



ORIGINAL ARTICLE

Renal denervation using carbon dioxide renal angiography in patients with uncontrolled hypertension and moderate to severe chronic kidney disease

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Abstract

Background: Chronic kidney disease (CKD) is the most common cause of secondary hypertension. More than half of the patients have uncontrolled hypertension ($\geq 140/90$ mmHg on three or more antihypertensive agents at optimum doses). Renal sympathetic denervation (RSDN) has been shown to reduce blood pressure (BP) in patients with resistant hypertension. Although patients with CKD have high sympathetic drive, all major clinical trials have excluded patients with estimated glomerular filtration rates (eGFRs) <45 mL/min/1.73m² for risk of contrast-induced nephropathy.

Methods: In this pilot study, carbon dioxide (CO₂) was used as the sole contrast agent to carry out renal angiography and RSDN in patients with moderate to severe CKD (eGFR 15–44 mL/min/1.73m²) and uncontrolled hypertension.

Results: Eleven patients (eight males) underwent RSDN. The median age was 57 years [interquartile range (IQR) 49–66]. The median number of antihypertensives being taken at baseline was 4 (IQR 3–4). No statistically significant difference was observed in serum creatinine in the serial follow-ups until at 6 months [median difference 0.25 mg/dL (IQR 0.09–0.53); $P=0.008$]. There was a non-significant reduction in median clinic BP from baseline to 6 months [–14 mmHg (IQR –24–5)] and a significant increase in daytime ambulatory systolic BP [7 mmHg (IQR –2–12); $P=0.045$]. A trend towards a serial reduction in albuminuria was observed. Procedure-related complications included a groin haematoma ($n=1$) and reported flank ($n=1$) and groin pain ($n=1$).

Conclusions: This pilot study shows that CO₂ renal angiography can be used to perform RSDN in patients with significant renal impairment and may lead to associated improvements in clinic BP and albuminuria.

Key words: carbon dioxide angiography, chronic kidney disease (CKD), contrast nephropathy, renal sympathetic denervation, uncontrolled hypertension

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Background

Hypertension is a risk factor for cardiovascular disease and chronic kidney disease (CKD). If it remains uncontrolled it can lead to rapid progression of CKD and is a leading cause of end-stage renal disease (ESRD). On the other hand, CKD itself can exacerbate hypertension, often necessitating the use of a combination of antihypertensive drugs of different classes to bring elevated blood pressure (BP) under control. Compared with people without CKD, the prevalence of treatment-resistant hypertension (TRH) is reported to be twice as high in patients with CKD. In the 3612 Chronic Renal Insufficiency Cohort study participants with CKD, 42% had apparent TRH [1].

Patients with CKD have a much higher risk of cardiovascular disease when compared with patients without CKD; meta-analyses show impaired renal function to be an independent risk factor for cardiovascular disease [2]. Vascular calcifications are more pronounced in CKD and may be partly responsible for the excess cardiovascular morbidity and mortality observed in CKD patients [3]. Moreover, improvement in BP control is known to slow the decline of renal function in patients with CKD [4].

The pathophysiology of hypertension in CKD is multifactorial, with sodium retention and excessive activation of the renin-angiotensin system (RAS) being the most important. Symmetric renal involvement is important for the uncontrolled progression of the RAS because if a single kidney is affected, the other one compensates [5]. CKD is the perfect example of symmetric involvement. The sympathetic nervous system is also overactive and has been implicated to play role in the progression of CKD [6]. In ESRD, sympathetic nerve activity is substantially increased and elevated noradrenaline plasma levels have been linked with poor cardiovascular outcomes [7, 8]. Recently, procedure-based approaches have been investigated in patients with TRH to achieve BP control. Percutaneous catheter-based radiofrequency ablation of afferent and efferent sympathetic nerves of renal arteries is one such technique and is the most widely researched to date. It is purported to address certain interorgan crosstalk pathways that may be upregulated in non-atherosclerotic nephrogenic hypertension [9]. Due to the risk of contrast-induced nephropathy associated with the use of iodinated contrast materials, patients with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m² have been excluded from major trials of renal sympathetic denervation (RSDN). Only a handful of pilot studies thus far have investigated the use of RSDN in patients with moderate to severe eGFR (15–44 mL/min/1.73 m²) [10–14].

Carbon dioxide (CO₂) angiography is a well-recognized and safe alternative to iodine-based contrast material in patients with CKD or iodinated contrast agent allergy [15–17]. A negative contrast image with digital subtraction angiography is produced when the directly injected CO₂ displaces blood intravascularly. CO₂ angiography has been shown to prevent deterioration of renal function in patients with known renal impairment and has been successfully used in such patients for various diagnostic and therapeutic indications [10, 16–18].

