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REVIEW

The autonomic nervous system and renal physiology

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Abstract: Research in resistant hypertension has again focused on autonomic nervous system denervation – 50 years after it had been stopped due to postural hypotension and availability of newer drugs. These (ganglionic blockers) drugs have all been similarly stopped, due to postural hypotension and yet newer antihypertensive agents. Recent demonstration of the feasibility of limited regional transcatheter sympathetic denervation has excited clinicians due to potential therapeutic implications. Standard use of ambulatory blood pressure recording equipment may alter our understanding of the diagnosis, potential treatment strategies, and health care outcomes – when faced with patients whose office blood pressure remains in the hypertensive range – while under treatment with three antihypertensive drugs at the highest tolerable doses, plus a diuretic. We review herein clinical relationships between autonomic function, resistant hypertension, current treatment strategies, and reflect upon the possibility of changes in our approach to resistant hypertension.

Keywords: resistant hypertension, renal sympathetic ablation, autonomic nervous system, ambulatory blood pressure monitoring, blood pressure control

Introduction

In the Paton Lecture for 2010, Murray Esler[1] of the Baker IDI Heart and Diabetes Institute, Melbourne, Australia, reviewed work from the von Euler lab at the Karolinska Institute in Solna, Sweden, which identified norepinephrine as the neurotransmitter of sympathetic nerves,[2] whose total body activity could be estimated by an assay from a 24-hour urine collection.[3] Esler referred to anatomical studies of Thomas Willis, published in 1664, in which a detailed dissection of the sympathetic nervous system appeared.[4] Esler also referred to studies from the Cannon Lab[5] at Harvard Medical School that gave insight into control of blood pressure and blood glucose in cats, dogs, and other species by measurements before and after surgical resections of major sympathetic ganglia above and below the diaphragm (Table 1). These observations would eventually have a role in proposed treatments for resistant hypertension.

Willis and Cannon would have been very attentive at the Starling Lecture for 2000, delivered by Gerald DiBona, of the University of Iowa School of Medicine, who described renal effector innervation as a selective unmyelinated fiber within myelinated fibers, permitting coordination of information emanating from kidney/heart with continuous reflexes moving through the brainstem.[6]

Studies by DiBona, Kopp, and Sawin focused on kidney function by means of fluorescent histochemical and electron microscopic methods,[7] demonstrating nerve endings in proximity to glomerular, tubular, and vascular structures.[8] Surgical renal

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Table 1 Brief history of the physiology of the autonomic nervous system

Dissection	Century	Relevant to physiology of organ systems			
		Neuro	Cardiovascular	Renal	Hepatic
Total					
Willis[4]	17th	+			
Macro					
Cannon[5]	20th		+		+
Smithwick[47]	20th		+	+	
Parmley[35]	20th	+	+		
Mini					
Von Euler[2]	20th	+			
Micro					
DiBona[6]	21st		+	+	
Esler[1]	21st		+	+	

denervation interfered with conservation of sodium during low-salt diet[9] and with excretion of sodium during infusion of normal saline.[10] In further studies, Osborn, Thames, Sawin, and DiBona used micropuncture techniques, along with nerve stimulation/denervation, to locate a sodium-exchange site between the end of the proximal tubule and the beginning of the distal tubule, ie, the loop of Henle, and to demonstrate direct neurological control of this function.[11] A secondary finding was sodium exchange in the distal tubule as a result of neurostimulation of the juxtaglomerular apparatus with activation of the renin–angiotensin–aldosterone system (Table 2).[12]

Observations on the relationship between autonomic control and resistant hypertension (Table 3)

With respect to heredity

There is evidence for inherited enhanced sympathetic activity in essential hypertensive families,[13] as well as in families with diabetes in pregnancy.[14] Normotensive offspring of hypertensive parents have increased activation of the sympathetic nervous system in response to mental stress.[13]

Table 2 Impact of autonomic nerve innervation on renal physiology

Norepinephrine constricts glomerular efferent arteriole
Decreased renal blood flow stimulates renin-angiotensin-aldosterone
Retains sodium in distal tubule
Activates sodium/potassium adenine triphosphatase in thick ascending limb of proximal tubule (loop of Henle) to increase interstitial osmolality promoting antidiuresis at collecting duct
Epinephrine increases expression of renin
Erythropoietin secreted by peritubular interstitial cells derive from a neural cell line that respond to hypoxia[53]

Table 3 Mechanisms of resistant hypertension

Secondary forms of hypertension
Renal artery stenosis
Adrenal adenoma/hyperplasia
Pheochromocytoma
Primary = essential hypertension = hyperactivity of the sympathetic nervous system
Inherited
Hyperactivity of the sympathetic system without a decrease in the parasympathetic system
Salt-sensitivity in African-Americans susceptible to focal glomerulosclerosis
Acquired
Sympathetic hyperactivity with a decrease in parasympathetic function in diabetic nephropathy
Excess white adipose tissue associated with sleep apnea-induced hypoxia
Activation of inflammation + oxidative stress = >stimulation of sympathetic system
Activation of cortical pathways to basal ganglia and brainstem by repeated episodes of hypoglycemia in type 1 diabetes
Acute/chronic glomerular or tubulointerstitial renal disease

A general mechanism for essential hypertension involves accelerated turnover of norepinephrine in the midbrain and medulla.[15] An animal model demonstrated that male offspring of diabetic mothers have greater enhancement of renal sympathetic activity.

