The 6-year anniversary of the first catheter-based renal denervation procedure for resistant hypertension has passed, and the 3-year follow-up results of the Symplicity HTN-1 are now published. At the ‘end of the beginning’, it is timely to reflect on the observations to-date for this revolutionary therapy, and to predict the next phase in its development and clinical application in hypertension treatment. In essence, on observations to hand, the procedure is efficacious and seems safe and durable. But will the blood pressure lowering truly be permanent (or might it be cancelled out by renal sympathetic nerve regrowth)? How can patient selection for the renal denervation procedure be optimized, given that some patients do not respond with a blood pressure fall? Will blood pressure lowering with renal denervation reduce the rate of clinical cardiovascular endpoints? Will long-term safety be acceptable? Can milder hypertension be cured? And there are unresolved procedural and technical questions: how much renal denervation is optimal; is unilateral denervation, now commonly used, beneficial; will renal denervation show a ‘class effect’, with the different energy forms now used for renal nerve ablation producing equivalent blood pressure lowering? At the 12-year anniversary, I expect these questions will be answered, and catheter-based renal denervation will have an established clinical role in the care of patients with severe grades of hypertension. Less certain is the common prediction of its application in early, mild hypertension, in parallel with, or even before anti-hypertensive drug prescribing.

Keywords
Renal denervation • Hypertension pathogenesis

Introduction

It was Thomas Willis and the seventeenth century London neuroanatomical school he led who provided the first identifiable illustrations of the sympathetic nervous system. Stimulation of the sympathetic nerves, by Claude Bernard and Charles Brown-Sequard, demonstrated them to be vasoconstrictor, and to elevate blood pressure, leading to their categorization as the ‘pressor nerves’. In the first two decades of the twentieth century, these observations were integrated by Geisbock into a proposal that human hypertension was neurogenic, initiated and sustained by the sympathetic nervous system. The aim at first was to surgically sever sections of the sympathetic chain, and all sympathetic nerves of the thorax and abdomen within reach, cutting as many ‘pressor nerves’ as possible to remove their systemic vasoconstrictor influence. Selective renal sympathectomy was not performed, as no theory existed suggesting importance of the sympathetic nerves of the kidneys in the pathogenesis of hypertension. Surgical sympathectomy for the treatment of hypertension was applied in the years 1935–1960, and was demonstrably of value in prolonging life in patients with severe and malignant hypertension, but at the cost of disabling side effects, most notably postural hypotension and syncope.

Ganglionic blocking drugs, discovered by Paton and Zaimis, ended the period of surgical sympathectomy for hypertension, and ushered in an era of anti-adrenergic drugs. Ganglion blockers constituted the first anti-adrenergic pharmacotherapy for hypertension and could achieve what surgery achieved minus surgical risk, but regrettably not minus complications, which as expected were almost identical with those of sympathectomy, and equally frequent and disabling. But a new principle for hypertension drug development had been established, and neurone-blocking drugs such as guanethidine, centrally acting sympathetic nervous inhibitors including methyldopa and clonidine, beta-adrenergic receptor blocking drugs such as propranolol, and alpha-adrenergic receptor blockers followed in quick
succession, with ganglion blockers rapidly becoming obsolete. These anti-adrenergic drugs, coupled with diuretics and direct-acting vasodilators such as hydralazine, were the preferred anti-hypertensive therapy from 1960 to 1990.

In the modern era, drugs antagonizing the renin–angiotensin system have become the dominant anti-hypertensive therapy. ACE-inhibitor drugs and angiotensin receptor blocking drugs gradually replaced anti-adrenergic drugs as the preferred anti-hypertensive agents because they were at least equally efficacious, and substantially better tolerated. Subsequently joined by dihydropyridine calcium channel blocking drugs, the anti-renin drugs, calcium channel blockers, and diuretics came to occupy the preferred position, at the top of international cardiovascular society hypertension guidelines ‘league tables’, with anti-adrenergic anti-hypertensive drugs edging towards the bottom of the lists. The sympathetic nervous system lost its earlier prominence in discussions of essential hypertension pathogenesis and treatment, and became to be considered as passé, and of only marginal relevance in hypertension care.

