REVIEW ARTICLE

The denervation or activation of renal sympathetic nerve and renal blood flow

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The denervation or activation of the sympathetic nerve in the kidney can affect renal hemodynamics. The sympathetic nervous system regulates the physiological functions of the kidneys. Stimulation of sympathetic efferent nerves affects various parameters related to renal hemodynamics, including sodium excretion, renin secretion, and renal blood flow (RBF). Hence, renal sympathetic fibers may also play an essential role in regulating systemic vascular resistance and controlling blood pressure. In the absence of renal nerves, the hemodynamics response to stimuli is negligible or absent. The effect of renal sympathetic denervation on RBF is dependent on several factors such as interspecies differences, the basic level of nerve activity in the vessels or local density of adrenergic receptor in the vascular bed. The role of renal denervation has been investigated therapeutically in hypertension and related disorders. Hence, the dynamic impact of renal nerves on RBF enables using RBF dynamic criteria as a marker for renal denervation therapy.

Key words: Renal blood flow, renal sympathetic denervation, renal sympathetic nerve activity

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INTRODUCTION

The sympathetic nervous system regulates a wide range of physiological functions within the body. The sympathetic nervous system innervates the kidneys through the vasculature, tubules, and juxtaglomerular apparatus. Since, the kidneys play an important role in adjusting blood pressure, the neural control of the kidneys is critical for regulating the body's fluid volume, sodium homeostasis, and renin release.[1] It has been suggested that animals' basal renal sympathetic nerve activity (RSNA) is at a minimum level under normal conditions. However, this activity is raised in pathological conditions, such as hypertension.[2] In addition, the RSNA fluctuations affect sodium reabsorption from renal tubular cells and renin release from juxtaglomerular cells. Due to the involvement of renal adrenergic nerves in regulating renal vascular resistance (RVR) and renal hemodynamics such as renal blood flow (RBF), the kidneys can adapt to both physiologic and pathologic stimulants.[3] The activity of sympathetic nerves of afferent and efferent renal arteries affects RBF and glomerular filtration rate (GFR).[4] Furthermore, stimulating renal efferent nerves change renal hemodynamics by increasing renin secretion, enhancing tubular fluid and electrolyte absorption, and reducing water and sodium excretion.[5] The renal nerves are inactive under normal conditions and based on the steady state measurement of RBF. However, they respond to experimental stimuli or several diseases where the RSNA exceeds the physiological level. In general, the dynamic measurement of RBF indicates that renal nerves are incessantly regulating RBF.[6]

Central sympathetic signals from the kidneys target various organs, such as the heart and lead the peripheral arteries to constrict and increasing of

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blood pressure.[7] The role of renal denervation has been investigated therapeutically in hypertension, chronic kidney insufficiency, and chronic heart failure (HF) conditions.[8] This review intends to evaluate the effects of renal nerve sympathetic activity or renal sympathetic denervation (RSDN) on RBF in physiological and pathological conditions based on basic and clinical evidences.

SYMPATHETIC RENAL INNERVATION

There are sympathetic inputs and outputs in the kidneys; the efferent sympathetic nerves from the central nervous system (CNS) and the afferent sympathetic nerves from the kidneys to the CNS constitute the sympathetic innervation of the kidneys. The sympathetic nerves innervate the kidneys through a dense network of postganglion neurons. Along the renal artery, preganglionic nerves enter the kidney from the hilus[9] and the branches of the renal sympathetic efferent nerves innervate glomerular arterioles, proximal tubules, and the juxtaglomerular system.[10] Activation of the sympathetic nerve increases the production of noradrenaline (NA) from the nerve terminals and denervation of the kidney causes a significant reduction in NA (by 95%).[11] The release of increased NA has three primary outcomes as follows:

1. NA stimulates beta-adrenergic receptors (β1-ARs) of juxtaglomerular granular cells, which in turn release renin and increase the activity of the renin-angiotensin-aldosterone system (RAAS)
2. NA reduces sodium and water excretion by increasing tubular reabsorption
3. NA reduces RBF and GFR by contracting renal arteries.[11][Figure 1].

