Obesity and natriuretic peptides, BNP and NT-proBNP: Mechanisms and diagnostic implications for heart failure

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1. Introduction

The obesity pandemic is a leading cause of morbidity and mortality across the world. In the United States an estimated one-third of Americans are obese, presenting a significant and growing public health concern [1]. Obesity is a risk factor for systemic hypertension, hyperlipidemia, diabetes mellitus, and left ventricular hypertrophy. These conditions, in turn, are associated with an increased prevalence of chronic heart failure (CHF), which results in the death of about half of the patient population within 5 years of diagnosis [2,3]. An estimated 5.1 million people are living with CHF in the United States, costing about $32 billion in health care costs and loss of productivity [3]. CHF is a progressive disease whose management requires close monitoring of the patient’s clinical status.

Obese patients, however, present unique challenges in the diagnosis of CHF, particularly in the emergency department (ED) setting [4–6]. Obesity may mask signs of edema and auscultation may be difficult during physical examination [6]. Obese patients may also present dyspnea and orthopnea, characteristic symptoms of CHF, from deconditioning and abdominal size, respectively. In addition, body habitus also diminishes the image quality of echocardiograms and chest radiographs [7,8]. Consequently, the use of molecular biomarkers to aid in the diagnosis and management of CHF would be particularly valuable in obese patients. The circulating biomarkers for myocardial stiffness, the brain natriuretic peptides BNP and NT-proBNP, are used to establish or exclude the diagnosis of CHF in patients with acute dyspnea in the ED. Higher natriuretic peptide levels increase the likelihood that etiology of dyspnea is due to HF [9]. However, the use of these markers is compromised in obese patients as their levels tend to be lower. In this review, we will discuss the biochemistry, physiology, and clinical use of BNP and NT-proBNP in obese patients with CHF. Finally, we will explore the biological basis underlying the inverse relationship between BNP and NT-proBNP levels and obesity.

2. B-type natriuretic peptide

BNP belongs to a family of natriuretic peptides, which includes atrial natriuretic peptide (ANP) and C-type natriuretic peptide (CNP), with the latter mainly secreted by vascular endothelium. ANP and BNP are cardiac natriuretic peptides secreted by myocytes, with BNP mainly secreted by atrial myocytes in the normal heart [10,11]. Ventricular BNP secretion increases drastically in CHF, indicative of greater ventricular stress and serious cardiac dysfunction [12–14]. The precursor of human BNP, preproBNP, is 134 amino acids (aa) in length and is a theoretically deduced form which does not exist as a separate entity [14]. PreproBNP is processed to 108 aa proBNP by the cleavage of N-terminal 26 aa signal peptide. The proBNP is cleaved by serine endoproteases corin and furin into an inactive 76 aa N-terminal peptide, NT-proBNP and a C-terminal 32 aa long active hormone, BNP [15]. BNP contains a ring structure formed by a disulfide bond between the cysteine residues Cys10 and Cys26, which is essential for receptor binding.

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and biological activity [16]. In addition to NT-proBNP and BNP, unprocessed proBNP also circulates in the plasma, whose levels may be more compared with the cleavage products in severe HF [14].

Cardiac natriuretic peptides are released from the heart under physiological conditions and are involved in cardiovascular homeostasis [17–19]. This is achieved, in part, by integrating the function of the renal system. Natriuretic peptides induce dilation of afferent and constriction of efferent renal arteries, resulting in increased glomerular filtration and enhanced natriuresis and diuresis [20,21]. In addition, these peptides decrease cardiac preload by shifting intravascular fluid into the interstitial space [22]. Natriuretic peptides suppress renin–angiotensin–aldosterone system (RAAS) and the release of renin from the kidney and aldosterone from the adrenal gland, which enhances natriuresis and the reduction of extracellular volume [23–25].

