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DIFFERENTIAL REGULATION OF ANP AND BNP IN ACUTE DECOMPENSATED HEART FAILURE - DEFICIENCY OF ANP

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Abstract

Background—The endocrine heart releases the cardiac hormones, atrial natriuretic peptide (ANP) and b-type natriuretic peptide (BNP) that play a key role in cardiovascular (CV), renal and metabolic homeostasis. In heart failure (HF), both plasma ANP and BNP are increased as a compensatory homeostatic response to myocardial overload.

Objectives—We investigated the differential regulation of circulating ANP and BNP in acute decompensated heart failure (ADHF) patients and tested the hypothesis that a relative deficiency of ANP exists in a subgroup of ADHF patients.

Methods—We measured ANP and BNP in a small group of ADHF patients (n=112). To support our goal, we also prospectively recruited 129 healthy subjects to establish contemporary normal values for ANP and BNP. Plasma cGMP, ejection fraction (EF) and body mass index (BMI) were measured in these subjects.

Results—In ADHF, 74% of patients showed elevated ANP and BNP. Importantly, 26% of patients were characterized as having normal ANP (21% of this subgroup having normal ANP and elevated BNP). Cyclic GMP was lowest in the ADHF group with normal ANP ($p<0.001$), whereas BMI and EF were inversely related to ANP levels ($p=0.003$).

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Conclusions—Among a subgroup of patients hospitalized with ADHF, the presence of an ANP deficiency is consistent with a differential regulation of ANP and BNP and suggests the existence of a potentially compromised compensatory cardiac endocrine response. Our findings have implications in the pathophysiology, diagnostics and therapeutics of human HF.

Keywords

natriuretic peptides; acute decompensated heart failure; atrial natriuretic peptide; and deficiency

INTRODUCTION

The discovery by deBold and colleagues that the heart produces a peptide hormone, called atrial natriuretic peptide (ANP), established the heart as an endocrine organ (1,2). Further studies by Sudoh revealed that the heart also produces a second structurally similar, but genetically distinct peptide, named b-type natriuretic peptide (BNP) (3). Both hormones play a key role in cardiovascular (CV), renal and metabolic homeostasis via activation of the particulate guanylyl cyclase A receptor (pGC-A) with increased generation of the second messenger 3,5, cyclic guanosine monophosphate (cGMP) (4). The activation of the pGC-A/cGMP pathway results in a number of CV and renal actions including natriuresis, diuresis, vasodilation, and suppression of the renin-angiotensin-aldosterone system (RAAS). They mediate cardioprotective actions such as inhibition of cardiomyocyte hypertrophy, suppression of cardiac fibrosis and enhancement of diastolic function as well as metabolic actions such as lipolysis and browning of white adipocytes (5). ANP is thought to be a more potent activator of pGC-A than BNP (6), however is also more susceptible to enzymatic degradation by neprilysin (NEP) (7).

A hallmark of heart failure (HF) is the elevation of ANP and BNP (8–12). From a biological perspective, studies have supported the concept that the elevation of ANP and BNP in HF may serve as a beneficial compensatory physiological response (13). Importantly, in a murine model of dilated cardiomyopathy (DCM), mice that were genetically ANP deficient with concomitant dilated cardiomyopathy had reduced survival compared to mice with DCM and an intact ANP system (14). Further, consistent with the protective role of natriuretic peptides (NPs) in HF is the success of sacubitril/valsartan, which augments circulating NPs through inhibition of NEP, a major enzyme that degrades both cardiac hormones. Of note however is that ANP is the principal NP elevated by sacubitril/valsartan with little change in BNP (7,15–18).

An emerging concept in hypertension and obesity is the presence of a NP deficiency state (19). Indeed, studies demonstrate low levels of BNP as well as ANP in hypertension and in obesity (20,21). Further, a relative NP deficiency state exists in African Americans, which may increase the risk for CV disease (22,23). It would not be surprising that the heart, like the thyroid gland in hypothyroidism or the pancreas in diabetes, may be associated with an inadequate endocrine response to organ stress, such as that induced by acute decompensated HF (ADHF).

