Metabolic Effects of Natriuretic Peptide Hormones

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1.0 Background

Obesity and obesity-related complications constitute serious public health problems. Obese individuals experience a markedly increased risk of cardiovascular and metabolic ("cardiometabolic") diseases– including diabetes, hypertension, and coronary artery disease. The rising prevalence of these problems despite current therapies supports that obesity is a multifactorial disease, and highlights the need for novel approaches to treat obesity-related cardiometabolic dysfunction.

A large body of evidence suggests that the natriuretic peptide (NP) hormonal system has important effects on metabolism, including increased energy expenditure and lipolysis. NPs are hormones produced by the heart in response to increased cardiac wall stress. NPs are well-known for their important role in blood pressure regulation. However, accumulating evidence suggests that the NPs have significant metabolic effects as well. For instance, administration of B-type natriuretic peptide (BNP) to wild-type mice leads to increased energy expenditure, increased thermogenic gene expression in brown as well as white adipose depots (a process referred to as "beiging" of white fat), and reduced fat accumulation.[1]

Thus, the NP system may protect against cardiometabolic risk. NP-overexpressing mice are protected from obesity and insulin resistance induced by a high-fat diet.[2] In humans, common genetic variants resulting in higher NP concentrations are associated with lower prevalence of hypertension, obesity, metabolic syndrome, and myocardial infarction, and a lower risk of developing Type 2 diabetes mellitus.[3, 4]

NP levels are reduced in obesity. NP levels are reduced in obese individuals in large cohort studies.[5] The low circulating NP levels appear to reflect a relative "NP deficiency," which could contribute to the adverse cardiometabolic outcomes observed in obese individuals. Further, surgical weight loss, increased physical activity, and treatment with insulin-sensitizing medications are each associated with increased circulating NPs in obese individuals.

2.0 Rationale and Specific Aims

Although recent studies in rodents suggest that NPs have important metabolic effects, there are few prospective data on the metabolic effects of NPs in humans. We propose a physiologic, proof-of-concept study to determine the acute effects of recombinant human B-type natriuretic peptide$_{1-32}$ on energy expenditure and adipose tissue gene expression in humans. Our primary hypothesis is that the administration of BNP will increase energy expenditure in humans. Our secondary hypothesis is that BNP administration will promote changes in gene expression in adipose tissue suggestive of a "beige" fat phenotype in humans. Thus, we propose the following specific aims:

Primary Aim: To investigate the acute effects of administration of BNP on energy expenditure in humans. We propose a randomized, placebo-controlled, cross-over study in 50 adults (25 lean and 25 obese) without significant medical problems. Subjects will be randomized to intravenous infusion of recombinant human BNP$_{1-32}$ or normal saline

(control), with assessment of energy expenditure and other physiologic measures. After a minimum of a 14-day washout period, subjects will then undergo the other intervention.

Secondary Aim: To determine the acute effects of BNP on gene expression in white adipose tissue in humans. We will assess markers suggestive of fat "beiging" in subcutaneous white adipose tissue biopsies after BNP infusion vs. control. This secondary aim will allow us to explore potential mechanisms underlying the hypothesized changes in energy expenditure.

3.0 Animal Studies and Previous Human Studies

The natriuretic peptide (NP) system and metabolism

The NP system is classically known for its role regulating of blood pressure and volume status. In response to increased cardiac wall stress, the heart secretes atrial natriuretic peptide (ANP) and BNP, which both cause natriuresis, vasodilation, and inhibition of the renin-angiotensin-aldosterone system.

Recent studies have shown that NPs have important metabolic actions as well. Administration of NPs stimulate lipolysis in animals and humans.[6-9] Transgenic mice that overexpress BNP are protected against weight gain, visceral fat accumulation, and insulin resistance induced by high-fat diets.[2] Moreover, Bordiccia et al. demonstrated in wild-type mice that BNP administration over 7 days significantly increases energy expenditure and oxygen consumption.[1] The increases in energy expenditure and oxygen consumption appear to be mediated by increased expression of thermogenic genes (including UCP1) in brown adipose tissue, as well as white adipose tissue (suggesting a "beiging" effect).[1]

Whether many of the metabolic effects of NPs observed in animals also occur in humans is not well established. Two small studies have examined the effects of ANP administration on energy expenditure in humans, but these lacked a control arm, and no data exist on the effects of BNP. In studies of 12 and 14 lean men, respectively, Birkenfeld et al. reported that systemic ANP infusion increased postprandial energy expenditure[8] and caused a shift from carbohydrate oxidation to lipid oxidation.[7] There are also no data on the effects of NPs on beige fat markers.