Natriuretic peptides suppress sympathetic nerve activity in the peripheral vasculature, perhaps by lowering the activation threshold of baroreceptors, by suppressing catecholamine release from the nerve endings, and by the inhibition of the sympathetic outflow [21,26–28]. Because these peptides lower the activation threshold of vagal afferents, reflex tachycardia and vasoconstriction that follow reduction in the preload are suppressed, effecting a sustained decrease in mean arterial pressure. Relaxation of smooth muscle cells and suppression of RAAS induced by the natriuretic peptides decrease systemic and peripheral vascular resistance [29]. Furthermore, natriuretic peptides may function as endogenous inhibitors of cardiac hypertrophy and fibrosis [30,31].

Natriuretic peptide secretion increases in proportion to the severity of the left ventricular dysfunction, suggesting that end-diastolic wall stress is the main regulatory mechanism [32,33]. However, increased peptide levels are also found in patients with renal failure or pulmonary hypertension and may increase in arterial hypertension or liver cirrhosis [34]. Increased BNP levels were reported in patients with acute coronary syndrome or during exercise-induced ischemia, in the absence of significant ventricular dilation [35–38]. Plasma ANP levels were chronically elevated following cardiac transplantation even after the return of cardiac function and normalization of RAAS [39]. These observations suggest an active involvement of the neurohormonal and immune systems in the regulation of the natriuretic peptide levels, which is supported by in vitro and animal model studies. For example, angiotensin II and endothelin induced BNP synthesis in rat cardiomyocytes as well as in anesthetized rats [40]. Similarly, plasma natriuretic peptide levels were increased in rat experimental autoimmune myocarditis [41]. In addition, proinflammatory cytokines tumor necrosis factor-α, interleukin-1β, and interleukin-6 induce BNP synthesis in cardiomyocytes [42,43]. These data suggest a complex interaction among mechanical, neurohormonal, and immunological components in the regulation of cardiac endocrine response involving natriuretic peptide synthesis/secretion.

Compared with the healthy subjects, a progressive increase in median BNP levels of up to 57-fold and median NT-proBNP levels of up to 107-fold was observed in patients with HF (discussed later) in NYHA class IV/stage D [44]. Despite the direct diuretic and natriuretic effects of natriuretic peptides, congestion, sodium retention, and edema are the hallmarks of CHF [14]. This cardiac endocrine paradox suggests a blunted biological effect of the peptides, mainly on natriuresis, which can be attributed to three main mechanisms [38,45]. First, the blunted effect may result from impaired post-translational processing of biosynthetic precursors of BNP [14,46–50]. Consistent with this, Dong et al. [49] reported a significant decrease in the plasma levels of corin involved in proBNP processing in CHF patients compared with the healthy controls, with the decrease in the enzyme level correlated with the severity of the disease. Increased levels of proBNP, with reduced efficacy in the activation of NPR-A receptor (discussed later) compared with BNP, can impair natriuresis [51]. In addition, the resistance of proBNP to degradation may result in the increased proBNP: BNP ratio observed in CHF patients, contributing to peripheral resistance to the biological activation of natriuretic peptides. Second, altered expression of natriuretic peptide receptors might also contribute to resistance to the biological effect of the peptides in CHF [52–55]. Another potential mechanism of resistance includes homologous desensitization of the NPR-A receptor [38], protein kinase C-dependent heterologous desensitization of NPR-A by vasoconstrictive hormones [56], increased activity of phosphodiesterases that hydrolyze cGMP [57,58], and the refractory nature of NPR-A to natriuretic peptide stimulation [59].