With respect to type 1 diabetes

There are significant differences between type 1 diabetic patients (insulin sensitive) and type 2 diabetic patients (insulin resistant) with respect to the preponderance of parasympathetic dysfunction. In lean hypertensive type 1 nephropathy patients, preservation of estimated glomerular filtration rate through control of blood pressure with angiotensin-converting-enzyme (ACE) inhibition and control of blood glucose with intensive insulin protocols, has been demonstrated.[16] In this population, there was a high incidence of loss of parasympathetic function.[17] Loss of parasympathetic function was associated with higher levels of blood pressure and more rapid rise in serum creatinine.[18] When baseline impairment of cardiac autonomic function was considered to be severe or advanced, there was no improvement during intensive blood pressure/blood glucose treatment for 6–18 months. However, improvement in parasympathetic function was found if baseline impairment of cardiac autonomic function was not severe or advanced.[19] In addition, reduction in left ventricular mass was notable among patients with improved glycemia control.[20] The simultaneous improvement in cardiac autonomic function and left ventricular mass may have more than coincidental implications, since

renal function was stabilized in the process.[21] With loss of parasympathetic stimulation, sympathetic stimulation predominates in type 1 diabetic nephropathy patients; platelet adhesion and aggregation are highly activated with no improvement noted, despite optimal blood pressure and glycemia control over a period of 6–18 months.[22] Given the high prevalence of microvascular and parasympathetic dysfunction in our type 1 diabetic population, it is understandable that researchers in the field of resistant hypertension would avoid this group for initial studies. But, in an attempt to promote parasympathetic stimulation, investigators at the University of Mississippi Medical Center have been working with carotid sinus stimulation in human studies, demonstrating lower blood pressures and – in animal studies – showing decreased plasma norepinephrine concentration,[23] which might have been anticipated to be helpful based upon earlier studies by Eckberg, Drabinsky, and Braunwald.[24]

With respect to type 2 diabetes, obesity, and other insulin-resistant states

Studies of obese animals demonstrate resistance to leptin binding to midbrain satiety centers. Resistance to usual concentrations of leptin results in higher secretion rates from white adipose tissue. As midbrain autonomic centers close to satiety centers are activated, an increase in rate and amplitude of sympathetic nerve discharge is noted.[25] A localized renin–angiotensin system has been described in white adipose tissue.[26] Triglyceride stores in white adipose fat cells are susceptible to lysis by epinephrine with release of free fatty acids.[27] The adipocyte is associated with an oxidation product (epoxy-keto derivative) of linoleic acid, which can be released to stimulate adrenal aldosterone secretion.[28] White adipose secretion may also secrete specific adrenal mineralocorticoid releasing factors.[29] Vasoconstriction is partially ameliorated by white perivascular fat. But, in obesity, this protective effect appears to be lost[30] in association with altered mechanisms of inflammation and oxidative stress within the community of adipose cells.

Recent work by Yamada-Goto et al comes closer to an understanding of how an injection of leptin or associated compounds into the midbrain can stimulate the rate and amplitude of sympathetic nerve pulsation.[31] These investigators have been using compounds (including serotonin, natriuretic peptide C, and other pharmaceutical agents) to find a way of activating the leptin-resistant midbrain receptor as a treatment for obesity.[31] Clinical studies have, thus far, been thwarted by concerns raised by progressive elevations of blood pressure.

The possibility of activation of brain stem sympathetic centers from higher centers in the frontal or parietal cortex is another contribution to the list of mechanisms of resistant hypertension. In a series of studies from Harvard Medical School, Bolo et al[32] found areas of higher centers activated by the thought process as in the working-memory task. The investigators used a magnetic resonance imaging technique, known as the blood oxygen level-dependent function (BOLD) MRI. When blood glucose was in the normal range, there were no differences between type 1 diabetic patients and normal controls. But when blood glucose levels were slowly decreased through controlled infusion of insulin (hyperinsulinemic clamp), it was possible to identify a unique network involving thalamus, hypothalamus, and brain stem, expressing an increased functional connectivity with basal ganglia only in the type 1 diabetic individuals.[31] Cognitive function (including memory) was retained at full capacity in the type 1 diabetic study subjects compared to normal controls. However, the diabetic group was relatively inefficient in brain oxygen utilization required to achieve full capacity in thinking. Inefficiency was visualized as the need both to exceed usual levels of intensity in brain areas undergoing activation as well as the inability to come to complete rest in areas undergoing a deactivation cycle. Some data exist indicating these differences occur in older type 2 diabetic patients whose ability to perform working-memory tasks at full capacity may eventually diminish to a greater or lesser degree. In terms of intermittent hypoglycemia as a challenge to brain activation resources, there is now visualization of pathways that activate brainstem centers that activate release of epinephrine. Then, if a cortical circuit is not able to recover completely from an initial signal of hypoglycemia before a subsequent episode of low blood glucose emerges, there is a kind of latency gridlock in which the individual may not be fully aware of the hypoglycemia, which is driving a reflex that pulsates at rapid rate with increased amplitude. Latency gridlock may interfere with awareness, but not with the brain's demand for fuel. An extreme example of this may be seen when catechol-induced malignant hypertension of pheochromocytoma leads to sympathetic/parasympathetic imbalance that proceeds, despite hyperglycemia when a beta-blocker is introduced without concomitant alpha blockade.

