Translational medicine

The human sympathetic nervous system: its relevance in hypertension and heart failure

Gianfranco Parati[1,2]* and Murray Esler[3]

[1]Department of Cardiology, S.Luca Hospital, IRCCS Istituto Auxologico Italiano, piazza Brescia 20, 20149 Milan, Italy; [2]Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Milan, Italy; and [3]Hypertension Thrombosis and Vascular Biology Division, Baker IDI Heart and Diabetes Institute, Melbourne, Australia

Evidence assembled in this review indicates that sympathetic nervous system dysfunction is crucial in the development of heart failure and essential hypertension. This takes the form of persistent and adverse activation of sympathetic outflows to the heart and kidneys in both conditions. An important goal for clinical scientists is translation of the knowledge of pathophysiology, such as this, into better treatment for patients. The achievement of this 'mechanisms to management' transition is at different stages of development with regard to the two disorders. Clinical translation is mature in cardiac failure, knowledge of cardiac neural pathophysiology having led to the introduction of beta-adrenergic blockers, an effective therapy. With essential hypertension perhaps we are on the cusp of effective translation, with recent successful testing of selective catheter-based renal sympathetic nerve ablation in patients with resistant hypertension, an intervention firmly based on the demonstration of activation of the renal sympathetic outflow. Additional evidence in this regard is provided by the results of pilot studies exploring the possibility to reduce blood pressure in resistant hypertensives through electrical stimulation of the area of carotid baroreceptors. Despite the general importance of the sympathetic nervous system in blood pressure regulation, and the specific demonstration that the blood pressure elevation in essential hypertension is commonly initiated and sustained by sympathetic nervous activation, drugs antagonizing this system are currently underutilized in the care of patients with hypertension. Use of beta-adrenergic blocking drugs is waning, given the propensity of this drug class to have adverse metabolic effects, including predisposition to diabetes development. The blood pressure lowering achieved with carotid baroreceptor stimulation and with the renal denervation device affirms the importance of the sympathetic nervous system in hypertension pathogenesis, and perhaps suggests a wider role for anti-adrenergic antihypertensives, such as the imidazoline drug class (moxonidine, rilmenidine) which act within the CNS to inhibit central sympathetic outflow, although the lack of large-scale outcome trials with this drug class remains a very material deficiency.

Keywords   Chronic heart failure • Arterial hypertension • Sympathetic activity • Arterial baroreflex • Microneurography • Catecholamines • Baroreceptor stimulation • Renal denervation • Beta-blockers

Introduction

Willis, in 1664, provided the first anatomically correct depiction of the sympathetic nervous system.[1] Histological examination two centuries later demonstrated dense innervation of walls of blood vessels, leading Stelling in 1840[2] to correctly conclude that the vasomotor fibres were in sympathetic nerves carried from the central nervous system. In the mid-nineteenth century, building on these observations, Brown-Sequard, Waller, and Bernard[2] laid the foundation for modern concepts of neural circulatory control, through demonstration of vasoconstriction with electrical stimulation of the cut nerves, and vasodilatation on the nerve section, which indicated that sympathetic fibres exerted a tonic, vasoconstrictor influence.

The sympathetic nervous system was brought to public awareness in the early decades of the twentieth century by Cannon, through his research on, and popularization of the concept of the 'fight and flight' response to stress.[3] In the past three decades, the sympathetic nervous system has moved towards centre stage in cardiovascular medicine, with demonstration of the importance of aberrations of the sympathetic nervous system in heart failure, essential hypertension, disorders of postural circulatory control causing syncope, and 'psychogenic heart disease', heart disease attributable to mental stress and psychiatric illness.[4]

This review makes the claim that sympathetic nervous system activation is important in heart failure and hypertension, but in

* Corresponding author. Tel: +39 02 619112980, Fax: +39 02 619112956, Email: gianfranco.parati@unimib.it

contrasting ways. In heart failure, sympathetic activation occurs subsequently to the development of the heart failure, and then impacts adversely on the clinical outcome. In essential hypertension the causal chain is different, with sympathetic nervous system activation being important in the initiation, and then maintenance of the hypertension, on the background of a complex interaction between multiple other mechanisms. Despite these differences, the sympathetic nervous system becomes a 'culprit', and therapeutic target in both conditions. Clinical translation of these concepts is mature in cardiac failure, knowledge of cardiac neural pathophysiology having led to introduction of beta-adrenergic blockers, an effective therapy. With essential hypertension, the positive results obtained with more recently developed beta-adrenergic receptor blockers, and recent successful testing of a device for electrical carotid baroreceptor stimulation as well as of selective catheter-based renal sympathetic nerve ablation in patients with resistant hypertension, hint at pathophysiology to therapy translation that might occur.

The sympathetic nervous system: methods of measurement

Von Euler[5] definitively demonstrated the sympathetic transmitter to be norepinephrine, using bioassay systems allowing comparison of the biological actions of the sympathetic transmitter extracted from tissues with those of epinephrine and norepinephrine. This discovery quickly led to the application of neurochemical methods, initially measurement of norepinephrine excretion in urine, now largely obsolete, in efforts to quantify sympathetic nervous system activity in humans. The development of a sympathetic nerve recording technique applicable to humans (clinical microneurography) in 1968 by Hagbarth and Vallbo[6] and the publication of the first sensitive and specific plasma-catecholamine assay, also in 1968, by Engelman et al.[7] were subsequent milestones in the field. The application of these neurophysiological and neurochemical methods, and later refinements of them, came to dominate the investigation of sympathetic neural mechanisms in clinical research.

