In 1664, the first anatomically correct depiction of the sympathetic nervous system came from Thomas Willis and his circle of London anatomists, included in The Anatomy of the Brain and Nerves, 1664 (Figure 1). This, the first work dedicated completely to the nervous system, also described the arterial loops at the base of the brain, which we now know as the Circle of Willis. Christopher Wren, an anatomist member of the group, was the principal illustrator before being asked by the City Fathers to turn his talents to town planning, architecture, and cathedral building after the 1666 Great Fire of London.

Almost 2 centuries later, subsequent microscopic examination demonstrated that blood vessel walls were densely innervated, leading Stelling in 1840 to correctly conclude that these vasomotor fibers were in fact sympathetic nerves that were carried from the central nervous system to the blood vessels. In the mid-19th century, celebrated European physiologists, including Brown-Sequard, Waller, and Bernard, built on these observations, demonstrating vasoconstriction with electrical stimulation of the cut nerves and vasodilatation on nerve section, which indicated that the sympathetic fibers exerted a tonic, vasoconstrictor influence. The pressor nerves had gained recognition.

Identification of the sympathetic neurotransmitter proved to be difficult. Claims for epinephrine and the hypothetical sympathins I and E confused the picture. Ulf von Euler compared bioassay responses of epinephrine, norepinephrine, and dihydroxy norephedrine with those of cattle splenic nerve extract, by testing blood pressure (BP) responses in the anesthetized cat and contractile responses in the isolated pregnant rabbit uterus, to definitively demonstrate the primary transmitter to be norepinephrine. This discovery provided the theoretical knowledge for the development of pharmacological antagonists of the sympathetic nervous system. They elaborated this observation into a clinical method for measuring sympathetic nerve efferent multifiber traffic. This technique of clinical microneurography and by radiotracer-derived measurements of regional norepinephrine spillover to plasma.

**Microneurography**

Hagbarth and Vallbo, while studying sensory nerves in humans, noted interfering neural discharges which after comprehensive investigation they identified as originating from postganglionic sympathetic nerves. They elaborated this observation into a clinical method for measuring sympathetic nervous system activity in humans. In 1970, the first sensitive and specific plasma catecholamine assay by Engelman et al. was a milestone in the field. For a time, plasma norepinephrine measurements were the principal method for the investigation of sympathetic neuronal mechanisms in clinical medicine. Plasma norepinephrine measurements, although providing a useful guide to sympathetic nervous system function, have substantial limitations. The principal one was that this or in fact any other global index of sympathetic nervous function provides no information on the regional patterning of sympathetic nervous responses. This runs contrary to the organization of the sympathetic nervous system in which sympathetic nervous responses are regionally differentiated. Precise quantification of individual regional sympathetic nervous outflows was needed. This need came to be met by the sympathetic nerve recording technique of clinical microneurography and by radiotracer-derived measurements of regional norepinephrine spillover to plasma.
Regional Norepinephrine Spillover Measurements

A special impetus to the development of techniques for studying the rates of overflow of norepinephrine to the circulation was provided by the lack of clinical methods for studying human sympathetic nervous outflow to otherwise inaccessible organs, such as the heart and kidneys. The inapplicability of the neural recording methodology for clinical research on internal organs led to a continuing search for alternative techniques, especially biochemical ones.

For these reasons, I established techniques for measuring organ-specific norepinephrine release to plasma for studying regional sympathetic nervous function in humans, which I will now describe in some detail. The relationship that, in general, holds between the sympathetic nerve firing rate of an organ and the rate of spillover of norepinephrine into its venous effluent provides the experimental justification for using measures of regional norepinephrine release as a clinical index of sympathetic nervous tone in individual organs.

During constant rate intravenous infusion of tritiated norepinephrine, outward flux of endogenous norepinephrine from an organ (regional norepinephrine spillover) can be measured by isotope dilution:

\[
\text{Regional norepinephrine spillover} = \left( C_v - C_A \right) + C_A E \times \text{PF},
\]

where \(C_v\) and \(C_A\) are the plasma concentrations of norepinephrine in regional venous and arterial plasma, \(E\) is the fractional extraction of tritiated norepinephrine in transit of blood through the organ, and \(PF\) is the organ plasma flow. The theory of this was clear enough, but the implementation was complicated, specifically how could the central venous catheterization necessary for sampling from the veins draining internal organs receive ethics committee approval? The solution lay in adding the research study to clinically justified procedures. Sampling from the renal vein for renin measurements was performed for the evaluation of hypertension at the time to screen for a functionally significant renal artery stenosis. This provided an opportunity, with appropriate consent, to establish the renal norepinephrine spillover measurement methodology. In patients with heart failure, central venous catheterization was also common to measure pulmonary artery wedge pressure; this enabled the coronary sinus venous sampling required for cardiac norepinephrine spillover measurements.

