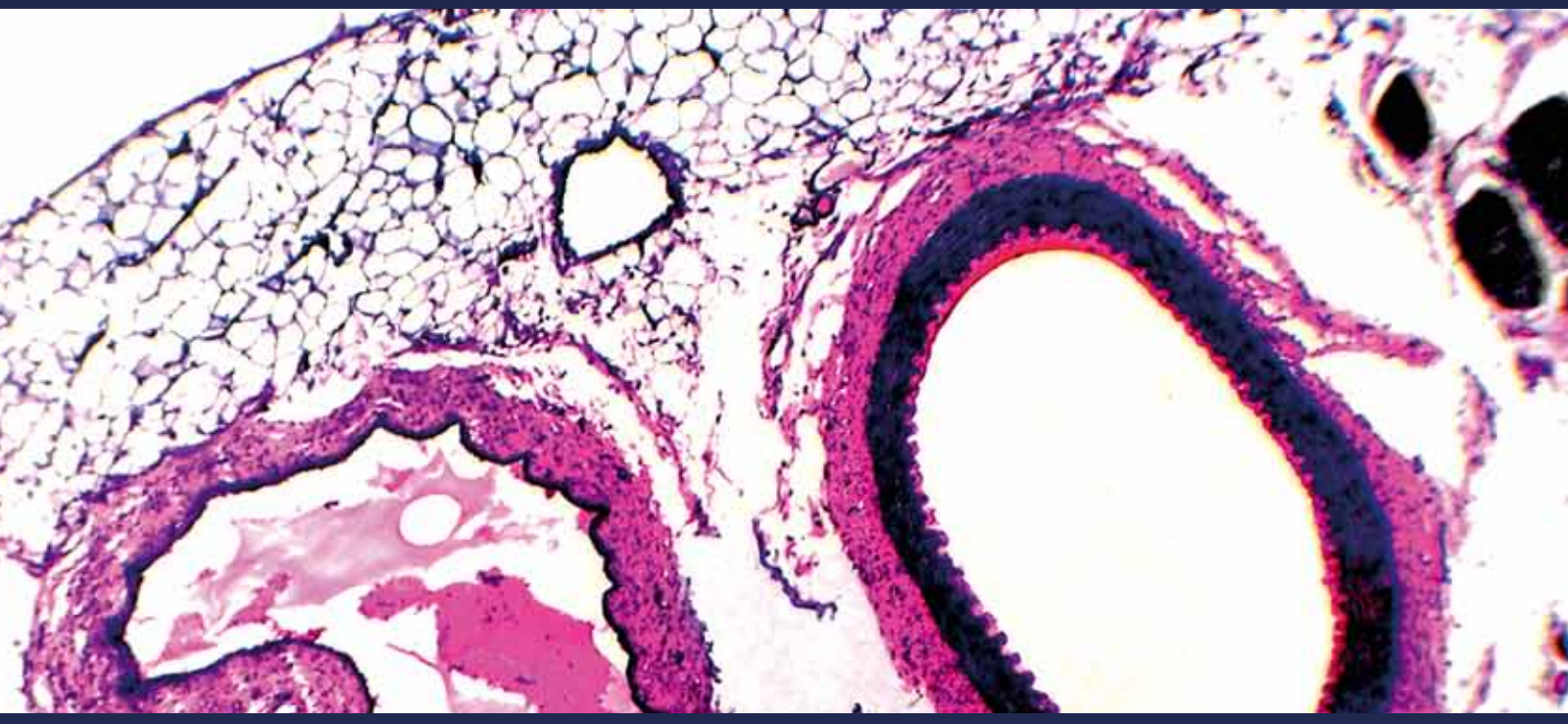
International Journal of Hypertension

Difficult-to-Treat or Resistant Hypertension: Etiology, Pathophysiology, and Innovative Therapies

Guest Editors: Vasilios Papademetriou, Costas Tsioufis, Alan Gradman, and Henry Punzi



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Editorial Board

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 438198, 4 pages
doi:10.4061/2011/438198

Editorial

Difficult-to-Treat or Resistant Hypertension: Etiology, Pathophysiology, and Innovative Therapies

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Received 23 March 2011; Accepted 23 March 2011

Despite the many therapeutic options available today for the treatment of hypertension, a sizable number of patients still remain resistant to treatment. The prevalence of resistant hypertension in the general population under optimal conditions is about 3–5%. Although several factors and conditions can be identified and corrected a percentage of hypertensive patients remain with unacceptably high blood pressure levels. The high prevalence of hypertension in the general population renders this small percentage significant, in terms of actual patient numbers. This special issue of the journal expoars a whole spectrum of topics related to resistant hypertension: several articles address pathophysiolog and secondary causes of resistant hypertension and modern approaches to therapy. Of interest is the referance to the newer interventional approaches, that is, Baroreceptor stimulation therapy and catheter based sympathetic renal denervation.

1. Approaches to Diagnosis and Treatment of Difficult-to-Treat or Resistant Hypertension

Resistant or difficult-to-control hypertension is becoming an increase burden in our society. Although with the many medical approaches available to us we can currently control the majority of patients with hypertension, a sizable number still remain resistant to treatment. The prevalence of resistant hypertension in the general population is difficult to determine accurately, but depending on the population and the center reporting it ranges from 5% to 30% [1, 2]. In specialized clinics utilizing optimal medical regimens the prevalence is closer to 3–5%. Although several factors and conditions can be identified and corrected (poor patient adherence, physician inertia, inappropriate drug combinations or inadequate dosing, drug-induced hypertension, and secondary causes), the fact is that a percentage of hypertensive patients remain with unacceptably high blood pressure levels. The high prevalence of hypertension in the general population renders this small percentage significant, in terms of actual patient numbers. The above, combined with several limitations in drug therapy (patient adherence, polypharmacy, and drug adverse effects), create the need for other therapeutic options, beyond existing antihypertensive medications, setting the basis for interventional approaches [3–5]. Recently two new innovative, still experimental interventional approaches to treat "resistant or difficult-to-control hypertension" have been explored: the baroreceptor stimulation with the Rheos device and sympathetic renal denervation using radiofrequency ablation techniques.

2. Pathophysiology

This special issue of the journal included papers covering the whole spectrum of issues related to "resistant or Difficult-to-treat hypertension."

In the first paper C. Tsioufis and coworkers reviewed the pathophysiology of resistant hypertension and the role of sympathetic nervous system. They emphasize that obesity, obstructive sleep apnea, and aldosterone are predisposing factors, but increased sympathetic nervous system activity

is paramount prevailing future of all these underlying conditions, supporting its crucial role in the development of treatment resistance. They also point out that current clinical and experimental data indicate an impact of several factors on SNS activation, namely, insulin resistance, adipokines, endothelial dysfunction, cyclic intermittent hypoxaemia, aldosterone effects on central nervous system, chemoreceptors, and baroreceptors dysregulation. V. M. Campese et al., examine the influence of sympathetic nervous system and the role of the kidney in the development of resistant hypertension. They point out not only that several factors have been implicated in the pathogenesis of hypertension such as sodium and water retention, total body volume expansion, and hyperactivity of the renin-angiotensin aldosterone system (RAAS) but also that increasing evidence suggests that afferent impulses from the injured kidney may increase sympathetic nervous system activity in areas of the brain involved in noradrenergic regulation of blood pressure and contribute to the development and maintenance of hypertension associated with kidney disease. Recognition of this important pathogenic factor suggests that antiadrenergic drugs or therapies should be an essential component to the management of hypertension in patients with kidney disease, particularly those who are resistant to other modalities of therapy.

3. Secondary Causes of Hypertension as a Cause of Resistance

M. C. Acelajado and D. A. Calhoun examine the role of primary hyperaldosteronism in the development of drug-resistant hypertension. They point out that the incidence of primary aldosteronism in patients with drug resistant hypertension is 14% to 23%, which is much higher than in the general hypertensive population. These patients have increased cardiovascular risk, as shown by higher rates of stroke, myocardial infarction, and arrhythmias compared to hypertensive individuals without primary hyperaldosteronism. Furthermore, resistant hypertension is associated with adverse cardiovascular outcomes. Addition of aldosterone antagonists to the antihypertensive regimen in patients with resistant hypertension produces a profound BP-lowering effect, and this effect is seen in patients with or without biochemical evidence of PA, highlighting the role of relative aldosterone excess in driving treatment resistance in this group of patients. S. Kshatriya et al. in an intriguing paper, examine the regulatory role of leptin in obesity hypertension. Leptin is a 16-kDa-peptide hormone that is primarily synthesized and secreted by adipose tissue. One of the major actions of this hormone is the control of energy balance by binding to receptors in the hypothalamus, leading to reduction in food intake, elevation in temperature, and energy expenditure. In addition, increasing evidence suggests that leptin, through both direct and indirect mechanisms, may play an important role in cardiovascular and renal regulation. While the relevance of endogenous leptin needs further clarification, it appears to function as a pressure and volume-regulating factor under conditions of health. However, in abnormal situations characterized by chronic hyperleptinemia such as obesity, it may function pathophysiologically for the development of hypertension and possibly also for direct renal, vascular, and cardiac damage. Z. Khawaja and C. S. Wilcox examine the role of the kidney in the development of resistant hypertension. They point out that the kidney plays a critical role in long-term regulation of blood pressure. Blunted pressure natriuresis, with resultant increase in extracellular fluid volume, is an important cause of resistant hypertension. Activation of the renin-angiotensin-aldosterone system, increased renal sympathetic nervous system activity, and increased sodium reabsorption are important renal mechanisms. Successful treatment requires identification and reversal of lifestyle factors or drugs contributing to treatment resistance, diagnosis, and appropriate treatment of secondary causes of hypertension, use of effective multidrug regimens, and optimization of diuretic therapy. Since inappropriate renal salt retention underlies most cases of drug-resistant hypertension, the therapeutic focus should be on improving salt depleting therapy by assessing and, if necessary, reducing dietary salt intake, optimizing diuretic therapy, and adding a mineralocorticoid antagonist if there are no contraindications.

A. Makris et al. addressed the issue of workup and treatment of patients with resistant hypertension. Evaluation of patients with resistant hypertension should begin by confirming that patients have true resistant hypertension. White coat hypertension, suboptimal blood pressure measurement technique, poor adherence to prescribed medication, suboptimal dosing of antihypertensive agents or inappropriate combinations, the white coat effect, and clinical inertia should be excluded. Management includes lifestyle and dietary modification, elimination of medications contributing to resistance, and evaluation of potential secondary causes of hypertension. Pharmacological treatment should be tailored to the patient's profile and focus on the causative pathway of resistance. D. Syrseloudis et al. address the crucial role of ambulatory blood pressure monitoring in the diagnosis and treatment of patients with resistant hypertension. The identification of white coat hypertension and masked hypertension is of great importance in the clinical management of such patients. Moreover, the various ABPM components such as average BP values, circadian BP variability patterns, and ambulatory blood pressure-derived indices, such as ambulatory arterial stiffness index, add significantly to the risk stratification of resistant hypertension. Obstructive sleep apnea is a frequent cause of resistant hypertension, and C. Thomopoulos and coworkers have done a wonderful job in exploring the interaction between the two entities and implications for successful treatment. Enhanced target organ damage and cardiovascular morbidity represent common issues observed in both resistant hypertension and obstructive sleep apnea. Common pathophysiological features and risk factors justify their coexistence, especially in individuals with increased upper-body adiposity. Impaired sodium handling, sympathetic activation, accelerated arterial stiffening, and impaired cardiorenal hemodynamics contribute to drug-resistant hypertension development in obstructive sleep apnea. Effective CPAP therapy qualifies as an effective

"add-on" treatment to the underlying antihypertensive pharmacological therapy, and emerging evidence underlines the favorable effect of mineralocorticoid antagonists on both resistant hypertension and obstructive sleep apnea treatment. Furthermore, A. Moraitis and C. Stratakis address adrenocortical causes if resistant hypertension.

4. Approaches to Treatment

C. Faselis and coworkers explored Common secondary causes of resistant hypertension and rational for treatment. They point out several secondary causes and a long list of factors contributing to resistant hypertension such as poor patient adherence, physician inertia, inadequate doses or inappropriate combinations of antihypertensive drugs, excess alcohol intake, and volume overload. They correctly point out that management of patients with resistant hypertension requires a combination of clinical acumen and common sense. An extensive workup of all patients with uncontrolled hypertension is scientifically unsound, very costly and requires immense human and technical resources. Therefore, they recommend practicing evidence-based medicine. The effective management of patients with resistant hypertension requires an appropriate combination of physiology and pharmacology, taking into account the unique characteristics of each case in order to tailor the therapeutic approach to the individual patient. They indicate that there are at least 14 endocrine disorders in which hypertension may be the initial clinical presentation. An accurate diagnosis of endocrine hypertension provides the clinician with a unique treatment opportunity, that is, to render a surgical cure or to achieve a dramatic response with pharmacologic therapy. In this paper the authors review mostly different aspects of primary hyperaldosteronism, which represents the most common cause of endocrine resistant hypertension.

In the following paper, M. Doumas et al. address potential benefits from the treatment and control of resistant hypertension. They point out that several factors have been identified as contributors to resistant hypertension: poor patient adherence, physician inertia, inadequate doses or inappropriate combinations of antihypertensive drugs, secondary forms of hypertension, drug-induced hypertension, excess alcohol intake, and volume overload. Life-style modifications including salt restriction are very important in these patients. Addressing some of the comorbid conditions, such as sleep apnea, primary aldosteronism, or addition of adjunct therapies such as spironolactone, can achieve blood pressure control. However, many patients remain uncontrolled despite the use of four, five, or six antihypertensive drugs, especially in everyday clinical practice, outside the "sterile" environment of clinical trials. It is surprising to realize that, although hypertension is among the most studied diseases, resistant hypertension which denotes the most severe, high-risk, and probably more scientifically interesting subgroup remains so much understudied. Unfortunately, data regarding the natural history of resistant hypertension is limited. Furthermore, the benefits of controlling blood pressure in patients with resistant hypertension are vaguely clarified, and it seems that they will continue to remain as such, since it is unethical to perform a randomized study with a control group of resistant hypertensives that will remain untreated. Since direct data is not available, only clinically meaningful assumptions can be made based on indirect information and using common sense. Therefore, for the purpose of this review, they use data from the past (before the era of antihypertensive therapy), data from clinical studies involving patients with severe or malignant hypertension, data from small clinical studies in patients with resistant hypertension, and from subgroups of patients included in large clinical trials.

In the next paper, P. M. Jansen et al. indicate that the long-term efficacy of aldosterone-receptor antagonists (ARAs) as add-on treatment in uncontrolled hypertension has not yet been elucidated. They present data from 123 patients (21 with primary aldosteronism, 102 with essential hypertension) with difficult-to-treat hypertension who received an aldosterone receptor antagonist over a four-year period. Results suggest a profound and sustained blood pressure reduction over a median follow-up period of 25 months.

In the last two papers, V. Papademetriou and coworkers review the role of devices and interventions in the management of patients with resistant hypertension. The first device to be used in the treatment of resistant hypertension was the Rheos baroreceptor stimulator. Baroreceptor stimulation is achieved through this pulse generator implanted subcutaneously (much like a pacemaker), which is connected to two leads rubbed around the carotid bulbs. The two early studies that include about 110 patients demonstrated significant efficacy of the device with up to 30/18 mmHg reduction in blood pressure, which can be maintained long term. A larger pivotal study, which included a blinded arm, recently completed recruitment of 300 patients. The study is still in progress, and results have not been announced.

Selective renal sympathetic denervation is an even more ambitious approach aiming to possibly cure hypertension. This new interventional approach provides the hope of an easy, long-term blood pressure control without significant adverse events. Using a specially designed catheter, this technique aims to interrupt the sympathetic fibers that interact with the kidney and kidney function. More importantly this technique also interrupts the efferent fibers from the kidney to the brain that may control peripheral vascular tone and peripheral resistance. The net effect of the sympathetic fiber network that runs along the renal arteries results in significant blood pressure reduction. A limited number of cases have been reported, but much larger studies are underway trying to evaluate the role of this new and innovative approach to treat resistant hypertension.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 642416, 7 pages
doi:10.4061/2011/642416

Review Article

Pathophysiology of Resistant Hypertension: The Role of Sympathetic Nervous System

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Received 4 October 2010; Accepted 22 December 2010

Academic Editor: Alan Gradman

Resistant hypertension (RH) is a powerful risk factor for cardiovascular morbidity and mortality. Among the characteristics of patients with RH, obesity, obstructive sleep apnea, and aldosterone excess are covering a great area of the mosaic of RH phenotype. Increased sympathetic nervous system (SNS) activity is present in all these underlying conditions, supporting its crucial role in the pathophysiology of antihypertensive treatment resistance. Current clinical and experimental knowledge points towards an impact of several factors on SNS activation, namely, insulin resistance, adipokines, endothelial dysfunction, cyclic intermittent hypoxaemia, aldosterone effects on central nervous system, chemoreceptors, and baroreceptors dysregulation. The further investigation and understanding of the mechanisms leading to SNS activation could reveal novel therapeutic targets and expand our treatment options in the challenging management of RH.

1. Introduction

A number of physiological mechanisms are involved in the maintenance of normal blood pressure (BP), and their derangement may play a key role in the development of hypertension (HTN). Amongst other factors, unfavorable genetic substrate, activated sympathetic nervous system (SNS) and renin-angiotensin system, excess sodium intake and disturbances between vasoconstrictors and vasodilators have been implicated in the pathophysiology of HTN [1]. Although the role of the above factors in the pathogenesis of essential HTN is well established, their involvement in mechanisms responsible for treatment resistance is not so thoroughly investigated.

According to World Health Report 2002, suboptimal BP control is the most common attributable risk for death worldwide, being responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease [2, 3]. Since resistance to treatment is one of the reasons for uncontrolled BP, it is obvious that resistant hypertension (RH) entails a major clinical and social impact. Consequently, understanding of the mechanisms involved in the pathophysiology of treatment resistance is crucial for the development of more effective therapeutic strategies. In the present paper, we will focus on the role of SNS in the pathophysiology of RH.

2. SNS and Patterns of Hypertension

The development of novel and sophisticated techniques for the direct and indirect assessment of adrenergic activity has changed our conception about the role of SNS in the regulation of BP, from a short-term regulator to a cornerstone of the pathogenesis and pathophysiology of HTN. Nowadays, the established theory is that SNS hyperactivity contributes to initiation, maintenance and progression of HTN. Several studies have correlated adrenergic hyperactivity with multiple patterns of HTN. More specifically, increased SNS activity has been documented in systole-diastolic and isolated systolic HTN [4, 5], in white coat and masked HTN [4, 6], in dipping, extreme dipping, nondipping and reverse dipping conditions [4, 7] and in pregnancy-induced HTN [4, 8]. Furthermore, SNS activity increases progressively and in parallel with HTN stages. This implies that the more

advanced the stage of HTN the greater is the adrenergic activity [4, 9, 10]. Whether this correlation could be extended to RH remains unclear given that the SNS activity in resistant hypertensives has been assessed in subgroups of populations of intervention studies without comparison with healthy controls.

3. The "Phenotype" of Resistant Hypertension

According to the AHA scientific statement for RH [11], based on the demographic data and the results of Framingham and ALLHAT studies, the strongest predictors of lack of BP control were older age, high baseline BP, obesity, excessive dietary salt ingestion and chronic kidney disease. Aging and its interface with SNS activation is well documented. A number of studies have shown that whole body sympathetic neural activity increases with aging [12–16] and indices of sympathetic activity, especially muscle sympathetic nerve activity (MSNA), become more linked to BP with older age [12, 17].

Beyond ageing, obesity, aldosterone excess and obstructive sleep apnea (OSA) are covering a great area of the mosaic of the characteristics of resistant hypertensives. In cohorts of patients with RH, the mean body mass index (BMI) was over 32 kg/m^2 and the prevalence of hyperaldosteronism was approximately 20% while the resistant hypertensives had a very high prevalence of known and suspected OSA [18–20]. Moreover, among subjects with RH, hyperaldosteronism was more likely to be present in patients with confirmed OSA than in those at low risk for OSA. The existing data support that OSA, aldosterone excess and obesity are not only common comorbidities in resistant hypertensives but that they also interact in this setting. Although the mechanisms that link these conditions in RH are not fully elucidated, SNS activation may be a major contributing factor (Figure 1).

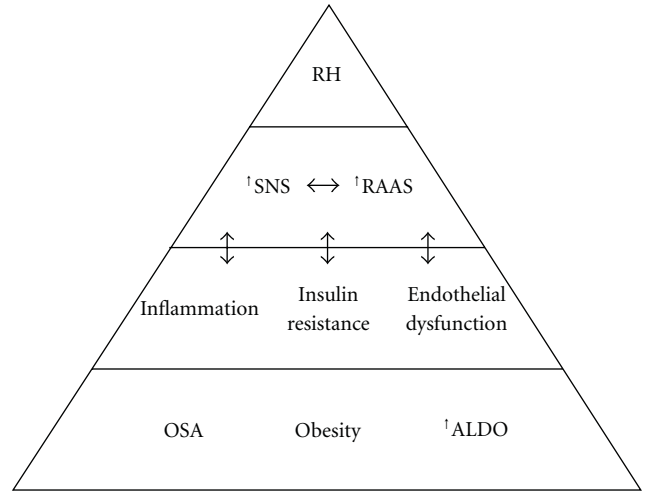

Figure 1: A proposed pathophysiologic pathway for the activation of SNS and the development of RH. Obesity, OSA and aldosterone excess are covering a great area of the mosaic of the phenotype of RH and are correlated with increased SNS activity, via multiple mechanisms. ↑ALDO: Aldosterone excess, OSA: Obstructive sleep apnea, ↑RAAS: Renin-Angiotensin-Aldosterone System activation, RH: Resistant hypertension, ↑SNS: Sympathetic nervous system hyperactivity.

4. The Interplay of SNS Activation and Resistant Hypertension

4.1. Obesity. Obesity is associated with more severe HTN, a need for an increased number of medications and a decreased likelihood of achieving BP control [11]. The Framingham study showed that subjects with BMI ≥ 30 kg/m^2 had 1.5-fold increased risk for uncontrolled systolic BP versus subjects with BMI < 25 kg/m^2 [21]. In addition, the HYDRA study, a cross-sectional study of 45,125 unselected consecutive primary care attendees conducted in Germany, showed that BP levels were consistently higher in obese patients and the odds ratios for BP control in diagnosed and treated patients were 0.8, 0.6, 0.5 and 0.7 for overweight and grade 1, 2, and 3 obese patients, respectively, compared to those with normal weight [22]. Among the mechanisms involved in obesity-induced hypertension, apart from impaired sodium excretion, fluid retention and activation of the renin-angiotensin-aldosterone system, the "neuroadrenergic hypothesis" should be taken into consideration.

Before the application of more specific methodology for the estimation of SNS activity, including the direct recordings of sympathetic nerve firings and the measurement of norepinephrine spillover to plasma, there was controversy concerning the state of SNS function in human obesity. These novel techniques applied to obese subjects with normal BP documented that the sympathetic outflow was increased to the kidneys and skeletal muscle vasculature, while it was normal to skin and the hepatomesenteric circulation and reduced to the heart [23–26]. This regional heterogeneity of SNS activation in obese normotensives is mitigated in hypertensives where a more homogenous activation of the SNS has been reported with absence of the suppression of cardiac sympathetic outflow [25–27]. Finally, the distribution of the adipose tissue seems to be crucial for the activation of the SNS since the central pattern of obesity with excess of visceral fat is accompanied by increased MSNA in contrast to men with peripheral obesity where MSNA is no higher than in lean men [23, 28, 29].

Several mechanisms have been proposed to explain the SNS activation in obese subjects; increased leptin concentration, hyperinsulinemia, OSA, decreased arterial baroreflex sensitivity, elevated plasma angiotensin, obesity-related kidney disease and lack of exercise [23]. Findings of increased MSNA after infusion of insulin in humans could suggest a triggering role of insulin for the SNS [30]. On the other hand, the same procedure in lean hypertensives does not seem to activate the renal sympathetic nerves [31]. Given that obesity is accompanied by increased renal sympathetic activity, mechanisms other than hyperinsulinemia should be considered, taking into account that insulin resistance might be an epiphenomenon of SNS activation. Furthermore, signals arising in adipose tissue that activate the brain have

been ascribed to adipokines such as leptin. The effects of leptin on the SNS are thought to be mainly driven by binding to leptin receptors in the hypothalamus [32]. Cross-sectional studies have shown positive correlations between leptin concentration and various indices of sympathetic activation [33–35]. However, the results of intervention studies examining the effects of leptin infusion on sympathetic activity status are controversial [36–38]. Additionally to these centrally driven effects, nonneural effects of leptin on the cardiovascular system mediated through receptors in the heart and endothelium are supported by the independent association between circulating leptin and heart rate in denervated hearts of transplanted patients [39]. Finally, evidence supports a bidirectional relationship between the renin-angiotensin system and SNS. The stimulation of renin release from juxtaglomerular granular cells through renal sympathetic nerves is well documented [40], while angiotensin facilitates adrenergic function at the level of central and peripheral nervous system [41, 42]. Grassi et al. reported substantial sympathetic inhibition by angiotensin receptor blockade in obesity-related hypertension [43] which is not produced in lean men with or without HTN [44, 45].

4.2. Obstructive Sleep Apnea. OSA and HTN are strongly associated, since OSA is an independent predictor for the presence and future development of HTN [46, 47]. The Wisconsin Sleep Cohort study, a prospective study of the association between sleep-disordered breathing and HTN in 709 subjects, reported a dose-response association between sleep-disordered breathing at baseline and the presence of HTN four-years later that was independent of known confounding factors [48]. This association is particularly strong in patients with RH. In a series of 41 resistant hypertensives, the prevalence of OSA, diagnosed by overnight polysomnographic study, was 83% and both the prevalence and the severity were significantly higher in men than in women [19]. In case-control studies, OSA was strongly and independently associated with RH and the apnoeic patients had 4- to 4.8-fold increased risk of having RH [49, 50].

Increased levels of norepinephrine, endothelin and aldosterone, vascular stiffening, activation of the renin-angiotensin system, endothelial dysfunction, oxidative stress and SNS hyperactivity have been suggested as explanations for sleep apnea-induced HTN [50–52]. According to the classic systematic review of Coy et al. all studies using MSNA revealed a relationship between sleep apnea and an increase in MSNA. Of the 21 catecholamine papers reviewed, only four failed to report a relationship between OSA and levels of either norepinephrine or epinephrine [53]. Assessment of MSNA has shown a sustained increase in sympathetic output which is increased even during the daytime and in the presence of normoxic wakefulness [54]. Furthermore, sympathetic traffic to peripheral blood vessels was higher in OSA subjects compared to controls with no difference between normotensives and hypertensives [55]. The independent activation of the SNS in apnoeics, regardless of comorbidities, is also documented in obesity. Sympathetic activity in lean men with OSA was elevated to a similar degree as in obese men without OSA, but less than in those with both OSA and obesity, in whom the two conditions exerted an additive effect [56]. Patients with OSA also have faster heart rates during resting wakefulness, suggesting an increased cardiac sympathetic outflow [57]. Further evidence of SNS activation by OSA is provided by studies reporting a reduction in SNS activity after continuous positive airway pressure (CPAP) therapy. In the study of Narkiewicz et al. the decrease of MSNA was evident after both 6 months and 1 year of CPAP therapy [58]. In another study, the decrease in sympathetic activity, estimated by peroneal microneurography at least 1 month after CPAP treatment, was limited to the patients with greater compliance with this device (>4.5 hours/night) [59]. On the other hand, when adrenergic activity was estimated by norepinephrine kinetics and the CPAP treatment was delivered for 14 days, the reduction in plasma levels of norepinephrine was attributed to increased norepinephrine clearance [60].

There seems to be a causal relationship between OSA and SNS activation, despite the lack of established mechanisms by which nocturnal upper airway obstructions leads to daytime sympathetic activation. Both the arousals from sleep and transient hypoxemia, the two major characteristics of OSA syndrome, have been proposed as a linkage between OSA and SNS hyperactivity. However, it is not clear if arousals can influence daytime adrenergic status independently from respiratory disturbances during sleep [61]. When daytime plasma norepinephrine levels were used as an index of daytime sympathetic tone, there was a correlation with movement, but not cortical arousals [62]. On the contrary, the data supporting cyclic intermittent hypoxaemia as the stimulus to SNS activation are more robust. The efferent sympathetic outflow is influenced by peripheral reflex activity, via chemoreceptors and baroreceptors, as well as by central sympathetic activity. Peripheral arterial chemoreceptors have a significant physiological activity in normoxia, the so-called "resting drive". Interestingly, administration of 100% oxygen, leading to chemoreflex deactivation, is accompanied by a decrease in both MSNA and BP in patients with OSA but not in nonapnoeic control subjects [63]. Thus, elevated MSNA in patients with OSA might be explained in part by tonic activation of excitatory chemoreflex afferents. Molecules such as endothelin and angiotensin II with a stimulating effect on chemosensitivity have been implicated in the mechanisms by which OSA results in increased chemoresponsivness through cyclic intermittent hypoxaemia [64]. Findings of increased expression of the endothelin receptor A and of preproendothelin, and also of upregulation of transcriptional and post-transcriptional expression of angiotensin type 1 receptors, in the carotid body after hypoxia, suggest that these molecules may influence sympathetic activity by modulating peripheral chemoreflex sensitivity after exposure to cyclic intermittent hypoxaemia [64, 65]. Furthermore, evidence support that these molecules can serve as neuromodulators of sympathetic activity in the central nervous system [64].

4.3. Excess of Aldosterone. A growing body of evidence suggests that aldosterone contributes broadly to the development and severity of HTN separately from the presence of classically defined primary aldosteronism. The ongoing Framingham Offspring study showed that serum aldosterone levels in normotensive subjects predicted the development of incident HTN and that the patients in the highest serum aldosterone quartile, relative to the lowest had a 1.6-fold risk of HTN during a four-year follow-up [66]. Moreover, a positive correlation was documented between plasma aldosterone and 24-hour ambulatory BP in cross sectional studies [67, 68]. Among untreated patients, the prevalence of primary aldosteronism increases with the stage of HTN (according to the JNC VI), from 2% in patients with stage 1 HTN to 8% in those with stage 2 HTN and 13% in those with stage 3 HTN [69]. The prevalence of primary aldosteronism is even higher in patients with RH, approaching 17–22% in multiple studies [70–72]. Furthermore, individuals with true RH but without primary hyperaldosteronism have higher aldosterone levels than control participants [73]. These findings suggest that aldosterone excess commonly underlies resistance to antihypertensive treatment.

The classic effects of aldosterone are exerted on the renal handling of sodium and potassium leading to expansion of intravascular volume and hypokalemia. In addition, aldosterone promotes RH by mediating maladaptive changes in the renal, cardiovascular and central nervous systems [74, 75]. SNS activation seems to be a basic component of the adverse impact of aldosterone excess in the central nervous system. In a cross-over study, sustained SNS stimulation was identified during chlorthalidone administration to hypertensives but not during spironolactone [76]. A recent double-blind, randomized study by Wray et al. reported a significant reduction in SNS activity after six months of therapy with an aldosterone receptor blocker, which was achieved without a change in end organ a-adrenergic responsiveness, implicating a central mechanism for the change in autonomic activity [77]. The above data extend earlier work in animal models demonstrating the ability of aldosterone receptor blockade to decrease SNS activity in hypertensive mouse models [78].

The mechanisms of aldosterone mediated central SNS activation are becoming clearer. The mineralocorticoid receptor is expressed in many cell types, including specific neurons. Mineralocorticoid receptors in the paraventricular nuclei are involved in the augmented neuronal activity in the nuclei leading to increased sympathetic drive [79]. Multiple studies in animal models are intensively investigating potential pathophysiological pathways. Indicatively, data arising from rats with heart failure demonstrate that mineralocorticoid receptor blockade reduces nicotinaminase adenine dinucleotide phosphate (NADPH) induced superoxide in the paraventicular nuclei of the hypothalamus and reduces descending sympathetic paraventricular nuclei output [80].

5. Clinical Applications

Although the clinical investigation has increased our knowledge about the function of the SNS and its involvement in the pathophysiology of several cardiovascular diseases including HTN, there is no current recommendation for the estimation of adrenergic activity in resistant hypertensives. Despite the methodological achievements in the assessment of adrenergic function, reflected in microneurographic measurement of MSNA and measurement of organ specific noradrenaline spillover, no technique can be viewed as the "gold standard" [81], and the above techniques are mainly used for investigational purposes. Regarding the most clinically applicable methods of hemodynamic parameters and noradrenaline measurement in urine and plasma, their limitations should be mentioned. Resting heart rate and heart rate responses to stimuli are regulated not only by the SNS but also by the parasympathetic nervous system and they are also depended on cardiac adrenergic receptors [81]. Furthermore, supine heart rate displays only a limited correlation with other indices of sympathetic activity, as plasma norepinephrine and sympathetic nerve traffic [82]. Concerning 24 hour urinary excretion of catecholamines, the inability of dynamic assessment of the SNS activity, the weakness to determine the systematic or renal origin of catecholamines and the dependence on renal function should be underlined [83]. As regards plasma noradrenaline levels, low reproducibility, low sensitivity and biological restrictions to discriminate between increased secretion or reduced clearance of elevated circulating neurotransmitter constitute substantial limitations [81, 84].

The therapeutic strategy in RH aims to block all possible mechanisms for BP elevation. Combination therapy with appropriate diuretic selection and dosing remains the cornerstone of treatment. According to the 2007 ESC/ESH guidelines for the management of arterial hypertension, patients with RH will need administration of more than three drugs [85]. Studies suggest that adding spironolactone or eplerenone to existing antihypertensive regimens for patients with RH provides significant BP reduction [11, 85, 86]. Most importantly, reductions in BP were similar in patients with and without primary aldosteronism and were not predicted by baseline plasma or 24 hour urinary aldosterone, plasma renin activity or plasma aldosterone to renin ratio [87]. With the usual therapeutic options the SNS hyperactivity is blocked to the peripheral level of adrenergic receptors with the use of alpha and beta blockers and it should be mentioned once more that rising data suggest a sympathoinhibitory effect of angiotensin and mineralocorticoid receptor blocking [43, 76, 77]. Centrally acting agents are effective antihypertensive agents but have a high incidence of adverse effects and lack outcome data [11]. Finally, promising results arrive from recent studies of interventional methods of sympathoinhibition including activation of the carotid baroreceptors using electrical stimuli [88] and selective renal sympathetic denervation [89].

