Study Protocol

The Impact on Central Blood Pressure and Arterial Stiffness Post Renal Denervation in Patients With Stage 3 and 4 Chronic Kidney Disease: The Prairie Renal Denervation Study

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Abstract

Background: Central aortic blood pressures and arterial stiffness are better indicators of cardiovascular outcomes than brachial blood pressures. However, their response to renal denervation (RDN) in patients with stage 3 and stage 4 chronic kidney disease (CKD) has not yet been examined.

Objective: To evaluate the impact of RDN on central blood pressures, brachial (office and ambulatory) blood pressures, arterial stiffness, glomerular filtration rate (GFR), 24-hour urine protein, and selective cardiac parameters observed on echocardiograms.

Design: Single-center, single-arm with pre-RDN/post-RDN follow-up.

Setting: Patients are being recruited from the multidisciplinary CKD clinic.

Patients: Fifty consecutive patients with stage 3 or stage 4 CKD and resistant hypertension, with no radiological or laboratory evidence of secondary causes of hypertension.

Measurements: The key measurements are central blood pressures, pulse wave velocity, ambulatory 24-hour blood pressure, office blood pressures on BP Tru, GFR, 24-hour urine protein and sodium, blood pressure medication, and doses.

Methods: For our primary outcome, we will compare changes in central blood pressures from baseline to 6 months post RDN using a paired t test or Mann-Whitney U test. Secondary outcomes will examine changes in central blood pressures from baseline to 3, 12, 18, and 24 months post RDN as well as changes in office pressures, GFR, 24-hour urine protein and sodium, and medications at all time points using mixed-model analyses of variance or Friedman test. Multiple regression may be used to control for potential covariates.

Limitations: Single-center study, with no sham arm.

Conclusions: Aortic blood pressure, rather than brachial blood pressure, optimally reflects the load placed on the left ventricle. Aortic blood pressure is also better associated with cardiovascular outcomes. If our study shows a preferential decrease in central blood pressures and improvements in cardiac parameters on echocardiograms post RDN, this may influence the way in which blood pressures are managed in clinics and offices.

Trial Registration: ClinicalTrials.gov (NCT01832233)

Abrégé

Contexte: La mesure de la pression centrale et de la rigidité artérielle sont de meilleurs indicateurs de troubles cardiovasculaires que la mesure de la pression sanguine par l’artère brachiale. Cependant, leur réponse à une dénervation rénale chez les patients atteints d’insuffisance rénale chronique (IRC) de stade 3 et 4 n’a pas encore été étudiée.

Objectif de l’étude: Évaluer l’effet d’une dénervation rénale sur les mesures de la pression artérielle centrale et brachiale (par le médecin ou ambulatoire), sur la rigidité artérielle, le débit de filtration glomérulaire (DFG), le taux de protéines dans les urines sur une période de 24 heures, de même que sur les paramètres cardiaques sélectifs observés sur les échocardiogrammes.

Type d’étude: Une étude à une seule branche avec un suivi des patients avant et après la dénervation rénale.

Cadre de l’étude: Les patients sont recrutés au sein d’une clinique multidisciplinaire spécialisée dans les soins offerts aux personnes atteintes d’IRC.

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 Patients: Cinqante patients atteints à la fois d’IRC de stade 3 ou de stade 4 et d’hypertension résistante, et pour qui il n’existe aucun signe radiologique ou biochimique de causes secondaires de l’hypertension.

Mesures: Les principaux paramètres qui seront analysés sont la pression centrale, la vitesse de l’onde de pouls, la pression artérielle mesurée par le patient lui-même (ambulatoire) sur une période de 24 heures, la pression sanguine mesurée par BP Tru dans le bureau du médecin, le DFG, le taux de protéines et de sodium dans les urines sur 24 heures, de même que la liste des médicaments prescrits pour traiter l’hypertension et les doses correspondantes.

