The role and management of sympathetic overactivity in cardiovascular and renal complications of diabetes

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Abstract

Feedback activation of neurohormonal pathways in the setting of kidney or heart failure contributes to the development and progression of dysfunction in the other. Diabetes and its management independently activate these same pathogenic pathways, feeding into this vicious cycle and contributing to a poor prognosis. One of the most important of these neurohormonal pathways is the sympathetic nervous system (SNS). The activity of the SNS is increased in patients with chronic kidney disease, even in the absence of renal impairment or heart failure. There is a strong relationship between SNS overactivity and prognosis, and evidence that blockade of SNS reduces morbidity and mortality in patients with diabetes. However, modulation of SNS is underutilised as a strategy to protect both the diabetic kidney and the heart. This is partly because of the historically poor tolerability, adverse haemodynamic and metabolic effects, lack of selectivity of β-blockers and the lack of specificity of other interventions that might modify SNS activation. The advent of “vasodilating β-blockers” with better tolerability as well as more favourable effects on renal function and metabolic profiles opens the door for their more widespread utility in patients with diabetes. Radiofrequency renal sympathectomy and baroreflex activation technologies also offer exciting new ways to tackle the challenge of sympathetic overactivity.

Keywords: Adrenergic; Beta-blocker; Chronic kidney disease; Cardiorenal syndrome; Diabetes; Heart failure; Sympathetic nervous system

Résumé

Le rôle et la gestion de l’hyperactivité du système nerveux sympathique chez des patients diabétiques atteints de complications rénales ou cardiovasculaires.


Mots clés: Béta-bloquant ; Système nerveux sympathique ; Insuffisance rénale ; Diabète ; Insuffisance cardiaque

1. Introduction

Feedback activation of the neurohormonal pathways in the setting of kidney or heart disease contributes to the development and progression of dysfunction in the other. This reciprocal
relationship forms part of the so-called “cardiorenal syndrome” (CRS), and is particularly relevant for the management of patients with diabetes in whom co-morbid disease is almost ubiquitous. Moreover, diabetes and its management may also independently activate these same pathogenic pathways, feeding into this vicious cycle (Fig. 1) and contributing to the worse prognosis of patients with diabetes and CRS [1].

One of the most important of these neurohormonal pathways is activation of the sympathetic nervous system (SNS). Because of the systemic nature of SNS, whether caused by diabetes, hypoglycaemia, stress, obesity, heart or renal failure, SNS activation has the potential to have far-reaching effects. For example, activation of the SNS following the induction of aortic regurgitation in rats directly contributes to intrarenal activation of the Renin Angiotensin Aldosterone System (RAAS), and subsequently podocyte loss and albuminuria [2]. Similarly, in patients with heart failure, renal sympathetic activation is correlated with all-cause mortality in patients with congestive heart failure [3]. The converse is also true as activation of the renal sympathetic output following phenol-induced renal damage is able to induce cardiac hypertrophy and dysfunction, even in the absence of volume expansion or hypertension [4]. Equally, recent evidence suggests that activation of the SNS in the setting of diabetes directly contributes to hypertension, cardiovascular and renal dysfunction. Taken together, these data highlight the SNS as a common pathway by which a host of different factors may promote adverse cardiac and renal outcomes in diabetes. Yet, despite unequivocal evidence for overactivity of the SNS in patients with CRS and/or diabetes, a clear relationship between SNS activation and prognosis [5], and evidence that blockade of excessive sympathetic activation reduces morbidity and mortality in patients with chronic heart failure (CHF) and diabetes [6], and those with CHF and chronic kidney disease (CKD) [7], modulation of SNS is underutilised as a strategy to protect both the diabetic kidney and the heart. This is partly because of the historically poor tolerability, adverse haemodynamic and metabolic effects, lack of selectivity of β-blockers and the lack of specificity of other interventions that might modify SNS activation. This review aims to explore the pathogenesis of the SNS overactivity in the CRS and diabetes, and highlight potential new opportunities for therapeutic intervention.