The activation of distinct adrenoceptor (ARs) subtypes found on the renal vasculature by the renal sympathetic nervous system mediates adrenergic control of the kidneys. ARs support renal hemodynamic and tubular functions and are found on the renal vasculature, nephrons, and proximal tubules in the kidneys. The α-ARs are the most important regulators of renal vascular tone among the different types of ARs.[12] During an adrenergic response, NA released into the circulation binds to the smooth muscle cells' α1 receptors, causing the smooth muscle to contract. By mediating catecholamine-induced effects on the ARs type α1 found on the renal vasculature, the renal sympathetic nervous system significantly affects the renal hemodynamics.[12]

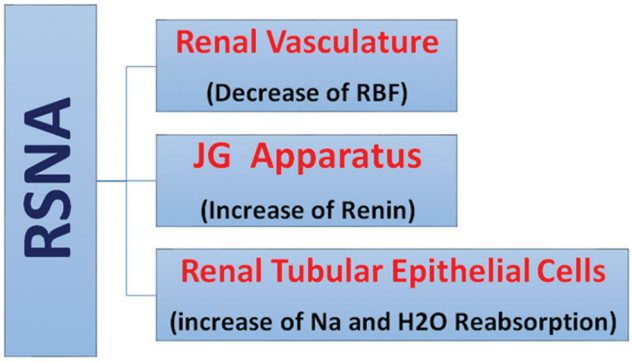

Figure 1: Schematic image of the effect of increased renal sympathetic nerve activity on different parts of the kidney. RSNA = Renal sympathetic nerve activity

Activation of the sympathetic efferent nerves of the kidney can occur in response to reinforced afferent signaling of the sensory nerve fibers of the kidney, which can be induced by various effectors such as renal hypoxia, ischemia, and oxidative stress.[8]

The pelvic area is the primary location of the afferent renal sensory nerves and the pressure in this area defines the activity of the nerves. Thus, as a reno-renal reflex response, enhancement in the urine flow rate raises the firing rate of renal afferent fibers, decreasing efferent RSNA and increasing sodium excretion from urine.[13] The renal afferent fibers are either chemo-sensitive and respond to nociceptive stimuli (such as inflammation, ischemia, acidosis, oxidative stress, adenosine, and angiotensin (Ang) (II)) or are mechano-sensitive (more common in the renal cortex) and respond to stretch.[14] The nervous system centers that received these signals include the nucleus tractus solitaries, paraventricular nucleus (PVN) of the hypothalamus, rostral ventrolateral medulla (RVLM), and subfornical organ.[15-17]

The neuronal activity in sympathetic premotor nuclei in the brain stem and hypothalamus, including RVLM and PVN, determines the degree of RSNA. Preganglionic neurons in the intermediolateral cell column of the spinal cord get input from the neurons in the RVLM; these neurons then project to postganglionic neurons, which in turn project to peripheral organs such the heart, arteries, and kidneys.[18] Figure 2 summarizes the central and peripheral pathways of sympathetic control of the kidney.

Activating of renal afferent sensory nerve (by modulation of posterior hypothalamic activity and secretion of oxytocin and vasopressin) affects the sympathetic outflow to highly innervated organs such as the kidneys, heart, and peripheral blood vessels.[19,20] Stimulation of the afferent system activates the cardiovascular regulatory centers in the CNS. The destruction of these nerves (in some diseases) reduces the central sympathetic flow to major organs regulating blood pressure, especially the kidneys, heart, and peripheral arteries.[14]

Renal denervation is believed to be effective in treating numerous diseases that are accompanied by increased