3. Clinical use of BNP and NT-proBNP

In the 1990s, the advent of assays for measuring serum levels of BNP allowed researchers to investigate the use of BNP as a clinical biomarker for CHF [60]. A large number of studies showed strong evidence for the use of BNP levels to aid in the diagnosis of HF in patients who present with acute dyspnea. In 2005, Wang et al. conducted a meta-analysis to evaluate the diagnostic value of circulating BNP levels [61]. They found that, across a pool of eleven studies, high BNP levels (>250 pg/mL) increased the chances of CHF by 2–4.5 times. Additionally, moderate to low BNP levels (<250 pg/mL) were associated with a 90% decrease in the incidence of CHF [60,61]. The validity of using BNP levels to diagnose HF in the emergent setting was also supported by the large-scale multi-center Breathing Not Properly (BNP) Study, which evaluated 1586 patients who presented with acute dyspnea [4]. This study found that patients diagnosed with CHF had significantly higher BNP levels (mean BNP 675 pg/mL) than patients with base-line left ventricular dysfunction but other causes of dyspnea (mean BNP 346 pg/mL) or no left ventricular dysfunction or HF (mean BNP 110 pg/mL). Based on this, Maisel et al. [4] established the widely used standard of BNP level >100 pg/mL as a cutoff for CHF as the etiology for acute dyspnea in the emergent setting (sensitivity 90% and specificity 76%) (Table 1).

Using a design similar to the above-mentioned BNP study, in the N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study Januzzi et al. [62] investigated the utility of NT-proBNP for the diagnosis of CHF in 600 dyspnea patients, a cohort with a final diagnosis of 35% acute CHF. An age-stratified analysis determined a rule-in cut-point of 450 pg/mL for patients <50 years (sensitivity 93% and specificity 95%) and 900 pg/mL for patients ≥50 years (sensitivity 91% and specificity 80%). More recently, Hildebrandt et al. [63] further refined age-based cut-points for NT-proBNP levels after analyzing data of 5508 primary care patients from 10 studies in several countries. NT-proBNP values of 50 ng/L (sensitivity 99.2%, specificity 57.2%, and negative predictive value 99.7%), 75 ng/L (sensitivity 95.9%, specificity 51.0%, and negative predictive value 96.8%), and 250 ng/L (sensitivity 87.9%, specificity 53.7%, and negative predictive value 92.4%) for <50, 50–75, and >75 years, respectively, were superior to a single cut-point to rule out HF. Emphasizing the importance of age stratification in improving diagnostic sensitivity, the data from the International Collaborative of NT-proBNP (ICON) study identified rule in cut-points for acute HF of 450, 900, and 1800 pg/mL for patients aged <50, 50–75, and >75 years, respectively (90% sensitivity and 84% specificity) [64] (Table 1). However, an age-independent cut-point of 300 pg/mL of NT-proBNP was sufficient to rule out acute HF, demonstrating 99, 60, and 98% of sensitivity, specificity, and negative predictive value, respectively.

Both the BNP and PRIDE studies show that BNP and NT-proBNP levels in combination with clinical judgment are superior to natriuretic factors levels or clinical judgment alone, indicating the importance of integrating the testing of these peptides with clinical assessment for the diagnosis of CHF in patients who present with dyspnea in the emergency department [62,65]. Supporting this notion, in a prospective study of 3870 older men NT-proBNP improved prediction of CHF above routine conventional risk factors and the Health ABC Heart Failure Score in all men and in men with and without established CVD.
glomerular fi re gender and age, hypertension, renal disease, and atrial fibrillation. Over a 15 month period, the group that received BNP-guided dosing had significantly higher plasma BNP levels, whereas those with the largest increase showed the lowest mortality.

Similarly, a study by Jourdain et al. examined the relative effectiveness of established dosing guidelines against dosing based on changes in BNP levels for angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics in the treatment of CHF. Over a 15 month period, the group that received BNP-guided dosing had significantly higher plasma BNP levels, whereas those with the largest increase showed the lowest mortality.

In addition to its utility in CHF diagnosis, several studies have established that circulating BNP levels are a powerful prognostic indicator in HF. Anand et al. analyzed data from the Valsartan Heart Failure Trial (Val-HeFT) of ~4300 patients to evaluate the predictive power of BNP levels. Their data revealed that levels above 97 pg/mL are associated with twice the risk of morbidity and mortality. Additionally, Tsutamoto et al. found, in a prospective study of 290 patients with asymptomatic or minimally symptomatic left ventricular dysfunction, that plasma BNP levels >56 pg/mL were an independent predictor for mortality.