2. Sympathetic nervous system overactivity in diabetes

It is well known that changes in plasma glucose levels mobilize neuro-endocrine responses that serve to prevent or correct hypoglycaemia. One of these responses is activation of alpha and beta adrenergic activity, which contributes to the classical symptoms of hypoglycaemia. However, this may not be the only consequence of SNS activation. Indeed, it has recently been suggested that recurrent events, even those that are subclinical or self-correcting, may contribute to cardiovascular morbidity and mortality, and antagonise the real benefits of optimal glucose control [8]. This has led to the recommendations that those medications that predispose patients to hypoglycaemia should be avoided if possible in patients with type 2 diabetes and cardiac disease [9]. The same rationale could be applied to patients with CKD in whom hypoglycaemia is much more common, and the impacts of SNS activation are equally important (see below).

However, SNS overactivity is not merely driven by glucose fluctuations in diabetes. Obesity, hyperinsulinaemia, activation of the RAAS, oxidative stress, dysfunctional nitric oxide synthesis and increased circulating non-esterified fatty acids and adipokines including leptin all potentially contribute to heightened adrenergic activity in patients with diabetes [10,11]. In addition, progressive damage to autonomic nerve fibres, affecting the longest fibres of the vagus nerve first, results in parasympathetic denervation and early augmentation of sympathetic tone [12]. Other complications of diabetes including obstructive sleep apnoea, depression and stress also feed in to promote and maintain excessive SNS activation in patients with diabetes.

3. Sympathetic nervous system overactivity in CVD

One of the most powerful compensatory mechanisms activated to support the failing heart is the reflex increase in cardiac adrenergic drive. Unlike many other mechanisms, adrenergic activation accesses all the known means by which myocardial performance can be stabilized or increased. Moreover, it is able to do so immediately by increasing cardiac output through an increased heart rate, augmented myocardial contractility, coronary vasodilatation, systemic arterial constriction and volume expansion through renal retention of sodium and water and activation of other neurohormonal systems including the RAAS. While these responses are vital in the short term, such adaptations may also have significant costs for the heart in the long term including secondary hypertension, vascular stiffening and remodelling, endothelial dysfunction, arrhythmogenicity [13], increased coagulation, and viscosity, increased oxygen consumption, left ventricular hypertrophy and fibrosis [14]. In patients with diabetes, these negative effects may be exaggerated, while positive actions are diminished. For example, in patients with type 2 diabetes, there may be an impairment of coronary microvascular dilation in

Fig. 1. Activation of the sympathetic nervous system by a host of factors contributes to the development and progression of diabetic complications, especially in the heart and the kidneys.
Fig. 2. Two faces of SNS activation in the heart. While acute sympathetic nervous activation is a vital haemodynamic support, chronic activation of the sympathetic nervous system may have a range of adverse actions that contribute to the development and progression of cardiac dysfunction.

response to sympathetic stimulation, even in the absence of macrovascular disease [15]. This imbalance may contribute to increased morbidity and cardiovascular mortality seen in patients with diabetes (Fig. 2) [5]. Indeed, there is a strong relationship between activation of the SNS (from any source) and adverse outcomes in patients with heart failure [16]. While it is often argued that SNS activation is an epiphenomenon (merely a response to increasing stress), data now support a causal relationship. Moreover, blockade of the SNS is able to improve morbidity and mortality in patients with heart failure and CKD [7].

4. SNS overactivity in CKD

There is a strong relationship between CKD and SNS overactivity. Plasma norepinephrine levels and sympathetic nerve activity directed to muscle (MSNA) are chronically elevated in patients with CKD, to levels approximately two-fold greater than in controls [17]. The greatest increase is seen in patients with end-stage renal disease (ESRD). However, SNS overactivity is also a feature of earlier stages of CKD as well, even in the absence of renal impairment [18–20].

