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CLINICAL RESEARCH

Chronic Peptide Therapy With B-Type Natriuretic Peptide in Patients With Pre-Clinical Diastolic Dysfunction (Stage B Heart Failure)

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ABSTRACT

OBJECTIVES This study determined whether there is development of tachyphylaxis to enhancement of cardiorenal response to acute volume loading (AVL) with B-type natriuretic peptide (BNP) after 12-week, twice-daily subcutaneous BNP administration in patients with preclinical diastolic dysfunction (PDD).

BACKGROUND PDD is characterized by normal systolic function and moderate or severe diastolic dysfunction but no symptoms of heart failure (HF). Impairment in cardiorenal endocrine response to stress by AVL exists in PDD and is corrected by acute administration of subcutaneous BNP.

METHODS A double-blinded, placebo-controlled proof-of-concept study was conducted to compare 12 weeks of twice daily subcutaneous BNP, 10 μg/kg ($n = 24$), versus placebo ($n = 12$) in PDD. Subjects underwent 2 study visits, at baseline and after 12 weeks. At each study visit, echocardiography, renal, and neurohumoral assessments were performed before and after intravascular AVL.

RESULTS Among those with PDD, there was a statistically significant improvement in diastolic function after 12 weeks of BNP, as measured by a decrease in the Doppler E/e′ ratio (where E is early mitral inflow velocity and e′ is mitral annulus early diastolic motion) ($p = 0.004$) and improvement of diastolic dysfunction grade ($p = 0.008$). After 12 weeks, there was statistically significantly greater sodium excretion, urine flow, and urinary cyclic guanosine monophosphate excretion to AVL (all $p < 0.001$), as well as a trend toward greater glomerular filtration rate ($p = 0.050$) in the BNP group as compared to the placebo group.

CONCLUSIONS In subjects with PDD, chronic BNP administration resulted in sustained improvement in diastolic function without development of tachyphylaxis to the enhancement of cardiorenal response to volume expansion with BNP. (Human Brain Natriuretic Peptide [BNP] [or Nesiritide] to Help Heart, Kidney and Humoral Function; NCT00405548) (J Am Coll Cardiol HF 2016;4:539–47) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AVL = acute volume loading

BNP = B-type natriuretic peptide

cGMP = cyclic guanosine monophosphate

DT = deceleration time

E = early mitral inflow velocity

e′ = mitral annulus early diastolic motion

EF = ejection fraction

GLP = glucagon-like peptide

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

NPR = natriuretic peptide receptor

PDD = preclinical diastolic dysfunction

RVSP = right ventricular systolic pressure

SQ = subcutaneous

Heart failure (HF) is a prevalent condition affecting more than 5 million Americans and is projected to increase as the population of the United States continues to age (1). Among those with HF, approximately one-half have preserved ejection fraction (pEF) (2). Despite significant advances in management of HF with reduced ejection fraction over the past decade, evidence-based therapeutic options in HFpEF remain limited.

Pre-clinical diastolic dysfunction (PDD) is defined as a subject with normal systolic function and moderate or severe diastolic dysfunction determined by Doppler criteria but no symptoms of HF (3). PDD falls within stage B HF as defined by American College of Cardiology/American Heart Association criteria for those without HF symptoms but who have structural heart disease. PDD prevalence is estimated to afflict 20% to 30% of the general adult population (3–5). There is known progression of PDD to symptomatic HF, with an estimated annual incidence of 2% (3). Furthermore, the 3-year cardiac hospitalization and mortality rates for those with PDD exceed 17% and 10%, respectively (6).

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Natriuretic peptides are secreted by the heart in response to volume expansion and cardiac distension and have multiple important cardiac and renal properties. B-type natriuretic peptide (BNP)'s beneficial cardiac effects include antihypertrophic, antifibrotic, and lusitropic effects (7,8). Natriuretic peptides are important in cardiorenal neurohormone regulation and homeostasis (9).

In a previous study, we demonstrated that, in patients with PDD, there is impairment in cardiorenal neurohormonal response to volume expansion and a subsequent lack in natriuretic response (10). The pathophysiology is due to impairment in renal cyclic guanosine monophosphate (cGMP) activation following acute volume loading (AVL), which is rescued with acute subcutaneous (SQ) BNP administration (10). The burden of PDD coupled with the lack of therapeutic interventions available for the prevention of HF leads to the search for novel therapies that may rescue the impaired cardiorenal physiology that may contribute to progression to symptomatic HF. Previous demonstration that acute SQ BNP administration improves cardiorenal response to AVL suggests a potential therapeutic option among those with PDD, but chronic peptide administration may lead to development of pharmacologic tolerance or tachyphylaxis (11,12).

