Natriuretic peptides, extracellular volume, and subclinical cardiovascular changes in chronic kidney disease stages 1–3: a pilot study

L Parker Gregg ,[1,2,3] Peter N Van Buren ,[4,5] David J Ramsey,[3] Amaris Maydon,[6] Subhash Banerjee,[7,8] Carl P Walther,[1] Salim S Virani,[3,9,10] Wolfgang C Winkelmayer,[1] Sankar D Navaneethan,[1,2,3,11] S Susan Hedayati[4]

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For numbered affiliations see end of article.

Correspondence to
Dr L Parker Gregg, Baylor College of Medicine Department of Medicine, Houston, Texas, USA; lucile.gregg@bcm.edu

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ABSTRACT

Natriuretic peptide levels are elevated in persons with chronic kidney disease (CKD) stages 1–3, but it remains unclear whether this is associated with extracellular volume excess or early cardiovascular changes. We hypothesized that patients with CKD stages 1–3 would have evidence of cardiovascular changes, which would associate with brain natriuretic peptide (BNP), amino-terminal-pro-BNP (NT-pro-BNP), and patient-reported symptoms.

Outpatients with CKD stages 1–3 and non-CKD controls were enrolled. Cardiovascular parameters included extracellular water (ECW) normalized to body weight measured using whole-body multifrequency bioimpedance spectroscopy, and total peripheral resistance index (TPRI) and cardiac index measured by impedance cardiography. Dyspnea, fatigue, depression, and quality of life were quantified using questionnaires.

Among 21 participants (13 with CKD), median (IQR) BNP was 47.0 (28.0–302.5) vs 19.0 (12.3–92.3) pg/mL, p=0.07, and NT-pro-BNP was 245.0 (52.0–976.8) vs 26.0 (14.5–225.8) pg/mL, p=0.08, in the CKD and control groups, respectively. Those with CKD had higher pulse pressure (79 (66–87) vs 64 (49–67) mm Hg, p=0.046) and TPRI (3721 (3283–4278) vs 2933 (2745–3198) dyn×s/cm^5/m^2, p=0.01) and lower cardiac index (2.28 (2.08–2.78) vs 3.08 (2.43–3.37) L/min/m^2, p=0.02). In the overall cohort, natriuretic peptides correlated with pulse pressure (BNP r=0.59; NT-pro-BNP r=0.58), cardiac index (BNP r=−0.76; NT-pro-BNP r=−0.62), and TPRI (BNP r=0.48), p<0.05 for each, but not with ECW/weight. TPRI and blood pressure correlated moderately with symptoms.

Elevated natriuretic peptides may coincide with low cardiac index and elevated peripheral resistance in patients with CKD stages 1–3. The role of these biomarkers to detect subclinical cardiovascular changes needs to be further explored.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with chronic kidney disease (CKD) stages 1–3 have elevated natriuretic peptides, which are associated with cardiovascular events and death; however, it remains unclear whether this is associated with extracellular volume excess or early changes in cardiovascular parameters.

WHAT THIS STUDY ADDS

⇒ Patients with CKD stages 1–3 had higher pulse pressure, higher total peripheral resistance index, and lower cardiac index compared with individuals without CKD.

⇒ In the entire cohort, elevated natriuretic peptides correlated with lower cardiac index and higher total peripheral resistance index but not with ECV normalized to total body weight.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Elevated natriuretic peptides may be associated with low cardiac index and elevated peripheral resistance.

⇒ The role of natriuretic peptides to identify patients with subclinical changes in cardiovascular parameters should be further studied.

INTRODUCTION

Patients with non-dialysis chronic kidney disease (CKD) stages 3–5 have a disproportionately higher risk for cardiovascular disease than age-matched non-CKD individuals, which contributes to considerable morbidity and mortality.[1–3] Those with advanced CKD also report a high burden of symptoms typical of cardiovascular disease, such as dyspnea and fatigue, as well as depressive symptoms and poor quality of life.[4–7] However, little is known about subclinical changes in cardiovascular parameters among individuals with earlier stages of CKD, who make up the vast majority of patients with CKD and in whom early targeted interventions may have a more substantial preventive impact on long-term outcomes.[8]

Brain natriuretic peptide (BNP) and amino-terminal-pro-BNP (NT-pro-BNP) are biomarkers used in clinical practice for

evaluation of disease severity, prognostication, and identification of states of acute volume overload in patients with heart failure.[9–11] We previously showed that in patients with stages 1–3 CKD, elevated BNP and NT-pro-BNP were independently associated with death and cardiovascular events more strongly than in those without CKD.[12] However, it remains unclear in this patient population whether elevated levels of these routinely measurable natriuretic peptides are associated with extracellular volume excess or early changes in cardiovascular parameters, both of which could mediate unfavorable associations with long-term adverse kidney and cardiovascular outcomes, and whether these biomarkers correlate with patient-reported symptom burden.[13–17]

We hypothesized that, compared with individuals without CKD, patients with CKD stages 1–3 would have biometric evidence of subclinical changes in cardiovascular parameters, including elevated extracellular water (ECW) relative to total body weight, higher total peripheral resistance index (TPRI), and lower cardiac index. We further hypothesized that elevated natriuretic peptides would be associated with higher ECW/total body weight, higher TPRI, and lower cardiac index. In an exploratory analysis, we also evaluated associations between cardiovascular parameters and patient-reported outcome measures (PROMs).