We first defined contemporary normal values of circulating ANP and BNP in a healthy adult population and then tested the hypothesis that a potential ANP deficiency exists in a

subpopulation of ADHF patients. Moreover, our study also sought to determine the clinical phenotype of ADHF patients based upon the elevation or lack of elevation of ANP and BNP. Our findings thus have significance to the pathophysiology, diagnostics and consequently, therapeutics of human HF.

METHODS

Study Populations

One hundred twenty nine (n=129) healthy subjects and one hundred twelve (n=112) ADHF patients were recruited.

Healthy, adult subjects were recruited from the Mayo Clinic Biobank that consists of over 75,000 subjects. Specifically, the Mayo Clinic Biobank is a comprehensive ongoing registry with Institutional Review Board (IRB) approval to collect volunteer DNA and blood samples to aid ongoing population studies focused on precision medicine and optimizing medical diagnostics and therapeutics. After screening subjects from the Mayo Clinic Biobank, we selected a clinically robust cohort of 129 healthy subjects who were defined as having neither CV nor metabolic disease and were not taking any CV medications. All participants provided written informed consent for participation, and the study was approved by the IRB at the Mayo Clinic.

Patients hospitalized for ADHF at Mayo Clinic Hospital - St. Marys Campus (Rochester, Minnesota) were prospectively identified and enrolled from an ongoing registry of consecutive admissions with the first patient recruited in 2009 and the last in 2016. Patients with a clinical diagnosis of HF consistent with the Framingham criteria (24) were included. All patients underwent a baseline history and physical examinations as part of routine clinical care. Plasma samples were collected for the assessment of ANP, BNP, cGMP, and creatinine within 72 hours of hospitalization. Utilizing the electronic medical record, we obtained ejection fraction (EF) by echocardiography, estimated glomerular filtration rate (eGFR), body mass index (BMI; kg/m^2) and length of stay (LOS) from this ADHF cohort. Medications at the time of blood sampling for ANP, BNP, cGMP and creatinine were also obtained.

Plasma Assays

Blood was drawn into EDTA tubes and centrifuged at 4°C and 2,500 rpm for 10 min. One milliliter of plasma was aliquoted and stored at −80°C until assayed. Hormonal measurements were conducted in the Mayo Clinic Cardiorenal Research Laboratory. ANP was obtained using an RIA (Phoenix Pharmaceuticals, Mountain View, CA) that had a standard curve range from 4.8 to 1250 pg/mL (8). ANP cross-reactivity was <1% with NT-ANP, BNP, CNP, endothelin, and adrenomedullin. BNP was measured using a 2-site immunoenzymatic sandwich assay (Biosite Incorporated, France) (25). The amount of analyte in the sample was determined from a stored, multi-point calibration curve with a range between 5 to 4000 pg/mL. There was no cross reactivity in the assay. Cyclic GMP was measured with an RIA (Perkin Elmer (NEX-133) with a standard curve range from 0.05 to 10 pg/tube (26). There was <0.001% with cAMP, GMP, GDP, ATP, GTP. Plasma creatinine

was measured by the Clinical Chemistry Core Laboratory at the Mayo Clinic using a Roche Cobas creatinine reagent (Roche Diagnostics, Indianapolis).

Statistical Analysis

Continuous variables were presented as median and quartiles while categorical variables were presented as number and percentage. In order to compare between groups while controlling for age and gender, regression models were fit including age, gender, and group as the independent variables and each characteristic of interest as the dependent variable. Specifically, linear regression was used for continuous characteristics, while logistic regression was used for binary characteristics. In these models, groups were used as a multiple level variable and a multiple degree of freedom test was used to test for differences across groups. In these analyses, biomarkers were log transformed to approximate normality. For categorical variables, logistic regression models were fit.

In order to classify ADHF patients into “Normal” and “Elevated” categories based upon their plasma ANP and BNP concentrations, the 95th percentile of the healthy subjects was used. If the plasma level of ANP and BNP was below that of the 95th percentile of the normal subjects, the ADHF patient was classified as “Normal” levels. Whereas if the ANP or BNP level were greater than or equal to the 95th percentile threshold of the normal subject’s concentration, the ADHF patient would be classified as having “Elevated” levels. SAS version 9.4 (Cary, NC) was used for analyses and two sided p-value ≤ 0.05 were used for statistical significance. For analysis of ADHF subgroups based upon “normal” and/or “elevated” ANP or BNP, we determined (Figure 2) the percentage of subjects with either normal or elevated ANP or BNP or both and in Table 3 report clinical features. We also assessed correlations of ANP and BNP in normal subjects and in patients with ADHF using Spearman rank correlations.