The objective of the current study was to determine whether there is development of tachyphylaxis to enhancement of cardiorenal response to AVL with BNP after 12-week, twice-daily SQ administration of BNP in patients with PDD. We hypothesized that chronic subcutaneous BNP administration for 12 weeks would lead to a sustained improvement of ventricular diastolic function without evidence of development of tachyphylaxis to the enhanced cardiorenal response with BNP following acute volume expansion in subjects with PDD.

METHODS

STUDY DESIGN. This proof-of-concept study was designed to determine safety and efficacy and to assess whether there is development of tachyphylaxis to long-term BNP therapy in PDD. The study was a randomized, double-blinded, placebo-controlled study designed to compare cardiorenal responses to AVL (0.9% normal saline, 0.25 ml/kg/min for 1 h) between those who received 12 weeks of twice-daily SQ BNP and those who received placebo. The study was approved by the Mayo Foundation Institutional Review Board and was performed at the Center for Clinical and Translational Science (NCT00405548).

PARTICIPANTS. Subjects with PDD (n = 49) were recruited between March 2008 and August 2012 at Mayo Clinic, Rochester, Minnesota, identified based on an echocardiographic database. Preclinical diastolic dysfunction was defined as subjects with normal systolic function (EF: >50%), moderate, or severe diastolic dysfunction as determined by Doppler criteria, and no symptoms and diagnosis of HF. Inclusion criteria included adults 18 years of age or older with EF >50% and moderate or severe diastolic dysfunction as identified by Doppler echocardiography. Subjects also could not have any signs, symptoms, or prior diagnoses of or hospitalization for congestive HF. Subjects' medical records were reviewed extensively for any previous diagnosis of HF, previous HF hospitalization, or symptomatic volume overload. Subjects had to achieve a 6-min walk distance of >450 m. Subjects who had a 6-min walk distance <450 m due to an orthopedic limitation but no dyspnea or fatigue as assessed by the investigators were included in the study. All subjects who were taking cardiovascular medications had to have stable dosages for at least 2 weeks. Informed consent was obtained and documented for all participants.

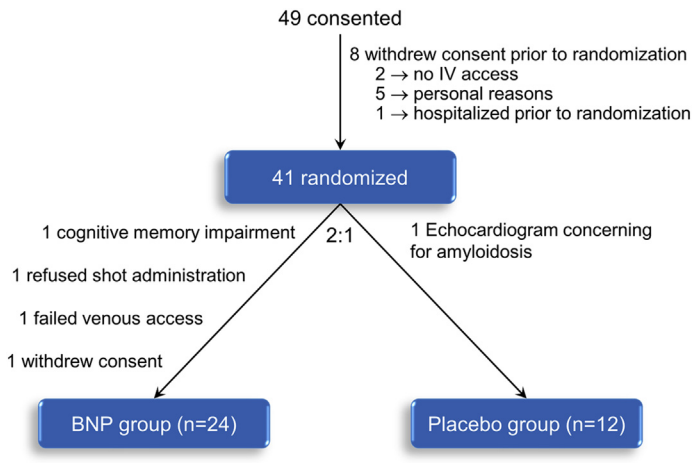
Exclusion criteria included myocardial infarction within 3 months, unstable angina within 14 days, or any evidence of myocardial ischemia. Additional exclusion criteria included significant valvular stenosis; hypertrophic, restrictive, or obstructive cardiomyopathy; constrictive pericarditis, primary pulmonary hypertension, biopsy-proven active myocarditis, severe congenital heart disease, sustained ventricular tachycardia, or ventricular fibrillation within 14 days; second- or third-degree heart block without a permanent cardiac pacemaker; stroke within 3 months of screening; or evidence of significantly compromised central nervous system perfusion. Laboratory exclusion criteria included total bilirubin concentration of >1.5 mg/dl, other liver enzyme levels >1.5 times the upper limit of normal, serum creatinine concentration >3.0 mg/dl, serum sodium concentration <125 mEq/l or >160 mEq/l, serum potassium concentration <3.5 mEq/l or >5.0 mEq/l, serum digoxin concentration >2.0 ng/ml, systolic pressure <85 mm Hg, or hemoglobin concentration <10 g/dl.

ECHOCARDIOGRAPHIC ASSESSMENT. Echocardiography was performed according to guidelines of the American Society of Echocardiography (where E is early mitral inflow velocity; A is the atrial component of mitral inflow velocity; e′ is mitral annulus early diastolic motion; DT is deceleration time; and PV S/D is pulmonic vein systolic flow-to-diastolic flow ratio) (13). Diastolic dysfunction was classified as grade 1 (impaired relaxation: E/A ≤ 0.75 or E/e′ <10), grade 1a (impaired relaxation: E/A ≤ 0.75 or E/e′ ≥10), grade 2 (pseudonormal: 0.75 < E/A < 1.5, DT >140 ms, and PV S/D <1 or E/e′ ≥10), or grade 3/4 (restrictive: E/A >1.5 or DT <140 ms and PV S/D <1 or E/e′ ≥10) (4). Right ventricular systolic pressure (RVSP) values were also measured.

