Renal Denervation

A Treatment for Hypertension and Chronic Kidney Disease

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Renal sympathetic overactivity contributes to the development and progression of hypertension and chronic kidney disease (CKD).[1–3] Conversely, progressive decline in renal function can exacerbate sympathetic overactivity.[4,5] Renal denervation (RDN) in experimental models of hypertension and CKD has been shown to reduce blood pressure (BP) and improve renal function, which laid the foundation for the introduction of RDN to clinical practice.[6] Although the efficacy of RDN as a treatment for hypertension has been disputed, the majority of data suggest that there is a place for RDN in the clinic and trials are ongoing (Table).[7–16]

Early Trials in Humans-Surgical Sympathectomy

In the early 1940s, therapeutic interventions for malignant hypertension were limited. Radical sympathectomy was trialled at this time and involved sectioning both the splanchnic nerve and thoracic dorsal sympathetic chain thereby interrupting sympathetic outflow resulting in decreased peripheral resistance and lowering of BP.[27–29] Follow-up studies in hypertensive patients that underwent sympathectomy demonstrated that BP was lowered without deterioration of renal function, and these outcomes were maintained in the long-term.[27–31] Despite the generally favorable results of sympathectomy, this highly invasive procedure was associated with significant side effects including postural-hypotension, hyperhidrosis, sensory and sexual dysfunction, and depression.[27,32,33] For these reasons, sympathectomy was abandoned, after the advent of antihypertensive drugs. However, assuming that interruption of the splanchnic nerve and thoracodorsal sympathectomy encompassed the renal sympathetic nerves, these studies provided proof-in-principle evidence that RDN may be an effective strategy for the treatment of hypertension and CKD if the renal nerves could be directly targeted.

Radiofrequency Catheter-Based RDN

The invention of a minimally invasive catheter-based technology to selectively destroy the renal nerves using radiofrequency energy reignited interest in exploring RDN as a therapy for hypertension and CKD in humans. This technique takes advantage of the location of the renal afferent and efferent nerves, embedded within the renal artery wall and directly adjacent to the wall of the renal artery, to destroy the nerves without damaging the arterial wall.[7] The catheter is floated into each renal artery in turn via standard femoral access, and multiple ablations (5–6 ablations) are applied circumferentially (longitudinal and rotational ablation points) within each artery to ensure adequate RDN.[34] In a study in 7 domestic swine, radiofrequency catheter RDN (≈4–5 ablations) was performed on 1 renal artery with the remaining renal artery acting as a control.[35] At the 6-month follow-up, 10% to 25% greater fibrosis, but no evidence of renal artery stenosis or thrombosis, was observed in the denervated compared with the nondenervated artery, indicating procedural safety.[35] The procedure was also demonstrated to reduce renal noradrenaline content by ≈85% in the kidney that underwent RDN, indicating a significant degree of destruction of renal nerves.[7]

Radiofrequency Catheter-Based RDN: Early Clinical Trials

In the first proof-of-principle study in humans (n=45) using the Symplicity catheter, radiofrequency RDN was demonstrated to reduce office systolic BP at 1 (≈14 mm Hg) and 12 (≈27 mm Hg) months after RDN.[7] This study also examined the effectiveness of the procedure and demonstrated in 10 patients that catheter RDN resulted in a ≈47% reduction in renal noradrenaline spillover at 15 to 30 days after procedure.[7] After this, SYMPLICITY HTN-1 recruited additional patients and demonstrated a sustained reduction in BP at 36-month post-RDN (Table).[17] In 12 patients, 24-hour ambulatory systolic BP was available at longer than 30 days after RDN, and in this subgroup, reduction in office systolic BP (≈32 mm Hg) and 24-hour systolic ambulatory BP (≈14 mm Hg) was observed.[7] Although the change in office BP correlated strongly with change in 24-hour ambulatory BP, the greater fall in office BP suggested a white coat effect and indicates that office BP may have overestimated the fall.[7,17] It should also be noted that in this and the next trials of RDN that subjects were maintained on their medications. Because of difficulties in documenting adherence to medication, in that people falsely report taking their medication or at study entry suddenly start taking their medication regularly, both these factors can confound interpretation of the data.[13]

