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B-type natriuretic peptide and obesity in heart failure: a mysterious but important association in clinical practice

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Summary

Since its discovery in 1988, B-type natriuretic peptide (BNP) and later its amino-terminal counterpart NT-proBNP have been thoroughly investigated and have become an essential clinical tool used in everyday practice for the diagnosis and prognostic assessment of patients with heart failure. However, one of the main pitfalls in the clinical interpretation of BNP/NT-proBNP levels is the concurrent presence of obesity. Many studies have demonstrated that BNP/NT-proBNP levels are lower than expected in obese patients even if the underlying mechanisms have not been fully elucidated yet. This article will review the physiology of BNP/NT-proBNP and their use in the clinical setting. We will then explore the pathophysiology of the association between obesity and low BNP/NT-proBNP levels to conclude with potential clinical consequences in patients with heart failure.

Keywords: *heart failure, natriuretic peptides, BNP, NT-proBNP, obesity, BNP handicap*

Physiology of BNP/NT-proBNP

B-type natriuretic peptide (BNP) was first isolated in porcine brain tissues in 1988 and therefore named initially "brain" natriuretic peptide. Several studies nicely demonstrated transcardiac step-ups of plasma BNP between the aortic root and the anterior interventricular vein, thus identifying ventricular cardiomyocytes as the main secretion site, hence the now preferred terminology "B-type" [1]. The mechanisms of BNP secretion have now been well elucidated [2, 3]. Wall stretch due to pressure or volume overload will induce the transcription of the natriuretic peptide precursor B gene to produce proBNP. This process has a certain delay, which explains, for example, the low BNP values observed in flash pulmonary oedema. Then, proBNP will be cleaved by two enzymes Furin and Corin into BNP and its biologically inactive amino-terminal counterpart N-terminal-pro-BNP (NT-proBNP) (fig. 1). The effects of circulating BNP are mainly mediated by a guanylyl cyclase receptor, natriuretic peptide receptor-A (NPR-A). As detailed in figure 1, BNP will act on many different target organs, but its primary effect is dilatation of afferent and constriction of efferent renal arterioles, resulting in increased glomerular filtration and enhanced natriuresis and diuresis. BNP also has metabolic effects, such as stimulation of lipolysis and increased insulin secretion (fig. 1) [4, 5].

There are three pathways of BNP clearance detailed in figure 1 [6]. In contrast, NT-proBNP seems to be eliminated only by glomerular filtration, which may contribute to its longer serum half-life (approximately 90 to 120 minutes compared with 20 minutes for BNP) and to its higher plasma concentration.

Clinical use of BNP/NT-proBNP

BNP and NT-proBNP are well-established biomarkers used in the diagnosis and prognostic assessment of patients with heart failure (HF) [7]. According to the latest European Society of Cardiology (ESC) heart failure guidelines, measurement of plasma BNP/NT-proBNP levels is recommended in all patients with acute dyspnoea and suspected acute heart failure [8].

Based on the existing evidence, specific cut-off values have been established to rule out heart failure depending on the type of presentation, acute or chronic. In the acute setting the rule-out cut-off points are <100 and <300 ng/l, respectively, for BNP and NT-proBNP. In the chronic setting, the respective values are <35 and <125 ng/l (table 1) [8]. Of note, these latter BNP/NT-proBNP levels are recommended in the same guidelines as diagnostic criteria (rule-in cut-off values) for two specific heart failure categories, namely heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF).

BNP/NT-proBNP concentrations have been repeatedly shown to have a strong prognostic value in patients admitted for heart failure and also in those with chronic heart failure [2, 9]. However, the medical value of using serial ambulatory BNP/NT-proBNP concentrations for guiding therapy in the follow-up of patients with heart failure remains controversial [7]. Finally, it is important to mention

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that BNP and NT-proBNP are used as inclusion criteria in most heart failure randomised clinical trials.