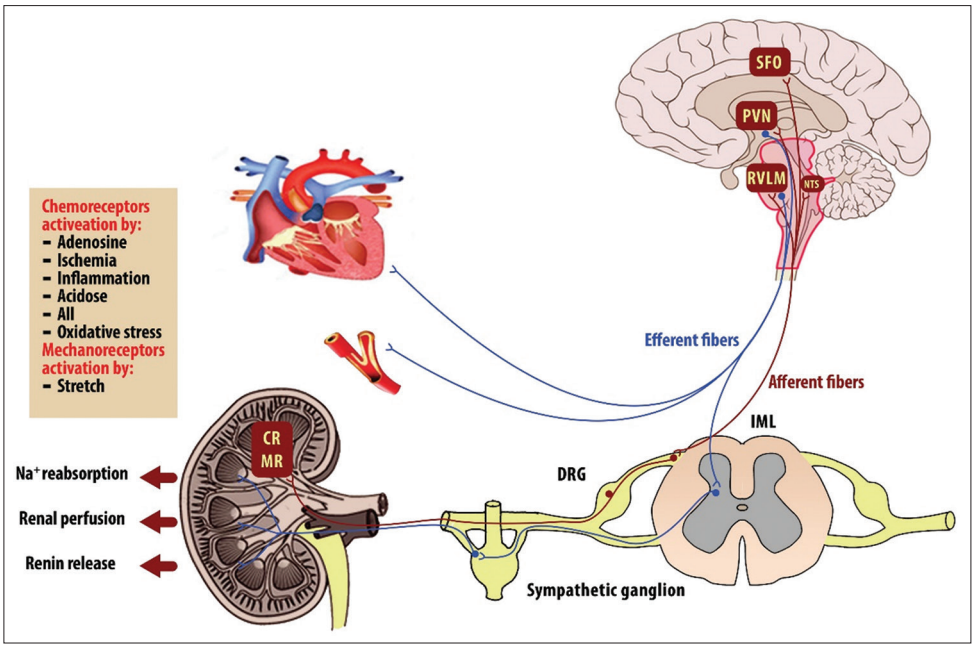

Figure 2: Schematic image of the connections between renal afferent sensory signaling and renal efferent sympathetic outflow on the kidney and other cardiovascular organs, which regulate blood pressure. Renal mechano and chemoreceptor reflexes, which are carried out by renal afferent nerves, regulate the activity of premotor neurons in the rostral ventrolateral medulla and paraventricular nucleus. CR = Renal chemoreceptors; DRG = Dorsal root ganglion; IML = Intermediolateral cell column; MR = Renal mechanoreceptors; NTS = Nucleus tractus solitarius; PVN = Paraventricular nucleus of the hypothalamus; RVLM = Rostral ventrolateral medulla; SFO = Subfornical organ

sympathetic renal activity, such as chronic and end-stage renal disease, hypertension, cardiac-renal syndrome, left ventricular hypertrophy, and improper fluid retention in HF.[19] In general, afferent sympathetic fibers may also play an essential role in regulating systemic vascular resistance and controlling blood pressure.[20]

RENAL SYMPATHETIC NERVE ACTIVITY AND RENAL BLOOD FLOW

The share of RBF from cardiac output is about 20% at rest, so its regulation plays a vital role in controlling blood pressure.[21] The kidneys have two robust auto-regulation mechanisms for regulating blood pressure, tubule-glomerular feedback, and myogenic response.[22] However, the importance of RSNA in the physiological regulation of RBF is still controversial based on the two findings. The first finding indicated that electrically stimulated renal nerves at different frequencies affect RBF differently, and in the pathophysiological range of RSNA, a significant decrease in RBF was observed.[6] Other findings violate the influence of renal nerves in the physiological regulation of RBF since renal denervation is not affecting basal RBF. However, both of these findings had significant drawbacks.[23] The electrical stimuli inherently cannot distinguish between physiological, pathophysiological, and supraphysiological effects. RSNA recruits special renal postganglionic fibers in response to specific stimuli with different effects.[23] In addition, the particular axons can electively innervate the vessels, juxtaglomerular cells, or tubules, and even axons that innervate juxtaglomerular arteries can be differentiated from those that innervate other renal vessels.[24] Eventually, by changing RSNA, which occurs through either stimulation or denervation, it must overcome powerful autoregulatory mechanisms to affect the steady state of RBF.[23]

It is stated that the vascular system is insensitive to slight changes in RSNA. In experimental models, RSNA was increased progressively by electrical stimulation of the renal nerves in anesthetized cats or dogs[25-27] or reflex activation in conscious dogs.[28,29] At low RSNA levels, only renin release occurred, and then, slightly increased levels have resulted in changes in sodium excretion, and still, RBF alteration was obtained only at much higher levels,[30] indicating that in daily life, changes in RSNA at near resting levels have minimal impact on RBF.[30]

Grady and Bullivant measured RBF during the daily activity in conscious rats, demonstrating that RBF decreased with increasing activity levels; however, this result was not obtained when RSNA was previously blocked with local anesthetics.[31] In alert rabbits, a moderate increase or decrease in RSNA affected RBF. However, sound stress, air-jet stress, and hypoxia increased RSNA by 12%–31%, reducing RBF by 8%–12% compared to controls.[32] In addition, an increase in blood volume, which reduces RSNA by 25%, leads to a 17% increase in RBF.[33] It is also reported that rapid and physiological changes in sympathetic output affect RBF during normal daily activities.[6]