SYMPLICITY HTN-2 was a randomized trial in which patients underwent catheter RDN (n=52) or were maintained on medication alone (control, n=54). At the 6-month follow-up,

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Table. Change in BP in Response to Catheter Ablation RDN in Major Clinical Trials and Studies in Large Animal Models of Hypertension

Human Trials	Experimental Design	Catheter Type, Ablations Per Renal Artery	BP Primary End Point, Duration	Change in Office SBP/DBP
Symplicity HTN-1,[7,17] 2009	Open-labeled	Symplicity flex	Office BP	RDN (n=88) −32/−14 mm Hg*
	No control	4 ablations (max 6)	36 mo	
Symplicity HTN-2,[18] 2010	RCT	Symplicity flex	Office BP	RDN (n=49) −32/−12 mm Hg*†
	Control-drug alone	4 ablations (max 6)	6 mo	Drug alone (n=51) +1/0 mm Hg
	No change in medication			
Symplicity HTN-3,[9] 2014	RCT	Symplicity flex	Office BP	RDN (n=353) −14/−7 mm Hg*
	Single blind, sham control	2 ablations (max 6)	6 mo	Sham (n=171) −12/−5 mm Hg*
	No change in medication			
Oslo RDN,[19] 2014	RCT	Symplicity flex	Office systolic BP	RDN (n=10) −8/−2 mm Hg
	Double-blind, sham control	8 ablations (range 6–11)	6 mo	Control (n=10) −28/−11 mm Hg*
	Control-SSHAT			
DENERHTN,[10,20] 2015	RCT	Symplicity flex	Day-time SBP	RDN (n=53) −15/−9 mm Hg*†
	Single blind, sham control	5.5 ablations (max 6)	6 mo	Control (n=53) −9/ 6 mm Hg*
	Control-SSHAT			
PRAGUE-15,[21,22] 2015	RCT	Symplicity flex	Office SBP	RDN (n=54) −12/−7 mm Hg*
	Single blind, sham control	5 ablations (max 6)	6 mo	Sham (n=52) −14/−7 mm Hg*
	No change in medication			
RESET,[23] 2016	RCT	Symplicity flex	24-h systolic AMBP	RDN (n=33) −4/−2 mm Hg
	Open-label, sham control	5.5 ablations (max 6)	6 mo	Sham (n=36) −2/3 mm Hg
	Intensified drug treatment			
INSPIRED,[12] 2017	RCT	EnligHTN; multielectrode	Systolic AMBP	RDN (n=9) −22/−13 mm Hg*†
	Control-drug alone	11 ablations	6 mo	Drug alone (n=6) +1/0 mm Hg
	No change in medication			
SPYRAL HTN OFF-MED,[14] 2018	RCT	Spyral; multielectrode	AMBP	RDN (n=37) −10/−5 mm Hg*†
	Single blind, sham control	20 ablations including proximal branches	3 mo	Sham (n=41) −2/0 mm Hg
	Off medication			
SPYRAL HTN-ON-MED,[16] 2018	RCT	Spyral; multielectrode	AMBP	RDN (n=40) −10/−5 mm Hg*†
	Single blind, sham control	20 ablations including proximal branches	6 mo	Sham (n=42) −3/−2 mm Hg
	On medication			
Radiance-HTN SOLO,[15] 2018	RCT	Paradise; multielectrode	Day-time AMBP	RDN (n=74) −11/−6 mm Hg*†
	Single blind, sham control	5.4 emissions	2 mo	Sham (n=72) −4/−1 mm Hg
	On medication			
Large animal studies				
Dog,[24] 2014	Obesity-induced hypertension	EnligHTN; multielectrode	Arterial catheter (18 h)	RDN (n=6) −24/−2 mm Hg*
	No sham control	8 ablations	2 mo	
Pig,[25] 2016	Spontaneous hypertension	Sniper	Tail-cuff	RDN (n=7) −73/−55 mm Hg*†
	Genetic inbreed	8 ablations	3 mol/L	Sham (n=7) +5/+5 mm Hg
	Sham control			
Sheep,[26] 2017	Hypertensive CKD	Symplicity flex	Arterial catheter (72 h)	CKD-RDN (n=7) −7/−5 mm Hg*†
	Induced by fetal uninephrectomy	6 ablations	5 mo	CKD+intact (n=7) +2/+3 mm Hg
	Sham and normotensive control groups			Control+RDN (n=8) +2/+3 mm Hg
				Control+intact (n=6) +4/+1 mm Hg

AMBP indicates 24-h ambulatory BP; BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic BP; RCT, randomized controlled trial; RDN, renal denervation; SBP, systolic BP; and SSHAT, standardized stepped-care antihypertensive treatment.