Méthodologie: Pour atteindre notre objectif principal, nous allons comparer les variations de la valeur de la pression centrale mesurée six mois après la dénervation rénale par rapport à la valeur initiale. Cette comparaison sera effectuée à l’aide d’un test T jumelé ou d’un test U de Mann-Whitney. Les résultats secondaires examineront les variations observées dans la mesure de la pression centrale initiale par rapport aux mesures faites à 3, 12, 18 et 24 mois après la dénervation rénale. On analysera également les variations dans les valeurs de la pression artérielle mesurées au bureau du médecin, dans les valeurs de DFG et dans les taux de protéines et de sodium mesurés dans les urines sur 24 heures. Tout au long de l’étude, les changements dans la médication seront analysés en utilisant le modèle mixte d’ANOVA ou le Test de Friedman. Un modèle de régression multiple pourrait aussi être utilisé pour tenir compte des possibles covariables.

Limite de l’étude: Les résultats seront limités par le fait qu’il s’agit d’une étude à une seule branche et qu’elle se tiendra dans un seul établissement.

Conclusions: La mesure de la pression centrale reflète, mieux que la mesure de la pression de l’artère brachiale, la charge imposée au ventricule gauche. La pression sanguine à la sortie de l’aorte est également associée de façon plus spécifique aux troubles cardiovasculaires. Si notre étude montre une diminution préférentielle de la pression centrale et une amélioration des paramètres cardiaques observés sur les échocardiogrammes pratiqués, ces résultats seraient susceptibles d’influencer la façon dont la pression artérielle est prise en charge dans les cliniques et les bureaux de médecins.

Keywords
central blood pressure, chronic kidney disease, chronic renal failure, resistant hypertension, renal denervation

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What was known before
In patients with stage 3 and 4 chronic kidney disease (CKD), there is an improvement in brachial blood pressures post renal denervation (RDN). However, no published studies have examined the improvement in central blood pressure post RDN in patients with CKD.

What this adds
At the conclusion of our study we will report the effects of RDN on central blood pressure and arterial stiffness, specifically in patients with resistant hypertension and G3 and G4 CKD.

Introduction
It has been shown that lowering of brachial blood pressure (BP) represents a surrogate endpoint that does not automatically lead to a parallel decrease in cardiovascular morbidity and mortality. Systolic BP varies across the arterial tree, and counterintuitively, central or aortic systolic pressures are lower than corresponding brachial values. While BP measured over the brachial artery is determined by cardiac output and peripheral vascular resistance, aortic (central) pressures are additionally determined by the stiffness of the conduit vessels and the timing/magnitude of pressure wave reflections. The central systolic BP places a direct burden on the left ventricle, and there is now overwhelming evidence that central hemodynamic indexes (which include aortic pressures, pulse pressures, and augmentation index [AIx]) are independent predictors of cardiovascular morbidity and mortality and are more closely correlated with cardiovascular risk than brachial pressures. Recent technological advances have led to central hemodynamics being reliably measured noninvasively with relatively inexpensive devices.

In the Conduit Artery Function Evaluation Study, a central systolic pressure of 125 mm Hg was associated with a
10% to 30% increase in cardiovascular risk compared with 121 mm Hg. In patients with chronic kidney disease (CKD), Townsend measured the central systolic and diastolic pressure in 2144 participants of the Chronic Renal Insufficiency Cohort (CRIC) study and the overall mean ± SD was 116 ± 21 and 71 ± 13 mm Hg, respectively. The corresponding office systolic and diastolic BPs were 126 ± 23 and 70 ± 13 mm Hg, respectively. The mean central systolic BP was 10 mm Hg lower, although the diastolic pressures were similar. The pulse wave velocity (PWV; m/s) in the same cohort was 9.49 ± 3.04 m/s and, when analyzed in diabetics, was marginally higher at 10.56 ± 3.27 m/s. Clinical studies have also shown that in addition to central pressures, increased aortic stiffness, as measured via aortic PWV, is an independent marker of cardiovascular risk and a major contributor to mortality in end-stage renal disease (ESRD).

Increased sympathetic activity has been found to be associated with essential hypertension, obesity-related hypertension, and hypertension associated with obstructive sleep apnea. There is evidence suggesting that increased afferent sympathetic activation is an early event in CKD and that various forms of renal damage lead to a heightened sympathetic drive. The ensuing efferent response contributes to propagation of hypertension and adverse cardiovascular events. Renal denervation (RDN) delivers radiofrequency energy to interrupt the afferent and efferent renal sympathetic nerve signaling and reduces total sympathetic nerve activity, leading to a decrease in BPs and improved cardiac outcomes.