An assumption underlying the use of the early neurochemical tests of the sympathetic nervous system was that the sympathetic nervous system acts in a global, undifferentiated fashion. This was in accord with the teaching of Cannon,[3] exemplified in his 'fight and flight' concept of sympathetic mass action, but is untrue. Sympathetic nervous system responses are often regionalized, activation in one sympathetic outflow commonly being accompanied by no change, or a reduction, in others.[8,9] Quantification of individual regional sympathetic nervous outflows can be achieved with the sympathetic nerve recording technique, and by radiotracer-derived measurements of regional norepinephrine spillover to plasma, from individual organs (Figure 1). These methods are complementary; neither is 'best'. The microneurography method is online, providing instantaneous data on electrical transmission in sympathetic nerves, with multi-unit or single-fibre recordings, but may be open to an investigator bias in case of studies based on manual and not blinded analysis of recordings obtained in small groups of subjects. The regional spillover method provides

objective information on neurotransmitter release in individual organs consequent to this firing, including in internal organs for which the nerve recording technique is not applicable. Another commonly used method to explore autonomic cardiovascular modulation is based on computer analysis of heart rate and blood pressure variability. However, while heart rate variability largely reflects selective autonomic control of the heart, blood pressure fluctuations are the result of complex interactions between multiple mechanisms, including cardiac and vascular neural regulation, mechanical influences of ventilation, humoral and endothelial factors, large arteries stiffening, and genetic factors. Nevertheless, when properly applied, methods based on time or frequency domain analysis of either blood pressure or heart rate variability can provide a valuable insight into integrated cardiovascular regulation. The advantages of this approach, in spite of a possible limited specificity in some circumstances, consist in its easy applicability also in daily practice and in the avoidance of any external intervention on subjects under evaluation.[10]

Microneurography

Hagbarth and Vallbo[6] in 1968 reported a method for measuring efferent multi-fibre traffic in sympathetic nerves. This technique of clinical microneurography provides a method for studying nerve firing in subcutaneous sympathetic nerves distributed to skin and the skeletal muscle vasculature. Multi-fibre recordings of 'bursts' of nerve activity, synchronous with the heart beat, are generated in skeletal muscle vascular efferents. More recently, single fibre sympathetic recording has also been successfully performed in humans.[11,12]

Noradrenaline spillover

A special impetus to the development of techniques for studying the rates of overflow of noradrenaline to the circulation was provided by the lack of clinical methods for studying sympathetic nervous outflow in humans to otherwise inaccessible organs, such as the heart and kidneys. Measurement of organ-specific norepinephrine release to plasma[8,9,13] became the gold standard for doing this. During constant rate infusion of tritiated norepinephrine, outward flux of endogenous norepinephrine from an organ (regional norepinephrine 'spillover') can be measured by isotope dilution:

$$\text{Regional norepinephrine spillover} = [(C_V - C_A) + C_A E]\ \text{PF},$$

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 noradrenaline in transit of blood through the organ, and PF is the organ plasma flow.

Heart rate variability, blood pressure variability, and arterial baroreflex sensitivity

Variability in cardiovascular parameters such as blood pressure and heart rate has been shown to reflect the activity of cardiovascular control mechanisms, including sympathetic cardiovascular modulation, both in health and disease.[14–16] Several methodological approaches are available to this aim, respectively focusing
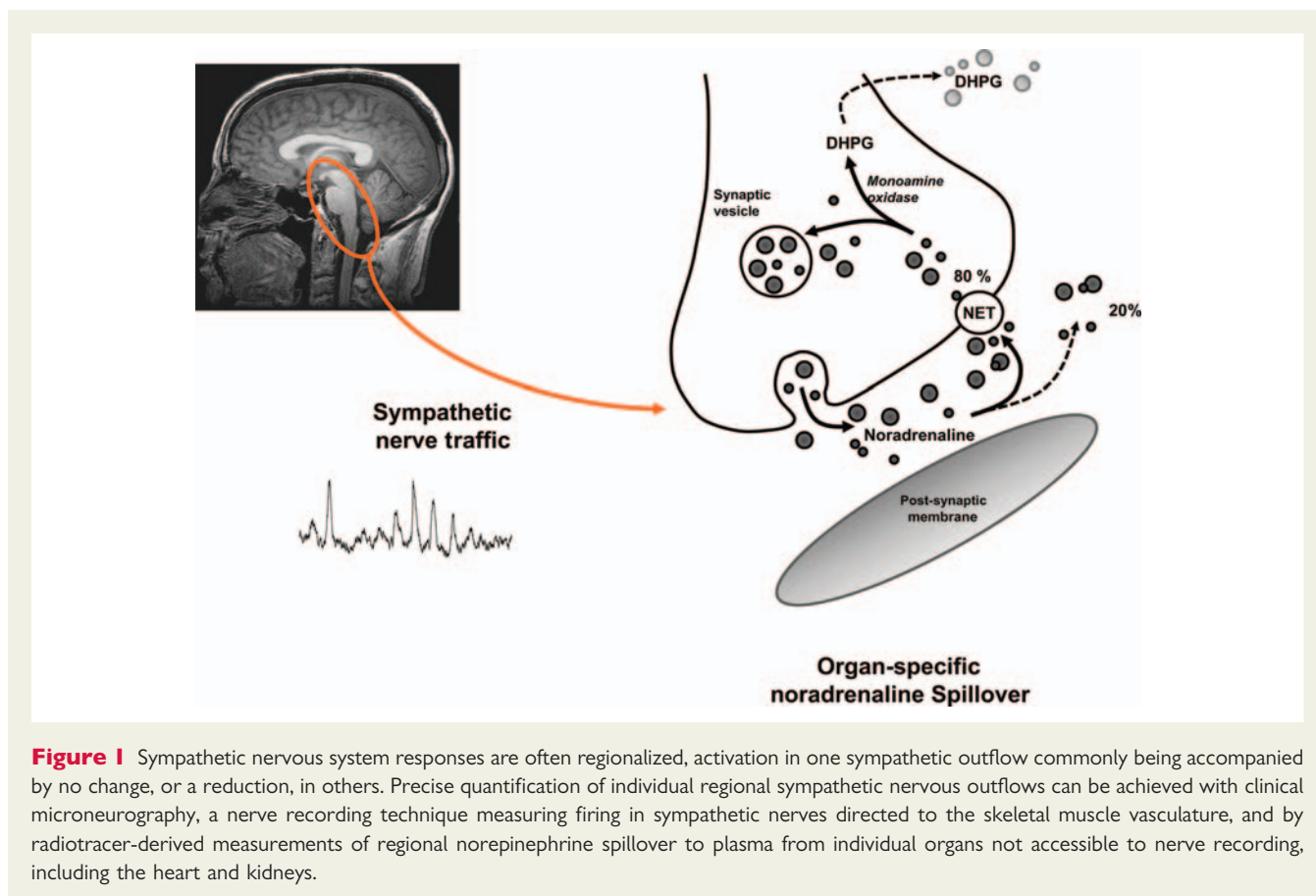
Figure 1 Sympathetic nervous system responses are often regionalized, activation in one sympathetic outflow commonly being accompanied by no change, or a reduction, in others. Precise quantification of individual regional sympathetic nervous outflows can be achieved with clinical microneurography, a nerve recording technique measuring firing in sympathetic nerves directed to the skeletal muscle vasculature, and by radiotracer-derived measurements of regional norepinephrine spillover to plasma from individual organs not accessible to nerve recording, including the heart and kidneys.