In this pilot study, we examined the safety and efficacy of RSDN performed using CO₂ as the sole contrast agent in patients with significant renal impairment (eGFR 15–45 mL/min/1.73 m²).

Materials and methods

All patients 18–75 years of age were recruited from screening patients attending the outpatient nephrology and specialist

hypertension clinic at Heart of England NHS Foundation Trust in Birmingham. Patients were screened based on their outpatient clinic systolic BP, number of antihypertensive medications used and outpatient eGFR. Only patients with TRH, outpatient clinic systolic BP ≥ 140 mmHg while taking at least three antihypertensive medications and an eGFR between 15 and 44 mL/min/1.73 m² were selected for RSDN. Patients with an eGFR ≥ 45 mL/min/1.73 m² or <15 mL/min/1.73 m², diagnosis of type 1 diabetes mellitus, substantial stenotic valvular heart disease, pregnancy or planned pregnancy during the study and a history of myocardial infarction, unstable angina or cerebrovascular accident in the previous 6 months were excluded.

At the baseline visit, clinic BP was assessed in a standardized manner following the British Hypertension Society guidelines. Briefly, an average of at least two systolic BPs was used to confirm systolic hypertension. BP was taken with patients resting in a chair for 5 min and a 1-min interval between the end of one measurement and the start of the next measurement. All patients had baseline serum electrolytes, urea and creatinine, urinary albumin:creatinine ratio (ACR) and 24-h ambulatory BP measured. Serum creatinine was used to calculate eGFR using the Modification of Diet in Renal Disease (MDRD) equation to confirm that the baseline eGFR met the inclusion criteria. Anatomical suitability for RSDN was confirmed using non-contrast computed tomography (CT) reconstruction of renal arteries. Baseline data recorded include basic demographics, comorbidities and the number and names of antihypertensive medications.

Renal angiography was performed utilizing CO₂ as the sole contrast agent to confirm the renal anatomy prior to performing RSDN [19]. The procedure was carried out in all patients by two interventional radiologists, both with considerable experience in both CO₂ angiography and RSDN. RSDN was performed using either the single or multi-electrode radiofrequency Symplicity catheter (Medtronic, Mountain View, CA, USA) in all patients as described previously [20]. The procedure was carried out as a day case.

All patients were followed up at 7 days and 1, 3 and 6 months post-procedure to assess renal function and BP response and to monitor any potential procedural complications. At each visit a medication review, clinic BP and urinary ACR was carried out. A repeat ambulatory BP monitoring (ABPM) was performed at the 6-month follow-up visit to assess clinical response. There was no a priori restriction on changes to antihypertensive medications after RSDN.

Statistical analysis was performed using SPSS Statistics 22 (IBM, Armonk, NY, USA). The Shapiro-Wilk test was applied to test for normality of distribution of data. Median and interquartile range (IQR) have been used to report the non-normally distributed parameters. Related-samples Wilcoxon signed rank test was used to compare baseline creatinine, eGFR and clinic and ABPM readings with follow-up readings to detect any statistically significant changes. A two-sided P-value <0.05 was considered statistically significant. Written informed consent was obtained from all patients. The study was reviewed by the local research ethics committee (NRES Committee West Midlands, Edgbaston) and granted approval. The study was registered with ClinicalTrials.gov (NCT02863510).

Results

Eleven patients with CKD underwent RSDN. The baseline characteristics for the patients are summarized in Table 1. There were eight (72.7%) men and the median age was 57 years (IQR

Table 1. Baseline characteristics

Characteristics	Results
Age (years), median (IQR)	57.0 (49.0–66.0)
Gender, n (%)	
Male	8 (72.7)
Female	3 (27.3)
Ethnicity, n (%)	
Caucasian	7 (63.6)
Afro-Caribbean	2 (18.2)
Asian	2 (18.2)
BMI (kg/m ²), median (IQR)	32.8 (25.7–38.7)
Comorbidities, n (%)	
Type 2 diabetes mellitus	5 (45.5)
Cerebrovascular disease	2 (18.2)
Antihypertensive medication, n (%)	
ACE inhibitor	4 (36.4)
Angiotensin receptor blocker	5 (45.5)
Aldosterone antagonist	1 (9.1)
α -adrenergic blocker	5 (45.5)
β -blocker	4 (36.4)
Calcium channel blocker	11 (100)
Loop diuretic	5 (45.5)
Thiazide/thiazide-like diuretic	2 (18.2)

49–66). Seven (63.6%) patients were Caucasian, two (18.2%) African Caribbean and two (18.2%) South Asian.