6. Conclusions

Obesity, OSA, and aldosterone excess are common comorbidities in resistant hypertensives. Screening of these underlying conditions in patients with RH is of major clinical

importance. SNS hyperactivity is a common characteristic of all the above conditions supporting its crucial role in the pathophysiology of antihypertensive treatment resistance. The further investigation and understanding of the mechanisms leading to SNS activation could reveal novel therapeutic targets and expand our treatment options in the challenging management of RH.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 814354, 6 pages
doi:10.4061/2011/814354

Review Article

Sympathetic Renal Innervation and Resistant Hypertension

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Received 1 September 2010; Accepted 1 November 2010

Academic Editor: Konstantinos Tsioufis

Hypertension in chronic renal disease and renovascular disease is often resistant to therapy. Understanding the pathogenic mechanisms responsible for hypertension in these conditions may lead to improved and more targeted therapeutic interventions. Several factors have been implicated in the pathogenesis of hypertension associated with renal disease and/or renal failure. Although the role of sodium retention, total body volume expansion, and hyperactivity of the renin-angiotensin-aldosterone system (RAAS) are well recognized, increasing evidence suggests that afferent impulses from the injured kidney may increase sympathetic nervous system activity in areas of the brain involved in noradrenergic regulation of blood pressure and contribute to the development and maintenance of hypertension associated with kidney disease. Recognition of this important pathogenic factor suggests that antiadrenergic drugs should be an essential component to the management of hypertension in patients with kidney disease, particularly those who are resistant to other modalities of therapy.

1. Hypertension Resistant to Therapy in Patients with Renovascular Disease and with Chronic Kidney Disease

Although the majority of patients with resistant hypertension have essential hypertension, secondary forms of hypertension are more commonly seen in patients with resistant hypertension. Among the most common causes of secondary hypertension are renovascular hypertension and hypertension secondary to chronic kidney disease (CKD). Renovascular hypertension accounts for 2-3% of patients with hypertension and is often difficult to control. Renovascular disease is present in 30% of patients with grade 3 or 4 hypertensive retinopathy [1]. In one study, 16.7% of clinically selected patients had renovascular hypertension, as documented by blood pressure response to correction of renal artery stenosis or removal of the involved kidney [2].

Hypertension is very prevalent among patients with CKD and it contributes to the high prevalence of cardiovascular disease and progression of kidney disease in these patients (Table 1) [3–6]. Hypertension associated with renal parenchymal disease constitutes approximately 5% of all forms of hypertension, and it becomes more frequent as patient progress toward end-stage renal disease (ESRD). Nearly 85% of ESRD patients have hypertension. Hypertension is the single most important predictor of coronary artery disease in ESRD patients, even more so than other known cardiovascular risk factors [7]. Often, treatment of hypertension in ESRD patients is difficult and inadequate. Understanding the mechanisms of hypertension may help improve therapy in such patient populations.

2. Evidence for Activation of the Sympathetic Nervous System (SNS) in Renovascular Hypertension and Kidney Disease

The renin-angiotensin-aldosterone system (RAAS) plays a key role in blood pressure (BP) elevation in the early phase of renovascular hypertension. Later on, other mechanisms such as sodium retention and activation of the sympathetic nervous system (SNS) may contribute to hypertension [8, 9]. In one study, sixty-five patients with hypertension and renovascular disease demonstrated by angiography underwent measurements of plasma renin activity and

Table 1: Factors implicated in the pathogenesis of hypertension in end-stage renal disease.

Sodium and volume excess
The renin-angiotensin-aldosterone system
The sympathetic nervous system
Endothelium-derived vasodepressor substances
Endothelium-derived vasoconstrictor substances
Erythropoietin use
Divalent ions and parathyroid hormone
Atrial natriuretic peptide
Structural changes in the arteries
Pre-existent essential hypertension
Miscellaneous
Anemia/ Hypoxia
A-V fistula
Vasopressin
Serotonin
Thyroid function
Calcitonin gene-related peptide

angiotensin II in conjunction with estimation of SNS activity by means of radiotracer dilution and intraneural recordings of muscle sympathetic nerve activity (MSNA) [8]. Total body norepinephrine (NE) spillover, an index of overall SNS activity, was increased by 100% and MSNA by 60% in the hypertensive patients compared with healthy subjects, which supports the role of SNS activity in the maintenance of hypertension in these patients [8].

The pathogenesis of hypertension in patients with CKD is multifactorial and may vary depending on the underlying disease (Table 1). Activation of the RAAS, sodium retention, and volume expansion have long been recognized as the most important factors [10, 11]. However, clinical experience indicates that volume depletion and inhibition of the RAAS do not necessarily result in normalization of BP. This suggests that other factors may play a role. Among those, activation of the SNS appears to have a prominent role.

Plasma NE levels are frequently increased in hemodialysis patients [12, 13] and in patients with early CKD and hypertension compared with healthy subjects and with normotensive CKD patients [14]. Direct recording of neuronal activity from postganglionic MSNA in the peroneal nerves of patients on chronic dialysis treatment has shown a greater rate of SNS discharge than in control subjects [15]. Moreover, MSNA in hypertensive hemodialysis patients with native kidneys were 2.5 times more frequent than those in hemodialysis patients after bilateral nephrectomy or in healthy subjects. Our studies on 5/6 nephrectomized rats have provided the most convincing evidence yet for a role of the sympathetic nervous system in the pathogenesis of hypertension associated with CKD [16]. The turnover rate of NE, which is a marker of SNS activity, was greater in two areas of the brain involved in the noradrenergenic control of BP (posterior hypothalamic (PH) nuclei and the locus coeruleus) of CKD rats compared to that of control rats. Moreover, microinjection of a neurotoxin, 6-hydroxydopamine, in the PH significantly reduced BP in CKD rats [17]. The secretion of NE from the PH was also greater in CKD rats than in control animals [16]. We postulated that the activation of these nuclei in the central nervous system results from impulses generated in the affected kidney which are transmitted to the central nervous system.

The kidney is richly innervated with baroreceptors and chemoreceptors [18–20]. Renal afferent nerves are connected directly or indirectly to a number of areas in the central nervous system that contribute to BP regulation [21]. Stimulation of renal receptors by adenosine, urea, or electrical impulses evoke reflex increases in SNS activity and BP [22, 23]. Renal afferent impulses play an important role in the genesis of hypertension in several other experimental models, including the one-kidney one-clip and two-kidney one-clip Goldblatt hypertension in rats, the one-kidney one-wrap Grollman hypertension in the rat, or in the spontaneously hypertensive rat (SHR) [24–27]. Furthermore, bilateral dorsal rhizotomy at the level T-10 to L-3 resulted in almost complete normalization of BP in 5/6 nephrectomized rats [28]. This suggests that increased renal sensory inputs from the injured kidney to the central nervous system may contribute to the development of hypertension in CKD rats.

Kidney damage can raise BP even in the absence of renal insufficiency. The injection of phenol in the lower pole of one kidney leads to an immediate elevation of BP and activation of the central SNS activity, which can be prevented by renal denervation [16, 29]. There is also convincing evidence that the SNS plays an important role in the pathogenesis of hypertension observed in patients with CKD caused by polycystic kidney disease [30].

However, not all types of injury to the kidney lead to an increase in blood pressure. For example, burning, administration of alkali, acids, or methanol caused no effects [29]. This is of relevance, since clinical experience indicates that not all renal injuries in humans are associated with hypertension. For example, in the absence of renal insufficiency, IgA nephropathy is more likely to be associated with hypertension than membranous glomerulonephritis or minimal change disease (Table 2) [31]. These findings support the notion that increased afferent nervous inputs from kidneys with renal diseases may send signals to integrative sympathetic nuclei in the central nervous system and contribute to the pathogenesis of hypertension. The normalization of BP that follows bilateral nephrectomy may be largely due to elimination of these afferent impulses.

Identification of the factor(s) responsible for the intrarenal activation of these afferent pathways, or for the stimulation of sympathetic output from the brain, may lead to a new understanding of the pathophysiology of sympathetic overactivity and hypertension in renal disease and, hopefully, to novel therapies based on specific inhibitors of these activating factors.

Table 2: Prevalence of hypertension secondary to underlying renal parenchymal disease.

Acute renal failure	40%
caused by glomerular-vascular disease	73%–90%
caused by tubulointerstitial disease	10%–15%
Acute poststreptococcal glomerulonephritis	60%–80%
Primary focal and segmental glomerulosclerosis	45% nephrotic 65% non-nephrotic
Minimal-change disease	Rare
Membranous glomerulonephritis	10%
Membranoproliferative glomerulonephritis	30%
Mesangial proliferative glomerulonephritis	33%
IgA nephropathy	25%–36%
Autosomal dominant polycystic kidney disease	50%–80%
Chronic pyelonephritis	33%
Wilms tumor	50%
Adenocarcinoma of the kidney	38%
Reflux nephropathy	20%
Renal tuberculosis	4%
End-stage renal disease	80%–90%
caused by chronic glomerulonephritis	78%
caused by hypertensive nephrosclerosis	100%
caused by diabetic nephropathy	80%

3. Mechanisms of SNS Activation in Kidney Disease

3.1. Angiotensin II. The activation of the SNS in CKD may be related to the effects of circulating angiotensin II (Ang II) released from the kidneys. We have previously shown that intracerebroventricular (ICV) infusion of Ang II raises BP, renal sympathetic nervous system activity (RSNA), and NE secretion from the PH compared to control rats. Pretreatment with losartan, an AT1 receptor blocker, given as an ICV infusion 20 min prior to the infusion of Ang II completely abolished the effects of Ang II on BP, RSNA, and NE secretion from the PH [32].

Antagonists of the renin-angiotensin system, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II AT1 receptor antagonists, inhibit the production of Ang II or its ability to bind to its receptor, resulting in partial inhibition of the sympathetic nervous system in 5/6 nephrectomized rats [33], in the phenol-renal injury model [34], as well as in humans with CKD [14, 30].

3.2. Oxidative Stress. Reactive oxygen species (ROS) are involved in the regulation of SNS activity [35]. Increased oxidative stress in key brain nuclei mediates the activation of the SNS in the phenol-renal injury model of hypertension [36] and in stroke-prone spontaneously hypertensive rats [37]. Increased oxidative stress within the rostral ventral lateral medulla (RVLM) and paraventricular nucleus (PVN) was associated with hypertension and sympathetic overactivity in the 2K 1C Goldblatt model of renovascular hypertension [38], and superoxide signaling in the RVLM was found to play a major role in sustained hypertension and sympathetic nervous system activation in this model.

ROS are also involved in the intracellular signaling mechanisms of Ang II in the brain. [39, 40], in central SNS activation and BP elevation in experimental models of obesity-induced hypertension [41], renovascular hypertension [38], and salt-sensitive hypertension [42]. Moreover, chronic antioxidant therapy improved oxidative stress and BP in a rat model of renovascular hypertension [38]. Despite these experimental data, antioxidants currently have no definitive role in the management of hypertension in CKD patients.

3.3. Hypoxia. Substantial evidence suggests that kidney ischemia may be responsible for sympathetic nervous system activation in renal hypertension. This is supported by studies in conscious rats with acute renal artery stenosis [21]. Restoration of renal perfusion in humans with renovascular hypertension reduces MSNA to control levels and leads to normalization of BP [43]. Regional hypoxia has also been demonstrated in polycystic kidney disease by immunostaining [44].

3.4. Nitric Oxide. Recent studies have provided convincing evidence that nitric oxide synthase (NOS) is present in specific area of the brain involved in the neurogenic control of blood pressure [45, 46]. Studies on experimental animals have also provided evidence that the neuronal isoform of NOS is an important component of the transduction pathways that tonically inhibit sympathetic outflow from the brain stem [47–50]. In normal rats, the basal activity of the central sympathetic nervous system is regulated by local NO production. Evidence from our laboratory also indicates that local production of NO may modulate sympathetic activity in brain nuclei involved in the neurogenic regulation of BP [51]. Reduced availability of NO in these brain nuclei, may result in increased SNS activity and hypertension.

3.5. Cytokines. Complex relationships exist between SNS, nitric oxide, and cytokines [52–55]. One possible mediator for the increase in NO expression is interleukin 1β (IL-1β). Our study has demonstrated for the first time that administration of IL-1β in the lateral ventricle of control and CKD rats lowers BP and NE secretion from the PH [56]. Moreover, we have shown that the modulatory action of IL-1β on SNS activity is mediated by increased expression of neuronal NOS mRNA in the brain. Several lines of evidence strongly support this conclusion. First, the administration of IL-1β in the lateral ventricle of control and CKD rats caused a dose-dependent decrease in BP and NE secretion from the PH and an increase in neuronal NOS mRNA abundance in the brain nuclei. Second, infusion of a specific anti-rat IL-1β antibody in the lateral ventricle led to an elevation in BP and secretion of NE from the PH of control rats, and to a

further rise in BP and NE secretion from the PH of CKD rats. Third, the administration of an anti-rat IL-1β antibody decreases NOS mRNA expression in the several brain nuclei (PH, locus coeruleus, and paraventricular nuclei) of both control and CKD rats. Finally, in CKD rats we observed an increase in the abundance of IL-1β mRNA in all brain nuclei tested. In all, these findings suggest that IL-1β modulates the activity of the SNS via activation of neuronal NOS and partially mitigates the rise in BP and SNS activity in CKD as well as in control rats.

3.6. Treatment of Resistant Hypertension with Antiadrenergic Agents. Given the evidence for the role of the sympathetic nervous system in hypertension, antiadrenergic agents may be considered in the treatment of hypertension, especially in the setting of difficult to control BP. The numerous antihypertensive agents that have become available over the last few decades have overshadowed the potential of centrally acting agents such as clonidine and guanfacine in conventional antihypertensive therapy. However, experimental evidence has demonstrated the ability for these agents to decrease peripheral SNS activity and BP. For example, in salt-sensitive SHR, intrahypothalamic infusion of clonidine abolished the hypertensive effect of dietary salt supplementation and decreased the salt-related increase in plasma NE seen in control rats supplemented with dietary salt [57]. In operative candidates, clonidine administration has been shown to decrease plasma NE levels typically associated with the stress of surgery in comparison to placebo [58]. We were the first to demonstrate that clonidine administration reduced SNS activity and caused natriuresis in salt-sensitive patients with essential hyperitension [59] and in patients with chronic kidney disease [60, 61]. Further studies are needed in the setting of resistant hypertension to determine the efficacy of antiadrenergic agents.

3.7. Catheter-Based Renal Denervation for the Treatment of Resistant Hypertension. New advances in technology recently have brought about the translation of basic science animal models of therapy for resistant hypertension into the forefront of current therapy for resistant hypertension. A recent case report by Schlaich et al. describes a 59-year-old patient on seven antihypertensive medications who underwent renal sympathetic ablation of the afferent renal nerves, which resulted in a BP reduction to 127/81 mg Hg from a baseline blood pressure of 161/107 mm Hg over a twelve-month period [62]. A concomitant reduction of total body norepinephrine spillover and plasma renin was noted.

A multicenter study involving 40 patients with resistant hypertension on an average of four or more antihypertensive medications who underwent ablation of the renal sympathetic afferent and efferent nerves was recently published [63]. An average BP reduction of 27 mm Hg systolic and 17 mm Hg diastolic was achieved, although the authors do clarify that BP medications were adjusted and in some patients, uptitrated after renal nerve ablation. Data on noradrenaline spillover in this study correlated closely with the reduction in BP, and the authors suggest that renal sympathetic nerve ablation is a safe and effective approach to the treatment of resistant hypertension. Long-term followup on patients undergoing renal sympathetic nerve denervation will be needed to determine the duration of benefit and long-term safety of such an approach.

4. Conclusions and Future Directions

SNS activation plays a major role in the pathogenesis of resistant hypertension, particularly when it is due to renal parenchymal or renovascular disease. Mechanisms responsible for increased SNS activity include intrarenal stimulation of renal afferent nerves, direct central effects of angiotensin II, oxidative stress, cytokines, and NO inhibition.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 837817, 7 pages
doi:10.4061/2011/837817

Review Article

Aldosteronism and Resistant Hypertension

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Received 3 October 2010; Revised 3 December 2010; Accepted 10 December 2010

Academic Editor: Konstantinos Tsioufis

Resistant hypertension (RHTN) is defined as blood pressure (BP) that remains uncontrolled in spite of intake of ≥3 antihypertensive medications, ideally prescribed at optimal doses and one of which is a diuretic. The incidence of primary aldosteronism (PA) in patients with RHTN is estimated in prospective studies to be 14 to 23%, which is higher than in the general hypertensive population. Patients with PA are at an increased cardiovascular risk, as shown by higher rates of stroke, myocardial infarction, and arrhythmias compared to hypertensive individuals without PA. Likewise, RHTN is associated with adverse cardiovascular outcomes, and the contribution of PA to this increased risk is undetermined. Similar to PA, obstructive sleep apnea (OSA) is closely associated with RHTN, and a causal link between PA, OSA, and RHTN remains to be elucidated. The addition of MR antagonists to the antihypertensive regimen in patients with RHTN produces a profound BP-lowering effect, and this effect is seen in patients with or without biochemical evidence of PA, highlighting the role of relative aldosterone excess in driving treatment resistance in this group of patients.

1. Introduction

Primary aldosteronism (PA) is characterized by the overproduction of the mineralocorticoid hormone aldosterone by the adrenal gland, a condition that is relatively autonomous of the renin-angiotensin system (RAS), and nonsuppressible by sodium loading [1]. The elevated circulating aldosterone levels lead to potassium loss, hypernatremia, metabolic alkalosis, and hypertension. The syndrome can be the result of bilateral hyperplasia of the adrenal glands, unilateral adrenal hyperplasia, aldosterone producing adrenal adenoma, or in rare cases, by glucocorticoid-remediable aldosteronism (GRA).

Early epidemiologic studies have determined the prevalence of PA to be <1% of hypertensive patients, particularly if hypokalemia was used as a sine qua non for its diagnosis [2–4]. Recent studies have challenged this assumption, which have reported the prevalence of PA to be about 5–10% in the general hypertensive population [5–8]. In a study done in Chile, using the aldosterone to renin ratio (ARR) to screen for PA and confirming its presence using fludrocortisone testing, the prevalence of PA was 6.1% in a population of unselected essential hypertensive patients [8]. This prevalence was noted to rise with increasing severity of hypertension, such that in patients with Stage III hypertension (classified according to Joint National Commission (JNC) 6 criteria, i.e., BP > 180/100 mmHg), the prevalence of PA was 13.2%, as opposed to 1.99% in patients with Stage I hypertension (systolic BP [SBP] 140–159 mmHg, diastolic BP [DBP] 90–99 mmHg). Further, patients with PA had a higher BP (164/102 ± 12/10 mmHg) than patients without PA (156/96 ± 16/9 mmHg, $P < .05$) and were taking more antihypertensive medications at baseline (1.6 ± 0.8 versus 1.2 ± 0.9, $P < .05$). In another study done at the Czech Republic involving over 400 patients with moderate to severe hypertension (BP > 166/101 mmHg), the prevalence of PA was 19% [9]. In this study, screening for PA was undertaken using the ARR and confirmed by non- or mild suppression of plasma aldosterone levels after saline infusion, and the elevated BP levels in the clinic were confirmed by 24-hour ABPM.

PA is particularly common in patients with resistant hypertension (RHTN), defined as BP that remains above goal

in spite of use of at least 3 antihypertensive medications, ideally prescribed at optimal doses and one of which is a diuretic [10]. In a large retrospective study involving 1,616 patients with RHTN who were referred to a specialty clinic in Greece, the prevalence of PA (screened for using the aldosterone-to-renin ratio [ARR] and confirmed by intravenous saline loading or fludrocortisone suppression and further confirmed by assessing response to spironolactone monotherapy) was determined to be 11.3% [11]. Prospective studies have found an even higher prevalence of PA in patients with RHTN. Among 88 patients with RHTN who were consecutively referred to the hypertension clinic of the University of Alabama at Birmingham (UAB), 18 patients (20%) were confirmed to have PA, based on a high 24-hour urinary aldosterone excretion (>12 μg/24 hr) paired with a suppressed plasma renin activity level (<1 ng/ml/hr) during a high sodium diet (urinary sodium excretion >200 mEq/24 hr) [12]. This high prevalence of PA in patients with moderate to severe hypertension has been confirmed in other prospective studies done elsewhere. Investigators from Oslo, Norway found a PA prevalence of 21% of patients with RHTN [13]. In a university-based hypertension clinic in Seattle, Washington, the PA prevalence was 17% in patients with severe and/or poorly controlled hypertension (BP > 140/90 mmHg) [14]. Lastly, in a study done on 100 diabetic patients with RHTN, PA was confirmed in 14% of the study patients, using oral or intravenous saline loading [15]. Overall, these studies show that PA prevalence is higher (14–21%) in patients with moderate to severe hypertension on multiple antihypertensive medications, compared to the general hypertensive population.

2. Prognosis

High aldosterone levels lead to increased sodium and water reabsorption (and consequently potassium loss) in the distal nephron, acting via mineralocorticoid receptors (MRs) that regulate gene transcription. Aldosterone also exerts rapid, nongenomic cellular effects on MRs found in nonepithelial tissue, thereby influencing cell volume, oxidation-reduction state, and vascular function [16]. These effects are linked to the development of vascular stiffness and fibrosis, particularly in large arteries, the heart, and the kidney [17]. Taken together, these effects act in concert to raise BP and contribute to target organ damage in hypertensive individuals with aldosterone excess and may partly explain treatment resistance in those with more severe hypertension.

Aldosterone excess has been linked to the development and progression of several cardiovascular diseases, notably hypertension, congestive heart failure, coronary artery disease, chronic kidney disease, and stroke. In the Framingham Offspring Study, higher baseline serum aldosterone levels were associated with an increased risk of BP elevation or development of hypertension after four years in 1688 normotensive individuals (mean age 55 years, 58% women) [18]. Using multivariate analysis, there was a 16% increased risk of an elevation in BP ($P = .002$) and a 17% increased risk of development of hypertension per quartile increment in the serum aldosterone level, and the highest quartile of serum aldosterone, compared to the lowest quartile, was associated with a 1.61-fold risk of development of hypertension (95% CI 1.05 to 2.46).

Beyond its effects on BP, the presence of PA is associated with increased carotid intima thickness, higher pulse wave velocity (a marker of increased arterial stiffness), and impaired flow-mediated brachial artery dilation (which is an indicator of endothelial dysfunction) compared to hypertensive patients without PA [19, 20]. Left ventricular wall thickness is higher, and there is greater incidence of diastolic dysfunction as measured by tissue Doppler imaging in patients with PA compared to matched hypertensive controls [21]. In the kidney, apart from its effects on renal sodium handling, excess aldosterone induces early kidney damage. Patients with PA have a higher urinary albumin excretion rate compared to matched hypertensive controls, with a preserved glomerular filtration rate (which is an early manifestation of kidney disease) [22].

Comparing hypertensive patients with PA to those without biochemical evidence of aldosterone excess, the former had a greater incidence of stroke (both hemorrhagic and ischemic, odds ratio [OR] 4.2, 95% confidence interval [CI] 2.0 to 8.6, $P < .001$), myocardial infarction (OR 6.5, 95% CI 1.5 to 27.4, $P < .005$), and atrial fibrillation (OR 12.1, 95% CI 3.2 to 45.2, $P < .0001$) [23]. Similarly, in another study, the presence of PA was associated with a higher incidence of myocardial infarction, stroke or transient ischemic attack, and sustained arrhythmias compared to patients with essential hypertension without PA [24]. In both studies, the differences were noted in spite of similar BP levels between the two groups, further supporting the concept that aldosterone excess produces additional adverse cardiovascular effects independent of BP. Moreover, the subtype of PA (aldosterone producing adenoma or bilateral adrenal hyperplasia) did not appear to influence the cardiovascular risk.

In the same regard, patients with RHTN have greater cardiovascular risk compared to those who do not have RHTN. Patients with RHTN have a higher incidence of concomitant diabetes, kidney disease, and obstructive sleep apnea, all of which are independent risk factors for the development of cardiovascular disease [25, 26]. RHTN is associated with the increased incidence of left ventricular hypertrophy, retinopathy, nephropathy, and carotid intimal disease, which are considered signs of target organ damage in hypertensive disease [27, 28]. Lastly, small outcome studies have shown that patients with RHTN have increased rates of stroke, myocardial infarction, and congestive heart failure compared to patients without RHTN [29, 30]. The extent to which PA contributes to this increased risk in patients with RHTN is unknown.

3. Primary Aldosteronism, Obstructive Sleep Apnea, and Resistant Hypertension

Obstructive sleep apnea (OSA) is strongly associated with the risk of having hypertension and the risk of developing

hypertension [31]. Moreover, it appears that greater severity of hypertension is associated with increased risk of OSA, such that OSA is particularly common in patients with RHTN. In a prospective study on 41 patients with RHTN, 83% were diagnosed with OSA (defined as apnea-hypopnea index [AHI] > 10 events/hour) after overnight polysomnography (PSG), and OSA was more prevalent (96 versus 65%, $P = .014$) and more severe (mean AHI 32 versus 14, $P = 0004$) in men than in women [25]. These results were confirmed in our study involving 71 patients with RHTN, where the prevalence of OSA was determined to be 85% and is also more common and more severe in men than in women [32].

Increasing severity of OSA also is associated with difficulty to control hypertension. In 257 patients with OSA who are adherent to a stable antihypertensive regimen for 6 months, those who were ineffectively treated (BP > 140/90 mmHg) had a higher AHI (44 events/hr) compared to those with controlled BP (33 events/hr, $P < .005$) in spite of having similar nocturnal oxygenation and after adjusting for age, gender, and body mass index [33]. As a corollary, in an observational study on patients with RHTN and OSA, treatment of OSA with continuous positive airway pressure (CPAP) allowed deescalation of antihypertensive drug therapy (by dose reduction or discontinuation of one or more drugs) in 71% of study patients [34]. This effect was not seen in patients without RHTN. The results of a prospective study in patients with RHTN and OSA largely confirm these findings. Treatment with CPAP (mean use of 5.8 hours/night) on top of the usual antihypertensive drug regimen significantly reduced mean 24-hour BP by 10/7 mmHg at the 3rd month followup, and the BP lowering effect was greatest for those who used CPAP longest each night (i.e., better compliance) [35]. While OSA is a known risk factor for the development of hypertension and likely contributes to treatment resistance, the above results also suggest that the reverse may be true; that RHTN may predispose to or aggravate OSA. Their common link, however, remains to be elucidated.

In 325 newly diagnosed hypertensive patients who were screened for the presence of OSA and evaluated by overnight polysomnography, 53 patients were confirmed to have OSA [36]. Out of these 53 patients, 18 patients had PA, based on results of saline infusion testing. Considering that both PA and OSA are common in patients with RHTN, it is interesting to note that in 71 patients with RHTN who underwent biochemical testing for PA and overnight PSG, the plasma aldosterone concentration was positively correlated with AHI (Pearson's $r = 0.44$, $P = .0002$) [32]. This association was not seen in 29 control patients without RHTN, where the median plasma aldosterone level was lower than in patients with RHTN and not correlated to the AHI. These results suggest that in patients with RHTN, PA may contribute to increased severity of OSA but does not exclude the reverse: that OSA stimulates aldosterone release in these patients. Currently, we are undertaking a prospective evaluation to test this hypothesis.

4. Treatment

Surgical treatment (unilateral adrenalectomy) should be offered to patients with unilateral adrenal disease who are eligible for surgery. In a number of reports, unilateral adrenalectomy has been shown to improve BP control and incidence of hypokalemia. In patients who are unable or unwilling to undergo surgery, treatment with an MR antagonist should be initiated.

Treatment of aldosterone excess with either spironolactone or unilateral adrenalectomy was found to reverse the increase in cardiovascular risk found in hypertensive patients with PA [23]. After a 12-year followup, patients with PA who were treated accordingly had similar rates of cardiovascular events as hypertensive patients without PA. Better cardiovascular outcomes were seen in younger patients and in those with a shorter duration of disease, highlighting the importance of early recognition and treatment to reverse the adverse effects of excess aldosterone.

4.1. Mineralocorticoid Receptor Antagonists. Spironolactone, a direct antagonist of the MR, is a formidable add-on agent to the antihypertensive regimen in patients with RHTN, who are taking at least 3 antihypertensive medications to control BP. When added to a regimen that typically already includes a diuretic, an RAS blocker and a CCB or BB, spironolactone (at a dose of 12.5 to 25 mg/day) lowers BP by as much as 21/10 ± 21/14 mmHg at 6 weeks and 25/12 ± 20/12 mmHg after 6 months (Figure 1) [37]. This effect was similar in patients with or without evidence of aldosterone excess, as well as in African American and Caucasian patients. In another study, incorporating the results of 24-hour ambulatory blood pressure monitoring, higher doses of spironolactone (25 to 100 mg/day) reduced 24-hour mean BP by 16/9 mmHg, and control (daytime BP < 135/85) was achieved in 48% of patients [38]. In both studies, similar degrees of BP reduction were achieved regardless of baseline plasma aldosterone or PRA values. This underscores the contributory role of relative aldosterone excess to treatment resistance in this group of patients, such that even those with presumably low levels of aldosterone benefit from MR blockade.

This importance of relative aldosterone excess in promoting treatment resistance is further emphasized in a comparison between spironolactone added to an ACE inhibitor or an ARB versus the combination of an ACE inhibitor and an ARB in treating patients with RHTN [39]. In this open-label prospective crossover study, 44 patients with RHTN received a second RAS blocker (ACE inhibitor or ARB) for 12 weeks, then subsequently given spironolactone (25 mg/day or higher) after a 4-week washout period. Greater BP reduction was achieved when spironolactone was added to an ACE inhibitor or an ARB (24-hour mean BP reduction of 21/9 mmHg, which is compatible with other trials of spironolactone as an add-on agent) versus dual RAS blockade (24-hour mean BP reduction of 7/3 mmHg), allowing 53.8% of patients receiving spironolactone to attain target BP, as opposed to only 25.6% of those on dual RAS blocker therapy. The results suggest that aldosterone excess plays a bigger role in the pathogenesis of treatment resistance,

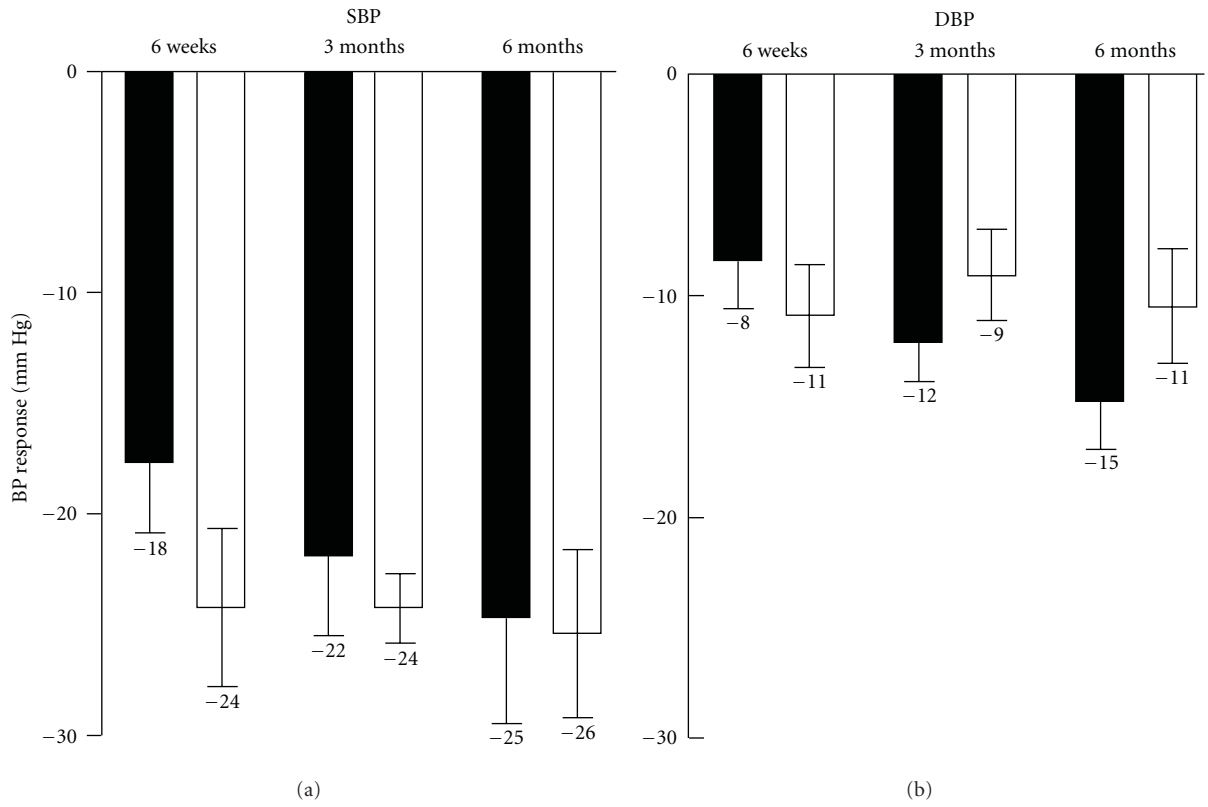

Figure 1: BP reduction achieved after low-dose spironolactone was added to the antihypertensive regimen in patients with RHTN, with (filled bars) or without (open bars) PA [37].

and that the hypersecretion of aldosterone is relatively autonomous of the RAS, so the magnitude of BP lowering is greater in patients given the MR antagonist compared to those on dual blockade. Further, since the study largely excluded patients with PA, the results show that resistant hypertensive patients in general have an element of relative aldosterone excess, even while measured aldosterone levels fall within the "normal" range.

Some of the more common adverse effects seen with spironolactone treatment are breast tenderness, gynecomastia, erectile dysfunction, and menstrual irregularities, which result from the binding of spironolactone to androgen receptors, preventing its interaction with dihydrotestosterone. The incidence of these adverse effects is rare, reported by about 2–9% of study patients, and is reversible after discontinuing treatment. Eplerenone, another MR antagonist, binds more selectively to the MR and has a lower affinity for androgen receptors and thus does not have the antiandrogen effects. It is effective in treating patients with RHTN. After receiving eplerenone (at a dose of 50 to 100 mg/day, titrated to achieve BP < 140/90 mmHg) on top of a three-drug regimen for 12 weeks, office BP was reduced by 18/8 mmHg, and 24-hour mean BP decreased by 12/6 mmHg ($P < .001$) [40]. Again, these effects were independent of baseline plasma aldosterone and PRA levels.

A head-to-head comparison between spironolactone and eplerenone in patients with primary (not resistant) hypertension and bilateral adrenal hyperplasia showed that the two agents achieved similar degrees of BP lowering in patients with PA [41]. Spironolactone was administered at 400 mg/day (which is a higher dose than usual), while eplerenone was given at 150 mg/day. In spite of the large dose used in the study, only 2 (out of 17) patients who received spironolactone developed painful gynecomastia after 16 weeks of followup, and this was resolved after the patients were shifted to eplerenone. A direct comparison of these two agents in patients with RHTN has not been conducted.

Hyperkalemia can also result from treatment with MR antagonists, particularly in the setting of multidrug therapy that includes RAS blockers, which can also raise serum potassium levels, or in patients with chronic kidney disease. This effect is likewise reversed by discontinuing the MR antagonist or reducing the dose. The incidence of hyperkalemia, however, is low. Out of 76 patients who were given spironolactone for 6 months, only 2 (2.6%) developed hyperkalemia ($K > 5.5$ mEq/L) [36]. In patients given eplerenone, the serum potassium increased by a mean of 0.30 $\pm$ 0.45 mEq/L after initiation of eplerenone treatment, and mild hyperkalemia (serum potassium 5.5 to 6 mEq/L) was seen in only two patients (out of 52, or 3.8%), despite being on an ACE inhibitor or an ARB concomitantly [39].

