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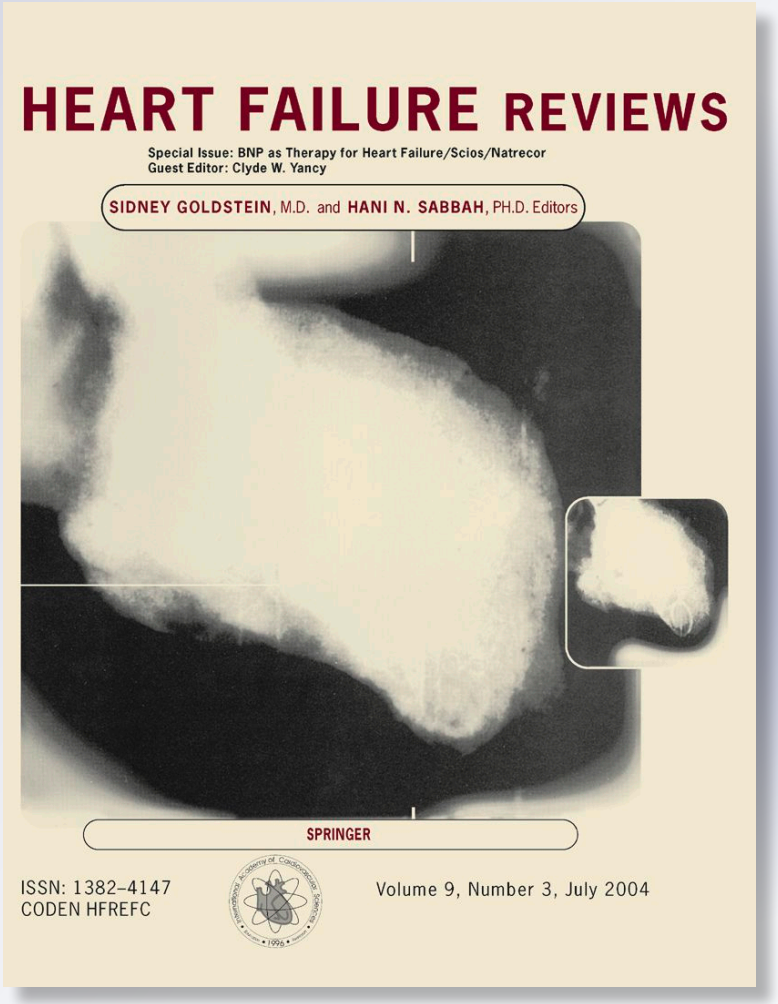

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The paradox of low BNP levels in obesity

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Abstract The aim of this review is to analyze in detail some possible pathophysiological mechanisms linking obesity and cardiac endocrine function, in order to try to explain the negative association previously observed between BMI and BNP values in both healthy subjects and patients with cardiovascular diseases. In particular, we discuss the hypothesis that the response of the cardiac endocrine system is the integrated resultant of several and contrasting physiological and pathological interactions, including the effects of peptide and steroid hormones, cytokines, cardiovascular hemodynamics, clinical conditions, and pharmacological treatment. Several studies suggested that gonadal function regulates both body fat distribution and cardiac endocrine function. Visceral fat expansion can increase the clearance of active natriuretic peptides by means of an increased expression of clearance receptors on adipocytes, and in this way, it may contribute to decrease the activity of the cardiac endocrine system. Moreover, obesity is associated with ectopic lipid deposition even in the heart, which may directly exert a lipotoxic effect on the myocardium by secreting *in loco* several cytokines and adipokines. Obese subjects are frequently treated for hypertension and coronary artery disease. Pharmacological treatment reduces plasma level of cardiac natriuretic peptides, and this effect may explain almost in part the lower BNP levels of some asymptomatic subjects with increased BMI values. At present time, it is not possible to give a unique and definitive answer to the crucial question concerning the inverse relationship between the amount of visceral fat distribution and BNP levels. Our explanation for these unsatisfactory results is that the cardiac endocrine response is always the integrated resultant of several pathophysiological interactions. However, only few variables can be studied together; as a result, it is not possible to perform a complete evaluation of pathophysiological mechanisms under study. We are still not able to well integrate these multiple information together; therefore, we should learn to do it.

Keywords BNP · NT-proBNP · Sex steroids · BMI · Obesity · Cardiovascular risk

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Background and article aim

The discovery of cardiac natriuretic hormones (CNH), namely atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), determined a radical conceptual revision of the heart function. CNH play a key role in the regulation of circulation and salt-water homeostasis and can exchange physiologically relevant information with other organs and systems.

Sarzani et al. [1, 2] suggested that obese individuals have an impaired natriuretic peptide response, and "natriuretic handicap" definition was used to describe this phenomenon. The existence of such a "handicap" was not definitively proven, although some experimental data suggest that ANP levels fail to rise appropriately in obese subjects after a saline load [3]. More recently, several studies have reported that circulating levels of BNP and its related peptide NT-proBNP are inversely related to body mass index (BMI) values in the general population [4, 5], as well as in patients

with heart failure (HF) [6–11]. These data seem to support the "natriuretic handicap hypothesis" indicating that the BNP levels are inappropriately low in obese subjects.

The main aim of this review is to analyze in detail some possible pathophysiological mechanisms linking obesity and cardiac endocrine function, in order to explain both the negative association, previously observed between increased BMI and BNP values in healthy subjects and patients with cardiovascular diseases. In particular, we discuss the hypothesis that the knowledge of the relationship between cardiac endocrine function and other neurohormonal and immune systems is crucial to accurately evaluate cardiovascular risk and mortality in all patients with cardiovascular disease, especially those with overweight or obesity.

The endocrine cardiac function: a pathophysiological overture

CNH share potent diuretic, natriuretic, and vascular smooth muscle-relaxing effects, and they have complex interactions with the hormonal and nervous systems [12, 13]. CNH are synthesized by cardiomyocytes as prepro-hormones (i.e., preproANP and perproBNP). In particular, human BNP is synthesized as a 134-amino acid (aa) precursor protein (preproBNP) and is subsequently processed during secretion to form a 108-aa peptide named proBNP (Fig. 1). The propeptide hormones of the cardiac natriuretic peptides can be enzymatically cleaved by proprotein convertases produced in the cardiomyocytes, such as corin and furin [14]. ProBNP is then processed to form the 76-aa N-terminal peptide (i.e., NT-proBNP) and the biologically active 32-aa C-terminal peptide (i.e., BNP). BNP has a shorter plasma half-life (about 15–20 min vs. 1 or 2 h) and consequently lower plasma concentration, compared with NT-proBNP. Moreover, the intact proBNP, an 108-aa peptide, is also present in plasma (especially of patients with heart failure) in both glycosylated and nonglycosylated form (Fig. 1) [14].