on estimates of blood pressure or heart rate variance, their spectral powers,[14–16] heart rate turbulence,[17] entropy, self-similarity and symbolic logic,[18] or on blood pressure−heart rate interactions to quantify the sensitivity of baroreflex control of heart rate (BRS).[19,20] Evidence that cardiovascular variability does represent an index of autonomic control of circulation comes from either animal or human studies, the latter performed both in normal subjects and in patients affected by diseases where the autonomic nervous system was primarily or indirectly affected.[10]

Heart rate variability

Vagal and sympathetic cardiac influences operate on the heart rate in different frequency bands. While vagal regulation has a relatively high cut-off frequency, modulating heart rate both at low and high frequencies, up to 1.0 Hz, sympathetic cardiac control operates only <0.15 Hz.[14,21,22] It has to be acknowledged, however, that although heart rate variability is certainly affected by sympathetic cardiac modulation, no individual heart rate spectral component is a specific marker of sympathetic cardiac modulation, because of the interference by other participating factors, including humoral mechanisms, gender, age, respiration and resonance in the baroreflex loop ∼0.1 Hz.[23] Normalization of LF powers by total variance, or computation of the LF/HF power ratio, may help increase the reliability of spectral parameters in reflecting sympathetic cardiac modulation.[14,15] Recent evidence suggests that also non-linear models for cardiovascular variability analysis, such as heart-rate self-similarity, may reflect autonomic

cardiovascular regulation.[24] The clinical relevance of the information on autonomic cardiac control provided by heart rate variability parameters is supported by the evidence that reduced heart rate variability and BRS is associated with increased mortality after myocardial infarction as well as in heart failure patients, and with increased risk of sudden arrhythmic death.[25]

Blood pressure variability

Blood pressure variability increases in conditions characterized by sympathetic activation. Indeed, increased daytime blood pressure variability in humans is associated with an increase in sympathetic efferent traffic in the peroneal nerve.[26] When considering blood pressure spectral powers, while HF fluctuations largely depend on the mechanical effects of respiration, LF and VLF powers are predominantly caused by fluctuations in the vasomotor tone and systemic vascular resistance and are influenced by complex interactions between neural, humoral, genetic and endothelial factors, by myogenic tone and by thermoregulation.[14] Thus, while blood pressure and heart rate LF powers have been repeatedly suggested as markers of sympathetic cardiovascular control,[16] their specificity in this regard is limited.[14]

Arterial baroreflex sensitivity

The ability of cardiovascular variability to reflect autonomic cardiovascular control is improved by use of multivariate models for its assessment. The simplest ones consider the relationship between spontaneous fluctuations in blood pressure and heart rate, either
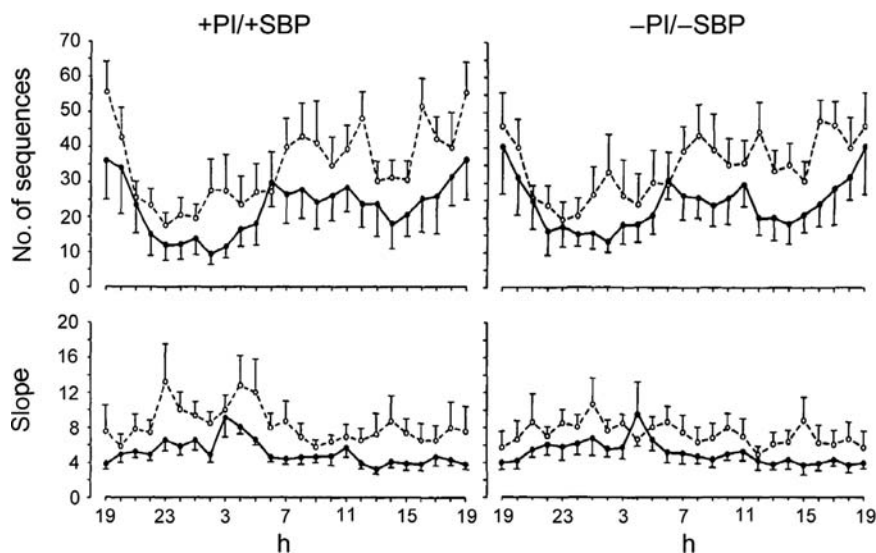
Figure 2 Number and slope of +PI/+SBP and −PI/−SBP sequences during each hour of a 24-h intra-arterial ambulatory blood pressure recording (means ± SE) for 10 normotensive (open circle) and 10 hypertensive (closed circle) subjects. (From Ref.[20], modified with permission). PI, pulse interval; SBP, systolic blood pressure.