Sommers et al of Boston University Medical Center listed pheochromocytoma of the adrenal gland as the most important secondary cause of hypertension.[33] This tumor may arise from the autonomic nervous system as it is related to paraganglioma cells that secrete catecholamines. A prolonged

release of epinephrine may increase renal expression of erythropoietin.

With respect to heart failure

DiBona and Sawin studied an experimental model of congestive heart failure in the rat.[34] They found control of cardiac pressure/volume relationships to be distorted with blunting of sympathetic activity that led to decreased renal perfusion with retention of fluid.

Blockade of the beta-adrenergic receptor preventing arrhythmia in ventricular muscle of the cat was the subject of experiments performed within the Cardiology Branch of the National Heart, Lung and Blood Institute (Bethesda, MD, USA). Using a blocker of systemic beta-adrenergic receptors (DL-propranolol), Parmley and Braunwald found protection from arrhythmia.[35,36] Vogel et al used a model of heart failure in calves surviving in Denver, CO, USA, at 5,280 feet, having undergone ligation of the pulmonary artery. As heart failure emerged, evidence of loss of norepinephrine secreting nerves was documented. When the animals were returned to sea-level air pressure, there was a reversal of heart failure associated with regrowth of adrenergic nerves.[37,38]

The importance of sympathetic neurostimulation in congestive heart failure was elucidated by Gaffney and Braunwald who used the ganglionic blocking agent, guanethidine, in both early (Stage II) and advanced (Stages III, IV) congestive heart failure (CHF). The drug was tolerated in early-stage CHF patients, but not in the advanced stage patients.[39] Francis et al of the Cardiovascular Division of the University of Minnesota Medical School measured plasma catecholamine of healthy subjects versus individuals under treatment for CHF. They found that to compete for equivalent amounts of low intensity exercise, the CHF group had to generate larger amounts of norepinephrine than healthy subjects.[40] Largely based upon the observation of Swedberg et al and Waagstein et al in Göteborg, Sweden, in the 1970s,[41,42] trials of beta blockade (metoprolol, carvedilol, bucindolol, and bisoprolol) in the 1980s and 1990s in Class III or Class IV heart failure have demonstrated benefits in functional capacity, ejection fraction, and morbidity/mortality. Severe heart failure is associated with elevated levels of norepinephrine, indicating hyperstimulation by the sympathetic nervous system ameliorated by beta-blockade.

A complicating feature of heart failure associated with obesity and often type 2 diabetes is obstructive sleep apnea. In obstructive sleep apnea, pathologic changes in cardiac pressure/volume relationships during hypoxemia are associated with increased sympathetic input to the kidney with potential pathologic consequence over time. When obstructive sleep apnea or heart failure[43] result from morbid obesity, increased sympathetic outflow from the brain stem is activated from within the adipose tissue itself.[44]

With respect to pregnancy

Since peripheral autonomic activity is often heightened in hypertensive women with obesity and diabetes mellitus, the additional stress of pregnancy may be inadvisable. When these risk factors are combined with hypoxia in the placenta, an excess of autonomic outflow causes resistant hypertension in association with a unique renal glomerular vascular pathology.[45] Placental hypoxia during eclampsia appears to result from inhibition of the receptor for the vascular endothelial growth factor responsible for adequate perfusion of the rapidly growing intensely metabolic organ.[46] At a time when there were limited pharmacological choices, Newell and Smithwick[47] at the Boston University School of Medicine, used extensive surgical resection of autonomic nerves to prevent arterial vasoconstriction to the heart, kidney, and placenta by disrupting pathologically intensive reflex activity in women with resistant hypertension.

These observations were precursors to the work of Harington, Kincaid-Smith, and McMichael,[48] who used early ganglionic blocking agents to successfully treat malignant hypertension over a 7-year period. Irreversible postural hypotension was severe enough to contraindicate the Smithwick procedure when further antihypertensive agents became available.

