Effects of sympathetic modulation in metabolic disease

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Abstract

Sympathetic overdrive contributes to the derangement of glucose metabolism evident in clinical conditions such as obesity, metabolic syndrome, type 2 diabetes, obstructive sleep apnea and others. Targeting the sympathetic nervous system directly therefore appears as an attractive therapeutic approach to restore impaired glucose metabolism. Indeed, lifestyle interventions including healthier diets and exercise have been shown to exert their beneficial effects at least in part by reducing sympathetic nervous system activity. Pharmacologic inhibition of exaggerated central sympathetic outflow has also been demonstrated to beneficially impact on body weight, glucose and lipid metabolism. More recently, catheter-based renal denervation, an intervention applied predominantly to lower elevated blood pressure in patients with resistant hypertension, revealed salutary effects on glucose metabolism. Here, we review the mechanisms that contribute to the beneficial effects of targeting the sympathetic nervous system directly and discuss how these approaches may best be embedded in routine clinical practice.

Introduction

The sympathetic nervous system (SNS), once thought to predominantly cater for the extreme flight and fight responses, in fact plays an integrative regulatory role to sustain cardiovascular and metabolic homeostasis. Central sympathetic overdrive is the hallmark of several important clinical conditions including hypertension (HTN) and cardiovascular, renal and metabolic disorders. Under normal circumstances, sympathetic outflow to the heart increases cardiac output and facilitates neurally mediated vasoconstriction of the peripheral vasculature to maintain blood pressure (BP) levels. Renal sympathetic outflow impacts renal hemodynamics, increases renin release thereby activating the renin angiotensin system (RAS) cascade, and causes sodium and water retention to regulate BP¹. Of note hypertension often coexists with obesity and other metabolic disorders². In addition to well-described effects on cardiometabolic conditions, SNS activation differentially regulates immune-mediated pathways to sustain the inflammation³ implicated in the derangement of metabolic homeostasis and is evident in patients with diabetes, patients with obesity, and patients with the metabolic syndrome⁴. Sympathetically -induced chronic inflammation⁵ seems to contribute substantially to both acute and long-term BP elevations and its adverse consequences^{6,7} [Fig 1].

Targeting sympathetic activation therapeutically appears as a logical approach not only in the management of cardiovascular disorders such as hypertension and its complications but likely also in metabolic conditions associated with sympathetic activation. Aside from lifestyle interventions, the strategies used to achieve SNS inhibition are pharmacotherapy and device-based approaches. Though the pharmacological approaches are safe, management of resistant hypertension becomes increasingly difficult with metabolic co-morbidities partially due to inadequate targeting of the SNS⁸. Hence sympathetic ablation using device-based therapeutic strategies such as renal denervation and carotid body ablation gained interest as hypertension in many patients remained poorly controlled with pharmacotherapy alone. Whilst carotid body

ablation is still at its nascent stages, accumulating evidence suggests that renal denervation is a viable option to target sympathetic activation in the management of treatment-resistant hypertension and other clinical conditions associated with increased sympathetic drive⁹ with the benefit of salutary effects on glucose metabolism.

Renal Sympathetic Denervation for targeting sympathetic overdrive.

Renal artery denervation (RDN) though reported as early as 1924¹⁰, has re-emerged as a promising treatment for hypertension recently owing to its multitude of cardiovascular and metabolic benefits including improved blood pressure control, regression of left ventricular hypertrophy and diastolic dysfunction, as well as improved insulin sensitivity and lipid profile¹¹⁻¹⁴. However, the clinical studies that assessed the overall effect of RDN as a possible therapeutic option has shown diverse results^{12,15-17}. The first proof-of-concept trial, SYMPPLICITY HTN-1 that evaluated RDN, demonstrated that catheter-based denervation led to a substantial BP reduction without any serious adverse events,¹¹ both at 6 months and subsequent follow ups compared with standard antihypertensive pharmacotherapy^{18,19}. Following this, SIMPLICITY HTN-2 trial showed similar significant blood pressure reduction in the RDN group compared to the control subjects¹². However, both these were limited in that not blinded and did not include a sham-controlled design. Other limitations included incomplete standardisation of blood pressure measurement and absence of assessment of adherence to antihypertensive medication. The SYMPPLICITY HTN-3 trial, designed as a prospective, sham controlled study thereby addressing the shortcomings of the initial RDN trials failed to demonstrate a more pronounced BP lowering effect of RDN compared to a sham-procedure^{19,20}.