Owing to its strong diagnostic and prognostic power, there has been great interest in using BNP to guide individual patient management. In the aforementioned Val-HeFT study, patients with the largest increase in BNP from the pre-treatment baseline had the highest mortality, whereas those with the greatest decline the lowest mortality. Similarly, a study by Jourdain et al. examined the relative effectiveness of established dosing guidelines against dosing based on changes in BNP levels for angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics in the treatment of CHF. Over a 15 month period, the group that received BNP-guided dosing had significantly higher plasma BNP levels, whereas those with the largest increase showed the lowest mortality.

### 4. The relationship between BMI and BNP

There are many variables that affect BNP levels in a patient, including gender and age, hypertension, renal disease, and atrial fibrillation. The increase in natriuretic peptide levels with age likely reflects age-related decreases in left ventricular compliance and glomerular filtration rate. Recently, researchers have demonstrated a consistent inverse relationship between obesity (defined as a BMI of 30 or greater) and circulating BNP levels. Wang et al. were the first to describe the inverse relationship between obesity and BNP levels in a study of 3389 subjects from the original Framingham Heart Study offspring cohort, none of whom had HF. Multivariable regression analysis was adjusted for echocardiographic variables such as left ventricular mass and left atrial size. The mean plasma BNP levels were 21.4, 15.5, and 12.7 pg/mL in lean (BMI < 25), overweight (BMI of 25 to 29.9), and obese (BMI greater than or equal to 30), respectively.

#### 5. The biological link between obesity and BNP

A number of hypotheses have been put forth in an attempt to explain the inverse relationship between obesity and circulating BNP levels. However, to date there has been no conclusive evidence in favor of any particular hypothesis.

#### 6. Kidneys

Renal function, more specifically glomerular filtration rate, has been reported to depress BNP levels in obese CHF patients because

<table>
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<tr>
<th>BNP All patients</th>
<th>Cut-point</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
<th>reference</th>
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<tbody>
<tr>
<td>BNP</td>
<td>100 pg/mL</td>
<td>90</td>
<td>76</td>
<td>79</td>
<td>89</td>
<td>76 [4]</td>
<td>[6]</td>
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<tr>
<td>BMI &lt; 25</td>
<td>170 pg/mL</td>
<td>90</td>
<td>70</td>
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<tr>
<td>BMI ≥ 25</td>
<td>110 pg/mL</td>
<td>90</td>
<td>70</td>
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<tr>
<td>BMI &gt; 35</td>
<td>54 pg/mL</td>
<td>90</td>
<td>70</td>
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<td>NT-proBNP</td>
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<td>Confirmation (rule in) cut-points</td>
<td>&lt;50 years</td>
<td>450 pg/mL</td>
<td>97</td>
<td>93</td>
<td></td>
<td>94 [66]</td>
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<tr>
<td>50–75 years</td>
<td>900 pg/mL</td>
<td>90</td>
<td>82</td>
<td>83</td>
<td>88</td>
<td>85</td>
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<td>&gt;75 years</td>
<td>1800 pg/mL</td>
<td>85</td>
<td>73</td>
<td>92</td>
<td>55</td>
<td>83</td>
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<td>Rule in, overall</td>
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<td>84</td>
<td>88</td>
<td>66</td>
<td>85</td>
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<tr>
<td>Exclusionary (rule out) cut-point</td>
<td>All patients</td>
<td>300 pg/mL</td>
<td>99</td>
<td>60</td>
<td>77</td>
<td>98</td>
<td>83 [66]</td>
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obesity is associated with substantially higher glomerular filtration rates [90]. This suggests that obese patients may have depressed circulating BNP levels simply because they are clearing these molecules more effectively. Given the short half-life of BNP (~23 min), this explanation is plausible. However the Suita study argues against this theory as their multivariable regression analysis was adjusted for serum creatinine among other variables, and still found the inverse relationship between BMI and BNP [88].