Although reduction in peripheral, ambulatory BPs and renal outcomes in patients with stage 3 and 4 CKD post RDN has been published, the relationship of central BP and arterial stiffness in patients with CKD before and after RDN has thus far been unexplored, and there is a paucity of relevant data in the literature. In our single-center prospective study, we aim to follow 50 patients with stage 3 and 4 CKD for 2 years post RDN and to chronologically document changes in central BPs, PWV, peripheral BPs (office and ambulatory), renal biochemical parameters (estimated glomerular filtration rate [eGFR] and 24-hour urine for protein), and fasting glucose and insulin levels as well as the change in the dose and number of medications.

### Methods

**Study Design and Patients**

This study is being conducted under a 2-year prospective preintervention/postintervention design. Fifty consecutive stage 3 and 4 CKD patients with resistant hypertension from the Regina Qu’Appelle Health Region multidisciplinary CKD clinic who agree to undergo RDN will be included in the study. Patients are considered eligible if they are older than 18 years and exhibit a systolic BP of greater than 140 mm Hg despite maximal doses of 3 agents (1 of which is a diuretic). Exclusion criteria are documented in Table 1. Once identified as having resistant hypertension based on chart review, the patients undergo evaluation for eligibility to participate in the study (Figure 1). Our Research Ethics Board (Institutional Review Board) granted approval for the study (REB-12-73). Patients on clonidine and other sympatholytic agents will not be excluded from the study.

#### Demographic Information

During the same clinic visit, the patient’s age, height, weight, waist circumference, race, gender, current medications being taken, and current medical conditions (peripheral artery disease, diabetes mellitus, coronary heart disease, cerebrovascular disease) are recorded. A quality-of-life questionnaire (EuroQol Five Dimensions Questionnaire [EQ-5D], a short standardized instrument to measure health-related quality of life) is also administered, which is to be completed prior to the procedure.

#### Laboratory Measures

The patient receives a requisition to have blood taken at a laboratory within 1 month prior to the RDN procedure to measure the following parameters: serum fasting glucose and insulin, a fasting lipid panel, eGFR, electrolytes, osmolality, complete blood count, and 24-hour urine for sodium, protein, creatinine clearance, potassium, osmolality, and the albumin/creatinine ratio.

#### Procedure

During renal nerve ablation, a catheter connected to a Medtronic (Santa Rosa, CA, USA) radiofrequency generator is inserted percutaneously through the groin via the femoral artery and advanced up the aorta to the renal arteries. A total of 4 to 6 discrete radiofrequency ablations lasting up to 2 minutes, of 8 watts or less each, are performed, separated both longitudinally and rotationally within each renal artery. The catheter system monitors tip temperature and impedance, altering radiofrequency energy delivery in response to a predetermined algorithm. The procedure takes approximately 40 minutes to complete the ablations bilaterally. The patient receives intravenous opiates and sublingual anxiolytics, as

### Table 1. Exclusion Criteria.

| Exclusion criteria: |
|-------------------|
| Functional adrenal adenoma |
| Renal artery length (on either side) of <20 mm and diameter of <4 mm |
| Pregnant or planning pregnancy during the study period |
| Moderate to severe aortic stenosis |
| Cardiac event necessitating introduction of clopidogrel during the prior 12 months |
| Current warfarin use |
| History of cerebrovascular accident (CVA) 6 months prior to the procedure |
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per the institutional protocol, to reduce visceral pain as well as 3000 IU of intra-arterial heparin in each renal artery prior to the ablations. Post procedure, the patient is monitored in the ambulatory care unit for 4 hours.

The procedure time and contrast volume are documented. The number of successful ablations in each renal artery is also recorded. All adverse events and complications are recorded during each study visit. Specific intervention-related safety data include bleeding or a femoral pseudoaneurysm requiring intervention, renal artery dissection, myocardial infarction, stroke, and death.

Follow-up Schedule

Seven days after the ablation procedure, the patient receives a phone call from the study coordinator to assess his or her clinical condition. Following appropriate orientation to home BP monitoring, he or she is encouraged to continue to check his or her BP routinely at home (2 times/wk) and inform the attending physician whether his or her BP falls below 100 mm Hg systolic or remains higher than 180/90 mm Hg.