MATERIALS AND METHODS

Participants and setting

In this prospective cohort study, participants were recruited from outpatient nephrology and primary care clinics at the Veterans Affairs (VA) Medical Center in Dallas, Texas, which is the academic tertiary care hospital in the VA North Texas Health Care System. Medical records were reviewed to identify individuals who had a recent clinic visit with a measured systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg. Estimated glomerular filtration rate (eGFR) was calculated using the creatinine-based CKD Epidemiology Collaboration (CKD-EPI) equation.[18] Individuals were considered eligible for inclusion in the CKD group if they had CKD stages 1–2, defined as an eGFR ≥60 mL/min/1.73 m^2 and a spot urine albumin-to-creatinine ratio (UACR) ≥30 mg/g, or CKD stage 3, defined as an eGFR 30–59 mL/min/1.73 m^2.[19] Individuals with eGFR ≥60 mL/min/1.73 m^2 and UACR <30 mg/g were included as the non-CKD control group. Exclusion criteria included CKD stages 4–5 (eGFR <30 mL/min/1.73 m^2), chronic dialysis-dependence, kidney transplantation, cirrhosis, or known left ventricular ejection fraction <40% by previous transthoracic echocardiogram, as these conditions are known to affect extracellular volume. Individuals with pacemakers, defibrillators, pregnancy, limb amputations, or metal prostheses such as joint replacements were also excluded, as these conditions affect the safety or accuracy of the study measures. The intention was to recruit 15 participants with CKD stages 1–3 and 15 non-CKD control participants, frequency matched for the presence of diabetes mellitus and age within ±5 years. Recruitment began on December 10, 2018. Due to the COVID-19 pandemic, recruitment was stopped early on March 17, 2020 when the VA Office of Research and Development halted non-essential in-person research visits.

Clinical and laboratory variables

Eligible participants who expressed interest in the study attended an initial visit. After completing informed consent, demographic and clinical information was gathered from the medical record and confirmed with the participant. Total body weight was measured using a seated scale. Blood pressure was measured two times in a seated position after 5 min of rest using an automated sphygmomanometer. A single investigator conducted a brief physical examination to evaluate for jugular venous distention, lower extremity edema, and pulmonary rales. Phlebotomy was performed the same day as the other study procedures to measure plasma creatinine, electrolytes, BNP, and NT-pro-BNP. Freshly voided urine samples were collected to measure UACR. These study measurements were repeated at a follow-up visit 4 weeks after the baseline visit.

Extracellular water, cardiac index, and total peripheral resistance index

ECW was measured by whole-body multifrequency bioimpedance spectroscopy (Impedimed SFB7). Participants were asked to lie supine for 5 min while electrodes were attached to their ipsilateral foot, ankle, hand, and wrist. Five consecutive measurements of ECW and total body water were collected and averaged. Measurements of ECW were normalized to total body weight, consistent with prior studies.[20 21] ECW, total body water, and total body weight were measured at both of the study visits.

Cardiac index and TPRI were measured by impedance cardiography using a Cheetah Non-Invasive Cardiac Output Monitor (NICOM). Impedance cardiography has been validated against more invasive measurements of cardiac output in patients requiring intensive care.[22 23] This tool has also been used in studies of outpatients to inform management of hypertension, heart disease, and end-stage kidney disease on hemodialysis.[20 24–27] Electrodes were attached to the participant's chest and a sphygmomanometer was attached to their arm. Three consecutive measurements of blood pressure and cardiac output were taken over 5 min while the participant was lying supine. The NICOM software uses the participant's height, weight, blood pressure, and cardiac output (stroke volume×heart rate) to calculate cardiac index (cardiac output/body surface area) and TPRI (proportional to the mean blood pressure/cardiac index). Due to equipment availability, NICOM measurements were only taken at one of the two study visits.

