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REVIEW

Sympatho-renal axis in chronic disease

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Abstract Essential hypertension, insulin resistance, heart failure, congestion, diuretic resistance, and functional renal disease are all characterized by excessive central sympathetic drive. The contribution of the kidney's somatic afferent nerves, as an underlying cause of elevated central sympathetic drive, and the consequences of excessive efferent sympathetic signals to the kidney itself, as well as other organs, identify the renal sympathetic nerves as a uniquely logical therapeutic target for diseases linked by excessive central sympathetic drive. Clinical studies of renal denervation in patients with resistant hypertension using an endovascular radiofrequency ablation methodology have exposed the sympathetic link between these conditions. Renal denervation could be expected to simultaneously affect blood pressure, insulin resistance, sleep disorders, congestion in heart failure, cardiorenal syndrome and diuretic resistance. The striking epidemiologic evidence for coexistence of these disorders suggests common causal pathways. Chronic activation of the sympathetic nervous system has been associated with components of the metabolic syndrome, such as blood pressure elevation, obesity, dyslipidemia, and impaired fasting glucose with hyperinsulinemia. Over 50% of patients with essential hypertension are hyperinsulinemic, regardless of whether they are untreated or in a stable program of treatment. Insulin resistance is related to sympathetic drive via a bidirectional mechanism. In this manuscript, we review the data that suggests that selective impairment of renal somatic afferent and sympathetic efferent nerves in patients with resistant hypertension both reduces markers of central sympathetic drive and favorably impacts diseases linked through central sympathetics—insulin resistance, heart failure, congestion, diuretic resistance, and cardiorenal disorders.

Keywords Sympathetic nervous system · Hypertension · Insulin resistance · Sleep apnea · Congestion · Heart failure · Cardiorenal syndrome · Tachycardiac arrhythmias · Renal denervation · Symplicity HTN-2

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Introduction

The contribution of renal somatic afferent nerves to central sympathetic drive and the impact of excessive efferent sympathetic signaling to the kidney are intimately linked to the development of several chronic diseases associated with such sympathetic excess [1, 2]. These chronic

ailments, essential hypertension, insulin resistance, congestion, diuretic resistance and cardiorenal disorders, have a multiplicity of underlying etiologies, yet their shared link with elevated central sympathetic drive identifies a common therapeutic target [3–5]. Therefore, treatment of the elevated sympathetic activity would be anticipated to provide significant clinical benefit. Recently, a new approach to selectively denervate the kidneys by ablation of efferent sympathetic and afferent somatic fibers has been established in clinical practice [6]. This article summarizes the chronic diseases linked by increased central sympathetic drive by describing the organ specific consequences of increased efferent signaling, and further suggests a common role of renal somatic afferents in elevation of central drive.

Renal somatic afferent nerve activity as a source of central sympathetic drive

The sophisticated network of afferent and efferent sensory, chemo- and baroreceptor nerve fibers, lie netlike in the adventitia of the renal artery (Fig. 1) and throughout the kidney [7]. Their signaling pathway to the hypothalamus provides the basis for targeting these nerves' as modulators of central integration in the brain stem [2] (Fig. 2). Altering the signals from the kidney to the hypothalamus is expected to impact peripherally, including on arterial resistance, the venous capacitance vasculature, peripheral and central chemoreceptors, sympathetic activity of the kidney, the liver and of course the heart itself [8]. Reduction of central sympathetic tone is therefore expected to simultaneously impact the plethora of systemic disorders linked through inappropriately high central sympathetic activity. Activation of renal sensory afferent signaling is likely caused by various stimuli such as renal ischemia, hypoxia, and oxidative stress as well as intrinsic renal

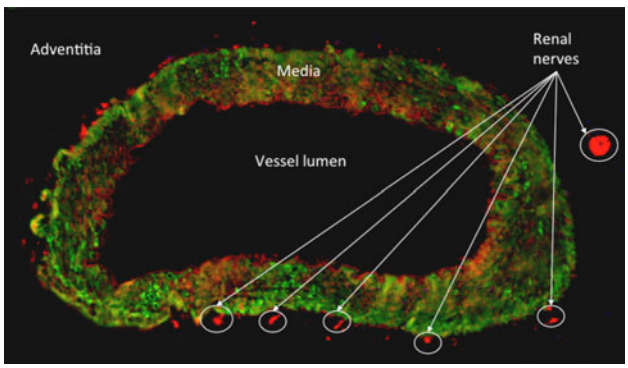

Fig. 1 Renal artery of a Sprague–Dawley rat, stained with tyrosin hydroxylase antibody. *Red* tyrosine hydroxylase, *green* α-smooth muscle actin, *blue* DAPI. Unpublished data by Mahfoud F, Kasakow A, Böhm M