As in CHF, the changes induced by SNS activity may be considered adaptive in the short term, including increases in systemic blood pressure, promote sodium retention and maintain filtration pressure, and therein support the homeostatic functions of the kidney. However, these same changes in the long term potentially contribute to renal dysfunction, including a rightward shift of the relationship between blood pressure and sodium excretion (to maintain hypertension rather than prevent it), activation of the RAAS, volume expansion, diuretic resistance, glomerular hypertension, glomerulosclerosis and ultimately nephron dropout in the kidney [21]. A causal relationship between SNS overactivity and renal damage in diabetes is further suggested by anti-albuminuric actions of the centrally acting sympatholytic agent, moxonidine [22], over and above its effect on blood pressure regulation. Beta-blockers and radiofrequency renal denervation have also been ascribed independent anti-albuminuric effects (see below) [23,24].

The mechanisms underlying this sympathetic dysregulation in CKD are complex and multifactoral, encompassing alterations in autonomic reflex pathways, central autonomic neuroanatomical sites as well as hormonal factors. For example, baroreflex sensitivity is decreased in the microalbuminuric patients, even in the absence of neuropathy [25]. In recent times, most interest has focused on reflex activation of the SNS by afferent signals arising in the injured or dysfunctional kidneys. This hypothesis was originally suggested by studies measuring of SNS overactivation in patients on haemodialysis [26] and observing its attenuation following bilateral nephrectomy. While such improvements may have also reflected removal of humoral factors, like renin, the advent of more selective means to target the nerves leaving the kidney including dorsal rhizotomy (in animals) [27] and radiofrequency ablation (in humans) [28] now clearly demonstrates that afferent signals coming from the kidney and returning to the cardiovascular areas of the brainstem lead to centrally regulated sympathetic outflow. Moreover, these signals appear to be enhanced in patients with CKD, as well as those with CHF, diabetes and/or obesity [29].

The precise trigger of this afferent signal coming from the kidneys remains to be firmly established. Certainly, the renal afferents connect to sophisticated network of chemoreceptors and baroreceptors both in the renal vasculature and renal parenchyma. It was originally hypothesised that accumulated ‘uremic toxins’ activated chemoreceptors on these afferent nerves and subsequently downstream SNS in the setting of renal impairment. However, the lack of improvement in SNS overactivity following kidney transplantation despite restoration of renal function suggests that functional changes induced by the remaining diseased kidneys directly contributes to SNS overactivity in patients with CKD. From a clinical stand point, this also means that SNS overactivity and its consequences can also be observed in patients with renal damage in the absence of renal functional impairment [30].

One hypothesis suggests that renal hypoxia in the setting of kidney disease is a key trigger for SNS activation. Hypoxia has increasingly been viewed as common cause and result of progressive renal injury, as microvascular obliteration, tubulointerstitial inflammation and fibrosis lead to hypo-perfusion and reduced oxygen delivery into the renal medulla, while at the same time residual nephrons have increased energy demands due to their increased filtered sodium load. However, the relationship between hypoxia and CKD is far from straightforward. Indeed in the remanent kidney model, which is also associated with SNS activation, renal tissue oxygen levels are paradoxically increased [31]. Similarly, Michaely et al. found no correlation between renal oxygenation on BOLD-MRI and renal function, concluding that progressive renal disease was not associated with reduced intrarenal oxygenation [32]. Taken together, these results suggest that reflex responses to hypoxia are not the
straightforward cause of SNS overactivity in patients with CKD.

Intrinsic renal diseases association with interstitial fibrosis and/or oedema may also be an important trigger for SNS overactivity. Interestingly, purely glomerular disease is less commonly associated with hypertension and SNS overactivity unless there is nephron dropout or interstitial changes as well. A classic example of this phenomenon is the hypertension caused by phenol injection into one kidney which 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, which is prevented by renal denervation of the phenol-treated kidney [33]. Similarly, hypertensive patients with polycystic kidney disease but with normal renal function have been reported to have significantly increased levels of sympathetic activity [30].

Another hypothesis is that increased secretion of adenosine in the damaged kidney leads to increased efferent renal sympathetic nerve activity. Indeed renal hypertension can be replicated by an intrarenal infusion of adenosine, which is eliminated after renal afferent denervation, implicating a role for adenosine in renal nerve stimulation. A number of adenosine receptor antagonists have recently been explored as potential adjunctive treatments for CHF, including rolofylline and tonapofylline. However, further testing of tonapofylline has recently been terminated because of side effects.