Beyond BP lowering, treatment with MR antagonists also reverses or attenuates cardiovascular injury mediated by excess aldosterone, particularly the nongenomic effects,

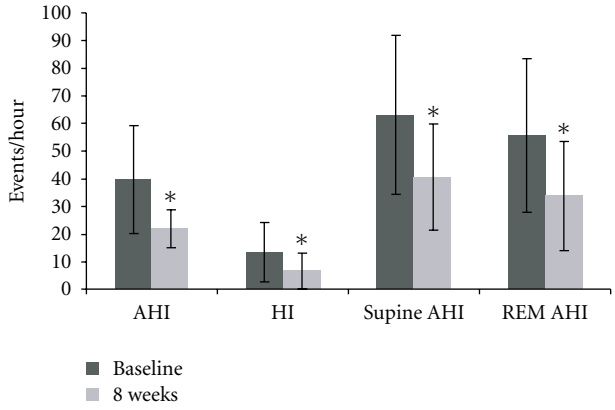

Figure 2: Changes in the apnea-hypopnea index (AHI), hypoxic index (HI), and AHI during supine position or rapid-eye movement (REM) sleep in patients with resistant hypertension before (baseline) and after 8 weeks of add-on spironolactone. $^*P < .05$ compared to baseline [44].

which lead to tissue fibrosis, arterial stiffness, and increased oxidative stress. In patients with RHTN (with or without PA), spironolactone (at an initial dose of 25 mg/day then forcetitrated to 50 mg/day after 4 weeks) reduced left ventricular mass index at the 3rd and 6th month followup [42]. The degree of LV regression achieved with spironolactone treatment was greater for patients with PA compared to those without PA (22 versus 12%, resp., $P < .001$ relative to baseline values). Further, spironolactone given to patients with both RHTN and PA for 6 months significantly decreased brain natriuretic peptide values from baseline, an effect that was not seen in those with normal or low aldosterone levels, indicating a prominent diuretic effect even when administered on top of chronic thiazide diuretic treatment. In another study involving patients with RHTN and PA, treatment with low-dose spironolactone (12.5 to 25 mg/day) for 3 months significantly increased flow-mediated dilation of the brachial artery, indicating improvement of endothelial function, and this effect was independent of the change in BP [43].

Lastly, spironolactone reduced the severity of OSA in patients with RHTN [44]. In a prospective evaluation involving 12 patients with RHTN in whom spironolactone (25–50 mg/day) was added to a stable antihypertensive regimen, there were significant reductions in the AHI (39.8 ± 19.5 versus 22 ± 6.8 events/hour, $P < .05$), hypoxic index (13.6 ± 10.8 versus 6.7 ± 6.6 events/hour, $P < .05$), and clinic and 24-hour ambulatory BP on the 8th week followup, and plasma renin activity was increased (Figure 2). Although the study was small and did not have an active control group, this study lends support to the concept that aldosterone excess contributes to the severity of OSA in patients with RHTN.

5. Summary

RHTN and PA are each associated with increased cardiovascular risk in hypertensive patients. Aldosterone excess is believed to contribute significantly to uncontrolled BP in patients with RHTN, as shown by a higher prevalence of PA in patients with RHTN and a significant BP-lowering effect produced by MR antagonists, particularly spironolactone, when added to a multidrug antihypertensive regimen that typically already includes a diuretic and an RAS blocker. This effect was seen in both patients with and without PA, showing that even in those patients without elevated aldosterone levels (by current laboratory standards), there is some element of relative aldosterone excess that contributes to the raised BP. Further, treatment with MR antagonists produces cardiovascular benefits beyond BP lowering (including reduction of the severity of OSA), showing that aldosterone also plays a direct role in the development of target organ damage, arterial stiffness, and endothelial dysfunction, mostly mediated via nongenomic mechanisms.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 270624, 8 pages
doi:10.4061/2011/270624

Review Article

Obesity Hypertension: The Regulatory Role of Leptin

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Received 27 September 2010; Accepted 15 December 2010

Academic Editor: Vasilios Papademetriou

Leptin is a 16-kDa-peptide hormone that is primarily synthesized and secreted by adipose tissue. One of the major actions of this hormone is the control of energy balance by binding to receptors in the hypothalamus, leading to reduction in food intake and elevation in temperature and energy expenditure. In addition, increasing evidence suggests that leptin, through both direct and indirect mechanisms, may play an important role in cardiovascular and renal regulation. While the relevance of endogenous leptin needs further clarification, it appears to function as a pressure and volume-regulating factor under conditions of health. However, in abnormal situations characterized by chronic hyperleptinemia such as obesity, it may function pathophysiologically for the development of hypertension and possibly also for direct renal, vascular, and cardiac damage.

1. Introduction

The prevalence of obesity in the adult population of the United States has risen markedly in the last three decades, contributing to the increased incidence of diabetes, hypertension, and heart disease [1–3]. Indeed, epidemiological studies suggest that 65–75% of the risk for hypertension is attributed to excess weight [4, 5]. Recently, a novel and most promising area of research in obesity and hypertension that links these two pathologic conditions is the endocrinology of adipose tissue. It is now apparent that adipose tissue is a prolific organ which secretes several immunomodulators and bioactive molecules [3, 6]. Of these various factors, leptin has emerged as an important hormone with significant pleiotropic actions on several organ systems [7, 8].

The first described major action of leptin was on the hypothalamus to control body weight and fat deposition through its effects on appetite inhibition, as well as stimulation of the metabolic rate and thermogenesis [9, 10]. However, increasing evidence suggests that the biology of leptin extends to other organs including the kidney, the heart, the sympathetic nervous system, and the systemic vasculature, areas in which it may have prominent effects [7, 8, 11–14].

2. Leptin Receptors: Localization and Function

The leptin receptor (LR), a product of the lepr gene, is a member of the extended class I cytokine receptor family having at least six splice variants LR (a-f) [15–19]. Significant expression of the lepr gene occurs in the lung and adipocytes, while only moderate levels appear in the kidney, with relatively lower levels demonstrated in other tissues like the heart, brain, spleen, liver, and muscle [20]. Though the extracellular domain of the leptin receptor and the short splice variant (LRa) have been detected in many peripheral tissues, the long splice variant (LRb) is expressed in fewer organ systems including the adrenal gland, kidney, and heart [20]. This long splice variant leads to activation of the Janus Kinases (a family of tyrosine kinases)

to promote transcription through activation of the STAT-3 (signal transduction and activator of transcription) and PI3K (phosphoinositol-3 kinase), and inhibition of AMPK (AMP-activated protein kinase) [15–20]. LRa and LRb can also stimulate MAPK (mitogen activated protein kinase) which may be involved in the induction of hypertrophy [21]. Finally, SOCS-3 (suppression of cytokine signaling protein) and PTB1b (protein tyrosine phosphatase 1b) have been identified as negative regulators of leptin signaling [15–19].

3. Leptin, Sympathetic Nervous System, and the Regulation of Arterial Blood Pressure

It is now well established that leptin can activate the sympathetic nervous system both by local peripheral actions as well as through centrally mediated effects on the hypothalamus [22]. Studies with direct infusion of leptin into the cerebral ventricles of normal rats have demonstrated a slow increase of mean arterial pressure (MAP) of approximately 10% [13]. Moreover, recent investigations have suggested that leptin signaling in the nucleus tracti solitarii increased renal sympathetic flow in normal rats but not in obese Zucker rats, indicating that intact leptin receptors are essential for this vasoactive response [22]. In agreement with these concepts, human studies have suggested that genetically mediated leptin deficiency is associated not only with morbid obesity, but also impairment in the sympathetic nervous system activity and postural hypotension in homozygous children and adults [23].

However, it is important to point out that in other investigations conducted both in normotensive as well as hypertensive rats [12, 14, 24], the acute systemic administration of leptin was associated with the peripheral activation of the sympathetic nervous system without elevation in MAP. This raises the possibility of the simultaneous local activation of counter-regulatory vasodilatory mechanisms [14, 25, 26]. *In vitro* studies have demonstrated a dose-dependent leptin-induced vasorelaxation in the aortic rings of Wistar-Kyoto rats [25] which is mediated by nitric oxide (NO) and possibly by endothelial-derived hyperpolarizing factor (EDHF). An elevation in plasma NO with intravenous administration of synthetic leptin in normal rats has also been demonstrated [26]. In these studies blockade of NO led to a leptin-induced enhancement of arterial blood pressure while blockade of the sympathetic nervous system led to leptin-mediated reduction in blood pressure [26]. Thus, leptin's lack of effect on arterial blood pressure in normal subjects may represent a balanced action of vasodilatation primarily mediated by NO and vasoconstriction primarily mediated by the sympathetic nervous system, with a resultant neutral hemodynamic effect [26, 27]. This concept requires further validation because the vasodilatory actions of leptin in other vascular beds have been found to be inconsistent [28, 29]. In high-calorie fed obese rats, however, recent studies by Beltowski et al have indicated that acutely infused leptin was associated with a hypertensive effect related, at least in part, to impaired vascular NO and EDHF production characteristic of obesity [30].

4. Chronic Hyperleptinemia, Leptin Resistance, and Hypertension

In chronic hyperleptinemic conditions such as obesity, the potential neutral effect of leptin on peripheral vascular resistance may no longer be present. It has been previously demonstrated that the agouti yellow obese mouse model is resistant to the satiety actions of leptin but not to the effects of leptin on the sympathetic nervous system [31, 32], although this stimulation may be attenuated with the progression of obesity [33]. From these findings, the concept of "*selective leptin resistance*" as a mechanism for the development of hypertension in obesity has emerged [31, 32]. The precise factors behind this selectivity are yet to be fully defined [32, 34], but may involve alterations in the SOCS3 signaling pathway or IRS-1 (insulin receptor substrate-1) serine residue phosphorylation [30, 35, 36].

Independent of the possibility of selective leptin resistance in obesity, studies in normal rats have demonstrated that chronic hyperleptinemia leads to a persistent elevation in MAP and this hypertensive effect is rapidly reversed upon cessation of the hormone administration [37]. Similar increases in systolic blood pressure have been demonstrated in transgenic mice overexpressing leptin where the endogenous level of the hormone was elevated twenty-fold [38]. In this regard, it is pertinent to point out that hyperleptinemia may increase vascular smooth muscle cell proliferation [38], an effect that could contribute to the development and/or perpetuation of hypertension. Moreover, mice with leptin deficiency (ob/ob) or with a leptin receptor defect (db/db) exhibit significant obesity but do not develop hypertension, suggesting that at least in animal models, leptin may play a role in the regulation of systemic hemodynamics [32]. In humans, emerging evidence suggests a direct relationship between hyperleptinemia and hypertension in both men and women [39, 40], and this effect may be independent of BMI and insulin resistance. In a recent study by Shankar and Xiao of 5,599 Americans, higher plasma leptin levels were positively associated with hypertension after adjusting for multiple covariates including age, sex, race/ethnicity, education, smoking, body mass index, diabetes mellitus, and serum cholesterol [41]. In this regard, recent studies indicating a reduction in serum leptin levels with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers suggest a potential interaction between leptin and the renin-angiotensin-aldosterone system for hemodynamic regulation in obesity [42, 43].

Finally, an additional potential mechanism involved in leptin's regulation of blood pressure implicates the melanocortin system [44]. Recent investigations have suggested that the acute actions of leptin to raise renal sympathetic activity are abolished in Melanocortin 4 receptor-(MC4R-) deficient (−/−) mice, suggesting that the MC4R may mediate the sympathoexcitatory actions of leptin [45]. To this end, Greenfield et al. demonstrated a lower prevalence of hypertension in obese subjects with a loss-of-function mutation in MC4R gene compared to obese controls with the intact gene again implicating melanocortinergic signaling in the control of systemic hemodynamics [46].

5. Leptin and the Regulation of Sodium-Volume Balance

Previous studies have indicated that the LRb leptin receptor is localized in the renal medulla [20, 47] which suggests a functional role of this hormone in renal biology. In the last 5–10 years, numerous studies have demonstrated that acute administration of synthetic leptin in the rat produces a significant elevation in urinary sodium and water excretion [14, 47–49].

Villarreal et al. [14] demonstrated that in normotensive rats, an intravenous bolus of leptin produced a robust six to sevenfold elevation in urinary sodium excretion and fractional excretion of sodium; in contrast, hypertensive rats were refractory to the renal effects of leptin. Interestingly, the natriuretic effect was attenuated in obese Zucker rats [14]. MAP and creatinine clearance remained unchanged in all of the rat strains with the acute infusion of the hormone. Collectively, these findings were interpreted to suggest that leptin might be a natriuretic hormone primarily acting at the tubular level for promotion of sodium and water excretion in normal rats, and that leptin may function pathophysiologically in obesity and hypertension, where chronic hyperleptinemia may contribute to a preferential stimulation of the sympathetic nervous system with further elevation in blood pressure and reduced sodium and water excretion [2, 7, 50]. Moreover, in a rat model of diet-induced obesity, initial studies by Patel et al. have shown markedly attenuated natriuretic and diuretic effects of synthetic leptin as well as reduced urinary excretion of NO [51]. These findings suggest that in obesity, alterations in leptin-induced renal NO production and/or metabolism may account, at least in part, for the blunted natriuretic effects. However, additional observations in diet-induced obese rats indicate that caloric restriction was associated with the restoration of the natriuretic actions of leptin as well as with the renal generation of NO [51]. In the aggregate, these studies are consistent with the concept that obesity is associated with renal leptin resistance [14, 52], and this resistance, at least in part, is reversible with caloric restriction and weight loss.

The significance of NO in the direct modulation of leptin-induced sodium excretion has been investigated in rats chronically treated with L-NAME to inhibit NO production [53]. L-NAME-treated rats failed to produce significant natriuresis. However, there was a two to threefold elevation in sodium excretion induced by leptin with the restoration of NO by sodium nitroprusside [53], indicating that NO may play an important role in mediating or modulating the tubular natriuretic effects of leptin. These observations are supported by the studies of Beltowski et al., [52] which demonstrated that leptin produces a time- and dose-dependent reduction of renal medullary Na-K-ATPase, which may in part be regulated by NO [53, 54]. Beltowski et al., [52] also reported that in diet-induced obese rats, leptin-induced stimulation of plasma NO, reduction of renal Na-K-ATPase, and natriuresis are all significantly impaired.

The mechanisms for renal resistance to leptin in obesity and hypertension are not completely defined but may include receptor down regulation [12, 51], postreceptor signaling alterations [12, 16, 17], excessive degradation of NO produced by oxidative stress [55], or increased activation of the efferent renal sympathetic nervous system leading to antinatriuresis [49]. Indeed, studies which [49] have examined this latter hypothesis using an animal model of renal denervation indicate that the renal efferent sympathetic nervous system is an important counter-regulatory mechanism impeding leptin-induced sodium excretion in hypertension, and perhaps also during obesity, which is similarly characterized by a heightened sympathetic nervous tone [2, 7].

The relevance of endogenous leptin as a distinct sodium-volume regulatory hormone has been examined in normal Sprague Dawley rats that were in a state of mild sodium/volume expansion [56]. Urinary sodium and volume excretion were significantly reduced by approximately 20–25% after blockade of leptin with a polyclonal antibody, indicating an important physiologic role for this hormone in the daily renal control of salt and water balance. The importance of leptin as a regulator of sodium and volume is further supported by recent investigations [56, 57] which have demonstrated that leptin expression in adipose tissue is directly proportional to dietary sodium, a response that would be expected for mechanisms regulating sodium balance.

Thus, the available information to date suggests that leptin's net effect on renal sodium metabolism and ultimately systemic hemodynamics may reflect both direct natriuretic and indirect antinatriuretic actions. The responsiveness to leptin at neural, renal, and other sites which regulate natriuresis and vascular resistance may differ under diverse physiological and pathophysiological conditions, and this in turn, will be a determinant for the overall magnitude of leptin-induced sodium, water, and hemodynamic balance.

6. Leptin and Chronic Renal Insufficiency

Leptin's role in renal physiology and pathophysiology is complex. As previously discussed, leptin may play a significant role in the regulation of sodium and water balance in normal situations. However, in conditions of chronic hyperleptinemia, the hormone has been linked to renal structural changes that specifically have been associated with obesity [58]. Elegant studies by Wolf et al. [59] have determined that in glomerular endothelial cells, leptin can stimulate cellular proliferation, expression of TGF-β1 and type IV collagen synthesis leading to fibrosis. Indeed, chronic infusion of leptin in normal rats promoted the development of glomerulosclerosis and proteinuria [59]. It is of interest that similar renal abnormalities have been found in mice with chronic high fat diet and the metabolic syndrome [60], which is characterized by sustained elevations of circulating leptin [61].

Inappropriate elevation in serum leptin levels has been demonstrated in patients with chronic kidney disease [62–64]. The origin and significance of hyperleptinemia in these patients are not completely defined, but it is important to emphasize that the marked elevation of leptin is out of

proportion to obesity and persists after correction for body mass index [65]. Since the kidney is involved in clearance of leptin, its elevated levels in renal insufficiency are primarily due to reduced renal filtration and metabolism [62, 66]. It remains to be determined whether an increased rate of leptin production also contributes to the high serum leptin levels in renal insufficiency.

Leptin levels appear to be higher in patients receiving peritoneal dialysis (PD) compared to hemodialysis (HD) [67]. The reasons for this phenomenon are multifactorial. It is likely that the elevated body fat mass in patients with PD contributes to the increase in serum leptin [67]. However, other factors are probably involved. For instance, the continuous glucose load in PD results in chronic hyperinsulinemia, an important finding considering that insulin upregulates lepr gene expression [63]. In this regard, it is of interest that even higher leptin levels are observed in patients with renal insufficiency with elevated insulin levels compared to patients with low insulin levels [63, 68].

The pathophysiological significance of hyperleptinemia in renal insufficiency is not completely understood. High levels of leptin have been associated with weight loss in dialysis patients [65, 69–71], and therefore it has been suggested that hyperleptinemia may be a contributing factor in uremic-induced cachexia [64, 69–74]. Other suggested actions in patients with end-stage renal disease which include leptin-induced reduction in erythropoiesis [75, 76], promotion of renal osteodystrophy [77, 78], and chronic inflammation [63, 78, 79].

7. Leptin and the Heart

It is now well recognized that the role of leptin in energy homeostasis extends into cardiac metabolism. The effects of leptin mediated by the LRb receptor include a reduction of insulin signaling with enhanced lipid oxidation and therefore inhibition of anabolic pathways [80]. Similar to the kidney, chronic hyperleptinemia may be indirectly important in the development of cardiac disease via sympathetic activation, pressor effects, enhancement of platelet aggregation, impairment of fibrinolysis as well as proangiogenic actions [12, 35, 81, 82] and systemic inflammation via leptin-induced expression of C-reactive protein [83, 84].

In addition, and although still controversial, leptin may be involved in the pathogenesis of myocyte hypertrophy and cardiac dysfunction [85–87] through direct effects. Indeed, leptin can proliferate, differentiate, and functionally activate hemopoietic and embryonic cells to promote myocyte growth [88–90]. Moreover, in rats with myocardial infarction, cardiac hypertrophy has been shown to be attenuated with the blockade of leptin receptors [91]. Among the suggested mechanisms of leptin-induced hypertrophy are the stimulation of endothelin-1, angiotensin II [92], and reactive oxygen species [93]. Additional studies in rats with myocardial infarction have also indicated that long-term continuous administration of leptin promoted the development of eccentric cardiac hypertrophy [94].

In contrast to these investigations, studies in leptin-deficient mice (ob/ob) with [94, 95] or without myocardial infarction [96] have suggested that leptin can exert protective cardiac effects with reversal of baseline myocyte hypertrophy during leptin supplementation [96]. Also, Tajmir et al. [97] have indicated that leptin can activate ERK 1/2 (extracellular signal-regulated kinase) and phosphoinositol-3 kinase-dependent signaling pathways in cardiomyocytes to promote physiological repair of myocardium. Presently, the reasons for the apparent discrepant effects of leptin on myocyte growth are unclear, but may be related to different experimental conditions, including the variable response of leptin in neonatal compared to adult cells [82–97].

In addition to its potential actions on myocardial cell growth, leptin has been shown to exert direct negative inotropic effects on adult rat ventricular myocytes [98]. The suggested mechanisms involve activation of fatty acid oxidation leading to decreased triglyceride content or an altered adenylate cyclase function [96, 99]. Alternatively, Nickola et al. [98] reported that leptin may abnormally increase expression of Nitric Oxide Synthases in cardiac myocytes promoting oxidative stress and depressed cardiac function. However, similar to the controversy related to cardiac hypertrophy, more recent studies in ob/ob mice [95] or rats [94] with myocardial infarction have suggested that leptin may attenuate adverse cardiac remodeling by reducing apoptosis [95], which may improve left ventricular contractile function, and at least in part, increase survival [94–96].

The relevance of these studies in humans is unclear. Although there is evidence to suggest a direct relationship between the hyperleptinemia of obesity with cardiac hypertrophy [96, 100], and possibly heart failure [101], these are not consistent findings [8, 11]. Additional *in vitro* and *in vivo* studies are needed to define and characterize the potential beneficial or deleterious effects of leptin in cardiac physiology and pathophysiology.

8. Summary and Conclusions

It is well established that cardiovascular and renal functions require the activation of multiple neuro hormonal mechanisms designed to maintain homeostasis. The hormone leptin has multiple actions that may be important not only for energy metabolism, but also in physiological and pathophysiological cardiovascular and renal regulation (Figure 1). Potentially prominent are its effects on renal sodium excretion, NO, sympathetic nervous system activation, and vascular tone. The interaction among the vasoconstricting, vasodilatory, and natriuretic effects of leptin to help achieve volume and pressure homeostasis in normal conditions may be disrupted during chronic hyperleptinemia, and this effect could likely contribute to hypertension and possible cardiac and renal dysfunction. Further research awaits the additional characterization of both direct and indirect mechanisms of action of leptin, including its interface with other important hormonal sodium-volume-pressure regulatory systems, in both health and disease states, particularly obesity and related comorbidities.

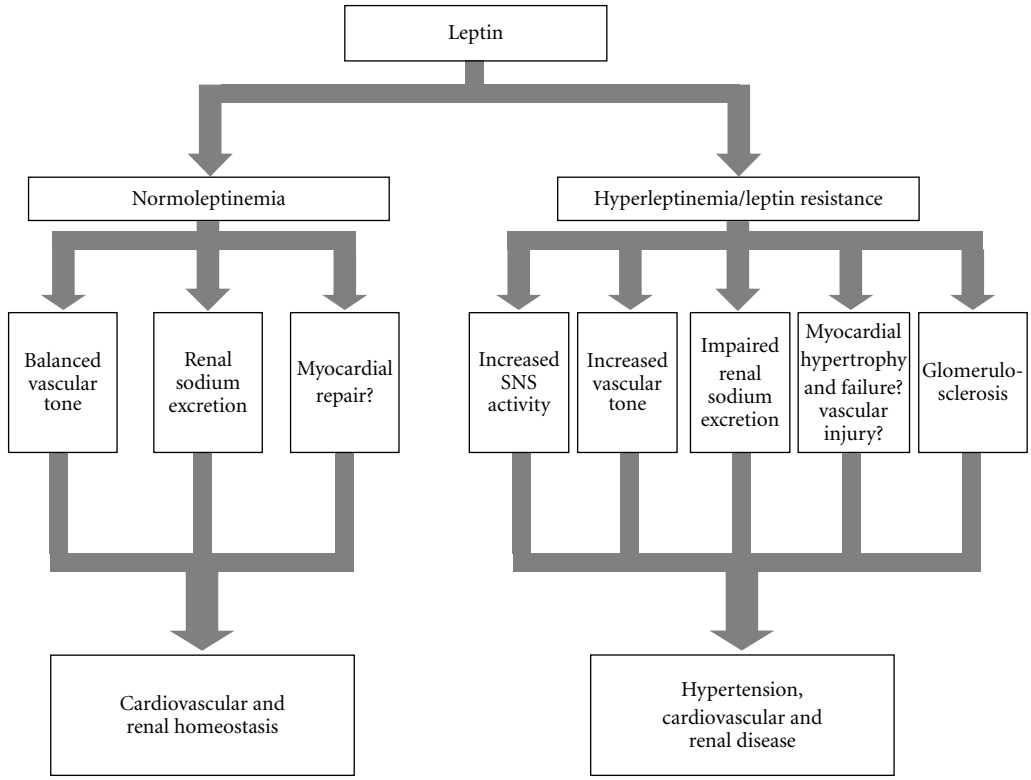

Figure 1: Cardiovascular and Renal Actions of Leptin. SNS: sympathetic nervous system. Adapted from Kshatriya S, Reams GP, Spear RM, Freeman RH, Dietz JR, Villarreal D. Current Opinion in Nephrology and Hypertension, 2010 Jan; 19 (1): 72−8. With Permission from Wolters Kluwer/Lippincott, Williams & Wilkins.

Acknowledgments

This paper is supported in part by the Veteran Affairs Research Program (Merit Review), the Joseph C. Georg Research Award, and the Hendricks Research Award. The authors wish to acknowledge the expert technical assistance Jeffrey Montalbano.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 143471, 8 pages
doi:10.4061/2011/143471

Review Article

Role of the Kidneys in Resistant Hypertension

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Received 29 November 2010; Revised 30 December 2010; Accepted 13 January 2011

Academic Editor: Vasilios Papademetriou

Resistant hypertension is a failure to achieve goal BP (<140/90 mm Hg for the overall population and <130/80 mm Hg for those with diabetes mellitus or chronic kidney disease) in a patient who adheres to maximum tolerated doses of 3 antihypertensive drugs including a diuretic. The kidneys play a critical role in long-term regulation of blood pressure. Blunted pressure natriuresis, with resultant increase in extracellular fluid volume, is an important cause of resistant hypertension. Activation of the renin-angiotensin-aldosterone system, increased renal sympathetic nervous system activity and increased sodium reabsorption are important renal mechanisms. Successful treatment requires identification and reversal of lifestyle factors or drugs contributing to treatment resistance, diagnosis and appropriate treatment of secondary causes of hypertension, use of effective multidrug regimens and optimization of diuretic therapy. Since inappropriate renal salt retention underlies most cases of drug-resistant hypertension, the therapeutic focus should be on improving salt depleting therapy by assessing and, if necessary, reducing dietary salt intake, optimizing diuretic therapy, and adding a mineralocorticoid antagonist if there are no contraindications.

1. Introduction

The Joint National Committee (JNC) 7 defined resistant hypertension as failure to achieve goal blood pressure (BP) (<140/90 mm Hg for the overall population and <130/80 mm Hg for those with diabetes mellitus or chronic kidney disease) in a patient who adheres to maximum tolerated doses of 3 antihypertensive drugs including a diuretic. An increasing number of patients, especially the aged, those with diabetes or who are African American, meet this definition. However, it is important to rule out white coat hypertension by asking the patient to record their own home blood pressures and undertaking an ambulatory blood pressure monitor if the results are equivocal. A careful enquiry about whether the patient is taking the prescribed medications and if there are adverse effects that are causing concern may give clues to noncompliance. In some cases, it may be useful to measure blood or urine drug levels, for example of diuretics, to check for noncompliance. A recent study of African Americans with hypertensive focal segmental glomerulosclerosis [1] has linked a single nucleotide polymorphism for the apolipoprotein L1 gene to the disease but this is not yet available as a diagnostic test. Since aging increases the burden of vascular disease, resistant hypertension and its consequences are more common in elderly people. The kidneys play a critical role in long term regulation of blood pressure. In this paper, we discuss the renal mechanisms which contribute to the development of resistant hypertension, which are summarized in Table 1, and their management.

2. Blunted Pressure Natriuresis

Pressure natriuresis [2] describes the increased sodium excretion that occurs with elevated blood pressure. A normal pressure natriuresis should prevent hypertension because any elevation of blood pressure would elicit an increased sodium and water excretion that would reduce the blood volume and venous return and retain a normal level of blood pressure. Patients with hypertension have a defective pressure natriuresis. The relationship between sodium excretion and blood pressure is shifted to higher levels of blood pressure, which implies an abnormal response in the kidney that

Table 1: Renal mechanisms of drug-resistant hypertension.

(1) Blunted pressure natriuresis
(a) Chronic kidney disease
(b) Renal artery stenosis
(2) Renal nerve activation
(3) Renal nitric oxide deficiency
(4) Medications acting adversely on the kidney
(a) Non steroid anti inflammatory drugs (NSAIDs)
(b) Cox-2 inhibitors
(c) Corticosteroids
(d) Cyclosporine
(e) Erythropoietin
(f) Licorice
(5) Extra renal factors causing salt retention
(a) Hyperaldosteronism
(b) Vasodilator medications
(c) Obstructive sleep apnea (OSA)
(d) Endothelin type A receptor antagonists.
(6) Inappropriately high salt intake
(7) Ineffective diuretic usage

maintains hypertension. Salt retention occurs when intake exceeds excretion. This leads to extracellular fluid (ECF) volume expansion which is common in chronic kidney disease (CKD) and is an important cause of resistant hypertension. The salt retention is typically subtle and does not lead to edema. Even a normal rate of sodium excretion in a patient with hypertension is inappropriate and implies a renal mechanism of hypertension since a normal kidney increases the sodium excretion above intake and reduces ECF volume when blood pressure is increased to restore a normal level of BP. The mechanism of renal sodium retention usually entails a combination of reduced glomerular filtration rate (GFR) and increased tubular sodium reabsorption. Since the GFR may be normal or only reduced modestly, the renal defect in resistant hypertension is predominantly a failure to appropriately suppress tubular sodium reabsorption [3].

Large increases in ECF volume may arise if sodium intake is very high or reduction in GFR is severe (e.g., chronic kidney disease stage 4-5). Patients with resistant hypertension had higher brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) levels confirming that they had increased intrathoracic blood volume [4].

Heart failure may aggravate sodium retention. Drugs that include fludrocortisone (mineralocorticoid receptor agonist), estrogens, and nonsteroidal antiinflammatory drugs (NSAIDS) [5] cause sodium retention and therefore are important renal causes of resistant hypertension.

Other renal mechanisms implicated in the pathogenesis of resistant hypertension include: increased renin-angiotensin-aldosterone system (RAAS) activity, increased renal sympathetic nervous system (SNS) activity, nitric oxide (NO) deficiency, oxidative stress, renal artery stenosis, hyperaldosteronism, obstructive sleep apnea and vasodilator medications (Table 1).

An important renal mechanism of resistant hypertension is renal artery stenosis. As first described by Goldblatt [6] in animal models, the reduction in renal perfusion pressure increases renin release by the kidney perfused by the stenosed artery. The ensuing increases in angiotensin II and aldosterone cause vasoconstriction and inappropriate renal salt retention. Moreover, the kidney downstream from the stenosis has a reduced renal perfusion pressure which is a further potent mechanism for salt retention. Numerous studies established the causal relationship between angiotensin II–mediated vasoconstriction and hypertension in the early phase of experimental renovascular hypertension [7, 8]. The high levels of angiotensin II stimulate the adrenal cortex to produce excessive aldosterone (secondary aldosteronism), promoting renal sodium retention by both kidneys. Moreover, angiotensin directly enhances renal salt and fluid reabsorption. Both the direct pressor effects of angiotensin II and the sodium retention restore the renal perfusion pressure at the stenosed kidney at the expense of systemic hypertension. However, during the chronic phase of experimental renovascular hypertension, which may be a better model for many patients with prolonged renal artery stenosis, plasma renin activity returns to baseline levels. The hypertension is sustained by hypertensive damage in the contralateral kidney. This may explain the disappointing results of controlled trials of renal revascularization of the stenosed kidney [9, 10]. The recently published STAR [11] trial, reported no overall benefit in renal function in patients with renal artery stenosis randomized to intervention, compared to the control group that received medication only. However, the number of antihypertensive medications taken by the patients was reduced after intervention. The CORAL [12] study is testing the effect of intervention for patients with renal artery stenosis on cardiovascular events, but it is not yet completed. Another trial, RAS-CAD [13] is studying the effect of medical therapy alone versus medical therapy plus renal artery stenting on left ventricular hypertrophy progression (primary end point) and cardiovascular morbidity and mortality (secondary end points) in patients affected by ischemic heart disease and renal artery stenosis.

Patients with bilateral renal artery stenosis are at an increased risk for developing severe renal salt retention. If the stenosis is unilateral, the unaffected kidney can eliminate the salt and water retained by the stenosed kidney via the pressure natriuresis mechanism. However, if both kidneys have a functional stenosis, the pressure natriuresis may be curtailed sufficiently to lead to episodic fluid retention that causes flash pulmonary edema.

Clues to the presence of bilateral renal artery stenosis in resistant hypertension include an abdominal bruit, atherosclerosis elsewhere, pulmonary edema with preserved ejection fraction and worsening renal function during therapy with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). Recurrent flash pulmonary edema due to bilateral renal artery stenosis

is dangerous for the patient and should prompt consideration of renal revascularization by angioplasty and stenting [14].

3. Renal Nerve Activation

Intense renal efferent nerve stimulation causes renal vasoconstriction with decreases in renal blood flow (RBF) and increases in renal vascular resistance (RVR). However, more subtle increases in renal nerve activity increase renal tubular sodium reabsorption and increase renin secretion without changes in renal hemodynamics [15]. Renal nerves make functional contact with many parts of the nephron including the tubules and the juxtaglomerular apparatus, where these effects are manifest. The effects of renal nerve stimulation on renin secretion are direct and not secondary to volume depletion or hemodynamic changes.

Renal denervation decreased blood pressure in many animal models of hypertension. But this may be a response to preventing renal nerve traffic from the kidney (deafferentation) and/or to the kidney (deefferentation).

The renal afferent sensory nerves are located primarily in the renal pelvic wall where they exhibit mechanosensitive (responding to increases in renal pelvic pressure) or chemosensitive (responding to changes in chemical composition of the urine) properties. Physiological stimulation of renal afferent mechanosensitive nerves by increasing ureteropelvic pressure increased afferent renal nerve activity and decreased efferent renal sympathetic nerve activity, resulting in a diuresis and natriuresis. This was termed the renorenal reflex [16]. Selective interruption of the afferent pathway has been achieved by removal of the kidney (presumed source of the signal) or section of the dorsal roots conveying afferent renal nerve input to the neuraxis (T9-L1). Dorsal root section reduced the blood pressure in rat models of renovascular hypertension, which testifies to the importance of the renal afferent nerves in maintaining hypertension in this setting.

Muscle sympathetic nerve activity and calf muscle vascular resistance were increased in patients with hypertension receiving hemodialysis therapy [17]. Bilateral nephrectomy abolished these changes. This important study identified the chronically diseased kidney as the source of afferent renal input resulting in increased muscle sympathetic nerve activity, calf vascular resistance, and hypertension.