But there was a problem. Despite the widespread availability and prescribing of a ACE-inhibitors, angiotensin receptor blockers, diuretics, and calcium channel blockers, in a substantial minority of patients with essential hypertension, perhaps 10%, goal blood pressure were not achieved. In these drug-resistant hypertensives, a new strategy was needed, and in fact, devised. This was the development of device-based therapies targeting the sympathetic nervous system, the surgically implanted barostimulator device, and catheter-based renal denervation, the latter being the subject of this review.

Central to the development of radiofrequency renal denervation was knowledge of the physiology of the renal sympathetic nerves, and their pathophysiology in experimental and human hypertension. In untreated essential hypertensive patients, the application of regional noradrenaline isotope dilution methodology, to measure the outward flux of the transmitter from renal sympathetic nerves to plasma (renal noradrenaline spillover), demonstrated that a high level of activation of the renal sympathetic outflow was present. (Figure 1). The sympathetic nervous outflow is commonly activated also to the heart, shown with selective cardiac noradrenaline spillover measurements, and to the skeletal muscle vasculature, demonstrated with microneurography recording, but it is the renal sympathetic activation which is central to hypertension pathogenesis.

In elegant studies in rodents, the renal nerves have been demonstrated to stimulate secretion of renin from the juxtaglomerular apparatus, to promote renal tubular reabsorption of sodium, and to cause renal vasoconstriction, reducing renal blood flow, all potentially blood pressure elevating responses. The renal tubules receive a dense sympathetic innervation, at all tubular levels. Analysis of sympathetic nerve stimulus–response curves demonstrates that the mid-range responses for renin secretion, sodium reabsorption, and renal vasoconstriction differ, being seen at renal sympathetic nerve firing frequencies of ~1, 2, and 3 Hz respectively (Figure 2). Single-fibre sympathetic nerve recordings in fibres distributed to the skeletal muscle vasculature in patients with essential hypertension (human renal nerve recordings are not available) indicate that nerve firing frequencies in the 1–2 Hz range are frequently encountered, particularly when individual fibres discharge in multiple salvoes within a cardiac cycle. As a consequence, in younger patients with essential hypertension, the renal sympathetic activation present commonly is sufficient to drive increased secretion of renin by the kidneys. Patients with high levels of renal sympathetic activation have increased secretion of renin by the kidneys, and often elevated plasma renin

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**Figure 1** Spillover of noradrenaline from the sympathetic nerves of the kidneys in untreated patients with essential hypertension and in healthy people. Activation of the renal sympathetic outflow was commonly present in hypertension. Unpublished data from the laboratory of the author.

**Figure 2** Relationship between stimulated renal nerve firing frequency in the rat and components of the renal response. The maximum responses for renin secretion (increase), urinary sodium excretion (decrease), and renal blood flow (decrease) are shown. From with the permission of the authors and publisher.
concentrations. A relation of renal tubular sodium reabsorption to sympathetic outflow has not been measured directly in human hypertension, but also presumably exists. In contrast, in essential hypertension renal blood flow at rest is not demonstrably linked to renal sympathetic outflow; the sympathetic nerve firing frequencies (3 Hz and above) needed for renal vasoconstriction, higher than for renin secretion and sodium reabsorption apparently do not exist in hypertensive patients under quiescent conditions.

A specific and important relation of the renal sympathetic nerves to renal tubular sodium reabsorption, key to hypertension pathogenesis, concerns pressure natriuresis, the normal capacity of the kidneys to excrete sodium at higher arterial perfusion pressures. Impairment of pressure natriuresis is believed to be a central element in the development of hypertension. Renal sympathetic denervation shifts the renal pressure-natriuresis curve to the left, promoting urinary sodium excretion and lowering of blood pressure. With this background, it was logical for the effect of surgical renal denervation on the development and maintenance of blood pressure elevation to be evaluated in experimental forms of hypertension. As for human hypertension, in these the renal sympathetic outflow is commonly activated. With few exceptions, the denervation favourably modified the hypertension, an effect lost when reinnervation occurred, as it usually did. Demonstrating the specificity of the surgical effect, the blood pressure was lowered if the sympathectomy was repeated.