5. Central hyper-responsiveness of the SNS in diabetes and the CRS

While renal afferent signalling may be a key initiator of activation of the SNS, overactivity may also result from the loss of central regulation, leading to an unbalanced or excessive response to tonic signals supplied by the renal afferents. Many diabetic patients respond to stressors with an excessive increase in their blood pressure, due to dysregulation of central control mechanisms. As renal afferent represents the major afferent stimulus to these same areas, in this setting, denervation of the renal afferents would still be effective in reducing SNS activity, although overactivity was driven by central dysfunction. In support of this hypothesis, a number of studies have documented changes in the posterior hypothalamus. For example, nitric oxide has a tonic inhibitory effect on central SNS outflow. Decreased bio-availability of nitric oxide associated with diabetes, CHF and/or CKD potentially contributes increased sensitivity (or resetting) to afferent stimuli, of which the kidney and the baroreceptors of the carotid bodies represent key sources. Similarly, oxidative stress, inflammation and activation of the RAAS also potentially serve to promote centrally mediated (renally-stimulated) SNS overactivity.

6. Reducing SNS overactivity – Therapeutic considerations

6.1. β-blockade

There is limited evidence that pharmacological blockade of β-adrenoreceptors (β-blockade) improves cardiac outcomes in patients with CHF and CKD. Some observational studies in patients with CKD have demonstrated better survival and cardiovascular outcomes in those treated with β-blockers [7,34]. Post hoc analyses from larger studies, like the SENIORS, have also suggested that the relative benefits of β-blockade may be at least similar in patients with the CRS when compared to those with isolated CHF [35]. A recent meta-analysis also suggested improvements in all-cause and cardiovascular mortality with β-blocker therapy in patients with heart failure and CKD [7], which in absolute terms may be greater than other clinical settings given the greater absolute risk of adverse outcomes in diabetic patients with both CHF and CKD. Such data further add support to calls for an increased use of β-blockers in diabetic patients with CRS, although randomised controlled trials are still to be performed.

One of most important challenges of using β-blockers in diabetes care is the considerable heterogeneity between different agents within the same class. Each may have different pharmacology, cardio-selectivity, route of excretion, and adjunctive properties such as vasodilatory, antioxidative, calcium-blocking activity and metabolic factors including glucose, lipoprotein, serum potassium levels that influence their efficacy or tolerability in different settings. This means exercising a careful choice of both the right drug and the right patient for β-blockade, and initiating with a slow, careful titration. For example, some patients with relatively fixed stroke volume maintain their cardiac output by an elevated heart rate and SNS-induced inotropy, in whom sympathetic blockade may precipitate a dangerous decline in cardiac output.

The first generation β-blockers, like propranolol, are non-selective competitive inhibitors of both β₁ and β₂ adrenoreceptors. They are generally not used in CHF or CKD as these agents can reduce kidney function, partly by reducing cardiac output. Moreover, unopposed activation of α₁ adrenoreceptors when blocking both β₁ and β₂ adrenoreceptors may induce causes reflex changes in both SNS activity and kidney function by increased peripheral vascular resistance [36].

Second generation β-blockers, like atenolol and metoprolol, have a higher affinity for β₁ adrenoreceptors than β₂, so have less effect on renal blood flow or renal function. However, each has adverse actions on glucose and lipid control, hypoglycaemic awareness and weight gain [37,38] which limit their acceptability for the treatment of patients with diabetes. In addition, some second generation agents like atenolol or sotalol are cleared by the kidney and may accumulate in patients with acute-on-chronic renal impairment, like following a heart attack, surgery or angiographic procedure, and precipitate bradycardia, especially if combined with non-dihydropyridine calcium antagonists [39]. Atenolol is commonly used once daily although its pharmacology (a half-life of 6–9 hours) is more consistent with twice daily. It has been recently argued that the inclusion of atenolol, which is probably not an ideal representative of β-blockers as a class (and exclusion of vasodilating agents like carvedilol), may explain why meta-analyses with β-blockade in patients with CHF have not been as positive as might have been expected [40].