Epidemiologic and genetic evidence linking the NP system with cardiometabolic health

Data from population genetic studies suggest that the NP system may protect against cardiometabolic risk. In humans, a common genetic variant resulting in ~10-20% higher NP concentrations (still within the physiologic range) is associated with lower prevalence of hypertension (by 15%),[4] obesity (by 46%), and metabolic syndrome (by 42%), and a lower risk of developing Type 2 diabetes (by 12%).[3, 10] Moreover, this genetic variant that causes higher NP levels is associated with favorable cardiovascular biomarkers and a lower prevalence of myocardial infarction.[3]

Circulating NP levels are inversely associated with presence of metabolic syndrome components, insulin resistance, and risk of developing Type 2 diabetes. In a large cohort study, BNP levels were 24-29% lower in individuals who met ≥3 criteria for the metabolic

syndrome, even after adjustment for BMI.[11] Moreover, higher NP levels are associated with lower levels of insulin resistance (as measured by homeostatic model assessment of insulin resistance, HOMA-IR) as well as lower risk of future Type 2 diabetes in large cohort studies.[12, 13]

Obese individuals have low circulating NP levels,[5] which appears to reflect a relative "NP deficiency." Obese individuals have lower NP levels than lean individuals in large cohort studies.[5] Obese individuals have a propensity toward hypertension and hypervolemia, which would be expected to cause higher circulating NP concentrations. Thus, the lower NP concentrations in obese individuals are physiologically inappropriate and may reflect a relative NP deficiency in obesity. Whether the low NP levels in obesity are due to decreased NP production, increased NP clearance, or both is unknown. Obese individuals have higher expression of the NP clearance receptor in adipose tissue compared with lean individuals,[14] which could conceivably lead to greater clearance of circulating NPs in obese individuals. As the NP axis appears to protect against cardiometabolic risk, a relative NP deficiency could contribute to the adverse cardiometabolic outcomes observed in obesity.

4.0 Inclusion/Exclusion Criteria

Inclusion Criteria:

- Men and women ages 18-40 years
- Body Mass Index (BMI): $18.5 \leq BMI < 25$ kg/m^2 (lean)
  or BMI ≥ 30 kg/m^2 (obese)

Exclusion Criteria:

- Significant cardiovascular disease (including heart failure and atrial fibrillation)
- Significant pulmonary, liver, or renal disease
- Diabetes Mellitus
- Significant hypertension (systolic blood pressure ≥ 170 mmHg and/or diastolic blood pressure ≥ 110 mmHg)
- Hypotension
- Thyroid dysfunction
- Active malignancy
- Current or recent use of glucocorticoids
- Current use of antihypertensive medications, including diuretics
- Current use of medications affecting glucose metabolism, including metformin
- Current use of amphetamines or other medications known to affect energy homeostasis
- Currently pregnant or breastfeeding, or unwilling to avoid becoming pregnant or breastfeeding during study duration
- Significant claustrophobia that would prevent the use of the metabolic cart as part of the study protocol

- Currently abnormal serum or plasma sodium or potassium level
- Known hypersensitivity to recombinant human b-type natriuretic peptide, $BNP_{(1-32)}$ (nesiritide)
- Hemoglobin A1c (HbA1c) ≥6.5%
- Liver Function Tests (LFTs) elevated >2x upper limit of normal
- Estimated Glomerular Filtration Rate (eGFR) <60 ml/min
- Currently abnormal thyroid stimulating hormone (TSH)