Patient-reported outcome measures

PROMs were quantified using self-report questionnaires previously validated in patients with CKD. Fatigue was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), which is a 13-item measure yielding scores ranging from 0 to 52, with higher scores indicating less fatigue.[28 29] Depressive symptoms were measured using the 16-item Self-Reported Quick Inventory of Depressive Symptomatology (QIDS-SR16), which reports scores ranging from 0 to 48, with higher scores indicating worse depression.[30] We previously validated a score of 11 or higher as consistent with a major depressive episode in patients with CKD.[31] Quality of life (QOL) was measured using the Kidney Disease Health Related Quality

of Life-Short Form 36 (KDQOL), which reports multiple domains on adjusted scales from 0 to 100, with higher scores indicating more favorable QOL.[7 32] Dyspnea was measured using a visual analog scale ranging from 0 to 10, with 10 being the most severe.[33]

Statistical analysis

A sample size of 30 participants was planned to establish feasibility of recruitment and would be able to demonstrate a clinically meaningful correlation (with a correlation coefficient of 0.50) with 80% power and $\alpha=0.05$. Baseline characteristics and cardiovascular parameters were compared between the CKD and control groups using χ^2 or Fisher's exact tests for categorical variables and Kruskal-Wallis tests for continuous variables. Univariable Spearman's correlations were calculated between natriuretic peptides and cardiovascular parameters. Variables with fewer than 18 observations in the entire cohort were excluded from correlation analysis. Hypothesis testing of correlations was performed using r to Z transformation, accounting for lack of normal distribution. The family wise error rate was adjusted using the Holm-Bonferroni method. Analyses of cardiac index and TPRI compared these measurements with other measures that were collected on the same date, whether at the first or second visit. In an exploratory analysis, correlations of symptom domains with cardiovascular parameters were also assessed, but no hypothesis testing was done due to concerns about multiple comparisons testing and overinterpretation of the results. The repeatability of BNP, NT-pro-BNP, and ECW/total body weight between the two visits 4 weeks apart was measured using paired Student's t-tests and expressed graphically.

RESULTS

Baseline characteristics

Ultimately 21 participants were enrolled, including 13 participants in the CKD group and 8 participants in the control group. Participants with CKD were older and were more likely to be black or have diabetes than the non-CKD control participants, although the comparisons did not reach statistical significance (table 1). A history of depression was present in 38.5% of participants in the CKD group and 62.5% of the non-CKD control group. There were nine (69.2%) individuals in the CKD group with peripheral edema on physical examination, compared with two (25.0%) of the non-CKD control participants, p=0.08. In the CKD group, 10 (77%) participants had CKD stage 3 and 3 (23%) had CKD stage 2.

Cardiovascular parameters

Median (IQR) BNP was 47.0 (28.0–302.5) pg/mL in the CKD group vs 19.0 (12.3–92.3) pg/mL in the control group, p=0.07, and NT-pro-BNP was 245.0 (52.0–976.8) pg/mL in the CKD group vs 26.0 (14.5–225.8) pg/mL in the control group, p=0.08 (figure 1A,B). Systolic blood pressure and diastolic blood pressure were not significantly higher in the CKD group (figure 1C,D). Pulse pressure was 79.0 (66.0–87.0) mm Hg in the CKD group vs 63.5 (49.0–67.4) mm Hg in the non-CKD group, p=0.046 (figure 1E). ECW normalized to total body weight was 0.27 (0.25–0.30) L/kg in the CKD group and 0.25 (0.23–0.26) L/kg in the control group, p=0.13 (figure 1F). Cardiac index was significantly lower and TPRI significantly higher in the CKD group compared with controls, with cardiac index 2.28 (2.08–2.78) vs 3.08 (2.43–3.37) L/min/m^2, p=0.02, and TPRI 3721 (3283–4278) vs 2933 (2745–3198) dyn×s/cm^5/m^2, p=0.01 (figure 1G,H).

Correlations of natriuretic peptides with cardiovascular parameters

BNP correlated with pulse pressure, cardiac index, and TPRI in the entire cohort (figure 2A–C). However, BNP was not significantly correlated with ECW/total body weight, with p=0.45 in the entire cohort, p=0.64 in the non-CKD

Table 1 Baseline characteristics by CKD status

Variable description, median (IQR) or N (%)	Non-CKD N=8	CKD N=13	P value
Estimated GFR, mL/min/1.73 m^2	92 (84–99)	40 (35–57)	<0.001
Age, years	56.5 (48.0–72.5)	70.0 (58.5–75.0)	0.38
Race			0.67
Black	4 (50.0)	8 (61.5)	
White	4 (50.0)	5 (38.5)	
Hispanic ethnicity	1 (12.5)	0 (0.0)	0.38
Diabetes	3 (37.5)	8 (61.5)	0.39
Hypertension	8 (100.0)	13 (100.0)	N/A
Hyperlipidemia	5 (62.5)	12 (92.3)	0.25
Heart failure with preserved ejection fraction	0 (0.0)	2 (15.4)	0.51
Peripheral vascular disease	1 (12.5)	3 (23.1)	1.00
Depression	5 (62.5)	5 (38.5)	0.39
Tobacco use			
Any history of tobacco use	5 (62.5)	9 (69.2)	1.00
Current tobacco use	2 (25.0)	5 (38.5)	0.66
Body weight, kg	104.5 (76.8–112.7)	90.6 (71.6–125.3)	1.00
Edema on physical examination	2 (25.0)	9 (69.2)	0.08

.CKD, chronic kidney disease; GFR, glomerular filtration rate; IQR, interquartile range; N/A, not applicable.