Review of attempts to interrupt or suppress the deleterious effects of sympathetic autonomic nervous stimulation

From 1926–1929, the Physiology Laboratory of Walter B Cannon,[5] working with cats, observed erection of dorsal hair as an endpoint for intact sympathetic innervation, with loss of erection as a sign of successful surgical interruption of the circuit. The procedure involved removal of sympathetic ganglia from the superior cervical ganglion to the pelvic brim. If the procedure were performed on the right side, then there would be hair erection only on the left if the animal were to enter the cold room. Other than the change in dorsal hair movement, the general impression was that of a normal laboratory cat. In subsequent operations, an approach through a lower rib space allowed for removal of sympathetic nerves below the diaphragm.

Measurement of blood pressure demonstrated blockade of the usual hypertensive response to stress or excitement, fulfilling the hypothesis that blood vessel muscles were under control of the nervous system. They also found that shivering in the cold had been eliminated. Other usual responses to stress were a rise in blood glucose and an increase in red blood cell count. Both of these responses were blocked by the sympathectomy. The ratio of carbon dioxide exhaled to oxygen inhaled (respiratory quotient) at the time used to estimate total body basal metabolic rate did not change.

The next inquiry was to determine whether kidneys activate sympathetic nerves leading to hypertension, or if activation of sympathetic nerves cause vasoconstriction with injury to renal vessels, or both. Benjamin Castleman, pathologist from the Massachusetts General Hospital, and Reginald Smithwick, thoracic surgeon from Boston University, did extensive studies of renal biopsy and nephrectomy specimens to determine if hypertension was of renal origin or if hypertension of extrarenal cause did injury to kidneys. In 500 instances, they were able to classify the renovascular pathology of hypertensive patients. They found 68% of specimens demonstrated grade II to III vascular pathology. Thus, 32% had low-grade changes or no vascular pathology. They concluded the kidney was the source of high blood pressure, which might occur long before the onset of vascular injury.[49] But Smithwick might also have concluded that some portion of the resistant state of high blood pressure had originated above the level of the cardiorenal axis capable of being disarmed by the procedures that he and Cannon had performed. DiBona and Esler, 60 to 80 years later, could state that renal denervation surgery in hypertensive animals with increased sympathetic nerve activity resulted in diminished release of epinephrine from the denervated kidney.[50] So, the stage was set at Boston City Hospital for extensive surgical intervention to bring down blood pressures that were not responsive to medication. Since the Smithwick procedure was destructive of lower thoracic and upper abdominal ganglia, there was a clinically significant degree of postural hypotension. But, since it prevented eclampsia in young women,[46] it serves as a challenge for current age technologies, which are not likely to cause postural hypertension, anhydrosis, constipation, or male sexual dysfunction.

A relevant experimental model of renal denervation in the Dahl salt-sensitive hypertensive rat was used by Nagasu et al[51] at Kawasaki Medical School to demonstrate preservation of glomerular structures that would usually undergo fibrosis since this animal is highly susceptible to salt in the diet. A cellular mechanism for renal glomerular fibrosis was an oxidative stress reaction, secondary to excess activity of the oxidase of nicotinamide adenine dinucleotide phosphate (NADPH). The investigators point to research indicating that reactive oxygen species have been shown to enhance sympathetic nervous system activity. Salt-sensitive hypertension models (Table 4) are needed in studies of African-American groups prone to glomerulosclerosis.[52] Glomerular and tubular diseases often have associated interstitial fibrosis, which determines the duration of useful kidney function. In an animal model of ureteral obstruction, followed by the generation of reactive oxygen species with development of interstitial fibrosis, Kim and Padamilam found renal denervation to be protective from oxidative stress and interstitial fibrosis in this setting.[53]

While radiofrequency stimulation of the carotid body increases sympathetic nerve activity, stimulation at the pericarotid sinus area activates a parasympathetic signal without injury to the nerve. Experiments in dogs from the laboratory of Lohmeier and Illescu at the University of Mississippi Medical Center, found carotid sinus stimulation lowered blood pressure while decreasing plasma norepinephrine, suggesting that both a stimulation of parasympathetic and an inhibition of sympathetic activity had occurred.[23] Further studies found neither a central nor a peripheral sympathetic reflex that could return blood pressure back to baseline. And, since there was no retention of sodium chloride, it was reasoned there had been an inhibition of renin that requires epinephrine stimulation. So when angiotensin II was infused to bypass renin-inhibition, then an aldosterone-related salt retention was able to restore blood pressure back to baseline