5.0 Enrollment/Randomization

Recruitment will take place at Tennessee Valley Healthcare System outpatient clinics, community-based outpatient clinics, veteran centers, veteran service organizations, and Vanderbilt University Medical Center (VUMC). All patients coming for outpatient services at TVHS may be considered. We will place IRB approved flyers and brochures in target clinics, veteran centers, and community boards (electronic and physical) with basic study information and study team contact information for potential subjects to signal potential interest. Working with the VA Public Affairs office, we will utilize their advertisement services such as waiting lobby TV advertisements, VA web homepage announcements, and newspaper. A link may also be posted on My HealtheVet. We will also screen medical records in CPRS system. VA subjects, once identified through the CPRS system, will be sent recruitment letters about participation in the study. The recruitment letters may be followed by a phone call to the participant. Study personnel may also approach possible study participants in clinic once permission is received by that subject's provider. Subjects may also be recruited using My HealthEVet and the VINCI system. Subjects may also be recruited via the Vanderbilt Broadcast email system (research.notifications@vanderbilt.edu). ResearchMatch.org may be utilized as a recruitment tool for this protocol. ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository.

Subjects will be randomized in a 1:1 ratio to each treatment sequence (BNP followed by control; or control followed by BNP) with the use of stratified permuted block randomization (blocks of size 4). Subjects will be stratified by BMI category (lean vs. obese). Randomization occurs after the screening visit to determine eligibility. Prior to study initiation, block size and randomization schemes will be determined by a biostatistician.

6.0 Study Procedure

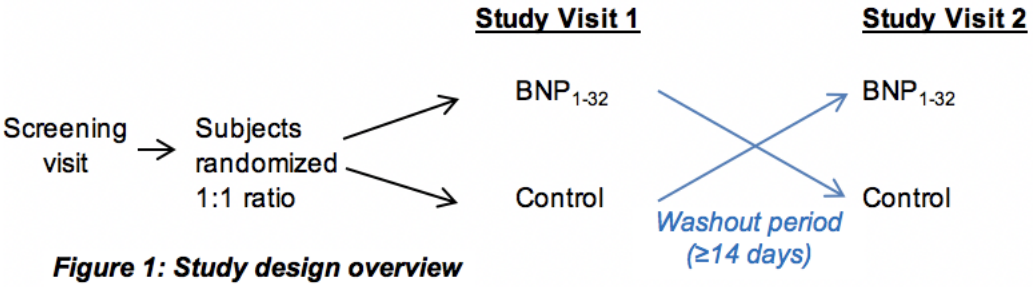

Figure 1: Study design overview

Screening Visit

After informed consent has been obtained, the subject's medical history and medications will be discussed and documented. A physical exam, including measurement of height, weight, and vital signs, will be performed. Blood will be collected for a comprehensive metabolic panel, complete blood count (CBC), Hemoglobin A1c, thyroid stimulating hormone (TSH) test, and free T4. A urine or serum pregnancy test will be completed on female subjects of child-bearing potential. Whenever possible, we will combine these research screening tasks and procedures with standard of care tasks and procedures to decrease the burden placed on the patient. This information will be acceptable from standard of care visits as far back as 6 months prior to the day the patient is identified as a possible candidate. Even if the patient has had these assessments completed during a standard of care visit, it is up to the discretion of the Principle Investigator to use them or require an updated set of assessments. Inclusion/exclusion criteria will be reviewed to confirm that the subject meets study eligibility requirements. Subjects will be given instruction on how to perform 24-hour urine collections, which will be collected at two study time points (immediately prior to study visits 1 and 2).

Study Visits 1 and 2

After the Screening Visit, eligible subjects who wish to participate in the study will be scheduled for two additional outpatient visits at the Vanderbilt CRC (Clinical Research Center): Study Visits 1 and 2. The two visits will be scheduled ≥14 days apart. For women, Study Visits 1 and 2 will be scheduled to coincide with the follicular phase of the menstrual cycle to minimize the impact of hormonal changes on energy expenditure (EE) and on measurements of renin-angiotensin-aldosterone (RAAS) system. In the 24 hours prior to each study visit, subjects will collect urine for quantification of urine sodium, urine creatinine, and other metabolic endpoints. Each subject will receive a BNP infusion at one study visit and a control (saline) infusion at the other visit ***(Figure 1)***. Other than the drug received, the study procedures and timeline are identical for both study visits (***Figure 2***).