in the time (sequence technique)[19,20] or frequency domain (alpha-coefficient, transfer function analysis) to assess BRS and its modulation in daily life[19,27,28] (*Figure 2*).

Cardiovascular variability and autonomic cardiovascular regulation

In conclusion, while spontaneous variations in blood pressure and heart rate clearly depend on autonomic mechanisms, caution is needed in taking their assessment as a quantitative index of sympathetic nervous efferent activity to the vessels and the heart. In fact, in a variety of clinical situations, including heart failure, LF heart rate spectral power has little or no relation to rates of noradrenaline spillover from the heart and sympathetic nerve firing quantified by microneurography. Indeed, in heart failure, LF heart rate spectral power is reduced, but cardiac noradrenaline spillover is remarkably increased.[29]

Heart failure

Sympathetic nervous system activation in heart failure

The contemporary picture of the neural pathophysiology of heart failure emerged slowly over three decades, with the first evidence for activation of the sympathetic nervous system being the finding of increased excretion of noradrenaline in urine.[30]

Urine and plasma noradrenaline

Noradrenaline in urine derives primarily from two sources, filtration at the glomerulus of noradrenaline in plasma originating systemically from sympathetic nerves, and preferentially, from noradrenaline released within the kidneys by the renal sympathetic nerves. The activation of the renal sympathetic outflow,

subsequently demonstrated in cardiac failure,[12,31] meant that measurement of the transmitter in urine was well placed to identify the sympathetic activation present. There was an early report of high concentrations in plasma of the sympathetic transmitter,[32] but the plasma noradrenaline assays in use at the time were non-specific and unreliable, giving values 5−10-fold higher than those documented later with valid assays.

The modern era commenced when Marks and colleagues,[33] applying a newly developed, valid plasma noradrenaline assay, demonstrated elevated plasma concentrations of the transmitter in heart failure patients. But that was not the end of the story; there is a drawback with plasma noradrenaline concentration measurements. The application of isotope dilution methodology with tritiated noradrenaline to heart failure research subsequently demonstrated that the rate of removal of noradrenaline from plasma in heart failure patients is, in fact, slowed due to reduced cardiac output and regional blood flows; the elevation in the plasma concentration of noradrenaline is partly attributable to this reduction in noradrenaline plasma clearance.[13] Plasma noradrenaline measurements in fact overestimate the degree of sympathetic nervous activation present in heart failure.

Myocardial β-adrenoceptors

The next milestone was the demonstration by Bristow *et al.*[34] of a reduction in the concentration of adrenoceptors in failing human myocardium, this being selective for β1 adrenoceptors, and excluding β2 adrenoceptors. The results were interpreted by the authors to signify that, most likely, the β1 adrenoceptors, which are in close proximity to sympathetic nerve varicosities, had been selectively down-regulated by increased rates of sympathetic nerve firing and transmitter release in the failing heart. β2 adrenoceptors are extrajunctional and are excluded from this neural influence.[34] But a paradox existed, as an earlier, pioneering study by

Chidsey et al.[35] had demonstrated that the concentration of noradrenaline in failing human myocardium was markedly lowered, which they took to be indicative of the presence of cardiac sympathetic denervation.

Cardiac noradrenaline spillover

This theoretical impasse was overcome with application of regional noradrenaline kinetics methodology, which demonstrated very high rates of noradrenaline spillover from the heart in cardiac failure.[13] The low tissue noradrenaline content was misleading; cardiac sympathetic tone is actually remarkably elevated in heart failure patients. Parallel studies demonstrated activation of the sympathetic outflows to the kidneys, evident in high rates of renal noradrenaline spillover,[13,31] and to the skeletal muscle vasculature, documented with microneurography.[36]

Adverse effects of chronic sympathetic activation

Inappropriate and excessive activation of the sympathetic nervous system has been invoked as a cause of heart disease. This pathophysiological linkage can take two forms. The most direct and explicit is when acute sympathetic nervous activation triggers adverse cardiac events (myocardial infarction, atrial fibrillation, ventricular arrhythmias, and Takotsubo cardiomyopathy have all been documented) during acute severe mental stress.[37] The case is no less strong that chronic sympathetic activation similarly is adverse. Research in patients with heart failure was central to establishing this principle.