STUDY PROTOCOL. Visit 1. Each subject had 2 study visits, visit 1 at the beginning of the study and visit 2 after 12 weeks of subcutaneous BNP or placebo therapy. At visit 1, subjects reported to the Center for Clinical and Translational Science at 7:00 AM after 1 week of salt-restricted diet (120 mEq/day). Subjects were given their usual morning medications and then placed in a supine position for 60 min, with spontaneous bladder emptying every 30 min. Subjects who were unable to spontaneously void every 30 min were given a urinary catheter, and bladder emptying was determined by bladder ultrasonography. Subjects drank amounts of water equivalent to the sum of blood and urine losses every 30 min. Baseline Doppler echocardiography was performed, followed by a 30-min clearance period that included neurohormone measurements, renal studies, and urine collection, including glomerular filtration rate, urine flow, urinary sodium excretion, and urine cGMP excretion. These measurements were followed by 60 min of volume expansion (normal saline: 0.25 ml/kg/min) and repeated echocardiographic measurements, urine collection, and blood sampling.

Subjects were randomized in a 2:1 fashion to the SQ BNP group or the placebo group (Figure 1). Randomization was provided by the Mayo Clinic Division of Biomedical Statistics and Informatics in conjunction with the Mayo Clinic Pharmacy, and investigators were blinded to which therapy the subjects received. Subjects, caregivers, and investigators were blinded during the trial and had no knowledge of whether the contents of the vial used for subcutaneous injections, as dispensed by pharmacy, contained placebo or BNP. Those in the SQ BNP group self-administered subcutaneous BNP at 10 μg/kg twice daily for 12 weeks (Scios Inc., Mountain View, California). Those in the control group self-administered subcutaneous placebo twice daily for 12 weeks. Subjects were given instructions for the proper abdominal wall SQ administration technique. The first and second doses were self-administered but under supervision and were monitored for 12 h. If hypotension occurred (systolic BP <85 mm Hg) after the first dose, the second dose was decreased by one-half. Subjects were discharged from the clinical research unit 12 h after the second dose with 12 weeks of supplies. Subjects had to be stable on their medication therapy for at least 3 weeks prior to enrollment, and during the trial, subjects were highly encouraged not to change their other medications.

FIGURE 1 Consort Diagram



BNP = B-type natriuretic peptide; IV = intravenous.

There were no significant changes in the background medical therapy during the 12 weeks of the trial in both the BNP and placebo groups.

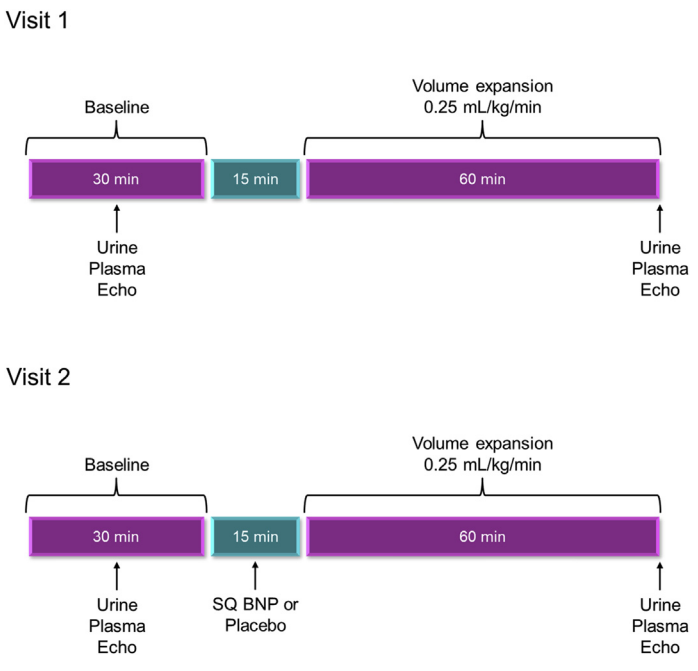
Visit 2. Subjects returned for study visit 2 after 12 weeks. In a protocol identical to study visit 1, the subjects underwent repeated echocardiographic, plasma, and renal clearance studies. They received their last subcutaneous BNP or placebo dose and then submitted to further measurements after volume expansion (Figure 2).