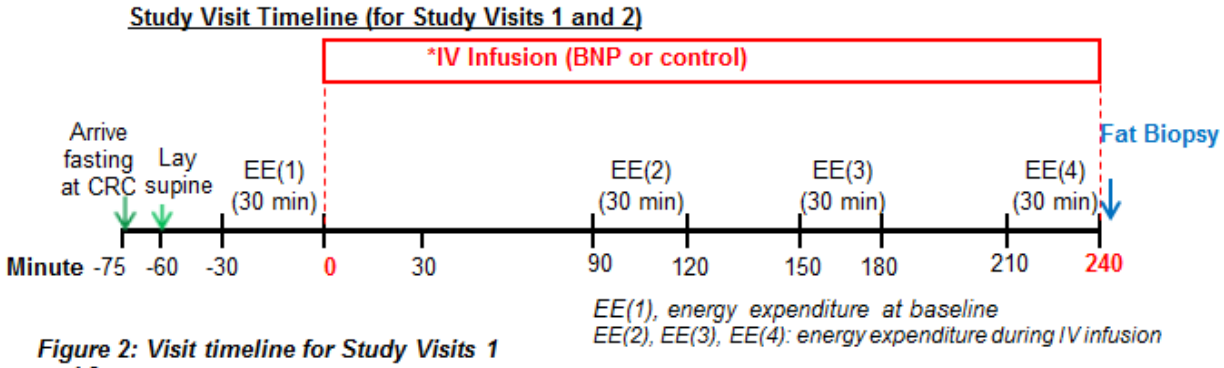

Figure 2: Visit timeline for Study Visits 1 and 2

Subjects will arrive at the Vanderbilt CRC after having fasted for at least 8 hours. Upon arrival, subjects will return the 24 hour urine collection, two peripheral intravenous (IV) lines will be placed and subjects will lie supine. Women of childbearing potential will undergo a pregnancy test. Subjects will need to remain supine during the entire study visit, with exceptions for urine collection timepoints, as some of the hormone measurements are affected by body position. Baseline resting energy expenditure will be assessed using indirect calorimetry (metabolic cart, described below) after approximately 30 minutes of lying supine (t= -30 to 0 minutes, ***Figure 2)***. A baseline blood draw, including measurements of NPs and measurements of the RAAS system (renin and aldosterone), will occur after subjects have been supine for approximately 60 minutes. Next, subjects will undergo IV infusion of either BNP_{1-32} (nesiritide) or control (normal saline) for 240 minutes. The IV infusion rate (whether BNP infusion or control infusion) will be the same (a rate of 10 ng/kg/minute for 240 minutes, preceded by an IV bolus of 100 ng/kg). In addition, during each visit (both BNP visit and control visit), subjects will receive a small amount of normal saline through the IV lines to maintain the integrity of the IV lines and to provide hydration. During the infusion the subjects will undergo hemodynamic monitoring, as described below. Energy expenditure will be measured during the infusion again from t=90-120 minutes, t=150-180 minutes, and t=210-240 minutes with the metabolic cart. At the completion of the infusion, the subjects will then undergo the subcutaneous adipose tissue biopsy procedure, as described below. The subjects will undergo a dual-energy x-ray absorptiometry (DXA) scan at one of the study visits. At the end of Study Visit 1, subjects will be given another 24 hour urine collection kit, to be turned in upon arrival for Study Visit 2.

Other study procedures

Phlebotomy: Blood draws will occur at Minutes 0, 60, 120, 180, 240 ***(Table 1).***

Endpoints	Timepoints
NP system markers (ANP, BNP, and their propepties)	Min 0, 240
RAAS system markers (direct renin, aldosterone)	Min 0, 240
Plasma catecholamines	Min 0, 60, 120, 180, 240
Glucose metabolism (glucose, insulin)	Min 0, 60, 120, 180, 240
Lipolysis (glycerol, free fatty acids)	Min 0, 60, 120, 180, 240

Table 1: Time points for blood draws

In addition, renal function will be checked at the end of Study Visits 1 and 2.