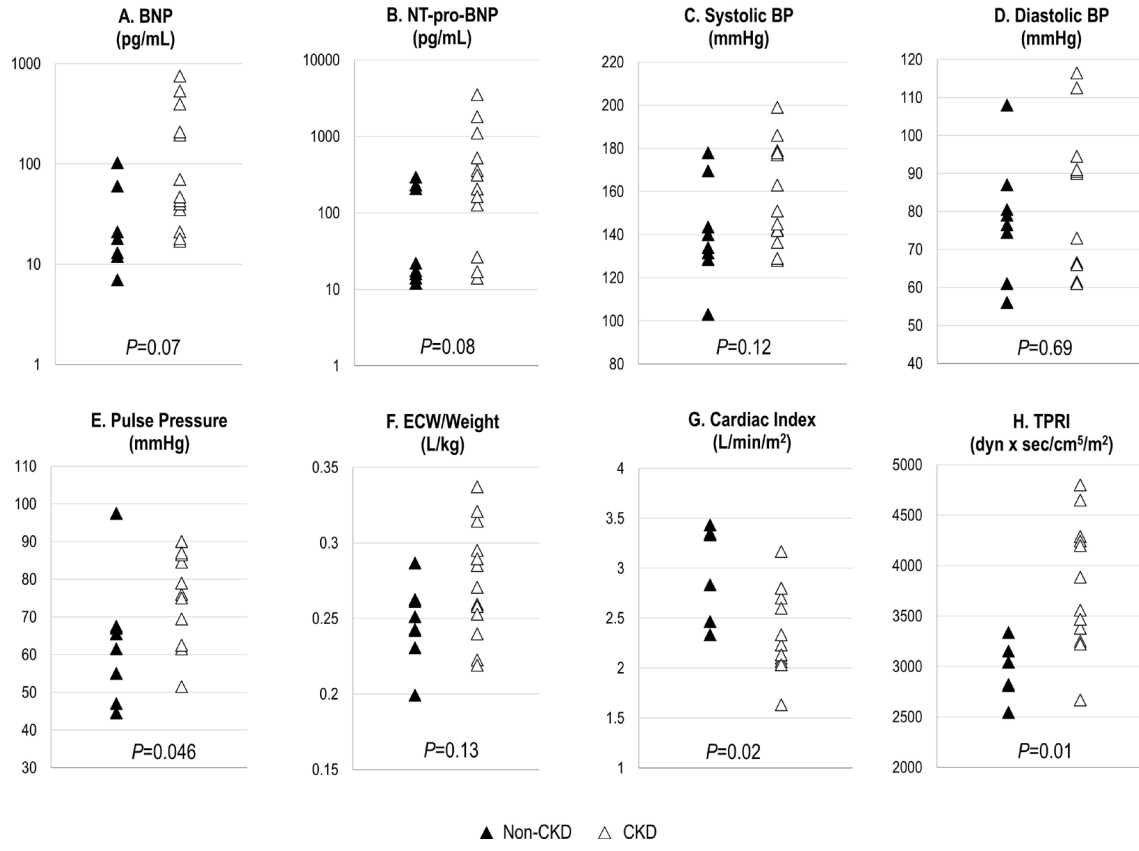

Figure 1 CKD was associated with higher pulse pressure, lower cardiac index, and higher peripheral resistance. Dot plots show the individual data points for BNP (A), NT-pro-BNP (B), systolic blood pressure (C), diastolic blood pressure (D), pulse pressure (E), ECW/total body weight (F), cardiac index (G), and TPRI (H). BNP, brain natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; ECW, extracellular water; NT-pro-BNP, amino terminal pro-BNP; TPRI, total peripheral resistance index.

group, and p=0.68 in the CKD group (online supplemental table 1). It similarly did not correlate with systolic blood pressure (p=0.28 in the entire cohort, p=0.48 in the non-CKD control group, and p=0.97 in the CKD group) or diastolic blood pressure (p=0.28 in the entire cohort, p=0.53 in the non-CKD control group, and p=0.18 in the CKD group). NT-pro-BNP correlated with pulse pressure and cardiac index in the entire cohort (figure 2D–E), but did not correlate with other cardiovascular parameters (online supplemental table 1).