Many conditions other than heart failure *per se* may either increase or decrease BNP/NT-proBNP levels and should be taken into account when interpreting them (table 2) [10]. Older age, renal insufficiency, atrial fibrillation or pulmonary embolism are associated with increased BNP/NT-proBNP values even if they do not meet all criteria for heart failure. However, these conditions should not be considered as false positives since they share a common pathophysiological process of increased cardiac filling pressures. Another unique condition associated with disproportionate levels of BNP/NT-proBNP compared with the clinical picture is cardiac amyloidosis, where extracellular amyloid deposits cause direct damage on the cardiomyocytes increasing BNP secretion [11]. In contrast, BNP/NT-proBNP may be lower than expected in conditions such as obesity and flash pulmonary oedema [10]. Among all these factors, the main confounder in the interpretation of BNP/NT-proBNP values in patients with heart failure is obesity [12], which is the focus of the present review.

Figure 1: Physiology of B-type natriuretic peptide. Wall stretch is the main trigger of proBNP production. ProBNP will then be cleaved into BNP and biologically inactive NT-proBNP. The effects of circulating BNP are mainly mediated by NPR-A. When NPR-A is activated, the production of cGMP is stimulated which, in turn, activates PKG that mediates the different target tissue effects. BNP increases glomerular filtration, natriuresis and diuresis. BNP also suppresses the RAAS, inhibits cardiac hypertrophy and fibrosis, and reduces sympathetic nerve activity. BNP also has metabolic effects, such as stimulation of lipolysis and increased insulin secretion. There are three pathways of BNP clearance. First, BNP binding to the clearance receptor NPR-C will lead to its internalization and lysosomal degradation. Second, BNP is cleaved by circulating endopeptidases, such as neprilysin, and finally it is excreted by the kidneys.BNP = B-type natriuretic peptide; cGMP = cyclic guanosine monophosphate; GFR = glomerular filtration rate; GTP = guanosine triphosphate; NPR = natriuretic peptide receptor; NT-proBNP = N-terminal-pro B-type natriuretic peptide; PKG; protein kinase G; RAAS = renin angiotensin aldosterone system