A proof of concept study in 45 patients with resistant hypertension reported that renal sympathetic denervation by renal artery radiofrequency ablation reduced the BP by 24/10 mm Hg at 3 months and 29/16 mm Hg at 12 months [18]. It is not clear whether this remarkable effect of renal nerve ablation on reducing BP is due to deafferentation or deefferentation of the renal nerves, or a combination of those. Symplicity HTN-2 trial [19] assessed 106 patients with treatment-resistant hypertension (i.e., systolic blood pressure $\geq$160 mm Hg or $\geq$150 mm Hg for patients with diabetes despite the use of three or more antihypertensive drugs). Patients were randomly assigned to renal sympathetic denervation (52) or control (54) groups. Renal denervation resulted in impressive reductions in mean office-based measurements of blood pressure (32/12 mm Hg at 6 months), whereas blood pressure remained almost unchanged in the control group. Home and ambulatory measurements of blood pressure followed a similar pattern; the corresponding reductions were 20/12 mm Hg and 11/7 mm Hg with renal denervation, whereas no significant reductions were observed in the control group. However, there were several limitations of the study design. The control group could not undergo sham operation, which would have provided double-blinding and reduced potential bias. Furthermore, secondary and white-coat hypertensions were not defined as exclusion criteria.

The increase in renin secretion with renal nerve stimulation is mediated via beta-1 receptors and is therefore blocked by cardioselective and noncardioselective beta blockers. The increase in tubular reabsorption and renal vascular resistance are mediated via alpha receptors and are diminished by alpha blockers. Central agents such as clonidine reduce renal nerve activity and renin secretion. Thus, several drugs used to treat hypertension interrupt some of the renal mechanisms that underlie resistant hypertension.

4. Nitric Oxide Deficiency

Studies in rodents have established that inhibition of nitric oxide synthase (NOS) causes systemic and glomerular hypertension, glomerular ischemia, glomerulosclerosis, tubulointerstitial injury, and proteinuria [20].

Most evidence suggests a decreased total nitric oxide (NO) production in human renal disease and hypertension. NO deficiency occurs in the presence of oxidative stress, due both to inactivation of NO by superoxide anion and to uncoupling of nitric oxide synthase, which then produces superoxide rather than NO. There is evidence that oxidative stress occurs early in the course of CKD and hypertension and is amplified as the disease progresses [21].

Oxidative stress can precede the development of hypertension and cause nitric oxide (NO) deficiency [22]. In a study of patients with early essential hypertension, Wang et al. [21] reported severe endothelial dysfunction and inhibition of microvascular nitric oxide synthase accompanied by elevated plasma reactive oxygen species and elevated plasma levels of asymmetric dimethyl arginine that can inhibit and uncouple nitric oxide synthase [23].

In almost all rodent models of hypertension, there is oxidative stress that if corrected, lowers BP, whereas creation of oxidative stress in normal animals can cause hypertension. Reactive oxygen species (ROS) can enhance afferent arteriolar tone and reactivity both indirectly via potentiation of the tubuloglomerular feedback mechanism [24] and directly by microvascular mechanisms that diminish endothelium-derived relaxation factor/nitric oxide responses, generate a cyclooxygenase-2-dependent endothelial-derived contracting factor that activates thromboxane-prostanoid receptors, [25] and enhance vascular smooth muscle cells reactivity [26]. Drugs that improve NO activity in blood vessels include nebivolol, nitrates and bidil. The hydralazine component in

bidil may act as a vascular antioxidant that preserves the NO generated by the nitrate component. It has been used primarily to treat resistant heart failure in African Americans. In a randomized, placebo-controlled, double blind study involving six subjects, Oliver et al. [27] showed that the combination of phosphodiesterase type 5 inhibitor, sildenafil and isosorbide mononitrate decreased BP by 26/18 mm Hg as compared with placebo. However, it should not be forgotten that sildenafil has been considered to be contraindicated in patients taking nitrates. Therefore, further evidence will be needed before this new therapeutic combination can be recommended for treatment of hypertension.

5. Medications Acting Adversely on the Kidney

5.1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). NSAIDs are an important remediable cause of drug-resistant hypertension. They increase BP by an average of 5 mm Hg, but the effect can be more pronounced in resistant hypertension. They inhibit renal prostaglandin production, decrease renal blood flow and retain sodium [28]. They diminish the BP-lowering effect of all antihypertensive drug classes except calcium antagonists [29]. The effect of NSAIDs on BP is more pronounced in patients with CKD. Selective cyclo-oxygenase-2 inhibitors have effects generally similar to those of NSAIDs [30].

5.2. Glucocorticoids. Glucocorticoids such as prednisone induce a modest sodium and water retention but the mechanism by which they increase BP is uncertain [31]. Corticosteroids with mineralocorticoid effect (e.g., hydrocortisone, cortisone) produce significant fluid retention, but even agents without mineralocorticoid activity (e.g., dexamethasone, betamethasone, and triamcinolone) can exacerbate hypertension in susceptible subjects. Licorice, a common ingredient in oral tobacco products, can raise blood pressure by suppressing the metabolism of cortisol by beta hydroxysteroid dehydrogenase resulting in increased stimulation of the mineralocorticoid receptor [32].

5.3. Erythropoietin Stimulating Agents (ESA). Erythropoietin stimulating agents increased blood pressure in both normotensive and hypertensive patients with CKD. Epogen may raise BP by expanding blood volume, increasing the hematocrit and hence the viscosity of the blood and increasing vascular production of the vasoconstrictor prostaglandin, thromboxane. However, in studies in rats these prohypertensive effects of epogen were offset by increased NO generation in the endothelial cells of the kidney [33]. Since CKD impairs NO generation, this offsetting effect may be diminished and this may explain why the hypertensive effects of epogen are more pronounced in patients with CKD and hypertension [34].

5.4. Cyclosporine. As summarized in a Cochrane review, [35] cyclosporine, in lower doses (1–4 mg/kg/d) increases BP by an average of 5 mm Hg and in higher doses (>10 mg/kg/d) by 11 mm Hg. The mechanisms are not established and may include enhanced sympathetic nervous system activity, renal vasoconstriction, sodium/water retention, [36] impaired peripheral vasodilatation and decreased vascular compliance. Calcium channel blockers (CCBs) attenuate cyclosporine induced vasoconstriction [37]. Verapamil, diltiazem and the dihydropyridine nicardipine reduce the hepatic metabolism of cyclosporine, thereby increasing its blood level by 40–50%. Although some investigators have found this interaction beneficial as it leads to a reduction in the dose of cyclosporine, other investigators prefer nifedipine or isradapine, which have little effect on blood levels of cyclosporine or tacrolimus. Amlodipine has an intermediate effect on cyclosporine metabolism, and the dose does not usually need adjustment [38].

6. Extra Renal Factors Causing Salt Retention

6.1. Aldosterone. Aldosterone is secreted by the zona glomerulosa of the adrenal cortex under the influence of angiotensin II, potassium, metabolic acidosis and adrenocorticotropic hormone (ACTH). The genomic pathway for aldosterone action in tubular cells regulates the transport of sodium and potassium. Aldosterone binds to mineralocorticoid receptors in the cytoplasm of the principal cells of the collecting duct, which activate genes for specific protein synthesis. This results in an increase in apical epithelial sodium entry channels, basolateral sodium/potassium ATPase for cellular sodium extrusion and potassium entry, and apical ROMK channels for passive movement of cellular potassium into the lumen that facilitates K^+ secretion.

Thus, aldosterone promotes sodium reabsorption and potassium secretion by the collecting ducts. Recent studies have shown that aldosterone is important in resistant hypertension. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [39] of 1141 patients with resistant hypertension, 25 mg daily of spironolactone over 1.3 years decreased the mean systolic BP by 21.8 mm Hg and the diastolic BP by 9.5 mm Hg. Adverse effects included gynecomastia or breast tenderness (6%) and hyperkalemia (2%). In another study of patients with resistant hypertension (mean baseline BP 163/91 mm Hg), spironolactone decreased BP to a similar degree as the ASCOT trial. The decrements in systolic and diastolic BP were similar to patients with primary hyperaldosteronism [40] and were comparable in black and white patients. Although much of the antihypertensive effect is likely secondary to reduced sodium reabsorption, there is a nongenomic effect mediated through the action of spironolactone to block mineralocorticosteroid receptors on the cell membranes of blood vessels. Evidence for a nonrenal action comes from a study in which spironolactone (50 mg) twice daily reduced pre-dialysis systolic BP from 142 to 131 mm Hg in patients who had end stage renal disease (ESRD) [41]. These patients had anuria and therefore the effect of spironolactone must have been independent of changes in sodium balance by the kidneys. Moreover, aldosterone can injure the vascular endothelium, which could contribute to elevated BP. Amiloride is a potassium-sparing diuretic that can reduce BP and combat hypokalemia

in patients with resistant hypertension. Eplerenone is a more selective aldosterone antagonist than spironolactone and is a good choice for patients who have responded to spironolactone, but developed adverse effects of breast enlargement or loss of libido.

6.2. Vasodilatory Edema. Drug-induced edema with vasodilatory drugs can involve nonrenal mechanisms, including direct arteriolar dilatation (causing an increase in intracapillary pressure) in addition to stimulation of the RAAS and renal fluid retention. Vasodilatory edema is most commonly encountered with direct arteriolar dilators such as minoxidil or hydralazine, but also with dihydropyridine calcium antagonists and alpha-blockers. The addition of an ACE inhibitor or an ARB to a dihydropyridine calcium antagonist reduced vasodilatory edema, whereas the addition of a diuretic had little effect [42].

6.3. Obstructive Sleep Apnea (OSA). OSA causes intermittent hypoxemia and increased upper airway resistance that can increase sympathetic nervous system activity, [43] raise blood pressure and increase fluid retention. OSA has been associated with increased reactive oxygen species with concomitant reduction in nitric oxide bioavailability and with an increase in serum aldosterone [44]. A recent open-label study provided preliminary evidence that treatment with a mineralocorticoid receptor antagonist substantially reduced the severity of OSA [45]. Importantly this treatment also reduced the BP of these patients.

6.4. Endothelin Type A (ET-A) Receptor Antagonists. Circulating endothelin-1 is elevated in patients with essential hypertension [46]. The selective ET-A antagonist darusentan reduced mean office blood pressure (systolic/diastolic) by 18/10 mm Hg [47]. Adverse events of fluid retention and edema occurred in 14% of patients in the placebo group, 25% in the 50-mg group, 32% in the 100-mg group, and 25% in the 300-mg group. The mechanism of fluid retention is unclear, but may involve renal sodium retention. In a recent trial [48], darusentan decreased clinic systolic BP at 14 weeks by 15 mm hg ± 14 mm Hg as compared to guanfacine (12 ± 13 mm Hg; $P < .05$). However, analysis of ambulatory blood pressure concluded that darusentan reduced mean 24-hour systolic BP (9 ± 12 mm Hg) more than placebo (2 ± 12 mm Hg) or guanfacine (4 ± 12 mm Hg). Unfortunately, the study was considered to be negative because it did not meet the prespecified goal of reducing office blood pressure, although the drug did have a clear-cut effect in reducing ambulatory blood pressure, whether compared to placebo or to active control.

7. Excessive Salt Intake

Excessive dietary salt intake contributes to the development of resistant hypertension both by increasing blood pressure and by blunting the blood pressure lowering effects of most classes of antihypertensive agents, [49] including diuretics. These effects are more pronounced in some subjects who are termed salt-sensitive. Salt sensitivity is more common in the elderly, African Americans and in patients with CKD. Among patients referred to a university hypertension center for resistant hypertension, the average dietary salt ingestion based on 24-hour urinary sodium excretion exceeded 10 g or (230 mmol of sodium) a day [50].

Sodium intake should be assessed from sodium excretion in a 24-hour urine collection. Urine sodium: creatinine ratio is inaccurate since sodium excretion varies during the day. Dietary sodium reduction to less than 3 g/day is associated with modest BP reductions, which are larger in African-American and elderly patients. Current guidelines suggest that dietary sodium for a hypertensive patient should be less than 100 mmol/day (2.4 g sodium or 6 g sodium chloride) [51]. This guideline is applicable to all patients with resistant hypertension. Pimenta et al. [52] randomized twelve subjects with resistant hypertension to low versus high sodium diet (50 versus 250 mmol daily for 7 days). The low compared to the high salt diet decreased office systolic and diastolic blood pressure by 22.7 and 9.1 mm Hg, respectively. Further reductions in dietary salt can produce further antihypertensive effects, but are not usually practicable.

8. Ineffective Diuretic Usage

The correct use of diuretics is a critical step in the management of resistant hypertension. Diuretics not only reduce ECF volume but also potentiate the effects of ACE inhibitors, ARBs, and other antihypertensive agents. Based on the results of the ALLHAT trial, JNC 7 recommended thiazide diuretics as preferred agents in the general population with essential hypertension to lower blood pressure and reduce CVD risk [51].

There are three major classes of diuretics: thiazides, loop diuretics, and potassium-sparing agents. The choice of diuretic agents depends on the level of GFR, electrolyte status and the degree of ECV expansion [53].

Thiazide diuretics inhibit the apical Na^+-Cl^- cotransport system in the first part of the distal tubule. Thiazides given once daily are recommended in patients with GFR ≥ 30 mL/min/1.73 m^2. Chlorthalidone was used in a dose range of 12.5 to 25 mg/d in the ALLHAT trial. It is longer-acting than hydrochlorothiazide (HCTZ), resulting in better blood pressure control, but also a higher incidence of hypokalemia. A small study of patients with resistant hypertension demonstrated that switching from the same dose of hydrochlorothiazide to chlorthalidone resulted in an additional 8 mm Hg drop in systolic BP and increased the number of subjects at goal [54]. Chlorthalidone in a daily dose of 25 mg provided greater ambulatory BP reduction, with the larger difference occurring overnight compared with hydrochlorothiazide 50 mg [55].

Thiazides become more effective in subjects accommodated to loop diuretics likely because of functional and structural hypertrophy of the early distal tubule. Thus, this segment becomes of great importance for sodium reabsorption and thiazide drugs acting at this site therefore have increased natriuretic efficacy [56]. However, any increase in

sodium chloride (NaCl) delivery to the collecting duct can increase distal sodium retention via the epithelia sodium channel (ENaC) which enhances the luminal electronegative potential and therefore enhances potassium (K^+) secretion. This can be countered by use of a distal, potassium-sparing diuretic or a mineralocorticosteroid antagonist.

Metolazone and thiazide diuretics retain some effectiveness at GFR levels below 30 mL/min/1.73 m^2. Metolazone is used primarily for resistant edema in patients receiving loop diuretics.

If blood pressure control worsens, or if volume expansion occurs as CKD progresses during treatment with a thiazide diuretic, a loop diuretic should be substituted [57]. Furosemide or bumetanide should be given twice daily, as they have short durations of actions of 3 to 6 hours, although these are increased in patients with renal impairment [58]. Torsemide is longer acting and is eliminated by hepatic metabolism. Therefore, it does not accumulate in renal insufficiency. It may be preferable with patients with CKD. The natriuretic effects of loop diuretics are offset by post-diuretic sodium retention [59]. Patients with advanced CKD (GFR <30 mL/min) who are unresponsive to thiazide alone have a marked natriuresis when a loop diuretic is added, [60] probably by blockade of enhanced distal tubular Na^+ reabsorption. However, such combination therapy should be initiated under close surveillance because of a high incidence of hypokalemia, excessive ECV depletion, and azotemia [61].

There are two principal classes of potassium-sparing diuretics, those that inhibit epithelial sodium channels (triamterene and amiloride) and those that inhibit mineralocorticoid receptors (aldosterone and eplerenone). For both types, the site of action is in the collecting tubule.

The role of spironolactone in resistant hypertension [62] was discussed earlier. Addition of spironolactone to therapy with other diuretics should always be considered in patients with drug-resistant hypertension providing that there is no hyperkalemia. Serum potassium must be monitored regularly during drug therapy. If adverse effects such as gynecomastia or breast tenderness develop, eplerenone should be substituted as it lacks progesterogenic and antiandrogenic effects. A combination of HCTZ/Triamterene or HCTZ/Amiloride is very effective [63], produces less hypokalemia than HCTZ alone and should be considered in patients with a GFR of >30 mL/min/1.73 m^2. Hood et al. [64], crossed over 51 patients with primary hyperaldosteronism between normal and high-dose therapy with bendroflumethazide, amiloride or spironolactone. Remarkably, when used at high-dose, the drugs were equally effective in reducing the blood pressure.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 598694, 10 pages
doi:10.4061/2011/598694

Review Article

Resistant Hypertension Workup and Approach to Treatment

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Received 30 September 2010; Accepted 18 November 2010

Academic Editor: Konstantinos Tsioufis

Resistant hypertension is defined as blood pressure above the patient's goal despite the use of 3 or more antihypertensive agents from different classes at optimal doses, one of which should ideally be a diuretic. Evaluation of patients with resistive hypertension should first confirm that they have true resistant hypertension by ruling out or correcting factors associated with pseudoresistance such as white coat hypertension, suboptimal blood pressure measurement technique, poor adherence to prescribed medication, suboptimal dosing of antihypertensive agents or inappropriate combinations, the white coat effect, and clinical inertia. Management includes lifestyle and dietary modification, elimination of medications contributing to resistance, and evaluation of potential secondary causes of hypertension. Pharmacological treatment should be tailored to the patient's profile and focus on the causative pathway of resistance. Patients with uncontrolled hypertension despite receiving an optimal therapy are candidates for newer interventional therapies such as carotid baroreceptor stimulation and renal denervation.

1. Introduction

Hypertension is the most common chronic disease in the developed world affecting up to 25% of the adult population [1]. It remains the most important modifiable risk factor for coronary heart disease, stroke, congestive heart failure, renal disease, and peripheral vascular disease. Suboptimal blood pressure control is responsible for 62% of cerebrovascular disease, 49% of ischemic heart disease, and an estimated 7.1 million deaths a year [2]. Because of the associated morbidity, mortality and economic cost to society early diagnosis and treatment within the established guidelines is imperative. A sizeable percentage of the hypertensive population does not manage to achieve adequate control in spite of receiving 3 or more antihypertensive medications. These are the patients with resistant hypertension.

Resistant hypertension is defined by the Joint National Committee 7 as blood pressure that is above the patient's goal despite the use of 3 or more antihypertensive agents from different classes at optimal doses, one of which should ideally be a diuretic [3]. Patients whose blood pressure is controlled but require 4 or more medications to do so should also be considered resistant to treatment. However, the definition does not include newly diagnosed hypertensives. Resistant hypertension is not synonymous with uncontrolled hypertension. The latter includes both patients with inadequately treated blood pressure due to poor adherence or inadequate treatment, as well as those with true resistant hypertension [3, 4]. The importance of resistant hypertension lies in the identification of patients who are at high risk of suffering complications from reversible causes of hypertension and patients who may benefit from a particular diagnostic or therapeutic approach [3].

The exact prevalence of resistant hypertension is unknown, in part because of its arbitrary definition. However, small studies estimate prevalence from 5% in general medical practice up to 50% in nephrology clinics [5]. In a prospective analysis of Framingham study data, a higher baseline systolic blood pressure along with older age, the presence of LVH and obesity (BMI $> 30\,kg/m^2$) were the strongest predictors of lack of blood pressure control [6, 7]. Results were similar in ALLHAT where the older, obese patients with higher baseline systolic blood pressure and LVH required 2 or more antihypertensive agents [8]. The strongest predictor

however was serum creatinine over 1.5 mg/dL. Other patient characteristics associated with resistant hypertension include excessive salt ingestion, diabetes, black race, and female gender. Both studies showed greater difficulty in controlling systolic blood pressure compared to diastolic. Up to 92% of patients achieved target diastolic blood pressure while only 60%–67% achieved systolic blood pressure goals [6, 8]. It is likely that this condition will become increasingly common because of the aging population and a progressive increase in obesity and comorbidities such as diabetes.

There are also a few studies implicating gene mutations. A Finnish study found that certain variants of the β and γ subunits of the epithelial sodium channel gene ENaC were significantly more prevalent in patients with resistant hypertension [9]. Other studies associate the allele of the CYP3A5*1 enzyme with both higher blood pressure levels in normotensive people of black race, as well as with hypertension resistant to treatment [10, 11]. This particular enzyme is involved in the metabolism of cortisol and corticosterone. These and other genes that may be identified in the future hold the potential for the development of novel therapeutic targets.

2. Pseudoresistance Evaluation

The workup of patients with suspected resistant hypertension is summed up in Table 3.

The first step in evaluating a patient with uncontrolled blood pressure is to establish whether it is a case of true resistant hypertension or just pseudoresistance. The latter refers to a lack of blood pressure control despite receiving treatment without true resistance. This can be caused by easily reversible causes such as suboptimal blood pressure measurement technique, poor adherence to prescribed medication, suboptimal dosing of antihypertensive agents or inappropriate combinations, the white coat effect, and clinical inertia. It is important to exclude these causes before labeling a patient as having resistant hypertension.

Poor blood pressure measurement technique is quite common, usually the result of not letting the patient rest before measurement and using a small cuff [12]. Patients should always rest in a chair with their back supported for a minimum 5 minutes prior to measurement and the cuff's air bladder must encircle at least 80% of the arm circumference. The average of two readings taken a minute apart represents the patient's blood pressure.

Approximately 40% of newly diagnosed patients will discontinue their antihypertensive medication the first year of treatment [13, 14]. Eventually, less than 40% will continue taking their medication after 5 to 10 years [13, 15]. The most common causes are poor patient-physician communication concerning blood pressure goals and the importance of achieving them, potential side effects, high cost of treatment, and complex regimens [16, 17]. Adherence can be improved by choosing affordable agents with minimal side effects that are given once daily alone or in fixed dose combinations. Older patients with memory deficits or psychiatric illness can benefit from using pill boxes.

Clinical inertia can be described as a physician's ignorance of treatment guidelines or reluctance to adhere to them due to lack of training or inexperience in antihypertensive medication, underestimation of cardiovascular risk, and overestimation of the treatment provided [18, 19]. This results in suboptimal dosing or inappropriate combinations of agents. A large part of this problem could be resolved if physicians familiarize themselves with one or two drugs in each class of antihypertensives. Proper training is imperative so that physicians realize the importance of treating to reach a goal blood pressure level of less than 140/90 mmHg and knowing when to refer patients to a hypertension specialist.

A white coat effect should be suspected in patients whose clinical blood pressure measurements are consistently and significantly higher than reliable out of office measurements. Other signs include repetitive symptoms of overtreatment such as orthostatic hypotension and persistent fatigue as well as absence of target organ damage including left ventricular hypertrophy, retinopathy, and chronic kidney disease [20, 21]. These cases must be confirmed with 24-hour ambulatory blood pressure monitoring. One study found that 20 to 30% of a patient population believed to have resistant hypertension was actually well controlled when measured by 24-hour ambulatory blood pressure monitoring [22]. Accurate home blood pressure values are the best guide for therapy. In elderly patients, especially diabetics, arterial stiffness may cause pseudoresistance because less compressible arteries cause falsely elevated blood pressure [23].

3. Concomitant Conditions

As was previously mentioned, obesity is associated with resistant hypertension. Obese patients have increased sympathetic activity, higher cardiac output, and a rise in peripheral vascular resistance due to reduced endothelium-dependent vasodilation. Plasma aldosterone and endothelin are also increased, while excessive surrounding adipose tissue results in increased intrarenal pressures and changes in renal architecture [24]. As the body mass index increases, progressively higher doses of antihypertensive drugs are required to control blood pressure [25]. Weight loss has been found to reduce both systolic and diastolic blood pressure [3, 26].

Another common concomitant condition in hypertensive patients is diabetes. Insulin resistance increases sympathetic nervous activity, vascular smooth muscle cell proliferation, and sodium retention leading to elevated blood pressure resistant to treatment [3]. The common comorbidities of obesity, hypertension, and diabetes induce renal dysfunction, further hindering blood pressure treatment.

Dietary factors include increased salt and alcohol consumption. Although small amounts of alcohol (2 drinks/day) have vasodilating effects and may lower blood pressure, consumption of more than 30 mL daily raises blood pressure and may increase cardiovascular risk. Older patients, patients of African origin, and patients with chronic kidney disease are particularly susceptible to salt intake [3]. Current guidelines

recommend that dietary sodium for a hypertensive person should be under 100 mmol/day (2.4 g sodium or 6 g sodium chloride) and even lower in salt sensitive patients [27]. Excessive salt intake can be assessed by measuring sodium excretion in a 24-hour urine collection.

Several common medications can cause elevated blood pressure and hinder treatment. Perhaps the most common are nonsteroidal anti-inflammatories including COX-2 inhibitors and aspirin, decongestants (phenylephrine and pseudoephedrine), stimulant agents used for weight loss, narcolepsy or attention deficit disorder, contraceptives, cyclosporine, and erythropoietin [3]. Corticosteroids increase blood pressure through fluid retention, particularly but not limited to those with increased mineralocorticoid activity. Licorice and herbal medication that contains stimulants such as ephedra can also cause hypertension.

4. Assessment of Secondary Causes of Hypertension

Secondary causes of hypertension are common in patients with resistant hypertension, particularly in the elderly. These include obstructive sleep apnea, renal parenchymal disease, renal artery stenosis, and primary aldosteronism [28, 29] (Table 1).

Obstructive sleep apnea is particularly frequent in patients with resistant hypertension. A small study of 41 patients with resistant hypertension discovered that 83% suffered from sleep apnea [30]. The severity of sleep apnea is positively associated with the likelihood of resistant hypertension [31, 32]. Several mechanisms are believed to contribute to this effect. Intermittent hypoxemia and increased upper airway resistance induce a sustained increase in sympathetic nervous system activity [33, 34]. Also, there seems to be a significantly higher prevalence of primary aldosteronism in patients with sleep apnea [35, 36]. Alternatively, obesity may be the common factor that increases risk for both obstructive sleep apnea and excess aldosterone production [35]. A sleep study is indicated in patients with resistant hypertension and other signs and symptoms of sleep apnea including obesity, large neck size, excessive loud snoring, interrupted sleep, daytime somnolence, polycythemia, and carbon dioxide retention [37, 38]. Treatment with a continuous positive airway pressure device (CPAP) has been shown to reduce blood pressure and thus is beneficial in resistant hypertension patients with obstructive sleep apnea [3].

The recent studies suggest that primary aldosteronism is a much more common cause of hypertension than originally believed. Particularly in patients with resistant hypertension, the prevalence of primary aldosteronism has been found between 10% and 20% [3, 39, 40]. Aldosterone exerts a number of effects leading to increased systemic vascular resistance, such as endothelial dysfunction, vascular remodeling through collagen deposition, vascular damage, impairment of the baroreflex leading to loss of compensation for elevated blood pressure, and hypovolemia [41–43]. It has been suggested that obesity is involved, causing a generalized activation of the renin-angiotensin-aldosterone system, perhaps through excretion of cytokines from adipocytes [44, 45].

Table 1: Causes of resistant hypertension.

Exogenous substances
Drug related (see Table 2)
Herbal preparations (licorice, ephedra, ginseng, yohimbine, ma huang, and bitter orange)
Alcohol consumption
Excess sodium intake
Concomitant conditions
Obesity
Insulin resistance
Smoking
Pseudoresistance
White-coat hypertension
Pseudohypertension in the elderly
Measurement artifact
Physician inertia
Secondary causes of hypertension
(i) Common causes
Renovascular disease
Renal parenchymal disease
Primary aldosteronism
Pheochromocytoma
Cushing syndrome
Thyroid and parathyroid disease
Coarctation of the aorta
(ii) Rare causes
Aneurysm located at the bifurcation of the right renal artery
Arterial thrombosis from abdominal aorta to both common iliac arteries
Occlusion of the left renal artery
Hypercalcemia
Carcinoid syndrome
Central nervous system tumors
Premenstrual syndrome

Primary aldosteronism may be suggested by hypokalemia; however this is often a late manifestation preceded by the development of hypertension [46–48]. Screening should be done with plasma renin and serum aldosterone ratio measurement (which has a high sensitivity but low specificity) and confirmed with sodium loading or fludrocortisone suppression testing [39, 49].

Renal parenchymal disease is both a cause and a complication of poorly controlled hypertension [50, 51]. As was previously mentioned, in ALLHAT serum creatinine above 1.5 mg/dL was the strongest predictor of failure to achieve goal blood pressure [8]. Resistant hypertension in chronic kidney disease is mainly due to activation of the renin-angiotensin system, sodium retention, and the resulting intravascular volume expansion [52]. Other factors include activation of the sympathetic nervous system due to decreased blood flow to the kidney, alterations in vasoconstrictor and vasodilator excretion from the endothelium, and increased arterial stiffness [52].

Table 2: Drug related causes of resistant hypertension.

Drug-related causes
Nonadherence
Suboptimal medication regimen
Inappropriate combinations
Drug actions and interactions
(i) Drugs that regularly raise blood pressure:
Anabolic steroids
Sympathomimetic amines (midodrine)
Cocaine
Nicotine
(ii) Drugs that often raise blood pressure:
Ethanol (in excess)
Corticosteroids
Cyclosporin
Erythropoietin
Anorectics
NSAIDs including COX-2 inhibitors
Ergot alkaloids
(iii) Drugs that occasionally raise blood pressure:
Caffeine
Phenothiazines
Tricyclics
Oral contraceptives
(iv) Drugs that cause hypertension on withdrawal:
Clonidine
B-blockers
(v) Drugs that cause hypertension by interaction:
MAOIs

Table 3: Resistant hypertension workup.

Identify and correct pseudoresistance
(i) Perform proper measurements of blood pressure.
(ii) Evaluate white coat hypertension with reliable home or 24-hour blood pressure measurements.
(iii) Evaluate patient adherence and improve it with education, prescription of the least costly effective drug regimen with the fewest potential adverse effects. Prefer once daily fixed-dose combination products.
Lifestyle modifications
(i) Ask the patient about use of any pharmacological/herbal substances that may increase blood pressure.
(ii) Evaluate of the amount of alcohol intake.
(iii) Evaluate dietary salt intake and recommend sodium restriction to <100 mmol (2.4 g) per day.
(iv) Assess the degree of obesity, abdominal obesity, and physical activity and recommend weight reduction and regular aerobic exercise (at least 30 min/day, most days of the week).
Identify factors contributing to true resistance
(i) Evaluate renal function with estimation of glomerular filtration rate and modify treatment accordingly.
(ii) Search for causes of secondary hypertension
Tailor treatment according to patient characteristics using optimal doses of appropriate medications. If all fails refer to hypertension specialist.

Renal artery stenosis is a relatively common finding in hypertensive patients undergoing cardiac catheterization with approximately 20% of patients having unilateral or bilateral stenosis above 70% [53]. However the causative role of these stenosis in hypertension remains unknown since only a few patients actually benefit from surgical or endovascular revascularization [54, 55]. The majority of cases (90%) are due to atherosclerotic lesions and are seen in older patients, smokers, patients with known atherosclerotic disease and unexplained renal insufficiency [56]. The other 10% are fibromuscular lesions, commonly in women under 50 years of age, and these are the patients that will usually improve blood pressure control after revascularization [3]. Bilateral renal artery stenosis should be suspected in patients with a history of "flash" pulmonary edema with preserved systolic heart function. Screening can be done using magnetic resonance angiography (MRA), computer tomographic angiography (CTA), Doppler ultrasonography, or angiotensin converting enzyme (ACE) inhibitor renography [49, 57].

Pheochromocytoma is a rare cause of resistant hypertension with a prevalence of 0.1%–0.6% among hypertensives [58, 59]. The average time between initial symptoms and diagnosis is 3 years, and many cases are missed altogether according to autopsy studies [60]. Clinical signs include episodic headaches, palpitations, and sweating. The best screening test for pheochromocytoma is 24-hour urinary metanephrines or plasma free metanephrines (normetanephrine and metanephrine) which carries a 99% sensitivity and an 89% specificity [61].

Hypertension is a common manifestation of Cushing's syndrome. Up to 90% of patients are hypertensive and 17% have resistant hypertension [62, 63]. The primary mechanism is increased mineralocorticoid activity that leads to increased intravascular volume [64]. However, other factors such as obstructive sleep apnea and insulin resistance also contribute substantially [65, 66]. Target organ damage in Cushing's syndrome is more severe than in primary hypertension because it is associated with many other cardiovascular risk factors such as diabetes, obstructive sleep apnea, obesity, and dyslipidemia [67, 68].

Thyroid and parathyroid dysfunction are common reversible causes of secondary hypertension. Patients with hyperthyroidism usually present with systolic hypertension and those with hypothyroidism have diastolic hypertension. Most patients with primary hyperparathyroidism are diagnosed because of routine findings of hypercalcemia [69, Table 1-2].

5. Pharmacological Treatment

Pharmacological treatment should be based on the most common causes of resistant hypertension and focused on blocking all the physiological pathways to blood pressure elevation [18, 70]. Antihypertensive agent doses should be titrated upward until blood pressure is controlled or the maximum recommended dosage is reached, unless the patient experiences dose related adverse effects. It is then appropriate to add a drug from another class that has additive or synergistic effects with the first drug. In general, a typical regimen should include a diuretic, an ACE inhibitor

or angiotensin receptor blocker (ARB), a calcium channel blocker (CCB), and a β-blocker.

The timing of medication administration can also affect blood pressure control. Switching one of 3 or more medications from morning to bedtime administration can result normalization of blood pressure in 21.7%–37% of patients [71, 72]. This is particularly important in nondippers. Since volume overload is the most frequent underlying pathophysiology and suboptimal dosing the most frequent cause of resistant hypertension, adding, increasing or changing diuretic therapy is the key to successful treatment and will help over 60% of patients achieve target blood pressure [18, 73–77].

Patients with normal kidney function should receive 12.5–25 mg/day of hydrochlorothiazide although some will benefit from doses up to 50 mg/day [73]. Chlorthalidone at 25 mg/day is an alternative that offers greater 24-hour blood pressure reduction than 50 mg/day hydrochlorothiazide with the greatest difference occurring overnight and may be preferred in certain patients with resistant hypertension [78]. When given at the same dose as hydrochlorothiazide, chlorthalidone will reduce blood pressure an additional 8 mmHg according to a small study [79]. Patients should be monitored for hyponatremia and hypokalemia, and caution is warranted in patients with a history of prediabetes and gout. A common pitfall is not realizing that the patient's kidney function is deteriorating and not switching diuretic class when it does. Thiazide diuretics are not effective in chronic kidney disease. Therefore, they must be replaced with loop diuretics when the estimated glomerular filtration rate (eGFR) falls below 40 mL/min/1.73 m^2 [27, 73, 80]. In a study of 12 elderly patients with hypertension whose blood pressure was uncontrolled on multidrug regimens the use of furosemide significantly improved blood pressure control [81]. Furosemide and bumetanide have a relatively short half-life and should be dosed twice daily in order to avoid reactive sodium retention due to intermittent natriuresis and consequent activation of the renin-angiotensin system [73, 80, 82].

When optimal diuresis fails, other medications should be considered. Since subclinical aldosteronism is a common occurrence in resistant hypertension, low doses of spironolactone (25–50 mg/day) or eplerenone can be particularly helpful. Patients most expected to benefit from mineralocorticoid blockade include those with primary hyperaldosteronism, the obese, and those suffering from obstructive sleep apnea. According to one study, the addition of spironolactone 12.5–25 mg/day to 76 patients with uncontrolled hypertension taking an average of 4 antihypertensive agents resulted in an average 25/12 mmHg reduction after 6 months [83]. The blood pressure lowering arm of the ASCOT study had similar results for patients who were unselected for aldosterone/plasma renin activity. When spironolactone was added as a fourth line agent, blood pressure dropped by 21.9/9.5 mmHg. At this dosage spironolactone is safe, well tolerated and provides significant additive blood pressure reduction [84, 85]. Eplerenone may be more suitable for patients requiring spironolactone doses above 25 mg/day because breast tenderness is a common adverse effect at higher doses [86]. Hyperkalemia is another risk that must be monitored.