7. Adipose tissue

Adipose tissue expansion is one of the defining characteristics of obesity. Adipocytes are known to highly express natriuretic peptide clearance receptors-C (NPR-C), causing some to speculate that this is the basis for low serum BNP levels associated with obesity [91,92]. However, the Dallas Heart Study showed that obesity is also linked with lower levels of NT-proBNP, which is not cleared by the NPR-C [84]. Additionally, the Dallas Heart Study found that BNP and NT-proBNP levels were more closely correlated with lean mass than with BMI, suggesting that adipose tissue itself may not be the driving force in this relationship. The authors postulate that a substance produced in the lean mass either suppresses the synthesis or release of the natriuretic peptides or an androgen coordinately regulates natriuretic peptide synthesis and body composition. Alternatively, the fat mass measured by dual energy X-ray absorptiometry in this study might mostly consist of subcutaneous adipose tissue [89]. In a study of 1873 community-based individuals, Cheng et al. [94] found an inverse relationship between NT-proBNP levels and visceral adipose mass, which was attenuated after adjustment for HOMA-IR (homeostasis model assessment of insulin resistance), indicating a role for hyperinsulinemia in lower natriuretic peptide levels in obesity. These data are consistent with the reports that hyperinsulinemia attenuates natriuretic peptide secretion and activity [95,96]. However, acute insulin administration has either no significant effect [97] or increased [98] natriuretic peptide levels, indicating perhaps the differential physiological effects of acute vs chronic hyperinsulinemia on natriuretic peptide levels.

Interestingly, several investigators have postulated a ‘bidirectional relationship’ between BNP and adiposity because BNP has been shown to cause lipolysis in adipocytes (Fig. 1). They point out that low levels of BNP could lead to less lipolysis and thus promote obesity [92,93]. Supporting this hypothesis, Cabiatii et al. [99] recently reported significantly lower levels of BNP and a reduction of ANP and CNP mRNA levels in the hearts of obese compared with the control rats. Furthermore, BNP induced lipolysis may underlie the wasting (cardiac cachexia) seen in patients with severe HF [92]. Natriuretic peptides exert their biological effects via stimulation of NPR-A (GC-A/NPR-1) and NPR-B (GC-B/NPR-2), two receptors which act as membrane-bound guanylyl cyclases [100]. ANP and BNP preferentially bind to NPR-A, whereas CNP is a physiological ligand for NPR-B [101]. Stimulation of these receptors generates cyclic guanosine monophosphate (cGMP) and subsequent activation of cGMP-dependent protein kinase 1 (cGK1), which constitutes the nitric oxide signal transduction pathway [102].

Using three types of genetically engineered mouse models – BNP transgenic, cGK transgenic and NPR-A heterozygous knockout mice – Miyashita et al. [102] demonstrated that increased natriuretic peptide levels prevent accumulation of abdominal fat in mice on high fat diet, by promoting mitochondrial biogenesis in skeletal muscle, through increased expression of peroxisome proliferator-activated receptor (PPAR)-γ coactivator (PGC)-1α and PPARδ, via the activation of cGMP/cGK1 signaling cascade (Fig. 1). In addition, BNP transgenic mice were protected against diet-induced insulin resistance. Cardiac natriuretic peptides also induced mitochondrial biogenesis by increasing the expression of PGC-1α and PPARδ in C2C12 myotubes. More importantly, high fat diet decreased the expression of NPR-A and NPR-B.

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**Fig. 1.** A proposed bidirectional relationship between BNP and obesity. Under normal conditions, BNP acting through the NPR-A receptor induces cGMP signaling which promotes lipolysis in adipose tissue and mitochondrial biogenesis and fat oxidation in skeletal muscle. These physiological actions provide protection against obesity and insulin resistance. In contrast to this, in obese patients and people with insulin resistance BNP secretion and activity are decreased and NPR-A:NPR-C ratio is altered, impairing NPR-A/cGMP/cGK1 signaling, as also reported during high fat feeding and/or physical inactivity (adapted from Moro and Smith [104]).
and increased the expression of NPR-C in skeletal muscle, brown and white adipose tissue. A low NPR-A:NPR-C ratio could decrease natriuretic peptide induced cGMP/cGK1 signaling pathways as well as natriuretic peptide levels within the tissue [103,104].