Routine activities such as sleeping or grooming have increased RSNA and concomitantly decreased RBF.[34] Furthermore, a small increase in heart rate and RSNA in unilaterally renal denervated rabbits showed considerable differences in the RBF of innervated and denervated kidneys. These findings suggested that RSNA changes in the physiological range affect RBF, so further research is needed to elucidate the role of renal nerves in the dynamic regulation of resting RBF.[23]

Sympathetic activity has two components: frequency and amplitude. The frequency shows baroreceptor modulation and central generation and the amplitude indicates the number of recruited nerves. Since various afferent stimuli can change these components, changes in the frequency or number of recruited nerves or multiple activation patterns can affect kidney function.[35,36] It is shown that dilatation of a pig's uterus reduced RBF by sympathetic nerves without altering blood pressure.[37] In Mancia *et al.*'s experiments, RBF decreased by 8%, 15%, and 19% in the three states of confrontation; without movement, forelimb movement, and hind limb and forelimb movement, respectively.[38] An experiment on conscious baboons demonstrated that RBF decreased in response to psychological stress.[39] Another study found that acute psychological stress in conscious monkeys reduced RBF by increasing RSNA.[40] Furthermore, RSNA increases and RBF decreases in moderate heat stress.[41-43]

RBF decreases in response to a slight increase in RSNA, but whether RBF increases in response to a slight decrease in RSNA is ambiguous. In the alert rabbits, an increase in plasma volume caused a moderate reduction in RSNA (by 25%) and a significant rise in RBF. In contrast, this response was not obtained in the renal denervated animals.[33]

RBF in the cortex and medulla was also decreased after the electrical stimulation of the sympathetic nerves.[44] Stimulation of the renal sympathetic nerve creates a different pattern in medullary perfusion and renal cortex, attributed to the less sensitive medulla in the anesthetized rat.[45] In rabbits, activation of the renal sympathetic nerves resulted in a greater increase in RBF and cortical perfusion than in medullary perfusion.[46,47] They were similar at each stimulation level of perfusion changes in the inner and outer medulla.[48]

In humans, renal function is measured in response to stimuli related to RSNA change instead of direct RSNA assay, while it is impossible to measure RSNA directly.[35] Psychological stress increases the activity of the sympathetic muscle nerve by up to 30% and decreases cortical blood flow by up to 36%.[49] Submerging in water and neck suction increases RBF due to decreased RSNA levels.[50,51] To sum up, it is clear that the stimulation of the sympathetic nerves of the kidney reduces RBF, and many studies proposed that the alterations in RSNA induced by natural behavioral activities had a remarkable effect on RBF [Table 1].

RENAL SYMPATHETIC DENERVATION AND RENAL BLOOD FLOW

The RSDN is performed to determine the nonneurological effects on the kidney. In this case, either the response is weak and difficult to measure or there is no response at all. Studies indicated that RBF increases in alert and resting animals after renal denervation, so RSNA is responsible for supplying the tonic level of renal vasoconstriction.[31,32] Furthermore, GFR was increased in patients with refractory hypertension with bilateral renal denervation.[53] In contrast, there was no difference in RBF between innervated and denervated kidneys in alert and resting rats.[34] Similarly, in anesthetized rats during the 1st h after unilateral renal denervation, no difference in RBF was observed in the denervated and innervated kidneys.[3] Such findings were also detected in rabbits on days 14–21[54] or after 7 weeks.[30] Similarly, there was no change in RBF after administrating an adrenergic blocker (dibenamine) to relaxed and stress-free state patients.[55] In general, the effect of RSNA on RBF differs in anxiety and pathophysiological conditions from calm and restful conditions. Anxiety and pathophysiological conditions reduce RBF, but in calm conditions, there is a slight tonic effect on RBF.[48] The tonic result of basal RSNA on RBF seems to be negligible, and acute surgical denervation has little impact on renal hemodynamics.[48] Overall, the basal renal nerve activity does not affect renal hemodynamics; for example, it is specified that in alert dogs and humans, renal denervation with medication or surgery does not affect RBF,[56,57] and in nondiuretic rats after acute unilateral denervation, renal plasma flow (RPF) remains unchanged in the kidneys.[58]