Amiloride is an alternative indirect aldosterone antagonist that is better tolerated than spironolactone. One small study found that the addition of 2.5 mg/day amiloride decreased blood pressure by 31/15 mmHg [40]. However, it has been shown that 10 mg of amiloride has half the blood pressure reduction capability of 25 mg spironolactone and therefore should be considered only when spironolactone is not tolerated [87].

Blockade of the renin angiotensin system with ACE inhibitors or ARBs in patients that are intolerant of ACE inhibitors is particularly recommended in patients with diabetes mellitus, heart failure, postmyocardial infarction, chronic kidney disease, high coronary disease risk, and recurrent stroke prevention [27, 88]. Dosage should be increased to the maximum recommended dosage as long serum creatinine does not increase more than 35% above baseline and hyperkalemia does not develop [1–11]. Dual ACE and ARB therapy is no longer recommended in most cases because of the possibility of adverse renal outcomes [89, 90].

Aliskiren, the only available direct renin inhibitor, is at least as effective as ARBs in reducing end target organ damage but has not been directly tested in resistant hypertension. The ALLAY trial showed that aliskiren monotherapy was as effective as losartan in reducing LVMI, although the combination of both did not achieve a statistically significant further LVMI regression [91]. The addition of aliskiren to losartan did however seem to have additional renoprotective effects in another study, reducing the mean urinary albumin creatinine ratio by 20% in patients with diabetic nephropathy [92]. The additional blood pressure reduction was marginal and therefore the role of direct rennin inhibitors in resistant hypertension remains undetermined.

Polypharmacy is difficult to avoid because blood pressure can be controlled by using one drug in only about 50% of patients. Fixed dose combinations offer the convenience of taking fewer pills, combining antihypertensive agents with additive or synergistic effect and reducing dose-dependant adverse effects of individual components. The latter is evident in ACE inhibitor or ARB combinations with CCBs, as the ACE inhibitors/ARBs reduce the peripheral edema that frequently develops with dihydropyridine calcium channel blocker therapy. Another popular fixed dose combination with synergistic effects is ACE inhibitors/ARBs with diuretics, since the latter enhance the antihypertensive efficacy of all the other classes. The recent introduction of triple agent combinations containing dihydropyridine CCBs as well is expected to lessen the burden of polypharmacy and further improve adherence [86].

CCBs are particularly indicated in black and elderly patients. The ACCOMPLISH study suggested that combining ACE inhibitors with CCBs was more effective at preventing major cardiovascular and renal events than ACE inhibitors with diuretics despite achieving similar blood pressure control rates [93]. Both regimens are available as fixed dose combinations and are useful options in different

circumstances. In cases of true resistant hypertension, there are also data to support adding a complementary non dihydropyridine CCB to a regimen including a RAS blocker, diuretic, and dihydropyridine CCB. Such a combination of complementary CCBs results in additive BP reduction with a low-side effect profile and makes pharmacological sense [94, 95].

Beta-blockers are indicated in the setting of coronary artery disease, congestive heart failure, and postmyocardial infarction. When adding on combinations already including a diuretic, an ACE inhibitor or ARB and a calcium channel blocker, vasodilating β-blockers should be preferred [73, 96]. Beta-blockers as well as loop diuretics are also usually necessary when administering direct vasodilators to overcome the reflex tachycardia and fluid retention, respectively [97]. If BP control is still not achieved with full doses of a 4-drug combination, use of other agents such as centrally acting alpha-agonists (methyldopa and clonidine) or vasodilators (hydralazine or minoxidil) is needed. These agents are very effective for lowering BP but have poor tolerability, require frequent dosing, and lack positive outcome data [27]. At this stage, the intervention of a hypertension specialist is warranted. Besides these established treatments, new antihypertensive agents are being developed.

Endothelin receptor antagonists are a new family of antihypertensive medications that are currently being evaluated. Darusentan is a selective antagonist for type A endothelin receptors, activation of which causes vasoconstriction and proliferation of vascular smooth muscle [98]. It has demonstrated significant dose-dependant reductions in both systolic and diastolic blood pressures and has been positively evaluated in resistant hypertension [98, 99]. Unfortunately, another unpublished phase 3 clinical trial failed to meet its coprimary end point and the drug's future remains uncertain [100]. Atrasentan is another highly selective endothelin receptor antagonist that has shown positive results in blood pressure reduction for 72 patients [101]. Interestingly, it also had a positive influence on the patients metabolic profile. Another promising category under development is medication that combines inhibitors of vasoconstrictive mediators with drugs that potentiate vasodilating mediators by inhibiting their breakdown by neutral endopeptidases (NEPs). Omapatrilat is such an agent that has been evaluated favorably in the OCTAVE trial [102]. Vaccines targeting angiotensin I and II are also being developed and tested [103, 104].

In any case, treatment should be tailored to the patient's profile, lifestyle, and comorbidities. Constructing a regimen that is acceptable to the patient, well tolerated and will maintain long-term compliance is important. Yet in some patients, optimal blood pressure control will not be achieved even with the most carefully designed regimen. In these cases, new device-based approaches for blood pressure control are being evaluated (Tables 1 and 2).

One of these devices is the Rheos device (CVRx, Maple Grove, Minn) which stimulates the carotid baroreceptors for better blood pressure control by taking advantage of chronic electrical activation of the afferent limb of the carotid baroreflex. The device consists of a pulse generator and bilateral perivascular carotid sinus leads that are implanted under narcotic anesthesia. According to the findings from the Device-Based Therapy of Hypertension (DEBuT-HT) study that were recently presented, after four years of treatment, Rheos reduced systolic blood pressure by an average of 53 mmHg (193 mmHg versus 140 mmHg). Blood pressure was reduced significantly each year, with the largest decrease occurring in year four. Many of these patients were able to reach their blood pressure goal and reduce the number of medications that patients were taking to treat their hypertension from an average of 5 at baseline to 3.4 medications at 4 years. Baroreflex activation therapy also improved functional capacity and reduced left ventricular mass without any evidence of carotid injury or stenosis [105].

Another target for the interventional treatment of resistant hypertension is catheter-based renal nerve ablation. Renal sensory afferent nerve activity directly influences sympathetic outflow to the kidneys and other highly innervated organs involved in cardiovascular control, such as the heart and peripheral blood vessels, by modulating posterior hypothalamic activity [106, 107]. All these components are stimulated in hypertension and contribute to blood pressure elevation.

Renal sympathetic nerve ablation is achieved percutaneously via the lumen of the renal artery, using a catheter connected to a radiofrequency generator. Treatment has been administered to 45 patients with resistant hypertension taking a median of 4.7 antihypertensive agents. Followup at 1 and 2 years has shown a sustained blood pressure reduction of 27/11 mmHg [108, 109]. The multicentre Simplicity HTN-1 study that was recently presented at the European Society of Hypertension's 20th meeting included 108 patients with persistently elevated blood pressure despite treatment with an average of five medications. Catheter-based renal denervation produced a mean blood pressure reduction of 33/15 mmHg at 24 months without evidence of vascular or renal abnormalities. Results from the Simplicity HTN-2 study comparing renal denervation treatment to rigorous medical therapy are expected by the end of 2010.

6. Conclusions

Resistant hypertension remains a challenging clinical problem that will increasingly become more common. Causes of resistance should be considered when blood pressure does not respond satisfactorily to a rational triple antihypertensive regimen that includes a diuretic. The workup of patients with resistive hypertension should be a two-step approach (Table 3): first, confirmation that it is indeed true resistant hypertension by ruling out or correcting factors associated with pseudoresistance, and second, identification of the true factors involved in treatment resistance. The cornerstone of therapy remains a rigorous evaluation followed by correction of contributing causes and appropriate pharmacological treatment. Newer interventional therapies may become a viable option in the future for those patients with uncontrolled hypertension despite receiving an optimal multiple

medication antihypertensive regimen and those who cannot tolerate the medication.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 285612, 4 pages
doi:10.4061/2011/285612

Review Article

Ambulatory Blood Pressure Monitoring in Resistant Hypertension

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Received 4 October 2010; Revised 23 December 2010; Accepted 18 January 2011

Academic Editor: Alan Gradman

ABPM constitutes a valuable tool in the diagnosis of RH. The identification of white coat RH and masked hypertension (which may fulfill or not the definition of RH) is of great importance in the clinical management of such patients. Moreover, the various ABPM components such as average BP values, circadian BP variability patterns, and ambulatory BP-derived indices, such as ambulatory arterial stiffness index (AASI), add significantly to the risk stratification of RH. Lastly, ABPM may indicate the need for implementation of specific therapeutic strategies, such as chronotherapy, that is, administration-time dependent therapy, and the evaluation of their efficacy.

1. Introduction

Ambulatory blood pressure monitoring (ABPM) is the method of obtaining automated brachial blood pressure (BP) measurements at fixed time intervals, during a 24-hour period away from a medical environment. This represents a more "realistic" approach to BP assessment since it involves BP measurement during the usual daily activities and sleep. In this sense, the overall haemodynamic load and BP variability is more accurately estimated. Numerous studies have shown that ambulatory BP compared to office BP is more reproducible and superior in predicting target organ damage and incidence of cardiovascular events in both the general hypertensive population and in subjects with chronic kidney disease [1, 2]. All these advantages of ambulatory BP in comparison to office BP, along with the ability to identify the white coat phenomenon, that is, the combination of increased office BP with normal ambulatory BP, and masked hypertension, that is, the combination of normal office BP with increased ambulatory BP, resulted in the transition of ABPM from a research tool to a clinical modality.

The indications for ABPM in the clinical management of hypertensives include among others the resistance to treatment [3]. This has been defined as BP above goal despite the use of three agents of different classes in optimal doses, ideally including a diuretic. More recently hypertension controlled with four or more agents has been proposed to be included in the spectrum of resistant hypertension [4]. Although the prognosis of resistant hypertension (RH) is inadequately substantiated in the literature due to lack of sufficiently powered studies, there is plenty of evidence relating target organ damage and cardiovascular outcomes to BP levels. Uncontrolled BP along with a clustering of other risk factors is a harbinger of poor outcome in RH. Consequently, ABPM has implications in both the diagnosis and management of RH.

2. ABPM As a Tool for the Diagnosis of Resistant Hypertension

One of the crucial points in the identification of RH as a unique hypertension-related phenomenon that warrants special management is the distinction of true RH from "pseudoresistance" [3]. The latter term is used to describe clinical situations with increased BP readings because of

improper BP measurement technique, heavily calcified arteries, white coat effect, and lack of compliance to the prescribed medication. White coat RH, a phenomenon that is characterized by elevated office BP but normal ambulatory and home BP [2] ranges from 25 to over 50% in subjects with apparent resistance to treatment [5–7].

Muxfeldt et al., in a cohort of 286 hypertensive subjects with uncontrolled BP, found that 43.7% had white coat RH, (office BP > 140/90 mmHg and daytime BP < 135/85 mmHg) and less target organ damage compared to the true resistant hypertensives [6]. In support, Pierdomenico et al. [7] in a cohort of 742 treated hypertensive subjects, 426 apparently responders and 276 apparently resistant, found that 126 subjects (29.5% of the apparently responders) had masked hypertension and 146 (52.8% of the apparent resistant) had white coat RH. In the same study, in the follow-up period cardiovascular risk was higher in masked hypertensives (masked versus responder hypertensives, relative risk (RR) 2.28, 95% confidence interval (CI) 1.1–4.7, $P < .05$) and in true resistant hypertensives (true resistant versus responder hypertensives, RR 2.94, 95% CI 1.02–8.41, $P < .05$) [7]. According to the above, a significant proportion of treated subjects with apparently controlled hypertension may actually "mask" their poor response to treatment and some of them could possibly be classified as subjects with resistant hypertension. Therefore, ABPM identifies patients with white coat RH or masked hypertension contributing to avoiding overtreatment in the first case and achieving optimal management in the second one.

Regarding BP measurement at home and at the office, the established guidelines are not always followed resulting in false BP readings [8]. This cause of pseudoresistance could be identified with ABPM usage.

Consequently, the physician having confirmed the adherence to the prescribed therapy that includes three antihypertensive agents at full doses, including a diuretic, should use ABPM in order to label the patient as truly resistant hypertensive [9].

3. ABPM Characteristics of Resistant Hypertensives

Since ABPM is a fundamental tool to differentiate true RH from white-coat RH, it has been widely used in the identification of the BP pattern that characterizes patients with RH. Muxfeldt et al. demonstrated that subjects with true RH compared to white coat RH had lower nocturnal systolic BP reductions (6.4 ± 8.8 versus 9.8 ± 7.5 mmHg, $P = .0004$), lower nocturnal diastolic BP (10.4 ± 9.6 versus 13.6 ± 9.2 mmHg, $P = .001$), and a higher percentage of nondippers (i.e., subjects nighttime BP fall <10% of the corresponding daytime BP values) (68.7% versus 49.6%, $P = .001$) [6]. Similarly Friedman and Logan showed that the prevalence of nondipping among normotensive, controlled hypertensive, and resistant hypertensive subjects was 25.0%, 42.3%, and 61.5%, respectively, ($P = .006$) [10]. It should be emphasized that in terms of pathophysiology, both RH and nondipping status have been linked to sympathetic overactivity, subclinical inflammation, and volume overload [11–14]. Furthermore, the failure of the once daily administration of antihypertensive drugs to provide 24-hour coverage has been identified as a cause of high nighttime BP, nondipping pattern and true RH [15].

By definition, subjects with true RH compared to those with white-coat effect present significantly higher ambulatory BP. Apart from this, certain studies demonstrate that patients with true RH have also increased ambulatory pulse pressure in comparison with those with white coat RH [6, 16]. Interestingly ambulatory 24-hour, daytime, and nighttime heart rate is higher in true resistant hypertensives, supporting the notion that increased sympathetic activation may be present in true RH [16].

4. ABPM and Cardiovascular Prognosis in RH

Although it is well known that the risk for cardiovascular hard end points in hypertension disease rises as the BP levels rise [17], there is a lack of evidence on the cardiovascular prognosis of RH. There is one study demonstrating the higher risk of patients with true RH compared to those with white-coat RH for fatal and nonfatal cardiovascular events [7]. On the other hand, there are studies evaluating the prognostic role of ABPM and its indices in patients with RH, highlighting its significance in the clinical management. In particular, Salles et al. in a cohort of 556 subjects with resistant hypertension demonstrated that 24-hour (HR: 1.32; 95% CI: 1.08–1.60; $P < .01$), daytime (HR: 1.26; 95% CI: 1.04–1.53; $P < .005$), and nighttime systolic BP (HR: 1.38; 95% CI: 1.13–1.68; $P < .01$), 24-hour (HR: 1.33; 95% CI: 1.06–1.66; $P < .01$), daytime (HR: 1.31; 95% CI: 1.05–1.63; $P < .01$), and nighttime (HR: 1.36; 95% CI: 1.10–1.69; $P < .05$) diastolic BP, and 24-hour (HR: 1.22; 95% CI: 1.00–1.48; $P < .01$) and nighttime (HR: 1.27; 95% CI: 1.04–1.55; $P < .01$) pulse pressure were independent predictors of fatal and nonfatal cardiovascular events and of cardiovascular and total mortality irrespectively of the office BP values [18]. Of note, there was no difference between systolic and diastolic BP, while pulse pressure was a weaker predictor and nighttime BP was superior to daytime BP [18].

Similarly Redon et al. exhibited that in 86 subjects with RH daytime diastolic BP predicted cardiovascular events (lower tertile versus higher tertile of daytime diastolic BP; RR: 6.42; 95% CI: 1.39–29.7; $P = .017$), while office BP had no prognostic significance [19].

Concerning the prognostic information of nondipping pattern in RH, Muxfeldt et al. demonstrated that, in a cohort of 556 subjects with RH, BP nondipping predicted a composite end point of fatal and nonfatal cardiovascular events, cardiovascular and total mortality (HR: 1.74; 95% CI: 1.12–2.71, HR: 2.31; 95% CI: 1.09–4.92, HR: 1.67; 95% CI: 0.95–2.94, resp.) above and beyond other traditional cardiovascular risk factors and mean ambulatory BP levels [20]. However, these results were not confirmed in other studies [21].

Although there are scarce data on the comparative value of the aforementioned indices derived from ABPM as

potential prognostic markers in RH, in a study of Magnanini et al. in women with RH, uncontrolled daytime BP was the stronger independent risk factor (RR: 1.67; 95% CI 1.00–2.78) [21].

Adding to the cluster of components of ABPM that carry valuable prognostic information, ambulatory arterial stiffness index (AASI), which has been defined as the regression slope of diastolic on systolic BP [22], emerges as a potential predictor of cardiovascular morbidity and mortality in RH (HR: 1.46; 95% CI: 1.12–1.92), after adjustment for traditional risk factors and other ABPM parameters [23].

5. Association of ABPM Components with Target Organ Damage in RH

ABPM can be useful as the components derived from it have been associated with target organ damage surrogates in hypertension. More specifically, high-pulse pressure and nondipping status in resistant hypertensives have been associated with a high-cardiovascular risk profile including greater age, higher prevalence of cerebrovascular disease and nephropathy, increased serum creatinine and microalbuminuria, and higher left ventricular mass index [24]. Moreover, a blunted nocturnal reduction in BP, a widened 24-hour pulse pressure and AASI have been independently associated with increased aortic stiffness in resistant hypertensive patients [21, 24]. Finally, according to some studies 24-hour pulse pressure presents a closer correlation to target organ damage compared to the other ABPM indices [23, 25].

6. ABPM Implications in the RH Treatment

ABPM emerges nowadays as a useful tool in the evaluation of the efficacy of antihypertensive treatment in clinical trials [26]. The conrtibution of ABPM in the assessment of treatment effectiveness, could be more prominent in the setting of RH, where it has been shown to possess a pivotal role in haemodynamic load evaluation [27]. Additionally, apart from just testing the efficacy of different drugs, ABPM has been used in the evaluation of the implementation of certain therapeutic strategies in resistant hypertensives by evaluating patients' compliance [28].

Furthermore, as ABPM reveals the unfavorable circadian BP pattern of patients with RH, namely, the nondipping profile, APBM has been used in the investigation of the efficacy of therapeutic strategies aiming at administration-time-dependent effects (chronotherapy) on the circadian BP pattern and on the degree of 24-hour BP control in RH [29]. Because a possible cause of the unfavorable BP pattern in RH is the short-acting antihypertensive treatment that is based on a single morning dosage, administration of one of the three drugs at bedtime may result in better clinic and ambulatory BP control as well as in lower prevalence of nondipping pattern [30, 31].

Some of the disadvantages of ABPM such as cuff discomfort or procedure-related disturbed sleep may be overcome with the use of home BP as a means of out of office assessment of BP. However, evidence of the superiority of home BP over office BP, for the assessment of RH, is scarce while there are no data regarding any comparisons with ABPM, which for the present represents the most reliable tool in this setting.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 947246, 5 pages
doi:10.4061/2011/947246

Review Article

Resistant Hypertension and Obstructive Sleep Apnea: The Sparring Partners

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Received 14 October 2010; Accepted 8 December 2010

Academic Editor: Vasilios Papademetriou

Enhanced target organ damage and cardiovascular morbidity represent common issues observed in both resistant hypertension and obstructive sleep apnea. Common pathophysiological features and risk factors justify their coexistence, especially in individuals with increased upper-body adiposity. Impaired sodium handling, sympathetic activation, accelerated arterial stiffening, and impaired cardiorenal hemodynamics contribute to drug-resistant hypertension development in obstructive sleep apnea. Effective CPAP therapy qualifies as an effective "add-on" to the underlying antihypertensive pharmacological therapy, and emerging evidence underlines the favorable effect of mineralocorticoid antagonists on both resistant hypertension and obstructive sleep apnea treatment.

1. Introduction

In the recent years several original articles and review papers have focused on the association between arterial hypertension and obstructive sleep apnea syndrome (OSA) [1–4]. Such an association is supported by the interplay of common risk factors and pathophysiological pathways affecting both the vascular wall and the upper airway [5]. Regarding risk factors, the obesity epidemic has prompted the recognition of an interaction between OSA and increased blood pressure (BP) [6]; additionally, as the population ages and gains weight, resistant hypertension is becoming more prevalent [7].

Up to date few small epidemiological studies have shown a significant association between resistant hypertension and OSA, and based on that both the Seventh Report of the Joint National Committee and the 2007 European Society of Cardiology-European Society of Hypertension guidelines for the management of arterial hypertension recognized OSA as an identifiable and not uncommon cause of resistant hypertension [8, 9]. Surprisingly, the European guidelines added OSA to the causes of secondary hypertension, thus creating some confusion; indeed, it is yet unresolved whether OSA could represent just a bystander of essential hypertension and whether the gold standard therapeutic approach for OSA, namely, continuous positive airway pressure (CPAP), is accompanied by efficacious treatment of hypertension [4, 5]. Either way, misdiagnosed or inappropriately treated OSA may prevent pharmacological treatment of drug-resistant essential hypertension from reducing BP levels within the goal [10].

In the present paper, we illustrate the pathophysiological and epidemiological evidence that supports the interrelationship between resistant hypertension and OSA and how these observations could be translated in clinical decisions in the context of an outpatient hypertension clinic.

2. Pathophysiological Issues

2.1. Obesity. Subjects with increased body size are more likely to suffer from hypertension and exhibit difficult-to-control hypertension compared to nonobese controls

[11–13]. Increased free leptin is at least partly associated with increased central and peripheral sympathetic firing in experimental animal models [14, 15], while nonapneic and nonobese subjects with out-of-office hypertension are characterized by hyperleptinemia with respect to their normotensive counterparts [16]. Therefore, it is plausible that leptin could represent an accelerator of sympathetic activation in both obesity and hypertension alone. Obesity itself is frequently observed in OSA patients in whom sympathetic activation is further augmented by episodic nocturnal hypoxia and hypercapnia due to the repetitive collapse of the upper vulnerable airway, yet whether leptin levels are raised in normotensive nonobese patients with OSA is still debated [17]. Additionally, sympathetic overactivity *per se* is accompanied by BP and heart rate increases, as well as by enhanced sodium retention. The above operating mechanisms in obese hypertensive patients with OSA are at least partly responsible for the increased hemodynamic load, and frequently three or more drugs in the maximum tolerated doses are insufficient to effectively reduce BP levels.

2.2. Kidney Function. Focusing on the kidney in obese subjects, "pressure natriuresis" is impaired, and higher BP levels are required to achieve sodium balance [18]. Additionally, urinary albumin excretion is increased in obese OSA patients with hypertension compared to hypertensive nonOSA controls [19]. A further hypothetical mechanism by which OSA affects renal hemodynamics is that the continuous nocturnal intrathoracic pressure swings are accompanied by changes in systemic and renal venous pressure, as it has been shown that renal venous congestion is accompanied by a decline in kidney function in patients with both preserved and impaired cardiac function undergoing right heart catheterization [20]. Considering the above, kidney impairment in OSA subjects may contribute to the development of drug-resistant hypertension, and diuretics implementation may be accompanied by better antihypertensive results by promoting both sodium excretion and venous decongestion.

2.3. Aldosterone. Plasma aldosterone levels are increased in both obese hypertensive patients and those with OSA [6]. Renin-angiotensin-aldosterone axis activation is implicated in most hypertensive states, and apart from sympathetic overdrive, visceral adiposity could also participate in that phenomenon by mechanisms that have not yet been fully elucidated [21]. In patients with resistant hypertension who were referred to an outpatient hypertensive unit, those with a high clinical suspicion for OSA exhibited increased plasma aldosterone levels with respect to those with no symptoms of OSA. In those with a final positive diagnosis of OSA as well as in obese hypertensive subjects, renin activity was suppressed, a finding that suggests that aldosterone secretion is at least partly plasma renin independent; thus, in resistant hypertensive patients with OSA targeting of renin inhibition seems pathophysiologically a less justified therapeutic strategy compared to blockers of subsequent steps of the renin-angiotensin-aldosterone cascade. Such a concept is further supported by the finding that hyperaldosteronism prevalence in resistant hypertension is as high as 20%, with obesity and suspected OSA being the two extremely common clinical features in this setting [21, 22].

2.4. Arterial Stiffening. Arterial stiffening constitutes a pathophysiological substrate that promotes acceleration of vascular aging observed in both hypertension and OSA [23]. Increased levels of circulating vasoconstrictors [24], enhanced subclinical inflammation [25], endothelial dysfunction [25], and repetitive increases of left ventricle afterload may separately or in combination contribute to the increasing magnitude of arterial stiffening. Even though it is known that resistant hypertension is more prevalent in the elderly, increased arterial stiffness observed in OSA may also precipitate the development of the drug-resistance phenomenon in younger ages.

3. Epidemiological Issues

3.1. Noninterventional Studies. In the beginning of the present millennium Logan et al. [26] demonstrated for the first time in the literature the striking prevalence (82.9%) of OSA in 41 middle-aged obese patients with "true drug-resistant hypertension" recruited from a hospital university hypertension clinic. Although most men with resistant hypertension suffered from OSA (95.8%), among women those not affected by the syndrome (35.3%) were younger, received less drugs, presented with a longer sleep time by 30% and less arousal movements per hour of sleep by 80%, and finally demonstrated a higher 24-hour pulse pressure, compared to those not affected by OSA. Another surprising finding in the same study was that almost one third of OSA patients with resistant hypertension had a normal dipping profile, suggesting that the nondipping phenomenon in resistant hypertension may be driven by OSA-independent pathophysiological mechanisms.

In another cross-sectional case-control study from the same investigational group [27], patients with drug-resistant hypertension were compared with a group of patients with controlled hypertension matched for age, sex, and body mass index. Accordingly, Ruttanaumpawan et al. [27] reported that those with controlled hypertension—as expected—received fewer antihypertensive medications and the use of diuretics was 60% less frequent with respect to those with resistant hypertension. Moreover, the prevalence of OSA was almost 50% more frequent in those with resistant hypertension. Total time asleep, sleep efficiency, and time of rapid-eye movement sleep were significantly higher in those with controlled hypertension compared to their resistant hypertension counterparts; interestingly, only the two latter parameters in tandem with the presence of OSA were unadjusted determinants of resistant hypertension in the total study population. After adjusting for confounders, OSA and reduced time of rapid-eye movement sleep qualified as independent significant determinants of resistant hypertension. Among antihypertensive medications, calcium blockers implementation was associated with a lower amount of rapid-eye movement sleep, suggesting that disruption of sleep architecture might be associated in some degree with the selection of antihypertensive drugs.

In a case-control study, Gonçalves et al. [28] demonstrated that patients with resistant hypertension are affected almost 5 times more frequently by OSA—diagnosed by portable sleep monitors—compared to their well-controlled hypertensive counterparts matched for age, sex, and body mass index. Finally, in a Spanish article by Martínez-García et al. [29], the severity of OSA diagnosed by polysomnography as measured by the apnea/hypopnea index was associated with the magnitude of BP levels in elderly patients with difficult-to-control hypertension and OSA after adjustment for age and sex.

Another study reported that, among resistant hypertension patients, there is a positive association between plasma aldosterone levels and severity of OSA. However, no correlation was noted between OSA and aldosterone levels in subjects without resistant hypertension with equally severe OSA [30]. These findings confirm the high prevalence of OSA in resistant hypertension (85%) and are consistent with the hypothesis that hyperaldosteronism in resistant hypertension might exacerbate OSA—by promoting upper airway edema due to sodium and fluid retention—or inversely, OSA stimulates aldosterone release, while there might even be a bidirectional relationship in that phenomenon.

3.2. Interventional Studies. Logan et al. [31] tested the therapeutic impact of CPAP therapy on ambulatory BP levels in 11 patients with drug-resistant hypertension and OSA both at a single night's application and after a period of two months. CPAP efficiently applied for one night was accompanied by a significant reduction in nocturnal BP levels. More specifically, nocturnal systolic BP exhibited a more pronounced acute reduction compared to a more limited reduction of the nocturnal diastolic component (138.3 ± 6.8 to 126.0 ± 6.3 mmHg versus 77.7 ± 4.5 to 72.9 ± 4.5 mmHg, resp.). Additionally, CPAP use for 2 months was accompanied by an 11.0 ± 4.4 mmHg decrease in 24-hour systolic BP, whereas the nocturnal diastolic BP was reduced significantly by 7.8 ± 3.0 mmHg. In these lines, efficiently treating OSA in resistant hypertension might be a therapeutic "add-on" option to the underlying antihypertensive treatment to reduce BP levels within the goal.

In a subsequent work on 33 elderly patients with difficult-to-treat hypertension and OSA [32], Martínez-García et al. highlighted, along with the beneficial effect of CPAP on systolic ambulatory BP levels, the fact that compliance to CPAP therapy (>4 hours at night on CPAP) is crucial for the efficient reduction of BP. Indeed, those who tolerated CPAP ($n = 23$) showed a significant drop in mean 24-hour systolic BP of 7.6 mmHg without significant changes in mean 24-hour diastolic BP; however, in those who were CPAP intolerant ($n = 10$), there were no significant changes in either mean diurnal or nocturnal, either systolic or diastolic BP.

Lozano et al. [33] in a randomized prospective controlled study evaluated the change in mean 24-hour systolic and diastolic BP at the three-month follow-up in two groups of patients with resistant hypertension and OSA: 29 patients under well-tolerated CPAP and appropriate pharmacological treatment (i.e., CPAP arm) and 35 patients under appropriate pharmacological treatment alone (i.e., conventional arm). The use of CPAP for three months was accompanied by a mean reduction of almost 5 mmHg in 24-hour diastolic BP in the CPAP arm, whereas no significant change was observed in the arm of conventional therapy. In those wearing the mask for at least 5.8 hours per day significant changes were registered in diurnal and 24-hour diastolic BP and in 24-hour systolic BP. It is worth noting that the beneficial effect of CPAP on BP levels was only seen in those with resistant hypertension confirmed with ambulatory BP monitoring, but not in those with resistant hypertension diagnosed only by office BP measurements. The number of patients in the CPAP arm with a nondipping pattern decreased significantly from 51.7% at baseline to 24.1% at the three-month follow-up, whereas no changes were observed in patients of the conventional arm of the study, in line with previous findings. A final important issue in the Lozano et al. [33] study was that, among those who accepted to wear the mask, the Epworth Sleepiness scale scoring did not differ between those who used CPAP for more and less than 5.8 hours/day, suggesting that even asymptomatic patients with resistant hypertension had similar reductions in BP levels especially if CPAP was applied for more than the cut-off of 5.8 hours/day.

In a retrospective chart review study [34], medical records of patients who had a polysomnography with CPAP study were reviewed and among them the researchers selected those with hypertension; OSA compliant with CPAP; office BP measurements obtained within three months of enrollment, every three months for six months and at one year after CPAP initiation. In subjects exhibiting resistant hypertension, the use of CPAP therapy was accompanied by a decrease in daytime BP at both 6 and 12 months after treatment initiation, while in almost 70% of these patients a reduction in either the dose or the number of antihypertensive drugs used at baseline was observed. On the contrary, patients with controlled hypertension and OSA demonstrated no significant change in BP levels over the same period of time, suggesting that the effect of CPAP on BP, when the latter has been already controlled with medication, is at least less pronounced or even absent in line with previous findings [35, 36].

4. Clinical Decisions: Lost in Translation or a Simple Rationale?

In patients with hypertension a thorough sleep history confirmed—if applicable—by the bed partner, identification of daytime symptoms, and a physical examination including visualization of the pharynx are all essential steps in order to separate those with a high clinical suspicion of OSA. However, in patients with drug-resistant hypertension establishing a high or low clinical suspicion for OSA might be futile. For example, in the context of resistant hypertension, the use of clinical prediction tools, like the Epworth Sleepiness Scale could not be as helpful [33] as it may be for the general population of hypertensive patients [4]. Therefore, in clinical practice, those with true drug-resistant hypertension should be counseled to undergo polysomnography.

Along with the other diagnostic exams, in true drug-resistant hypertension, a 24-hour ambulatory BP monitoring should be considered valuable as it confirms the office evaluation of BP levels and possibly helps the clinician assess the hemodynamic responsiveness to CPAP treatment better [33]. Furthermore, evaluating the dipping pattern and nighttime BP levels in resistant hypertension is vital for a more comprehensive approach of the circadian BP variability, its response to therapy, and the potential implementation of chronotherapy issues [4].

Lifestyle modifications should always stand at the first line of the therapeutic procedure in resistant hypertension associated with OSA. The importance of appropriate weight control must be underlined, and bariatric surgery should be encouraged if morbid obesity coexists. Additionally, the underlying pathophysiological mechanisms activated in the duo of resistant hypertension and OSA prompt to rigorous sodium intake restriction [4].

In resistant hypertension complicated by OSA, CPAP is imperative as it proved an efficacious "add-on" to the conventional pharmacological treatment and succeeded to reverse nondipping profile in most of the patients [31, 33]. In these lines, patients should be encouraged to wear their mask every night and possibly for the whole night. The antihypertensive effect of CPAP seems to be more prominent in those with more severe OSA or hypertension, though there is limited evidence whether sleepy and nonsleepy patients with drug resistant hypertension benefit the same in terms of BP reduction when compliant to CPAP treatment. Although, there is limited clinical evidence for the potential benefit of mineralocorticoid antagonists in resistant hypertension and OSA [37], their use should be considered as an additional promising therapeutic strategy with a plausible pathophysiological background [6, 21].

Since resistant hypertension and OSA are accompanied either separately or in combination with highly increased prevalence of target organ damage and adverse cardiovascular outcome, combined treatment seems to be of the highest clinical priority. Targeting on both the maximum individual doses of antihypertensive drugs and the effective implementation of CPAP should remain the main awareness of the physician dealing with this compound difficult-to-treat hypertensive disorder.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 236239, 17 pages
doi:10.4061/2011/236239

Review Article

Common Secondary Causes of Resistant Hypertension and Rational for Treatment

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Received 8 November 2010; Accepted 11 January 2011

Academic Editor: Konstantinos Tsioufis

Resistant hypertension is defined as uncontrolled blood pressure despite the use of three antihypertensive drugs, including a diuretic, in optimal doses. Treatment resistance can be attributed to poor adherence to antihypertensive drugs, excessive salt intake, physician inertia, inappropriate or inadequate medication, and secondary hypertension. Drug-induced hypertension, obstructive sleep apnoea, primary aldosteronism, and chronic kidney disease represent the most common secondary causes of resistant hypertension. Several drugs can induce or exacerbate pre-existing hypertension, with non-steroidal anti-inflammatory drugs being the most common due to their wide use. Obstructive sleep apnoea and primary aldosteronism are frequently encountered in patients with resistant hypertension and require expert management. Hypertension is commonly found in patients with chronic kidney disease and is frequently resistant to treatment, while the management of renovascular hypertension remains controversial. A step-by-step approach of patients with resistant hypertension is proposed at the end of this review paper.

1. Introduction

Hypertension represents a major public health problem affecting more than one billion individuals worldwide [1]. The advent of antihypertensive therapy has substantially reduced the occurrence of cardiovascular events. However, antihypertensive therapy failed to achieve blood pressure control in all patients, with hypertension control rates remaining in general disappointingly low. Blood pressure goals are not attained in some patients despite the simultaneous use of several antihypertensive medications. Several terms have been used to define this condition: "refractory hypertension", "difficult-to-treat hypertension", "difficult-to-control hypertension"; however, the term "resistant hypertension" seems to prevail.