Of all measurements of regional norepinephrine spillover, it was those in the heart and the kidneys that have had most direct clinical relevance. Measurements of cardiac norepinephrine spillover in heart failure documented activation of the cardiac sympathetic outflow in patients with heart failure, providing key theoretical background for the testing and introduction of \(\beta\)-adrenergic blockers as therapy. Measurements of renal norepinephrine spillover in essential hypertension documented preferential activation of the renal sympathetic outflow, key to the development of catheter-based renal denervation as therapy for drug-resistant hypertension. The measurement of cardiac norepinephrine spillover in a patient with heart failure did provide a Eureka moment in 1982, with detection of an inexplicably high value. This was surprising because the content of norepinephrine in the failing human myocardium is markedly reduced, the failing heart at that time being thought to be sympathetically denervated. This finding in a single patient was reinforced by further studies, with publication of the finding 4 years later, establishing that in reality the cardiac sympathetic outflow in heart failure is activated at a high level.

Human Neural Cardiovascular Pathophysiology: Translation to Patient Care

This review provides evidence that abnormalities of the sympathetic nervous system are commonly crucial in the development and clinical expression of cardiovascular disorders. Examples include congestive heart failure, the disorders of postural circulatory control causing orthostatic syncope and essential hypertension. These abnormalities involve ongoing activation of the sympathetic outflows to the heart and kidneys in hypertension and heart failure and impaired postural sympathetic circulatory responses in orthostatic intolerance disorders.

The translation of knowledge of pathophysiology such as this into better medical care for patients is an important goal for clinical scientists. The achievement of this transition, from mechanisms to medical management, is at differing stages of development with the different conditions. With cardiac failure, clinical translation is mature, knowledge of cardiac neural pathophysiology having led to the introduction of \(\beta\)-adrenergic blockers. With essential hypertension, translation has emerged in the application of catheter-based renal sympathetic nerve ablation for treatment of patients with severe drug-resistant essential hypertension resistant to pharmacological treatment. With postural syncope syndromes, knowledge of the neural pathophysiology is preliminary only, and any clinical translation remains for the future.

Cardiac Failure

There were 3 important historical antecedents to contemporary knowledge of sympathetic nervous pathophysiology in heart failure. The first was the observation that the concentration of the sympathetic nervous neurotransmitter, norepinephrine,
is reduced in the failing human heart,\textsuperscript{79} usually taken to signify that the heart was sympathetically denervated. The second was the finding that the concentration of norepinephrine in peripheral venous plasma was elevated in patients with heart failure,\textsuperscript{81} providing evidence for systemic sympathetic nervous activation, although presumably not in the heart. And third was the observation that survival in patients with heart failure is related to their venous plasma norepinephrine concentration, with diminished survival being present in those with the highest norepinephrine concentrations.\textsuperscript{42} But these crucial observations left a paradox: why is clinical outcome in heart failure related to sympathetic activation when the heart, through its sympathetic denervation, should be protected? It was research by Bristow et al\textsuperscript{39} that challenged these concepts, causing a paradigm shift in the conceptualization of the neural pathophysiology of heart failure—the finding of a selective reduction in $\beta_1$-adrenoceptors in failing human myocardium, these receptors being in close proximity to sympathetic nerve varicosities. In contrast, normal extrajunctional $\beta_2$-adrenoceptor numbers suggested to these investigators\textsuperscript{39} that the sympathetic nerves of the failing heart must, in fact, be intact and actually release norepinephrine at an increased rate. The expected finding in sympathetic denervation of $\beta_1$-adrenoceptor upregulation definitely was absent.

When my laboratory applied organ-specific tracer kinetic techniques using radiolabeled norepinephrine, this hypothesis was confirmed with demonstration that the sympathetic nervous outflow to the heart is actually preferentially stimulated in severe congestive cardiac failure (emphatically, the failing heart is not sympathetically denervated).\textsuperscript{17,21,27} Rates of norepinephrine spillover from the failing human heart to plasma are approximately equal to the rate of norepinephrine release observed transiently in the healthy heart during near-maximal exercise. Furthermore, a strong link was demonstrated between the level of cardiac sympathetic nervous stimulation in heart failure and the development of ventricular arrhythmias, progressive left ventricular deterioration, and reduced survival.\textsuperscript{21,27}

Informed with this knowledge, Packer et al\textsuperscript{40} devised and conducted the first definitive $\beta$-adrenergic blocker trial for congestive heart failure, the Carvedilol trial. This trial established that chronic $\beta$-adrenergic blockade in cardiac failure could be life-saving.