Associations of BNP and NT-pro-BNP with PROMs

There was a trend toward worse patient-reported severity of dyspnea, fatigue, depression, and QOL among those with CKD versus without, although none reached statistical significance (table 2). The KDQOL sexual function subscale was excluded from analysis due to low response rate, as the majority of participants reported no sexual activity in the preceding 4 weeks. Exploratory Spearman's correlations of symptom severity with cardiovascular parameters are shown in figure 3. TPRI and systolic blood pressure and diastolic blood pressure were moderately correlated with multiple symptom domains. Fatigue on the FACIT-F and as a domain of the KDQOL moderately correlated with ECW/total body weight, such that higher ECW was associated with more favorable fatigues scores. Higher BNP was associated with more favorable scores on the KDQOL domains of effect of CKD (Spearman's r=0.24, p=0.04) and burden of CKD (Spearman's r=0.20, p=0.01). NT-pro-BNP was not significantly correlated with any symptom scores in the overall cohort.

Repeatability of natriuretic peptides and ECW

There were no changes from baseline to 4 weeks in BNP, NT-pro-BNP, or ECW/total body weight measurements. In the entire cohort, median (IQR) BNP was 41.5 (18.0–171.3) pg/mL at baseline and 49 (12.0–123.0) pg/mL at follow-up (p=0.36); median (IQR) NT-pro-BNP was 151.0 (22.5–526.0) pg/mL at baseline and 195.0 (15.0–313.0) pg/mL at follow-up (p=0.54); and median (IQR) ECW/total body weight was 0.259 (0.241–0.288) L/kg at baseline and 0.256 (0.245–0.287) L/kg at follow-up (p=0.20) (figure 4). There were no differences from baseline to follow-up in these measurements in either the CKD or non-CKD groups.

DISCUSSION

In this pilot prospective cohort study, we found that individuals with CKD stages 1–3 had higher total peripheral resistance and lower cardiac index than individuals without CKD. Natriuretic peptides correlated with higher pulse pressure and TPRI and lower cardiac index, but not with ECW/total body weight. Higher blood pressure and TPRI were associated with increased symptom burden. Natriuretic

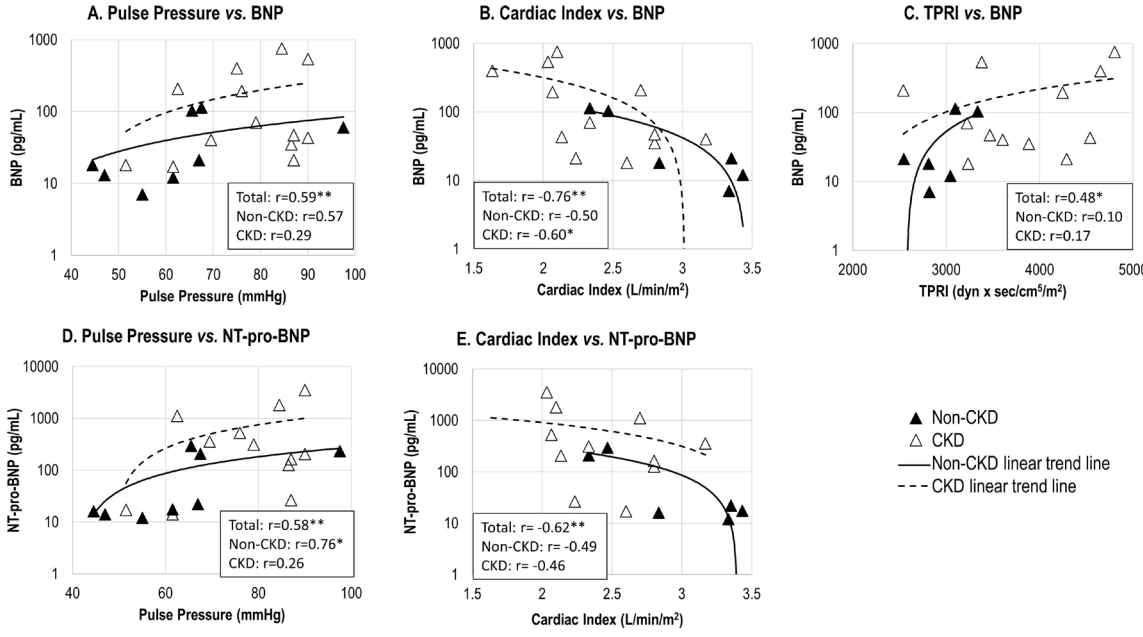

Figure 2 BNP and NT-pro-BNP were associated with cardiovascular parameters. Scatter plots show the linear associations of BNP with pulse pressure (A), cardiac index (B), and TPRI (C) and of NT-pro-BNP with pulse pressure (D) and cardiac index (E). Natriuretic peptides and blood pressure values were measured the same day as the available cardiac index and total peripheral resistance index measurement for each participant. BNP, brain natriuretic peptide; CKD, chronic kidney disease; NT-pro-BNP, amino terminal pro-BNP; TPRI, total peripheral resistance index. *p<0.05, **p<0.01.

peptides and ECW/total body weight measurements were consistent within individuals when repeated after 4 weeks.