Table 4 Resistant hypertension occurs in association with a number of factors

Resistant hypertension occurs in association with:
Acute/chronic glomerular or tubulointerstitial renal disease
Salt sensitivity, particularly if inherited with focal glomerulosclerosis
Individuals with a body mass index >30 kg/m^2, particularly if:
Over the age of 40 years
Leading sedentary lives
Demonstrating insulin resistance
Susceptible to sleep apnea-induced hypoxia
Excreting increased levels of urine albumin/creatinine
Type 1 diabetic patients with Body Mass Index <20 kg/m^2
Susceptible to repeated attacks of hypoglycemia
Demonstrating loss of parasympathetic function
Chronic inflammation/oxidative stress, including repeated use of:
Cigarettes
Cocaine
Pseudoephedrine, dextroamphetamine
Ma huang herbal preparation
Licorice root (*Glycyrrhiza glabra*) ⇨ aldosterone-like effect

through expansion of plasma volume. Since obesity-related hypertension involves enhanced sympathetic nerve activity with increased renin secretion, chronic stimulation of carotid sinus would be expected to improve blood pressure. A 2-year clinical trial of carotid sinus baroreflex activation has found significant diminution in systolic and diastolic pressure in patients with resistant hypertension[54] without the troublesome side effect of postural hypotension that had been the downside of the Smithwick procedure.[47] There are no follow-up studies on the combined use of radiofrequency ablation in the renal artery area plus radiofrequency stimulation of the carotid sinus area.

The mechanism of action of antihypertensive agents may impact on the autonomic nervous system. Differences are observed within pharmaceutical antihypertensive medication groups. The dihydropyridine calcium channel blocker nifedipine is associated with increased muscle sympathetic nerve activity and plasma norepinephrine as a reflex response to vasodilation and a fall in blood pressure (also seen with isosorbide and hydralazine). Nondihydropyridine calcium channel-blocking agents, however, are observed to decrease plasma norepinephrine (verapamil, diltizem); amlodipine had no impact on plasma norepinephrine.[55] Among angiotensin-converting enzyme inhibitors, which block the peripheral autonomic nervous system response to angiotensin 2, although use of captopril is associated with a fall of plasma norepinephrine and muscle sympathetic nerve activity, use of enalapril is not.[56] Research has also revealed that use of clonidine, which acts to inhibit the central autonomic nervous system results in a fall of plasma norepinephrine and muscle sympathetic nerve activity.[57]

Definition and prevalence of resistant hypertension

Without the use of 24-hour ambulatory blood pressures

A 2011 review of data from participants in the National Health and Nutrition Surveys (NHANES) found 52.5% of individuals receiving no antihypertensive medication to have a blood pressure of 140/90 mmHg or higher. Among participants on antihypertensive medications, 28% were not in optimal control, and 12.8% were defined as resistant (blood pressure ≥140/90 mmHg despite ≥three antihypertensives) to medications.[58] Prevalence of resistance however was reduced to 7.3%, if the requirement was for ≥four antihypertensive medications.[59] Thus, prevalence was largely definition based. The place of diuretic in the definition of resistant hypertension was not clear. Within the resistant-hypertension group, 85.6% were receiving a diuretic (hydrochlorothiazide, 64.4% of the time). Drugs inhibiting sympathetic nervous stimulation (Table 5), included beta-blocking agents (received by 75.5% of participants), alpha-adrenergic blocking agents (17.5%), and central acting adrenergic agents (10%).[59] Chronic kidney disease, defined by estimated glomerular filtration rate ≤60 mL/minute or by spot check urine albumin level of ≥0.030 mg/mg creatinine was noted in 38% of participants. In 71% of participants, a greater than 20% risk for coronary events (Framingham score) was observed. The demographics of resistant hypertension include age >40 years, body mass index >30 kg/m^2 with the presence of diabetes mellitus, chronic renal disease, and cardiovascular complications.

Important reflections by Calhoun et al,[58] Alderman,[60] and Egan et al[61] have sought to clarify the definition of resistant hypertension. There is no universal consensus regarding documentation of compliance inclusion/exclusion of certain medication groups, which might be seen as first-line medication choices. There is no concern regarding the need to document exclusion of drugs like dextroamphetamine, pseudoephedrine, and nonsteroidal analgesics – some of which are available without prescription.

An additional issue that requires resolution is physicians' reluctance to resort to spironolactone or eplerenone before declaring resistance of hypertension to medications. The reluctance to use spironolactone in males is based on risk

Table 5 Classification of hypertension control

From office setting
Greater than 130/80, but less than 140/90 on a diuretic, plus a number of antihypertensive medications
One (mild)
Two (moderate)
Three (severe)
Greater than 140/90 on a diuretic plus three antihypertensive agents
Without papilledema or rapid loss of renal function ⇨ resistant hypertension
With papilledema or rapid loss of renal function ⇨ malignant hypertension
Greater than 140/90 on no antihypertensive, but less than 140/90
If taken outside of the office setting ⇨ white coat hypertension
Less than 140/90 on no antihypertensive, but greater than 140/90
If taken outside of the office setting ⇨ masked hypertension
From 24-hour ambulatory recording on diuretic, plus three antihypertensives
Greater than 140/90 both day and night ⇨ resistant hypertension
Greater than 140/90 during day, less at night ⇨ pseudoresistant hypertension
Less than 140/90 during day, greater at night ⇨ persistent hypertension

of growth of breast tissue; the high cost of eplerenone is also a hindrance. The obese salt-sensitive rat (SHR/CP) was used to elucidate the mechanism of salt-induced hypertension as an experimental metabolic syndrome model. After a period of salt loading, the level of aldosterone was appropriately decreased, associated with development of kidney injury and proteinuria. Despite the decrease in serum aldosterone, there was a paradoxical nuclear activation of the mineralocorticoid receptor, along with enhanced expression of aldosterone effector kinase in the kidney. Renal pathology included glomerular sclerosis, tubulointerstitial scarring, and depletion of nephrin from glomerular podocytes. Use of eplerenone by Nagase et al at Tokyo Graduate School of Medicine prevented the development of hypertension and this renal pathology.[62]