Three facts provided the intellectual framework for the development of catheter-based renal denervation for the treatment of essential hypertension (Table 1). The first two, described above, were the presence of activation of the renal sympathetic outflow in hypertensive patients, and the blood-pressure lowering effect of surgical renal denervation in experimental models of hypertension. The third was the anatomy of the postganglionic renal sympathetic nerves in their passage to the kidneys. In humans, the nerves pass from the sympathetic chain and ganglia to the kidneys via the outer wall of the renal arteries, or just outside in perirenal adipose tissue and connective tissue, within reach of radiofrequency energy delivered by a catheter in the artery lumen. Drawing on these concepts, the first to suggest that essential hypertension might be treated with a renal nerve ablation catheter were Howard Levin and Mark Gelfand in USA (provisional patents 60/370190 (April 2002), 60/415575 (October 2002), and 60/442970 (January 2003)).

The California start-up company, Ardian, acquired the patent rights, and commenced a developmental program to design a radiofrequency ablation catheter suitable for human use, testing this purpose-designed catheter for safety and renal denervation capacity in pigs. The first-in-man studies were conducted in Melbourne. The initial proposition was, in a small study, to test in humans only for safety and effectiveness of renal denervation, but plans were then extended to expand the trial into a larger open-label evaluation of the anti-hypertensive effect also, in drug-resistant essential hypertension. This patient class, of resistant hypertension, was selected because of the very evident clinical need, and because the potential benefit-risk balance made the study defensible ethically. The entry blood pressure selected, a clinic systolic pressure above 160 mmHg, is not the conventional defining pressure for drug resistance (which is >140 mm Hg), but was based on agreement reached between the trial investigators and the Alfred Hospital Institutional Ethics Committee, Melbourne, which had ethics jurisdiction over the study. This trial, which commenced in June 2007, became known as Symplicity HTN-1.

### Endovascular renal denervation: observations

**Simplicity HTN-1 and symplicity HTN-2 clinical trials**

The Symplicity trials in endovascular renal nerve ablation, HTN-1, and HTN-2 have opened a door to a new future in the treatment of drug-resistant hypertension. Six years after the first patient was treated with the Symplicity radiofrequency catheter system, these initial trials, their continuation to later specified endpoints, accompanying resistant hypertension renal denervation registry files, and trials with other, newly engineered renal denervation devices have established important therapeutic principles:

1. Efferent sympathetic renal denervation can be achieved with luminal delivery of radiofrequency energy.
2. The treatment can be delivered with very minimal procedural complications, these being typical of invasive cardiological procedures in general, and not consequential on RF energy delivery.
3. The mean BP reduction across the trials shows consistency, office systolic BP falling on average by 20–30 mm Hg at the primary endpoints. Renal function is preserved.
4. The BP reduction is durable, demonstrably persisting for 3 years and beyond, despite initial concerns that regrowth of renal sympathetic nerves might cancel out the pressure lowering.
5. The blood pressure fall is sometimes delayed; the treatment response rate improves over time.
6. New renal artery stenoses in the field of RF energy delivery are very uncommon. RF-induced aneurysm has not been reported.
7. Treatment failure does occur (estimated at 15–30% in the trials); this cannot be predicted from patient clinical characteristics. A higher baseline blood pressure is the only consistent predictor.
8. Postural hypotension is not observed, indicating that, under gravity, reflex sympathetic responses in veins remain intact after renal denervation, this being crucial in the avoidance of postural hypotension.

### Table 1 Observations providing the theoretical underpinning for the development of the catheter-based renal denervation treatment for hypertension

| (1) | The sympathetic outflow to the kidneys is activated in essential hypertension, demonstrable in isotope dilution measurements which show increased renal noradrenaline spillover to plasma.
| (2) | Surgical denervation of the kidneys in most experimental models of hypertension opposes the development of hypertension and lowers blood pressure in established hypertension.
| (3) | The renal nerves pass to and from the kidneys in the adventitia of the renal arteries, and in the adjacent perirenal connective and adipose tissue, within reach of ablative energy released in the renal artery lumen. |
Mechanism of the blood pressure fall

The expectation was that disruption of the postganglionic efferent sympathetic nerves directed to the kidneys would provide the anti-hypertensive mechanism, by reducing renal tubular reabsorption of sodium (and shifting the pressure-natriuresis curve to the left, favouring urinary excretion of sodium) and by inhibiting renin secretion. This no doubt is important, but efferent nerve ablation is almost certainly not the sole anti-hypertensive mechanism. The first renal denervation procedure performed was unexpectedly painful (adequate analgesia is now uniformly used) due to stimulation of pain fibres in the renal afferent nerves, prior to their destruction. Renal afferent nerve disruption is now seen to contribute to the anti-hypertensive effect of endovascular RF renal nerve ablation.