Our exploratory results generate hypotheses that subclinical changes in cardiovascular parameters may exist in patients with CKD stages 1–3. Participants with CKD had significantly higher pulse pressure and TPRI and lower cardiac index compared with non-CKD controls. It was notable that despite the exclusion of individuals with known left ventricular ejection fraction <40%, the majority (58%) of individuals in the CKD group had a cardiac index <2.5 mL/min/m^2, which is considered below the normal range. Heart failure and decreased glomerular filtration rate (GFR) are strongly associated,[34–36] which could explain this finding, as the majority of the CKD group was classified as stage 3 with a median (IQR) eGFR of 40 (35–57) mL/min/1.73 m^2. The median cardiac index of 2.28 L/min/m^2 (IQR 2.08–2.78) in our study was similar to prior estimates measured by bioelectrical impedance in patients with non-dialysis-dependent kidney disease, such as one small study of seven individuals with mean inulin-based GFR of 25 mL/min, with mean cardiac index of 2.3±0.2 L/min/m^2.[37] Our results were also similar to a study of 85 older adults with eGFR ≤20 mL/min/1.73 m^2, in which median cardiac index measured by cardiac MRI was 2.5 L/min/m^2 (IQR 2.1–3.0).[38] However, these numbers differ from another study, in which mean cardiac index by Doppler ultrasonography was 3.86±1.57 L/min/m^2 among 24 younger individuals with CKD stages 2–4 (mean age 50.5±16.8 years).[39] Despite this, even if the absolute cardiac index cannot be compared among studies due to differences in their methods for measuring stroke volume,[40 41] this would not account for the difference seen in our study between the CKD and non-CKD groups, indicating that cardiac index may indeed be lower in those with early stage to moderate-stage CKD than those without kidney disease.

Building on these results, we sought to identify cardiovascular parameters associated with natriuretic peptides to provide further insight into interpretation of elevated BNP or NT-pro-BNP in CKD. Our study was likely underpowered to demonstrate that individuals with CKD had higher natriuretic peptides, higher ECW/total body weight, or more peripheral edema than those without CKD, as previously demonstrated in larger studies.[12 42–44] Natriuretic peptides are known to associate with decreased eGFR due to urinary clearance of these biomarkers, which affects BNP to a greater degree than NT-pro-BNP.[42 45 46] BNP and NT-pro-BNP are ultimate products of cleavage of pre-proBNP, which is generated by cardiomyocytes in response to increased pressure and stretch, often in the setting of acute states of extracellular volume excess.[47] In the clinical setting, elevated levels of these biomarkers are frequently interpreted as indicating states of acute volume overload in patients with heart failure presenting with symptoms of dyspnea.[10 11 45] However, natriuretic peptide release is also stimulated by other factors, including elevated angiotensin II and sympathetic nervous system activity.[48] Our exploratory results support the notion that elevated natriuretic peptides in stable outpatients may be more strongly associated with low cardiac index and high total peripheral resistance than elevated ECW/total body weight. This raises the question of whether low cardiac index may explain the previously demonstrated relationships between elevated BNP and NT-pro-BNP and adverse outcomes in CKD, but further investigation is needed into this point.

Table 2 Baseline symptom scores by CKD status

Variable description, median (IQR)	Non-CKD N=8	CKD N=13	P value
Dyspnea*	0.0 (0.0–2.4)	1.0 (0.0–5.0)	0.39
Fatigue†	24.0 (18.0–43.0)	28.0 (24.0–43.0)	0.38
Depression‡	6.0 (3.0–12.5)	8.0 (3.5–13.0)	0.49
Quality of life§			
Symptom burden	73.9 (57.8–90.3)	65.9 (52.3–77.3)	0.29
Effect of CKD	98.4 (73.4–100.0)	93.8 (53.1–100.0)	0.30
Burden of CKD	100.0 (70.3–100.0)	75 (21.9–84.4)	0.05
Work	50.0 (0.0–100.0)	50.0 (0.0–100.0)	0.70
Cognitive function	76.7 (53.3–96.7)	80.0 (26.7–93.3)	0.51
Social	73.3 (51.7–86.7)	66.7 (36.7–93.3)	0.94
Sex	37.5 (28.1–84.4)	93.8 (40.6–100.0)	0.45
Sleep	66.3 (40.6–71.9)	57.5 (37.5–72.5)	0.66
Social support	66.7 (33.3–83.3)	50.0 (41.7–100.0)	0.80
Physical functioning	42.5 (22.5–83.8)	45.0 (17.5–70.0)	0.80
Role physical	12.5 (0.0–93.8)	0.0 (0.0–100.0)	1.00
Pain	45.0 (22.5–56.9)	32.5 (22.5–67.5)	0.94
General health	47.5 (36.3–67.5)	30.0 (22.5–57.5)	0.17
Emotional	69.0 (57.0–82.0)	64.0 (44.0–86.0)	0.54
Role emotional	66.7 (0.0–100.0)	66.7 (0.0–100.0)	0.69
Social functioning	50.0 (50.0–87.5)	50.0 (37.5–100.0)	0.80
Fatigue	37.5 (16.2–67.5)	40.0 (30.0–72.5)	0.47