The pivotal observation was made by Cohn et al.,[38] who demonstrated that the prevailing plasma concentration of noradrenaline was a predictor of heart failure patient survival, survival being worse at the highest plasma concentrations of the transmitter. Direct demonstration of a strong relation of cardiac sympathetic activity specifically to survival followed in a prospective study, with high sympathetic activity, independent of the severity of the heart failure, causing death both by arrhythmias and by progressive left ventricular failure.[39] In a later instructive study, both high cardiac noradrenaline spillover and reduced myocardial noradrenaline stores (measured with radiolabelled noradrenaline) were shown to impact on survival in heart failure, the high cardiac sympathetic activity being linked to risk of death from arrhythmias and reduced myocardial noradrenaline content to death from progressive left ventricular failure.[40]

Subsequently, when most heart failure patients were under treatment with β-adrenergic blockade, high renal sympathetic activity (gauged from renal noradrenaline spillover measurements) emerged as a predictor of early death.[31] Excessive retention of sodium from activation of the renal sympathetic nerves directly innervating the renal tubules[41] may be the culprit here. Whether the level of activation in the sympathetic outflow to the skeletal muscle vasculature, which is accentuated when hypertension, obesity, and the metabolic syndrome co-exist with heart failure[42,43], also predicts survival in heart failure patients is less clear. In this case, the mechanism by which risk would be conferred is not as obvious as with activation of the cardiac and renal sympathetic outflows. Perhaps the burden of heightened cardiac afterload from skeletal muscle vasoconstriction is important.

Heart rate variability and baroreflex sensitivity

In patients with chronic heart failure heart rate variability and baroreflex sensitivity are markedly reduced, and their reduction has been found to be a predictor of arrhythmic mortality both in univariate and multivariate analysis.[44] A few studies on cardiac patients have also suggested a predictive value of heart rate turbulence.[45] Finally, when examined in conjunction with depressed LVEF, also BRS contributes to risk stratification.[25] In spite of these results, however, the evidence linking impaired short-term HRV to sudden death in heart failure patients is still limited, which implies caution with the clinical use of HRV for arrhythmic risk stratification in these conditions.

Antagonism of sympathetic activation in heart failure

These observations linking sympathetic activation to clinical outcome in heart failure provided the theoretical basis for trials of pharmacological antagonism of the sympathetic nervous system.

Beta-adrenergic blockade

An apparently favourable response to propranolol had been reported in several small series of heart failure patients treated with propranolol in the mid-1970s, but these and subsequent more formal trials remained underpowered to show benefit. Then with the strong theoretical foundation that β_1-adrenoceptors were selectively down-regulated in the failing heart, and noradrenaline release from cardiac sympathetic nerves was markedly increased,[46] subsequent large, randomized beta-blocker trials followed, demonstrating clear prolongation of survival, with carvediolol,[47] metoprolol,[48] bisoprolol,[49] and nebivolol,[50] in turn. Benefit was demonstrated in moderate heart failure, severe heart failure, and heart failure in the elderly. But this is not a 'class effect', holding for all beta-blockers. Bucindolol and xamoterol provide no benefit with long-term dosing.[51] An explanation lies in the fact that these drugs share the property of possessing intrinsic agonist activity, which causes cardiac adrenergic stimulation.
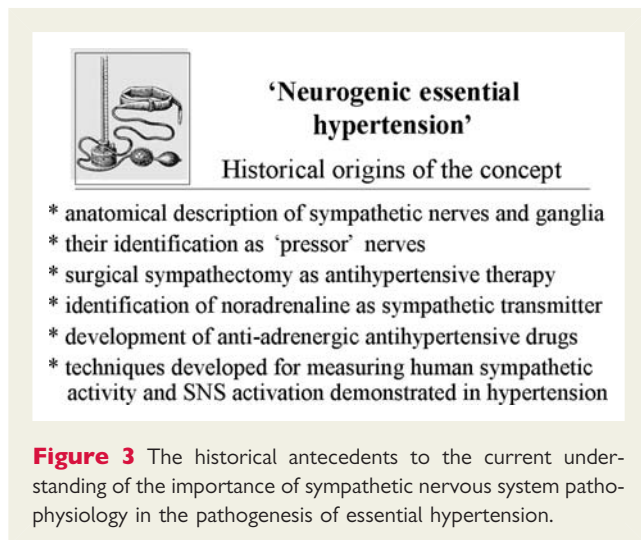
Central inhibition of sympathetic outflow

A logical extension of these beta-blocker trials was the evaluation of central inhibition of sympathetic outflow in heart failure, which was performed with the imidazoline agent moxonidine.[52] Central sympathetic inhibition with moxonidine actually increased mortality in heart failure patients, for uncertain reasons. Whether this was because the central premise that inhibition of central outflow would be beneficial was in fact false, or was due to a faulty trial design, specifically the adoption of a fixed, forced titration to high doses,[52] remains an unsettled question.

Hypertension

History: early ideas that essential hypertension might be 'neurogenic', the pressure rise being initiated and sustained by the sympathetic nervous system

In the early decades of the twentieth century, faced with the high mortality of severe hypertension, and the absence of effective
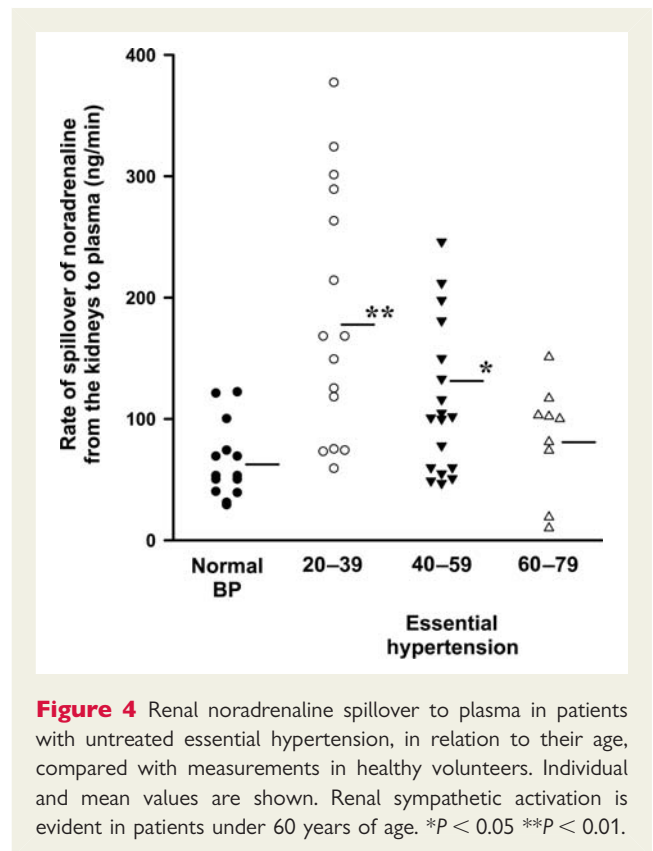
Figure 3 The historical antecedents to the current understanding of the importance of sympathetic nervous system pathophysiology in the pathogenesis of essential hypertension.