Third generation agents have the additional advantage of inducing peripheral vasodilatation via α₁ adrenoreceptor...
blockade or by augmenting nitric oxide production. This has led to them being called “vasodilating β-blockers”. These agents generally have better tolerability profile than older β-blockers, as well as more favourable effects on renal function and metabolic profiles in patients with diabetes.

Carvedilol is the best studied in CKD of all the third generation β-blockers. It provides non-selective (vasodilating) β-blockade along with α1 adrenoceptor antagonism. At high concentrations, it also has ion channel–blocking activities and potentially useful extra-adrenergic properties including antioxidant, anti-inflammatory, and anti-apoptotic actions and a more favourable metabolic profile [41]. Small studies have suggested benefits in early CKD, including reductions in albuminuria and improvements in renal function [23,37,42]. In the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial, fewer patients on carvedilol progressed to microalbuminuria than those on metoprolol [37]. Carvedilol has also shown a reduction in cardiovascular events in CKD patients with hypertension [43] and survival benefits in patients with CKD and chronic heart failure [44]. Carvedilol is also 96% protein bound, hepatically cleared and is not lost in the dialysate making it a potentially useful agent in patients with severe or rapidly progressing renal disease [39].

Bisoprolol is also a selective β-1 receptor blocker, with a suitable pharmacokinetic profile for use in mild to moderate renal impairment. The CIBIS trials have recently confirmed bisoprolol as a frontline agent for the management of heart failure, although its utility in CRS is presently unknown. Post hoc analysis from CIBIS II trial suggested that improvements in mortality and/or heart failure hospitalisation following treatment with bisoprolol were consistent across all strata of renal function, meaning that the absolute benefit of bisoprolol was greater for patients with chronic kidney disease compared with those without CKD [45]. However, rates of discontinuation were also higher in those with CKD, reflecting the challenge of treating this hemodynamically frail patient group.

Nebivolol is the most selective β1 adrenoceptor antagonist, with a much higher affinity for beta-1 adrenergic receptors than for beta-2 adrenergic receptors [41]. It also has additional extra-adrenergic actions including nitric oxide mediated vasodilatory properties via direct stimulation of endothelial nitric oxide synthase [46]. It is also the only β-blocker whose structure differs fundamentally from that of the first generation agent, propranolol. In addition, the liver predominantly excretes it, although dose reduction is still warranted in patients with severe renal impairment or ESRD. In the SENIORS study, which examined the safety and efficacy of nebivolol in elderly patients with heart failure (HF), a large number had co-morbid renal dysfunction. Again, renal impairment did not influence the relative benefit of nebivolol with respect to all-cause mortality or cardiovascular hospital admission, meaning the absolute benefits were greater in those with CKD [35]. As with bisoprolol, patients with CKD had higher rates of drug-discontinuation, mostly due to bradycardia or hypotension. Recent studies have also explored the potential for direct renoprotective effects, including actions in contrast nephropathy.

6.2. Centrally acting sympatholytic agents

These agents act on the brainstem to inhibit central sympathetic outflow directly by stimulating central α2-adrenergic receptors and/or imidazoline receptors. Clonidine and methyl-dopa, both predominantly central α2 receptor agonists, are effective in reducing SNS overactivity, but may be limited with rebound effects on hemodynamics [47]. Most study has been carried out with moxonidine and rilmenidine, which act predominantly on central imidazoline receptors. Experimental studies have demonstrated that this strategy is able to attenuate glomerulosclerosis over and above its effects on blood pressure control [48]. Similarly, non-hypotensive doses of moxonidine have been documented to improve urinary albumin excretion in patients with diabetes [22] and/or hypertension [49]. Moderate improvements in glucose and lipid control have also been demonstrated [50], partly mediated by improvements in insulin sensitivity [51]. However, the MOXCON trial using high dose moxonidine (3 mg/day) was associated with an early increase in mortality and adverse events (hospitalization for heart failure, myocardial infarction and other adverse events) [52]. Whether conventional dosing (0.2–0.6 mg/day) delivered in slow release formulations offers more favourable effects on the heart and the kidney remains to be established. Moxonidine is contraindicated in patients with renal disease, although low dose alternate day formulations of moxonidine and rilmenidine have both been studied in patients with ESRD [53,54].