The outcome of the SYMPPLICITY HTN-3 trial tossed RDN into hibernation despite criticism relating to study conduct, incomplete denervation and lack of circumferential, four quadrant sympathetic fibre interruption. The SYMPPLICITY HTN-4 clinical trial that was planned to follow SYMPPLICITY HTN-3 to investigate patients with moderate uncontrolled HTN was halted as SYMPPLICITY HTN-3 failed to meet its primary efficacy endpoint. However, the DENER-HTN trial, designed to address the major concern of lack of antihypertensive standardization and adherence in the SYMPPLICITY HTN-3 trial clearly demonstrated the supremacy of RDN when delivered with a standardized stepped-care antihypertensive treatment approach over the same standardized stepped-care antihypertensive treatment alone²¹. Clearly, SYMPPLICITY HTN-3 and DENERHTN trials identified the need to characterize patient populations that may benefit most from RDN²². In support of this view, the study by Kario et al indicated that patients with concomitant obstructive sleep apnea seemed to respond more favourably to RDN²³.

Importantly, trial designs were adjusted to overcome issues identified in previous studies and three rigorously executed sham controlled studies with similar protocol design were recently published (SPYRAL HTN-OFF MED, SPYRAL HTN-ON MED, and RADIANCE-HTN SOLO²⁴⁻²⁶) and all consistently demonstrated a significant BP effect compared to sham control [Fig 2]. However, the magnitude of BP reduction achieved was smaller in comparison to the uncontrolled, unblinded RDN studies and was similar to changes expected from drug therapy modification^{19,22,27}.

In addition, these studies excluded patients with isolated systolic hypertension who form around 70% of the elderly population, thereby data from these studies are not applicable to this important group. Hence, future trials are still warranted to reconcile the true efficacy of RDN in the treatment of hypertension and various other cardiac and metabolic conditions. Nevertheless, RDN is again considered a valuable alternative to lower BP in clinical practice.

Indeed, results from these studies prompted a meeting of the US Food and Drug Administration Circulatory System Devices Panel in December 2018, to discuss recommendations regarding clinical evaluation of anti-hypertensive devices ²⁸. It is hence worthwhile to revisit the mechanisms underlying the effects of renal denervation, and its potential in the management of cardio metabolic disorders.

Mechanisms of RDN-induced clinical benefits

The innervation of the kidneys includes efferent sympathetic fibres originating from central nervous system nuclei traversing to the kidney as well as afferent sensory fibres from the kidneys projecting to integrating nuclei in the brainstem [**Fig 3**]. Increased central sympathetic outflow directed towards the kidneys reduces renal blood flow, stimulates renin release, and enhances the tubular reabsorption of sodium and water ²⁹. Studies in rat models reported that RDN decreases blood pressure independent of renin release or sodium-water balance and did not impact the salt sensitivity of arterial pressure³⁰⁻³³. In addition, the afferent sympathetic signalling also contributes to the off target antiarrhythmic effect and other metabolic and long-term effects of RDN. Animal studies have shown that bilateral RDN led to substantial neuronal remodelling in the brain stem and stellate ganglia following RDN procedure³⁴⁻³⁷. The renal efferent sympathetic nerves arising from the second sympathetic ganglion, form a network within the renal artery adventitia³⁸ which is regulated by the rostral ventrolateral medulla (RVLM), the destruction of which substantially reduces blood pressure³⁹. Accordingly, the RDN procedure was introduced to disrupt the sympathetic cross-talk from the kidneys to the brain and vice versa as well as between the two kidneys⁴⁰. Sympathetic ablation by RDN, evident from the reduction in markers of sympathetic activity such as MSNA and noradrenaline spillover⁴¹, reduces vasoconstriction, improves metabolism and cardiac performance, with favourable renal effects⁴². Moreover, RDN blocks adverse renal stimuli

(i.e. renal ischemia, electrolyte imbalance, oliguria, high adenosine levels) from being projected to the relevant brain regions in turn attenuating central sympathetic outflow to other organs.