Table 1: The effect of renal sympathetic nerve activity on renal blood flow

RSNA in animal or human	RBF	Reference
Anesthetized cat	Decrease	[25]
Anesthetized dog	Decrease	[26]
Conscious dog	Decrease	[28,29]
Conscious rat	Decrease	[31,34]
Conscious rabbit	Decrease	[32]
Anesthetized pig	Decrease	[37]
Conscious cat	Decrease	[38]
Conscious baboon	Decrease	[39,42]
Anesthetized rat	Decrease	[43,52]
Conscious monkey	Decrease	[40]
Human	Decrease	[49]

RSNA=Renal sympathetic nerve activity; RBF=Renal blood flow

All stimuli that significantly reduced RBF in renal innervated rabbits, such as air-jet stress, hypoxia, or noise stress, failed to elicit an RBF response after renal denervation.[32] Similarly, following baroreflex alteration of RSNA, the response of RBF was significantly altered in response to change in arterial pressure after administering a calcium antagonist or an Ang II antagonist following renal denervation in rats.[59] In the same way, in conscious cats, RBF responses to confrontation following renal denervation were eliminated.[38] Other studies have shown that acute denervation causes diuresis and natriuresis in anesthetized dogs and rats without significantly affecting renal hemodynamics parameters.[58,60,61] No alteration in RBF was reported with renal denervation performed on unconscious pigs[62] and cats[63,64] and no difference was observed in anesthetized monkeys in renal excretory function after renal denervation.[65] However, in conscious baboons, RBF responses to psychological stress following renal denervation were persisted.[39] The impact of RSDN on RBF at different times after RSDN in patients with resistant hypertension indicated a 20% increase in total blood flow per cardiac cycle and a significant decrease in blood pressure, without any changes in RBF.[66] It is also stated that under normal sympathetic tone, the sympathetic nerve fibers of the kidney have little effect on the dynamic auto-regulation of renal vascular tone and, consequently, on RBF.[3] In a study on a pig model, RBF increased acutely after RSDN and remained at the same acute peak even after a month, while RBF reserve remained lower, and based on these observations, it can be concluded that such changes in RBF parameters can be a valuable biomarker for successful denervation.[67] Hemodynamic measurements in renal arteries of healthy pigs after RSDN, immediately, 3 weeks, and 3 months after RSDN indicated that RBF at rest propends to increment.[68] This results agree with relative increase in RBF after renal denervation in dogs.[69] However, as contradictory results in this regard, in anesthetized nondiuretic rats, RBF and GFR remained unchanged after denervation.[58] Furthermore, some studies have reported that renal basal sympathetic nerve resection in normal dogs and rats does not affect RBF.[70,71] A study on rats determined the regional blood flow in the cortex and medulla of the left kidney, and they did not observe a significant effect on intracortical blood distribution after renal denervation,[72] However, acute unilateral renal denervation increased RBF and RPF without altering GFR. In general, renal denervation did not affect intracortical blood flow distribution and renal hemodynamics.[72] Otherwise, it is suggested that renal denervation causes a rapid (approximately 25%) increase in cortical perfusion in anesthetized rats.[73] In hypertension and congestive HF (CHF) rat model, RSDN increased basal RBF.[70] However, in Sprague Dawley rats (SD), RSDN did not affect RBF.[3] These disagreements may be due to differences among animal species or the RSDN method.[30]

It has been reported that renal denervation does not significantly alter arterial pressure in spontaneously hypertensive rats (SHR) over a short period of 1 h, despite interfering with intrarenal function (such as increasing RBF, dynamic autoregulation of RBF, and variability of RBF).[74] Meanwhile, despite causing systemic hypotension, RSDN does not affect perfusion and renal function at various intervals (directly and after 3 months) and does not alter RBF in patients with hypertension.[75] Hence, it can be deduced that the effect of RSDN is negligible on acute or chronic renal perfusion.[75] However, a case report indicated that RSDN was associated with increased RPF.[76]

In Wistar Kyoto (WKY) and SHR, acute renal denervation under genetic control resulted in continuous diuresis and natriuresis in SHR and not in WKY, and there was no significant change in RBF.[77] Also, in SD and Munich-Wistar (MW) rats, similar to SHR, renal hemodynamics remained unchanged.[77] Acute denervation studies have shown a negligible tonic effect of renal efferent nerves on renal arteries in SHR, WKY, and SD-MW rats.[77] Strain differences have been identified between SHR and WKY in renal excretory response to acute unilateral renal RSDN.[77] Also, the effect of acute renal RSDN on RBF or GFR is not noticeable in normal adult rats in hydroponic, euvolemic, or volume-expanded conditions.[58,78] Table 2 shows the effect of RSDN on RBF in some studies models.