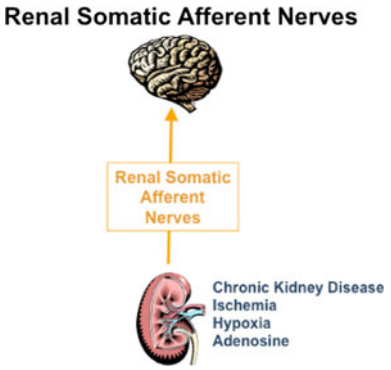

Fig. 2 Renal somatic afferent nerve activity, a source of elevated central tone

diseases [2]. In the 5/6 nephrectomy rat model of chronic renal failure and hypertension dorsal rhizotomy prevented blood pressure elevation indicating that afferent signaling from the diseased kidney to central integrative structures contributes to the rise in blood pressure in kidney disease [9]. Renal injury caused by unilateral phenol injection reliably causes hypertension in rats and is associated with both an increase in norepinephrine secretion from the posterior hypothalamus and increased renal sympathetic efferent and afferent nerve activity of both kidneys [10]. Surgical renal denervation of the phenol-treated kidney prevents hypothalamic-mediated rises in noradrenaline and increases in blood pressure, while restoring vascular resistance to normal. These findings have been confirmed in several other models of renal disease as well as interventions targeting the sympathetic nervous system, thereby demonstrating the crucial role of both efferent and afferent renal nerve signaling in hypertension associated with chronic kidney disease [11]. Experiments based on the same principles conducted in humans using nephrectomy in end stage renal disease patients with and without transplant have demonstrated similar findings [12]. Nephrectomy of the native non-functioning kidney has resulted in reduction of muscle sympathetic nerve activity, reduction of total body noradrenaline spillover, reducing blood pressure and calf vascular resistance, confirming the role of the diseased kidney in mediating central sympathetic tone.

The invasive nature of nephrectomy or spinal rhizotomy has recently been superseded by endovascular renal specific denervation of native kidney using low power radiofrequency in end stage renal disease patients either on dialysis or post transplant as well as patients with hypertension resistant to pharmacologic therapy [13]. Following endovascular denervation, blood pressure fell significantly, and, when measured, muscle sympathetic nerve activity had returned to normal post denervation [14–16]. Similar findings of reduced total body noradrenaline spillover and

reduced muscle sympathetic nerve frequency in resistant hypertension patients without evident renal disease suggest the renal chemo- or baroreceptors are responding to stimuli other than overt renal damage, possibly local metabolites of ischemia or hypoxia [14]. While renal generated NO, adenosine, and angiotensin II may be responsive to changes in central nervous system status, these animal and human experiments strongly identify a direct neurologic link. These numerous observations, confirm the native kidney as a neurologic progenitor of signals to the central sympathetic nervous system.

Consequences of increased central sympathetic tone

Increased renal sensory afferent signaling, following its integration in the posterior hypothalamus, directly influences central sympathetic outflow, not only restricted to the kidneys but evident throughout the entirety of the sympathetic system [1] (Fig. 3). Outbound sympathetic nerve fibers innervate all organs that are involved in the direct control of peripheral vascular resistance, management of central and peripheral chemo receptors, directly influence cardiovascular contractility, heart rate and rhythm, management of total body salt and water through both renal mechanisms and control of intravascular circulating blood volume through alterations in tone of the splanchnic storage vessels and of course the kidney itself [2]. Thus, reduction of excessive central sympathetic activity, following the selective removal of renal signals to the hypothalamus, is therapeutically attractive in the treatment of disorders commonly linked by sympathetic over-activity [17]. The consequences of elevated central sympathetic drive underlie the many diseases that are found to cluster with hypertension and systolic heart failure, such as insulin resistance, sleep disorders, diuretic resistance and congestion [18].