6.3. α-adrenergic blockade

Blockade of α-adrenergic receptors with agents including prazosin, doxazosin terazosin and alfuzosin, is able to effectively reduce blood pressure through smooth muscle cell relaxation, reduced vascular tone and decreased peripheral resistance. It has been argued that when unopposed, these agents can cause reflex sympathetic stimulation of the heart. Consistent with this hypothesis, the Veterans Administration Cooperative Study [55] and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [56] suggested that α1-blockade may be associated with a higher incidence of heart failure [29]. By contrast, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) suggested that doxazosin was not associated with an increased risk of heart failure, and had the added advantage of a range of favourable metabolic effects [57]. The potential utility of alpha-blockade in diabetes and/or CRS remains to be formally explored. However, in patients with uncontrolled hypertension, alpha adrenergic blockade provides an important adjunct to other antihypertensive agents.

6.4. RAAS blockade and SNS overactivity

Activation of the RAAS also contributes to SNS activation in patients with CHF and CKD. Angiotensin (Ang) II has both intrarenal and central effects to potentiate SNS signalling. In the brain in particular, Ang II can stimulate SNA activity and reset reflex sensitivity by a direct effect on the vasomotor centres in the brain stem. At the adrenergic nerve terminal, Ang II can
also increase noradrenaline release and inhibit the presynaptic uptake of noradrenaline by nerve endings, thereby enhancing sympathetic adrenergic function. Ang II also resets the arterial baroreflex at a higher blood pressure level. Inhibition of the RAAS has been shown to reduce SNS overactivity in patients with CKD [58], and may represent one of their many pleiotropic benefits in the setting of diabetes. However, these actions on the SNS are partial and modest at best when compared to more direct interventions.

6.5. Statins and SNS overactivity

3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) are also known to have a range of “pleiotropic effects” on cardiovascular risk over and above their actions to lower LDL cholesterol levels. One of these actions has been suggested to be the attenuation of central sympathetic outflow [59], possibly mediated via inhibition of ROCK signalling or indirect effects through reduced vascular stiffness. Whether this is a clinical meaningful reduction in SNS activity remains to be established. Again any effect on SNS overactivity is partial, variable and modest at best.

6.6. Diet, lifestyle and SNS overactivity

Restricting the amount of salt in the diet is frequently recommended to patients with heart failure and/or CKD, chiefly as a means to modify attenuate fluid retention. However, dietary sodium intake is inversely associated with SNS and RAAS activity, such that individuals with a low-sodium intake have the greatest SNS and RAAS activity and vice versa [60]. Given the prognostic significance of such changes, recent work has begun to question the utility of sodium restriction in this context. Indeed, in patients with type 1 diabetes and CKD, a low-sodium intake is associated with an increased risk of ESRD compared to those with a normal or high intake [61]. Similarly, in some studies in patients with heart failure, adverse outcomes including mortality have been reported to be higher in patients on low-sodium diets [62]. However, other studies have suggested the opposite association [63,64]. Taken together, there is insufficient evidence to support or endorse the practice of sodium restriction. Indeed the European Heart Association has recently removed a recommendation for sodium restriction from their heart failure management guidelines.

Regular physical activity is also able to reduce central SNS activity, augment baroreceptor sensitivity and improve clinical outcomes in patients with CKD and CHF [65]. Whether this is a direct relationship or indirect benefit is largely moot in a clinical setting, and all diabetic patients are advised to maintain some physical activity within individuals’ tolerability and safety [66]. Smoking is also associated with SNS overactivity, as well as an increased risk of adverse outcomes in patients with diabetes. For this and many other reasons, smoking cessation should be encouraged. Effective management of sleep disorders like obstructive sleep apnoea, paroxysmal nocturnal dyspnoea and restless legs can also reduce SNS activity. Finally, stress is an important source of SNS overactivity for many people.