The median number of antihypertensive medications taken by the study population at baseline was 4 (IQR 3–4). All patients were taking a calcium channel blocker (CCB), nine (81.8%) were taking either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker and seven (63.6%) were taking at least one diuretic (loop, thiazide/thiazide-like or potassium-sparing). At 6 months, most patients [$n=9$ (81.8%)] were taking the same number of antihypertensive medications and two patients had at least one antihypertensive medication stopped.

Table 2 summarizes the results of renal function, albuminuria and BP parameters at the baseline and follow-up visits. The baseline median serum creatinine was 2.26 mg/dL (IQR 1.66–3.47) with a median eGFR of 29 mL/min/1.73 m² (IQR 18–41). The median of differences between serum creatinine at baseline and 6 months post-RSDN was 0.25 mg/dL (IQR 0.09–0.53), which was statistically significant ($P=0.008$). The median of differences between serum creatinine at baseline and the earlier follow-up visits were not statistically significant. Similarly, the median of differences between eGFR at baseline and the 6-month follow-up visit was statistically significant with a median difference of -4 mL/min/1.73 m² (IQR -11 to -1); $P=0.012$. The median albuminuria, measured as urine ACR, of the study population showed an improving trend (Table 2); however, the median of differences in ACR at the baseline and follow-up visits was not statistically significant.

At baseline the median clinic BP was 170 mmHg (IQR 158–180) systolic and 89 mmHg (IQR 74–99) diastolic. The median clinic systolic BP was lower at 6 months but the median of the difference, -14 mmHg (IQR -24 – 5), was not statistically significant. The apparent reduction in the median clinic BP was not accompanied by a corresponding reduction in ambulatory BP parameters, where the median systolic BP was higher at 6 months overall and when separated into day and night (Table 2). Statistically, however, the median of the difference was only found to be significant for daytime systolic BP, which was 7 mmHg (IQR -2 – 12), $P=0.045$. The change in all other ambulatory BPs was not statistically significant.

The mean total number of radiofrequency ablations delivered during the RSDN procedure was 11.3 (SD 2.4). There were no minor atherosclerotic findings, which could have limited the radiofrequency ablation probe contact with the true wall of the artery, in any of the patients who underwent RSDN. Patients with significant renal artery stenosis due to any atherosclerotic lesions were excluded at the screening stage by CT renal angiogram. Procedure-related complications observed included one patient with flank pain that was managed with simple analgesics, another patient with groin pain that did not require any analgesics and another patient with a groin haematoma requiring overnight admission but no intervention. Two patients progressed to end-stage renal disease requiring dialysis; one patient commenced on peritoneal dialysis at 6 months and 10 days after the procedure and the other required haemodialysis at 5 months and 27 days.

Discussion

This is the first reported study to perform RSDN with the sole use of CO₂ as a contrast agent. This pilot study shows that CO₂ renal angiography can be used safely to perform RSDN in patients with significant renal impairment where there is a risk of contrast-induced nephropathy commonly associated with iodinated contrast agents. We showed that at 7 days after the procedure there was no significant change in the median serum creatinine and eGFR. There was no significant improvement in BP control, but there was a trend towards an improvement in albuminuria at 6 months.

The primary aim of this study was whether the use of iodinated contrast agents could be avoided in patients with significant renal impairment and uncontrolled hypertension to successfully perform RSDN using CO₂ angiography. CO₂ angiography is not completely risk free; however, the adverse events associated with CO₂ angiography are uncommon and are usually limited to the organs being injected [21]. In particular, a vapour lock phenomena can occur where the large doses of CO₂ can cause obstruction to blood flow and hence ischaemia downstream if unresolved. Contamination of CO₂ with room air can result in air embolus. Neurotoxicity, pain, nausea, vomiting and an urge to defecate are among the other possible complications. The risk of these rare complications can be reduced through understanding the unique properties of CO₂ and making sure appropriate precautions are observed when preparing and administering it [21, 22]. No patients in this study cohort suffered any adverse events that could be attributable to CO₂ angiography and the only observed adverse events were secondary to puncture site complications, which are common to any percutaneous angiographic procedure. CO₂ with digital subtraction angiography allowed adequate placement of the RSDN catheter to allow radiofrequency ablation, which was confirmed by the impedance drops observed for each ablation.