*Significantly different to baseline.

†Significantly different to control.

patients who underwent RDN, had a reduction in office BP (−32/−12 mm Hg) compared with baseline, whereas in the control group, BP did not differ from baseline (Table).[8] However, ≈35% of the control group also had a decrease in office systolic BP of >10 mm Hg, possibly related to change in medication.[8] At this time, patients in the control group were allowed to crossover and undergo RDN (n=37), 6 months after crossover, it was observed that office BP decreased in these patients (−26/−10 mm Hg). It was also noted that the reduction in BP in the patients who underwent RDN at the beginning of the study (initial RDN group) was sustained at 12-month follow-up. In both groups that underwent RDN (initial and crossover) the reduction in office BP was sustained at 36-month follow-up.[18] The primary safety end points in these trials were renal vascular complication or new-onset renal disease. Overall, the SYMPLICITY HTN-1 and HTN-2 trials suggested that radiofrequency catheter RDN was effective in reducing and sustaining reduction in BP in hypertensive patients and was relatively safe, without serious adverse events.[17,18] Although the sustained reductions in BP were remarkable, both HTN-1 and HTN-2 lacked a sham control group which meant that a placebo effect could not be discounted, and significant concerns were raised about drug adherence and compliance during the trials, which could have influenced outcomes.[13]

SYMPLICITY HTN-3 was a prospective, randomized, single-blind, sham-controlled trial conducted at 88 sites in the United States in patients with severe resistant hypertension undergoing either catheter-based RDN or a sham procedure (Table).[9] In this study, at 6 months after RDN, no difference in reduction in office systolic BP was observed between the RDN (≈14 mm Hg) and sham (≈11 mm Hg) groups (Table).[9] The fall in 24-hour ambulatory systolic BP at 6 months after procedure from baseline was also similar between the RDN (≈7 mm Hg) and sham (≈5 mm Hg) groups.[9] At the 12-month follow-up, the reduction in office BP was similar in the RDN and sham groups,[36] though post hoc analysis suggested RDN might be effective in lowering BP in specific subpopulations of hypertensive patients.[37] However, considerable procedural issues were identified in HTN-3. For successful denervation, it was (at that time) recommended that 4 to 6 ablations be delivered to each renal artery.[37] In HTN-1 and HTN-2 an average of 4 ablations, with a maximum of 6, were performed (Table).[7,8] Post hoc analysis of procedural data for HTN-3 demonstrated that the majority of patients had only 1 or no ablation notches (acute vessel wall edema after radiofrequency ablation) suggesting inadequate denervation.[37,38] There were 535 patients enrolled in the trial and 111 operators (the majority untrained) performed 364 RDN procedures, therefore, the inexperience of the interventionists likely contributed to ineffective denervation in HTN-3.[2,9] Furthermore, no tests were undertaken to assess the degree of denervation achieved (eg, change in noradrenaline spillover). To date, SYMPLICITY HTN-3 remains the largest clinical trial of RDN, but its lack of efficacy is attributed almost entirely to procedural failure.[1,2,13] Recognition that multiple lesions were required to ensure effective RDN led to the development of multielectrode devices with the capability of performing multiple ablations simultaneously.