In addition, RDN ameliorates SNS-dependent modulation of immune pathways that causes metabolic perturbations such as insulin resistance and hyperinsulinemia and vice versa. Sympathetic activation triggers inflammation of the skeletal muscle vasculature, brain, and kidneys and contributes to chronic elevation in BP⁴³⁻⁴⁵ along with metabolic disturbances. In clinical conditions associated with high sympathetic drive, a chronic systemic low-grade inflammatory environment is established and sustained by activated immune cells and increased cytokines in the circulation⁴⁶⁻⁵⁰. Distinct clinical states such as obesity, metabolic syndrome and type 2 diabetes as well as obesity related hypertension are characterised by immune activation and increased circulating inflammatory cytokines and interleukins exerting metabolic stress, perturbing systemic homeostasis⁴⁹⁻⁵⁴. Bilateral chemical ablation of renal sympathetic nerves in mice inhibited immune activation, renal inflammation and attenuated Ang II-induced hypertension⁵⁵. Similarly, RDN attenuated hypertension and renal inflammation in the rat deoxycorticosterone acetate-salt model of hypertension, which was driven by renal inflammation-induced augmented afferent sympathetic trafficking⁵⁶. In addition, catheter-based renal denervation induced reduction in SNS activity not only lowered BP but also reduced monocyte activation and inflammatory cytokines in patients with arterial hypertension⁵⁷.

The metabolic effects of RDN

Heightened sympathetic activation induces insulin resistance⁵⁸ and obesity⁵⁹ and contributes to the development of diabetes mellitus⁶⁰ and metabolic syndrome⁶¹ with the resultant hyperinsulinemia causing further sympatho-excitation^{62,63}. Around 50% of patients with

essential hypertension are insulin resistant,⁶⁴ and hypertension often coexists with obesity^{65,66}. Increased adiposity, insulin resistance and hyperinsulinemia have been directly related to enhanced muscle sympathetic nerve activity (MSNA) activity^{67,68}. The vascular resistance induced by sympathetic activation causes a shift of blood flow from striated muscle to viscera, which is less insulin sensitive than striated muscle. In addition, the prevalence of hypertension is associated with impaired postprandial insulinemia⁶⁹. Sympathetic inhibition by dietary measures predicts the weight loss in metabolic syndrome^{70,71}. These findings form the pathophysiological rationale for the introduction of RDN as potential strategy for amelioration of perturbed metabolic homeostasis.

Inhibition of central sympathetic outflow with the centrally acting imidazline receptor agonist moxonidine is associated with improvement of glucose metabolism by increasing the skeletal blood flow, decreasing glucagon secretion that accompanies reduced glycogenolysis and gluconeogenesis⁷². However, the use of centrally acting sympatholytic agents can be limited by side effects, leading to relatively high non-adherence rates.⁷³ In this context RDN is a potential option to ameliorate glucose metabolism⁷⁴. RDN reduces norepinephrine release, attenuates α -adrenergic tone, and reduces RAS activation with salutary consequences on striated muscle blood flow⁷⁵. This improvement in peripheral blood flow in turn facilitates insulin delivery to the skeletal muscle enhancing glucose uptake and utilisation⁷⁶. Sympathetic overactivity renders hypertensive patients more susceptible to weight gain associated with reduced responsiveness of adrenoceptors⁷⁷. Increased SNS activity promotes insulin resistance and central adiposity, which in turn has been associated with higher rates of sleep apnea⁷⁸ and further exacerbation of impaired glucose metabolism. In obese patients with resistant hypertension and concomitant obstructive sleep apnea, attenuation of sympathetic overdrive induced significant weight

loss⁷⁹, ameliorated BP and improved metabolic parameters^{76,78}. Taken together, RDN could provide a sustainable therapeutic option in obesity related hypertension, particularly in those with concomitant sleep apnea, to improve BP and possibly metabolic homeostasis.