**Postural Circulatory Dysregulation and Syncope**

Orthostatic intolerance is the descriptive umbrella term for a heterogeneous group of disorders characterized by recurrent postural syncope. The syncope is a transient loss of consciousness and postural tone developing secondary to a fall in cerebral perfusion, this cerebral perfusion fall being commonly caused by a precipitous drop in BP. In health, standing leads to $\approx 700 \text{ mL}$ of the circulating blood volume being displaced into capacitance vessels of the lower limbs and pelvis.\textsuperscript{44} This sequestration of blood results in the activation of compensatory neural reflexes. The sympathetic nervous system provides the pivotal reflex neurocirculatory adjustments that stabilize BP during standing.\textsuperscript{44}

The origins of recurrent postural syncope, no doubt diverse, remain rather obscure, despite extensive investigation. In clinical practice, 2 broad clinical phenotypes of recurrent postural syncope are identified, either with or without neural degeneration\textsuperscript{45,46}:

1. **Neurodegenerative disorders causing postural hypotension:** Patients with sympathetic nerve degeneration (pure autonomic failure), degeneration of brain regions regulating the circulation (multiple system atrophy), and the Parkinson disease (where both mechanisms may apply) often experience disabling postural hypotension and syncope, commonly so severe that prolonged standing and walking are impossible. Diagnostic distinction between these conditions is difficult but is important, as prognosis differs (pure autonomic failure typically is stable for decades, whereas multiple system atrophy inevitably progresses to multisystem involvement and death), as do treatment responses.\textsuperscript{45,46}

2. ** Syndromes of autonomic circulatory dysregulation:** More common than the neurodegenerative autonomic illnesses, and described here are impairments of functional sympathetic circulatory responses to the gravity challenge imposed by standing.

**Postural Tachycardia Syndrome**

This syndrome is typified by an exaggerated reflex sympathetic nervous system response to standing, apparently underlying the tachycardia.\textsuperscript{32,34,35,45,46} Neuromediately mediated cerebral vasoconstriction with reduction of cerebral blood flow seems to be common and is the cause of syncope.\textsuperscript{47} Postural hypotension is usually absent. The research of my group implicates augmentation of the postural sympathetic neural signal as a result of severe deficiency of the noradrenaline transporter protein\textsuperscript{45} as a mechanism of the postural tachycardia and excessive postural fall in cerebral blood flow. The human cerebral blood vessels do have a functional sympathetic innervation.\textsuperscript{15}

**Recurrent Vasovagal (Neurocardiogenic) Syncope**

Recurrent postural fainting can occur in apparently healthy people. There are 2 variants: the first of these being patients with low supine BP, individuals whose supine systolic BP is at the extreme lower end of the normal range, 75 to 90 mm Hg. In my clinical practice, I find this to be a common form of recurrent postural vasovagal syncope.\textsuperscript{38} These patients commonly present at postural syncope clinics, but their low supine BP is often discounted as a basis for the syncope, although previously identified as deleterious in the medical literature.\textsuperscript{45} These patients are commonly informed that low BP is actually healthy, protecting against the development of strokes and myocardial infarction. The second recurrent vasovagal syncope variant involves patients with recurrent syncope and normal supine BP. This is the commonest and most perplexing clinical variant. Clinical examination discloses no abnormalities. The primary pathophysiology of this disorder remains unknown, and treatment is usually ineffective.

The knowledge base for precise diagnosis and treatment of the postural circulatory control disorders has until recently remained dismally deficient.\textsuperscript{45,46} My group has recently made some progress in delineating the neural circulatory pathophysiology of recurrent postural vasovagal syncope, with the
Sympathetic nervous system has been the inaccessibility of nerve firing rates and norepinephrine release from sympathetic nerves, and analysis of sympathetic nerve proteins, accessed via a subcutaneous vein biopsy and quantified with Western blotting. These findings suggest a disconnect between nerve firing and norepinephrine release. Reproduced from Vaddadi et al. with permission.