It is generally believed that ANP is preferentially produced in atria, while BNP in ventricles, particularly in patients with chronic cardiac diseases [13]. Synthesis and

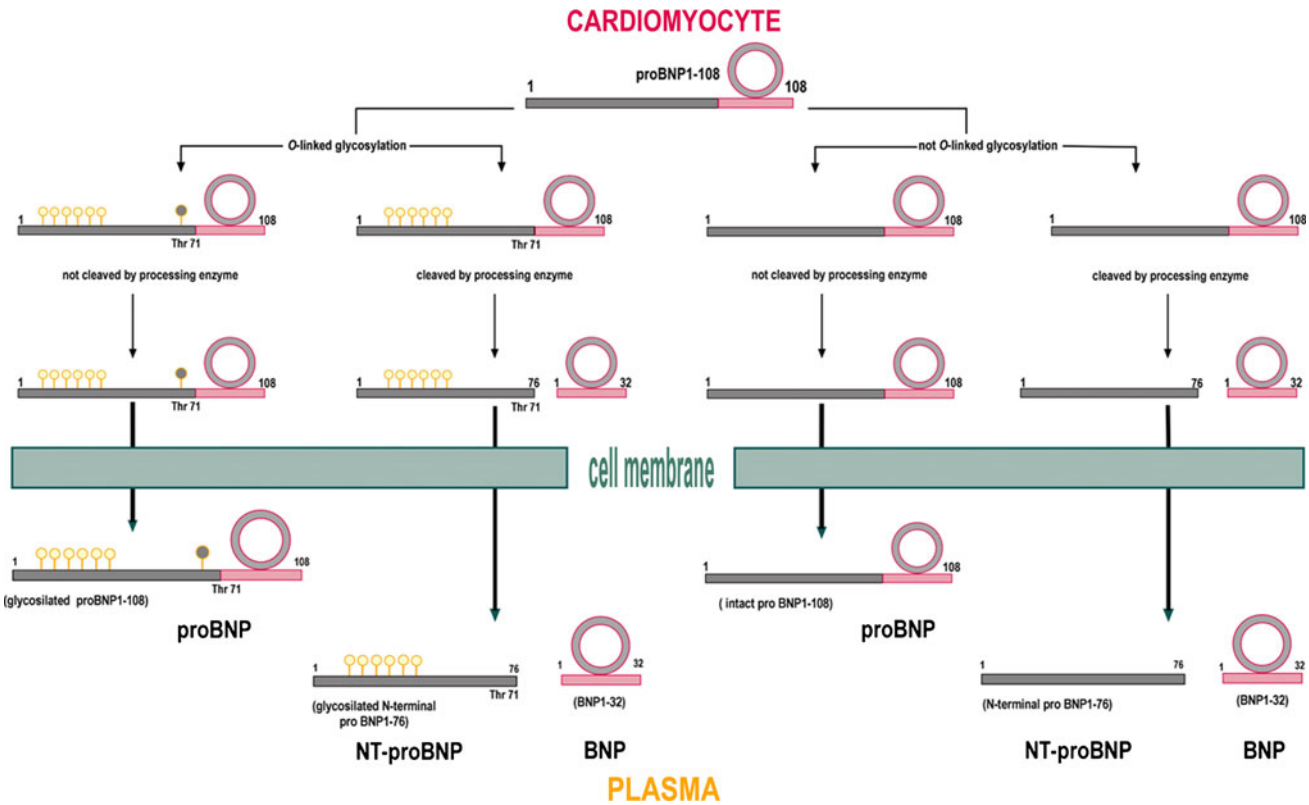

Fig. 1 Schematic representation of maturation and secretion of B-type-related natriuretic peptides by cardiomyocytes. Some of the biosynthesized pro-hormone (proBNP-108) is *O*-glycosylated within the Golgi apparatus. If *O*-glycosylation does not occur, proBNP-108 can be cleaved to BNP-32 and NT-proBNP-76 by the processing enzymes within the trans-Golgi network. If *O*-glycosylation occurs, glycosylated proBNP-108 cannot be cleaved, and uncleaved glycosylated proBNP-108 is secreted into the circulation. Finally, a smaller part of intact pro-hormone is not glycosylated and cleaved, and so this peptide can be present into circulation in intact form as proBNP-108. As indicated in the figure, the glycosylation on the threonyl residue in position 71 (Thr 71) could regulate pro-hormone cleavage by either blocking or guiding endoproteolytical enzymes (see reference [14] for more details)

secretion of the two peptides may by differently regulated in atrial versus ventricular cardiomyocytes, and, probably, during neonatal versus adult life [15–17]. The circulating levels of CNH are greatly increased in patients with cardiac disease, especially those with HF [13, 18, 19]. The measurement of B-type-related peptides is now considered a useful marker of myocardial function [13, 18–26]. Recent systematic reviews and meta-analyses demonstrated that both BNP and NT-proBNP assays have not only a high degree of diagnostic and prognostic accuracy in cardiovascular diseases [19–23] but also that BNP/NT-proBNP-guided therapy is able to significantly improve the outcome of patients with HF [27–29].

Wall stress (distension) is generally considered the main mechanical stimulus for BNP production by ventricular tissue (Fig. 2). However, mounting evidence from both in vivo and ex vivo studies is providing supports to the hypothesis that the production/secretion of CNH is regulated by complex interactions with neurohormonal and immune systems, especially in patients with cardiac disease [13, 14, 30–33]. Endothelin-1 and angiotensin II are considered the most powerful stimulators of production/secretion of both ANP and BNP; similarly, glucocorticoids, thyroid hormones, some growth factors, and especially some cytokines (such as TNF-alpha, interleukin-1, and interleukin-6) share stimulating effects on the cardiac endocrine function (Table 1 and Fig. 2) [13, 15, 16, 30–32]. Several studies indicate that BNP production/secretion may be differently regulated in the normal compared with the diseased ventricular myocardium [11, 30, 31, 34]. Indeed, ventricular hypertrophy and especially the concomitant presence of mechanisms related to inflammation and fibrosis can stimulate BNP production in the diseased ventricular myocardium [34–36]. Furthermore, experimental and clinical studies indicated that also myocardial ischemia, and perhaps hypoxia, *per se*, could induce the synthesis/secretion of BNP and its related peptides by ventricular cells, even if isolated and cultured [33, 37–43] (Fig. 2).