Safety data were collected, including identification of development of HF symptoms, gastrointestinal side effects, hypersensitivity reaction at the injection site, joint pains, dyslipidemia, and hypotension with blood pressure monitoring.

NEUROHORMONE, ELECTROLYTE, AND RENAL ASSESSMENT. Plasma and urine cGMP were measured by radioimmunoassay. Plasma BNP was measured by fluorescence immunoassay.

For measurement of renal parameters, intravenous catheters were placed in each arm of the subjects. Continuous iothalamate was infused to achieve a plasma concentration of 15 to 20 mg/l. After 60 min of equilibrium, urine and blood samples were collected for determination of glomerular filtration rate. Measurements were made by the Mayo Clinic Core Renal laboratory.

FIGURE 2 Methods and Visit Flowchart



SQ = subcutaneous; other abbreviations as in Figure 1.

STATISTICAL METHODS. Sample size calculations were based on our previous study of acute cardiorenal and humoral effects of acute SQ BNP in PDD. Sample size was calculated by construction of the magnitude of difference that could be detected for sodium excretion and urine flow in response to volume expansion (10). It was assumed that the standard deviation (SD) in the untreated group would be only one-half that in the treated group, because the untreated group response data were due largely to biological and measurement variability between 2 occasions, with little or no actual signal. Hence, subjects were randomized in a 2:1 fashion to treatment or placebo to optimize the precision of the group comparison. Power calculations were done with these assumptions. With a total of 40 subjects, the values given below give detectable change (with 85% power) between group mean changes, both as raw numbers and as percentages of baseline mean. For sodium excretion, the detectable change was 131 μEq/min, and the detectable percentage of change was +100%. For urine flow, the detectable change was 1.89 ml/min, and the detectable percentage of change was +54%. Continuous variables are means ± SD, and categorical variables are percentages. Comparisons between the 2 treatment groups (SQ BNP vs. SQ placebo) were made by Student *t* test for normally distributed continuous variables, the rank-sum test for continuous variables with a skewed distribution, and the chi-square test for independence for categorical variables. Comparisons within groups (between visit 1 and visit 2) were made using a paired Student *t* test. For all analyses, statistical significance was accepted as $p < 0.05$.

RESULTS

PATIENT POPULATION. There were 49 subjects who consented to the study. Eight subjects withdrew consent before randomization due to lack of intravenous access, hospitalization before randomization, or for personal reasons. Forty-one subjects were randomized in a 2:1 fashion to the BNP group or the placebo group. Four subjects withdrew from the BNP group due to existing cognitive impairment, failed venous access, refusal of subcutaneous administration, and withdrawal of consent. One subject was withdrawn from the placebo group due to echocardiographic findings suspicious for amyloidosis. Hence, in the final analysis there were n = 24 subjects in the BNP group and n = 12 subjects in the placebo group.

The baseline characteristics shown in Table 1 demonstrate that age, sex, and comorbidities were

similar between the BNP and placebo groups. Echocardiographic and neurohormone measurements including left atrial volume index, and left ventricular filling pressures were also similar between the 2 groups. Mean ± SD left atrial volume indices were 35.9 ± 7.4 ml/m^2 and 33.2 ± 8.5 ml/m^2 in the BNP and placebo groups, respectively. Mean ± SD E/e′ ratios, representing left ventricular filling pressure, were 14.9 ± 4.1 and 14.9 ± 4.5 in the BNP and placebo groups, respectively.

EFFECTS OF CHRONIC SQ BNP ON LV DIASTOLIC FUNCTION. After 12 weeks, there was a statistically significant reduction in the E/e′ ratio in the BNP group (baseline: 14.9 ± 4.1; after 12 weeks: 12.6 ± 3.5, p = 0.004), whereas it remained unchanged in the placebo group (baseline: 14.9 ± 4.5; after 12 weeks: 14.0 ± 5.1, p = 0.43). Of the 24 subjects in the BNP group, 17 had reduction in E/e′, 2 had no change, and 5 had increases in E/e′ over the 12-week period. The average change in E/e′ was −2.4 with ±3.7 SD. Of the 12 subjects in the placebo group, 6 had reduction in E/e′, 3 had no change, and 3 had increases in E/e′ over the 12-week period. The average change in E/e′ was −0.9 with ±3.8 SD. Furthermore, after 12 weeks, there was also improvement in the diastolic grade in the BNP group (38% with improvement in diastolic grade as assessed by Doppler echocardiography, p = 0.008), whereas it remained unchanged in the placebo group (8% with improvement, p = 1.0), as shown in Figure 3.

CARDIORENAL RESPONSE TO ACUTE VOLUME EXPANSION. Data were collected on sodium excretion, urine flow, glomerular filtration rate, and urinary cGMP excretion both before and after volume expansion at both visit 1 and visit 2, as shown in Figure 4.