RESULTS

Study Populations

Baseline demographic data are presented in Table 1. When compared to healthy subjects, ADHF patients were older, were mostly of male gender, had higher BMI, with CV and metabolic co-morbidities including hypertension, diabetes, atrial fibrillation, ischemic heart disease, myocardial infarction, hyperlipidemia, and stroke. In ADHF patients, EF showed reduced systolic function, angiotensin converting enzyme inhibitors (ACEI’s), angiotensin II type 1 receptor blocker (ARB’s), beta-blockers, loop diuretics and statins were prescribed during hospitalization and at time of blood draw for ANP, BNP and cGMP. Median length of stay in ADHF patients was 5 days while eGFR was mildly reduced.

Natriuretic Peptides in Healthy Subjects and in ADHF Patients

Figure 1 reports median plasma levels of ANP and BNP in healthy subjects (n=129) and ADHF patients (n=112). In the healthy subjects, median circulating levels were 4 pg/mL for ANP and 26 pg/mL for BNP. In ADHF, the median plasma levels of ANP were significantly higher than healthy subjects at 106 pg/mL. Circulating BNP was increased compared to

healthy subjects at a level of 503 pg/mL. The correlation coefficients for ANP and BNP in healthy subjects was 0.51 and in ADHF patients was 0.54.

ANP and BNP 95th Percentile Levels in Healthy Subjects

Table 2 reports the median (Q1, Q3) values and 95th percentile for ANP and BNP levels obtained from healthy subjects. The 95th percentile for ANP was 39 pg/mL while for BNP it was 73 pg/mL. The 95th percentile cut-off points were used to determine “Normal” or “Elevated” ANP and BNP levels in ADHF patients.

Analysis of “Normal” and “Elevated” ANP and BNP in ADHF

As shown in Figure 2, we observed that 74% of ADHF patients had “Elevated” levels of both ANP and BNP (n=83). Importantly, we observed that 21% of ADHF patients had “Normal” levels of ANP with “Elevated” levels of BNP (n=23). A small number of 5% of ADHF patients exhibited “Normal” levels of both ANP and BNP (n=6). Thus, 26% of ADHF patients demonstrated “Normal” levels of ANP. Finally, there were no ADHF patients that had an “Elevated” level of ANP and “Normal” level of BNP.

Clinical Characteristics of the ADHF Patients according to ANP and BNP

Table 3 reports characteristics of the ADHF patients divided into subgroups based upon normal or elevated ANP and BNP levels.

The subgroup with “Elevated” ANP/ “Elevated” BNP accounted for 74% of the study population with the majority being male at an average age of 73. Median ANP and BNP levels were 184 pg/mL and 641 pg/mL, respectively. This cohort had median cGMP levels at 5.6 pmol/mL, BMI of 31 kg/m^2, and the lowest EF among the subgroups at 35% with 40% having an EF<=40 with trend for the longest LOS.

The subgroup with “Normal” ANP/ “Elevated” BNP levels accounted for 21% of the study population, with 52% being males, at an average age of 71 years. Median ANP and BNP levels were 22 pg/mL and 354 pg/mL, respectively. These patients had median plasma cGMP levels of 3.4 pmol/mL, BMI of 35 kg/m^2, and EF of 40%. 52% had EF<=40.

The subgroup with “Normal” ANP/ “Normal” BNP levels represented 5% of ADHF patients all of whom were male with an average age of 63 years. Median ANP and BNP levels were 7 pg/mL and 49 pg/mL, respectively. This group had the lowest level of plasma cGMP of 2.5 pmol/mL (P<0.001) and the highest BMI of 44 kg/m^2 (p=0.003). Additionally, these ADHF patients had an EF of 54% with 25% EF<=40.

As reported in Table 3, plasma cGMP was positively associated (p<0.001) with elevated ANP and BNP levels. In contrast, BMI and EF displayed a negative association (p=0.003). There were no differences in eGFR among subgroups.