Table 1 Some biological factors suggested to stimulate or inhibit the production/secretion of CNH in vivo or in cell culture of cardiomyocytes

Suggested stimulating factors
Angiotensin II
Endothelin-1
α-Adrenergic agents
Arginine vasopressin
Cytokines (including IL-1, IL-6, TNF-α)
Growth factors (such as fibroblast growth factor, FGFb, and transforming growth factor-b1, TGF b1)
Prostaglandins (such as PGF2α and PGD2)
Lipopolysaccharide (LPS)
Chromogranin B
Thyroid hormones
Corticosteroids
Estrogens
Suggested inhibiting factors
Androgens
IGF-I
Nitric oxide (NO)

The Inverse Relationship between BNP and BMI

Obesity is a complex metabolic disorder, with an increasing epidemiologic impact in the European and the US population [44, 45]. BMI is usually considered to be a reliable index of overweight and obesity by some International Organizations, including the World Health Organization [44] and the National Institute of Health [45]. Several studies reported an inverse (negative) correlation between BMI and BNP/NT-proBNP values, both in healthy subjects and in patients with HF. In Table 2, we listed these studies, including some information regarding the study protocols and the main findings obtained. Although there is no doubt that an inverse correlation between BMI and BNP values is present, there is not a general consensus about the pathophysiological mechanisms responsible of this relationship. We will discuss in detail some pathophysiological mechanisms, suggested by different research groups in order to explain thus relationship, in the following paragraphs.

Role of peripheral clearance and degradation of cardiac natriuretic peptides

The first proposed explanatory hypothesis for the inverse correlation between BMI and BNP values concerned a possible increase in the peripheral clearance of natriuretic peptides [7]. It is theoretically conceivable that an increased expression of the C-type natriuretic peptide receptor (NPR-C) in the adipose tissue, which has a clearance function on natriuretic peptides, may increase the peripheral removal of BNP throughout this specific way (Fig. 3) [7]. However, an increase in NPR-C in the adipose tissue should have no influence on NT-proBNP concentration, because this inactive peptide cannot bind this receptor. Recent data from our laboratory [46] confirmed that there are significant variations among groups of patients with different BMI, associated with a negative correlation between BMI and BNP values (Spearman rank correlation coefficient Rho $= -0.240$, $P < 0.0001$), as well as between BMI and NT-proBNP values (Rho $= -0.243$, $P < 0.0001$). Moreover, the ratio between

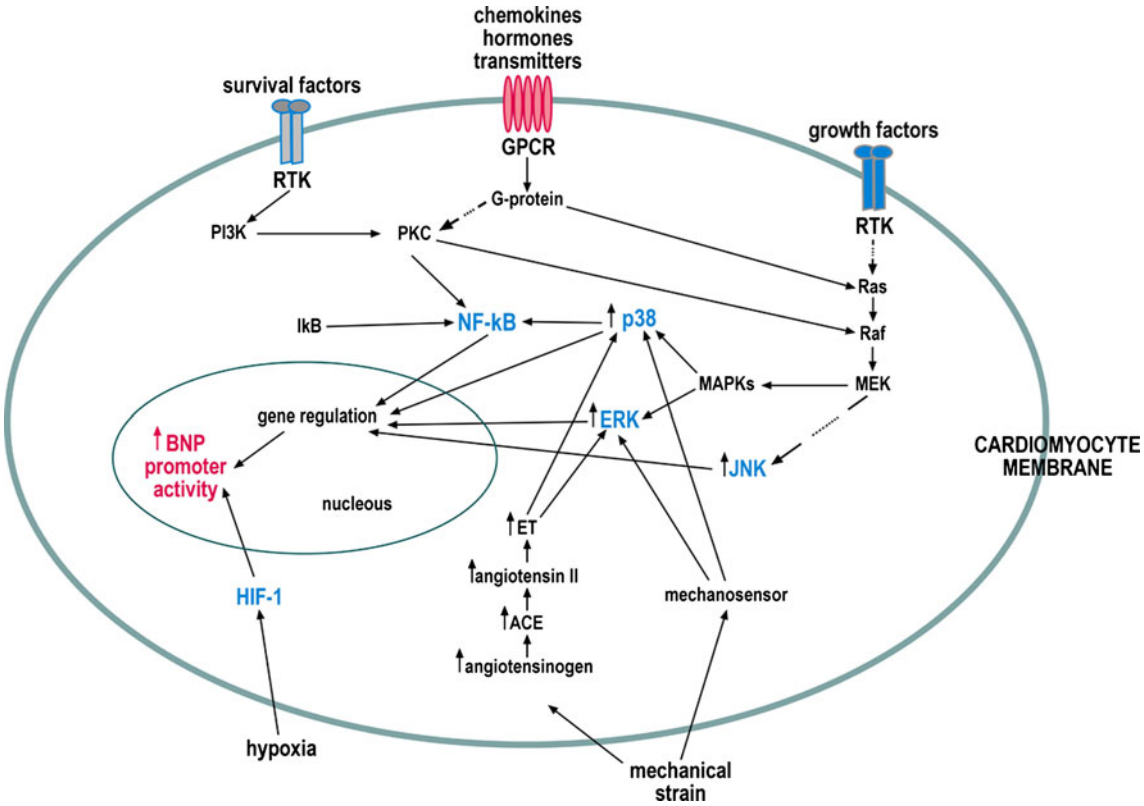

Fig. 2 Highly schematic representation of regulation of BNP gene expression. BNP production may be affected by a huge number of neurohormones, cytokines, survival, and growth factors (see Table 1 for a complete list), as well as by mechanical strain and hypoxia. The stimulation (or inhibition) of the MAPK activity and the transcriptor factor NF-kB may play a relevant role in many of these regulatory pathways. As suggested in the Figure, neurohormones, cytokines, and other biological factors can regulate the CNH production throughout multiple and independent metabolic pathways, which can be activated (or inhibited) in different pathophysiological conditions (see the references [13–17] for more details). As a result, the response of the cardiac endocrine system is the integrated resultant of several and contrasting physiological and pathological interactions, including the effects of peptide and steroid hormones, cytokines, cardiovascular hemodynamics, clinical conditions, and pharmacological treatment. *CPCR* G protein-coupled receptor, *HIF* hypoxia-inducible factor, *PCK* protein kinase C, *PI3K* phosphoinositide-3-kinase, *RTK*: receptor of tyrosine kinase

NT-proBNP and BNP values showed no significant variations among groups of patients with different BMI, thus suggesting that the clearance of BNP and NT-proBNP is similar among groups of HF patients with different BMI [46]. In conclusion, although an increased number of NPR-C into adipocyte membranes may contribute to decrease the BNP levels, it is very difficult that this increase may also play an important role in modulating the NT-proBNP levels in obese subjects.