Urine collection: All urine during the visit will be collected. All subjects will utilize a bedside commode to collect urine. CRC staff will be available to assist the subject from the bed to the bedside commode to ensure the subject's safety. Urine will be collected at baseline and at Minutes 120, and 240, and urine volume will be measured at each timepoint. Ideally urine will be collected at these exact timepoints. If subject is unable to void at this exact timepoint, urine should be collected as close as possible to the exact timepoint and the time documented. Urine will be tested for urine sodium, urine creatinine, and other metabolic endpoints.

Ins/Outs: Strict Ins/Outs will be recorded throughout the study visit, and total ins/outs will be recorded.

Hemodynamic monitoring: During both Study Visits 1 and 2, blood pressure will be measured frequently via sphygmomanometer and/or volume clamp method (finger photoplethysmography). Heart rate and rhythm will be monitored throughout infusions using cardiac telemetry. Temperature will be monitored using a thermometer.

Indirect Calorimetry (Metabolic Cart): At each visit, resting energy expenditure will be determined by indirect calorimetry, using a metabolic cart. We will measure energy expenditure (EE) four times during the infusion (***Figure 2***): baseline (30 minutes leading up to start of infusion), EE2 (Minute 90-120), EE3 (Minute 150-180), and EE4 (Minute 210-240). For each energy expenditure assessment, we will measure energy expenditure over the course of 30 minutes.

Substrate oxidation (lipid oxidation and carbohydrate oxidation): Respiratory exchange ratio will be determined using VO2 and VCO2 measurements, which is determined via indirect calorimetry, and collected at the same time points as energy expenditure.

Subcutaneous adipose tissue biopsy: Participants will undergo percutaneous subcutaneous adipose tissue biopsies on the abdomen (peri-umbilical region) after the BNP infusion and after the control infusion. This procedure will be performed by a trained study physician. After the completion of the 4-hour infusion (of either BNP or saline, as described above), the subject will remain supine, and an approximately 10cm diameter area will be cleaned with a chlorhexidine swab lateral to the umbilicus. A fenestrated sterile drape will be placed to establish the sterile field. Approximately 20 ml of 1% lidocaine will be applied to anesthetize the skin. A small (approximately 0.5 cm) incision is made through the skin with a scalpel, a few centimeters lateral to the umbilicus. A TULIP 2.7mm liposuction cannula with a syringe attached is inserted and moved parallel to the skin at a rate of approximately 1 Hz without breaking suction and with a twisting motion. The sampling continues until approximately 10 ml of tissue (approximately 9.5 g) is collected. The syringe is then removed, antibiotic ointment applied, a steri-strip is placed, and the incision is covered with an adhesive bandage. The tissue will be washed in physiologic serum and then placed immediately in liquid nitrogen and stored at -80 degrees Celsius until analysis. The bandages will be removed after 24 hours, and steri-strips are left in place until they fall off.

Biomarkers

Blood, urine, and tissue samples will be coded for subject confidentiality. Additional samples will be frozen and stored for possible future investigation.

7.0 Possible Side Effects

Fasting: Inconvenience and hypovolemia. To minimize risks of hypovolemia, subjects will be instructed to drink plenty of fluids the day before the visits, and we will measure subjects' blood pressure and heart rate upon arrival for their study visits and frequently throughout the study visits. Also, there is a potential risk of hypoglycemia while fasting. However, the risk of hypoglycemia in healthy individuals while fasting for this amount of time is low. Subjects will be monitored for signs and symptoms of hypoglycemia throughout the study visits.

Intravenous Lines: Risks related to the placement of peripheral intravenous lines are minimal. Risks include pain, hematoma formation, bruising, rarely fainting, and phlebitis

Phlebotomy: Volume depletion and anemia are possible risks of phlebotomy. The risks associated with phlebotomy in healthy individuals are minimal. Risks will be minimized by excluding subjects with anemia or history of hypotension. Subjects will be advised to drink plenty of the fluids the night before the study visit, and after the study visit.

Hemodynamic monitoring (blood pressure monitoring using sphygmomanometer and finger photoplethysmography, and heart rate monitoring by cardiac telemetry): A non-invasive technique with no symptoms aside from possible minimal discomfort.