At 3, 6, 12, 18, and 24 months after the procedure (within ±1 month), the study coordinators perform/request the tests documented in Table 2. The patient also undergoes an echocardiogram to examine cardiac function at 12 and 24 months (within ±2 months). The insulin sensitivity index is calculated from fasting glucose and insulin values as follows: homeostatic model assessment–insulin resistance (HOMA-IR) (FPG/FPI), where FPG and FPI are fasting plasma glucose and fasting plasma insulin, respectively.

**Ambulatory BPs and office BPs.** Patients will undergo 24-hour BP monitoring (Welch Allyn, Skaneateles Falls, New York), and the following information will be documented: 12-hour daytime systolic pressure (mm Hg), 12-hour daytime diastolic pressure (mm Hg), 12-hour nighttime systolic pressure (mm Hg), and 12-hour nighttime diastolic pressure (mm Hg). The following day, the patients will have the 24-hour arm cuff removed, and they will sit in a quiet room for 10 minutes before the study coordinator can take further peripheral BP measurements using BP Tru (BPM-100, BPTru Medical Devices, Coquitlam, British Columbia, Canada) on the nondominant arm, which measures 6 consecutive BPs (the first is excluded, and the average of the last 5 readings will be documented).

**Central BP.** After obtaining the mean of the 5 BP readings, radial artery waveforms will be recorded with a high-fidelity micromanometer from the wrist of the dominant arm and calibrated to the previously measured mean of 5 BP readings. Waveforms will be processed with dedicated software (SphygmoCor CPV [EM3] software version 9; AtCor

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**Table 2. List of Investigations at Baseline and at Follow-ups.**

| Patient demographics | Age, sex, weight, height, waist circumference, and medication review (Baseline and 3, 6, 12, 18, and 24 months) |
| Laboratory investigations: blood | Serum urea, creatinine, electrolytes, complete blood count (CBC), fasting panel (glucose, insulin, and lipids), serum osmolality, and HbA1c (Baseline and 3, 6, 12, 18, and 24 months) |
| Laboratory investigations: urine | Early morning spot urine (for sodium, potassium, osmolality, and the albumin/creatinine ratio) and 24-hour urine (for protein) (Baseline and 3, 6, 12, 18, and 24 months) |
| Blood pressure | 24-hour ambulatory blood pressure and office blood pressure (average of 6 readings on BP Tru), central blood pressure (augmentation index [%], augmentation pressure [mm Hg], central pulse pressure [mm Hg], central systolic pressure [mm Hg], central diastolic pressure [mm Hg], pulse pressure amplification [mm Hg], and time to reflection [Tr] in ms), and pulse wave velocity (Baseline and 3, 6, 12, 18, and 24 months) |
| ECHO | Left ventricle volume, left ventricle hypertrophy, left ventricle function, left atrial mass, E-wave velocity, and E-prime velocity (Baseline and 12 and 24 months) |

Note. ECHO = echocardiogram.
Medical, Inc., Itasca, IL, USA). The integral system software will be used to calculate an average radial artery waveform and to derive a corresponding central aortic pressure waveform using a previously validated generalized transfer function. Aortic waveforms will be subject to further analysis using the SphygmoCor software to identify the time to the peak/shoulder of the first and second pressure wave components \( T_1, T_2 \) during systole. The pressure at the peak/shoulder of the first component will be identified as the \( P_1 \) height, and the pressure difference between this point and the maximal pressure during systole \( \Delta P \), or augmentation) will be identified as the reflected wave during systole. The \( \Delta x \), defined as the ratio of augmentation to the central pulse pressure \( CPP \), is expressed as a percentage: \( \Delta x = (\Delta P / PP) \times 100 \), where \( P \) is pressure and \( PP \) is pulse pressure. Pulse pressure amplification \( \text{PPA} \) is expressed as the ratio \( \text{CPP} \) to brachial pulse pressure \( \text{PPP} \): \( \text{PPA} = \frac{\text{PPP}}{\text{CPP}} \). At least 2 consecutive radial pressure wave samplings will be recorded for each patient, and the mean will be used for analysis. The collected data will include the \( \Delta x \) (\%), augmentation pressure \( \text{mm Hg} \), \( \text{CPP (mm Hg)} \), central systolic pressure \( \text{mm Hg} \), central diastolic pressure \( \text{mm Hg} \), \( \text{PPA (mm Hg)} \), time to reflection \( \text{Tr} \) in milliseconds, and \( \text{PWV} \).