A significant limitation to clinical investigation of the human sympathetic nervous system has been the inaccessibility of tissues containing sympathetic nerves. We have recently developed a technique to extract sympathetic nerve proteins from subcutaneous forearm vein biopsy specimens. Figures 2 and 3 detail some of these findings:

1. Sympathetic nerve firing rates: Paradoxically, nerve firing rates during tilt were much higher in patients with the low BP phenotype, despite their low BP, than in healthy controls and subjects with the normal supine BP vasovagal syncope phenotype (Figure 2).

2. Total norepinephrine spillover rates: In healthy subjects, total norepinephrine spillover to plasma rose incrementally in proportion to the tilting angle (Figure 2). Norepinephrine spillover during tilting was subnormal in the 2 vasovagal syncope syndrome variants.

3. Quantification of sympathetic nerve proteins: Testing for a possible mechanism of the disjunction between nerve firing and norepinephrine release to plasma? Norepinephrine is synthesized by a series of enzymatic steps. Tyrosine hydroxylase (TH) is the rate-limiting step in NE synthesis. The release of NE into synaptic cleft is triggered by sympathetic nerve activity originating in the brain. This neural signal is effectively terminated by the norepinephrine transporter, which clears NE from the synaptic cleft. The vesicular monoamine transporter 2 is critical to the reincorporation of NE into synaptic vesicles, whereas dynamins are responsible for vesicle fusion with the plasma membrane and vesicle recycling. It is plausible that dysfunction of the neural signal or any of these molecular systems governing sympathetic varicosity function could reduce the spillover of NE and account for the propensity to recurrent syncope.

To summarize, recurrent vasovagal syncope in the low and normal systolic BP phenotypes is characterized by an impaired neurovascular response to standing, apparently taking the form of an electrochemical disconnect in sympathetic nerves, with normal nerve firing being accompanied by markedly reduced neurotransmitter spillover. In planned research, the norepinephrine prodrug dihydroxyphenylserine, which is converted to norepinephrine within sympathetic nerves by dihydroxyphenylalanine-decarboxylase, is to be administered to vasovagal patients with the low supine pressure phenotype.
Agreement was initiated by pivotal studies of Julius et al.38 This contemporary agreement that overactivity of the sympathetic nervous system commonly initiates and sustains the BP elevation in patients with essential hypertension.11,22–26,28,30,53 This contemporary agreement is based on both the proportion of untreated patients with essential hypertension who have demonstrable sympathetic excitation and the number in whom substantial BP lowering is achieved, and the extent of this lowering, with antidiuretic drugs. In a truly international endeavor from many research groups, the application of sympathetic nerve recording and norepinephrine spillover methodologies11,22–26,28,30,56–59 has identified activated sympathetic outflow to the skeletal muscle vasculature and kidneys. Sympathetic nervous system activation is evident in both lean and obese patients with hypertension11,24,25,30,59; sympathetic activation demonstrable with microneurography is particularly prominent in the metabolic syndrome and obesity-related hypertension.11,24,25,59 In the heightened sympathetic activation seen when hypertension is accompanied by obesity, hyperinsulinemia, hyperleptinemia, and obstructive sleep apnea have all been invoked as prime movers, but in reality the precise mechanism remains uncertain.50

Does this sympathetic activation initiate and maintain the BP elevation as has been suggested?53 There is strong evidence to support this claim. In patients with resistant hypertension, responding inadequately to concurrent treatment with multiple antihypertensive drug classes, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, and diuretics, catheter-based radiofrequency ablation of the renal sympathetic nerves targeting the activation of the renal sympathetic outflow lowers BP remarkably.18,19 And this sympathetic nervous activation present in essential hypertension has microcirculatory effects beyond BP elevation, causing the insulin resistance central to the commonly comorbid metabolic syndrome.61 Renal denervation, through the central sympathetic inhibition it causes by the ablation of renal afferent nerves,62 breaks this link, reducing insulin resistance.63

Essential Hypertension

For the past 3 decades, the major focus in high BP research has been the renin–angiotensin system. Angiotensin-converting enzyme inhibitors and angiotensin receptor blocking drugs have been the dominant antihypertensive therapy, leading to neglect of other BP-raising systems, including the sympathetic nervous system. Despite this, there is a new general agreement that overactivity of the sympathetic nervous system commonly initiates and sustains the BP elevation in patients with essential hypertension.11,22–26,28,30,53 This contemporary agreement was initiated by pivotal studies of Julius et al.38,55 commencing 4 decades ago, in which heart rate and hemodynamic response to pharmacological adrenergic blockade indicated the clear presence of excessive neural drive to the cardiovascular system in essential hypertension.