Experimental studies of Campese and Kogosov demonstrated that with renal injury, in this particular instance intra-renal phenol injection, nociceptive receptors are stimulated on afferent fibres which project centrally to the hypothalamus, stimulating sympathetic outflow. A similar mechanism operates in human renal disease, best demonstrated in patients with end-stage renal disease maintained on dialysis. The marked sympathetic nervous activation present in these patients, which contributes substantially to their hypertension, is abolished by bilateral nephrectomy (removing the afferent nerve signal to the brain), but not by renal transplantation when the disease kidneys are left in situ. Catheter-based renal denervation in patients with drug-resistant hypertension causes central sympathetic nervous system inhibition, with an ~35% reduction in single fibre sympathetic nerve firing being registered with microneurography. Presumably, a renal injury signal is present in drug-resistant essential hypertension, abolished by afferent nerve disruption, which is contributing to the sympathetic nervous activation present. This renal injury must be cryptic, in that it is typically not reflected in proteinuria or reduced glomerular filtration rate.

The blood pressure lowering with renal denervation is presumed to represent a summation of the effects of ablation of efferent and afferent renal nerves. Some have suggested that the afferent nerve ablation and resultant central sympathetic inhibition is the primary anti-hypertensive mechanism, outranking ablation of the efferent renal sympathetic nerves. This is unlikely. Centrally acting anti-hypertensive drugs such as the imidazolines reduce central sympathetic outflow by 30–35%, similar in degree to that achieved with afferent nerve ablation, but have much less anti-hypertensive potency than renal denervation. And there is an additional point; while after renal denervation in resistant hypertension both sympathetic activity and blood pressure fall materially, the magnitude of the fall in blood pressure is not tightly linked with the degree of central sympathetic inhibition (Figure 3).

‘Which’ blood pressure falls?

With the Symplicity trials, office blood pressure fell substantially more with renal denervation than did 24-h ambulatory blood pressure. This has been interpreted to mean that a reflexive, sympathetic nervous system-mediated component of blood pressure is selectively lowered. This may not be true, however, as renal denervation does not dampen cardiovascular reflexes across the board; those accompanying exercise and upright posture are undiminished. A further, allied, suggestion has been that renal denervation works in particular in white coat hypertension, a special form of reactive hypertension, but this has been disproven. In a comprehensive study, office BP was demonstrated to fall similarly in ‘pseudo’ resistant (white coat) hypertension and bona fide resistant hypertension, while 24 h ambulatory blood pressure did not fall at all in white coat hypertension.

The disparity between office and 24 h ambulatory blood pressure with renal denervation may, perhaps, not be unique, being reported also with pharmacological treatment of severe hypertension. This phenomenon might derive from the severity of the hypertension in patients treated with renal denervation, rather than being due to the specific anti-hypertensive modality of renal denervation. But an important clinical point remains; reduction in ambulatory blood pressure is more closely linked with improved cardiovascular outcomes than is lowering of office BP, so that at some point future renal denervation trials in resistant hypertension may need to evaluate reduction in cardiovascular clinical endpoints, not just blood pressure-lowering efficacy.

Why is the blood pressure fall with renal denervation gradual?

In occasional patients, the blood pressure fall following renal denervation is abrupt and excessive, but this is very unusual. Much more typically, the blood pressure reduction is progressive, through to 12 months post-denervation and beyond. Why is this so? It has been suggested that the explanation lies in a matching, progressive fall in central sympathetic inhibition from renal afferent nerve ablation, but this appears not to be the case. After renal denervation, inhibition of CNS sympathetic outflow is fully expressed at 3 months. More likely is slow reversal of hypertensive cardiovascular remodelling; this remodelling can be extreme in severe hypertension.
Hypertensive arteriolar hypertrophy reverses gradually with effective blood pressure lowering. Reversal of compliance changes in the arterial wall, and reversal of left ventricular hypertrophy have been documented after renal denervation. An analogous phenomenon is seen after definitive treatment of secondary hypertension where the blood pressure fall is slower, and sometimes less complete than anticipated. With removal of the primary cause of the blood pressure elevation, the remaining maladaptive cardiovascular elements remain, contributing to the continuing pressure elevation.