pharmacological therapy, a number of operations on the sympathetic nervous system were devised in an attempt to lower blood pressure (*Figure 3*). Notable among these was radical lumbodorsal splanchnicectomy, developed in 1938 by Smithwick,[53] which lowered blood pressure and reduced mortality, but at the cost of often incapacitating side effects. By the late 1960s, of the available antihypertensives, which by then had been developed, most antagonized the autonomic nervous system, either generally, with ganglionic blockers, or specifically its sympathetic division, with central sympathetic inhibitors methydopa and clonidine, sympathetic neuronal blockers such as guanethidine, and alpha- and beta-adrenergic blockers. The potency and clinical usefulness of these drugs helped sustain the argument that the sympathetic nervous system was important in the pathogenesis of essential hypertension.

For the past three decades, the major focus in high blood pressure research has been the renin–angiotensin system. The proven value of anti-hypertensive drugs that block this system has led to neglect of other blood pressure-raising systems, including the sympathetic nervous system. Despite this, undeniable evidence now exists for the importance of chronic activation of the sympathetic nervous system in essential and renal hypertension.

Sympathetic nervous system activation in essential hypertension

Application of the norepinephrine spillover methodology has demonstrated activation of the sympathetic nervous outflows to the kidneys and heart.[8,54] Renal norepinephrine spillover, on average, is elevated two- to three-fold in both normal weight patients with essential hypertension and in obesity-related hypertension.[8,54] Multi-unit recordings from sympathetic nerve fibres directed to the skeletal muscle vasculature similarly show a doubling or trebling of the sympathetic outflow.[12,55–57] Single-fibre sympathetic recording demonstrates increased fibre firing frequencies, and multiple firings within a cardiac cycle (firing salvos), not seen in health.[12,56]

The syndrome of neurogenic essential hypertension appears to account for $\geq$50% of all cases of high blood pressure. This estimate is based on both the proportion of untreated patients with

Figure 4 Renal noradrenaline spillover to plasma in patients with untreated essential hypertension, in relation to their age, compared with measurements in healthy volunteers. Individual and mean values are shown. Renal sympathetic activation is evident in patients under 60 years of age. *$P < 0.05$ **$P < 0.01$.

essential hypertension who have demonstrable sympathetic excitation, and the number in whom substantial blood pressure lowering is achieved, and the extent of this lowering, with anti-adrenergic drugs. The application of sympathetic nerve recording and norepinephrine spillover methodologies, in multiple studies from different research groups,[8,12,54–57] has identified activated sympathetic outflow to the skeletal muscle vasculature and kidneys in ~50% of patients (*Figure 4*).

If we consider, even with the limitations mentioned above, an overall measure of autonomic cardiac modulation such as the sensitivity of arterial baroreflex control of the heart rate, both laboratory and 'spontaneous' methods for arterial baroreflex sensitivity analysis provide consistent evidence of reduced cardiac baroreflex sensitivity in hypertension, mainly due to impaired parasympathetic cardiac control.[19,20] Given the reciprocal interactions between sympathetic and parasympathetic cardiovascular regulation, reduced cardiac parasympathetic activity implies an increase in the activity of the sympathetic nervous system to the heart. The occurrence of such a systematic imbalance between parasympathetic and sympathetic cardiac modulation in hypertensive patients was demonstrated not only in the laboratory, but also over the 24 h in ambulatory conditions[20] (*Figure 2*).

Does this sympathetic activation cause blood pressure elevation?

Once it was thought that the sympathetic nervous system exerts minute by minute circulatory control only, and was not important in the pathogenesis of hypertension. This is not correct. It now

seems certain that the renal sympathetic nerves are pivotal in the pathogenesis of experimental and essential hypertension, through influences on renin release, glomerular filtration rate and renal tubular reabsorption of sodium.[41,58] Experimental studies establish the important concept that sub-vasoconstrictor levels of renal sympathetic activity can increase renin secretion and renal sodium retention, without changing renal haemodynamics.[41] A parallel is seen in essential hypertension. Younger patients with mild essential hypertension very commonly have 'high renin essential hypertension', where renal sympathetic activity is sufficiently elevated to increase renal secretion of renin, but not to reduce renal blood flow.[54] In patients with resistant hypertension, responding inadequately to concurrent treatment with multiple anti-hypertensive drug classes, including ACE inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, and diuretics, radiofrequency ablation of the renal sympathetic nerves lowers blood pressure remarkably,[59,60] as described below.