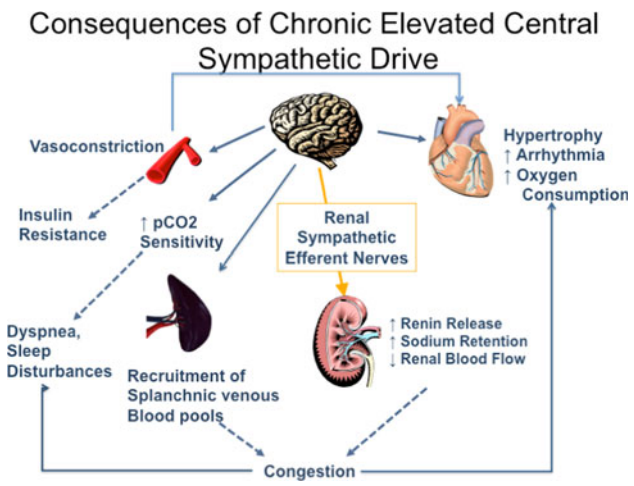

Fig. 3 Cardiovascular consequences of chronic elevated central sympathetic signaling

Specific consequences of increased sympathetic efferent signaling to the kidney

The sympathetic nerves to the kidneys terminate in the blood vessels, the juxtaglomerular apparatus, and the renal tubules [19]. Stimulation of the renal sympathetic nerves cause increased renin release, increased sodium reabsorption, and a reduction of renal blood flow [2]. These nerves, exclusively noradrenergic, have a graded response to nerve stimulation including increased renin secretion rate; increased proximal tubular sodium reabsorption; and direct adrenergic-mediated increases in renal vascular resistance. It has been discussed that essential hypertension is largely neurogenic, both initiated and sustained by sympathetic nervous system over-activity proved with studies using radiotracer dilution methodology measuring spillover of noradrenaline from the kidney to plasma [3, 20–22]. Beyond essential hypertension, efferent sympathetic traffic is logically linked with the three major physiologic features identified as the renal component of the "cardiorenal syndrome" [23, 24]: excess renin release, rightward shift of the pressure-natriuresis relation and reduced renal blood flow and glomerular filtration rates. These three consequences of heightened sympathetic tone to the kidney portend heightened morbidity and mortality rates.

Efferent sympathetic nerve activity is increased in systolic heart failure, as demonstrated by an excessive increase of noradrenaline synaptic spillover to plasma from both the heart and kidney [23]. Intravenous infusion of the centrally acting alpha adrenoceptor agonist clonidine, at modest doses, significantly attenuates cardiac and renal sympathetic tone in heart failure patients [25]. Beyond the noted beneficial cardiac effects of antiadrenergic therapy in heart failure, the renal sympatholytic effects counteract direct neuro-mediated tubular salt retention. Consistent with this notion is the predictive value of renal sympathetic activation on all-cause mortality or need for heart transplant in patients with congestive heart failure [26]. The contribution of increased renal noradrenaline spillover in heart failure as a predictor of mortality is independent of overall sympathetic activity, glomerular filtration rate, and left ventricular ejection fraction [23]. Evidence-based treatment with beta-blockers in patients with chronic heart failure reduces morbidity and mortality, due to blockade of the effects of excessive sympathetic activation on the heart [27, 28]. These findings suggest treatment strategies that further reduce renal sympathetic activation, and in particular renal sympathetic efferent signals, have the potential to improve survival in patients with heart failure.

Both advanced chronic kidney disease and end stage renal disease are characterized by heightened efferent sympathetic nervous system activation [29]. Centrally acting sympatholytic agents, such as moxonidine delay the progression of renal failure, and reduces MSNA in normotensive patients with type I diabetes mellitus, in the absence of blood pressure changes [7, 30, 31].

Consequences of chronic elevated central sympathetic tone

Essential hypertension

Bilateral renal denervation prevents or attenuates the development of hypertension in a large number of diverse animal models of experimental hypertension including genetic, salt sensitive, obesity related, renovascular, and other hypertension models [2, 32–34]. Only models of volume expansion with hormonal activation, such as the one-kidney, one-clip model of hypertension, are associated with elevated blood pressure in the absence of involvement of the renal sympathetic axis [35]. In other models, the renal sympathetic axis causes, promotes or sustains blood pressure across species and hypertension models. These findings corroborate the notion that renal sympathetic nerves represent a critical link between the sympathetic nervous system and the kidney in essential hypertension.