Study Medications: ***Of note, Dr. Bachmann (Principal Investigator) has obtained an IND exemption for all drugs in the proposed protocol from the Food and Drug Administration (FDA).** VUMC Investigational Drug Services (IDS) Pharmacy will provide the intravenous medications for this study because IDS Pharmacy is co-located at the VUMC Clinical Research Center (CRC) where all the study visits will take place. The study medications provided by IDS Pharmacy are intravenous medications that need to be prepared locally due to drug stability requirements and study timeline procedures.

- $BNP_{(1-32)}$ (nesiritide): The main potential side effect of nesiritide is hypotension. However, in healthy controls, BNP administered at doses and durations similar to what we will administer has been shown to be safe and well-tolerated, without significant hypotension or other significant adverse events.[15, 16] Other symptoms reported by subjects with heart failure who received nesiritide in prior trials include headache (8%), nausea (4%), and angina (2%). Furthermore, in the proposed study, hypotension is extremely unlikely as trained study personnel will remain at bedside and closely monitor blood pressure during the entire infusion. Because of the very low risk of hypotension, firm stopping rules for the BNP infusion will be implemented: The BNP infusion will be stopped if systolic blood pressure decreases by 30 mmHg or greater from baseline, if absolute systolic blood pressure drops below 80 mmHg, or if the subject demonstrates symptomatic hypotension as clinically assessed by the investigator. If these unlikely cases occur, any changes in blood pressure should resolve extremely quickly (within a few minutes) because the half-life of BNP is very short. If the infusion is stopped, remaining study procedures (e.g. blood and urine collections, energy expenditures, and fat biopsy procedure) may be resumed with the permission of the subject and at the discretion of the study team. Finally, as with any drug,

there is a potential risk of hypersensitivity. We will not enroll any subject with history of hypersensitivity to BNP, and subjects will be closely monitored during the infusions.

Percutaneous subcutaneous adipose tissue biopsy: The biopsy procedure will be performed by the study physician. The percutaneous subcutaneous adipose tissue biopsy procedure is associated with low risk. Possible risks of the biopsy procedure include pain, local skin irritation, bleeding, bruising, and hematoma at the site. There is potential risk for local or systemic infection, more severe bleeding, or a small scar; however, the risk of these events is extremely low.

Lidocaine: May cause local discomfort during injection, or a rash, redness or soreness at the injection site. In rare cases, lidocaine could potentially cause hypersensitivity reactions, confusion, or induce a transient alteration in heart rhythm; to reduce this risk, suction will be applied to the syringe prior to injection to ensure the lidocaine is not being injected into a vessel.

Dual Energy X-ray Absorptiometry (DXA): Radiation risk is very minimal. DXA uses very low dose radiation, and the expected total exposure for each participant is in the range of 7 millirem, which is equivalent to approximately 9 days of background radiation.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Participants should and will be instructed to notify study personnel regarding any adverse events or unanticipated problems. Adverse events will be reported to the IRB per IRB policy. Also, all serious and unanticipated adverse events or problems involving risks to subjects that may possibly be or are known to be related to the research activity will be reported promptly to the IRB office per IRB policy.

Any adverse event associated with the use of drug that is serious, unexpected and possibly or definitely study-related will be reported promptly to the IRB per IRB policy.

The Data Monitoring Committee (DMC) of the U.S. Department of Veteran Affairs' Office of Research and Development will monitor the study, per instruction by the administrators with Clinical Science Research and Development (CSR&D). The DMC will provide ongoing evaluation of studies' progress including patient accrual and retention, monitoring of adverse events, and the adequacy and efficiency of the analysis plan to discern outcomes that might require study modifications, or result in early cessation of the study due its benefits or harms. Reports will be submitted to the DMC for review approximately every 4 months.

9.0 Study Withdrawal/Discontinuation

Subjects may withdraw from the study at any time and should notify study personnel if they wish to withdraw from the study. Subjects may request their biological samples to be destroyed at any time. However, any data or biological samples that have already been used for research cannot be destroyed.

Subjects may be discontinued from the study at the discretion of the investigators' (possible reasons listed below).