Consequences of sympathetic nervous system activation in hypertension, beyond blood pressure elevation: left ventricular hypertrophy, insulin resistance

A growth promoting effect of high cardiac sympathetic activity on human myocardium was evident in a clinical study that demonstrated proportionality between increases in LV mass (normalized for blood pressure) and cardiac noradrenaline spillover in patients with essential hypertension.[57] Glucose utilization by skeletal muscle through the action of insulin, which is the process largely determining measured insulin resistance, is influenced by sympathetic nervous outflow to the limbs and skeletal muscle blood flow and glucose delivery to muscle. Reduced skeletal muscle blood flow in essential hypertension resulting from sympathetically mediated vasoconstriction is the probable primary cause of insulin resistance and attendant hyperinsulinaemia commonly present.[61,62]

Sympathetic nervous system activation in secondary forms of hypertension

In *end-stage renal disease* sympathetic nervous activation is at a very high level, higher than in essential hypertension and equal to or exceeding that seen in cardiac failure.[63] Renal transplantation restores renal function but does not abolish the hypertension. Nephrectomy on the other hand does reduce blood pressure, through normalization of sympathetic tone[63] via removal of the sympathetic excitatory influence of renal afferents from the diseased kidneys.[64] In experimental models of renal injury, involving, for example, injection of phenol into the renal parenchyma, projection of activated renal afferent imputs to the hypothalamus has been demonstrated to activate CNS sympathetic outflow, causing hypertension.[64] The hypertension of renal failure is explicitly a neurogenic hypertension.[63] Less studied are renovascular hypertension and pregnancy hypertension, where the sympathetic nervous system is activated, and primary aldosteronism and Cushing's syndrome, where the sympathetic system is suppressed.

Obstructive sleep apnoea is another cause of resistant hypertension associated with increased sympathetic activity to cardiac and vascular targets,[65] acknowledged by Hypertension Management Guidelines.[66] The blood pressure increase associated with obstructive sleep apnoea is due to a complex interaction of different mechanisms, among which changes in autonomic cardiovascular regulation play a major role.[65] Indeed, obstructive apnoea, besides determining sleep fragmentation and periodic changes in intra-thoracic pressure, activates hypoxic and hypercapnic chemoreflexes involving central autonomic neural mechanisms that generate a profound elevation in sympathetic nerve activity and cyclical changes in parasympathetic nerve activity.[67–69] The pathogenetic role of sympathetic activation in the obstructive sleep apnoea (OSA)-related blood pressure increase is clearly supported by the finding of enhanced muscle sympathetic nervous activity during wakefulness and sleep in patients with OSA.[70,71]

The origins of sympathetic nervous system activation in essential hypertension

These do remain enigmatic. For obesity-related hypertension the list of possible causes is long, but for none of these is the supporting evidence totally convincing. Does the sympathetic activation represent an ongoing response to continuing overfeeding, which is suggested by the experimental models, or is it perhaps a consequence of sedentary life style, or chronic mental stress?[61] Or is it driven by the pathophysiological and clinical changes that accompany obesity once it has developed, including hyperinsulinaemia, high plasma leptin levels, or obstructive sleep apnoea?[61] Research by Noll *et al.*[72] identified accentuated sympathetic nervous system responses to mental stress in normotensive offspring of parents with essential hypertension. Patients with essential hypertension do have demonstrable increases in forebrain noradrenaline turnover,[73] suggesting that brainstem noradrenergic projections to the hypothalamus and amygdala, and presumably behavioural mechanisms, are commonly operative in activation of their CNS sympathetic outflow.

Neurogenic essential hypertension: research translation via anti-adrenergic therapies

The sympathetic nervous system is the 'forgotten pathway' in the treatment of hypertension in the modern era where anti-hypertensive drugs antagonizing the renin–angiotensin system is the dominant therapeutic mode. Despite the importance of neural pathophysiological mechanisms in pathogenesis, therapy specifically targeting the sympathetic nervous system is currently underutilized.

Non-pharmacological treatment

Two commonly applied non-pharmacological therapies for hypertension, aerobic exercise training and calorie restriction, inhibit the sympathetic nervous system. We have learned *post hoc* that this effect is congruent with the neural pathophysiology of essential hypertension, and perhaps explains why, of all non-pharmacological therapies, these two seem to be the most effective. This targeting of the pathophysiology is particularly apt for the metabolic syndrome and obesity-related hypertension, where there is a contribution of sympathetic inhibition to reductions in both blood pressure and insulin resistance.[61] Another non-pharmacological approach with an anti-adrenergic component is the regular application at night of continuous positive air pressure (CPAP) ventilation in patients with obstructive sleep-apnoea-related resistant hypertension. This therapeutic approach has been shown to prevent nocturnal

obstruction of upper airways, reduce sympathetic activity and favour blood pressure reduction.[65,74–76]

Anti-adrenergic drugs

The early anti-hypertensive drugs were commonly anti-adrenergic, and potent, but fell out of favour because of their side effects. Beta-adrenergic blocking drugs are currently following a similar path, due to their adverse effects on plasma lipids and insulin resistance. Alpha-adrenergic blocking drugs similarly are now used less, due to common side effects of postural and exercise hypotension, and their presumptive linkage with heart failure risk in patients with hypertension.

What anti-hypertensive drugs are available to specifically target the sympathetic nervous activation of essential and renal hypertension? Should centrally acting sympathetic suppressants, imidazoline-binding agents, such as moxonidine and rilmenidine, be specifically prescribed in patients with essential hypertension? Both drugs produce the desired sympathetic inhibition in the sympathetic outflows to the heart, kidneys, and skeletal muscle vasculature. They are largely free of the side effects of their progenitor, clonidine, most notably the rebound hypertension seen with clonidine when doses were missed. These drugs are third or fourth tier in most national and professional society guidelines. Sometimes they do not make the list at all. Logic would, perhaps, dictate that this might change, and especially in obesity hypertension, where sympathetic inhibition in skeletal muscle reduces the existing insulin resistance.[62] A substantial barrier to wider prescription of this drug class, however, remains, this being the absence of large-scale outcome studies.