In tune with the above data, natriuretic peptides activated PGC-1α, induced mitochondrial biogenesis, and increased respiration in human adipocytes [105]. Additionally, infusion of BNP into mice significantly increased the expression of uncoupling protein 1, a mediator of thermogenic energy expenditure and PGC-1α in adipose tissue, suggesting a role in regulation of obesity. In this context, it is of interest to note that calorie restriction promotes muscle mitochondrial biogenesis in rodents [106] as well as humans [107] by increasing the levels of nitric oxide, the upstream activator of cGMP/cGK1 pathway. Emerging evidence suggests that natriuretic peptides control lipolysis and lipid mobilization in physiological and pathological conditions [108]. Further supporting the protective effect of natriuretic peptides against obesity, Sengenès et al. [92] reported that cardiac natriuretic peptides induce strong lipolysis in isolated human fat cells by producing cGMP via the NPR-A receptor. Activation of cGMP/cGK1 pathway increases the phosphorylation of perilipin-A and hormone-sensitive lipase, a rate-limiting enzyme in lipolysis [109]. Perilipin-A phosphorylation results in the physical alteration of the surface of the lipid droplet, facilitating the binding of the hormone-sensitive lipase and hydrolysis of triglycerides into free fatty acids and glycerol.

Concurrent with this data, a meta-analysis of 49,279 subjects from seven case-controlled studies showed that BNP promoter T-381C polymorphism (rs198389), associated with higher BNP levels, has modest protective effect against type 2 diabetes [110]. However, this polymorphism is not associated with a decreased HF risk in large population-based cohort studies, indicating that increase in BNP levels because of the genetic variation might not be large enough to cause clinically detectable risk reduction [111,112]. Supporting the role of natriuretic peptides in adiposity, significant increases in the levels of BNP and NT-proBNP were observed in obese patients following gastric bypass surgery [113,114]. Similarly, weight loss as a result of comprehensive lifestyle changes in patients with coronary heart disease and coronary heart disease risk factors and/or diabetes mellitus decreased insulin and increased BNP levels [115], suggesting that loss of natriuretic peptide clearance pathways as well as hyperinsulinemia regulate natriuretic peptide levels.

8. Validity of BNP as a marker for CHF in obese patients

Because obese subjects have BNP levels below the traditional cutoff used to diagnose CHF, lower thresholds should be used to diagnose HF in this patient population [6]. Based on the established clinical threshold of 100 pg/mL, BNP testing yielded false negative results in 20% of obese HF patients [6,116]. Hence, a cut-point of BNP ≤ 54 pg/mL is recommended for ruling out CHF in severely obese patients (BMI ≥ 35) (Table 1) [6]. It is also suggested that a higher BNP cut-point of ≥ 170 pg/mL in lean patients increases specificity. In contrast to BNP cut-points, relatively lower concentrations of NT-proBNP in overweight and obese patients with acute dyspnea retain their diagnostic and prognostic capacity [117]. A cut-point of 300 ng/L NT-proBNP had highly significant negative likelihood ratio of 0.02, 0.03, and 0.08 for BMI of <25.0, 25.0–29.9, and ≥ 30.0, respectively, ruling out acute HF. Also, a NT-proBNP cut-point of >986 ng/L remained strongly prognostic across all 3 BMI groups.

9. Conclusions

HF has become the most common cardiovascular diagnosis in hospitalized patients and, at the same time, the proportion of HF patients with significant obesity has increased dramatically due to the increase in obesity in the general population. For this reason, more precise understanding of the inter-relationship between BMI and BNP measurements is of critical importance and will facilitate more accurate diagnosis of HF in obese patients. In this review, we have illustrated new knowledge on important relationships that exist between natriuretic peptides and lipid metabolism as well as the regulation of natriuretic peptide secretion and activity in normal body weight and obesity. Further basic and translational research offers the possibility of formulating new therapeutic strategies for treatment of vascular and metabolic diseases in general and CHF in particular.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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