With the use of 24-hour blood pressure monitoring

Use of the 24-hour ambulatory blood pressure apparatus proves instructive in allocation of patients with resistant hypertension to effective treatment (Table 6). An individual receiving no antihypertensive medications whose blood pressure is above 140/90 mmHg in the office, but below 140/90 mmHg in outside settings, is referred to as having "white coat hypertension," but is referred to as "pseudoresistant hypertension," if receiving an antihypertensive medication. This group should be considered at risk for unnecessary medication side effects, which might include loss of energy, postural hypotension, mental dullness, and emotional depression. If failure to utilize 24-hour ambulatory blood pressure information is based on the lack of resources provided by insurance carriers, then there is a need to point out just how much money is being wasted on expensive medication. In an important study by de la Sierra et al,[63] 40% of individuals under treatment for resistant hypertension could be reclassified to pseudo resistant by the finding of lower pressures overnight. An important subsequent study by De Nicola et al[64] demonstrates that among patients with chronic renal disease reclassification from resistant hypertension to pseudoresistant by ambulatory blood pressure monitoring identified a subgroup with fewer cardiac and renal endpoints (Table 6). An ambulatory blood pressure study similar to that from Spain[63] and Italy[64] has been published from several centers in Japan. Iimuro et al[65] classified types of hypertension in chronic renal disease. A 26% incidence of persistent hypertension was reported (22%, 27%, and 36% if the estimated glomerular filtration rates were 30–45, 15–30, and <15 mL/min, respectively). The incidence of drug resistant hypertension could not be determined precisely from the tables, but since only 26% of persistent hypertension patients received either diuretics or antihypertensives, on average, a maximum of 7% could have been drug resistant.

Table 6 Consequences of being labeled with the diagnosis of chronic resistant hypertension and reclassification by the use of ambulatory blood pressure monitoring observed in a high-risk group (chronic renal disease)

	Elevated office blood pressure	Controlled office blood pressure
Elevated ambulatory blood pressure	**True resistant** 25% CV events: +++ Renal events: ++++ Consider discontinuation of ineffective medications, change medications, enroll in a trial	**Sustained** 40% CV events: ++ Renal events: +++ Increase in appropriate therapy to reduce risk
Controlled ambulatory blood pressure	**Pseudoresistant** 10% CV events: ++ Renal event: + Consider whether any problems result from overtreatment	**Controlled** 25% CV events: ++ Renal events: +

Abbreviation: CV, cardiovascular; +, number of events.

When an individual receiving no medication for high blood pressure has an office reading of less than 140/90 mmHg, but readings greater than 140/90 mmHg in outside settings, then this is usually referred to as "masked hypertension," as it carries with it an increased risk of cardiac and renal pathology (compared to the normotensive individual). For the individual already taking medication to control high blood pressure this pattern would more appropriately be labeled "persistent" hypertension. In the study by de la Sierra et al, as many as 31% of individuals classified as "hypertension controlled by treatment" were reclassified as "persistent hypertension," due to the finding of higher pressures overnight.[63] It was not unexpected that this group had left ventricular hypertrophy with progressive loss of estimated glomerular filtration rate. Failure to utilize such 24-hour ambulatory blood pressure data may lead to premature use of end-stage renal disease (ESRD) resources.[66]

Measurement of effectiveness of blood pressure control

While effectiveness of antihypertensive procedures and medications has traditionally been reported on the basis of mmHg of blood pressure lowering, large-scale trials have recently focused on soft and hard endpoints.[67] Analysis of hard endpoints in multiple trials has led to discontinuation

of some drugs that initially looked promising with respect to surrogate endpoints (eg, flosequinan, rofecoxib). There remains a need for short-term trials of such biologic markers as changes in systolic and diastolic blood pressures, left ventricular wall thickness, etc. However, longer-term trials must determine whether endpoints, such as all cause and cardiac mortality, cardiovascular events (eg, hospitalization for heart failure, myocardial infarction, coronary intervention, stroke, nontraumatic amputation), ESRD requiring renal replacement therapy (dialysis, filtration, transplant), or blindness,[63] are favorably impacted.