There was a statistically significantly greater sodium excretion response to volume expansion at visit 2 in the BNP group compared with the placebo

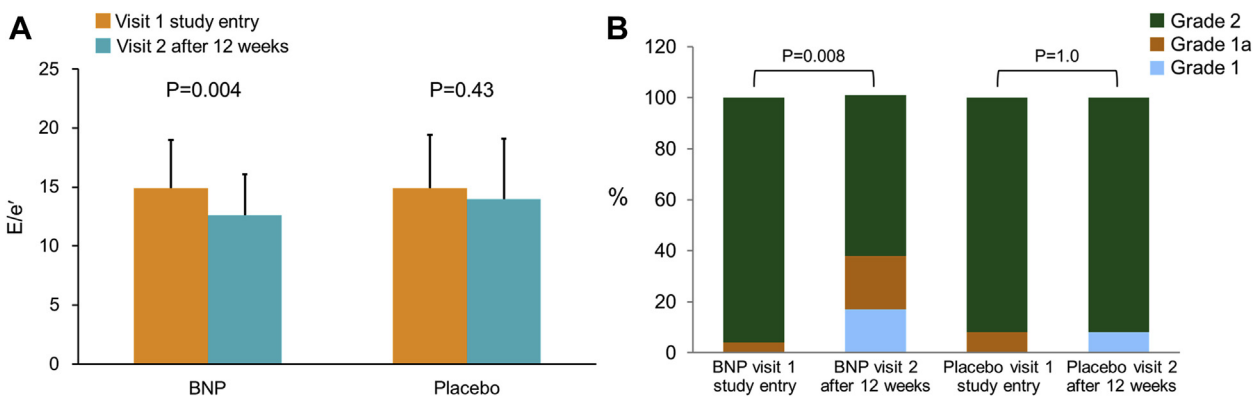
TABLE 1 Baseline Characteristics

	BNP (n = 24)	Placebo (n = 12)
Age, yrs	68.8 ± 8.1	69.6 ± 10.9
Females, %	9 (38)	7 (58)
BMI, kg/m^2	33.5 ± 6.6	30.8 ± 7.3
Heart rate, beats/min	61.7 ± 9.5	63.1 ± 13.0
Blood pressure		
Systolic BP, mm Hg	134.0 ± 14.5	132.5 ± 14.3
Diastolic BP, mm Hg	75.9 ± 9.0	76.0 ± 7.5
Patients with hypertension, %	18 (75)	8 (67)
Creatinine, mg/dl	1.0 ± 0.2	0.9 ± 0.3
BUN, mg/dl	20.2 ± 5.2	20.0 ± 7.5
Patients with hyperlipidemia, %	18 (75)	10 (91)
Patients with diabetes mellitus, %	9 (38)	3 (27)
Patients with coronary artery disease, %	12 (52)	9 (75)
Patients with myocardial infarction, %	5 (22)	3 (25)
Patients taking cardiovascular medications, %		
ACEI or ARB	16 (67)	7 (58)
Beta blocker	10 (42)	6 (50)
Thiazide diuretic	6 (25)	2 (17)
Loop diuretic	3 (13)	0 (0)
Statin	18 (75)	9 (75)
LVEF	62.6 ± 4.9	62.3 ± 4.4
LA volume index, ml/m^2	35.9 ± 7.4	33.2 ± 8.5
E/e′	14.9 ± 4.1	14.9 ± 4.5
RV systolic pressure, mm Hg	32.4 ± 6.0	30.1 ± 12.1

Values are mean ± SD, or n (%). There were no statistically significant differences between the 2 groups.