The syndrome of neurogenic essential hypertension accounts for no <50% of all cases of high BP.53 This estimate is based on both the proportion of untreated patients with essential hypertension who have demonstrable sympathetic excitation and the number in whom substantial BP lowering is achieved, and the extent of this lowering, with antidiuretic drugs. In a truly international endeavor from many research groups, the application of sympathetic nerve recording and norepinephrine spillover methodologies11,22–26,28,30,56–59 has identified activated sympathetic outflow to the skeletal muscle vasculature and kidneys. Sympathetic nervous system activation is evident in both lean and obese patients with hypertension11,24,25,30,59; sympathetic activation demonstrable with microneurography is particularly prominent in the metabolic syndrome and obesity-related hypertension.11,24,25,59 In the heightened sympathetic activation seen when hypertension is accompanied by obesity, hyperinsulinemia, hyperleptinemia, and obstructive sleep apnea have all been invoked as prime movers, but in reality the precise mechanism remains uncertain.50

Renal Denervation for Drug-Resistant Hypertension: Observations of a Founder

The sympathetic nervous system is the forgotten pathway in the treatment of hypertension. Despite the importance of neural pathophysiological mechanisms in pathogenesis, therapy specifically targeting the sympathetic nervous system is currently underused. This has changed with the testing of device-based therapies for reducing sympathetic nervous system activity and consequently BP.65

In earlier times, before the availability of antihypertensive drugs, extensive surgical sympathectomy was used as a treatment for severe hypertension66; survival benefit was demonstrated, but complication rates were high as was morbidity from the extensive denervation, which did not specifically target the kidneys. In that era, there was no theory that the renal nerves were a prime mover in hypertension pathogenesis. In many experimental models of hypertension, the sympathetic outflow to the kidneys is activated, and renal sympathectomy typically prevents the development of the hypertension.67

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 BP-elevating responses. The renal tubules receive a dense sympathetic innervation at all tubular levels. A specific and important relationship 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 thought to be a central element in the development of hypertension. This has been documented with inherited, monogenetic abnormalities in renal tubule sodium transport but also occurs with stimulation of the renal sympathetic nerves, which opposes pressure natriuresis.

Renal sympathetic denervation shifts the renal pressure–natriuresis curve to the left, promoting urinary sodium excretion and lowering of BP.

Initiation of the treatment strategy of catheter-based radiofrequency renal nerve ablation for drug-resistant hypertension was based on these experimental observations and the demonstration that the renal sympathetic outflow is activated in human hypertension. 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 end points, accompanying resistant hypertension renal denervation mechanism studies and 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 and ultrasound energy.
2. The treatment can be delivered with minimal procedural complications, these being typical of invasive cardiological procedures in general and not consequent on energy delivery.
3. The mean BP reduction across the trials shows consistency, office systolic BP falling on average by 20 to 30 mm Hg at the primary end points. Renal function is preserved.
4. The BP reduction is durable and perhaps permanent, demonstrably persisting for 3 years and beyond, despite initial concerns that regrowth of renal sympathetic nerves might cancel out the pressure lowering.
5. The BP fall is sometimes delayed; the treatment response rate improves over time.
6. New renal artery stenoses in the field of radiofrequency energy delivery are uncommon. Radiofrequency-induced aneurysm has not been reported.
7. Treatment failure does occur (estimated at 15%–30% in the trials). This might, perhaps, be because of the absence of neural mechanisms of BP elevation in individual patients but cannot be predicted from patient clinical characteristics. A higher baseline BP 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 the postural venous pooling that underlies postural hypotension.

Renal Denervation for Resistant Hypertension: the End of the Beginning

The first catheter-based renal denervation procedure for drug-resistant hypertension was performed on June 6, 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.” Many questions remain. Will the BP lowering be permanent (or will it be canceled out by renal sympathetic nerve regrowth)? How can patient selection for the renal denervation procedure be optimized, given that pressure reduction is not achieved in all patients? Will BP lowering with renal denervation reduce the rate of clinical cardiovascular end points? 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 in newer denervation devices being equally effective with radiofrequency energy in lowering pressure? I hope the second 6 years of catheter-based renal denervation will answer these questions.

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Sympathetic Nervous System Moves Toward Center Stage in Cardiovascular Medicine: From Thomas Willis to Resistant Hypertension

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