It is well known that the risk of developing contrast-induced nephropathy is associated with the volume of contrast used. CO₂ renal artery angiography has been used to reduce but not completely eliminate the amount of iodinated contrast given when carrying out intravascular procedures in individuals with significant renal function impairment [10]. In our study, the use of iodinated contrast agents has been wholly replaced by CO₂, completely negating the risk of developing contrast-induced nephropathy. There are no reported studies comparing the safety of CO₂ versus radio-iodine contrast with pre-procedural hydration in patients undergoing RSDN. However, a recent

Table 2. Study parameters at baseline and serial follow-up

Parameter	Baseline (n = 11)	Week 1 (n = 11)	Week 4 (n = 11)	Week 12 (n = 10)	Week 26 (n = 11)
Creatinine (mg/dL)	2.26 (1.66–3.47)	2.02 (1.91–3.45)	2.27 (1.75–3.35)	2.21 (1.75–4.07)	2.24 (1.71–3.81)
eGFR (mL/min/1.73m ²)	29 (18–41)	33 (19–36)	29 (20–38)	28 (16–38)	25 (17–34)
Urine ACR (mg/mmol)	203 (63–412)	231 (55–283)	136 (23–386)	146 (15–382)	137 (6–370)
Clinic SBP (mmHg)	170 (158–180)	169 (158–175)	157 (135–170)	159 (152–177)	164 (149–174)
Clinic DBP (mmHg)	89 (75–95)	87 (78–87)	83 (74–91)	86 (71–103)	86 (74–94)
24-h ambulatory SBP (mmHg)	155 (149–161)				161 (149–168)
24-h ambulatory DBP (mmHg)	86 (73–94)				86 (84–101)
Day ambulatory SBP (mmHg)	159 (149–164)				163 (152–167)
Day ambulatory DBP (mmHg)	89 (75–95)				88 (84–100)
Night ambulatory SBP (mmHg)	147 (141–163)				155 (144–169)
Night ambulatory DBP (mmHg)	82 (73–86)				83 (74–90)

All values are given as median (IQR). Conversion factor for creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$. DBP, diastolic blood pressure; SBP, systolic blood pressure.

meta-analysis comparing the incidence of acute kidney injury with CO₂ versus iodinated contrast media reported that CO₂ use is associated with a modestly reduced rate of AKI despite the patients with iodinated contrast media being optimized with pre-hydration [23]. Furthermore, a recent randomized controlled trial of prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy found no prophylaxis to be non-inferior and cost saving in preventing contrast-induced nephropathy compared with intravenous hydration [24]. Patients with CKD are at a higher risk of developing contrast nephropathy and any measures that help reduce the risk of contrast-induced nephropathy should be considered for patients undergoing interventional procedures.

Unlike other studies of RSDN [25, 26], only a modest reduction in clinic systolic BP was observed 6 months after RSDN. Conversely, ambulatory systolic BP readings were higher at 6 months. The most likely explanation for this observed rise in ambulatory systolic BP could be progression of CKD and the consequent sodium and water retention. In nine (82%) of the patients serum creatinine was higher, and accordingly a lower eGFR, at 6 months after RSDN when compared with baseline values.

The median serum creatinine at 7 days after RSDN showed no significant decline and, if anything, a trend towards improved creatinine. However, by 6 months the decline in kidney function was statistically significant, suggesting a continued progression of CKD. Given the small number of patients in the study, a detailed analysis of whether RSDN affected the rate of decline in kidney function was not performed. A recent study in 46 patients with CKD (baseline eGFR ≤ 60 mL/min/1.73m²) has provided some evidence that RSDN can slow further deterioration of renal function irrespective of BP-lowering effects [14]. These results build on similar findings reported by others [13, 27].

There is some evidence to suggest that RSDN may have a beneficial effect in reducing urinary albumin excretion that may be unrelated to improvement in BP control [27]. In this study, a non-significant trend towards improved urinary excretion appeared at 4 weeks post-procedure and was maintained at subsequent follow-ups until 6 months.

Conclusions

This is the first study of RSDN in patients with moderate to severe CKD that has avoided the use of traditional iodinated

contrast media altogether by replacing it with CO₂ angiography. However, this was a pilot single-arm study with no sham comparator and was not powered to detect a meaningful reduction in clinic or ambulatory BPs. The results have shown that there were no adverse procedural events associated with CO₂ angiography and any future trials of RSDN should not exclude patients with moderate to severe CKD on the basis of the risk of contrast-induced nephropathy associated with the conventional methods. Further research, with a larger study population, is needed to investigate whether RSDN can achieve substantial reductions in BP and albuminuria and have any effect on the rate of decline of CKD.

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Conflict of interest statement

None declared.

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