Medication use was similar across all subgroups although there was a trend for lower use of BB in the “Normal ANP” / “Normal BNP” subgroup.

DISCUSSION

The major objective of our study was to investigate the hypothesis that there is a lack of elevation of circulating ANP in a subpopulation of patients hospitalized for ADHF. To test this hypothesis, we prospectively recruited ADHF patients from the Mayo Clinic Hospital and healthy subjects from the Mayo Clinic Biobank. We first established contemporary normal levels for plasma ANP and BNP from our healthy subjects. We utilized the 95th percentile for cut-off values to set the threshold for normal circulating values of NPs, which then provided us with the ability to determine “Normal” or “Elevated” values of circulating ANP and BNP in ADHF patients. Indeed our results, for the first time, support the existence of a relative ANP deficiency state in a subgroup of patients with ADHF despite an increase of BNP.

Our findings extend previous NP biomarker studies by providing a comprehensive investigation of both mature cardiac hormones, which are biologically active (ANP and BNP) in both healthy and ADHF cohorts. A universal hallmark is the elevation of circulating BNP in HF. Indeed, in our ADHF population with the exception of 6 patients, BNP was elevated in all ADHF patients. In contrast, 26 ADHF patients lacked elevation of ANP, which is thought to be the more potent activator of their commonly shared receptor, pGC-A (6). All together, these findings support the existence of a relative deficiency of the cardiorenal protective hormone, ANP, possibly due to reduced production, altered release with or without enhanced enzymatic degradation by neprilysin (NEP). This latter mechanism may play a role given ANP is much more susceptible to degradation by NEP than BNP (7, 27). Indeed, recent studies report that the principal NP that is increased by sacubitril/valsartan in HFrEF is ANP, and not BNP, although there may an early increase in BNP with sacubitril/valsartan which supports an important role for enzymatic degradation of ANP more than BNP to also explain our findings (16–18).

Our observation is also highly relevant to the seminal work of Nakagawa (28) showing that in isolated cardiomyocytes, BNP demonstrated much more rapid transcriptional activation, early mRNA turnover, and greater secretion compared to ANP when cells were stimulated by neurohumoral factors known to be increased in HF. Importantly, the study by Nakagawa concluded that the myocardial gene expression of BNP is distinctly regulated from ANP, at transcriptional and posttranslational levels. The properties of BNP gene expression demonstrated by Nagakawa et al. also support BNP as a hormone that may function as an “emergency” cardiac hormone in HF while ANP functions more as the regulator of body fluid homeostasis under physiological conditions. Such differential regulation also underscores our concept of an ANP deficiency in HF as we observed in a subpopulation of ADHF patients in our study. It is intriguing to speculate on a mechanism of reduced ANP production compared to BNP also may be active in the current study. There exist two key microRNAs (mir425 and/or mir155), which downregulate ANP gene expression and ANP production (29). In, addition, it is also possible that those without an increase in ANP have less severe HF. Suggestive of this is a trend for less duration of hospitalization in the ANP deficient group yet there was no difference in eGFR or use of medications among the subgroups. Further mechanistic studies are clearly warranted to understand the basis of this

potential ANP deficiency in the failing heart with a focus on ANP production as well as potential role of enhanced NEP activity resulting in increased ANP degradation.

Relevant key clinical data collected in ADHF patients provided insight into the phenotype of the subgroups defined by an “Elevated” or “Normal” ANP and BNP as shown within the Central Illustration. Key parameters included cGMP, the second messenger of pGC-A activated by ANP or BNP, BMI which is associated with lower ANP and BNP levels and EF for which BNP is reported to be lower with HFpEF compared to HFrEF. Importantly, among ADHF patients without elevated ANP, plasma cGMP levels were lower, BMI was higher and both HFrEF and HFpEF were represented in all subgroups.

Recognizing that the current study involves a small cohort of ADHF patients, we cautiously speculate on the causality for the clinical phenotype and associations observed as follows. The role of BMI and adipose tissue in NP regulation is well known and in the setting of obesity, in which decreased production and/or increased metabolism including increased clearance by NP clearance receptor (NPR-C) could be a mechanism for the relative ANP deficiency (30). Alternatively, a primary ANP deficiency could have contributed to obesity considering that the metabolic actions of ANP include lipolysis and browning of white adipocytes (31). Indeed, obesity and metabolic syndrome are less prevalent among the carriers of the ANP genetic variant rs5068, which is associated with higher circulating levels of ANP (32). Further, it is of interest that the ANP deficiency group also had more preserved EF and lower levels of cGMP although patients with both preserved and reduced EF were observed among all subgroups.