Other smaller trials have also produced conflicting results. In the RESET (n=69) double-blind sham-controlled trial, no effect of catheter RDN on BP in patients with resistant hypertension was reported (Table).[23] However, although evidence of successfully RDN (presence of ablation notches) was shown, it was conceded that the findings could have been affected by changes in medication during the trial.[23] In a study investigating the relationship between catheter RDN and drug compliance, removing the data of patients with poor drug compliance canceled the antihypertensive effect seen with RDN, suggesting that changes in drug protocol have a greater effect than catheter ablation.[39] In addition, some prospective trials demonstrated that although RDN reduced BP, drug therapy may be as effective or better than RDN. In the Oslo study, no significant reduction in 24-hour ambulatory systolic BP was observed at the 6-month follow-up in patients who underwent RDN, whereas BP (≈28 mm Hg) was reduced in patients randomized to receive adjusted drug treatment (Table).[19] Prague-15, an open-labeled, randomized, multicenter trial compared the effectiveness of RDN (n=52) with intensified antihypertensive therapy (n=54) in patients with true resistant hypertension and demonstrated similar reduction in 24-hour ambulatory systolic BP in patients from both groups (≈8 mm Hg) at 6-month follow-up (Table).[21] At the 12-month follow-up, it was demonstrated that the reduction in BP in the RDN and antihypertensive therapy groups were comparable, but addition of spironolactone to the antihypertensive group caused a greater decrease in 24-hour systolic BP (6 mm Hg in RDN versus 15 mm Hg in antihypertensive with spironolactone).[22] In DENERHTN, another open-labeled multicenter trial, the effect of RDN on 24-hour ambulatory BP in patients with resistant hypertension on standardized stepped-care antihypertensive treatment (SSHAT, n=48) were compared with patients on SSHAT alone (n=53). It was demonstrated that patients who underwent RDN and were maintained on SSHAT had ≈6 mm Hg greater decrease in BP at the 6-month follow-up compared with patients on SSHAT alone (Table).[20] Furthermore, when adherence to antihypertensive medication during the follow-up period was accounted for, RDN in combination with SSHAT still produced a greater reduction in ambulatory BP than SSHAT alone (Table).[10] Pilot data released from the INSPIRED randomized control trial using the newer multielectrode EnligHTN catheter, demonstrated that BP decreased more in the RDN group maintained on optimized drug therapy than drug therapy group alone (Table).[12] Although the majority of these studies suggest that RDN is effective in reducing BP in combination with drug therapy, these studies where in large part poorly controlled and thus the efficacy of catheter-based RDN remains to be substantiated.

Methods to Assess the Effectiveness of Catheter RDN Procedure

The shortcomings of HTN-3 placed the spotlight on a major challenge about the clinical application of catheter-based RDN, which is that there are no reliable methods to demonstrate effective destruction of the renal nerves at the time of procedure. In experimental studies in animals, renal tissue noradrenaline content has been used as a measure of effectiveness of the catheter ablation RDN procedure. In the spontaneously hypertensive rat, RDN performed by delivering radiofrequency energy directly over the renal artery, in contrast

to the intraluminal approach in humans, resulted in reductions in BP (≈20 mm Hg), plasma renin activity (≈34%), and renal tissue noradrenaline (≈50%) 12-week post-RDN compared with sham procedure.[40] In a canine model of obesity-induced hypertension, catheter RDN resulted in ≈42% less renal noradrenaline content 2 months after RDN compared with normotensive dogs.[24] Unfortunately, these studies did not determine renal noradrenaline content at an earlier time point, and thus it was not possible to differentiate between the extent of the denervation versus the possibility of nerve regrowth. In normotensive sheep, renal tissue noradrenaline content was reduced by ≈80% at 1-week,[41] ≈47% at 5.5-month, and ≈10% at 11-month post-RDN compared with sham-operated controls,[42] clearly indicating successful RDN and significant reinnervation after catheter-based RDN.