**What determines the magnitude of blood pressure fall with renal denervation?**

The magnitude of the blood pressure fall achieved with renal denervation differs between individual patients, clinically manifest in a response rate of 50–85% in published reports. A higher baseline blood pressure is the only consistent predictor for response. The facile, but incorrect, explanation of this phenomenon is that it solely represents regression to the mean, a statistical artefact based on sampling error, in essence catching some patients on a ‘bad day’ at the point of trial entry, when their blood pressure happens to be at its highest. This ignores the undoubted presence and impact of biological factors present in patients with the most severe hypertension, such as the renal injury signal which drives central sympathetic activation by renal afferent nerves.

Failure to respond might be caused by technical failure of the denervation procedure, which due to the absence of valid detection methodology cannot be documented at present. But it could arise because the hypertension is not neurogenic, the blood pressure elevation not being initiated or sustained by neural mechanisms, which no doubt applies in a significant minority of patients with essential hypertension. It might apply that in the absence of activation of the renal sympathetic outflow, catheter-based renal denervation is fruitless as an anti-hypertensive treatment. This point, although probable, has not been established with certainty, because in some of the experimental models of hypertension in which surgical renal denervation is effective sympathetic nervous activation is absent. It could possibly be that renal sympathetic denervation, in moving the renal pressure–natriuresis curve to the left such as to offload sodium, can sometime lower blood pressure regardless of prevailing renal sympathetic activity.

**Safety of catheter-based renal denervation**

Despite experimental studies with radiofrequency ablation of renal nerves in pigs showing some vascular damage, with clinical follow-up now as long as 6 years the long-term safety in patients is good, perhaps exceeding expectations. Procedural complications, primarily of access site femoral artery haematomas are not uncommon, as might be expected from femoral artery puncture in severely hypertensive and often obese patients. Despite some endothelial damage during the denervation procedure, sometimes accompanied by microthromboses detected with optical coherence tomography, renal artery stenoses from renal artery atherosclerosis or perhaps fibrous stricture at the site of energy delivery are very uncommon. Renal artery aneurysm is not described, nor is renal thromboembolism.

A particular concern is whether renal loss of function might occur. Certainly, this is not evident with clinical renal function tests. But could renal denervation interfering with renal mechanisms of sodium conservation have adverse consequences in the setting of illnesses with acute diarrhoea, such as intercurrent salmonella or shigella infection? The medical registries provide no clear evidence of deaths attributable to this. An additional concern is that blunting of systemic neural vascular reflexes might impair the cardiovascular adjustment to blood loss, from trauma or a bleeding ulcer, perhaps. But as mentioned, neural cardiovascular reflexes seem not to be impaired by renal denervation; certainly those accompanying exercise and upright posture are normal. Direct removal of renal vasoconstriction by efferent nerve ablation would have little influence on the homeostatic cardiovascular response to blood loss, as renal vascular resistance constitutes only ~20% of total peripheral resistance.

**Renal denervation pleiotropism**

Multiple benefits have been reported with renal denervation in patients with resistant hypertension, in addition to blood pressure lowering. The procedure has been claimed to benefit diabetes, atrial fibrillation, obstructive sleep apnoea, and psychological well being. Most effects have been attributed to central sympathetic inhibition from ablation of renal afferent nerves.

Anti-hypertensive drugs (imidazolines) causing inhibition of central sympathetic outflow reduce insulin resistance. A similar mechanism may be operating here; with renal denervation reduction in neural vascular tone in skeletal muscle increasing blood flow and glucose delivery to muscle has been proposed. This effect of renal denervation is best seen as a clinical bonus, in that so many resistant hypertensive patients are obese, and have metabolic syndrome or type II diabetes. Renal denervation is not a new, stand-alone treatment of diabetes. Atrial fibrillation is commonly triggered by sympathetic nervous activation; central sympathetic inhibition from renal afferent nerve ablation might be the mechanism of benefit in atrial fibrillation, although reduction in arterial pressure and end-diastolic left ventricular and atrial pressure certainly would contribute. In patients with obstructive sleep apnoea, benefit possibly derives from natriuresis and improved sodium balance. With fluid overload in patients with heart failure, peripheral to central blood volume redistribution when supine at night contributes to the upper airways obstruction. Favourable effects on salt and water balance from renal denervation possibly acts similarly. Quality of life questionnaires show benefit in mental health scores from renal denervation. The mechanism is no doubt complex, but ablation of renal afferent nerves projecting to the hypothalamus has been invoked as one component.