Overall, there is a degree of uncertainty in these studies. The reasons for the above inconsistent results are not specific, because the studies were performed either under anesthesia or consciously. Factors such as differences between animal species, the method of RSDN, the degree of RSNA required to impact on RBF, final evaluation of renal hemodynamics, and validation of renal denervation are factors that can be involved in these differences.[82] Studies in normal animals presented where basal RSNA was sub-vasoconstrictor, basal RBF and dynamic RBF auto-regulation were not altered by the elimination of basal RSNA by renal denervation.[70] Also, under a number of physiological and pathological circumstances, there may be a change in the functional participation of a1– ARs.[12] In the deoxycorticosterone acetate-salt (DOCA)-salt-hypertensive rats, a local change in the density of α1-ARs may be responsible for the increased responsiveness of the mesenteric vascular bed to α1-AR agonists, and Suzuki *et al*. discovered that the mesenteric vasculature of DOCA-salt hypertensive rats had increased α1-AR density and affinity.[83] Compared to normotensive WKY rats, SHR rats showed enhanced affinity of the small mesenteric artery α1–AR.[84] Both Dahl salt-sensitive rats and SHR rats showed higher renal densities of α1-AR and α2–AR.[85] Additional research in various salt-related hypertension animal models has shown that a local change in the α1-AR density may be the cause of the increased

Table 2: he effect of renal sympathetic denervation on renal blood flow

RSDN	Model	RBF	References
Transmission blocking drug (xylocaine)	Conscious rat	Increase	[31]
Bilateral	Conscious rabbit	Increase	[32]
Bilateral	Conscious sheep	Increase	[79]
Acute and chronic	Anesthetized rat	No change	[48]
-	Anesthetized rat	Increase (cortical RBF)	[73]
Chronic (14–21 days)	Rabbit	No change	[54]
Chronic (7 weeks)	Rabbit	No change	[30]
-	Conscious rat	No change	[34]
Adrenergic blocking drug (dibenamine)	Human unstressed	No change	[55]
Adrenergic blocking drug (dibenamine)	Anxious human	Increase	[55]
Surgical or pharmacological	Conscious dogs and humans	No change	[56,57]
Acute unilateral	Nondiuretic rats	No change	[58]
-	Rats	No change	[59]
-	Conscious cats	No change	[38]
Unilateral	Anesthetized rats and dogs	No change	[58,60,61]
Acute	Anesthetized pigs	No change	[62]
-	Cat	No change	[63,64]
Chronic bilateral	Anesthetized monkeys	No change	[65]
-	Conscious baboons	No change	[39]
Acute unilateral	Rat	Increase	[72]
-	Hypertensive patients	No change	[66]
Acute	Rat	No change	[3,77]
-	Porcine model	Increase	[67]
Chronic	Pig	Increase	[68]
-	Normal dog	No change	[70,71]
Acute	Hypertensive rats	Increase	[70,74]
Acute	Congestive heart failure rat	Increase	[70]
Acute	Spontaneously hypertensive rats	No change	[77]
Acute	Wistar-Kyoto genetic control rats	No change	[77]
Chronic	Normotensive rats (Sprague–Dawley strains)	No change	[80]
Acute	Volume-expanded Rat	No change	[78]
Acute	Hydropenic, euvolemic rat	No change	[58]
-	Pacing-induced heart failure rabbit	Increase	[81]
Chronic	Resistant hypertension patient	No change	[75]

RSDN=Renal sympathetic denervation; RBF=Renal blood flow

reactivity of the vasculature to catecholamine.[86] The neurovascular transduction mechanisms may vary as a result of these variations in vascular beds' sensitivity.[86] Aging modifies the distribution of the vascular α1-AR subtype in humans, which differs from animal models, changes with vessel bed.[87] These discoveries provide possible new therapeutic targets that might be used in a variety of clinical scenarios.