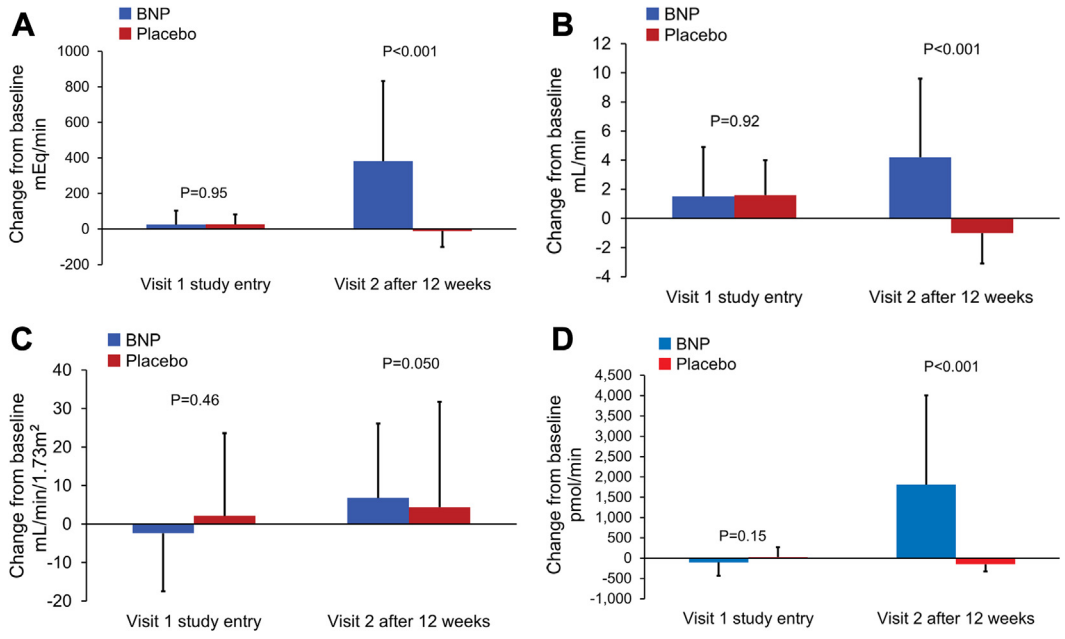
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; BUN = blood urea nitrogen; LA = left atrium; LVEF = left ventricular ejection fraction; RV = right ventricle.

FIGURE 3 E/e′ and Diastolic Grade at Study Entry and After 12 Weeks



(A) E/e′ from visit 1 to visit 2. **(B)** Diastolic grade from visit 1 to visit 2. Abbreviations as in Figure 1.

FIGURE 4 Excretion Response



(A) Sodium excretion, **(B)** urine flow, **(C)** glomerular filtration rate, and **(D)** urinary cyclic guanosine monophosphate excretion.

group (381.6 ± 450.8 mEq/min vs. −10.5 ± 90.1 mEq/min, respectively, $p < 0.001$), whereas there were no differences between the 2 groups at visit 1 ($p = 0.95$).

There was a statistically significantly greater urine flow response to volume expansion at visit 2 in the BNP group than in the placebo group (4.2 ± 5.4 ml/min vs. −1.0 ± 2.1 ml/min, respectively, $p < 0.001$), whereas there were no differences between the 2 groups at visit 1 ($p = 0.92$).

There was a trend toward greater glomerular filtration rate response to volume expansion at visit 2 in the BNP group than in the placebo group (6.8 ± 19.3 ml/min/1.73 m² vs. 4.4 ± 27.3 ml/min/1.73 m², respectively, $p = 0.050$), whereas there were no differences between the 2 groups at visit 1 ($p = 0.46$).

Importantly, there was no evidence of development of tachyphylaxis to BNP as demonstrated by significant increases in both plasma cGMP and urinary cGMP excretion responses following SQ BNP administration in the BNP cohort at visit 2. There was a statistically significantly greater urinary cGMP excretion response to volume expansion at visit 2 in the BNP group than in the placebo group (1,810.1 ± 2,195.6 pmol/min vs. −148.0 ± 174.5 pmol/min, respectively, $p < 0.001$), whereas there were no differences between the 2 groups at visit 1 ($p = 0.15$). Similarly, plasma cGMP response to volume expansion at visit 2 in the BNP group was significantly greater than that in the placebo group (7.3 ± 6.5 pmol vs. 0.0 ± 0.5 pmol, respectively, $p < 0.001$), whereas there were no differences between the 2 groups at visit 1 (−0.2 ± 1.0 pmol vs. 0.2 ± 0.7 pmol, respectively, $p = 0.27$).

Upon sensitivity analysis, assuming the 4 dropped patients in the BNP group had no changes, the results remained statistically significant for cardiorenal response and diastolic grade.

Furthermore, RVSP was measured in both groups before and after volume expansion, at both visit 1 and visit 2. Although there were no changes in RVSP responses in the placebo group from visit 1 to visit 2 (4.4 ± 4.5 in visit 1 to 4.7 ± 8.9 mm Hg in visit 2, $p = 0.36$), there was a statistically significant reduction in RVSP response in the BNP group from visit 1 to visit 2 (1.0 ± 3.9 to −3.7 ± 4.9 mm Hg, respectively, $p = 0.002$).