**Renal denervation for resistant hypertension: ‘The End of the Beginning’**

The first catheter-based renal denervation procedure for drug-resistant hypertension was performed on 6 June 2007. More than 6 years later, there remain many unanswered questions. To paraphrase the memorable wartime quote of Winston Churchill (November 1942), out of context, ‘this is, perhaps, the end of the beginning’. How durable will the blood pressure lowering be (will it be cancelled out by renal sympathetic nerve regrowth)? How can patient selection for the renal denervation procedure be optimized?
given that some patients do not respond with a blood pressure fall? Will blood pressure lowering with renal denervation reduce the rate of clinical cardiovascular endpoints? Will long-term safety be acceptable? Can milder hypertension be cured? And there are unresolved procedural and technical questions: how much renal denervation is optimal; is unilateral denervation, now commonly used, beneficial; will renal denervation show a ‘class effect’, with the different energy forms now used producing equivalent blood pressure lowering? It is time for some predictions.

Endovascular renal denervation: predictions

Blood pressure lowering with endovascular renal denervation will be permanent

With surgical renal denervation in experimental hypertension the blood pressure lowering is temporary, being cancelled out when renal sympathetic nerve regrowth occurs, which happens in less than 6 months.18,19 The expectation was that in human hypertension, the anti-hypertensive effect might also be of rather limited duration, but perhaps last long enough to be of clinical benefit. It was anticipated that after perhaps 1 or 2 years, the denervation procedure might need to be repeated, and even repeated again, subsequent to this. What has transpired is that with catheter-based RF denervation the blood pressure lowering is durable, with documentation of no loss of anti-hypertensive effect at 3 years of follow-up,26 and almost certainly permanent, based on persistence of blood pressure reduction in patients now followed for as long as 6 years. Is this contrast in anti-hypertensive duration a species difference (rats vs. humans) or attributable to denervation methodology, surgery vs. electromagnetic energy delivery? Perhaps RF thermal tissue damage obliterates pathways needed for re-innervation more completely than does surgery. Regardless of these speculations, I project that blood pressure lowering with endovascular renal denervation will be permanent.

Patient selection will remain problematic

Failure of blood pressure to fall might be caused by technical failure of the denervation procedure, which due to the absence of valid detection methodology cannot be documented at present. It could also arise because in a particular patient the blood pressure elevation is not initiated or sustained by neural mechanisms. If the response rate with renal denervation is as low as 50%, as some trials suggest, it will become important to predict which patients will show a good response. Tests screening sympathetic nervous system activity might, perhaps, be applied preparatory to the decision to use renal denervation as treatment. But the readily available tests of sympathetic activity such as urine and plasma norepinephrine measurements are imprecise, and probably will be of no utility. Anything less that testing for activation of the renal sympathetic outflow, with renal noradrenaline spillover measurements12,13 might not help.

Prevention of clinical cardiovascular endpoints will equal or exceed that achieved with drugs

To this point, there has been no evaluation of whether blood pressure lowering by renal denervation reduces rates of the adverse clinical outcomes of hypertension, of myocardial infarction, sudden death, stroke, heart failure, and renal failure. I do not believe this represents a material deficiency in the denervation trials. Antihypertensive drugs in general show a ‘class effect’, with the achieved blood pressure reduction being of overwhelming importance in reducing clinical outcomes, rather than the drugs used.53,54 Claims of specific benefit being achieved by specific drug classes are now largely discounted.52,53 Resistant hypertension is associated with high-grade clinical risk.54 The large blood pressure falls achieved with renal denervation will be life-saving.