Indeed, clinical data suggest that RDN is a potentially valuable intervention in metabolic diseases associated with BP elevation with a likely reduction in cardiovascular risk. RDN besides reducing BP, improved glycosylated haemoglobin levels and attenuated sleep apnea severity with improvement in indices of insulin action and metabolic parameters in patients with resistant hypertension^{72,79}. The EnligHTN I trial⁸⁰ showed that RDN could potentially benefit patients with heart failure as there was a significant reduction of average heart rate⁸¹. In addition, RDN was associated with reduction in left ventricular mass, improvement of atrial and ventricular arrhythmias⁸² and diastolic parameters as well⁸³. Moreover, RDN improved indices of renal resistance and ameliorated the severity of macroalbuminuria and microalbuminuria⁸⁴. Interestingly, in hypertensive patients with diabetes mellitus, RDN improved glucose metabolism and insulin sensitivity^{72,78}. Furthermore, the benefits of RDN has been extended to combined metabolic and endocrine disorders. In polycystic ovary syndrome, RDN improved blood pressure and fasting glucose with parallel improvement in insulin sensitivity along with a reduction in glomerular hyperfiltration and urinary albumin excretion⁸⁵. RDN also slows the progression of renal injury in diabetes which had already been proven in an animal model⁸⁶.

However, the DREAMS-Study⁸⁷, investigating the effects of RDN on blood pressure and insulin sensitivity in patients with metabolic syndrome neither showed a change in fasting glucose, insulin sensitivity nor improved sympathetic activity⁸⁸. The DREAMS-Study included nearly drug-naïve patients with higher sympathetic activity compared to other studies^{89,90} and would have been expected to demonstrate at least a reduction in

sympathetic activity⁹¹. Whether insufficient denervation may have contributed to this finding is uncertain but remains a possibility. The study lacked a control group and the small size of the cohort makes it difficult to draw any firm conclusions. Further evaluation in the form of rigorously designed clinical trials are mandatory and ongoing to confirm the previously reported beneficial effects of RDN in diabetes mellitus.

Limitations and potential complications of renal denervation

It is now exactly 10 years ago that the results from Symplicity HTN-1, the first safety and proof-of-concept study applying RDN in patients with resistant hypertension was published¹¹. However, longer term follow up data is thus far only available for up to three years from Symplicity HTN-1¹⁸, Symplicity HTN-2⁹⁴, and from the Global Symplicity Registry⁹⁵. This is mainly due to the fact that follow up was only planned for three years following the procedure. Although safety of the procedure was demonstrated in all these studies, longer term follow up data together with reporting of cardiovascular and renal endpoints would be useful. The Global Symplicity Registry is collecting these data and will help to close this gap in the future. A very recent meta-analysis reviewing the efficacy and safety of renal denervation within the 6 trials that had a sham-control arm⁹⁶, reported that no major peri-procedural adverse events were reported in either group in 5 of the 6 trials and that the SYMPPLICITY HTN-3 trial reported major adverse events in 1.4% of the RDN group and 0.6% of the sham controlled group. They concluded that patients treated with RDN experienced significantly greater reduction in 24-h ambulatory systolic blood pressure and that adverse events associated with the RDN procedures were rare⁹⁶. While these findings are reassuring long term safety and efficacy will have to be monitored in ongoing studies.