BLOOD PRESSURE. Systolic and diastolic blood pressure and heart rate values for the BNP group were similar to those in the placebo group throughout the study, at both visit 1 and visit 2 and

both before and after volume expansion ($p > 0.05$). At visit 1 before AVL, systolic blood pressure was 133 ± 14.9 mm Hg for the BNP group and 123.5 ± 11.9 mm Hg for the placebo group. At visit 1 after AVL, systolic blood pressure was 130.6 ± 14.9 mm Hg for the BNP group and 127.5 ± 20.0 mm Hg for the placebo group. At visit 2 before AVL, systolic blood pressure was 127.4 ± 11.5 mm Hg for the BNP group and 128.6 ± 17.9 mm Hg for the placebo group. At visit 2 after AVL, systolic blood pressure was 126.5 ± 14.4 mm Hg for the BNP group and 130.8 ± 19.9 mm Hg for the placebo group (Table 2).

ADVERSE EVENTS. Adverse events, which included hypotension, diarrhea, symptoms of HF, hyperglycemia, joint pains, and rash, were similar between the 2 groups, as shown in Table 3. There were 2 subjects in the BNP group and 2 subjects in the placebo group that developed hypotension, requiring reduction in subsequent subcutaneous injections ($p = 0.45$).

TABLE 3 Adverse Events

	Overall (n = 36)	BNP (n = 24)	Placebo (n = 12)	p Value
Decreased dose of SQ injection	4 (11)	2 (8)	2 (17)	0.45
Diarrhea	1 (3)	1 (4)	0	0.47
Heart failure symptoms	1 (3)	0	1 (8)	0.15
Hyperglycemia	1 (3)	1 (4)	0	0.47
Hypotension	4 (11)	2 (8)	2 (17)	0.45
Joint pains	2 (6)	2 (8)	0	0.30
Rash	1 (3)	1 (4)	0	0.47

Values are n (%).
BNP = B-type natriuretic peptide; SQ = subcutaneous.

DISCUSSION

This proof-of-concept study is the first investigation to determine the benefits of chronic administration of SQ BNP among those with PDD. Findings suggest 12 weeks of chronic SQ BNP administration resulted in significant improvement in both left ventricular filling pressures and diastolic function as evident in the change in Doppler E/e′ ratio and diastolic dysfunction grade without tachyphylaxis or development of tolerance to the enhancement of cardiorenal response to acute volume loading with BNP administration. Further studies are warranted to determine if these physiologic observations with chronic natriuretic peptide system augmentation can be translated into a delay in the progression of PDD (stage B HF) to symptomatic HF with preserved EF (stage C HF).

TABLE 2 SBP, DBP, and Heart Rate

	BNP Group (n = 24)	Placebo Group (n = 12)	p Value
SBP, mm Hg			
Visit 1 before AVL	133 ± 14.9	123.5 ± 11.9	0.06
Visit 1 after AVL	130.6 ± 14.9	127.5 ± 20.0	0.60
Visit 2 before AVL	127.4 ± 11.5	128.6 ± 17.9	0.81
Visit 2 after AVL	126.5 ± 14.4	130.8 ± 19.9	0.49
DBP, mm Hg			
Visit 1 before AVL	67.1 ± 9.9	62.2 ± 10.4	0.18
Visit 1 after AVL	65.3 ± 10.4	62.3 ± 9.1	0.41
Visit 2 before AVL	65.4 ± 9.0	62.4 ± 10.6	0.39
Visit 2 after AVL	64.6 ± 12.5	66.7 ± 10.3	0.63
Heart rate, beats/min			
Visit 1 before AVL	58.9 ± 8.9	62.8 ± 14.7	0.33
Visit 1 after AVL	61.9 ± 12.3	59.5 ± 14.5	0.62
Visit 2 before AVL	60.5 ± 9.5	58.1 ± 11.4	0.51
Visit 2 after AVL	60.8 ± 12.7	59.3 ± 6.7	0.74

Values are mean ± SD.
AVL = acute volume loading; BNP = B-type natriuretic peptide; DBP = diastolic blood pressure; SBP = systolic blood pressure.

The beneficial effects of chronic BNP on diastolic function, as demonstrated by reduction in diastolic filling pressures and improvement in diastolic grade, are a result of the pro-lusitropic properties of the cGMP system. In vitro studies have shown that cardiomyocytes in response to exposure to BNP have greater relaxation and cell length (14). In canine studies, BNP has been shown to enhance left ventricular relaxation (7). When BNP, with its action on natriuretic peptide receptor A (NPR-A) and cGMP system, is infused in humans with HFpEF, it has hemodynamic enhancement and beneficial neurohormone effects in response to exercise (15). The left atrial filling pressures, as measured by pulmonary capillary wedge pressure, demonstrated an attenuated increase during exercise among those with diastolic HF who received BNP compared with those who received placebo.