However, some alterations in the peripheral turnover of CNH may exert a pathophysiological role. Higher amounts of unprocessed proBNP have been found in HF patients compared with healthy subjects [14, 47–52]. As a result, proBNP may be considered a circulating pro-hormone [14], which can be degraded into circulation to form the active peptide (i.e., BNP) by some plasma proteases, such as the enzymatic protein corin [53]. It is important to note that an impaired processing of proBNP in carriers of the corin I555 (P568) allele, almost exclusively expressed in individuals of African ancestry (allelic prevalence 6.7%), is associated with lower plasma BNP and with an increased cardiovascular risk as compared to noncarrier (control) subjects [54, 55]. In conclusion, some alterations of peripheral degradation of CNH may play a role also in the explanation of the lower BNP values observed in obese patients; however, further studies are necessary to test this hypothesis. In particular, the use of specific methods for the assay of unprocessed (intact) proBNP [48, 49, 52] will allow better knowledge of production/secretion as well as peripheral metabolism of B-type natriuretic peptide system, even in obese individuals and HF patients [56].

Role of sex steroid hormones

It is well known that development and distribution of body fat is closely regulated by gonadal function

Table 2 Summary of study protocol and results of studies concerning the relationship between BMI and cardiac natriuretic peptides discussed in the review

Authors	Journal	Year of publication	Population studied	Study design	Main findings
Licata G et al. [3]	Hypertension	1994	Young normotensive obese human subjects	Experimental—saline load	Absence of ANP increase after intravascular volume expansion
Wang TJ et al. [4]	Circulation	2004	General population (from the Framingham study)	Cross sectional study—multivariate analysis	Lower BNP and N-ANP plasma levels in obese subjects (according to BMI)
Mehra MR et al. [6]	JACC	2004	Chronic HF population	Cross sectional study—multivariate analysis	Lower BNP in obese subjects (according to BMI)
McCord J et al. [10]	Arch Intern Med	2004	Patients presenting with acute dyspnea	Cross sectional study—multivariate analysis	Lower BNP values in obese subjects with or without HF, but BMI not indipendently related to BNP
Krauser DG et al. [9]	American Heart J	2005	Acute HF population	Cross sectional study—multivariate analysis	Lower BNP and NT-proBNP in obese subjects (according to BMI)
Das SR et al. [62]	Circulation	2005	General population (from the Dallas Heart Study)	Cross sectional study—multivariate analysis	Negative correlation between BMI and BNP/NT-proBNP with CNH more related to lean than fat mass
Kanda H et al. [113]	J Hum Hypertension	2005	General population (Japanese)	Cross sectional study—multivariate analysis	No significant correlation between BNP and BMI
Olsen MH et al. [136]	Hypertension	2005	General population (Danish)	Cross sectional study—multivariate analysis	Negative correlation between BMI and BNP/NT-proBNP
Daniels LB et al. [8]	American Heart J	2006	Human population of patients presenting with acute dyspnea	Cross sectional study—ROC analysis	Lower BNP cut-offs for diagnosis of HF in obese patients (defined by BMI)
Horwich TB et al. [107]	JACC	2006	Chronic HF population	Cross sectional study—multivariate analysis	Negative correlation between BMI and BNP
Taylor JA et al. [108]	Am J Cardiol	2006	Patients undergoing cardiac catheterization	Cross sectional study—multivariate analysis	Negative correlation between BMI and BNP, independently of left ventricular end diastolic pressure
van Kimmenade R et al. [109]	JACC	2006	Patients undergoing bariatric surgery	Observational study-weight loss after surgery	Negative correlation between BMI and BNP/NT-proBNP, with CNH increase after BMI decrease following bariatric surgery
St Peter JV et al. [110]	Clin Chem	2006	Obese patient population	Cross sectional study—multivariate analysis	Negative correlation between BMI and BNP/NT-proBNP, with gastric bypass surgery predictor of increased BNP/NT-proBNP
Iwanaga Y et al. [111]	J Card Fail	2007	Chronic HF population	Cross sectional study—multivariate analysis	Negative correlation between BMI and BNP, independently of end diastolic wall stress parameters
Sarzani R et al. [1]	J Hypertension	2008	Cultures of human and in vitro-differentiated preadipocytes and visceral mature adipocytes	Experimental—exposure to ANP (and to angiotensin II)	Inhibition of cell growth by ANP (and stimulation by angiotensin II)
Park SJ et al. [11]	Korean Circ J	2009	Patients with chest pain and/or dyspnea undergoing cardiac catheterization	Cross sectional study—multivariate analysis	Negative correlation between BMI and NT-proBNP observed only in non diabetic patients

Table 2 continued

Authors	Journal	Year of publication	Population studied	Study design	Main findings
Pervanidou P et al. [112]	Horm Res Pediatr	2010	Healthy children	Cross sectional study—multivariate analysis	Lower NT-proBNP values in obese than non obese males, with no difference in females
Sugisawa T et al. [169]	Diabetes Res Clin Pract	2010	Patients with advanced type 2 diabetes	Cross sectional study—multivariate analysis	Negative correlation between BMI and BNP. BNP inversely related to visceral fat (from CT scan)
Chainani-Wu N et al. [137]	Am J Cardiol	2010	Subjects with or at high risk of coronary artery disease	Observational study-weight loss after life-style modification	A decrease in BMI following lyfestile modifications is associated with BNP increase
Christenson RH et al. [105]	Clin Chem	2010	Patients presenting with dyspnea	Cross-sectional study—multivariate analysis	Negative correlation between BMI and NT-proBNP
Sugisawa T et al. [5]	Endocrinology J	2010	General population (Japanese)	Cross-sectional study—multivariate analysis	Lower BNP in obese subjects (according to BMI)

[57, 58]. Women have a higher percentage of body fat than men. Moreover, women tend to accumulate fat around the hips, buttocks, and thighs, while men have a larger intra-abdominal (visceral) fat mass. After menopause, there is a redistribution of fat depots, and postmenopausal women develop increased amounts of visceral fat [57]. This sex difference in body fat distribution was identified as the main determinant of the differing metabolic profiles and cardiovascular disease risk in men and women [57, 58]. Indeed, the risk of developing obesity-related diseases is significantly lower in premenopausal women compared to men, a difference that is abolished after menopause [57].