**Pulse wave velocity.** The carotid to femoral pulse wave velocity \( \text{CF-PWV} \) will be measured in all patients during every clinic visit. \( \text{PWV} \) will be determined immediately after the central BPs. This parameter is determined by simultaneous measurement of arterial pressure waves at the carotid and femoral arteries with a pressure transducer. The surface distance from the suprasternal notch to the distal (femoral) recording site will be measured, and the pressure wave transit time will be calculated by dividing the distance to the distal site by the pressure wave transit time. The data are collected by a single trained coordinator (R.J.), and the mean of 2 \( \text{PWV} \) measurements will be taken for each patient.

**Echocardiogram.** The following parameters will be documented: left ventricular end-diastolic volume, left ventricular hypertrophy, left ventricle function, left atrial mass, E-wave velocity, and E'-prime velocity.

**Endpoints**

The primary outcome of interest is the change in central BP from baseline to 6 months post RDN. The secondary outcomes of interest include the change in central BP from baseline to 3, 12, 18, and 24 months post RDN as well as changes in 24-hour peripheral BP, \( \text{PWV} \), cardiac parameters, renal biochemical parameters, fasting insulin and glucose levels, and the number of medications.

**Sample Size Considerations**

With a 1-sided type 1 error rate of 5%, a sample of 50 subjects will provide 90% power to detect a 10/5 mm Hg change in systolic/diastolic central pressures from baseline with a standard deviation of 23/12, which would be clinically significant.

**Statistical Analyses**

Baseline data will be summarized descriptively. The primary outcome will be evaluated using a 1-sided paired samples \( t \) test for normally distributed data or Mann-Whitney \( U \) test for nonnormally distributed data. Secondary outcomes will be examined using repeated-measures or mixed-model analyses of variance with correction for multiple comparisons (continuous outcomes), chi-square test (categorical outcomes) for normally distributed data, and Friedman test (continuous) or McNemar test (categorical) for nonnormally distributed data and 2-sided alpha set to .05. Multiple linear regression may be used to account for potential covariates such as age, body mass index, gender, or comorbidities on changes in BP, cardiac or renal parameters, and insulin/glucose.

**Results**

To date, 26 subjects have been enrolled into the trial. Interim findings are reported. Demographic data are provided in Table 3 and medications in Table 4. The number of antihypertensives by CKD stages is provided in Table 5.

**Discussion**

In CKD, stimulation of renal afferent nerves by various mechanisms, including ischemia and uremic toxins, increases the systemic sympathetic outflow via central integrative pathways in the hypothalamus. Targeting renal sympathetic nerves in patients with CKD via luminal delivery of radiofrequency energy therefore appears to be a valid therapeutic option for blocking the cycle between renal sympathetic nervous hyperactivity and deterioration of kidney function.

Sympathetic denervation by thoracic and lumbar sympathectomy improved BPs and long-term outcomes and supported the physiological basis for RDN. On the contrary, the results of percutaneous catheter–based denervation in patients without CKD have been less definitive. While Symplicity HTN-1 and HTN-2 showed superiority of RDN, the results of Symplicity HTN-3 and the Oslo RDN trial showed no advantage of RDN in BP control. In CKD patients, smaller observational studies by Ott et al and Hering et al have shown benefit with office BP and improvement in GFR post procedure. This is the first study to our knowledge to evaluate central pressures post RDN. This study aims to address the knowledge gap that exists regarding differential central and brachial pressures post RDN and will provide commentary on the stiffness of the conduit vessels.