Although renal noradrenaline content is a useful indicator of denervation in experimental models, it is not feasible clinically. Other methods have been used in human studies to demonstrate the extent of nerve destruction. The most predictive being renal noradrenaline spillover, an index of renal sympathetic activity. To date renal noradrenaline spillover has only been measured in 10 patients showing ≈47% reduction post-RDN.[7] However, in this study renal noradrenaline spillover was determined several weeks after RDN surgery and therefore leaves unanswered questions about whether RDN was incomplete given the remaining level of noradrenaline spillover or if nerve regrowth had occurred in the intervening weeks. Investigation into other methods to evaluate the intra or acute postprocedural effectiveness of RDN in patients are ongoing. In terms of biochemical markers, brain-derived neurotrophic factor levels were shown to be decreased in patients 2 hours after catheter RDN.[43] A promising method to test the effectiveness of the RDN procedure intraoperatively is an examination of the cardiovascular and renal responses to electric stimulation of the renal nerves before and immediately after RDN. In normotensive sheep electrical stimulation of renal nerves increased mean arterial pressure (≈110%) and reduce renal blood flow (≈50%) but after radiofrequency catheter RDN these responses were abolished.[42] In dogs, electrical stimulation of renal nerves via a quadripolar open irrigation catheter before RDN increased systolic BP (≈24 mm Hg) and this increase in BP was attenuated immediately after RDN (≈2 mm Hg).[44] In contrast, renal nerve stimulation using the same procedure did not produce an increase in BP before RDN in pigs, suggesting this response may be species dependent.[45] However, renal nerve stimulation in patients with hypertension using the radiofrequency EnligHTN catheter has been demonstrated to increase systolic BP by ≈50 mm Hg, but immediately after RDN, this response was significantly attenuated (≈13 mm Hg).[46] Moreover, the decrease in 24-hour ambulatory BP at 4.5 months after RDN in patients with hypertension correlated strongly with the difference in BP response to renal nerve stimulation before and immediately after RDN.[47] This suggests that BP responses to renal nerve stimulation before RDN and immediately after RDN maybe a method to assess effectiveness of the procedure, to provide immediate feedback to the surgeon about the need for additional ablations. However, the degree to which the response to renal nerve stimulation needs to be attenuated to demonstrate effective RDN remains to be determined. In addition, the enhanced BP response to renal nerve stimulation before RDN may predict, which patients are likely to benefit the most from the RDN procedure.[47]

Regrowth of Renal Nerves and Return of Renal Nerve Function After RDN

Although we await information on long-term efficacy of RDN from sham-controlled clinical trials, the sustained reductions in BP up until 3 years after RDN, in the early SYMPLICITY trials were surprising, given evidence that both sympathetic efferent and sensory afferent renal nerves regrow after RDN.[42,48,49] In normotensive Sprague Dawley rats after RDN (unilateral surgical section, with or without application of phenol), immunolabeling for renal sympathetic nerves (tyrosine hydroxylase and neuropeptide Y) and sensory nerves (CGRP [calcitonin gene-related peptide] and substance P) were demonstrated to be similar to the contralateral innervated kidney at 12-week post-RDN suggesting complete restoration of nerve growth.[48,50] Interestingly, in the nondenervated kidney (used as the control), at 12 weeks after RDN, immunolabeling for tyrosine hydroxylase and CGRP had doubled suggesting either crosstalk between the kidneys or that an age-related increase in renal innervation had occurred.[50] This finding may explain why in hypertensive models unilateral, or partial, RDN is not effective for the treatment of hypertension.[51] Moreover, the method of denervation may affect nerve regrowth. For example, it has been shown that nerve regrowth was enhanced after RDN induced via freezing as compared with surgical section in the rat tail artery.[52] Interestingly, in this model it was also demonstrated that partial denervation (≈50%) was not sufficient to reduce vasoconstrictor responses to nerve stimulation.[53] This data suggests that there is a redundancy in sympathetic nerve response because activation of all nerves was not required to produce maximal physiological responses to nerve stimulation and indicates that the majority of renal nerves may need to be ablated to effectively reduce BP. There is a significant gap in knowledge about the extent of renal nerve regrowth after RDN and whether the nerves connect to the effectors cells (renin cells, vascular smooth muscle, and tubules) to produce normalized functional responses in terms of release of renin, vasoconstriction, and tubular sodium reabsorption.

Regrowth of renal nerves has also been examined in those studies that used radiofrequency catheter-based RDN via percutaneous access similar to that used in the clinic. In normotensive pigs, after unilateral radiofrequency nerve ablation, there was a trend for renal noradrenaline content to increase between 7 (≈88% reduction in noradrenaline) and 28 days (≈58%) after RDN, suggestive of reinnervation.[54] In normotensive sheep renal nerve regrowth and function were examined over an 11-month period after catheter-based RDN.[42] Immunolabeling for tyrosine hydroxylase and CGRP, and renal noradrenaline content were markedly reduced 1 week after RDN, but ≈20% to 60% return had occurred by 5.5 months, with evidence of further regrowth at 11-month post-RDN. Visualization of the renal nerves at 11-month post-RDN indicated that the renal nerves had penetrated to the glomerular arterioles.[42] The renal response to electrical stimulation of