Our findings of a deficiency of ANP may be characteristic of a unique form of cardiac failure that warrants further investigations. This form is analogous to Type 1 diabetes mellitus in which there is a deficiency of insulin warranting insulin replacement therapy. While the exact mechanism of this ANP deficiency in the presence of elevated BNP is unclear (reduced production and/or increased degradation), the potential of ANP based therapy is an attractive area for further exploration. One such therapy is inhibition of NEP with a drug such as sacubitril/valsartan in which ANP was reported to be increased in contrast to little change in BNP (16–18). Further, ANP (carperitide) is approved in Japan for the treatment of ADHF with beneficial outcomes (33). MANP (also called ZD100) also holds promise as a long acting ANP analogue that is more potent than ANP and is currently in clinical trials for CV disease thus also representing a potential ANP/cGMP therapy in HF (33). Further, the current study underscores the importance and need to better understand the ANP system in HF. Our study also may suggest that, in addition to measuring BNP in ADHF, it may also be important to determine ANP levels.

In conclusion, this investigation provides new insights into the endocrine role of the heart in human ADHF. Specifically, our data suggest that there may be differential regulation of ANP and BNP in ADHF and there is an existence of a relative ANP deficient subpopulation, an observation that has not previously been reported until now. Our findings lay the foundation for future prospective studies aimed to better understand the mechanisms of the ANP deficiency observed in a subpopulation of ADHF patients. Further studies should also define the natural history of ANP deficiency in ADHF including outcomes such as

rehospitalization and death, the possible need for ANP/pGC-A/cGMP therapeutic strategies as well as the need for measuring circulating ANP, in addition to BNP, in ADHF.

LIMITATIONS

Our study has limitations: it is observational; therefore, what is cause versus effect remains unclear. Our study population also was small and future larger studies should confirm the current findings and further define the clinical phenotype of such an ANP deficient subpopulation as well as its association with outcomes. Further studies are also needed with more patients to fully characterize if ANP deficiency is more prevalent in either HFrEF or HFpEF or found equally in both. It should be noted that understanding cGMP levels in the healthy population would have provided even more insight into cGMP in HF patients. Finally, recognizing that African Americans have lower levels of NPs, a limitation to our study was that all ADHF patients were Caucasians (22,23).

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Abbreviations

ADHF	acute decompensated heart failure
ANP	atrial natriuretic peptide
BMI	body mass index
BNP	b-type natriuretic peptide
cGMP	3’,5’ cyclic guanosine monophosphate
EF	ejection fraction
eGFR	estimated glomerular filtration rate
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
pGC-A	particulate guanylyl cyclase A receptor
NP	natriuretic peptide