Measurement of office blood pressure, though standard and well-established, is often misleading. Its use to define resistant hypertension has been supplanted by availability of devices that permit 24-hour blood pressure monitoring. Although use of such devices is required to demonstrate adequacy and duration of the blood pressure-lowering effect in trials of medications, they are not often clinically used. Refinement of the definition of resistant hypertension, and ultimately improvement in the effective monitoring of blood pressure by these devices is possible,[62–64] with the use of ambulatory monitoring.

Based upon outcome studies, we believe it most appropriate to define blood pressure control under the following categories: normotensive, untreated office or "white coat" hypertension, untreated masked hypertension, controlled hypertension, pseudoresistant hypertension, sustained hypertension, and resistant hypertension. Fortunately, properly defined, the latter category represents only a small proportion of the hypertensive population. Few reasons exist to avoid using diuretics in hypertensive patients, and thiazides must be supplemented or replaced by spironolactone, eplerenone, or loop diuretics as kidney and heart function deteriorate. Patients should not be considered resistant unless exposed to optimal timing and dosage of agents from each of the six following classes: (1) diuretic; (2) ACE (angiotensin converting enzyme inhibitor)/ARB (angiotensin receptor blocker)/DRI (direct renin inhibitor); (3) beta-blockade; (4) calcium-channel blockade; (5) ganglionic blocking agents/Alpha 2 agonists; and (6) vasodilator.

Hypertension should also not be considered resistant to control in the presence of inadequate compliance or comorbidities, such as glycohemoglobin greater than ten, recurrent hypoglycemic episodes, or systemic inflammatory syndromes. Documentation of absence of substances that contribute salt, calories, sympathetic stimulation (dextroamphetamine, pseudoephedrine, cocaine, ephedra/ma huang), licorice root (*Glycyrrhiza glabra*), or analgesia (nonsteroidal analgesics, herbal preparations) is required.

Proposed treatments and sympathetic control targets for control of resistant hypertension

Medications currently undergoing preclinical trials for antihypertensive treatment are not presumed to have predominant sympathetic autonomic effects.[68] At this point, drug-resistant hypertension is being studied by means of radiofrequency[69] or cryoablation[70] of nerves surrounding the renal arteries, testing the hypothesis that interruption of pathological reflexes with relaxation of stiff vessels, plus excretion of excess salt, would forestall cardiovascular events by restoring homeostatic relationships.

In 2012, Savard et al published criteria for use of renal denervation.[71] The criteria included age >18 and <80 years; absence of pregnancy; absence of secondary causes of hypertension, such as renal artery stenosis; continuous fulfillment of the conditions of resistant hypertension, which were stated to be blood pressure greater than 140/90 mmHg on three antihypertensive medications and a diuretic (Table 7). When the 1,034 patients seen in their Hypertension Clinic were reviewed, only 15 individuals (1.5%) met these criteria.[71]

The Symplicity Hypertension-2 (HTN) Trial[68,72] meets these criteria, as far as we can tell. In 2010, the Symplicity Investigators, led by Murray Esler, reported a study[72] that involved 106 subjects randomized to standard treatment ($n = 54$) versus standard treatment and radiofrequency renal nerve ablation ($n = 52$). Average blood pressure on three antihypertensive agents was 178/96 mmHg at baseline. At 6 months, data were available on 51 of 54 control patients (94%) versus 49 of 52 denervation patients (94%). Blood pressure average was not different in the control group. The denervation group recorded a fall of 32/12 mmHg on average ($P < 0.001$). At 6 months, there were 18 of 51 control study subjects (35%), whose systolic pressure had fallen by 10 mmHg or more. At 6 months, there were 41 of 49 denervation study subjects (84%) whose systolic pressure had fallen by 10 mmHg or more ($P < 0.001$). There were no serious side effects of the procedure.

In 2012, Hering et al published a series of patients with resistant hypertension complicated by Stages 3 to 4 chronic renal insufficiency. This study[73] involved 15 study subjects with a baseline average blood pressure of 174/91 on an average of 5.6 antihypertensive medications. The mean creatinine clearance was 31 ± 9 mL/min, with a range of 15–43 mL/min. At the 12-month follow-up, there was no decrease in mean creatinine clearance. There were no serious side effects of the procedure. To our knowledge, this is the only longitudinal

Table 7 Renal artery sympathetic radiofrequency ablation for resistant hypertension

Study inclusion criteria
• Blood pressure greater than 140/90 both day and night while complying with three or more antihypertensive medications of which one is a diuretic
• Between the ages of 18 and 80 years
• Appropriate renal artery anatomy (single renal artery greater than 4 mm diameter, >20 mm length to each kidney)[75,76]
Study exclusion criteria
Anatomic
• Renal arterial anatomic exclusions (prior renal arterial intervention or evidence for renal artery stenosis, vessel smaller than 4 mm diameter, or <20 mm length)
Related to systemic disease
• Primary pulmonary hypertension
• Chronic oxygen support or mechanical ventilation
• Type 1 diabetes mellitus
• Chronic kidney disease with eGFR <45 mL/min or active focal sclerosis
• MI, angina, CVA within 6 months
• Prior history of autonomic dysfunction
Related to hypertension
• Secondary forms of hypertension
• Requirement for, or use of, medication or recreational substance known to raise blood pressure
Other
• Pregnancy or plan for pregnancy
• Prior keloid formation
• ICD or pacemaker, or any other metallic implant not compatible with MRI

Abbreviations: eGFR, estimated glomerular filtration rate; MI, myocardial infarction; CVA, cerebrovascular accident; ICD, implantable cardioverter-defibrillator; MRI, magnetic resonance imaging.

report addressing the problem of preservation of renal function over time.