Approximately 70% of incident hypertension is associated with overweight and obesity [36]. The potential for renal denervation to treat obesity-related hypertension has been investigated in a chronically instrumented, high-fat fed dog model, which is characterized by sodium retention and increased sympathetic nervous system activation [34]. Whilst the high fat diet resulted in a 50% increase in body mass in both control and denervated dogs, blood pressure increased significantly only in the control but not in the denervated dogs. Furthermore, sodium retention was reduced by 50% in the denervated dogs. Extension of this principle to man has been demonstrated in the Symplicity HTN-2 trial of therapeutic renal denervation in resistant hypertension. Patients failing to attain blood pressure control, despite an average of more than five medications, experienced a 6 months reduction of office blood pressure by −32/−12 mmHg compared to well-matched controls [16]. With a mean body mass index of 31 kg/m [2] most of the included patients were overweight or obese. The reduction of blood pressure alone is anticipated to have significant impact on the risk of developing cardiovascular diseases in these patients.

Obstructive sleep apnea in resistant hypertension

Obstructive sleep apnea, often considered a cause of resistance in patients with essential hypertension, may also be a consequence of increased central sympathetic tone [37, 38]. A recent observational series of patients with sleep study pre and post renal denervation for resistant hypertension suggests that denervation and/or blood pressure reduction alone reduces the frequency of apneic–hypopneic episodes [39]. Reduction of renal mediated salt and water expansion, a consequence of reducing renal sympathetic efferent signaling and neurologic mediated volume expansion [38], could be expected to reduce the occurrence or severity of obstructive sleep apnea in patients with overt or those with subtle volume expansion. Patients with obstructive sleep apnea have elevated muscle sympathetic nerve activity [40], which is reduced following adequate treatment of the obstruction. The suggestion that it is the over-activity of the sympathetic system that underlies some of the obstruction needs further testing.

Insulin resistance

That insulin resistance has been found in lean as well as in weight matched hypertensives suggests that insulin resistance is related to the basic determinates of blood pressure [41]. Julius et al. [42] proposed in 1991 that pressure induced restriction of the microcirculation limits nutritional flow, and thereby impairs glucose uptake in the skeletal muscle. While other factors are likely operative, two recent studies have observed profound changes in insulin resistance following renal denervation for the treatment of resistant hypertension [43, 44]. Euglycemic hyperinsulinemic clamp studies in conjunction with assessment of total body noradrenaline spillover and muscle sympathetic nerve activity before and after renal denervation in patients with polycystic ovary syndrome demonstrated an association between reduction of total body spillover, sympathetic nerve activity and improved insulin sensitivity measured with clamp [44]. A second and larger series, in resistant hypertensive patients undergoing renal denervation has documented a dramatic change in fasting insulin, C-peptide and calculated HOMA-IR with 20% of patients were documented to improve diabetic status (from glucose intolerance to normal or from diabetes to glucose intolerance) 3 months after renal denervation [43]. Beyond questions of insulin level and diabetic risk, the application of renal denervation to prevent development of structural renal changes due to early diabetic nephropathy has previously been explored [45]. Functional and anatomic studies performed 2 weeks after the onset of streptozotocin-induced diabetes in denervated rats revealed attenuation of

physiologic and anatomic findings of early diabetic nephropathy. Studies in humans demonstrated that sympathoinhibition with the centrally acting drug moxonidine reduced microalbuminuria in normotensive patients with type 1 diabetes, in the absence of any significant blood pressure changes [30]. Both the change in diabetic state and the profound reduction of insulin levels in these initial reports may have profound implications on cardiovascular risk. The calculated 10-year change in cardiovascular risk associated with blood pressure reduction and improvement in diabetic state appears to be more than additive. Preclinical observations on renal protection against diabetic glomerular sclerosis coupled with the human data on renal denervation resulting in reduced blood pressure with improved insulin sensitivity justify additional study in this area.