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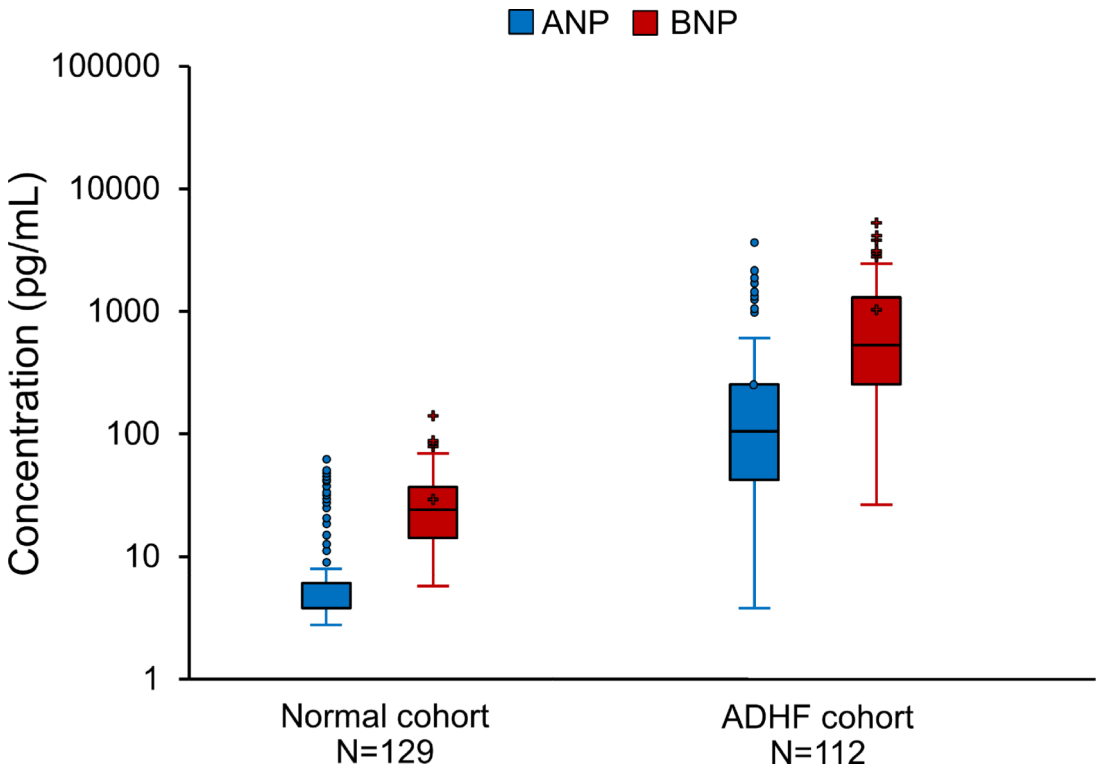
CLINICAL PERSPECTIVES

- There exists a relative deficiency of ANP in a unique cohort of ADHF patients.
- The circulating levels of the cardiac hormones ANP and BNP are differentially regulated in ADHF.
- Those with a relative ANP deficiency have lower cGMP levels and higher BMI.
- These findings may have implications for the need to treat such patients with ANP-based drugs or drugs that increase levels of circulating ANP.

Translational Outlook

From bench to bedside, we discovered a deficiency of ANP in ADHF. Such a deficiency suggests a loss of the cardio-protective effects of ANP and cGMP. To address this dysregulation, we believe therapeutically augmenting the ANP/pGC-A/cGMP system may improve outcomes, which will need to be tested in a larger study. This study thus sets the framework to delve deeper into exploring the mechanisms of this cardiac hormone deficiency together with supporting the development of potential drugs or small molecules that potentiate the ANP/pGC-A/cGMP pathway, to exogenously increase ANP levels and/or activate pGC-A (the ANP/cGMP receptor). Thus, the pioneering of innovative advancements in the field of therapeutics, by harnessing the biological utility of ANP, to improve patient care in HF is on the horizon.



Central Illustration.

Presence of an ANP deficiency in acute decompensated heart failure and pathological implications