Resistant hypertension is currently defined as uncontrolled blood pressure despite the use of optimal doses of three antihypertensive medications, of which one is a diuretic [2]. Several factors have been identified as contributors to resistant hypertension. Poor patient adherence, physician inertia, inadequate doses or inappropriate combinations of antihypertensive drugs, excess alcohol intake, and volume overload are some of the most common causes of resistance [2–10]. Secondary forms of hypertension represent another very important contributor to drugresistance. The list of secondary forms of hypertension is long and covers a large variety of conditions (Table 1). Most of these conditions may result in resistance to pharmacologic therapy of hypertension.

The management of patients with resistant hypertension requires a gratifying combination of clinical acumen and common sense. An extensive workup of all patients with uncontrolled hypertension is scientifically unsound, is very costly and requires immense human and technical resources. Therefore, practicing physicians need to implement evidence-based medicine. The effective management of patients with resistant hypertension requires an appropriate combination of physiology and pharmacology, taking into account the unique characteristics of each case in order to tailor the therapeutic approach to the individual patient.

This paper will address the most common secondary causes of resistant hypertension (drug-induced, obstructive sleep apnea, primary aldosteronism, and chronic kidney

Table 1: Secondary forms of hypertension (disease categories).

(i) Endocrine disorders
(ii) Renal disease
(iii) Neurological disorders
(iv) Acute stress
(v) Drug-induced hypertension
(vi) Miscellaneous

disease), which are frequently encountered in hypertensive patients and are, therefore, the most interesting from the clinical point of view. In addition, this paper will attempt to provide a rational for the workup and treatment of patients with resistant hypertension.

2. Prevalence and Prognosis of Resistant Hypertension

The exact prevalence of resistant hypertension in the general population remains unknown. Data from small observational studies show a wide variation (from 5% to 50%) according to the studied populations [2–10]. Data from large clinical trials point towards a relatively high prevalence of resistant hypertension (20–35%). It has to be noted, however, that atypical drug combinations have been used in most of these studies as required by study protocols. Therefore, the evaluation of the prevalence of resistant hypertension requires a large, prospective, population-based study, specially designed for this aim.

Similarly, the prognosis of resistant hypertension is currently unknown [2–10]. Available evidence addressing the prognosis of resistant hypertension is scarce, since virtually no longitudinal study has addressed this topic. Data from small clinical studies point towards an increased cardiovascular risk in patients with resistant hypertension. In addition, patients with resistant hypertension frequently have comorbidities that are known to increase cardiovascular morbidity and mortality, such as chronic kidney disease, diabetes, and obesity. Moreover, patients with resistant hypertension have higher rates of target organ damage than the general hypertensive population and are thus at increased cardiovascular risk.

3. Lifestyle Factors

Resistance to antihypertensive treatment is affected by several lifestyle factors. Excessive dietary salt intake is common in patients with resistant hypertension and contributes to treatment resistance by blunting the blood pressure reduction of most antihypertensive drugs, including diuretics and inhibitors of the renin-angiotensin axis [2–10].

Obesity can also contribute to treatment resistance [2–10]. It has been shown that blood-pressure control is more difficult to be achieved in obese than lean hypertensive patients. Several lines of evidence indicate a graded positive correlation between body mass index and blood pressure levels, while weight loss results in blood pressure reduction. Insulin resistance, sympathetic nervous system overactivity, sodium retention, and activation of the renin-angiotensin system have been implicated in the pathogenesis of obesity-induced hypertension.

Alcohol consumption is another important factor [2–10]. Large alcohol consumption (>3 drinks per day) has been shown to result in blood pressure elevation. In addition, blood pressure control might be achieved more difficult in heavy drinkers due to poor adherence in antihypertensive therapy. The role of physical inactivity in patients with resistant hypertension has not been adequately studied.

Table 2: Drugs inducing or exacerbating hypertension.

(i) Nonsteroidal anti-inflammatory drugs
(ii) Oral contraceptives
(iii) Sympathomimetics
(iv) Illicit drugs
(v) Glucocorticoids
(vi) Mineralocorticoids
(vii) Cyclosporine, tacrolimus
(iix) Erythropoietin
(ix) Herbal supplements
(x) VEGF inhibitors

4. Drug-Induced Hypertension

A variety of prescription or over the counter medicines as well as other exogenous substances may induce hypertension or contribute to treatment resistance. Drug-induced hypertension is among the most common causes of secondary hypertension and is frequently encountered in everyday clinical practice. However, despite the frequent occurrence of drug-induced hypertension, primary care physicians frequently miss the opportunity to detect and appropriately manage this iatrogenic form of secondary hypertension. Therefore, a detailed and meticulous medical history is of utmost importance in patients with resistant hypertension, since the identification and subsequent withdrawal of the offending drug may alleviate treatment resistance. However, withdrawal of the responsible agent is not always possible; in such cases, dose reduction and/or search for alternate treatment may substantially improve or even control blood pressure levels. Another very important aspect relates to the great variability of the effects of administered drugs on blood pressure. The administration of offending drugs can result in excessive blood pressure elevation in some individuals, while most individuals will experience little or no increases of blood pressure. This variability represents a rule without exception. Therefore, it would be very important to identify predictors of blood pressure elevation, in order to individualize drug treatment. Up to now, however, no such reliable predictors have been identified.

A descriptive list of all exogenous agents capable of inducing or exaggerating hypertension is presented in Table 2. However, this paper will focus on the drugs that are

widely used, represent the most common causes of drug-induced hypertension, and are thus of major clinical importance: nonsteroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives. In addition, a brief comment regarding specific antineoplastic agents (anti-VEGF) that have emerged as inducers of hypertension is presented at the end of this chapter, since many clinicians are not aware of this condition.

4.1. NSAIDs-Induced Hypertension. By far, the most common cause of drug-induced hypertension is the use of NSAIDs. In 265 patients with resistant hypertension identified during a one-year period, treatment resistance was drug-related in 36% of the cases, with NSAIDs being responsible in 88% (personal unpublished data). Osteoarthritis is highly prevalent in the general population, and its prevalence would be even greater due to population aging and the obesity epidemic [11, 12]. Osteoarthritis and hypertension often coexist, since both conditions are age related. It has been reported that approximately 50% of patients with osteoarthritis suffer from hypertension [13]. Although lifestyle modification, exercise, and weight loss are considered as first-line therapeutic measures for patients with osteoarthritis, the vast majority of such patients require the systematic or intermittent use of either acetaminophen or NSAIDs for pain relief.

Data regarding the effects of NSAIDs on blood pressure continue to accrue. Two large prospective cohort studies in normotensive women reported higher risks of subsequent hypertension among NSAIDs users than in women without regular NSAIDs administration [14, 15]. In the first study, the risk of developing hypertension was increased about two times in women using acetaminophen or NSAIDs [14]. Acetaminophen consumption for 1–4 days per month and NSAIDs consumption for 5–14 days per month was necessary for the risk to be apparent. In the second study, women with frequent use of nonnarcotic analgesics (>22 days/month) had statistically significant higher risk for developing hypertension; in particular, the hazard ratios were 1.20 for acetaminophen, 1.21 for aspirin, and 1.35 for NSAIDs [15]. It has to be noted that although acetaminophen is considered to have a better safety profile than NSAIDs [16, 17], its use was associated with a moderate increase in the risk for incident hypertension in both males and females [18, 19]. Another large, case-control study revealed a 66% increased risk for initiating antihypertensive drugs in NSAIDs users compared to nonusers [20]. These detrimental effects of NSAIDs on blood pressure have been also observed in two older meta-analyses of randomized trials with NSAIDs [21, 22]. In the first meta-analysis, mean arterial pressure was increased by 3.3 mmHg in hypertensive patients whereas the increase in normotensive subjects was negligible (1.1 mmHg) [21]. In the second meta-analysis, NSAIDs resulted in a significant mean arterial pressure elevation of 5.0 mmHg; blood pressure elevation was apparent in hypertensive patients with controlled blood pressure, whereas normotensive individuals did not experience such an effect [22].

On the contrary, data reporting no or little effect of NSAIDs on blood pressure exist in the literature as well. In two cross-sectional studies, no association between use of NSAIDs and hypertension was found [23, 24]. Similar findings were observed in two small randomized studies regarding the effects of acetaminophen on blood pressure [25, 26], as well as in studies evaluating the effects of aspirin on blood pressure in hypertensive patients [27, 28]. In addition, in a large prospective cohort of 8,229 male normotensive physicians, analgesic use was not associated with increased risk of developing hypertension (hazard ratio: 1.12; 95% CI: 0.97–1.31) [29]. The corresponding hazard ratios were 1.08 (95% CI: 0.87–1.34) for acetaminophen, 1.16 (95% CI: 0.92–1.48) for aspirin, and 1.05 (95% CI: 0.89–1.24) for NSAIDs.

This apparent heterogeneity of available data on the effects of traditional NSAIDs on blood pressure becomes even more complicated when recent data with selective COX-2 inhibitors are taken in account. In a meta-analysis of randomized trials, use of COX-2 inhibitors was associated with a significant increase in blood pressure compared to placebo (3.85/1.06 mmHg) and nonselective NSAIDs (2.83/1.34 mmHg) [30]. However, it was shown that a great part of blood pressure elevation could be attributed to rofecoxib. Indeed, rofecoxib use is associated with greater blood pressure elevations than celecoxib in both hypertensive and normotensive individuals [31].

The above-mentioned study highlights another important aspect: the potential differences on blood pressure effects between the various NSAIDs. In a meta-analysis of randomized trials, conducted mainly in hypertensive patients, naproxen and indomethacin were associated with the largest blood pressure elevations, while piroxicam, sulindac, ibuprofen, and aspirin exhibited little if any effect on blood pressure [21]. On the contrary, a randomized study in patients with controlled hypertension showed that the blood pressure was significantly higher with ibuprofen than with lumiracoxib [32]. Moreover, in 34,701 participants at the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long term) program, patients assigned to etoricoxib discontinued the study due to hypertension more frequently than patients randomized to diclofenac [33].

Finally, the potential differences of the effects of NSAIDs on blood pressure according to the various antihypertensive agents coadministered are of great clinical importance. In a study of elderly hypertensives with osteoarthritis, indomethacin had no effect on blood pressure in patients taking calcium antagonists whereas significant blood pressure elevations were detected in patients taking ACE-inhibitors [34]. On the contrary, celecoxib exerted similar to placebo effects in patients taking ACE-inhibitors [35]. Another study among hypertensive patients with osteoarthritis, comparing the effects of rofecoxib and celecoxib, revealed no differences on blood pressure between the two drugs in patients taking diuretics or calcium antagonists, whereas larger blood pressure elevations were observed with rofecoxib than with celecoxib in patients taking ACE-inhibitors or beta blockers [36].

The above presented information clearly indicates that available data on the effects of NSAIDs on blood pressure are sometimes contradictory and in total far from conclusive. Convincing data coming from carefully designed randomized studies are necessary to: (a) detect potential differences between the various NSAIDs on blood pressure, (b) clarify the effects of coadministering each NSAID with each one of the various antihypertensive drug categories, and (c) identify predictors of blood pressure response to NSAIDs use.

Withdrawal of NSAIDs is indicated in patients with resistant hypertension, exacerbation of prior hypertension, or incident hypertension. Substituting NSAIDS with acetaminophen can usually solve the problem. Pain relief is more likely in patients with osteoarthritis and pain of muscular skeletal origin. However, this is not always possible in everyday clinical practice, since patients with chronic inflammatory arthritic diseases (rheumatoid arthritis) respond better to anti-inflammatory agents. In such cases, hydrocodone, tramadol, or nerve blocking might be of help, constituting effective alternatives to NSAIDs. In cases, however, where NSAIDs are still necessary, the lower effective dose should be administered, since existing data point towards dose-related effects of NSAIDs on blood pressure.

NSAIDs affect blood pressure levels via different mechanisms: activation of the renin-angiotensin-aldosterone system, sodium and water retention, induction of vasoconstriction through endothelin-1 and arachidonic acid metabolites, and mainly inhibition of renal vasodilatory prostaglandins (E_2 and I_2) [37–43]. These detrimental effects of NSAIDs may lead to deterioration of renal function and acute kidney injury, especially in patients of older age, preexisting hypertension, chronic kidney disease, or diabetes. In such patients, calcium antagonists seem to be more suitable than drugs inhibiting the renin-angiotensin system, since the concomitant administration of NSAIDs and calcium antagonists is not accompanied by blood pressure elevation [36, 39]. The development of NSAIDs that apart from cyclo-oxygenase inhibition possess nitric oxide promoting properties might significantly ameliorate current situation and alleviate the effects of NSAIDs on blood pressure. CINODs (Cyclo-oxygenase Inhibiting Nitric Oxide Donating drugs) represent a new class of NSAIDs; CINOD molecules consist of a traditional NSAID and a nitric oxide-donating chemical group connected by a linker. Naproxcinod is the first CINOD in clinical trials with very promising preliminary results [44–47].

4.2. Oral Contraceptives. Oral contraceptives represent another class of drugs that are widely used and are capable of inducing hypertension [48, 49]. The larger study evaluating the effects of oral contraceptives on blood pressure was the Nurses' Health Study, in which more than 60,000 normotensive women were prospectively followed for 4 years [50]. Women using oral contraceptives had an 80% higher risk of developing hypertension compared to women that were not using such drugs. However, withdrawal of oral contraceptives abolished this increased risk, underlining the need for close monitoring in women taking oral contraceptives. Another important aspect of "pill"-induced hypertension regards the contribution of oral contraceptives in uncontrolled hypertension. A study in hypertensive women revealed that those taking oral contraceptives had more severe hypertension and lower blood-pressure control rates than women using other contraceptive methods [51].

The type of oral contraceptives seems also to be of clinical importance. Combined oral contraceptives (progestin and estradiol), which were widely used in the past, were associated with blood pressure elevations more frequently than progestin-only oral contraceptives. On the contrary, drospirenone (a fourth generation progestin) reduces blood pressure when combined with estradiol [52]. Therefore, current guidelines recommend the use of progestin-only oral contraceptives in women with established cardiovascular disease, or major cardiovascular risk factors (such as hypertension) [53, 54].

It can, therefore, be summarized that oral contraceptives may contribute to resistance in hypertensive women, but the type of oral contraceptive is important. Close monitoring of women and withdrawal of oral contraceptives may alleviate the effects on blood pressure.

4.3. Anti-VEGF Agents. Another class of agents that emerged as inducers of hypertension are the antineoplastic drugs that target the VEGF pathway. A monoclonal antibody (bevacizumab) binding to the VEGF-A isoform, as well as small molecules inhibiting the intracellular tyrosine kinase domains of all three VEGF receptors, is used or is under clinical testing for the treatment of various malignancies [55–57]. Hypertension was encountered very frequently in patients receiving treatment with VEGF-inhibitors [58]. In particular, 20–30% of patients treated with bevacizumab, and 15–60% of patients treated with VEGF kinase inhibitors developed hypertension [59]. Three meta-analyses with drugs inhibiting the VEGF pathway uncovered a high relative risk for incident hypertension with these agents: 7.5 (95% CI: 4.2–13.4) with bevacizumab, 6.11 (95% CI: 2.44–15.32) with sorafenib, and 21.6 (95% CI: 18.7–24.8) with sunitinib [60–62]. Interestingly enough, the development of hypertension has been correlated with the efficacy of these drugs [63–65], suggesting that hypertension could be used as a surrogate marker of anti-VEGF efficacy. A phase III trial evaluates this concept in patients with pancreatic cancer receiving anti-VEGF agents. Clearly, more data are needed to clarify the blood pressure effects of the various drugs acting on the VEGF pathway.

Experimental studies have shown that VEGF upregulates endothelial nitric oxide synthase [66, 67], enhances nitric oxide production [68], and induces nitric oxide-dependent vasorelaxation [69]. Moreover, VEGF was shown to result in enhanced prostacyclin production and release [70, 71]. It can be therefore anticipated that VEGF inhibition may lead to reduction of nitric oxide and prostacyclin bioavailability, a subsequent increase of systemic vascular resistance, and finally blood pressure elevation. In addition, arteriolar rarefaction has been observed in animals treated with VEGF kinase inhibitors, proposing another pathogenetic

mechanism of hypertension with these drugs [72–74]; preliminary studies in humans reported similar findings [75, 76]. Finally, enhanced arterial stiffness has been suggested as another contributing factor in the development of hypertension [77].

The recognition of the pathogenetic mechanisms that contribute to blood pressure elevation with VEGF-inhibitors might be helpful in identifying the most appropriate drugs for the management of these patients. Reliable data evaluating the efficacy of the various antihypertensive drug categories in anti-VEGF-induced hypertension are missing. Preliminary reports point towards restricted efficacy of diuretics [78] and beneficial effects of calcium antagonists [79]; however, appropriate prospective studies are needed in this topic.

5. Obstructive Sleep Apnea

A vast amount of evidence demonstrates an association between obstructive sleep apnea (OSA) and hypertension. Such an association has been shown in epidemiological, longitudinal, and cross-sectional studies, as well as in studies from specialized clinics [80–83]. In addition, it has been shown that OSA in normotensive subjects predicts future development of hypertension.

Sympathetic nervous system activation plays a crucial role in the pathogenesis of hypertension in patients with OSA. Enhanced upper airway resistance and intermittent hypoxia are considered to stimulate the sympathetic system, while the subsequent sympathetic overactivity may result in blood pressure elevation via vasoconstriction and increased systemic vascular resistance, increased cardiac output, and enhanced fluid retention. Aldosterone seems to be the other significant player in this field. Increased aldosterone levels have been observed in OSA patients with resistant hypertension. The exact nature of the association between OSA and aldosterone excess remains to be elucidated. Whether OSA results in aldosterone excess or aldosterone excess contributes to OSA, or another underlying factor (like obesity) promoting both aldosterone excess and OSA has not been clarified.

Several studies have reported an extremely high prevalence of OSA in patients with resistant hypertension. Two decades ago, a Swedish study of 16 patients with resistant hypertension reported a 56% prevalence of OSA in these patients compared to 19% in patients with controlled hypertension [84]. In a study of 41 consecutive resistant hypertensives, an 83% prevalence of unsuspected OSA was found; OSA was defined as an apnea/hypopnea index (AHI) of more than 10 events per hour [85]. Another study of 71 patients with resistant hypertension revealed an 85% prevalence of OSA (AHI $\geq$ 5 events/h) [86]. A study from Spain in 62 resistant hypertensives reported a 90% prevalence of OSA (AHI $\geq$ 5 events/h) [87]. However, when the diagnosis of OSA was based on 30 or more episodes of apnea/hypopnea per hour, the prevalence was reduced to 70%, underlining the importance of accurate and homogeneous definition of OSA. Moreover, all the above-mentioned recent studies did not have a control group in order to exclude the potential effects of confounding factors. A recent study from Brazil evaluated 63 patients with resistant hypertension and an equal number of patients with controlled hypertension, matched for baseline parameters apart from blood pressure [88]. A strong and independent association between OSA and resistant hypertension has been described (odds ratio: 4.8; 95% CI: 2.0–11.7); OSA (AHI $\geq$ 10 events/h) in 71% of resistant hypertensives and in 38% of responders.

Continuous positive airway pressure (CPAP) represents the treatment of choice for patients with OSA. It has been shown that CPAP decreases the incidence of cardiovascular events in patients with OSA [89, 90].The acute application of CPAP attenuates blood pressure elevations during sleep [91]. However, the long-term effects of CPAP on blood pressure are controversial, from studies reporting a significant decrease in blood pressure to studies reporting small or no effects [92–106]. Three meta-analyses have tried to overcome these discrepancies and revealed that the beneficial effect is modest, with reductions in systolic blood pressure ranging from 1.38 mmHg to 2.46 mmHg [107–109]. It is, therefore, not surprising that in a recent randomized study, valsartan was more effective than CPAP in hypertensive patients with OSA [110].

It has to be noted, however, that most of the above-mentioned studies have not been performed exclusively in hypertensive patients, usually evaluating both normotensive and hypertensive subjects. In addition, larger blood pressure reductions were observed in OSA patients with higher baseline blood pressure levels [107, 111], as expected with any antihypertensive approach; the motto "the higher the blood pressure, the larger the reduction" has been verified over the years. Indeed, two small studies in OSA patients with resistant hypertension revealed significant blood pressure reductions (over 10 mmHg) [112, 113]. On the contrary, a study in 42 patients with resistant hypertension showed a smaller mean arterial pressure reduction (5.6 mmHg; 95% CI: 2.0–8.7 mmHg; $P < .03$) [114]. Interestingly enough, the benefits of CPAP were evident only at 1-year after CPAP application, suggesting that longer followup periods might be necessary for the benefits of CPAP treatment to become apparent in OSA patients with resistant hypertension. Another important factor is that CPAP treatment allowed de-escalation of antihypertensive treatment in the majority of participating patients (71%) [114]. A recent study in 96 patients with OSA and resistant hypertension showed a slight decrease in systolic blood pressure (1.3 mmHg) [115]. However, the reduction was significantly larger in patients with ABPM-confirmed resistant hypertension (7.6 mmHg). In addition, the reduction was even larger in CPAP users for more than 5.8 hours per day. The above-mentioned data delineate the complexity in identifying patients with resistant hypertension and OSA that will have the greater benefits with CPAP treatment.

An important issue challenging the efficacy of CPAP relates to patient adherence. Among patients prescribed CPAP therapy up to 50% failed to initiate it or did not use it at 3 years [116, 117]. Moreover, among CPAP users, 29–83% used it for less than 4 hours [118].

Another important aspect of treatment is the choice of antihypertensive drugs in patients with OSA. The crucial role

of SNS activation and the increased levels of aldosterone in patients with OSA, point towards potential advantages of drugs inhibiting these pathways on reducing blood pressure. Indeed, beta blockers were found to be more effective than other antihypertensive drugs in OSA patients [119]; however, relevant data is still far from conclusive. Even more interestingly, however, spironolactone was shown not only to significantly lower blood pressure in 12 patients with OSA and resistant hypertension, but to reduce the severity of OSA as well [120]. Further, larger studies are needed, however, to confirm these beneficial effects of spironolactone in patients with OSA.

Table 3: Endocrine causes of secondary hypertension.

(i) Primary aldosteronism
(ii) Pheochromocytoma
(iii) Hyperthyroidism
(iv) Hypothyroidism
(v) Cushing's syndrome
(vi) Acromegaly
(vii) Hyperparathyroidism
(iix) Carcinoid tumor
(ix) Congenital adrenal hyperplasia

6. Primary Aldosteronism

Primary aldosteronism (PA) was initially described by Conn in 1955 [121]. PA is characterized by autonomous production of aldosterone by adrenal glands and the subsequent decrease in renin levels though negative feedback. Aldosterone excess leads to hypertension, metabolic alkalosis, hypernatremia, and potassium loss resulting in hypokalemia; the latter is currently considered a late manifestation of PA. PA can result from an aldosterone producing adenoma, bilateral adrenal hyperplasia, glucocorticoid-remediable aldosteronism, or rare familial syndromes. Although the diagnosis of adrenal adenomas prevailed during the older times, recent reports reveal that hyperplasia is more frequent than adrenal adenomas.

The prevalence of PA in the general hypertensive population remains an unresolved issue [122, 123]. Historically, PA has been considered a rare disease, affecting about 1% of hypertensive patients [124–127]. However, several studies performed in the last decade report a much higher prevalence of PA (>10%), suggesting an "epidemic" of this condition [128–133]. These studies, however, were carried out in specialized referral centers, raising concerns of selection bias. Indeed, a study of more than 600 unselected patients with hypertension conducted in Chile, revealed a 6.1% prevalence of PA [134], suggesting that the true prevalence is somewhere in the middle. However, irrespective of its exact prevalence, PA has become fashionable again, with leading specialized centers appearing all over the world, from Alabama (D. Calhoun) to Italy (G. Rossi) and from Australia (M. Stowasser) to United Kingdom (M. Brown).

The prevalence of hypertension relates to the severity of hypertension. In the study from Chile, PA was found in 1.99% of patients with Stage I hypertension and in 13.2% of patients with stage III hypertension [134]. In another study of more than 400 Czech patients with moderate-to-severe hypertension, the prevalence of PA was even higher (19%) [135]. Data from clinical practice indicates that resistant hypertension represents the condition with the highest probability of detecting PA [136, 137]. Indeed, the prevalence of PA ranged from 14–23% in 5 studies conducted in resistant hypertensives [138–142]. A study of 88 patients with resistant hypertension in Alabama showed that 18 patients (20%) suffered from PA; PA prevalence was race independent [138]. The prevalence of PA was quite similar in two other studies, one from Seattle (17%) and one from Norway (23%) [139, 140]. A somehow lower prevalence was found in the remaining two studies. A study from Spain reported a 14% prevalence of primary hyperaldosteronism in patients with refractory hypertension; however, patients with hypokalemia were excluded from the study suggesting that the true prevalence of primary aldosteronism could be up to two times higher than the one reported [141]. Finally, a similar prevalence of 14% has been reported in diabetic subjects with resistant hypertension [142].

The above-mentioned studies have reported a PA prevalence of 14–23% in patients with resistant hypertension, suggesting that the true prevalence would be around 20%. However, it has to be recognized that all these studies included a small number of patients. In total, only 418 patients participated in these studies, underlining the need for larger studies. A recent study from Greece evaluated 2,032 patients with resistant hypertension, with 1,616 of them having "true" resistant hypertension [143]. It was found that about 21% of studied patients had a high aldosterone to renin ratio combined with high aldosterone levels, which were suggestive of primary aldosteronism. However, only half of them (11.3%) were suffering for primary aldosteronism, confirmed by salt suppression tests and response to spironolactone.

Another very interesting finding is the coexistence of PA and OSA in patients with resistant hypertension. In one study of 109 patients with resistant hypertension, OSA was found in 84% of patients with PA [144]. However, in another study, PA was found in only 34% of patients with OSA [145]. The pathophysiologic mechanisms underlining the co-occurrence of these conditions need further elucidation.

The other forms of endocrine hypertension, presented in Table 3, are less frequently encountered in hypertensive patients and, therefore, represent rare causes of resistant hypertension. In addition, the clinical presentation of these endocrine forms of secondary hypertension is usually so characteristic that is really hard to be missed. Since this paper addresses the most common secondary causes of resistant hypertension, readers interested in endocrine hypertension may refer to other recently published reviews [146, 147].

7. Chronic Kidney Disease

Hypertension is commonly found in patients with chronic kidney disease (CKD), with 75% of CKD patients taking antihypertensive drugs [148]. On the other hand, renal disease represents one of the forms of target organ damage induced by hypertension [149]. It seems that the relationship between hypertension and CKD is bidirectional; the kidney is both "the victim and the culprit" in this relationship.

All recent guidelines recommend lower blood pressure goals in patients with CKD, especially when frank albuminuria is present [149–151]. It has been shown, however, that the vast majority (>85%) of patients with CKD fail to achieve these goals; blood pressure control rates in CKD patients are lower than in other hypertensive patients despite the use of 3 antihypertensive drugs in average [152, 153]. It is, therefore, not surprising that the prevalence of resistant hypertension in patients with CKD is over 50% [154]. However, CKD is usually underappreciated as a cause of resistant hypertension, mainly because these patients are being followed at specialized nephrology clinics.

Several factors contribute to treatment resistance in patients with CKD. Sodium and fluid retention plays a cardinal role, while the increased activity of both the sympathetic and the renin-angiotensin-aldosterone systems greatly contribute to treatment resistance. Moreover, vascular alterations both at a structural and functional (increased endothelin-1, decreased nitric oxide bioavailability) level, combined with the consequences of renal ischemia play an additional role [155].

Another significant contributor to treatment resistance in patients with CKD regards the use of diuretics in these patients. It has been observed that restrictions in diuretic use were the primary cause of resistant hypertension in patients with CKD [156]. Restricted diuretic use includes either lower doses or inappropriate drug selection; thiazides are usually not effective when GFR is lower than 40 and should, therefore, be replaced by loop diuretics in such patients. In the case that furosemide is chosen, it has to be given at least twice daily due to its limited half-life. Finally, dietary salt reduction may effectively attenuate volume expansion and offer significant benefits in these patients.

Another important key aspect in patients with CKD is the assessment of urinary albumin excretion. Microalbuminuria and especially macroalbuminuria are related with marked increments in cardiovascular risk. Drugs inhibiting the rennin-angiotensin axis (ACE-inhibitors, angiotensin receptor blockers, and direct rennin inhibitors) should be included in the therapeutic regime, since their use is associated with reduction of albuminuria and end-stage renal disease [157]. The combination of ACE-inhibitors with angiotensin receptor blockers has not proven any benefits in high-risk patients at the ONTARGET study and was even associated with more adverse effects [158, 159]. However, this combination might still be beneficial in patients with CKD and overt albuminuria [160].

Renovascular hypertension is another common form of secondary hypertension. Renovascular hypertension is of atherosclerotic origin in the vast majority of cases, thus being more frequent in older individuals, diabetics, smokers, and in patients with atherosclerotic lesions at other vascular beds [161, 162]. Indeed, about 25% of patients undergoing cardiac catheterization are found to have renal artery stenosis (RAS) higher than 70%, which could be of clinical significance [163, 164]. On the other hand, fibromuscular dysplasia is a much less frequent cause of RAS (approximately 10%) than atherosclerosis, and is more frequently encountered in younger females.

Renovascular hypertension is common among patients with resistant hypertension. Older studies suggested that 1 out of 3 patients with secondary hypertension has renovascular hypertension [165, 166]. Unfortunately, recent studies in patients with resistant hypertension usually focus on OSA and PA and do not even mention RAS. It seems that RAS came out of fashion, mainly because its diagnosis with noninvasive methods remains tricky. Although several methods are used for the detection of RAS (duplex ultrasound, renal scintigraphy, ands CT and MR angiography) with rather good sensitivity and specificity [167], the diagnosis of renovascular hypertension represents an unfulfilled challenge for primary care physicians and remains mainly restrained in specialized centers.

Another important aspect regards the management of patients with RAS. Three choices are available nowadays: surgical treatment, balloon angioplasty (with or without stenting), and conservative drug treatment. The surgical approach has subsided during the last decades and is now reserved for specific indications. Available data regarding the remaining two methods are inconclusive. Balloon angioplasty was not found superior to optimal drug treatment in the recently published ASTRAL study; several drawbacks, however, limit the interpretation of study findings [168]. Another ongoing trial, the CORAL study, will provide hard-endpoint data with the two different approaches [169].

8. Rational for the Management of Resistant Hypertension

The management of resistant hypertension represents a challenge for the astute clinician. Although it seems rational for patients with resistant hypertension to be referred to specialized hypertension clinics, the initial evaluation can be performed by primary care physicians. We will, therefore, attempt to provide a step-by-step approach for the evaluation and treatment of patients with resistant hypertension. The first steps may take place at the primary care level, in the attempt to substantially reduce the number of referred patients and prevent unnecessary costs and patient discomfort.

In summary, the following steps need to be followed in the management of resistant hypertension.

(i) Verification of "true" Resistant Hypertension. Patients with "pseudoresistance" should be identified and excluded from further evaluation. Three main problems require special attention at this step: patient-related problems, physician-related problems, and blood-pressure technique-related problems.

(a) *Patient-Related Problems.* Adherence to antihypertensive treatment is of utmost importance for the effective management of arterial hypertension. Both epidemiological and clinical data strongly indicate that patient adherence to antihypertensive therapy is poor [170–175]. Almost half of treated hypertensive patients discontinue drug administration during the first year of treatment whereas long-term adherence rates are even lower. In addition, small studies in patients with resistant hypertension suggest that poor patient adherence represents one of the most common causes of treatment resistance [176, 177]. Detailed medical history, information by relatives, and use of specific questionnaires might help in identifying patients with poor adherence; these methods can be easily applied by primary care physicians with obvious benefits. The pursuit of improved patient adherence attracts great scientific interest. Modern technology is used with good results (electronic pill boxes, internet monitoring) but is not widely applied yet. Special programmes using close contact of health care professionals (doctors, nurses, and pharmacists) with patients seem also effective but lack wide application as well. Finally, simplification of dosing schedule and use of drugs with superior safety profile may be of benefit.

(b) *Physician-Related Problems*. Physician inertia is another important factor contributing in treatment resistance. It has been shown that doctors are frequently reluctant to maximize drug therapy, either by adding antihypertensive drugs or by switching drug category, in order to achieve blood pressure goals [178–181]. Indeed, a gap between guideline recommendations and their implementation in everyday clinical practice has been recognized and represents a significant obstacle in achieving satisfying blood pressure control rates [149, 150]. Another contributor to treatment resistance is the use of inappropriate drug combinations or suboptimal doses of antihypertensive drugs. Indeed, a study of patients with resistant hypertension revealed that simple measures, such as increasing diuretic dosing or switching to appropriate diuretics, can result in significant blood pressure reductions [156].

In our opinion, however, the most important line of evidence suggesting physician inertia on treatment resistance, comes from recent studies reporting significantly higher control rates of hypertension [182–185]. In these studies, various measures have been used to motivate physicians in achieving blood pressure goals, resulting in improved control rates. Therefore, physicians need to be the focus of future efforts for the effective management of resistant hypertension.

(c) *Blood Pressure Technique-Related Problems*. The requirements for proper blood pressure measurement have been standardized [186] and incorporated in the guidelines for the management of arterial hypertension [149, 150]. However, the measurement of office blood pressure in clinical practice frequently deviates from the recommendations. Therefore, falsely elevated blood pressure levels may be recorded due to several reasons: inappropriate cuff size, failure to comply with the recommendations regarding sufficient time before blood-pressure measurement, arm support at the heart level, assessment in a quiet room, triplicate recordings, and coffee intake or smoking before blood pressure measurement [187–189]. The above mentioned factors may contribute to overestimation of blood pressure and "pseudoresistance". Similarly, false elevations may be encountered in older patients, in whom adequate artery compression may not be achieved due to marked arterial calcification. Therefore, it is essential to assure proper techniques of blood pressure measurement in order to limit the rates of pseudoresistance.

Another important aspect of "resistance" is recognition of "white coat" hypertension. It has been noted that in 20–30% of patients with resistant hypertension, treatment resistance may be attributed to the "white coat" effect [143, 190–192]. Target organ damage is less frequent in these patients, who actually do not suffer from "true" resistant hypertension. Therefore, either ambulatory or home blood-pressure monitoring should be performed in every patient with resistant hypertension, in order to exclude the "white coat" effect and avoid unnecessary referrals.

(ii) Exclusion of Drug-Induced Hypertension. As discussed in the first section of this paper, several drugs may induce blood pressure elevations, with NSAIDs and oral contraceptives being the most common. Therefore, practicing physicians need to be very meticulous during medical history taking, in order to uncover the use of drugs inducing hypertension. The withdrawal of offended drugs usually results to the return of blood pressure at previous levels. In the case, however, that the drug is considered essential for the treatment of comorbidities, the substitution to another drug with a more friendly profile or the reduction of dose might be beneficial.