Congestion

Heart failure associated with reduced systolic function or congestion (or both) is characterized by substantial neurohormonal activation in heart, kidney and skeletal muscle [23, 46]. These neurohumoral responses include activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, further aggravating heart failure by increasing ventricular afterload and preload. Initial measures of serum noradrenaline verified an inverse relation between serum levels and mortality, which was initially hypothesized to be a hormonal marker of hemodynamic stress, and later with the appreciation of the value of beta blockers to improve morbidity and mortality in heart failure, felt to itself be a mediator of the increased mortality rates [47, 48]. Moreover, renal noradrenaline spillover is an independent predictor of heart transplant free survival; patients with elevated serum norepinephrine experience rates of mortality three times higher in untreated than treated heart failure patients [2, 23, 49]. Renal sympathetic efferent traffic can underlie congestion due to frequency dependent release of renin, sodium retention in the proximal tubules and elevation of renal vascular resistance [2]. Renin release, and subsequent generation of local angiotensin II directly stimulates proximal tubular sodium reabsorption by activating sodium bicarbonate co-transporters and sodium hydrogen exchange [50] and also by causing vasoconstriction of the efferent renal arteriole, lowering peritubular hydrostatic pressure [51]. Aldosterone, acting within the distal tubule and collecting duct, up-regulates and activates the basolateral Na/K pumps retaining remaining intraluminal Na. The clinical importance of the sympathetically mediated impact on fluid retention is evident even after standing, which increases renal sympathetic efferent signaling in heart failure and hepato renal syndrome [2]. Upright posture alone decreases eGFR and raises plasma concentrations of noradrenaline, renin and aldosterone in both hepato renal and heart failure patients [52]. The effects of chronic activation of efferent renal signaling on total body Na and water balance are likely critical in edema and congestion formation. The natriuretic peptides are considered markers of volume expansion, however, they may also serve as indicators of excess renal efferent signaling [53]. The natriuretic actions of natriuretic peptides are reduced in heart failure. Thematically, the family of natriuretic peptides may represent compensation to the anti natriuretic consequences of renal sympathetic activity and other activated vasoconstrictor systems. Experimental ligation of renal nerves protects against development of postprandial natriuretic resistance and the development of congestion or rises in ventricular filling pressures [54]. The therapeutic value of renal denervation in heart failure was evaluated in a similar experimental model of coronary ligation induced myocardial infarction in rats [55]. This study, in which renal denervation was performed pre-onset of myocardial infarction, demonstrated reduced ventricular filling pressure and improved ventricular function compared to non-denervated controls [55]. More recently, evidence from a rabbit model with pacing induced heart failure demonstrated that the reduction in renal blood flow and the increase in renal vascular resistance can be prevented by surgical renal denervation, indicating that renal sympathetic nerve activity elicits a detrimental effect on renal blood flow [56]. Equally important in this later study, expression of angiotensin receptors was found to be dependent on sympathetic innervation [57]. Beyond renal management of volume, the appreciation that circulating blood volume can abruptly be altered by neurologically recruiting splanchnic venous storage blood pools suggests that increased central sympathetic drive has potential to both increase total body salt and water through renal mechanisms as well as abruptly change circulating volume by recruiting splanchnic venous stores of blood [2]. This neurogenic mechanism may explain the often clinically frustrating finding in patients who experience dramatic increases in dyspnea and pulmonary congestion in the absence of either weight changes or abnormalities of ventricular function, i.e. sympathetically mediated changes in circulating volume.

Central sympathetic control of sensory afferent receptors—sympathetic underpinnings of central sleep apnea and dyspnea

Like the peripheral pO_2 receptor, the central pCO_2 receptor set point and gain are sympathetically modifiable [58]; suggesting that the clinical appreciation of dyspnea may reflect sympathetic hyperactivity quite independent of the

mechanism by which alveolar and interstitial lung water stimulate interstitial pulmonary juxtacapillary receptors. A leftward shifted set point of the central pCO_2 receptor in heart failure is well recognized, as the chronic metabolic alkalosis is ubiquitous, and on occasion the development of central sleep apnea, a manifestation of the shift being so leftward that the trigger point for inspiration is not reached [59]. Certainly, restoring a normal set point and gain of the central pCO_2 receptor from the pathological altered set point could obliterate central sleep apnea. Dyspnea is most often considered a consequence of increased alveolar and interstitial lung water, however, it is not significantly improved following diuretic therapy except in the patient with alveolar water [60]. On the other hand, dyspnea is principally a consequence of hypersensitivity to pCO_2. If renal denervation can restore normal minute ventilation response to pCO_2, then this direct consequence of diastolic and systolic heart failure, i.e. exercise intolerance, may be amenable by renal denervation.