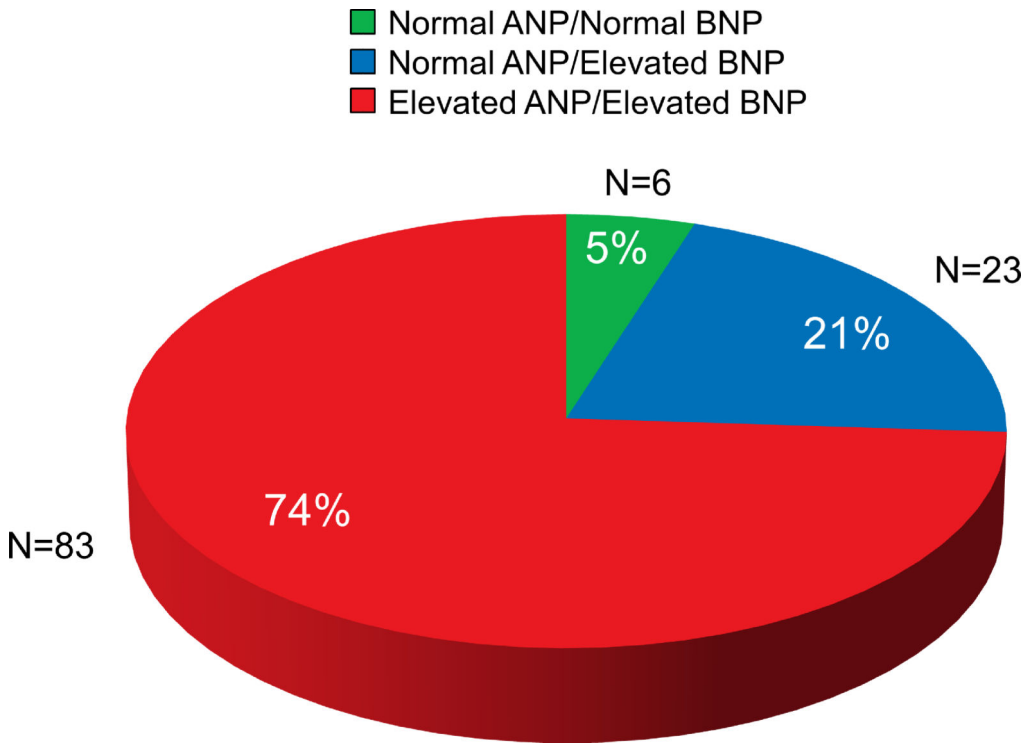


Figure 1.
Circulating levels of ANP and BNP in normal human subjects and patients with acute decompensated heart failure.

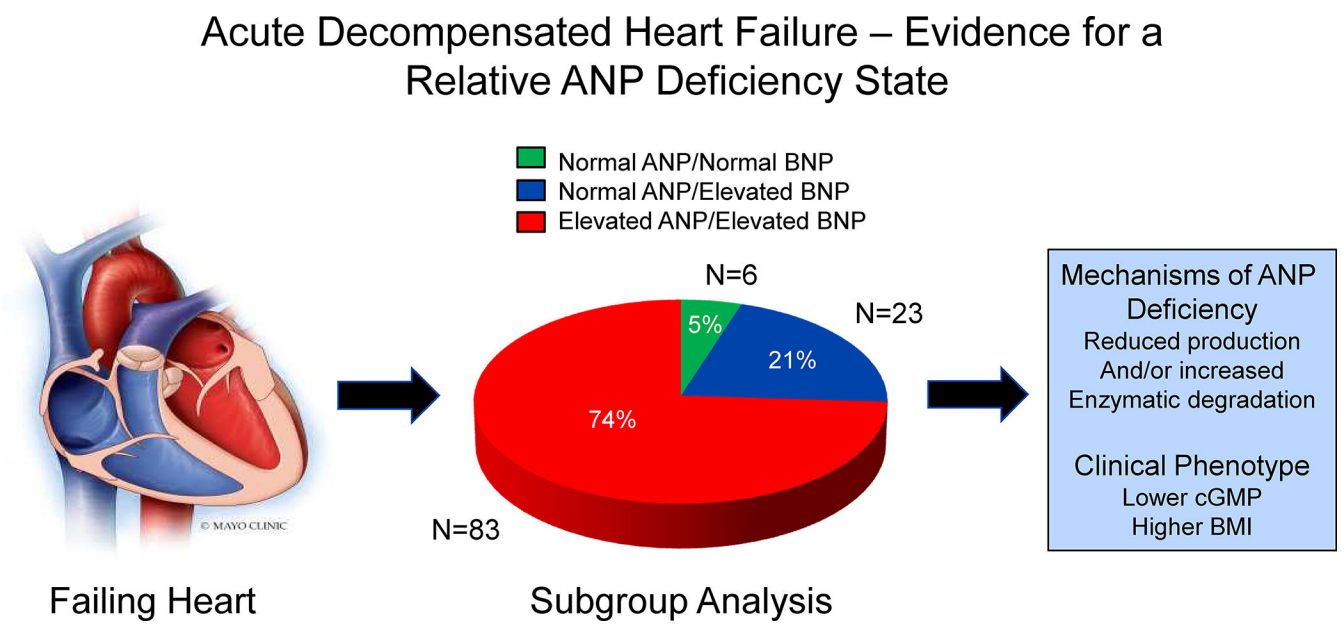


Figure 2.

Subgroup analysis of patients with acute decompensated heart failure. These subgroups include patients with “Elevated” ANP and BNP; “Elevated” BNP and “Normal” BNP; and “Normal” ANP and BNP.