The main focus of our study is to determine the differential change between central and peripheral BPs at 6 months and at different intervals for 2 years. From a pathophysiologic viewpoint, it is the aortic and not the brachial pressure...
that is “seen” by the heart and the coronary and cerebral arteries, which are the 3 specific sites where the main clinical events occur. It is the aortic systolic pressure that the left ventricle encounters during systole (afterload). Furthermore, the aortic pressure during diastole is a determinant of coronary perfusion. The technique for measuring the aortic central BP noninvasively via radial tonometry, along with the synthesis of an aortic pressure waveform, is reproducible, validated, and is regarded as a reference standard. However, it requires additional time and a basic level of operator skill. Several epidemiological studies have shown that tonometry-derived central BP is superior to brachial pressures in predicting cardiovascular outcomes.

Further to central pressures, we intend to measure pulse wave velocities at baseline and at different time points post RDN, as arterial stiffness has been associated with adverse clinical outcomes. Townsend recently published data from the CRIC study that demonstrated that among patients with CKD, CF-PWV is much greater (approximately 2 m/s higher) in the presence of diabetes and increases in tandem with the reduction of GFR (with each 10 mL/min per 1.73 m² decline in GFR being independently associated with an approximate 0.23-m/s increase in CF-PWV). It was therefore no surprise that higher CF-PWVs were associated with faster

| Table 3. Demographic Data and Results of Baseline Parameters (N = 26). |
|-------------|-----------------|-----------|
| Baseline characteristics | n | Mean | SD |
| Age, y | 26 | 62.9 | 12.2 |
| Height, cm | 26 | 173.0 | 9.4 |
| Weight, kg | 26 | 100.8 | 22.5 |
| BMI | 26 | 33.5 | 6.0 |
| Waist circumference, cm | 24 | 114.6 | 14.6 |
| Office BP Tru, mm Hg | 26 | 154.5/77.7 | 13.9/15.5 |
| Ambulatory 12 h day, mm Hg | 26 | 151.9/70.6 | 15.5/13.0 |
| Ambulatory 12 h night, mm Hg | 26 | 140.1/64.8 | 14.9/12.6 |
| Central blood pressure, mm Hg | 25 | 128.6/78.1 | 22.3/15.6 |
| Augmentation pressure, mm Hg | 25 | 12.5 | 11.5 |
| Central pulse pressure, mm Hg | 25 | 52.0 | 25.6 |
| Pulse wave velocity, m/s | 21 | 13.7 | 13.4 |
| 24-h urine protein, g/day | 24 | 1.4 | 2.0 |
| Creatinine, µmol/L | 26 | 176.5 | 65.4 |
| Albumin/creatinine ratio, mg/mmol | 25 | 97.3 | 156.2 |
| eGFR (MDRD, mL/min per 1.73 m²) | 26 | 3.70 | 12.3 |
| Urea, mmol/L | 26 | 12.8 | 6.8 |
| Fasting insulin, pmol/L | 13 | 175.8 | 131.3 |
| Fasting glucose, mmol/L | 23 | 7.7 | 2.9 |
| End diastolic volume, mL/m² | 26 | 108.2 | 24.6 |
| End systolic volume, mL/m² | 24 | 40.6 | 15.9 |
| Left atrial volume, mL/m² | 24 | 96.3 | 30.5 |
| Hypertensive medications, n | 26 | 4.9 | 1.1 |
| Stage 3 CKD | 18 | | |
| Stage 4 CKD | 8 | | |

Note. BMI = body mass index; eGFR = estimated glomerular filtration rate; MDRD = modified diet in renal disease; CKD = chronic kidney disease.