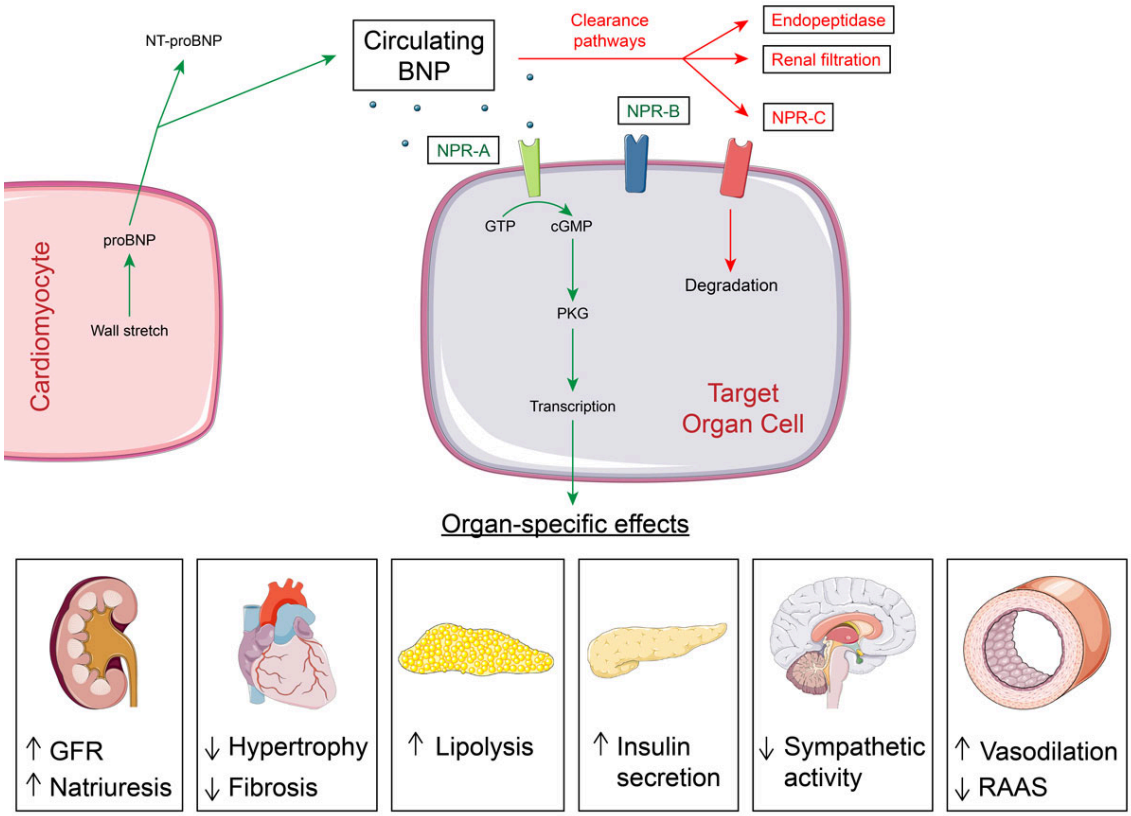


Table 1: Rule-out cut-off concentrations of natriuretic peptides in acute and chronic heart failure according to body mass index [8, 22].

			Rule-out cut-off points (ng/l)
Acute heart failure	BNP	All	<100
		If body mass index <25 kg/m^2	<170
		If body mass index 25-35 kg/m^2	<110
		If body mass index ≥35 kg/m^2	<54
	NT-proBNP		<300
Chronic heart failure	BNP		<35
	NT-proBNP		<125

BNP = B-type natriuretic peptide; NT-proBNP = N-terminal-pro B-type natriuretic peptide

Obesity and BNP/NT-proBNP: physiological link

The association between obesity and low BNP levels in heart failure has been first demonstrated in 2004 by Mehra et al [13]. They observed a clear inverse relationship between BNP and body mass index (BMI) in 318 patients with heart failure. The mean BNP level was more than 100 ng/l lower in obese patients compared with non-obese ones. This association was independent of all measured covariates including age, renal function, echocardiographic parameters and atrial fibrillation. Since then, many other observations have confirmed this finding, with both BNP and NT-proBNP [14]. In a recent analysis of a cohort of 11,637 heart failure patients, BMI was the strongest predictor of BNP levels, ahead of left ventricular ejection fraction [12]. A gender effect in the obesity-associated decrease in NT-proBNP levels was recently demonstrated in a large cohort from the general population, in the sense that this association was more pronounced in women than men [15].

The pathophysiological link between obesity and low BNP/NT-proBNP has not been fully elucidated yet, but several mechanisms have been proposed and are summarised in figure 2. Many of these mechanisms are related to the endocrine secretion by adipocytes of cytokines, known as adipokines [16].

Gentili et al. showed in their fundamental study that adipose tissue of obese adults had less NPR-A than those of lean adults. In contrast, they had higher concentrations of clearing receptors NPR-C. Thus, circulating BNP in obese patients would be more likely to have reduced cellular effects and increased clearance. They showed that this low NPR-A/NPR-C ratio was negatively correlated with BMI, insulinaemia and insulin resistance. Furthermore, adipose tissue of obese patients secreted more proinflammatory interleukin 6 (IL-6) and adipose tissue cells exposed to IL-6 expressed more NPR-C and nearly half NPR-A. IL-6 secretion may be one of the key components explaining the dysbalance in NPRs in obese patients. However, this mechanism cannot account for the reduction also observed for NT-proBNP, which is not cleared by those receptors (fig. 2). This condition of decreased BNP levels in obese patients has been termed “the natriuretic handicap” [17].

Besides IL-6, adipose tissue secretes other pro-inflammatory cytokines such tumour necrosis factor-alpha (TNF-α), IL-1β and resistin, which promote BNP degradation and enhance atheromatosis and cardiac fibrosis. However, adipocytes also produce adiponectin which has a completely opposite effect. It inhibits cardiac inflammation and fibrosis and antagonises the action of endogenous vasoconstrictors. In contrast to other adipokines, however, obesity leads to a decrease in adiponectin gene expression, promoting further inflammation, fibrosis and hypertension [18].

Standeven et al. demonstrated that another way of BNP degradation was enhanced in obesity via the neprilysin pathway. High intake of a high-fat diet increased circulating levels of neprilysin, and visceral fat contains high levels of the enzyme, which in turn results in low BNP circulating levels [19]. Obese patients may also have less patent intracellular activity after BNP stimulation. Miyashita et al. showed that transgenic mice with enhanced intracellular cascade after NPR-A and B activation, fed on high-fat diet, were protected against obesity and insulin resistance by promotion of mitochondrial biogenesis in skeletal muscle [20]. They even had reduced body weight on a standard diet.