renal nerves in anesthetized sheep was examined at 5.5 and 11 months after unilateral RDN. At 5.5-month post-RDN, the reduction in renal blood flow in response to electrical stimulation of the nerves was markedly attenuated, but by 11 months, the response was no longer different to controls with intact renal nerves.[42] These observations suggest that subsequent to RDN the kidney is reinnervated and neural control of renal function is restored in a normotensive setting in a large mammal, using the same RDN methodology as used in patients. These initial studies in animal models to determine the effectiveness of the catheter RDN procedure were limited to normotensive animals.[35,44] Coexistence of hypertension, which has been strongly associated with sympathetic overactivity and increased sympathetic innervation density (hence the rationale for RDN as a treatment for hypertension) may alter nerve regrowth.

There is no available histological evidence of regrowth of renal nerves after catheter-based RDN in humans. However, after renal transplant, anatomic regrowth of renal nerves has been demonstrated from as early as 28 days with abundant regrowth of nerves extending into interlobular arteries by 8-month postrenal transplant.[55] Moreover, Hansen et al[56] demonstrated that renal nerve function determined as reflex renal hemodynamic response to lower body negative pressure were present but markedly attenuated in subjects 6 to 8-week postrenal transplant compared with control subjects, with similar attenuation in responses observed in subjects that had a kidney transplanted for 25 months. Taken together this evidence suggests that the renal nerves undergo significant regrowth in humans after resection, but that the full functional response to renal nerve activation has not returned.

Thus, evidence clearly demonstrates that the kidney is reinnervated after RDN and that these nerves are functional. However, there is a lack of evidence to demonstrate whether this nerve regrowth and restoration of function is complete, particularly in the setting of hypertension. The presence of the nerves, as illustrated by immunostaining, does not provide information about nerve-effector connectivity or function. Nor, have studies convincingly demonstrated that the neural rewiring of the kidney has been finalized. Therefore, long-term studies in large animal models of hypertension are warranted to better examine the consequences of renal nerve regrowth and return of function on BP after RDN.

Consequences of RDN-Studies in an Ovine Model of Hypertensive CKD

It is also worth considering, given the pivotal role of the renal nerves in the maintenance of long-term BP homeostasis, whether patient who undergo RDN have a reduced ability to respond to physiological challenges such as, hemorrhage, thereby decreasing the chances of survival. Our studies addressed this question in an ovine model of hypertensive CKD, which has features similar to human essential hypertension; progressive hypertension,[57,58] reduction in glomerular filtration rate (GFR),[57,59] presence of albuminuria and left ventricular hypertrophy,[58] and enhanced responses to sympathetic activation.[60] These features and the fact that this large animal model allows the use of the same catheter-based approach to RDN as used clinically, make this an ideal model to examine the consequences of RDN. Radiofrequency catheter-based RDN or a sham procedure was performed in normotensive sheep with normal renal function or hypertensive CKD sheep using the Symplicity Flex catheter. All animals that underwent RDN received 6, 2-minute radiofrequency ablations per renal artery.[26] Our studies demonstrated that elevated BP was normalized at 2 and 5-month post-RDN in the hypertensive CKD as compared with the control group (Figure).[26] Additionally, we demonstrated a modest increase in basal GFR (≈15%) at 5-month post-RDN in hypertensive CKD sheep compared with intact counterparts.[26] RDN had no effect on basal BP or GFR in normotensive sheep.[26] Similarly, in small-scale uncontrolled clinical trials, catheter-based RDN slowed GFR decline in association with BP reduction in CKD patients over a 12-month period.[61,62] An increase in GFR after RDN is potentially of concern as it is indicative of hyperfiltration because of increased glomerular pressure,[26] which in the long-term may accelerate renal injury and this warrants further follow-up.