Possible reasons for withdrawal/discontinuation from study include, but are not limited to:

- Noncompliance with treatment or procedures
- Decision by participant/participant withdraws consent
- Lost to follow-up
- Change in patient's health status that makes them no longer eligible for study.
- Development of a significant medical condition specified in the exclusion criteria
- In female subjects, becoming pregnant during study
- Significant adverse event deemed by investigator to preclude continued participation

10.0 Statistical Considerations

The primary endpoint will be change in resting energy expenditure, calculated as final resting energy expenditure adjusted for baseline level, using linear regression. Secondary endpoints include adipose tissue gene expression and protein levels. We will test the effect of treatment (BNP vs. control) on the primary endpoint and secondary endpoints (all are continuous variables that are repeated and correlated) in a similar fashion. We will use mixed effects modeling, adjusting for treatment sequence, to assess the effect of treatment on each endpoint. The null hypothesis is that there will be no significant effect of treatment on each endpoint. In addition, we will assess for a period effect and a treatment-period interaction effect; the null hypothesis is that there will be no period effect and no interaction effect. We will adhere to intention-to-treat principles. No interim analysis is planned. In a secondary analysis, we will examine whether treatment effects differ between lean and obese individuals. We will perform exploratory analyses to investigate whether treatment effects differ by sex or race (white vs. non-white). To address missing data, we will apply multiple imputation methods.

11.0 Privacy/Confidentiality Issues

Strict confidentiality will be maintained to the fullest extent possible by the research team, including keeping all data in a secure location. All specimens will be de-identified and coded after they are obtained and the code key kept in a secure location. Only study personnel will access to the data and specimens. Samples may be shared with third parties outside of the VA and Vanderbilt for future testing but will remain anonymous to the recipient. Subjects may contact the principal investigator at any time to request that samples be destroyed. However, any data or biological samples that have already been used for research cannot be destroyed.

The Research Electronic Data Capture (REDCap) database is a secure web application housed on the TVHS VA secured computer network and is password protected. REDCap offers secure institutional data hosting and includes full audit-trails in compliance with HIPAA security requirements. Only members of the study team will have access to this database.

Adverse event reports and annual summaries will not include subject-identifiable material but only the assigned study identification numbers.

12.0 Follow-up and Record Retention

Anticipated study duration is 60 months. Research data will be maintained by the PI after study closure. After study closure, research data will be maintained for a minimum of 6 years and possibly indefinitely. Data will be stored on a secure computer network in a password-protected database. Only members of the study team will have access. Pertinent paper documentation will be kept in a locked office and only study personnel will have access. Only personnel directly involved with the study will have access to source data and the electronic database.

13.0 Relevance to VA Mission

Obesity represents a serious public health burden in our veteran population and in the general population. Over 30% of veterans are obese. Obese individuals experience increased risk of cardiovascular and metabolic ("cardiometabolic") diseases, including insulin diabetes, resistance, hypertension, and dyslipidemia, which markedly increase morbidity and mortality. Obesity is a major problem that spans across a wide age range, all race/ethnic groups, and both sexes. There are multiple approaches for tackling the problem of obesity at the VA: system-level factors, provider-level factors, and patient-level factors. All of these approaches are valuable. This particular study focuses on patient-level factors. Specifically, we are interested in improving the understanding of the pathogenesis of cardiometabolic risk, in order to identify novel therapeutic approaches.

Obesity and obesity-associated cardiometabolic dysfunction are significant contributors to morbidity and mortality in veterans. This indicates that obesity and cardiometabolic dysfunction are complex and multifactorial, and suggests that there are additional factors that contribute to the pathogenesis of obesity and its associated cardiometabolic risk that have not been discovered. Moreover, some of the pharmacologic therapies for obesity can have adverse cardiovascular effects (like phentermine, which can cause hypertension). Conversely, some of the treatments for cardiovascular disease can have adverse metabolic effects (like beta blockers, which can lead to weight gain). Thus, it is crucial to improve our understanding of the multiple pathways contributing to the pathogenesis of obesity and obesity-associated cardiometabolic risk, including the identification of novel relevant pathways, in order to develop more effective treatments for these diseases. Characterizing the metabolic effects of the natriuretic peptides in the present study has the potential to inform future studies aimed at assessing the natriuretic peptide system as a target for the treatment of obesity and obesity-associated metabolic dysfunction, a field of paramount importance to veterans.

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