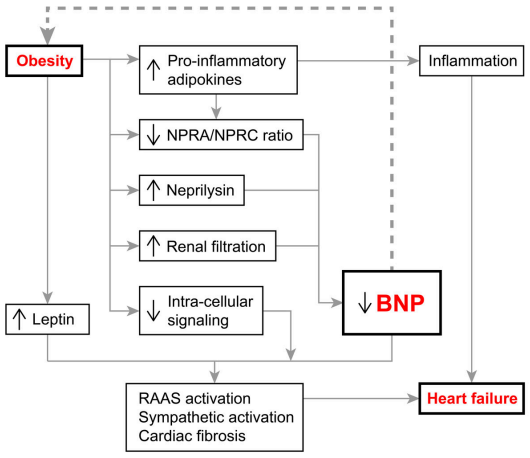
BNP itself is as potent as catecholamines in inducing lipolysis [21]. It explains, for example, the presence of cachexia in patients with severe heart failure. Therefore, there might be a bidirectional relationship between BNP and obesity, with obesity causing further lipid retention via low levels of BNP, which creates a positive feedback loop (fig. 2).

Another adipokine related to obesity and heart failure is leptin. Leptin is released by adipocytes when they are overfilled with lipids. It reduces food intake, promotes energy consumption, and also stimulates sympathetic nervous activity and renin angiotensin aldosterone system (RAAS) [16]. Thus, leptin and BNP have opposite effects. In obese adults, circulating levels of leptin are too high, whereas levels of BNP are low. Both mechanisms result in aldosterone secretion, and sodium and water retention. This high

Table 2: Typical conditions influencing the interpretation of natriuretic peptides concentrations beyond heart failure.

Higher concentrations than expected	Older age
	Chronic kidney disease
	Atrial fibrillation
	Pulmonary hypertension
	Pulmonary embolism
	Cardiac amyloidosis
	Severe sepsis/septic shock
Lower concentrations than expected	Obesity
	Flash pulmonary oedema
	Cardiac tamponade
	Mitral stenosis

Figure 2: Pathophysiological link between obesity, B-type natriuretic peptide and heart failure. Obesity leads to decreased BNP concentrations, mainly by enhancing its clearance through increased NPR-C and neprilysin concentrations, and increased renal filtration. Obesity also decreases BNP activity by decreasing NPR-A concentrations and BNP intracellular signalling pathways. In turn, reduced BNP levels and activity will lead to reduced lipolysis, thus promoting obesity, which creates a positive feedback loop. Besides the reduction of BNP levels and activity, obesity also has a negative impact on heart failure itself through increased secretion of pro-inflammatory adkipokines as well as leptin, which promotes neurohormonal activation and cardiac fibrosis.BNP = B-type natriuretic peptide; NPR = natriuretic peptide receptor; RAAS = renin angiotensin aldosterone system



volume state will then promote heart failure. The so-called leptin-aldosterone-neprilysin axis is now considered the centre of the complex physiology relating obesity and heart failure (fig. 2) [16].

Obesity and BNP/NT-proBNP: clinical implications

The association between obesity and low natriuretic peptides is highly relevant in clinical practice for many reasons. Obese patients are virtually all breathless and do not often unveil typical heart failure signs including increased jugular venous pressure, a third heart sound, displaced apical impulse and ankle oedema. The quality of their chest x-rays and transthoracic echocardiograms, both essentials in heart failure diagnosis, are, most of the time, reduced. Therefore, it would be ideal to rely on a biomarker in these patients. However, using the standard BNP threshold of 100 ng/l, the diagnosis of acute heart failure may be missed in one in five patients with a BMI ≥35 kg/m^2 [22]. Therefore, Daniels et al. have tried to define for each BMI groups the cut-off points corresponding to a sensitivity of 90% for diagnosing acute heart failure. They found a value of 54 ng/l in patients with a BMI of 35 kg/m^2 or more. In contrast, the cut-off point could be increased to 170 ng/l for lean subjects with a BMI <25 kg/m^2 (table 1) [22]. No specific cut-off value has been established for NT-proBNP in obese patients. In the inclusion criteria of a recent trial [23], another correction of BNP/NT-proBNP cut-off values according to BMI has been proposed. It consists of a 4% reduction of the BNP (≥300 ng/l) or NT-proBNP (≥1500 ng/l) cut-off for every 1 kg/m^2 increase in BMI above a reference BMI of 20 kg/m^2. However, the clinical value of such a correction has not yet been evaluated, neither in the diagnosis nor prognosis of heart failure patients. Finally, a recent review of the ESC proposed 50% lower BNP/NT-proBNP cut-off concentrations in obese subjects, but this correction remains controversial among experts [7].