THE SYMPATHETIC NERVOUS ACTIVITY IN PATHOLOGICAL CONDITIONS

Overactive sympathetic nerves are linked to hypertension and numerous cardiometabolic disorders, but the underlying mechanisms are poorly understood.[88] Sympathetic hyperactivity is associated with decreased GFR, RBF, and salt excretion, and this might affect systemic blood pressure. Renal denervation has been demonstrated to be an effective therapeutic method for lowering blood pressure. The relationship between renal sympathetic nerves and the pathophysiology of hypertension, HF, and chronic kidney disease has been highlighted.[89] Based on these phenomena, renal denervation helps lower blood pressure and may be used to treat insulin resistance,[90] obesity-related hypertension,[91] HF,[92] chronic kidney disease,[93] metabolic syndrome,[94] diabetes,[95] and obstructive sleep apnea.[96]

Hypertension

Sympathetic hyperactivity is a common trait in both human and animal models of hypertension. When compared to normotensive people, RSNA in hypertension patients is twice.[97] However, Gattone *et al*. demonstrated that renal damage is mitigated by sympathetic function suppression irrespective of systemic hypertension.[98] Antiadrenergic, diuretics, Ang-converting enzyme inhibitors (ACEi), AngII

receptor blockers (ARBs), calcium-channel blockers, and anti-renin medicines are just a few of the many efficient anti-hypertensive medications that are now on the market. However a significant portion of individuals with essential hypertension are drug-resistant, meaning they are unable to lower their blood pressure despite taking three separate antihypertensive medications at the recommended dose.[99] Renal denervation is a therapeutic option for severe resistant hypertension patients.[100,101] The rise in blood pressure was reduced in the DOCA-salt rat model of hypertension by surgically ablate both efferent and afferent renal neurons.[102] The afferent renal nerve activity in the clipped kidney was increased in the two-kidney-one-clip (2K1C) mouse and rat models, while afferent renal denervation (ARDN) and total renal denervation (TRDN) attenuated the increase in blood pressure.[103,104] The expression of Ang II receptors was assessed in both kidneys of the 2K1C rat model, and the results revealed a significant up-regulation of Ang II receptor mRNA in the clipped kidney; while, renal denervation led to a normalization of their expression in the ischemic kidneys.[105] TRDN reduced the rise of blood pressure during the emerging stage of hypertension in stroke-prone SHR (SHRSP), but such finding was not seen by ARDN.[106] It seems that the suppression of the development of hypertension in SHRSP is a result of the denervation of efferent renal nerves.[106] RSDN is helpful in the pathophysiological circumstances of sympathetically driven hypertension, such as obesity-related hypertension.[107] RSDN, lowered renin production and enhanced RBF in individuals with essential hypertension, indicating that the efferent renal nerves had been successfully targeted.[76] RSDN does not necessarily have antihypertensive effects in several animal models, such as Ang II salt-induced hypertensive rats, Wistar rats, and dogs whose hypertension was brought on by chronic nitric oxide (NO) synthase suppression.[108-110] Both ARDN and TRDN were unable to reduce blood pressure elevation in Ang II or high salt diet-induced hypertensive rats (AngII-salt rats).[111] AngII-salt rats show continually high blood AngII levels despite sympathetic nerve activity and vascular disorders such as arteriosclerosis, endothelial dysfunction, and impairment of vasodilator response to sympathetic suppression.[111] It seems that, RSDN may not lower blood pressure even if it lowers the sympathetic outflow from the brain. In addition, RSDN may be inefficient in lowering blood pressure in the presence of pathophysiological factors linked to the development of vascular diseases, such as advanced age and isolated systolic hypertension.[111] RSDN may be useful in treating certain types of hypertension and offers the potential for more individualized disease management.[112]

Heart failure

Sympathoexcitation is a feature of chronic HF, especially in the heart and kidneys.[113] Renal vasoconstriction, reduced RBF, increased water and salt reabsorption, and renal fibrosis are all brought on by increased RSNA.[114] Following stimulation of the sympathetic nerves that innervate the vasculature, the vasculature (macro-and microcirculations) is susceptible to endothelial cell malfunction, smooth muscle cell hypertrophy, and vasoconstriction. The release of renin from the kidneys, activation of the RAAS, and renal damage are all further enhanced by increased RSNA. RSNA causes pathological changes in the kidneys, which increase blood volume, cause tissue edema, and cause systemic vasoconstriction through Ang II to considerably worsen HF.[115] The success of neuro-hormonal modulators, including beta-blockers, ACEi, ARBs, aldosterone antagonists, diuretics, and neprilysin inhibition, as standards of care to treat CHF is a testimony to the substantial role the SNS plays in worsening HF severity.[116-119] Despite the fact that these pharmacotherapies have been effective in lowering morbidity and early death, pharmacotherapy resistance, unintended side effects, and patient nonadherence to medication regimens[120,121] continue to aggravate HF symptoms over time. Therefore, there is still a clinical unmet need for supplemental or alternative therapy approaches to treat HF. In animal model studies of the CHF, it was found that acute renal denervation in anesthetized rats, increased RBF,[70] so it can be concluded that the renal nerves may apply a tonic vasoconstrictive function in CHF.[122]