In our studies, hemorrhage was used to induce a homeostatic challenge to assess the return of neural control of renal function after RDN. The fall in BP during hemorrhage results in a reflex increase in sympathetic outflow, which in the kidney results in vasoconstriction, increased renin secretion, and sodium reabsorption.[63,64] Together these mechanisms promote restoration of blood volume and BP. In our studies, 20% blood volume was withdrawn >15 minutes, and the compensatory response monitored over the following 180 minutes (Figure).[26] BP fell at a faster rate, resulting in a greater fall in BP, in both normotensive and hypertensive CKD sheep post-RDN as compared with those with intact renal nerves at the end of hemorrhage, and these changes were remarkably similar at 2 and 5 months post-RDN.[26] A greater fall in BP in an ovine model of sepsis has also been reported following surgical RDN as compared with sheep with intact renal nerves.[65] The greater fall in BP was associated with a lesser increase in HR during hemorrhage in the RDN group (Figure), providing indirect evidence for the importance of afferent renal sensory pathways in this response. This is in agreement with previous studies demonstrating the direct role of renal afferents in other models of hypertension and CKD.[2,66] An alternative possibility, which warrants further examination, is that abnormal baroreflex function post-RDN may contribute to this response particularly in the CKD-hypertensive group. The greater fall in BP when hemodynamic homeostasis is challenged is of concern, as it demonstrates that patients that have undergone RDN may enter the decompensatory phase of hemorrhage more precipitously, resulting in vascular collapse and death if left unchecked.

In normotensive sheep with intact renal nerves during the 180 minutes recovery period after blood loss, BP was completely restored to prehemorrhage levels. This compensatory response was association with marked increases in plasma renin activity (Figure) and vasoconstriction and reductions in GFR and sodium excretion.[26] However, in sheep that had undergone RDN this compensatory response was markedly attenuated (Figure). Though not the main focus of the current review, it is interesting to note that the compensatory response to hemorrhage was also somewhat impaired in the CKD-intact group as compared with the control-intact group (Figure). In

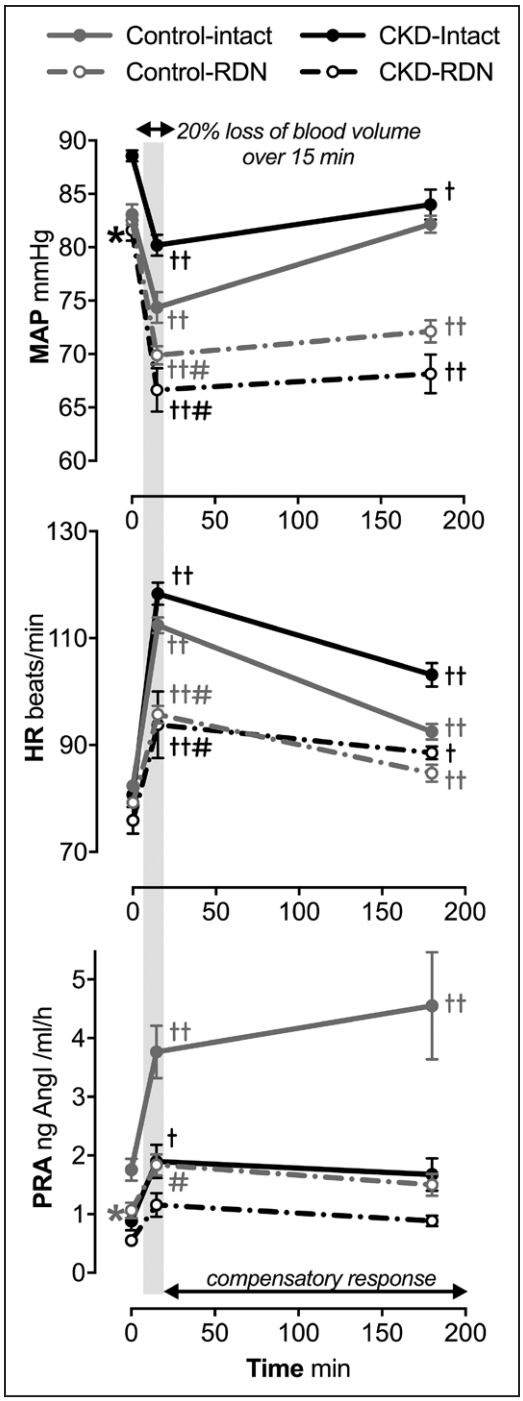

Figure. Hemodynamic response to hemorrhage after renal denervation (RDN). Mean arterial pressure (MAP), heart rate (HR), and plasma renin activity (PRA) at baseline (time zero), and 15 and 180 min after 20% blood volume withdrawal over a 15-min period. In normotensive (control; grey lines and symbols) or hypertensive chronic kidney disease (CKD; black lines and symbols) sheep 5 mo after sham (intact, closed symbols) or catheter-based renal denervation (RDN; open symbols). **P*<0.05 between intact and RDN groups at baseline; †*P*<0.05, ††*P*<0.01 compared with baseline within each respective group. #*P*<0.01 between intact and RDN groups at 15-min postblood loss. n=6 to 8 per group. Data derived from Singh et al.[26]