Effects of other interventional sympatholytic approaches on glucose metabolism

Baroreflex activation therapy (BAT) is another relevant intervention targeting sympathetic pathways. Indeed, the procedure has been demonstrated to significantly reduce arterial blood pressure (BP) by inhibition of the sympathetic nervous system. The effect of this approach on the metabolic state has been tested in patients with resistant hypertension. Wallbach et al.⁹⁷ prospectively assessed the effects of BAT in a cohort of 30 patients with resistant hypertension on blood pressure, BMI, weight, fasting glucose, insulin, C-peptide, HbA1c, HOMA-IR, HOMA-b, ISQuickI, and glucose levels during oral glucose tolerance test, both at baseline and 6 months after the procedure. While fasting glucose levels were significantly reduced at 6 months follow up, all other parameters remained essentially unchanged. The authors concluded that BAT is effective in reducing BP but may only have minimal effects on the metabolic state at 6 months. In line with these findings, a study in obese hypertensive dogs exposed to BAT revealed sustained reductions in BP, heart rate and plasma norepinephrine concentrations, but no changes in plasma glucose or insulin concentrations⁹⁸. Together, these findings may indicate that potential beneficial effects of interventions to lower sympathetic activity may have disparate effects on glucose metabolism.

Future Perspectives and Conclusions

The exact mechanisms by which RDN impacts on insulin metabolism and glucose homeostasis remain to be fully understood. They are likely to involve a concerted interplay of complex mechanisms such as modulation of afferent signaling to reduce central sympathetic outflow, interference with the RAS cascade, a decrease in alpha adrenergic vascular tone dilating skeletal muscle vasculature, increased insulin and non-esterified fatty acid sensitivity, and improved glucose uptake and transport to skeletal muscle⁹¹⁻⁹³. Recent studies applying RDN in patients with diabetes have several limitations including small sample size, lack of adequate control groups, short follow up and others. Beneficial

effect of the RDN induced BP reduction per se which could account for the improvements in glucose metabolism cannot be excluded. Future studies in the metabolic area are required to address these limitations and to confirm the previous results and enhance the understanding of the potential beneficial impact of RDN on metabolism in patients with metabolic syndrome and diabetes. The results of ongoing RDN clinical trials in diabetes (NCT 02081989) and metabolic syndrome (NCT 01911078) performed to determine the effects of sympathetic ablation by RDN on glucose metabolism and insulin sensitivity, will further define the role and applicability of RDN in metabolic disorders.

Disclosures

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Figure Legends:

Figure 1: Sympathetic overdrive induces immune activation that causes inflammation and organ damage. The immune cascade is sustained by the bidirectional interaction between the sympathetic nervous system and immune mechanisms causing immune infiltration and immune-mediated inflammatory damage in the organs regulating blood pressure to result in the derangement of cardiovascular and metabolic diseases.

Figure 2: Comparison of 24-hr systolic and diastolic blood pressure (SBP and DBP) changes in renal denervation vs sham-control groups in the 3 recent randomized, sham-controlled clinical trials showed. ABPM indicates ambulatory BP monitoring; CI, confidence interval; HTN-ON MED, Spyral Hypertension on Medication trial; HTN-OFF MED, Spyral Hypertension OFF Medication trial; and RADIANCE-HTN SOLO, RADIANCE hypertension solo (off medication) trial. *Reprinted from Kandzari et al, 1 Azizi et al, 2 and Townsend et al 3 with permission. Copyright © 2018, Elsevier.*

Figure 3: Renal Sympathetic Innervation includes efferent sympathetic fibres originating in the central nervous system and traversing to the kidney as well as afferent sensory fibres from the kidneys to hypothalamus. Increased sympathetic outflow to the renal vascular bed reduces renal blood flow, releases renin, thereby activating the renin-angiotensin-aldosterone (RAAS) cascade and enhances tubular reabsorption of urinary sodium and water. The cardiometabolic consequence of increased sympathetic flow includes cardiac hypertrophy and arrhythmias, endothelial dysfunction and insulin resistance in the skeletal muscle contributing to the development of diabetes mellitus and metabolic syndrome.