Long-term safety will be excellent

Although experimental studies with radiofrequency ablation of renal nerves in pigs showed some vascular damage,45 and optical coherence tomography46 demonstrates endothelial damage and sometimes microthromboses, clinical follow-up now as long as 6 years suggests excellent vascular safety. Renal artery stenoses from renal artery atherosclerosis or perhaps fibrous stricture at the site of energy delivery occur but are very uncommon,11,12,26,47 and renal artery aneurysm and renal thromboembolism are not described. There is in some quarters a lingering concern that hazardous renal loss of function, not evident with standard clinical renal biochemical testing, might occur. For example, involving interference with renal mechanisms of sodium conservation, or the blunting of systemic neural vascular reflexes might, perhaps, impair adjustment to sodium depletion or blood loss, but this is unlikely.

Patients with renal hypertension will benefit most

Blood pressure lowering with renal denervation has two mechanisms, ablation of the postganglionic sympathetic nerves directed to the kidneys, and central sympathetic inhibition resulting from destruction of renal afferent nerves.31,32 The renal afferents, when engaged by a renal injury signal, mediate sympathetic nervous activation through their projection to the hypothalamus.32 This applies in drug-resistant hypertension, and is no doubt even better expressed in renal hypertension, where sympathetic nervous system activation is at a high level.34 Pilot studies of renal denervation in resistant hypertension accompanying renal disease in patients with a mean eGFR of ~30 mL/min15 and in end-stage renal disease56 have been positive. The most logical application of the catheter-based renal denervation method is in renal hypertension, where sympathetic nervous activation can be extreme, and the renal afferent nerves are an important driver in pathogenesis.34

The current degree of denervation will be shown to be suboptimal

The level of renal sympathetic nerve ablation achieved clinically with the RF denervation procedure, ~50%,15 contrasts with that achieved surgically in experimental hypertension, 90–95%.17 Which is optimal? If the aim is to ‘normalize’ renal sympathetic activity, 50% ablation of
sympathetic nerves in patients who have on average a doubling of renal sympathetic activity,\(^\text{14,44}\) might perhaps be ideal. But as renal denervation lowers blood pressure in some experimental models of hypertension in which sympathetic nervous activity is actually normal,\(^\text{19}\) normalizing renal sympathetic activity is probably not the desired aim. Greater left shift in the pressure—natriuresis curve\(^*\) and resultant off-loading of more sodium would occur with a higher grade renal denervation than is currently achieved clinically. This could be achieved if delivered energy were to penetrate somewhat beyond 2–3 mm, as some renal sympathetic nerves are more remote from the lumen than this.\(^\text{24}\)

**Unilateral denervation will be discredited**

Renal artery anatomy sometimes does not allow bilateral renal denervation. This is most often due to the presence of multiple renal arteries on one side. Faced with this predicament, it has become common practice to perform a unilateral denervation, on the side where this is feasible. Surgical unilateral denervation in experimental hypertension lowers blood pressure minimally,\(^\text{19}\) and clinical registry data on unilateral denervation to this point are not available. A strong theoretical argument can be made against unilateral renal denervation in resistant hypertension, based on the disruption that this will produce in renorenal reflexes, which can potentially protect against the development of hypertension. Through renorenal reflexes, which are spinal reflexes providing communication between the kidneys, change in one kidney can reduce sympathetic activity in the contralateral kidney.\(^\text{57}\) This protective effect on the non-denervated kidney will be abolished by unilateral renal nerve ablation.

**Renal denervation with differing energy modalities may not show a ‘class effect’**

With some drugs used in cardiovascular medicine, an example being beta-adrenergic blockers in cardiac failure,\(^\text{58}\) all members of a drug class do not show equal benefit. What will apply with the differing energy forms used for renal denervation? Although early results suggest similar short-term blood pressure lowering occurs with RF and ultrasound catheter engineering,\(^\text{11,12,29,30}\) the existence of a ‘class effect’ has not been fully established. Crucial here is whether both denervation capacity and reinnervation potential, will be identical with radiofrequency, ultrasonic, and cryogenic methodologies. For example, nerve ablation with ultrasound devices relies on both thermal and sonication (mechanically disruptive) damage. Will the impact of this, on both nerve ablation and nerve regeneration be identical to that with RF energy, where there is thermal injury only? The magnitude of the clinical response, and importantly its durability, will depend on the relative influence of the different energy forms on both of these.