our study, the greater fall in BP in response to hemorrhage was associated with an attenuated increase in plasma renin activity and heart rate in sheep that underwent RDN compared with intact counterparts.[26] Renal hemodynamic responses to hemorrhage were also significantly impaired, with the expected reduction in GFR in response to hemorrhage being attenuated in denervated sheep.[26] This was associated with an attenuated increase in renal vascular resistance and fall in renal blood flow in both the normotensive and hypertensive CKD sheep that underwent RDN compared with intact counterparts.[26] These findings are compatible with observations in patients after renal transplant (thus denervated), in whom renal responses to moderate lower body negative pressure have been shown to be impaired.[56] The responses to hemorrhage in our study were remarkably similar at 2 and 5 months after RDN demonstrating that there was little return of renal nerve function during this time-frame.[26] This is despite evidence that the nerves have commenced to reinnervate the renal tissue at 5.5 months of age in sheep after RDN.[42] Together, this data suggests that the simple presense of nerve fibers is not an indicator of neuroeffector connectivity and function.

In summary, our studies demonstrated that catheter-based RDN was beneficial in terms of the treatment of hypertension and improvement of renal function in hypertensive CKD. However, RDN impaired the compensatory renal response to homeostatic challenge that compromised the maintenance of BP. It should be noted that there are mixed findings in patients after RDN with normal chronotropic competence during exercise and both normal and reduced orthostatic function during tilting reported,[67–69] though these challenges are less severe than 20% blood loss and are less dependent on the renal response. In this cohort of hypertensive CKD sheep, studies are ongoing to determine if return of nerve function occurs and whether the reduction in BP and improvement in GFR are sustained in the long-term.

Clinical Trials Revisited

Lack of appropriate control groups, changes in medication prescription, poor drug compliance, and procedural failures have combined to hamper studies examining the efficacy of catheter-based RDN for the treatment of hypertension and CKD in humans. This realization has brought about redesign of protocols to assess the efficacy of RDN.[13] Recently, data has been released from 3 sham-controlled clinical trials, which adhered to these principals. The first was the SPYRAL HTN OFF-MED trial conducted in mild to moderate hypertensive patients after removal of drugs (thus limiting the issue of adherence), which 3-month post-RDN reported a ≈5 mm Hg reduction in BP compared with the sham control (Table).[14] Next SPYRAL HTN ON-MED, with patients on 2 drugs at titrated doses with adherence monitored, reported a ≈10 mm Hg reduction in BP 6-month post-RDN (Table).[16] These trials used the new Spyral multielectrode catheter and performed RDN of the main renal artery and accessory branches as evidence demonstrated that this approach produced more effective RDN.[70] Finally, in the Radiance-HTN SOLO trial, using the Paradise system that uses ultrasound energy, reported a ≈7 mm Hg reduction in BP compared with the sham control (Table).[15] Importantly, in each of these 3 trials, BP was not significantly altered in response to the sham procedure as compared with baseline. A 10 mm Hg decrease in BP has been shown to reduce the relative risk of cardiovascular disease by 20%.[71] Thus, these observations in

sham-controlled trials are promising and indicate that there may be a place for RDN in the treatment of hypertension.

Perspectives

Catheter-based RDN is in clinical trial for the treatment of hypertension. However, it may also be effective for the treatment of heart failure and hypertensive CKD. Early trials of RDN were promising, but outcomes may have been affected by poor trial design and procedural failure. Ongoing clinical trials designed to overcome these problems will provide information on the long-term efficacy of the procedure. Given the large body of evidence that renal nerves regrow after RDN, studies in large animal models of hypertension are necessary to elucidate the full extent of reinnervation and whether return of nerve function will herald reoccurrence of hypertension after catheter-based RDN. Alternatively, such studies may provide evidence that catheter-based RDN has a legacy effect that normalizes renal sympathetic hyperinnervation, permanently lowering BP.

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