In 2012, Brinkmann et al published a report,[74] involving twelve individuals with difficult-to-control hypertension. They were 45–74 years of age. Following radiofrequency ablation of their renal artery nerves, the mean blood pressure did not change from a baseline of $157 \pm 7 \rightarrow 157 \pm 6$ mmHg systolic; $95 \pm 4 \rightarrow 95 \pm 4$ mmHg diastolic. Three of the twelve patients did experience a significant fall in blood pressure. Heart rate did not change significantly: $61 \pm 3 \rightarrow 58 \pm 2$ per minute. Muscle sympathetic nerve activity did not change significantly: $34 \pm 2 \rightarrow 32 \pm 3$ bursts per minute. Clonidine was associated with a fall in blood pressure of 27 ± 0 mmHg systolic; 13 ± 5 mmHg diastolic with a decrease in muscle sympathetic nerve activity of 8 ± 1 bursts/minute – suggesting these patients had the expected central sympathetic nerve activity increases seen in essential hypertension. But changes in blood pressure following renal denervation correlated with neither changes in muscle nerve sympathetic activity nor plasma norepinephrine concentration, placing doubt on the systemic effect of local denervation.

Long-term follow-up studies will be required to settle the question of cardiovascular benefit or risk related to ablation of renal artery sympathetic nerves and technologies that might be safely used to accomplish this end[75,76] (Table 8). Currently, investigations of various radiofrequency strategies for ablation appear to be enrolling more subjects than those for cryoablative strategies. More invasive (laparoscopic) or less-invasive (ultrasonic) strategies can be expected. We will, however, need several more years of experience to clarify benefits, if any, their durability, and side effects in clinical research follow-up studies. At this point in time, it is too early to claim procedural success, based only upon lower office blood pressures. Payment for these procedures will not be forthcoming from insurance carriers without statistical demonstration of a decrease in cardiovascular events in the absence of serious side effects, despite efforts to design a set of guidelines.[77]

Future studies

Success rates for radiofrequency ablations have consistently been overestimated in initial scientific reports. In the real world, ablation of arrhythmogenic foci and nerve connections are often incomplete, impermanent, and require repeated efforts. Exuberant adoption of ablative procedures has

Table 8 Pros and cons of radiofrequency ablation of renal artery sympathetic nerve endings

Pros
• Decrease in problems of compliance and drug side effects
• Long-term medication cost lower
• Potential for reducing hard outcomes (suggested by degree of blood pressure lowering in short trials)
• Potentially safe for chronic renal disease patients with ≥45 mL/min in whom antihypertensives are not working (Stage 3A or better)[79]
Cons
Absence of:
• Accurate cardiovascular outcome data
• Placebo or sham controlled studies
• Experience with patient groups listed under exclusions in Table 7
• Consensus on trial of ganglionic blocking agents prior to ablation
• Data on comparative cost of medications versus high-tech equipment (catheters, MRI, procedure)
Risks related to:
• Radiation and contrast exposure
• Potential for renovascular complications (perforation, dissection, atheroembolism, keloid, necrosis)[74,75]
• Possibility of orthostatic symptoms
• Potential for sympathetic renal dystrophy

Abbreviation: MRI, magnetic resonance imaging.

demonstrated that procedural "success" may be overstated, and that soft endpoint reduction (of arrhythmia burden) may not lead to reduction of hard endpoints. Current studies of nonsurgical renal sympathetic ablation by any modality[78] will need to learn from past observation. Durability of effect cannot be assumed from short-term studies, and permanence of effect may have unanticipated consequences (postcardiovascular or neurological event hypotension or autonomic dysfunction). To this point, the discomfort of renal sympathetic ablation has only been reported as a brief procedural consequence. Surgical regional sympathetic nerve ablation has been associated with regional side effects. We will have to be alert for the possible existence of renal sympathetic dystrophic symptoms.

Though there are many drugs in the pipeline anticipated to lower blood pressure and to reduce cardiovascular and all cause mortality, there are few that have a primarily autonomic target. Among those currently considered, side effect profiles have not permitted widespread use. Until drugs are developed that specifically target the sympathetic system, concentration on local peripheral sympathetic blockade is the most likely new tool to reduce cardiovascular and renal events. We should not consider one therapy as opposed to others, but rather what treatment strategies at our disposal produce the most long-term benefit with the least risk for patients with resistant hypertension.

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