Anti-adrenergic devices

The neglect of anti-adrenergic therapies for hypertension appears to be at an end, with the recent testing of anti-hypertensive devices for reducing sympathetic nervous system activity, and as a consequence blood pressure. One of these is the surgically implantable arterial barostimulator, which operates by continuous electrical stimulation of the carotid sinus buffer nerves.[77,78] Recent evidence indicates that such a stimulation is accompanied by a reduction in the 24-h mean blood pressure, although this issue still needs further investigation on a larger scale and over a prolonged follow-up time.[79]

Another revolutionary treatment principle, described in more detail here, which has been recently successfully tested in patients with resistant (uncontrolled) hypertension, involves ablation of the renal sympathetic nerves with a radiofrequency emitting catheter inserted percutaneously into the femoral artery in the groin, and advanced to lie, in turn, in the lumen of both renal arteries[59] (*Figure 5*). Sympathetic nerves enter the human kidneys in the walls of the renal arteries, within reach of ablative energy delivery.

In many experimental models of hypertension the sympathetic outflow to the kidneys is activated, and renal sympathectomy typically prevents the development of the hypertension.[41] Initiation of the new treatment strategy for hypertension was based on these observations, and the demonstration that the renal sympathetic outflow is activated in essential hypertension[8,54] (*Figure 4*). In participating patients with resistant hypertension, radiofrequency energy in 90° quadrants was delivered in a step-wise fashion to the full circumference of the walls of both renal arteries.
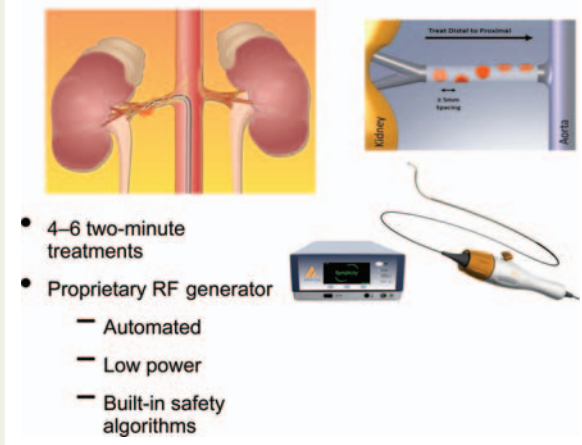

Figure 5 The renal sympathetic nerves pass to the kidney in the wall of the renal artery, within reach of radiofrequency energy delivered by the *Symplicity* catheter in the artery lumen. The radiofrequency energy is transmitted through the catheter from an external generator, delivered at four to six sites in both arteries, aimed at achieving a full circumference of dosing coverage, to ablate all nerves in passage, but not at a single point on the artery which might, perhaps, predispose to stenosis or aneurysm formation.

To establish whether the catheter ablates renal sympathetic nerves, measurements of renal norepinephrine spillover were made at baseline and at follow-up; sympathetic denervation does, in fact, occur. The level of blood pressure reduction achieved, a mean fall of 24/10 mmHg at 3 months and 29/16 mmHg at 12 months ($P < 0.001$), was actually greater than anticipated, but it should be emphasized that in this proof of principle trial the experimental design is not blinded. At this point, in those patients with the longest follow-up (2 years), blood pressure reduction is sustained, suggesting that renal sympathetic innervation, if it has occurred, is insufficient to cancel out the blood pressure benefit (*Figure 6*).

Perspective: a cure for essential hypertension?

It has been suggested that renal artery catheter-based renal denervation might, perhaps, provide a cure for essential hypertension in selected patients, those with milder hypertension than treated in the recent study. This speculation remains untested. For the procedure to be applied in milder forms of essential hypertension, a very high level of safety would be mandatory. Further, efferent sympathetic nerve regrowth is possible, although the degree to which this would fully restore sympathetically mediated function in the kidneys, and perhaps cancel out the observed anti-hypertensive effect, is problematic. Also relevant is the fate of renal afferent nerves, which project to the hypothalamus, and stimulate sympathetic outflow.[1] This CNS input from renal afferent nerves is critical in producing both the sympathetic activation and hypertension in patients with end-stage renal disease.[63,64] It is
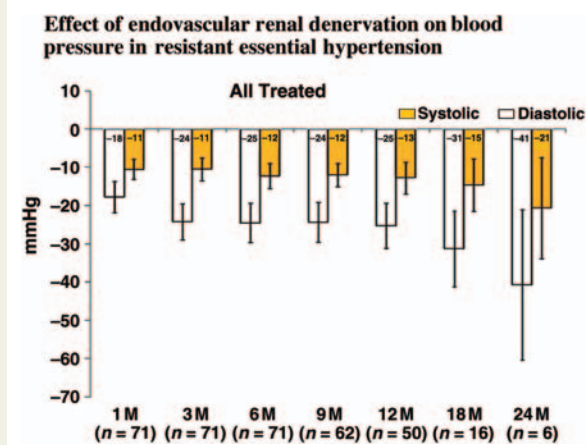
Figure 6 Effect on clinic blood pressures of bilateral denervation of the kidneys using endovascular radiofrequency ablation methodology in patients with essential hypertension resistant to multi-drug therapy. Shown here are the initial 45 patients,[63] and 26 additional patients, in whom follow-up results for a minimum of 1 month post-denervation were available. The procedure produced very substantial blood pressure lowering (P < 0.001). Pressures are shown, when available, from 1 to 24 months post-procedure.

almost certain that the radiofrequency procedure ablates the renal afferent nerves and that this, by inhibiting systemic sympathetic outflow, contributes to blood pressure lowering.[60] Regeneration of renal afferent nerves does not occur. Any blood pressure reduction attributable to renal deafferentation is likely to be permanent.

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