*Measured using the dyspnea visual analog scale, range 0–10. Higher scores indicate more severe dyspnea.
†Measured using the Functional Assessment of Chronic Illness Therapy-Fatigue, range 0–52. Higher scores indicate less severe fatigue.
‡Measured using the 16-item Self-Reported Quick Inventory of Depressive Symptomatology, range 0–48. Higher scores indicate more severe depression.
§Measured using the Kidney Disease Health Related Quality of Life-Short Form 36, range 0–100. Higher scores indicate more favorable quality of life.

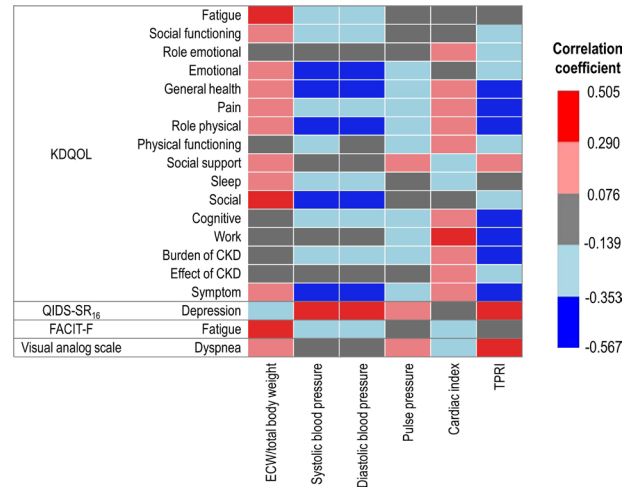

Figure 3 Higher systolic blood pressure and diastolic blood pressure and higher peripheral resistance may be associated with multiple patient-reported symptoms. In an exploratory analysis, the heat map represents correlations seen between symptom scores and cardiovascular parameters, with bright red representing the strongest positive correlations and bright blue representing the strongest negative correlations. Pale red and pale blue represent weaker correlations, and gray represents correlations near zero. Patient-reported symptoms, ECW/total body weight, and blood pressure were measured the same day as the available cardiac index and total peripheral resistance index measurement for each participant. CKD, chronic kidney disease; ECW, extracellular water; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; KDQOL, Kidney Disease Health Related Quality of Life-Short Form 36; QIDS-SR$_{16}$, 16-item Self-Reported Quick Inventory of Depressive Symptomatology; TPRI, total peripheral resistance index.

We further explored whether cardiovascular parameters may be associated with the high symptom burden experienced by patients with CKD. Higher blood pressure and TPRI both appeared to correlate with increased severity of multiple symptom domains. Given that TPRI is derived in part from blood pressure, it is not surprising that we found similar relationships between these variables and symptom severity. There were no apparent correlations between natriuretic peptides and symptom burden. Our results differ from prior studies in other patient populations, which showed that BNP correlated with depressive symptoms in patients with heart failure and that fluid overload was associated with fatigue and poor QOL among patients receiving chronic dialysis.[49–51] Although we are unable to draw conclusions about such relationships from our exploratory results, it is possible that changes in cardiovascular parameters may contribute to the unique symptom profile experienced by patients with CKD prior to the onset of uremic symptoms. More extensive studies are needed to further characterize these relationships and inform future interventions for these important patient-centered outcomes.

Finally, we measured the repeatability of BNP, NT-pro-BNP, and ECW/total body weight to assess whether these values remain stable over the course of 4 weeks without intervention. Our results suggest that these measurements are reliable over this window of time. Potential uses of repeated measures of natriuretic peptides in this population remain to be determined. One prior study in patients on chronic hemodialysis showed that although BNP only correlated moderately with bioimpedance spectroscopy measurements of ECW between individuals, within individuals it strongly correlated with variation in extracellular volume.[52] This suggests that repeated measures to assess change in natriuretic peptides over time may have a more important clinical role than their absolute values. With only two measurements of natriuretic peptides, we were unable to assess such relationships in this study.

