have until now. Consequently, we still need a great deal and more insight in order to understand the exact relationship between BMI and NPs in patients with CHF.

BNP and metabolically benign adipose tissue

Although obesity is associated with increased morbidity and CVD, studies have noted the paradoxical existence of lean but metabolically unhealthy individuals, as well as metabolically healthy but obese individuals. This suggests that adipose tissue accumulation is not always accompanied by detrimental metabolic effects. Approximately 12% of the obese individuals are considered metabolically healthy [62]. Contrariwise, approximately 18% of the general population were found to have normal bodyweight but suffered from severe metabolic abnormalities [62]. There is compelling evidence that a critical factor for the obesity-related metabolic disorders and type 2 diabetes is the degree of adipose tissue inflammation. In the absence of adipose tissue inflammation, obese patients are metabolically healthy [63, 64]. There is also known to be a large heterogeneity of fat distribution and function throughout the body, which plays a major role in the complex relationship between NPs and body fat. However, it appears that the opposite may also apply. NPs can affect both the quality and the behaviour of fatty tissue, making it more beneficial for the body, and can favourably affect body fat metabolism.

There are several adipocyte sub-types in human adipose tissues. The most important types are the white adipocytes, fat cells that are capable of storing large quantities of lipid, and the brown adipocytes, which have more mitochondria and perform a more thermogenic function [14, 65]. Brown adipose activation mediates pro-oxidative and anti-lipotoxic effects. Rather than oxidising substrates to produce ATP, cellular respiration

in brown adipocytes results in heat production [14]. A third sub-type, brown-in-white/beige adipocytes, arises within white adipose depots that come from the same progenitor population as white adipocytes, but functionally resembles brown adipocytes [14]. NPs increase brown adipocyte characteristics and energy expenditure in vivo. Both brown and beige adipocytes can express uncoupling protein 1 (UCP1), and their thermogenic activity can be induced by BNP [15]. UCP1 is responsible for the thermogenic action of brown and beige adipose tissue and uncouples cellular respiration from ATP synthesis, thereby dissipating energy that is normally used for cellular work in the form of heat [66]; it is considered specific to brown and beige adipocytes. Infusion of BNP increases UCP1 transcription through a p38 mitogen-activated protein kinase in mouse adipocytes [15]. This has been shown to offer a favourable cellular metabolic and energetic result.

Apart from its thermogenic properties, it has recently been recognised that brown adipose tissue has a systemic cardioprotective role and exerts beneficial effects against cardiomyocyte injury and adverse left ventricular remodelling [67]. A clinical study has indicated that brown adipose tissue activity driven by sympathetic nervous system stimulation is lower in older, but not in obese individuals [68]. However, in a recent experimental MRI study, brown fat adipose tissue was evaluated and found to be significantly lower in quantity in animal models with heart failure [69]. All these observations clearly raise the possibility that BNP activation may have therapeutic implications in CHF.

On the other hand, white adipose tissue is organised in discrete anatomical depots, which are identified as subcutaneous adipose tissue and visceral adipose tissue; their expansion contributes to obesity and related complications. NP levels have variable relationships with different adipose depots. The visceral fat compartment is considered as the more metabolically active, and hence pathogenic, fat depot [70]. Circulating NT-pro-BNP is more strongly related to visceral adiposity than subcutaneous adiposity, but this relation is attenuated by adjustment for homeostatic model assessment for insulin resistance (HOMA-IR), suggesting that hyperinsulinemia could be a mediator of the link between visceral adiposity and lower NP levels [71].

Nevertheless, excess adiposity in the lower body subcutaneous fat compartment is associated with a lower prevalence of metabolic risk factors [72, 73]. Loss of this fat reservoir may lead to hypertension, hyperlipidaemia and type 2 diabetes [74]. Increasing BNP levels may lead to a reduction of visceral fat and results in redistribution to more metabolically favourable adipose depots.

In recent years, special research interest has focused on epicardial and pericardial fat, whose role is particularly significant, though much remains to be clarified. Khawaja et al. have demonstrated that epicardial fat volume measured by CT decreases as left ventricular ejection fraction decreases [75]. Epicardial fat thickness, in a group of patients with non-ischaemic-dilated cardiomyopathy, was found to be significantly correlated with left ventricular ejection fraction and, inversely, related to BNP levels and functional class [76].

Although the existing literature shows that the role of BNP in relation to fatty tissue behaviour in HF is significant, many questions remain to be answered. We are still not able to fully interpret all the multiple types of information and the complex pathophysiological interplay between BNP activation, cardiovascular haemodynamics, clinical condition and the cardiac endocrine system.

Conclusions and future perspectives

The adipose tissue actively contributes in the pathophysiology of HF. However, while obesity in HF leads to reduced NP activity, the interactions and mechanisms are complex, making their significance difficult to determine. Enhancement of the action of natriuretic and vasodilatory peptides is a well-established therapy in patients with HF, and molecules that increase BNP levels have been included in the guidelines for the treatment of HF patients [4, 77]. However, more data are needed to determine which of these patients respond better to such types of therapy. The adipose tissue plays a key role in this setting, since it can modify the levels and function of NPs. Conversely, by augmenting the activity of NPs, the adipose tissue could be reprogrammed to prevent the accumulation of visceral and ectopic fat, and enhancing the deposition of metabolically benign adipose tissue.

In conclusion, the in-depth study of adipose tissue function and phenotype and the metabolic profile of each patient can provide information to guide diagnosis. Although the importance of the adipose tissue has been well-studied in HF, it has not been therapeutically targeted in appropriately designed studies. Future research in the field is warranted to uncover the therapeutic potential of this communication between the adipose tissue and the heart, which could be of particular importance for obesity-related cardiac disease and the treatment of obese patients with HF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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