(iii) Reduction of Dietary Sodium Intake. Sodium intake is excessive in the Western world, mainly due to the "hidden salt" in processed foods. The average sodium intake is far higher than the recommended 2.4 grams per day, reaching even 10 g/day in patients with resistant hypertension [193]. Plasma volume expansion represents one of the cardinal characteristics of resistant hypertension. The important role of sodium restriction in patients with resistant hypertension is highlighted by the findings of a recent study. It was found that reductions in sodium intake are accompanied by significant reductions in blood pressure levels in resistant hypertensives [194].

(iv) Evaluation for Secondary Causes of Hypertension. As previously discussed, obstructive sleep apnea, primary aldosteronism, and chronic kidney disease represent the most common secondary causes of resistant hypertension whereas several other conditions may be responsible for treatment resistance as well. The diagnostic workup for secondary hypertension is demanding, requires special knowledge and technology, and should be performed in specialized referral centers, which are familiar with secondary hypertension. Although a detailed description of the diagnostic workup is beyond the scope of this paper, some signs and/or findings raising the suspicion of secondary hypertension need to be mentioned. In particular: obesity, snoring, daytime sleepiness, and increased neck diameter raise the suspicion of obstructive sleep apnea; hypokalemia (either spontaneous or diuretic induced) is present in about half of cases with primary aldosteronism; active urine sediment, small kidneys, and impaired renal function point towards chronic kidney disease; abdominal bruit, difference in renal size raise the suspicion of renal artery stenosis..

(v) Pharmacologic Management of Resistant Hypertension. The pathophysiology of resistant hypertension provides the rational for the effective management of this clinical entity. The combination of increased systemic vascular resistance with marked volume expansion in many cases, renders the triple combination of a drug inhibiting the renin-angiotensin axis (ACE-inhibitors or angiotensin receptor blockers) with a calcium antagonist and a diuretic a very attractive combination for the majority of patients (unless these drugs are contraindicated or not tolerated, or other drugs are indicated due to comorbidities). However, reliable data verifying the superiority of this combination over other combinations is not available. Special attention has to be drawn in maximizing the dose of diuretics or switching to loop diuretics in patients with low GFR. The overactivation of the sympathetic nervous system renders beta blockers, alpha blockers, and centrally acting antihypertensive drugs (clonidine, alpha methyldopa) of potential benefit in many patients when added in previous therapy. Direct vasodilators, such as hydralazine and minoxidil, can be very effective for blood pressure management, especially in African Americans and patients with chronic kidney disease. A vast amount of evidence indicates that spironolactone is a drug of choice in the treatment of resistant hypertension. Several studies revealed impressive blood pressure reductions in patients with resistant hypertension when spironolactone was added in the therapeutic regime [195–205]. Chronotherapy represents an important approach for the management of resistant hypertension. Administration of one antihypertensive drug at bedtime has been shown to improve blood pressure control in patients with resistant hypertension [206–208].

(vi) Newer Drugs for the Management of Resistant Hypertension . Endothelin antagonists exhibited promising results in preliminary studies [209]. The future of darusentan remains unclear, however, since in another study in patients with resistant hypertension, darusentan failed to be more effective than placebo regarding office blood pressure reductions. It has to be mentioned, however, that in the latter study, significant differences were detected in ambulatory blood pressure between darusentan and placebo [210], indicating that further studies are needed with this drug category. Another interesting approach for the management of resistant hypertension is the administration of nitric oxide donors. In a recent small clinical study of six patients with resistant hypertension, the combination of nitrates with phosphodiesterase-5 inhibitors resulted in significant blood pressure reduction [211]. However, this finding has to be interpreted with caution, since the concomitant use of these medications is contraindicated due to the possibility of severe hypotension.

(vii) Interventional Management of Resistant Hypertension. Despite the wide application of antihypertensive therapy, a substantial portion of the hypertensive population remains uncontrolled although taking more than three drugs. This situation calls for testing alternative approaches in patients with resistant hypertension. Carotid baroreceptors and renal sympathetic overdrive play a significant role in blood pressure regulation [212, 213]. During the last decade, two new approaches have revived the use of interventional techniques for the management of resistant hypertension. Carotid baroreceptor stimulation and renal sympathetic denervation have shown promising preliminary results in patients with resistant hypertension [214, 215]. However, further studies are needed to establish their role in the management of resistant hypertension.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 624691, 10 pages
doi:10.4061/2011/624691

Review Article

Adrenocortical Causes of Hypertension

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Received 18 November 2010; Revised 9 January 2011; Accepted 13 January 2011

Academic Editor: Vasilios Papademetriou

Primary aldosteronism is the most common cause of secondary hypertension. In the past, screening for primary aldosteronism was offered only in patients with hypertension associated with hypokalemia. Recent studies showed that hypokalemia is seen in only 25% of the patients with primary aldosteronism, which has increased the prevalence of primary aldosteronism to 10–15% of all cases with new onset hypertension.

1. Introduction

Approximately 85 million people in the United States are estimated to be hypertensive. In the majority, the hypertension is "essential" or "idiopathic," but a subgroup of approximately 15% has secondary hypertension. The secondary causes of hypertension can be divided into renal (e.g., renovascular or renal parenchymal disease) and endocrine causes. There are at least 14 endocrine disorders in which hypertension may be the initial clinical presentation (Table 1).

A further classification of the adrenocortical causes of hypertension based on the levels of renin and aldosterone can be used for the diagnostic approach of a patient with suspected endocrine hypertension (Table 2).

An accurate diagnosis of endocrine hypertension provides the clinician with a unique treatment opportunity, that is, to render a surgical cure or to achieve a dramatic response with pharmacologic therapy. Primary hyperaldosteronism, which represents the most common cause of endocrine resistant hypertension, is reviewed here.

2. Aldosterone Biosynthesis and Control of Secretion

The differentiation of the adrenal cortex into distinct zones has important functional consequences. The *zona glomerulosa* comprises approximately 15% of the cortex (depending upon sodium intake). Cells are clustered in spherical nests and are small with smaller nuclei in comparison to other zones. The *zona fasciculata* comprises the 75% of the cortex; in this zone, the cells are large and lipid laden and form radial cords between the fibrovascular radial network. The innermost *zona reticularis* is sharply demarcated from both zona fasciculata and the adrenal medulla; cells are irregular with little lipid content. Three main types of hormone are produced by the adrenal cortex-glucocorticoids (cortisol, corticosterone), mineralocorticoids (aldosterone, deoxycorticosterone), and sex steroids (mainly androgens).

Aldosterone is synthesized from cholesterol in a series of six biosynthetic steps [1]. The first four steps are also involved in the synthesis of cortisol, whereas the last two pertain only to aldosterone [2]. The product of the *CYP11B2* gene is capable of catalyzing both the 11-hydroxylase and 18-hydroxylase and 18-hydroxydehydrogenase steps in aldosterone biosynthesis [2–4]. The *CYP11B2* gene is located on human chromosome 8q24.3-tel [5].

Aldosterone, the major circulating mineralocorticoid, is a steroid hormone produced exclusively in the *zona glomerulosa*. The major regulators of aldosterone biosynthesis and secretion are the renin-angiotensin system and potassium ion concentrations. Minor regulators include corticotrophin (ACTH) from the pituitary, atrial natriuretic peptide from the heart, and dopamine secreted locally in the adrenal. A number of aldosterone precursors,

Table 1: Endocrine causes of hypertension.

Adrenal dependent
(1) Pheochromocytoma
(2) Cushing's syndrome
(3) Primary hyperaldosteronism
(4) Other adrenocortical tumors (i.e., carcinoma, other)
(5) Genetic defects affecting adrenocortical function
(i) Congenital adrenal hyperplasia: 11β-Hydroxylase and 17α-Hydroxylase deficiency, primarily
(ii) Primary cortisol resistance
Apparent mineralocorticoid excess (AME)/11β-Hydroxysteroid dehydrogenase deficiency
Genetic
(i) Type 1 AME
(ii) Type 2 AME
Acquired
(i) Licorice or carbenoxolone ingestion (type 1 AME)
(ii) Cushing's syndrome (type 2 AME)
Thyroid dependent
Hyperthyroidism
Parathyroid dependent
Hyperparathyroidism
Pituitary dependent
(1) Acromegaly
(2) Cushing's disease

Table 2: Adrenocortical causes of hypertension.

Low renin and high aldosterone
Primary aldosteronism
(1) Aldosterone producing adenomas(APA)—35% of cases
(2) Bilateral idiopathic hyperplasia(IHA)—60% of cases
(3) Primary adrenal hyperplasia—2% of cases
(4) Aldosterone-producing adrenocortical carcinoma—<1% of cases
(5) Familial Hyperaldosteronism(FH)
(i) Glucocorticoid-remediable Aldosteronism(FH type I)—<1% of cases
(ii) FH type II(APA or IHA)—<2% of cases
(6) Ectopic aldosterone producing adenoma or carcinoma—<0.1% of cases
Low renin and low aldosterone
Hyperdeoxycorticosteronism
(1) Congenital adrenal hyperplasia
11β-hydroxylase deficiency
17α-hydroxylase deficiency
(2) Deoxycorticosterone producing tumor
(3) Primary cortisol resistance
(4) Apparent mineralocorticoid excess (AME) 11β-Hydroxysteroid dehydrogenase deficiency (Genetic or Acquired)
(5) Cushing's syndrome and Cushing's disease

including deoxycorticosterone and 18-hydroxycorticosterone, have mineralocorticoid activity, and their hypersecretion in various pathological states may produce or exacerbate features typical of mineralocorticoid hypertension. Aldosterone acts mainly on the distal nephron although several other sites of sodium reabsorption exist.

The classic functions of aldosterone are regulation of extracellular volume and control of potassium homeostasis. These effects are mediated by binding of free aldosterone to the mineralocorticoid receptor in the cytosol of epithelial cells principally in the kidney. Mineralocorticoid receptors have a tissue-specific expression. For example, tissues with

the highest concentration of these receptors are the distal nephron, hippocampus, and colon. Lower concentrations are found in the rest of the gastrointestinal tract and heart. Transport to the nucleus and binding to specific binding domains on targeted genes lead to their increased expression. Aldosterone-regulated kinase appears to be a key intermediary, and its increased expression leads to modification of the apical sodium channel, resulting in increased sodium ion transport across the cell membrane. The increased tubular negativity augments tubular secretion of potassium by the tubular cells and hydrogen ion by the interstitial cells.

Glucocorticoids and mineralocorticoids bind equally to the mineralocorticoid receptor. Specificity of action is provided by the presence of a glucocorticoid metabolizing enzyme, 11β-hydroxysteroid dehydrogenase (11BHSD2), which metabolizes cortisol to cortisone and prevents glucocorticoids from interacting with the receptor.

In addition to the classic genomic actions mediated by aldosterone binding to cytosolic receptors, mineralocorticoids have acute, nongenomic actions due to activation of an unidentified cell surface receptor. This action involves most likely a G protein-coupled receptor and probably a modification of the sodium hydrogen exchange activity.

Aldosterone has additional, nonclassic effects primarily on non epithelial cells. These include the expression of several collagen genes, genes controlling tissue growth factors, such as transforming growth factor β and plasminogen activator inhibitor type 1, and genes mediating inflammation. The resultant actions lead to microangiopathy, necrosis (acutely), and fibrosis in various tissues such as the heart, the vasculature, and the kidney.

At the level of the zona glomerulosa, the major stimulatory influences are angiotensin II and serum potassium [6, 7]. ACTH stimulates aldosterone secretion in an acute but transient fashion, but it is questionable whether ACTH plays a significant role in the chronic regulation of mineralocorticoid secretion [8]. The major inhibitory influences affecting the *zona glomerulosa* are exerted by circulating atrial natriuretic peptide (ANP) and locally by dopamine [9]. Although ANP levels are clearly increased in hyperaldosteronism, neither ANP nor dopamine has been implicated as primary causes of clinically significant defects in aldosterone secretion. Metoclopramide increases aldosterone secretion, suggesting dopamine may inhibit aldosterone release [10–12]. The physiologic roles of adrenomedullin and vasoactive intestinal peptide (VIP) on aldosterone secretion remain to be clarified; it appears that both these neuropeptides are produced in the rat *zona glomerulosa* [13, 14].

3. Primary Hyperaldosteronism

In his presidential address at the Annual Meeting of the Central Society for Clinical research, Chicago Illinois, October 29 1954, Dr. Jerome W. Conn stated: "I have prepared no comprehensive review of my personal philosophy of clinical investigation. Instead, I plan to make a scientific report to you about a clinical syndrome, the investigation of which has been most exciting to me since I initiated it in April of this year".

In April 1954, Conn was asked to see M. W., a 34-year-old woman with a 7-year history of muscle spasms, temporary paralysis, tetany, and weakness and a 4-year history of hypertension. Because there were no signs or symptoms of glucocorticoid or androgen excess, Conn suspected based on his prior research that M. W.'s clinical presentation could result from excess secretion of the adrenal salt-retaining corticoid. Conn planned for a bilateral adrenalectomy on December 1954. In 1955, Gittler and Fajans told of the surgical scene: To "the immense delight of Conn and those in the operating room, the surgeon, Dr. William Baum, encountered a right 13gr adrenal tumor which was removed while leaving the contralateral gland intact. The patient's post operative studies showed an almost total reversal of the preoperative metabolic and clinical abnormalities".

By 1964, Conn had collected 145 cases, and he suggested that up to 20% of patients with essential hypertension might have primary aldosteronism. Later, Conn decreased his predicted prevalence or primary aldosteronism to 10% of hypertensives, a prediction that was substantiated nearly 40 years later.

In the past, clinicians would not consider the diagnosis of primary hyperaldosteronism unless the patient presented with spontaneous hypokalemia, and then the diagnostic evaluation would require discontinuation of antihypertensive medications for at least 2 weeks. The spontaneous hypokalemia/no antihypertensive drug approach resulted in predicted prevalence rates of less than 0.5% of hypertensive patients.

However, it is now recognized that most patients with primary aldosteronism are not hypokalemic and that screening can be completed with a simple blood test (plasma aldosterone concentration[PAC]-to-plasma renin activity (PRA) ratio) while the patient is taking antihypertensive drugs. Using the PAC/PRA ratio as a screening test, followed by confirmatory testing, has resulted in much higher prevalence estimates (5% to 13% of all patients with hypertension) for primary aldosteronism.

Since Conn described the first case of an aldosterone-producing adenoma, several subtypes of primary aldosteronism have been described (Table 2). The differential diagnosis of these subtypes is crucial for the management and the prognosis.

4. Clinical Presentation

The diagnosis of primary aldosteronism is usually made in patients who are in the third to sixth decade of life. In cases associated with hypokalemia, patients may have muscle spasms, weakness, headaches, palpitations, polyuria, polydipsia, nocturia, or a combination of these. Periodic paralysis is a very rare presentation in Caucasians but not an infrequent presentation in patients of Asian descent. Sometimes, tetany can develop due to decreased ionized calcium from hypokalemic alkalosis. The nocturia and polyuria are a result of hypokalemia-induced renal concentrating defect,

and the presentation is frequently mistaken for prostatic disease in men.

There are no specific physical findings. Edema is not a common finding because of the mineralocorticoid escape phenomenon. The degree of hypertension may be moderate to severe and may be resistant to usual pharmacologic treatments. Patient with aldosterone producing adenoma tend to have higher blood pressure compared to patient with bilateral idiopathic hyperplasia. Hypokalemia is frequently absent; in some patients, the hypokalemia can become evident only with the addition of potassium-wasting diuretics, and some patients can develop profound hypokalemia with only small doses of diuretics. Because of a reset osmostat, the serum sodium concentration tends to be high normal or above the upper limit of normal. This clinical clue is very useful when initially assessing the potential for primary aldosteronism.

Patients with primary aldosteronism may be at higher risk than other patients with essential or secondary hypertension for target-organ damage of the heart and kidney. That can be explained from a direct effect of aldosterone on these organs.

5. Screening for Primary Aldosteronism

The diagnostic approach to primary aldosteronism can be considered in three phases: screening, confirmation, followed by subtype evaluation tests.

Physicians should always consider screening for primary aldosteronism in the following situations:

(1) hypertension and hypokalemia,

(2) resistant hypertension,

(3) adrenal incidentaloma and hypertension,

(4) onset of hypertension at a young age (<20 years),

(5) severe hypertension (>160 mm systolic or >100 diastolic),

(6) secondary hypertension,

(7) profound hypokalemia with usual doses of potassium wasting diuretics.

The initial screening tests include the measurement of plasma aldosterone concentration and plasma renin activity and calculation of the PAC/PRA (ARR) ratio. Like all biochemical case detection tests, the ARR is not without false positives and negatives. Table 2 documents the effect of medications and conditions on the ARR. The ARR should, therefore, be regarded as a detection test only and should be repeated if the initial results are inconclusive or difficult to interpret because of suboptimal sampling conditions.

If a patient is already on any of the medications listed in Table 3, he can be switched over to medications [15, 16] that do not affect or affect minimally the ARR. In Table 4 are listed the antihypertensive medications that have minimal effects on plasma aldosterone levels and can be used to control hypertension during case finding and confirmatory testing for primary aldosteronism [15, 16].

Table 3

	PAC	PRA	PAC/PRA
Medications			
β-Adrenergic blockers	↓	↓↓	↑(FP)
Central α-2 agonists	↓	↓↓	↑(FP)
NSAIDs	↓	↓↓	↑(FP)
K^+-wasting diuretics	→ ↑	↑↑	↓(FN)
K^+-sparing diuretics	↑	↑↑	↓(FN)
ACE inhibitors	↓	↑↑	↓(FN)
ARBs	↓	↑↑	↓(FN)
Ca^{2+} blockers (DHPs)	→ ↓	↑	↓(FN)
Renin inhibitors	↓	↓↑[1]	↑(FP)[1]
			↓ (FN)[1]
Potassium status			
Hypokalemia	↓	→ ↑	↓(FN)
Potassium loading	↑	→ ↓	↑(FP)
Dietary sodium			
Sodium restricted	↑	↑↑	↓(FN)
Sodium loaded	↓	↓↓	↑(FP)
Advancing age	↓	↓↓	↑ (FP)
Other conditions			
Renal impairment	→	↓	↑(FP)
PHA-2	→	↓	↑(FP)
Pregnancy	↑	↑↑	↓(FN)
Renovascular HTN	↑	↑↑	↓(FN)
Malignant HTN	↑	↑↑	↓ (FN)

The ARR is most sensitive when used in patients from whom samples are collected in the morning after patients have been out of bed for at least 2 h, usually after they have been seated for 5–15 min and without posture stimulation. Ideally, patients should have unrestricted dietary salt intake before testing. In many cases, the ARR can be confidently interpreted with knowledge of the effect on the ARR of continued medications or suboptimal conditions of testing, avoiding delay and allowing the patient to proceed directly to confirmatory/exclusion testing [15, 16]. Washout of all interfering antihypertensive medications is feasible in patients with mild hypertension but is potentially problematic in others and perhaps unnecessary in that medications with minimal effect on the ARR can be used in their place (Table 4).

A suggested approach [15, 16] for measurement of ARR as per the 2008 Endocrine Society guidelines follow.

(A) *Preparation for ARR Measurement: Agenda*

(1) Attempt to correct hypokalemia, after measuring plasma potassium in blood collected slowly with a syringe and needle (preferably not a Vacutainer to minimize the risk of spuriously raising potassium); avoid fist clenching during collection; wait at least 5 sec after tourniquet release (if used to achieve insertion of needle); ensure separation of plasma from cells within 30 min of collection.

Table 4

Drug	Class	Usual dose	Comments
Verapamil slow release	Nondihydropyridine calcium channel antagonist	90–120 mg twice daily	Use singly or in combination with the other agents listed in this table.
Hydralazine	Vasodilator	10–12.5 mg twice daily, increasing as required	Commence verapamil slow release first to prevent reflex tachycardia. Commencement at low doses reduces risk of side effects (including headaches, flushing, and palpitations).
Prazosin hydrochloride	α-Adrenergic blocker	0.5–1 mg two to three times daily, increasing as required	Monitor for postural hypotension
Doxazosin mesylate	α-Adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension
Terazosin hydrochloride	α-Adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension

(2) Encourage patient to liberalize (rather than restrict) sodium intake.

(3) Withdraw agents that markedly affect the ARR (48) for at least 4 weeks:

(a) spironolactone, eplerenone, amiloride, and triamtereneb,

(b) potassium-wasting diureticsc,

(c) products derived from licorice root (e.g., confectionary licorice, chewing tobacco).

(4) If the results of ARR of the above agents are not diagnostic, and if hypertension can be controlled with relatively noninterfering medications (see Table 4), withdraw other medications that may affect the ARR (48) for at least 2 weeks like

(a) β-Adrenergic blockers, central α-2 agonists (e.g., clonidine and α-methyldopa), nonsteroidal anti-inflammatory drugs,

(b) angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and dihydropyridine calcium channel antagonists.

(5) If necessary to maintain hypertension control, commence other antihypertensive medications that have lesser effects on the ARR (e.g., verapamil slow release, hydralazine (with verapamil slow release, to avoid reflex tachycardia), prazosin, doxazosin, and terazosin; see Table 4).

(6) Establish OC and HRT status, because estrogen-containing medications may lower DRC and cause false-positive ARR when DRC (rather than PRA) is measured. Do not withdraw OC unless confident of alternative effective contraception.

(B) *Conditions for Collection of Blood*

(1) Collect blood mid-morning, after the patient has been up (sitting, standing, or walking) for at least 2 h and seated for 5–15 min.

(2) Collect blood carefully, avoiding stasis and hemolysis (see A.1 above).

(3) Maintain sample at room temperature (and not on ice, because this will promote conversion of inactive to active renin) during delivery to laboratory and before centrifugation and rapid freezing of plasma component pending assay.

(C) *Factors to Take into Account when Interpreting Results (see Table 3)*

(1) Age: in patients aged >65 yr, renin can be lowered more than aldosterone by age alone, leading to a raised ARR.

(2) Time of day, recent diet, posture, and length of time in that posture.

(3) Medications.

(4) Method of blood collection, including any difficulty doing so.

(5) Level of potassium.

Level of creatinine (renal failure can lead to false-positive ARR).

Another important consideration when we are screening patients for primary aldosteronism is the reliability and the sensitivity of the assay we use for both aldosterone and plasma renin activity. Because the ARR is mathematically highly dependent on renin, renin assays should be sufficiently sensitive to measure levels as low as 0.2–0.3 ng/mL·h (DRC 2 mU/liter). Although most laboratories use radioimmunoassay (RIA) for plasma and urinary aldosterone, measured levels of standards have been shown to

be unacceptably different in some instances. Tandem mass spectrometry is increasingly used and has proved to be much more consistent in performance.

6. Interpretation of ARR

Secondary hyperaldosteronism should be considered when both PRA and PAC are increased and the ARR is less than 10 (e.g., Renovascular disease). If both PAC and PRA are suppressed, an alternate source of mineralocorticoid receptor agonist should be considered (e.g., hypercortisolism). Primary aldosteronism should be suspected when PRA is suppressed (<1 ng/mL/hr) and PAC is increased. It is important to understand that the lower limit of detection varies among different PRA assays and can have dramatic effect on the PAC/PRA ratio. For example, if the lower limit for detection of for PRA is 0.6 ng/mL/hr and the PAC is 16 ng/dL, then the ARR would be 27. However, if the lower limit for detection of PRA is 0.1 ng/mL/hr, then the ARR would be 160. Thus, the ARR cutoff for a high ARR is laboratory dependent and more specifically PRA assay dependent.

In a retrospective study [17], the combination of an ARR>30 and PAC >20 ng/dL had a sensitivity of 90% and a specificity of 91% for aldosterone producing adenomas. At Mayo clinic, an ARR of more than 20 and a PAC >15 ng/dL are found in more than 90% of patients with surgically confirmed aldosterone producing adenomas.

Most groups, however, use cutoffs of 20–40 when testing is performed in the morning on a seated ambulatory patient. Some investigators [18] require elevated aldosterone levels in addition to elevated ARR for a positive screening test for PA (usually aldosterone >15 ng/dL.) An alternative approach is to avoid a formal cutoff level for plasma aldosterone but to recognize that the likelihood of a false-positive ARR becomes greater when renin levels are very low.

Against a formal cutoff level for aldosterone are the findings of several studies. In one study, seated plasma aldosterone levels were less than 15 ng/d in 36% of 74 patients diagnosed with PA after screening positive by ARR defined as more than 30 and showing failure of aldosterone to suppress during fludrocortisone suppression testing (FST) and in four of 21 patients found by AVS to have unilateral, surgically correctable PA. Another study reported plasma aldosterone levels of 9–16 ng/dL in 16 of 37 patients diagnosed with PA by FST. Although it would clearly be desirable to provide firm recommendations for ARR and plasma aldosterone cutoffs, the variability of assays between laboratories and the divided literature to date makes it more prudent to point out relative advantages and disadvantages, leaving clinicians the flexibility to judge for themselves.

7. Confirmatory Tests

An increased ARR is not diagnostic by itself and confirmatory tests are required to demonstrate inappropriate aldosterone secretion. Treatment with spironolactone or eplerenone should not be started before the confirmation of primary aldosteronism. In patients already receiving treatment with spironolactone or eplerenone, the treatment should be held for at least 4–6 weeks before further diagnostic testing. Aldosterone suppression testing can be performed with orally administered sodium chloride and measurement of urinary aldosterone or with intravenous sodium chloride loading and measurement of PAC.

8. Oral Sodium Loading Test

After hypertension and hypokalemia are controlled, patients should increase their sodium intake to >200 mmol/d (~6 g/d) for 3 d, verified by 24-h urine sodium content. Patients should receive adequate slow-release potassium chloride supplementation to maintain plasma potassium in the normal range. Urinary aldosterone is measured in the 24-h urine collection from the morning of d 3 to the morning of d 4. Primary aldosteronism is unlikely if urinary aldosterone is lower than 10 μg/24 h (27.7 nmol/d) in the absence of renal disease, where primary aldosteronism may coexist with lower measured urinary aldosterone levels. Elevated urinary aldosterone excretion (>12 μg/24 h (>33.3 nmol/d) at the Mayo Clinic, >14 μg/24 h (38.8 nmol/d) at the Cleveland Clinic) makes primary aldosteronism highly likely. This test should not be performed in patients with severe uncontrolled hypertension, renal insufficiency, cardiac insufficiency, cardiac arrhythmia, or severe hypokalemia. The 24-h urine collection may be inconvenient. Laboratory-specific poor performance of the RIA for urinary aldosterone (aldosterone 18-oxo-glucuronide or acid-labile metabolite) may blunt diagnostic accuracy, a problem obviated by the currently available HPLC-tandem mass spectrometry methodology. Aldosterone 18-oxo-glucuronide is a renal metabolite, and its excretion may not rise in patients with renal disease.

9. Intravenous Saline Infusion Test

The test is done after an overnight fast. Patients stay in the recumbent position for at least 1 h before and during the infusion of 2 liters of 0.9% saline iv over 4 h, starting at 0800–0930 h. Blood samples for renin, aldosterone, cortisol, and plasma potassium are drawn at time zero and after 4 h, with blood pressure and heart rate monitored throughout the test. Postinfusion plasma aldosterone levels <5 ng/dL make the diagnosis of primary aldosterone unlikely, and levels >10 ng/dL are a very probable sign of primary aldosterone. Values between 5 and 10 ng/dL are indeterminate and can be seen in patients with bilateral idiopathic hyperplasia. This test should not be performed in patients with severe uncontrolled hypertension, renal insufficiency, cardiac insufficiency, cardiac arrhythmia, or severe hypokalemia.

10. Subtype Studies

All patients with primary aldosteronism (PA) should undergo an adrenal CT scan as the initial study in subtype testing and to exclude large masses that may represent adrenocortical carcinoma. The findings on adrenal

CT—normal-appearing adrenals, unilateral macroadenoma (>1 cm), minimal unilateral adrenal limb thickening, unilateral microadenomas (≤1 cm), or bilateral macro- or microadenomas (or a combination of the two)—are used in conjunction with adrenal venous sampling (AVS) and, if needed, ancillary tests to guide treatment decisions in patients with PA. Aldosterone-producing adenomas (APA) may be visualized as small hypodense nodules (usually <2 cm in diameter) on CT. Adrenal glands with bilateral idiopathic hyperplasia (IHA) may be normal on CT or show nodular changes. Aldosterone-producing adrenal carcinomas are almost always more than 4 cm in diameter, but occasionally smaller, and like most adrenocortical carcinomas have a suspicious imaging phenotype on CT.

Adrenal CT has several limitations. Small APAs may be interpreted incorrectly by the radiologist as IHA on the basis of CT findings of bilateral nodularity or normal-appearing adrenals. Moreover, apparent adrenal microadenomas may actually represent areas of hyperplasia, and unilateral adrenalectomy would be inappropriate. In addition, nonfunctioning unilateral adrenal macroadenomas are not uncommon, especially in older patients (>40 yr) and are indistinguishable from APAs on CT. Unilateral UAH may be visible on CT, or the UAH adrenal may appear normal on CT. Magnetic resonance imaging has no advantage over CT in subtype evaluation of PA, being more expensive and having less resolution than CT.

11. Adrenal Venous Sampling

Lateralization of the source of the excessive aldosterone secretion is critical to guide the management of PA. Distinguishing between unilateral and bilateral disease is important because unilateral adrenalectomy in patients with APA or UAH results in normalization of hypokalemia in all; hypertension is improved in all and cured in 30%–60% [19, 20]. In bilateral IHA and GRA, unilateral or bilateral adrenalectomy seldom corrects the hypertension, and medical therapy is the treatment of choice. Unilateral disease may be treated medically if the patient declines or is not a candidate for surgery.

Adrenal vein sampling was initially proposed as a way to localize catecholamine secreting neoplasms (Young 2009). In 1967, Melby et al. reported the use of adrenal vein sampling in primary aldosteronism, and it has since become the gold standard test to differentiate unilateral from bilateral disease (Young 2009). In his initial paper, he reported the comparison of aldosterone from the right and left adrenal veins in seven patients with primary aldosteronism and also in three normal patients. The authors found elevated aldosterone secretion and a higher aldosterone to cortisol ratio from the involved adrenal gland compared to the uninvolved adrenal gland. All primary aldosteronism patients in the study were operated for unilateral adrenalectomy and were found to have adenomas that correlated with the lateralization found on adrenal vein sampling (Melby 1967).

From this first report, adrenal vein sampling in primary aldosteronism has continued to evolve. Some controversies remain including whether the addition of cosyntropin to the test either as a bolus or constant infusion improves the diagnostic accuracy and what diagnostic criteria to use (Auchus 2010). In performing this test, there are some things that need to be considered. First, the patient needs to be prepared properly. They should be tested in a fasting state and be supine for at least one hour before testing (Young 2009). Additionally, certain antihypertensives should be avoided to prevent false results. Mineralocorticoid receptor antagonists in particular should be discontinued at least 6 weeks before testing. Preferred medications include extended release verapamil, α-adrenergic blockers, and hydralazine. Patients should also be potassium repleted as hypokalemia can lower the aldosterone levels (Rossi 2007).

In addition to patient preparation, the test should be performed by an experienced and skilled practitioner, especially given some of the technical difficulties that can arise in cannulating the right adrenal vein. Additionally, a well-defined protocol should be in place (Rossi 2007, Young 2009). Samples are obtained from the right adrenal, left adrenal, and from a peripheral source. This should be performed simultaneously or in rapid sequence to limit fluctuations in secretion that occur with time (Young 2009).

The NIH protocol for adrenal vein sampling in primary aldosteronism is as follows.

(1) Catheterization of bilateral femoral veins is performed with a 0.45 polyurethane catheter with 6 French sheath in the right, and Muller catheter in the left.

(2) Cannulation of both adrenal veins is obtained via the right femoral vein.

(3) Simultaneous baseline sampling for aldosterone and cortisol is performed from both adrenal veins, and a peripheral sample is drawn from the left femoral catheter at time −5 minutes and at time 0 minutes.

(4) After obtaining baseline samples, a 0.25 mg push of ACTH is given followed by steady infusion of ACTH of 1 mcg/ml at 150–200 ml/hr.

(5) At time +10 minutes and +15 minutes, simultaneous samples are again obtained from right adrenal vein, left adrenal vein, and left femoral vein.

(6) Upon completion of sampling, ACTH infusion is stopped and switched to normal saline at KVO, and catheters are removed.

It is important to note that all samples are stored on ice during sampling and are then transported to the laboratory on ice for processing.

Interpretation of the results of the sampling is dependent not only on the aldosterone concentration and on the cortisol concentration but also on whether ACTH stimulation was used. In the setting of ACTH stimulation during adrenal vein sampling, a few ratios need to be calculated. The first is the selectivity index (SI) which is used to determine if there was adequate cannulation of the adrenal veins. This is calculated

Table 5

Location	Aldosterone	Cortisol	Selectivity index	A : C ratio
Right adrenal	A	D	D/F	A/D
Left adrenal	B	E	E/F	B/E
Peripheral	C	F		

by taking the ratio of cortisol from the adrenal compared to the cortisol from the peripheral sample. This should be done for both right and left sided samples. With ACTH stimulation, a ratio of 5 : 1 indicates successful cannulation of the adrenal vein. Without ACTH stimulation, a ratio of 3 : 1 suggests successful cannulation though different cut-offs have been suggested (Young 2009).

After confirming successful cannulation, the next step is to determine unilaterality versus bilaterality. First, the aldosterone concentration needs to be corrected for possible dilution by dividing by the cortisol to get the A : C ratio. Next, the cortisol corrected values are compared to calculate the lateralization index (LI). The greater of A : C ratio is divided by the smaller A : C ratio. A ratio of >4 : 1 suggests lateralization, <3 : 1 suggests bilateral disease, and anything in between is inconclusive (Young 2009, Auchus 2010). An example of the calculation follows Table 5.

In this example, selectivity index (SI) should be >5 to indicate successful cannulation of the adrenal veins. Lateralization index (LI) would be calculated by taking the higher A : C ratio divided by the lower A : C ratio. If LI is > 4, then unilateral disease lateralizing to the numerator side is suggested. If LI is <3, then bilateral disease is suggested. If LI is between 3 and 4, then the results are indeterminate and a repeat study may need to be considered. Alternatively, repeating the assay on samples stored from the test or measuring 18-hydroxycorticosterone could be considered (Auchus 2010). The true sensitivity and specificity of the test is difficult to determine, as calculating this would require performing an adrenalectomy on all patients to verify the diagnosis.

12. Treatment

Unilateral laparoscopic adrenalectomy should be offered to patients with documented unilateral PA (i.e., APA or UAH). If a patient is unable or unwilling to undergo surgery, medical treatment with a mineralocorticoid receptor antagonist is recommended. Hypertension is cured (defined as blood pressure <140/90 mm Hg without the aid of antihypertensive drugs) in about 50% (range, 35%–60%) of patients with APA after unilateral adrenalectomy, with a cure rate as high as 56%–77% when the cure threshold was blood pressure less than 160/95 mm Hg.

There are two mineralocorticoid receptor antagonists that can be used for the management of patients with primary hyperaldosteronism: spironolactone and eplerenone. Usually, a low dose of either antagonist can significantly and effectively improve hypokalemia, but for the management of hypertension, high doses are required. In patients intolerant to mineralocorticoid receptor antagonists, dihydropyridine calcium channel blockers such as nifedipine can be used alternatively, since studies have been shown that it directly inhibits the synthesis of aldosterone and blocks the mineralocorticoid receptors.