Diuretic resistance and the cardiorenal syndrome

Escalating doses of diuretics are associated with worsening prognosis in heart failure [61, 62]. Although generally interpreted as a sign of worsening intrinsic heart function, the resistance to diuretics, in particular furosemide, may indeed reflect renal sympathetic mediated Na reabsorption proximal to the more distal sites of furosemide action [63]. Thus, congestion and natriuretic resistance may reflect underlying increased renal sympathetic activity. This principle has been previously observed following the increase of renal sympathetic signaling associated with standing in patients with either heart failure or hepatorenal syndrome [52]. The consequences of increased renin release associated with renal sympathetic activity, increased angiotensin II and aldosterone, both act to increase salt and water retention and interfere with pharmacologic intervention [1]. Worsening renal function observed in heart failure patients is associated with increased morbidity and mortality. In a pacing rabbit heart failure model, the elevations of renal resistance and reduction of blood flow observed with the development of heart failure were entirely restored to normal following renal denervation [57]. Additionally, renal AT1R expression was increased by approximately 67% and AT2R expression was decreased by approximately 87% in rabbits with heart failure. In contrast, kidneys from denervated rabbits with heart failure showed a near normalization in the expression of these receptors [57]; suggesting that the renal hormonal milieu is in large part consequent upon underlying renal sympathetic efferent state. The best-described consequence of cardiorenal disease is the staggering prevalence of cardiovascular mortality seen in patients with either chronic or end stage renal disease or both [24]. The possible clinical value of therapeutic native kidney denervation or nephrectomy for the attenuation of cardiovascular disorders remains entirely unexplored, yet the ease and reported safety of the endovascular therapeutic renal denervation may allow this experiment to be conducted with relatively little risk to the end stage renal disease patient.

Tachycardiac arrhythmias

Both atrial and ventricular arrhythmias are associated with sympathetic hyperactivity [64, 65]. The sinus tachycardia of heart failure may represent primary elevations of cardiac efferent signaling. Recent studies of drugs that reduce heart rate without additional systemic effects have demonstrated improvements of cardiovascular mortality in heart failure similar to the findings of beta-blockers, which also reduce heart rate [66, 67]. The ventricular response rate in atrial fibrillation is often an expression of sympathetic state. The underlying ventricular rate in atrial fibrillation has been observed to fall following renal denervation in resistant hypertension (Felix Mahfoud, personal communication). While this may represent changes in myocardial work and stress associated with blood pressure declines, there may also be reductions in direct cardiac sympathetic signaling. Similarly, left stellate cardiac ganglionectomy has been reported to both reduce heart rate and shorten the QT interval [68].

From theory to practice

Reduction of central sympathetic activity following baroreceptor stimulation has been reported with the Rheos baroreceptor stimulator, and this carotid strategy may indeed exhibit similar systemic properties. Further, the reduction of central sympathetic stimulation associated with nerve stimulation from the carotid sinus may result in substantially reduced renal sympathetic efferent signaling [69]. Therapeutic renal denervation has been applied in a controlled randomized trial for the treatment of resistant hypertension with a significant reduction of systolic blood pressure, diastolic pressure and pulse pressure at 6 months [16]. Reduction of insulin resistance has been anticipated in preclinical work, and confirmed in man using gold standard euglycemic hyperinsulinemic clamp and the calculated HOMA-IR in two different models of excess sympathetic state [43, 44]. While this confirms the hypothesis, prospective randomized clinical trials remain to be conducted and are currently underway. Sleep disorders, similarly may be a reflection of the underlying sympathetic state, and a logical diagnostic and treatment strategy may target

treatment of the sympathetic state, and later consideration of supplemental ventilator support. Certainly, the congestion that accompanies systolic and diastolic heart failure may be mediated in part by neurologic mechanisms. Removal of both the renal somatic afferent and sympathetic efferent conduction may address both the total body excess volume and the maldistribution of stored blood. Lastly, the functional renal component of cardiorenal syndrome, including diuretic resistance, may indeed be an immediate reflection of the functional efferent renal sympathetic activity, and a clinical trial to discern this physiology in humans is shortly to begin.

Conclusions

Afferent somatic signals arising from the kidney and efferent sympathetic activity to the kidney can mediate effects on wide range of chronic conditions. Interventional renal denervation has been shown to successfully reduce blood pressure and improve insulin resistance in patients with resistant hypertension. Further investigations are needed to study the effects of selective renal denervation in other entities linked by elevated sympathetic activity.

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