This pilot study has several strengths. We obtained detailed phenotypic cardiovascular information in a sample of patients with CKD stages 1–3 and demonstrated that many had developed underlying subclinical changes in cardiovascular parameters when compared with individuals without CKD. The results also generate hypotheses about whether underlying cardiovascular disease may explain known relationships between natriuretic peptides, symptom burden, and poor outcomes. This study also has important limitations that temper interpretation of the results. Most notably, the small sample size limits what can be concluded from the data. Correlations must be interpreted cautiously with such a small sample size and concerns of multiple comparisons testing. The incomplete frequency matching for age and diabetes of

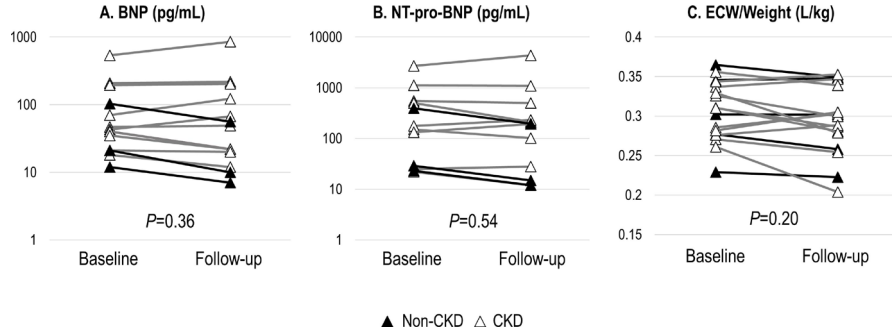

Figure 4 Repeated measurements of natriuretic peptides and extracellular volume were consistent over time. BNP (A), NT-pro-BNP (B), and ECW/total body weight (C) were consistent within participants from baseline to follow-up 4 weeks later. BNP, brain natriuretic peptide; CKD, chronic kidney disease; ECW, extracellular water; NT-pro-BNP, amino terminal pro-BNP.

control and CKD participants was unavoidable due to unanticipated early cessation of recruitment in the setting of the COVID-19 pandemic and subsequent unequal recruitment between the two groups. The majority of the CKD group had stage 3 CKD, limiting interpretation of alterations in cardiovascular parameters that may develop in CKD stages 1–2. Some of the results seen could be accounted for by the higher age, higher prevalence of diabetes, or slightly higher blood pressure observed in the CKD group than the control group, but the study was too small to conduct a sensitivity analysis excluding individuals whose measured blood pressure was <140/90 mm Hg. We did not evaluate the role of medications, such as beta-blockers, on the relationships studied. We did not obtain repeated measures of cardiac index or TPRI to evaluate the consistency of these measurements over time.

In conclusion, the presence of CKD stages 1–3 may be associated with higher pulse pressure and total peripheral resistance and lower cardiac index compared with individuals without CKD. Elevated natriuretic peptides may correlate with low cardiac index, elevated total peripheral resistance, and elevated pulse pressure. Elevated blood pressure and TPRI may also correlate with multiple symptom burden domains, but these results need to be confirmed in larger cohorts. Further evaluation of these relationships in larger studies will be of interest to determine more clinically accessible ways to identify patients with subclinical changes in cardiovascular parameters who may be at higher risk for future adverse outcomes.

Author affiliations
[1]Selzman Institute for Kidney Health, Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA
[2]Medical Care Line, Section of Nephrology, Michael E DeBakey Veterans Affairs Medical Center, Houston, Texas, USA
[3]Veterans Affairs Health Services Research and Development Center for Innovations in Quality, Effectiveness and Safety, Houston, Texas, USA
[4]Internal Medicine, Division of Nephrology, University of Texas Southwestern Medical Center, Dallas, Texas, USA
[5]Medical Service, Renal Section, Veterans Affairs North Texas Health Care System, Dallas, Texas, USA
[6]Mental Health Service, Veterans Affairs North Texas Health Care System, Dallas, Texas, USA
[7]Internal Medicine, Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, Texas, USA
[8]Medical Service, Cardiology Section, Veterans Affairs North Texas Health Care System, Dallas, Texas, USA
[9]Internal Medicine, Section of Cardiology, Baylor College of Medicine, Houston, Texas, USA
[10]Internal Medicine, Section of Cardiology, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA
[11]Institute of Clinical and Translational Research, Baylor College of Medicine, Houston, Texas, USA

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Twitter L Parker Gregg @LParkerGregg1

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ORCID iDs
L Parker Gregg http://orcid.org/0000-0002-5469-367X
Peter N Van Buren http://orcid.org/0000-0002-4392-1163

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