It was also suggested that the endocrine cardiac function is regulated by gonadal function [13, 46]. Indeed, BNP and NT-proBNP concentrations are low in the early years of extra-uterine life with similar values in both genders, while peptide levels increase progressively throughout the adolescence in girls, reaching the values in healthy premenopausal women about 2-fold higher than men at the same age [46, 59–61]. After 50 years of age, the difference in BNP and NT-proBNP values between sexes tends to decrease.

Several findings support the hypothesis that the gonadal function, and in particular the estrogens/androgens circulating ratio [46], may have a key role in the regulation of both body fat distribution and BNP production/secretion [62–65]. In women, estrogens may promote a gynoid distribution of body fat [58] and also increase the BNP production/secretion by cardiomyocytes [11, 46, 64, 65]. On the other hand, the results of the Dallas Heart Study [62, 63] suggested that androgens may regulate the cardiac endocrine function. Androgens may promote, at least in hyper-androgenic women, both the development of lean mass and the decrease in the natriuretic peptide production/secretion by cardiomyocytes. Moreover, the low circulating sex hormone-binding globulin (SHBG) levels found in women with abdominal obesity may indirectly indicate that elevated free androgens are related to increased visceral fat accumulation [58]. In men, androgens may increase cardiovascular risk because they promote a visceral (android type) fat distribution [58, 59], and they may also decrease the BNP production/secretion by cardiomyocytes [46]. However, data on androgen effects on cardiovascular risk in men are conflicting [66–75], probably because the relationship between testosterone concentrations and mortality risk is U-shaped [46, 58] with an increased risk for both high [68, 73, 74] and low [76–79] testosterone concentrations. Conversely, testosterone concentrations within the physiological range are usually associated with a more favorable metabolic profile and cardiovascular risk [58, 73].