Table 1:

Clinical Characteristics of the Study Populations

VARIABLE	ADHF PATIENTS (N=112)	NORMAL SUBJECTS (N=129)
Age *y	71 (±11)	57 (±12)
Male gender n (%)	74 (66)	31 (40)
BMI †	33 (27,40)	26 (23,29)
Hypertension n (%)	75 (67)	-
Diabetes mellitus n (%)	48 (43)	-
Atrial fibrillation n (%)	72 (64)	-
IHD n (%)	75 (67)	-
MI n (%)	30 (27)	-
Hyperlipidemia n (%)	72 (64)	-
Stroke n (%)	6 (5)	-
EF% †	36 (26,52)	
EF≤40 # n (%)	54 (56)	
ACEI n (%)	53 (47)	-
ARB n (%)	21 (19)	-
Beta-blocker n (%)	68 (61)	-
Loop diuretic n (%)	109 (97)	-
Statin n (%)	70 (63)	-
ANP † pg/mL	106 (39,271)	4 (4,6)
BNP † pg/mL	503 (268,1069)	26 (15, 39)
cGMP † pmol/mL	4.8 (3.0,6.9)	1.6 (1.2,2.4)
eGFR, ml/min	52.3 (39.8,75.9)	
LOS days	5 (3,8)	

*Values expressed as Mean (±SD)

†Values expressed as Median (IQR)

#EF data available in 97 subjects

ADHF: acute decompensated heart failure, SD= standard deviation, IHD= ischemic heart disease, MI= myocardial infarction, ACEI= angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, eGFR= estimated glomerular filtration rate, LOS= length of stay, IQR=interquartile range

Table 2:

Contemporary ANP and BNP Cut-Off Values

Variable	Median (IQR)	95th Percentile
ANP (pg/mL)	4 (4,6)	39
BNP (pg/mL)	26 (15,39)	73

IQR=interquartile range, pg=picogram, mL= milliliter, ANP=atrial natriuretic peptide, BNP= b-type natriuretic peptide

Table 3:

Clinical Characteristics of the ADHF Patients according to ANP and BNP Subgroups

Variable	Normal ANP/ Normal BNP (N=6)	Normal ANP/Elevated BNP (N=23)	Elevated ANP/ Normal BNP (N=0)	Elevated ANP/ Elevated BNP (N=83)	Age/Sex Adj P Value
Age,(y) *	63 (57,75)	71 (65,75)	-	73 (67,79)	0.29
Male, n (%)	6 (100%)	12 (52%)	-	56 (67%)	0.30
ANP (pg/mL) *	7 (5,10)	22 (16,31)	-	184 (81,369)	<.001
BNP (pg/mL) *	49 (36,57)	354(206,615)	-	641 (329,1260)	<.001
cGMP(pmol/mL) *	2.5 (2.3,3.0)	3.4 (2.1,4.5)	-	5.6 (3.7,21.3)	<.001
BMI (kg/m^2) *	44 (42,65)	35 (30,42)	-	31 (2637)	0.003
EF (%) *	54 (40,62)	40 (34,50)	-	35 (24,55)	0.08
EF≤40 n (%)	1 (25%)	11 (52%)	-	42 (40%)	0.32
eGFR (ml/min) *(ml/min/ $1.73m^2$) *	73 (45,106)	57 (36,79)	-	51 (40,75)	0.66
ACEI n (%)	2 (33)	13 (57)	-	38 (46)	0.48
ARB n (%)	0 (0)	3 (13)	-	18 (22)	0.68
Beta-blocker n (%)	2 (33)	19 (83)	-	47 (57)	0.04
Loop diuretic n (%)	6 (100)	23 (100)	-	80 (96)	>0.99
Statin n (%)	4 (67)	16 (70)	-	50 (60)	0.56
LOS (days) *	3.5 (2.0,4.0)	4.0 (2.0,8.0)	-	6.0 (3.0,8.0)	0.06

* Values expressed as Median (Interquartile Range)

ANP=atrial natriuretic peptide, BNP= b-type natriuretic peptide, cGMP = cyclic guanosine monophosphate, BMI= body mass index, EF= ejection fraction, eGFR=estimated GFR, LOS=length of stay.