A number of studies have demonstrated the benefits of stress management techniques including relaxation therapies, yoga, tai-chi and cardiovascular rehabilitation programs to improvement in clinical cardiovascular parameters (systolic function, heart rate variability, pulse pressure, need for antihypertensive, arterial stiffness), biochemical parameters (hematocrit levels, lipid and glucose profiles), physical parameters (improved aerobic capacity, reaction time, lower extremity muscle strength, de-conditioning), psychosocial well-being in patients with CHF and/or CKD.

7. Renal sympathetic denervation

Radiofrequency ablation of the renal nerves has recently emerged as a practical treatment for resistant hypertension [67]. However, for many years the removal of non-functional kidneys in patients with ESRD and resistant hypertension has been practiced as a means to both control blood pressure and improve cardiac function, usually prior to renal transplantation. The advent of radiofrequency ablation via a catheter-based technique offers obvious advantages for blood pressure control in its ability to selectively injure afferent and efferent sympathetic nerves located in the adventitia of the renal artery. The Symplicity studies have clearly demonstrated that reducing sympathetic tone via intravascular renal denervation is feasible in treatment-resistant hypertension, and that this procedure can achieve long-lasting improvements in the control of blood pressure in addition to other agents, most probably due to a reduction in both renal and central sympathetic activity [68]. Indeed reductions in cardiac and muscle sympathetic activity have been reported following renal sympathetic denervation [69], although its central effects may be variable [70]. In patients with established renal impairment and hypertension, the procedure has proved to be safe and efficacious, at least in the short term [71]. Reductions in albuminuria [24] and improvements in glucose control/insulin sensitivity have also been reported with this procedure [72–74]. Small pilot studies in patients with heart failure have also provided evidence of possible benefits [75]. However, its effects on CHF or in the CRS, or its impact on hard outcomes like mortality, ESRD or cardiovascular morbidity remain to be established and its use outside of refractory hypertension remains experimental at this stage.

8. Baroreceptor-activating therapy

Apart from the kidneys, the other major source of afferent input to the brainstem SNS centres is the arterial baroreceptors of the carotid sinus. Patients with diabetes, obesity, CKD and/or CHF have reduced baroreflex sensitivity, partly due to chronically increased SNS activity that accompanies these states [76]. Structural defects of the baroreflex pathway may also exist in diabetes. Impairment of the baroreflex inhibitory control is regarded as a cause of SNS overactivity. Consistent with this hypothesis, it is possible to reduce central SNS overactivity (and augment antagonistic parasympathetic stimulation) by stimulating the carotid baroreceptors, in effect signalling the brain that the pressure/volume is too high. To achieve this, an
electric device is implanted at the level of the carotid sinus to stimulate the vagus nerve. This strategy has been shown to be able to reduce blood pressure and SNS overactivity in patients with treatment-resistant hypertension [77]. Initial data in a small number of patients with severe heart failure have suggested subjective improvements associated with favourable changes in cardiac parameters [78]. Although the surgical procedure is more involved than endovascular renal denervation, it has the advantage in that it can be turned off and/or adjusted upward or downward, according to the patient’s overall clinical condition or to achieve different intensities during day and night. Its potential impact in patients with diabetes remains to be clarified.

9. Conclusions

There is a strong association between diabetic complications and reflex activation of the SNS. Although this is often perceived as a compensatory phenomenon, there is strong experimental and clinical evidence for a causal relationship between chronic SNS activation and the development and progression of both renal and cardiac complications in patients with diabetes. But while there is a strong physiological rationale for targeting the SNS, the best means to achieve safe and effective blockade remains to be established. Early therapies lacked specificity and were beset with numerous off-target effects and unintended clinical outcomes. While newer vasodilating β-blockers have addressed some of these limitations, many questions remain including the best site of blockade, the extent of blockade, the duration of blockade and the relative importance of extra-adrenergic properties in conferring clinical efficacy. The advent of radiofrequency renal sympathectomy and baroreflex activation technologies also offers exciting new ways to safely tackle the challenge of sympathetic overactivity. However, long-term studies with hard outcomes remain to be performed. Although the activities of the SNS has been understood now for many centuries, it is beginning to look that we may at last be coming to grips with it.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