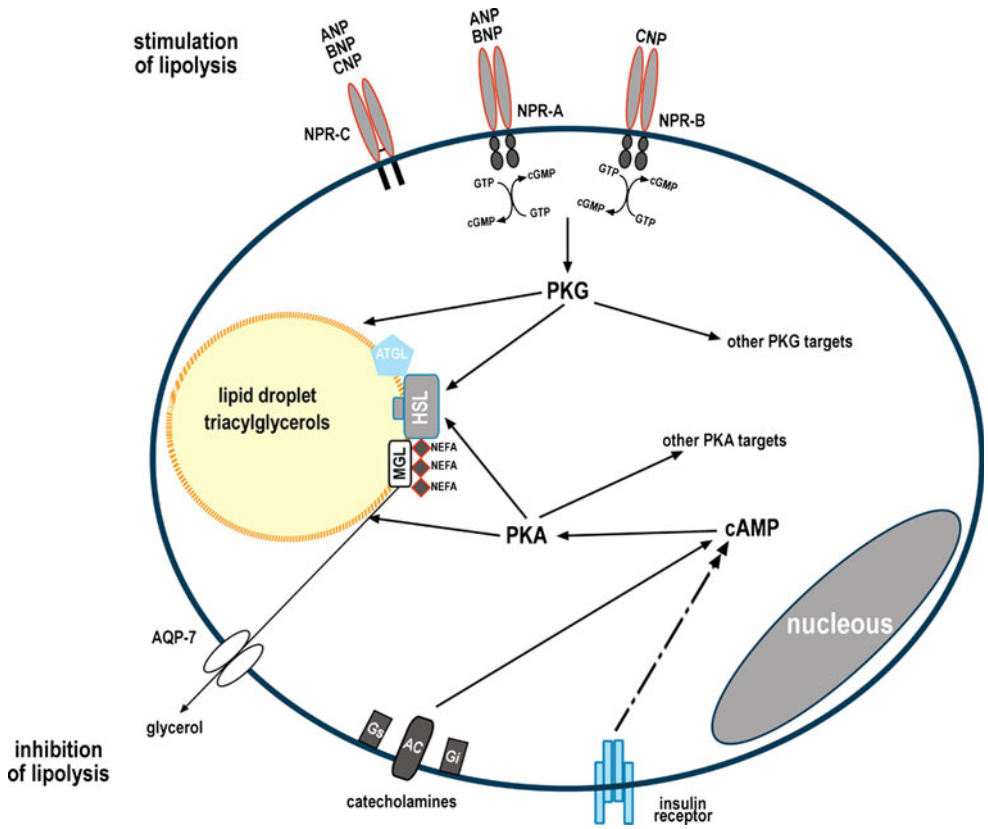

Fig. 3 Control of human fat cell lipolysis. Signal transduction pathways for catecholamines, for atrial natriuretic, and for insulin are summarized. In *the top of the figure*, the stimulating action of natriuretic peptides ANO, BNP, and CNP on adipocytes is shown. There are three known natriuretic peptide–specific receptors: **a** NPR-A, **b** NPR-B, and **c** NPR-C, also named clearance receptor. NPA-B and NPR-B contain an equally large intracellular signal domain catalyzing the synthesis of the intracellular signaling molecule cGMP. In contrast, NPR-C only contains a smaller residue intracellular domain and lacks guanylyl cyclase activity. It primarily controls local natriuretic peptide concentrations via receptor-mediated internalization and degradation. ANP, BNP, and CNP exert potent lipolytic effects in human fat cells, similar to those induced by the *β*-adrenoceptor agonist, isoproterenol, through a cGMP-dependent protein kinase signaling pathway independent of cAMP production. Intracellular cAMP concentrations are controlled by: (i) catecholamines through b-adrenoceptor-mediated adenylyl cyclase activation; (ii) inhibitory receptors (i.e., a2-adrenoceptors, adenosine, prostaglandin, neuropeptide Y and peptide YY, and nicotinic acid) through the inhibition of adenylyl cyclase activity, and (iii) insulin through PDE-3B activation. CNH stimulate NPR-A-dependent guanylyl cyclase activity and cGMP production. cAMP and cGMP both contribute to the protein kinase [PKA and PKG (cGK-I)]-dependent phosphorylation of HSL. Phosphorylation of HSL promotes translocation of HSL from the cytosol to the surface of the lipid droplet. PKA and PKG (cGK-I) phosphorylate several other substrates (enzymes and transcription actors, not shown in the diagram) and can also influence the secretion of various molecules from adipocytes. Stimulation of insulin receptors counteracts cAMP production by PDE-3B stimulation but has no effect on cGMP production. The products of the complete hydrolysis of triacylglycerols (i.e., NEFAs and glycerol) are released by fat cells. Docking of adipocyte lipid-binding protein (ALBP) to HSL favors the efflux of NEFA, whereas glycerol is channeled by aquaporin-7 (AQP-7), a water–glycerol transporter that is present in the plasma membrane. *AC* adenylyl cyclase, *A1* adenosine-R, *A1* adenosine receptor, *AR* adrenoceptor, *ATGL* adipose triglyceride lipase, *EP3-PGR* EP3 prostaglandin receptor, *Gi* inhibitory GTP-binding protein, *Gs* stimulatory GTP-binding protein, *GC* guanylyl cyclase, *HSL* hormone-sensitive lipase, *IRS-1* insulin receptor substrate 1, *MGL* monoacylglycerol lipase, *NEFA* nonesterified fatty acid, *NPY-Y1-R* type Y1 neuropeptide receptor, *PDE-3B* phosphodiesterase-3B, *PKA* protein kinase A, *PKB* protein kinase B (Akt), *PKG* (*cGK-I*) protein kinase G, *PtdIns3P-K* phosphatidylinositol-3-phosphate kinase, *PUMA-G* in mice, and HM74-R in humans, nicotinic acid receptor

Cross talk between endocrine function and adipose tissue: the role of adipokines

Recent findings support the hypothesis that the natriuretic peptide system (ANP, BNP, and, at a less extent, CNP) may have a role in the regulation of fat tissue function and development by exerting a potent lipolytic effect in human fat cells [80–83]. On the other hand, obesity is associated with salt retention [84] and increased cardiac output [85, 86], which are mechanisms that should increase (rather than decrease) the activity of cardiac endocrine function [1, 2]. The hypothesis of "natriuretic handicap" [1, 2] implies that obesity is characterized by the presence of one or more circulating or tissue factors able to depress the

activity of cardiac endocrine function. In other words, this hypothesis assumes that there is a continuous cross talk between endocrine function and fat tissue.

A huge number of bioactive substances are increased in plasma of patients with obesity, such as noradrenaline, angiotensin II, vasopressin, endothelins, and some cytokines, which typically increase (rather than reduce) the production/secretion of CNH by cardiomyocytes (Table 1 and Fig. 2) [11–13, 15–17]. Also insulin was reported in one study to increase ANP secretion and gene expression in cultured rat cardiomyocytes, while glucose has no effect [87]. Therefore, all these neurohormones and pro-inflammatory factors should not be considered good candidates as the pathophysiological link between increased visceral fat distribution and low plasma BNP levels.

It is well known that obesity is associated with ectopic lipid deposition in multiple tissues, including the heart [88, 89]. It is now well accepted that fat tissue produces and secretes a great number of bioactive peptides (named adipokines), which act as mediators between obesity-related exogenous factors (nutrition and lifestyle) and the molecular events that lead to metabolic syndrome, inflammation, lipotoxicity, and cardiovascular diseases [90, 91]. A recent list of adipokines includes leptin, adiponectin, visfatin, apelin, vaspin, hepcidine, chemerin, and omentin [90].

It is interesting to note that some pro-inflammatory adipokines (such as leptin, resistin, and visfatin), like as some cytokines, are able to activate the transcription factor NF-kB [92–98], and subsequently by this pathway, they may stimulate the ANP and BNP gene transcription (Fig. 2). As a result, it may be hypothesized that these adipokines may stimulate the ANP and BNP gene transcription throughout this metabolic pathway. However, some very recent studies indicate a more complex effect of adipokines (such as leptin) on CNH production/secretion by cardiomyocytes. Mascareno et al. [99] reported that the antihypertrophic action of leptin in vivo may be mediated by CNH, since this action requires the activation of some transcription factors (such as NFATc4) followed by an increase in the expression of the ANP gene in mice. On the other hand, Yuan et al. [100] reported that leptin infusion inhibits ANP secretion indirectly through nitric oxide without changing basal or isoproterenol-induced ANP secretion in Sprague–Dawley rats. These studies suggest that CNH production/secretion by cardiomyocytes can be differently regulated by the same biological factor (such as leptin) throughout multiple metabolic pathways activated (or inhibited) in different pathophysiological conditions.

On the other hand, recent findings indicated that the CNH have a role in the regulation of fat tissue function and development [80]. Furthermore, several data indicated that CNH exert potent lipolytic effects in human fat cells, similar to those induced by the β-adrenoceptor agonist, isoproterenol, through a cGMP-dependent protein kinase signaling pathway independent of cAMP production [83] (Fig. 3). Furthermore, ANP can increase the production of adiponectin [101], a polypeptide positively involved in glucose and free fatty acid metabolism (so to be protective from diabetes and metabolic syndrome), while the release of leptin is inhibited in culture of human adipocytes [102, 103]. These studies support the hypothesis that a continuous cross talk exists between cardiac endocrine function and adipose tissue system. From a pathophysiological point of view, further studies on the inter-relationship between CNH and adipokine systems may allow new insights into the link between metabolic disorders (such as diabetes mellitus, metabolic syndrome, and obesity), body fat distribution, and increased cardiovascular risk [46, 104].