| Table 4. Breakdown by Medication Class. |
|---------------------------------------|
| Medications | Mean dose/d, mg | CKD stage 3 (n = 18) | CKD stage 4 (n = 8) |
|---------------------------------------|
| Aldosterone antagonist | | | |
| Spironolactone | 50 | 6 | 0 |
| ACE inhibitors | | | |
| Perindopril | 8 | 7 | 4 |
| Quinapril | 40 | 0 | 1 |
| Ramipril | 10 | 1 | 0 |
| Angiotensin receptor blockers | | | |
| Irbesartan | 300 | 3 | 2 |
| Valsartan | 320 | 2 | 0 |
| Candesartan | 32 | 1 | 3 |
| Olmesartan | 40 | 1 | 1 |
| Telmisartan | 80 | 2 | 0 |
| Losartan | 100 | 1 | 0 |
| Thiazide diuretics | | | |
| Indapamide | 2.5 | 6 | 2 |
| Hydrochlorothiazide | 37.5 | 6 | 2 |
| Metolazone | 2.5 | 1 | 0 |
| Loop diuretics: | | | |
| furosemide | | | |
| Beta-blockers | | | |
| Metoprolol | 100 | 7 | 3 |
| Propranolol | 40 | 0 | 1 |
| Vasodilators | | | |
| Minoxidil | 7.5 | 4 | 0 |
| Hydralazine | 400 | 5 | 5 |
| Dihydropyridine Ca²⁺ blockers | | | |
| Nifedipine | 90 | 4 | 0 |
| Amlodipine | 10 | 9 | 5 |
| Nondihydropyridine Ca²⁺ blocker: diltiazem | | | |
| Alpha blocker | | | |
| Doxazosin | 16 | 7 | 1 |
| Centrally acting medications | | | |
| Clonidine | 0.6 | 5 | 3 |
| Alpha methyl dopa | 750 | 0 | 2 |

Note. CKD = chronic kidney disease; ACE = angiotensin converting enzyme.

| Table 5. Number of Medications by CKD Stage at Baseline. |
|---------------------------------------|
| Number of medications | Stage 3 CKD (n = 18) | Stage 4 CKD (n = 8) |
|---------------------------------------|
| 4 | 10 | 3 |
| 5 | 5 | 2 |
| 6 | 2 | 1 |
| 7 | 1 | 1 |
| 8 | 0 | 1 |

Note. CKD = chronic kidney disease.
progression of renal dysfunction. CF-PWV was also independently correlated with 24-hour protein excretion, particularly among participants with diabetes. The impact of PWV post RDN and its relationship with tonometrically derived central BPs have not yet been studied across the spectrum of CKD. We intend to address this knowledge gap.

Finally, we intend to assess the relationship between cardiac parameters and RDN. Left ventricular hypertrophy (LVH) and cardiac fibrosis are consequences of structural impairment of the left ventricle and are associated with cardiovascular morbidity and mortality.40,41 CKD and hypertension both independently increase the risk of heart failure.40,41 Rationally, regression of LVH has been shown to improve cardiovascular outcomes, independent of other risk factors.1,42 There is a paucity of studies addressing the impact of RDN on left ventricular mass in patients with CKD. We intend to address this gap. A detailed analysis of cardiac parameters will also be undertaken. We also intend to add to the existing literature regarding renal outcomes specifically, as well as glucose metabolism.

We expect to see a selective improvement in central BPs, in relation to the peripheral and ambulatory BPs. We hope to see stabilization in eGFR and a reduction in proteinuria.

The limitations of the study include lack of a control group, regression to mean of the treatment group, and given the small sample size, loss of patients to follow-up might influence the readings. Furthermore, we will not have the required technology to measure decrease in the renal sympathetic nerve activity by measuring renal norepinephrine spillover. The last limitation is critical, as with the first-generation catheters, the extent of circumferential ablation has been difficult to determine and suboptimal denervation has been reported.

This study is, to the best of our knowledge, the first to include a measure of central BP to assess the efficacy of RDN in controlling BP in patients with stage 3 and 4 CKD. Furthermore, it will contribute to the limited literature about the impact of RDN on LVH and will provide evidence for the relationship between PWV and central BP post RDN.

If we were to identify a relative decline in central BPs in comparison with brachial pressures, we hope it sets the stage for larger randomized controlled trials.

Ethics Approval and Consent to Participate
This study was approved by the Regina Qu’Appelle Health Region Research Ethics Board (REB-12-73). Informed consent was obtained from all participants before enrolling them into the study.

Consent for Publication
All authors read and approved the final version of this manuscript.

Availability of Data and Materials
The raw data from this study cannot be made publicly available in order to protect participant confidentiality, as per the requirements of the RQHR Research Ethics Board.

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Author Contributions
B.P. conceived the study. B.P., K.G., P.D., and J.R.S. designed the study procedures. B.P. led the drafting of the manuscript. All authors contributed to and approved the final version of the manuscript.

Declaration of Conflicting Interests
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