Whether the prognostic value of BNP/NT-proBNP concentrations remains valid in obese patients with heart failure has been examined in several studies. The first by Horwich et al. in 2006, examined the impact of BMI on the association of BNP with haemodynamics and outcomes in 316 patients with advanced heart failure and reduced ejection fraction. At each level of BMI, BNP not only predicted functional class and ventricular filling pressure, but also retained its prognostic capacity with regards to mortality [24]. One year later, Bayes-Genis et al. analysed the diagnostic and prognostic value of NT-proBNP in 1103 patients admitted for acute dyspnoea with and without heart failure. Despite lower concentrations in obese patients, NT-proBNP remained useful in the diagnosis or exclusion of acute heart failure and in the prediction of mortality in all BMI categories [25].

One of the most intriguing consequence of the association of natriuretic peptides and obesity is the diagnosis of HFpEF. As mentioned, BNP and NT-proBNP have been included in the diagnostic criteria of HFpEF in the latest ESC guidelines. The rationale was to rule out many other potential causes of dyspnoea in patients with preserved left ventricular ejection fraction. However, recent evidence indicates that BNP/NT-proBNP may be low in obese patients with HFpEF, who may represent a distinct HFpEF phenotype [26]. Two novel diagnostic scores have been recently proposed to diagnose HFpEF, the Mayo clinic H2FPEF score [27] and the HFA HF-PEFF score [28]. In the H2FPEF score, based on a large cohort of patients with a well-established diagnosis of HFpEF, notably including resting and exercise right heart catheterisation, BNP/NT-proBNP were not included because they were not shown to be significantly and independently associated with the diagnosis of HFpEF. The main hypothesis for this finding is the high prevalence in this cohort of obese patients (33 kg/m^2 of mean BMI), who had lower mean NT-proBNP values than expected (384 pg/ml). Low BNP/NT-proBNP were therefore not able to discriminate patients with and without HFpEF. In contrast, the ESC HF-PEFF score takes into account BNP/NT-proBNP levels. Besides the above-mentioned ESC diagnostic cut-off values, higher values were also introduced and considered as major diagnostic criteria (>80 ng/l for BNP and >220 ng/l for NT-proBNP). These cut-off values were tripled in the presence of atrial fibrillation and adapted to age, but curiously not to BMI. The scientific evidence supporting these cut-off values remains however low. The future use of these diagnostic scores will determine if BNP/NT-proBNP should be included and adapted to BMI in these definitions or not [29].

Conclusion

BNP/NT-proBNP are essential biomarkers in the diagnosis and management of heart failure. The main confounder in the interpretation of natriuretic peptides is the concurrent presence of obesity, which is associated with lower BNP/NT-proBNP levels than expected from heart failure severity. Increased BNP clearance and reduced intracellular signalisation pathways are the most important underlying mechanisms of this association. The endocrine role of adipose tissue seems to play a central role in this dysbalance. BNP has several metabolic effects that reduce body fat. Decreased BNP will therefore lead to a positive feedback loop of further increasing fat accumulation. The same effect is seen with the reduction of leptin. An unfavourable leptin-BNP-aldosterone axis may be a cornerstone in the pathophysiology linking obesity with heart failure. In the clinical setting, adapted cut-off values have been proposed in the acute setting to diagnose heart failure in obese patients. Further studies are needed to better define the role of BNP/NT-proBNP in the diagnosis of HFpEF in obese patients.

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