Pathophysiological conditions and pharmacological treatment as possible confounding variables

Many studies found significantly reduced circulating levels of BNP and NT-proBNP in individuals with BMI values $\geq$30 kg/m^2 compared with individuals with normal BMI values, resulting an inverse (negative) association between BMI and plasma BNP and NT-proBNP values [4, 5, 8–11, 62, 63, 105–112] (Table 2). Some studies were based on large population [4, 5, 62, 63, 106], including both healthy adult subjects and patients with various disorders (only patients with HF were excluded), while other studies included only patients with HF [8–11, 105] (Table 2). However, conflicting results were also reported; Kanda et al. [113] found no significant correlation between BNP to BMI values in a general Japanese population, including 686 apparently healthy subjects.

Overweight and obese individuals show an increased mortality risk and for this reason are more frequently treated for hypertension, coronary artery disease, or other cardiovascular disorders than lean subjects [114]. It is well known that ACE inhibitors, angiotensin receptor blockers (such as valsartan), diuretics, and nitrates are able to reduce plasma CNH levels in parallel with hemodynamic and clinical improvement [19, 27]. Moreover, although acute administration of some β-blockers may provide an early rise in plasma CNH, sustained treatment is associated with improvement in cardiac function, reduction in filling pressure, cardiac volumes, and a fall in CNH levels [19]. The decrease in plasma BNP and NT-proBNP under baseline median concentration is associated with treatment efficacy and clinical improvement, whereas unchanged or increased levels are associated with disease progression and worse prognosis [115, 116]. Some recent meta-analyses demonstrated that if BNP-guided treatment is able to significantly decrease the peptide levels, it is also effective

on prognosis [27, 28, 117]. In other words, treated patients who have low BNP/NT-proBNP values also have a lower mortality risk independently of other predictive variables (including the presence of obesity or metabolic syndrome).

From a theoretical point of view, pharmacological treatment for cardiac disease should be considered a possible candidate as the pathophysiological link between increased visceral fat distribution and low CNH levels. Indeed, patients at high risk (such as those with obesity, hypertension, and/or type-2 diabetes mellitus) are more frequently treated, and an efficacious treatment significantly reduces plasma BNP and NT-proBNP levels.

From a statistical point of view, the confounding effect of pharmacological treatment is difficult to estimate in a multivariable statistical analysis [118]. Indeed, type, dose, association, and interaction of drugs administered greatly vary among patients with cardiovascular diseases. Furthermore, pharmacological treatment is generally evaluated in multiple regression analyses as a dichotomized variable. Dichotomization produces loss of information, reduces statistical power, and introduces the possibility of erroneous results [119, 120]. Finally, several recent studies and meta-analyses have demonstrated that treatment response is clinically more relevant than the treatment itself in HF patients [19, 27, 28, 115–117]. An effective response to treatment is strongly dependent by clinical conditions: severe disease, old age, and presence of comorbidities are associated with both no response to treatment and higher mortality risk in HF patients [19, 26–29, 115–117]. These two variables (clinical condition and pharmacological treatment), being greatly variable among patients enrolled in the same population study and even more in different studies, may actually produce some conflicting results.

Role of possible confounding variables: are all individuals with BMI $\geq$30 kg/m^2 true obese?

Overweight is usually defined as a BMI of 25–29.9 kg/m^2, while obesity as a BMI of $\geq$30 kg/m^2 [44, 45]. BMI is a simple, common parameter for rating obesity level, but it may be misleading in some specific clinical conditions, because it is not able to assess the distribution of major components of body weight: fat, lean body mass, and fluid body content [121]. Indeed, BMI overestimates body fat in people who are very muscular (such as bodybuilders and athletes) or who have edema [122] and in young adult males compared to young adult females, because of the lesser percent body fat in men. As an example, in 1970, Arnold Schwarzenegger at age 23, when he won the Mr. Olympia contest for the first time, had a body weight of 113 kg and a height of 1.88 m [123], with a corresponding BMI of 32.0 kg/m^2; consequently, according to these data, we should assume that an obese men won the most important bodybuilder contest in 1970. Conversely, BMI underestimates body fat in people with muscle mass loss, such as the elderly.

Due to these BMI limitations, there is need to take into account more accurate investigations of major components of body weight (such as DEXA or computed tomography and magnetic resonance imaging) [124, 125], in order to understand the relationship linking circulating natriuretic peptides and sex steroid hormones to fat distribution and body weight. The results of large population studies, discussed above, which used only BMI for estimation of obesity [4–6, 8–11, 105, 106, 113, 114], should be taken into consideration only after an accurate analysis of the anthropometric characteristics of the individuals enrolled in the study. In the following paragraph, we will discuss more in detail the pathophysiological and clinical implication of this important issue.

Role of possible confounding variables: difference in analytical performance of BNP and NT-proBNP immunoassays

There is another possible important confounding variable in the evaluation and comparison of different studies on cardiac natriuretic peptides. It is well known that there are significant differences in the analytical characteristics and clinical results (including differences in reference ranges, decision levels, and cutoff values) among immunoassays for B-type-related peptides, and these differences might allow misleading clinical interpretation [126–128], as also recently confirmed by a multicentre study [129]. Since BNP and NT-proBNP have completely different biochemical structure, molecular weight, biological activity, and degradation pathways, it is not surprising that immunoassay methods considered specific for BNP or NT-proBNP show different analytical characteristics, quality specifications, and measured values [126–129]. However, the CardioOrmocheck study [129] has recently confirmed that there are large differences (up to 2.7-fold) even in measured values between the results obtained with the most popular fully automated platforms considered specific for BNP immunoassays, while less differences are found between the most popular fully automated platforms for NT-proBNP assay. These results are largely expected because all the commercial NT-proBNP methods actually use antibodies and standard materials from the same source (i.e., Roche Diagnostics), while BNP methods use different antibodies and standard materials [127–129]. These differences in measured values are probably due to relative poor specificity of all commercial assays for BNP and NT-proBNP peptides, due to presence of a significant cross-reactivity with the intact precursor proBNP$_{1\text{-}108}$, variable for each assay [130]. Unfortunately, at present time, it very

difficult to estimate the exact influence of proBNP in the BNP and NT-proBNP immunoassays, because there are no commercial methods specifically designed for the measurement of intact proBNP. These data suggest that the great part of peptides measured with commercial immunoassays for B-type natriuretic hormone probably is inactive peptides present in plasma samples (Fig. 1), and so the measurement of BNP may be an unreliable index of the true biological activity of the cardiac endocrine function [13, 14].