**Mild hypertension may never be cured**

In drug-resistant hypertension, blood pressure control is often achieved but never cured. What are the prospects for cure in milder grades of hypertension? Two key points are:

(i) whether the sympathetic outflow to the kidneys is activated in milder grades of essential hypertension; yes\(^\text{14,44}\)

(ii) whether a renal injury signal exists in mild hypertension, activating central sympathetic outflow via afferent nerve input to the CNS; presumably no.

If the renal injury signal is absent, one mechanism for blood pressure reduction by renal denervation will be absent. Counterbalancing this, unlike in severe hypertension treated with renal denervation, in milder hypertension less reversal of maladaptive hypertensive changes of arteriolar hypertrophy and arterial wall remodelling will be needed for the full expression of the anti-hypertensive effect. On balance, the expectation is that pressure will possibly be lowered, but less than in severe hypertension. Judging whether cure will be achieved cannot come from a theoretical synthesis of these potential conflicting influences. The answer must be empirical, based on experiments yet to be done.

**Endovascular renal denervation: concluding thoughts**

**Why did it take so long to develop endovascular renal denervation?**

The knowledge base for catheter-based renal denervation development, specifically the presence of renal sympathetic activation in essential hypertension, the utility of renal surgical denervation in experimental hypertension, and the anatomical knowledge of the proximity of the renal nerves to the renal arteries, was in place almost 30 years ago, but this novel therapy was slow to emerge. It might be asked: ‘Why was the sympathetic nervous system so neglected in essential hypertension treatment and research over the past three decades?’ and, ‘Why did this novel therapy take so long to materialize?’ I believe several factors contributed. One is that drugs blocking the renin–angiotensin system were the dominant anti-hypertensive therapy over recent decades, a pre-eminence based on their efficacy and low side-effect rate. Anti-adrenergic drugs tended to fall from favour. A second factor is that in recent years, clinical trialists have often been regarded as the international hypertension cognoscenti; they primarily conducted trials on drugs antagonizing the renin–angiotensin system and showed little interest in the sympathetic nervous system. And third, the funding of most experimental hypertension research by the major pharmaceutical companies was of the renin–angiotensin system; given it was their anti-renin drugs which were still in patent. Over time, the collective medical memory of the sympathetic nervous system faded. The knowledge and skills of cardiac interventionists, hypertension specialists, and neuroscientists needed to come together in discovery, but these groups usually follow different research and clinical paths. The lateral thinking was eventually provided by Howard Levin and Mark Gelfand [US provisional patents 60/370190 (April 2002), 60/415575 (October 2002), and 60/442970 (January 2003)].

**The renal sympathetic nerves provide a universal common pathway of hypertension pathogenesis**

How can it be that renal sympathetic denervation is so effectively anti-hypertensive in human and experimental hypertension? I suggest it is because renal nerve ablation cuts the legendary Gordian knot, at the intersecting influence in hypertension pathogenesis of the sympathetic nervous system, the kidneys, and dietary salt. Too often,
each of these three factors is thought of as a unitary progenitor of hypertension, but they act in concert.59

Renal sympathetic activation in human hypertension has multiple origins, obesity,60 sedentary life,61,62 and chronic mental stress1,6,23 being three, which explains its high prevalence. Obesity is proven to activate the renal sympathetic outflow,22 Aerobic exercise training preferentially causes renal sympathetic inhibition,60 an influence absent in sedentary people. Mental stress activates the renal and cardiac sympathetic outflows.61,62

In the presence of high dietary sodium intake, all too common in developed societies, this activation of the renal sympathetic outflow provides ‘neural’, ‘renal’, and ‘sodium’ mechanisms of hyper-tension development, through excessive renal tubular reabsorption of sodium, and rightwards shift in the renal pressure natriuresis curve.23 Endovascular renal denervation breaks the nexus between salt and the nervous system.

Footnote
On January 9th 2014, Medtronic, the sponsor of the US pivotal Sym-plicity HTN-3 trial of renal denervation in drug-resistant hyperten-sion, complying with US securities law, issued a press release informing that the primary efficacy endpoint had not been reached in the trial. The safety endpoint was achieved. No information beyond this was made available.

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