DiBona and Sawin investigated the tonic effect of basal RSNA on dynamic autoregulation of RBF in rats, and found that, RSDN increased basal RBF in CHF and SHR but not in SD and WKY rats[70] and notably ameliorated auto-regulation of RBF.[70] In the pacing-induced HF model in rabbits, decreased RBF, increased RVR, increased expression of Ang II receptor type 1 (AT1), and decreased expression of Ang II type II receptor (AT2) in renal cortical arteries, was specified.[81] These alterations were stopped by RSDN before induction of HF. Principally, the results of these animal studies cleared that the activity of renal sympathetic nerves has a deleterious effect on RBF and can be associated with changes in the expression of Ang II receptors so that renal denervation may be effective in the treatment of CHF.[92]

HF is linked to sleep apnea,[123] and RSDN counteracted the decrease of renal hypoperfusion during apnea and the activation of the RAAS in the kidney.[124] An improvement in sodium excretion, an increase in cardiac output, and an improvement in RBF mediating unfavorable responses were all seen in animal models of RSDN after myocardial infarction.[125,126]

Kidney diseases

Another research used an ovine model of hypertensive chronic kidney disease to show the efficacy of RSDN. In

comparison to sham controls animal, the hypertensive CKD accompanied with RSDN showed larger improvements in GFR, RBF, and albuminuria 5 months after the ablation.[127] Furthermore, RSDN recovered estimated GFR (eGFR) by changes of intrarenal hemodynamics in CKD patients.[128,129] The eGFR assessments could help to evaluate the exact renal functions.[130]

It has been shown that ischemic acute kidney injury changes renal hemodynamics and is associated with endothelial cell dysfunction brought on by an increase in the formation of reactive oxygen species, which reduces NO availability.[131] Numerous physiological functions of NO in the kidney include the control of RSNA.[132] By reducing NO synthesis may directly increase sympathetic nervous system activity in CKD patients.[133] The glomerular microvasculature becomes more constricted as a result of NO production inhibition and proximal tubular reabsorption decreases.[133] RSDN treatment has stopped these effects.[134] However, RSDN may not be suitable for lowering blood pressure in patients with polycystic kidney disease.[135]

Renal denervation and future challenge

Despite new data demonstrating the large benefits of RSDN, there are still numerous unsolved problems, including responder identification, procedural guidance, effects persistence, and the applicability of clinical outcomes. The identification of responders is a particularly important subject matter. The hypertensive patients who had a baseline plasma renin activity > 0.65 ng/ml/h or a baseline heart rate > 73.5 bpm were more sensitive to RSDN.[136,137] The preference of patients for RSDN is another crucial feature that has to be taken into account in addition to the identification of responders. A nationwide web survey in Japan revealed that the presence of side effects while taking antihypertensive medications, younger patient age, male sex, higher systolic blood pressure (at home or at the office), and poor antihypertensive drug adherence were all significant predictors of preference for RSDN.[138] This should be considered while deciding on a course of antihypertensive treatment. Finally, it is debatable whether renal nerve regeneration impacts the long-term responses to renal denervation. The re-innervation of the renal nerves may start in humans as early as 28 days.[139] Similar events were seen in dogs where, 3–6 months after transplantation, renal autografts were re-innervated.[139] On the basis of enough data, it is envisaged that the therapeutic use of RSDN would proceed completely.

CONCLUSION

Several afferent and central pathways are involved in inducing an increase in RSNA, all of which result in a significant reduction in RBF that is proportional to the increase in RSNA. Without renal nerves, the response to stimuli is minimal or absent. Based on experiments, the effect of RSDN on RBF varies. The dynamic impact of renal nerves on RBF enables using RBF dynamic criteria as a biomarker in renal denervation therapy.

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Conflicts of interest

There are no conflicts of interest.

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