BNP levels, obesity, and mortality risk in patients with heart failure

Two recent meta-analyses confirmed that overweight and obesity, as assessed by BMI, are associated with lower (rather than higher) all-cause and cardiovascular mortality rate in patients with congestive HF [122, 124]. These findings are consistent with other evidences in different chronic disease populations, which demonstrate improved mortality with higher BMI levels [125, 131–133]. This phenomenon, termed "reverse epidemiology" and involving about 20 million Americans, may be due to the overwhelming effect of the malnutrition–inflammation complex syndrome (MICS) [131]. The presence of MICS in some patients contributes to explain the inverse correlation between BMI and BNP values in HF [6, 8–11, 105]. BNP production/secretion is greatly increased in elderly HF patients with severe disease, hemodynamic impairment, and activation of counteracting neurohormone (including adrenergic, renin–angiotensin–aldosterone, and endothelin) and cytokine systems compared to asymptomatic subjects [13, 30–35]. On the other hand, BMI is significantly decreased in chronic HF patients with anorexia, malnutrition, and body wasting [131]. These patients usually show increased circulating levels of some cytokines (especially TNF-α), able to activate cardiac endocrine function, and have also more severe clinical disease and very poor prognosis [13, 30, 31, 134]. Furthermore, it is well known that androgen production is decreased in elderly male subjects and patients with severe chronic disease [135]; in turn, this condition may contribute to increase the production of CNH [46].

A huge number of studies reported the clinical usefulness of CNH as prognostic biomarker for all-cause and cardiovascular mortality both in the general population [136–143] and in patients with cardiovascular diseases [144–155]. Furthermore, several meta-analyses confirmed that BNP/NT-proBNP assay is a powerful prognostic marker in the general population, as well as in patients with cardiac diseases or undergoing cardiac and noncardiac surgery [19, 156–160]. These studies usually suggest that the mortality risk progressively increases according to the rise in plasma BNP and NT-proBNP concentration and also that there is no threshold value below which there is no risk [19, 156, 161]. In other words, the risk of death and cardiovascular events seems to rise even for small increments of BNP values in patients with HF [156], thus suggesting that to have low BNP values is always "a good thing" owing to the association with lower mortality risk.

In conclusion, high baseline BNP and NT-proBNP values and especially significant increased (or unchangeable) values with respect to baseline levels after treatment (i.e., no response to treatment) are powerful and independent (to other predictive variables, including obesity and metabolic syndrome) prognostic markers of all-cause and cardiovascular mortality risk in patients with HF [27, 115, 116], which is the natural and final end of all cardiovascular diseases [162]. As a result, this finding seems to be, almost in part, in conflict with the "natriuretic handicap" original hypothesis [1, 2, 7], which predicts that obese patients (characterized by lower plasma BNP and NT-proBNP values) should have an increased (rather than decreased) cardiovascular and mortality risk compared to lean individuals (characterized by higher peptide values).

Prospective remarks

At present time, it is not possible to give a definitive answer to the crucial question what the pathophysiological link between increased visceral fat distribution and low plasma BNP levels is. However, we would like to suggest some indications in order to restrict and to better direct the future researches in this field.

(1) While BMI is a simple, common parameter for rating obesity level [44, 45], it may be misleading in some specific clinical conditions [122, 123]. Due to these limitations concerning BMI, we need further studies using more accurate investigations of major components of body weight (such as DEXA or computed tomography and magnetic resonance imaging), in order to better understand the relationship linking CNH and body fat distribution [163].

(2) Obese individual or patients with metabolic syndrome are frequently treated for comorbidity or cardiovascular complications, such as hypertension, coronary artery disease, or other cardiac disorders. The standard pharmacological treatment tends to decrease the production/secretion of CNH. As a result, treated patients usually show lower plasma BNP and NT-proBNP than untreated individuals (lean or obese). The pharmacological treatment is usually considered a stubborn bias factor in multivariate analyses [118],

which should be taken specifically into account as possible confounding factor in future epidemiological or clinical studies evaluating the link between CNH system and body fat distribution.

(3) The response of the CNH system is always the integrated resultant of several and contrasting physiological and pathological interactions [13]. Although fascinating, the hypothesis that gonadal function regulates both body fat distribution and cardiac endocrine function needs further evidence. In particular, it is necessary the conclusive demonstration that sex steroids (especially androgens) are able to actually affect (increase or decrease) the production/secretion of BNP from mammalian (including human) cardiomyocytes both in cell cultures and in vivo [46]. Moreover, visceral fat expansion can increase the clearance of active natriuretic peptides (ANP and BNP) by means of an increased expression of NPR-C on adipocytes, and in this way, it may contribute, almost in part, to decrease the activity of the CNH system [1, 7]. Obesity is associated with ectopic lipid deposition even in the heart, which may directly exert a lipotoxic effect on the myocardium by secreting *in loco* several cytokines and adipokines. These substances can affect both the endocrine and the contractile function cardiomyocytes throughout a paracrine effect [88, 89]. We believe that future studies should be set up to evaluate especially this important issue: the possible effects of some specific adipokines on CNH system.

(4) Most diseases are the consequence of the breakdown of cellular processes, but the relationships among genetic/epigenetic defects, the molecular interaction networks underlying them, and the disease phenotypes remain poorly understood. The network concept may reveal a number of surprising connections among different clinical conditions [164–166]. Similarly, the effects of drugs are not limited to the molecules they directly bind to; instead, these effects can spread throughout the cellular network in which they act, causing unwanted side effects [165]. Furthermore, the more connected a disease is to other diseases, the higher is its prevalence and associated mortality rate [167].

In an integrated communicative network, several actors can play a role throughout several positive or negative feedback servomechanisms. A network topology-based approach may help to uncover potential mechanisms that contribute to cardiovascular diseases [167]. Peptide and steroid hormones, cytokines, cardiovascular hemodynamics, clinical conditions, and pharmacological treatment may all together contribute to the pathophysiological mechanisms linking endocrine function regulation and body fat growth and distribution. The response of the CNH system is always the integrated resultant of all these pathophysiological interactions. However, only few variables of a biological system are usually studied together. As a result, a lot of information is not taken into consideration, and so it is impossible to have an accurate interpretation and evaluation of all pathophysiological mechanisms under study. Unfortunately, we are still not able to well integrate these multiple information together [168]; therefore, we should learn to do it.

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