The important role of the cGMP system was also highlighted by recent studies with neprilysin inhibition, which resulted in reduction of natriuretic peptide degradation. The PARAMOUNT (Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion) study showed that LCZ696, an angiotensin receptor neprilysin inhibitor, when administered over 12 weeks to subjects with HFpEF, was well tolerated and resulted in reduction in NT-proBNP levels as well as reduction in left atrial volumes (16). Furthermore, there was also renal preservation with chronic use of LCZ696 compared with angiotensin receptor blocker alone in those with HFpEF (17). The PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients

With Preserved Ejection Fraction) study, a phase 3 HFpEF trial designed to evaluate the efficacy and safety of LCZ696, is currently ongoing with an estimated enrollment of more than 4000 subjects (NCT01920711).

Although we previously showed that acute administration of BNP resulted in short-term benefits on cardiorenal response to AVL in PDD, the development of tachyphylaxis or tolerance over time to chronic BNP administration remains a major concern (10). Sustained administration without evidence of pharmacologic tolerance is necessary for novel peptide therapy for chronic HF prevention. Receptor downregulation after continued exposure to a peptide is one potential mechanism of tolerance induction. Tachyphylaxis remains a concern for peptide therapy, such as with the incretin hormone glucagon-like peptide (GLP)-1 (11,12). The current study suggests that there is no development of pharmacologic tolerance as there is a sustained activation of its second messenger, cGMP, and improvement in cardiorenal response to acute volume loading with BNP after 12 weeks of chronic administration.

The natural history of PDD suggests progression to symptomatic HF at an annual incidence of 2%, which increases to 12% at 3 years (6). Importantly, renal dysfunction was independently associated with increased risk of progression to symptomatic HF, as those with glomerular filtration rate <60 ml/min/1.73 m^2 had a hazard ratio of 2 for HF development compared with those with normal renal function (6). Furthermore, PDD impairment of renal response to AVL may contribute to the progression of HF (10). Therefore, these observations suggest that preserving renal function may attenuate the development and progression of symptomatic HF.

In addition, targeting diastolic dysfunction is also essential in prevention of HF progression, as worsening diastolic dysfunction has been shown to be associated with increased HF development (18). Kane et al. (18) demonstrated that over a 6-year period, those with normal, mild, and moderate to severe diastolic function had incidence of progression to symptomatic HF of 3%, 8%, and 12%, respectively. Pre-clinical studies have demonstrated that improvement in cardiorenal parameters is important in prevention of cardiac apoptosis, fibrosis, and diastolic dysfunction progression (19). In a rodent model of renal insufficiency, Martin et al. (19) showed that impaired renal function resulted in neurohormone alterations that led to cardiac remodeling and hypertrophy with clinical outcome implications, by induction of transforming growth factor beta, apoptotic, inflammatory, and fibrotic pathways. The findings of the current study, which include improvement of LV diastolic function and the preservation of the enhanced response to AVL with chronic BNP therapy, suggest the potential of chronic SQ BNP as a novel therapeutic agent for improvement in diastolic function and cardiorenal parameters, and subsequent prevention of HF development.

STUDY LIMITATIONS. Although the study protocol randomized subjects in a 2:1 fashion to the BNP and placebo groups to maximize power, 1 limitation of the current study is the small study population. After randomization, 4 subjects dropped out of the BNP group before study protocol initiation. Additionally, there are limitations regarding multiple testing, so these factors remain a limitation in this small study population. Although there was no significant reduction in blood pressure from visit 1 to visit 2, the lack of invasive vital sign measurements remains a limitation of this study, as minor changes in systolic blood pressure could have contributed to the observed changes in E/e′.

Although the 12-week duration of this study is the first of its kind to analyze the chronic effects and possibility of pharmacologic tolerance or lack thereof from BNP administration, even longer studies are necessary to assess the effects of chronic BNP administration. Further studies are also necessary to characterize whether the observed beneficial echocardiographic and neurohormonal improvements in the BNP-treated group can translate to actual delay in progression of the development of symptomatic HF in this population of PDD.

CONCLUSIONS

In subjects with PDD, 12 weeks of chronic BNP administration resulted in sustained improvement in diastolic function without development of tachyphylaxis, to the enhancement of cardiorenal response to volume expansion with BNP. Further studies are warranted to determine whether these physiological observations with chronic natriuretic peptide system augmentation can be translated into a delay in the progression of PDD (stage B HF) to symptomatic HF with preserved EF (stage C HF).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with PDD, chronic BNP administration results in improvement in diastolic function and enhancement of cardiorenal response to volume expansion. Further studies are necessary to determine if there is correlation to disease progression, morbidity, and mortality outcomes.

TRANSLATIONAL OUTLOOK: Further large, prospective, randomized, and long-term studies are needed to investigate the utility of chronic low-dose BNP for the prevention of symptomatic HF development.

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KEY WORDS B-type natriuretic peptide, cardiorenal syndrome, diastolic dysfunction, heart failure with preserved ejection fraction