Factors associated with resolution of hypertension in the postoperative period include having one or no first-degree relative with hypertension and preoperative use of two or fewer antihypertensive drugs. Other factors have been reported to predict cure but have been evaluated by only univariate analysis or when the cutoff for blood pressure resolution was less than 160/95 mm Hg, duration of hypertension less than 5 yr, higher PAC to PRA ratio preoperatively, higher urinary aldosterone secretion, or positive preoperative response to spironolactone. The most common reasons for persistently increased blood pressure after adrenalectomy are coexistent hypertension of unknown cause and older age and/or longer duration of hypertension.

13. Pre- and Postoperative Management

In the patient scheduled for surgery, both hypertension and hypokalemia should be well controlled preoperatively. Obtaining such control may require a delay in surgery and the addition of a mineralocorticoid receptor antagonist.

Plasma aldosterone and renin activity levels should be measured shortly after surgery as an early indication of biochemical response, and on postoperative day 1, potassium supplementation should be withdrawn, spironolactone discontinued, and antihypertensive therapy reduced, if appropriate.

Postoperative iv fluids should be normal saline without potassium chloride unless serum potassium levels remain very low (i.e., <3.0 mmol/liter), and during the first few weeks after surgery, a generous sodium diet should be recommended to avoid the hyperkalemia that can develop from hypoaldosteronism due to chronic contralateral adrenal gland suppression. In rare instances, temporary fludrocortisone therapy may be required.

Blood pressure typically normalizes or shows maximal improvement in 1–6 months after unilateral adrenalectomy for unilateral APA but can continue to fall for up to 1 yr in some patients.

14. Familial Forms of Primary Aldosteronism

Glucocorticoid-remediable aldosteronism (GRA), also known as familial hyperaldosteronism type I (FH I), is a monogenic form of inherited hypertension, first described in 1966 by Sutherland et al. (1966). This disease is characterized by high plasma aldosterone levels, suppressed plasma renin activity, and abnormally high production of two rare steroids: 18-hydroxycortisol (18OHF) and 18-oxocortisol (18oxoF). The synthesis of these steroids requires the simultaneous presence of a 17-hydroxylase activity and the two C18 (18-hydroxylase and 18-oxidase) activities typical of the CYP11B2 (aldosterone synthase) enzyme.

In GRA, the secretion of aldosterone is primarily regulated by adrenocorticotropic hormone (ACTH) rather than

angiotensin II; in fact, the symptoms are exacerbated by ACTH administration and normalized by glucocorticoid administration. Despite the state of hyperaldosteronism, hypokalemia is not a common feature. In affected families, there is an increased frequency of early death from stroke and an increased risk for exacerbation of hypertension during pregnancy. However, the majority of affected family members has mild-to-moderate hypertension and normal biochemistry and is clinically indistinguishable from patients with essential hypertension. It is, therefore, possible that this condition is under diagnosed. This monogenic form of hypertension is noteworthy, because it is frequently unresponsive to standard antihypertensive medication but successfully managed by treatment with amiloride, spironolactone, or dexamethasone alone.

The GRA is inherited in an autosomal dominant fashion and is caused by the presence of a chimeric gene originating from an unequal crossover between the *CYP11B1* (11_-hydroxylase) and *CYP11B2* genes. The hybrid gene has the CYP11B1 sequence at the 5′ end, including the promoter, and the *CYP11B2* sequence at the 3′ end. The *CYP11B1* promoter ensures the expression of the hybrid gene throughout the adrenal cortex, whereas the *CYP11B2* sequence leads to the inappropriate synthesis of aldosterone, 18OHF, and 18oxoF. The exact position of the crossover site, occurring between intron 2 and exon 4, does not seem to affect the phenotype. Aldosterone suppression by dexamethasone, and high 18OHF and 18oxoF levels are used to differentiate glucocorticoid-remediable aldosteronism from the other forms of primary aldosteronism. Definitive diagnosis can only be reached by identification of the CYP11B1/CYP11B2 chimeric gene in genomic DNA using either Southern blotting or the long PCR technique.

FH-II is an inherited, nonglucocorticoid remediable form of hyperaldosteronism that was relatively recently recognized as a distinct entity. The onset of FH-II occurs usually in adulthood. Apart from its familial occurrence, FH-II is clinically, biochemically, and morphologically indistinguishable from apparently nonfamilial primary aldosteronism and also overlaps with essential hypertension. Pathologic aldosterone secretion may result from unilateral adenoma or bilateral hyperplasia with different subtypes sometimes occurring within different members of the same family. Diagnosis of FH-II can be suspected by documenting primary aldosteronism in two-to-three members (ideally two generations) of a family and excluding the CYP11B1/2 gene. Most, but not all patients could be linked to chromosome 7p22, consistent with the hypothesis that FH-II and maybe primary aldosteronism in general are likely to be genetically heterogeneous [21, 21]. Since FH-II lacks steroid sensitivity, therapeutic options resemble those of the sporadic forms of primary aldosteronism. Like in FH-I it is advisable to avoid genomic and nongenomic effects by removal of the source of aldosterone secretion. Of course, surgery is only indicated if lateralization can be demonstrated by adrenal vein sampling. The second-best approach is blockage of aldosterone effects with receptor antagonists.

15. Summary

Primary hyperaldosteronism is more frequent in hypertensive subjects than was previously believed. It is now recognized that the APA is just one of the seven subtypes of primary aldosteronism. APA and bilateral idiopathic hyperaldosteronism (IHA) are the most common subtypes of primary aldosteronism. Using the plasma aldosterone to plasma renin activity ratio as a case-finding test, followed by aldosterone suppression confirmatory testing, has resulted in much higher prevalence estimates of 5%–13% of all patients with hypertension. In patients with suspected primary aldosteronism, screening can be accomplished by measuring a morning (preferably between 0800 and 1000 h) ambulatory paired random plasma aldosterone concentration (PAC) and plasma renin activity (PRA). An increased PAC : PRA ratio is not diagnostic by itself, and primary aldosteronism must be confirmed by demonstrating inappropriate aldosterone secretion. Aldosterone suppression testing can be performed with orally administered sodium chloride and measurement of urinary aldosterone or with intravenous sodium chloride loading and measurement of PAC. Adrenal venous sampling performed by an experienced interventional radiologist is the gold standard for the differentiation between APA and non-APA-causes of primary aldosteronism. Distinguishing between unilateral and bilateral adrenal hypersecretion is critical in assessing treatment options.

Acknowledgment

This work was supported by the Intramural Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 318549, 8 pages
doi:10.4061/2011/318549

Review Article

Benefits from Treatment and Control of Patients with Resistant Hypertension

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Received 11 October 2010; Accepted 16 November 2010

Academic Editor: A. Gradman

Resistant hypertension is commonly found in everyday clinical practice. However, the risks of resistant hypertension, as well as the benefits of treatment and control of blood pressure in patients with resistant hypertension remain vaguely clarified. Data from small clinical studies and observational cohorts suggest that patients with resistant hypertension are at increased cardiovascular risk, while control of blood pressure offers substantial benefits. It has to be noted however that data from appropriate large randomized studies are missing, and resistant hypertension remains remarkably understudied. Resistant hypertension has attracted significant scientific interest lately, as new therapeutic modalities become available. The interventional management of resistant hypertension either by carotid baroreceptor stimulation or renal sympathetic denervation is currently under investigation with promising preliminary results. This review presents available evidence regarding the benefits of treatment and control of blood pressure in patients with resistant hypertension and offers a critical evaluation of existing data in this field.

1. Introduction

Resistant hypertension is defined as uncontrolled blood pressure despite the use of optimal doses of three antihypertensive medications, of which one is a diuretic [1]. Although this definition encompasses a large number of patients, many of these patients can be controlled with more careful adjustment of their regimen and implementation of good practices. Several factors have been identified as contributors to resistant hypertension: poor patient adherence, physician inertia, inadequate doses or inappropriate combinations of antihypertensive drugs, secondary forms of hypertension, drug-induced hypertension, excess alcohol intake, and volume overload [2]. Lifestyle modifications including salt restriction are very important in these patients [3]. Addressing some of the comorbid conditions, such as sleep apnea, primary aldosteronism [4], or addition of adjunct therapies such as spironolactone [5–11] can achieve blood pressure control. However, many patients remain uncontrolled despite the use of four, five, or six antihypertensive drugs, especially in everyday clinical practice, outside the "sterile" environment of clinical trials. It is surprising to realize that although hypertension is among the most studied diseases, resistant hypertension which denotes the most severe, high-risk, and probably more scientifically interesting subgroup remains so much understudied.

Unfortunately, data regarding the natural history of resistant hypertension is limited. Furthermore, the benefits of controlling blood pressure in patients with resistant hypertension are vaguely clarified, and it seems that they will continue to remain as such, since it is unethical to perform a randomized study with a control group of resistant hypertensives that will remain untreated. Since direct data is not available, only clinically meaningful assumptions can

be made based on indirect information and using common sense. Therefore, for the purpose of this paper we'll use data from the past (before the era of antihypertensive therapy), data from clinical studies involving patients with severe or malignant hypertension, data from small clinical studies in patients with resistant hypertension, and from subgroups of patients included in large clinical trials.

This paper attempts to present available evidence regarding the benefits of treatment and control of resistant hypertension, to highlight the significant scarcity of data in this population, and to critically evaluate the use of data from other hypertensive subgroups for extrapolation in resistant hypertension.

2. Data on Malignant Hypertension: Lessons from the Past

The risks of resistant hypertension and the benefits of its management remind one of the story of malignant hypertension. Although uncontrolled or resistant hypertension is a different entity from malignant hypertension, it is well known that in the long term, untreated or uncontrolled hypertension can lead to "accelerated/malignant" phase (VA studies). The term malignant hypertension was introduced by Volhard and Fahr in 1914 for patients with severe hypertension and renal insufficiency [12]. The term was abandoned until the landmark studies performed at Mayo Clinic by Keith and Wagener. It was observed that the prognosis of malignant hypertension was extremely grave. In the first study from Mayo Clinic, only 7 out of 81 patients with malignant hypertension were still alive after the fifty months of followup, while the average length of life was eight months [13]. Retinitis was highlighted as an essential part of malignant hypertension and was significantly associated with mortality; the average length of life in patients with Grade I retinitis was 17 months and that of patients with Grade IV retinitis was 2 months. In a later study of 146 patients, only 1 patient was alive at the end of five-year follow-up period [14]. Further reports of more than 1400 patients with malignant hypertension have confirmed the findings of Mayo Clinic and revealed that the five-year mortality was over 90%, even until the 60s [15–18]. It's worth noting that no therapy was available at that time. Protein and salt restriction, the rice diet, and mild sedatives were used for the treatment of hypertension; however, the results were all but hopeless regarding long-term improvements [19–23]. Therefore, other therapeutic approaches for malignant hypertension were considered.

Experimental and human studies have revealed the central role of SNS in the pathogenesis of arterial hypertension. Due to the lack of effective therapeutic measures for malignant hypertension, sympathectomy was proposed by many physiologists, such as Pende, Danielopolu, and Jonnesco. Sympathectomy was tested up, that point, for the management of peripheral vascular disease (Jaboulay and Leriche in France), angina pectoris (Jonnesco and Danielopolu in Romania), spastic paralysis (Royle and Hunter in Australia), and Raynaud's disease and scleroderma in Germany (Bruening). Sympathectomy for the treatment of malignant hypertension appears to have taken place for the first time in Germany as early as 1923 [24]. It was introduced in the US by Alfred Adson at the Mayo Clinic and by Max Peet at Ann Arbor. It was rapidly realized that sympathectomy dramatically increased the survival of patients with malignant hypertension. The five-year mortality rates of patients with Grade IV retinopathy fell from 99% at the Keith Wagener series to 66.5% in sympathectomized patients [25, 26]; similar impressive improvements were observed in patients with Grade III retinopathy (Figure 1).

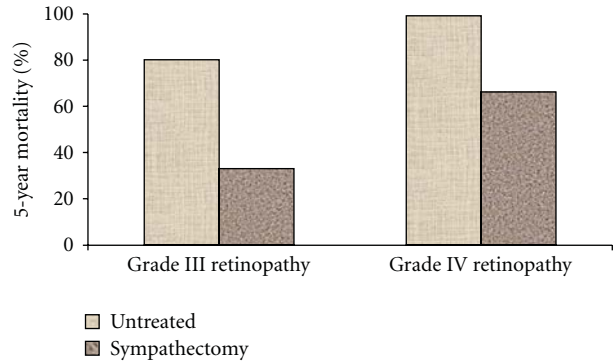

Figure 1: Five-year mortality rates (%) in untreated patients with malignant hypertension and Grade III or IV retinopathy compared to similar patients that underwent sympathectomy (modified from Keith et al. [25] and Peet et al. [26]).

The pioneer work of Peet, Adson Crile, Hener, Page, Grimson, Hinton, and others was reinforced by Reginald Smithwick, who established the operation worldwide as an effective method of lowering blood pressure in patients with malignant hypertension. Until 1960, a plethora of papers reported the effects of sympathectomy in several thousand patients with malignant hypertension all over the world [27–38], pointing towards dramatic improvements in the survival of operated patients [39] when compared to conservative management (Figure 2).

The indications for sympathectomy waxed and waned during this period. The operation was initially reserved for patients with severe hypertension without significant target organ damage (heart failure, chronic renal disease, angina), was later performed irrespective of the organ damage, and finally restricted to patients without chronic complications since the benefits were more apparent in such patients. Similarly, the extent of the operation varied between the different centers, due to the incomplete understanding of sympathetic anatomy and the absence of appropriate studies comparing the various surgical approaches. The common denominator of all operating techniques was the need for prolonged hospitalization and long recovery period. Another annoying aspect of sympathectomy was the lack of satisfactory predictors of blood pressure response to the operation. Although several tests have been used, the results were inconclusive and sometimes misleading.

The most important limitation of sympathectomy was the safety of the procedure. Adverse events were frequent

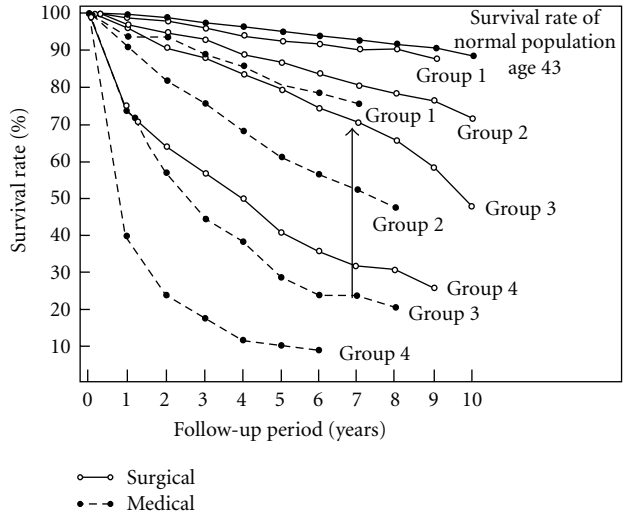

Figure 2: Survival rates in patients with malignant hypertension at various stages (Group 1–4) treated either medically or surgically (modified from Smithwick and Thompson [39]).

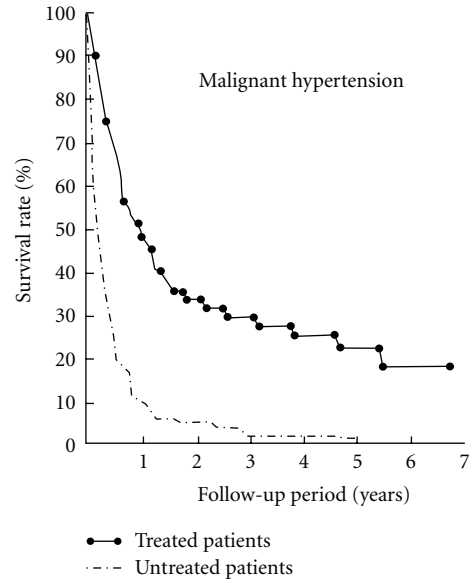

Figure 3: Survival rates in untreated and medically treated patients with malignant hypertension (modified from Harington et al. [40]).

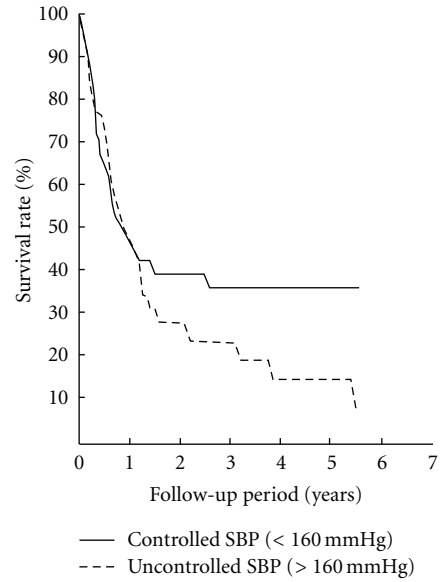

Figure 4: Survival rates in medically treated patients with malignant hypertension according to blood pressure control (modified from Harington et al. [40]).

and annoying, such as orthostatic hypotension, perioperative pain, orthostatic tachycardia, anhidrosis, intestinal and sexual problems, and palpitations, while more serious complications have been reported, such a perioperative death, stroke, myocardial infarction, paraplegia, and spinal cord injury. The operation was unpleasant and intolerant and many hypertension experts remained skeptical; Ed Weiss stated in 1937 "... and now to cap the climax of his difficulties the unfortunate person with hypertension seems about to fall into the clutches of the neurosurgeon who is prepared to separate him from his sympathetic nervous system", while Homer Smith used the words "investigation and desperation" for sympathectomy. It was not until the introduction of effective antihypertensive drug therapy that the benefits and risks of sympathectomy were fully reevaluated.

The interest in sympathectomy faded quite suddenly with the advent of antihypertensive therapy. Centrally acting drugs (ganglion-blocking agents, reserpine) have offered similar beneficial effects [40] (Figure 3). The introduction of diuretics has closed the circle of sympathectomy in the treatment of hypertension, highlighting that therapeutic options fade away when new, more promising treatments appear. Of note, blood pressure control significantly affected the survival of treated patients [40] (Figure 4), underlining that uncontrolled hypertension is associated with increased mortality rates.

3. Data from Trials in Severe Hypertension: The VA Study

Despite the impressive benefits of antihypertensive drugs that have established their use in the treatment of malignant hypertension, their role in the treatment of milder forms of hypertension remained controversial for a significant period of time. Even in 1966, it was stated in the book *Controversy in Internal Medicine* that drug treatment of essential hypertension was not beneficial [41]. Several reasons contributed to the "resistance" of hypertension specialists, primary care physicians, and relevant authorities to recognize the benefits of antihypertensive therapy. Those benefits include the following.

(a) The general belief that vascular changes represent a primary pathologic process that is independent of blood pressure levels. Hypertension was considered to be merely a symptom and not the cause of vascular

complications, therefore the motto "treat the patient, not the manometer" was adopted by the majority.

(b) The inheritance of Sir William Osler promoted therapeutic nihilism. The nihilistic attitude regarding the role of drug therapy may be attributed to Osler's quote: "one of the first duties of the physician is to educate the masses not to take medicine" [42]. However, this was probably a misinterpretation of Osler's beliefs, since Osler was referring to the drugs available at his time, the use of which reached the limits of charlatanism, and not modern antihypertensive drugs that were not available at his time.

(c) The special emphasis and the exaggerated focus that were given in secondary forms of hypertension, the prevalence of which was largely overestimated and absorbed the vast majority of available grants. The opinion that one has to find the cause before treating the disease has prevailed, thus rendering "empiric" antihypertensive therapy "a shot in the dark", an approach that was not appreciated at all. However, the cause of hypertension remained unknown for the vast majority of patients, and it was not unusual for such patients to remain untreated.

(d) The role of preventive medicine was not considered crucial and had not gained wide popularity at that time. Patients, physicians, and the media were not stuck by the benefits of prevention, since the whole society was not ready to move from therapy to prevention.

(e) Maybe the most important factor that restricted the wide adoption of antihypertensive drugs was the lack of convincing clinical studies to verify the benefits of treating essential hypertension.

The first organized data demonstrating benefit from the treatment of severe hypertension came from the Veterans Administration study group. Under the leadership of Edward Freis the first placebo controlled study was carried out in patients with severe hypertension. In that study (published in 1967), 143 patients with severe untreated hypertension (diastolic >115 mmHg) were randomized to either treatment or placebo [43]. In only 20 months, it became apparent that treatment of these patients with severe blood pressure elevation was dramatically beneficial. Twenty-six events occurred in the placebo arm and only 1 in the treated arm (Table 1). It is important to note that 12 out of 26 events were accelerated hypertension leading to malignant hypertension. Since then, the standard of care is to treat severe hypertension; it is unlikely that the study will be repeated. Although the study was placebo controlled, it is reasonable to assume that even treated patients who remain with severe blood pressure elevations (i.e., resistant to treatment) will have similarly bad prognosis.

Confirmation of this assumption comes from many longitudinal studies, cohorts, or subgroup analyses. In the Australian National Blood Pressure study, early in the antihypertensive therapy era, it was shown that patients with uncontrolled blood pressure despite triple therapy had a four-fold increased risk for cardiovascular events compared to patients with controlled blood pressure [44–46].

Table 1: Fatal and nonfatal events at the VA trial in patients with severe hypertension receiving active treatment (HCTZ, reserpine, and hydralazine) or placebo (modified from the VA collaborators [43]).

Events	Active treatment $n = 73$	Placebo $n = 70$
Deaths	0	4
Stroke	1	4
Coronary events	0	2
Heart failure	0	2
Renal damage	0	2
Accelerated hypertension	0	12

4. Data from Small Clinical Studies

Virtually no longitudinal study has addressed the particular prognosis of resistant hypertension. Relevant information may be extracted only from small clinical studies. Isakson and Ostergren studied 36 patients with resistant hypertension in Sweden for a 7-year follow-up period [47]. For each of these patients, two control patients were randomly selected from a reference group (retrospectively, matched for age and gender), and the outcomes of the two groups were compared. It has been shown that patients with resistant hypertension had an almost 3-fold increased risk for cardiovascular events (stroke, transient ischemic attacks, myocardial infarction, death, heart failure, renal failure, new onset diabetes) compared to patients with controlled hypertension (odds ratio 2.71; $P < .05$).

Redon conducted, in Spain, a prospective study of 86 patients with resistant hypertension (diastolic blood pressure >100 mmHg) and a long follow-up period (49 months average) using ambulatory blood pressure measurement (ABPM) [48]. It was reported that patients with poorly controlled blood pressure (daytime diastolic blood pressure >97 mmHg) had more than 6 times higher relative risk for morbid cardiovascular events (relative risk: 6.42; 95% CI: 1.39–29.7; $P = .017$) compared to patients with relatively controlled blood pressure (daytime diastolic blood pressure <88 mmHg) (Figure 5). It should be noted, however, that the number of patients and events were relatively small, office blood pressure was not independently associated with morbid events, data regarding systolic blood pressure were not provided, and the cut-off limit of daytime diastolic blood pressure (88 mmHg) was higher than what is currently considered normal (85 mmHg).

Pierdomenico in Italy studied a larger number of patients (130 resistant hypertensives) for a slightly longer follow-up period (4.98 ± 2.9 years) using ABPM as well [49]. Moreover, the study compared the outcomes of patients with true resistant hypertension (high clinic and ambulatory blood pressure) to the outcomes of patients with false resistant hypertension (high clinic and normal ambulatory blood

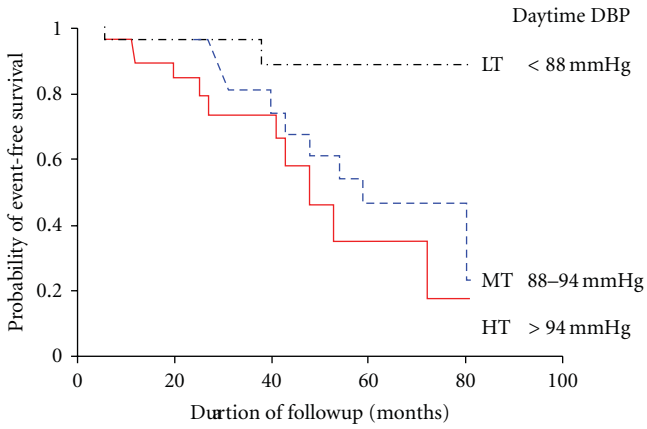

FIGURE 5: Probability of event-free survival in patients with resistant hypertension according to daytime diastolic blood pressure (modified from Redon et al. [48]).

pressure) and controlled hypertension (normal clinic and ambulatory blood pressure). It was shown that patients with true resistant hypertension had an almost 3-fold increased relative risk for cardiovascular events (relative risk: 2.94; 95% CI: 1.02–8.41; $P < .05$) compared to patients with controlled blood pressure.

More recently, Salles in Brazil studied an even larger number of patients with resistant hypertension (556 patients) for a median follow-up period of 4.8 years [50]. It was reported that resistant hypertension was an independent predictor for cardiovascular and all-cause mortality. Moreover, it was shown that patients with resistant hypertension had increased cardiovascular and all-cause mortality compared to patients with false resistant hypertension (hazard ratio: 2.30; 95% CI: 1.42–3.74). Recent studies from the same group have shown the prognostic value of nocturnal blood pressure, the ambulatory arterial stiffness index, the electrocardiographic strain, and the ventricular repolarization in patients with resistant hypertension [51–54]. The above findings along with the superiority of ambulatory over office blood pressure measurements in patients with resistant hypertension underline the importance of taking into account other factors, beyond office blood pressure, in the management of patients with resistant hypertension.

Magnanini studied 382 Brazilian women with resistant hypertension and found that cardiovascular events (death, ischemic heart disease, stroke, nephropathy) were higher in patients with uncontrolled hypertension, as compared to those with controlled blood pressure (5.8 versus 3.7 per 100 women/years, resp.), although the difference did not reach statistical significance ($P = .06$) [55]. However, daytime blood pressure was found to be an independent risk predictor (relative risk: 1.67; 95% CI: 1.00–2.78; $P < .05$).

5. Data from Large Clinical Trials

The lack of reliable data regarding the outcome of uncontrolled versus controlled blood pressure in patients with resistant hypertension using hard endpoints justifies other approaches. One can use data from other patient populations and make rational assumptions, although extrapolation carries inherent risks and has severe limitations.

For example, in a large cohort of hypertensive males (4,714 patients), it has been shown that cardiovascular mortality was almost twice as high in male patients with uncontrolled hypertension compared to patients with well-controlled blood pressure (risk ratio: 1.66; 95% CI: 1.04–2.64), although particular data regarding resistant hypertension are not provided [56]. In another cohort of 11,912 veteran male patients followed for 15 years, uncontrolled hypertension (systolic blood pressure >150 mmHg) was associated with increased risk of end-stage renal disease (risk ratio: 3.00; 95% CI: 2.09–4.55; $P < .001$) [57]. Is this exaggerated cardiovascular risk of uncontrolled hypertension applicable in resistant hypertension? Common sense dictates that there is no reason to assume the opposite. Until convincing data becomes available, it seems clinically wise to assume that controlling blood pressure in resistant hypertension is beneficial, and treating physicians should make every possible effort towards this direction.

Relevant information can be obtained from large clinical trials. Although no trial has been specifically designed to evaluate the benefits of blood pressure control in resistant hypertension, data from recent large trials regarding patients that fulfill the definition of resistant hypertension will be valuable until the conduction of a study devoted to resistant hypertension. We have to keep in mind, however, the inherent limitations of such studies, that besides the post-hoc analysis, they have used unusual antihypertensive regimes, which are seldom used in everyday clinical practice.

In the ASCOT trial, the combination of older drugs (diuretics + beta blockers) was compared to newer drugs (ACEinhibitors + calcium antagonists) [58]. In patients not achieving blood pressure control, alpha blockers have been added as third-line and spironolactone as fourth-line therapy. It is obvious that some patients from the diuretic/beta blocker group may be labeled as resistant hypertensives when the addition of alpha blockers was ineffective. It should be, recognized however, that the combination of a diuretic with a beta- and an alpha-blocker is uncommon in everyday clinical practice. Calcium antagonists or agents acting on the renin-angiotensin axis or a combination of both are used for the vast majority of uncontrolled patients.

Similar problems are applicable to the ACCOMPLISH trial, which compared the combination of an ACEinhibitor with diuretics or calcium antagonists [59]. Uncontrolled patients were allowed to use beta blockers. Therefore patients from the first group that remained uncontrolled with the triple combination of ACEinhibitors, diuretics, and beta-blockers can be characterized as resistant hypertensives and be used as a source of valuable data extraction. This combination is more clinically meaningful than the one used in the ASCOT trial, even this, however, excludes the use of calcium antagonists, which are among the most commonly prescribed drugs in the western world for the treatment of resistant hypertension.

The ALLHAT trial confronts similar problems. Patients were assigned to receive diuretics, ACEinhibitors, calcium

antagonists, or alpha-blockers, and were allowed to use beta-blockers, clonidine, or hydralazine in case the blood pressure remained above goal [60]. Patients included in the diuretic group that remained uncontrolled despite the use of two additional drugs meet the criteria of resistant hypertension. However, as one can easily notice, the drug combinations that were actually used in this study are seldom used in everyday clinical practice.

6. Conclusions

Data from large clinical trials in different subgroups of hypertensive patients suggest an increased prevalence of resistant hypertension. Data regarding the risks of resistant hypertension, as well as the benefits of treatment and control of blood pressure in resistant hypertensive patients is scarce. However, data from small clinical studies and observational cohorts consistently points towards an increased cardiovascular risk in patients with resistant hypertension. Moreover, available information suggests that there is substantial benefit from appropriate treatment and control of resistant patients. Recent randomized studies in resistant hypertension assessed the efficacy and safety of either new drugs (such as darusentan) [61, 62] or interventional techniques (such as carotid baroreceptor stimulation or renal sympathetic denervation) [63, 64]. We believe that appropriate large, long-term studies are needed to evaluate the prevalence and the risks of resistant hypertension, as well as the significant benefits of treating and controlling resistant hypertension.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 368140, 12 pages
doi:10.4061/2011/368140

Research Article

Long-Term Use of Aldosterone-Receptor Antagonists in Uncontrolled Hypertension: A Retrospective Analysis

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Received 30 September 2010; Accepted 24 January 2011

Academic Editor: Alan Gradman

Background. The long-term efficacy of aldosterone-receptor antagonists (ARAs) as add-on treatment in uncontrolled hypertension has not yet been reported. *Methods*. Data from 123 patients (21 with primary aldosteronism, 102 with essential hypertension) with difficult-to-treat hypertension who received an ARA between May 2005 and September 2009 were analyzed retrospectively for their blood pressure (BP) and biochemical response at first followup after start with ARA and the last follow-up available. *Results*. Systolic BP decreased by 22 ± 20 and diastolic BP by 9.4 ± 12 mmHg after a median treatment duration of 25 months. In patients that received treatment >5 years, SBP was 33 ± 20 and DBP was 16 ± 13 mmHg lower than at baseline. Multivariate analysis revealed that baseline BP and follow-up duration were positively correlated with BP response. *Conclusion*. Add-on ARA treatment in difficult-to-treat hypertension results in a profound and sustained BP reduction.

1. Introduction

Aldosterone-receptor antagonists (ARAs) have been shown to be effective in blood pressure (BP) reduction [1–11], but until recently their use was mainly limited to certain conditions such as liver cirrhosis, heart failure, and primary aldosteronism (PA). With the recognition of PA as a common cause of resistant hypertension [12], a renewed interest in the use of ARAs in hypertension has emerged. However, aldosterone has also shown to be an important factor in other forms of resistant hypertension. In patients with elevated aldosterone-to-renin ratios (ARRs) and plasma aldosterone levels, but without genuine PA based on suppression testing, BP control was harder to achieve than in essential hypertensives (EHs) [13]. Furthermore, a proportion of patients treated with angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) show aldosterone breakthrough [14–16], contributing to therapy resistance by partly counteracting the intended blockade of the renin-angiotensin-aldosteron-system (RAAS).

The use of ARAs in resistant hypertension, therefore, seems rational, and several publications have pointed out the potential of aldosterone blockade in difficult-to-treat or resistant hypertension [17–24]. In many of these studies, the addition of spironolactone resulted in an impressive drop in systolic BP (SBP) of up to 25 mmHg and 12 mmHg in diastolic BP (DBP). However, most of these studies were either open label [17, 18, 20, 22], or retrospective [19, 21, 23] in design. One randomized, placebo-controlled, double-blind trial was performed comparing spironolactone with amiloride, the combination of both drugs, and placebo in black hypertensive patients with uncontrolled hypertension despite treatment with at least a diuretic and a calcium-channel-blocker [24]. Interestingly, the BP response was considerably smaller than in the aforementioned studies (−7.3 in SBP and −3.3 mmHg in DBP for spironolactone versus placebo). De Souza et al. recently performed an open-label, prospective study on the BP-lowering benefits of spironolactone in patients with resistant hypertension. By using 24-hour ambulatory BP measurements, at least part of the potential white coat and placebo effect could be

accounted for. Twenty-four-hour SBP and DBP decreased by 16 and 9 mmHg, respectively, after a median treatment duration of 7 months, and in a subgroup, the persistence of this effect was confirmed up to 15 months [22]. So far, longer followup periods have not been reported and although a persistence of the effect in the long run is expected, this remains to be confirmed.

Predicting factors for the BP response to ARA treatment have been identified in several studies. Lower serum potassium levels were pointed out by several groups to be associated with a larger decrease in BP [19, 21, 22, 25]. Most studies found no relation between plasma renin concentration or activity and the BP lowering response to ARAs [5, 9, 17, 26]. Also neither plasma aldosterone levels nor ARR levels seem to predict the BP-lowering effect [22, 26], although this could have been caused by the interfering effects of multidrug antihypertensive regimens on the ARR in these patients [25]. Other factors possibly associated with a better response are the absence of diabetes [23], higher waist circumference, lower aortic pulse wave velocity [22], and a lower baseline high-density lipoprotein (HDL) cholesterol [21].

ARAs have been prescribed in our clinic to patients with difficult-to-treat hypertension for a long time now, often with good results even after many years. This study aims to retrospectively characterize the long-term response to ARA treatment in patients with difficult-to-treat hypertension and to identify factors associated with this response.

2. Methods

2.1. Patients. All patients who visited the outpatient hypertension clinic of the Erasmus Medical Center in Rotterdam and the TweeSteden Hospital in Waalwijk, the Netherlands, between May 2005 and September 2009 were screened for their eligibility for the study. Patients were selected when they had uncontrolled hypertension (BP > 140/90 mmHg, or >130/80 mmHg for patients with diabetes mellitus (DM) or manifest cardiovascular disease) despite the use of at least two antihypertensive drugs and were put on spironolactone or eplerenone during the study period. Patients who were already using an ARA when referred to our clinic were excluded. Patients of whom insufficient data was available to meet the primary objective (for instance insufficient data on medication use or the absence of a BP measurement at the start of treatment or last followup) or patients who were prescribed an ARA for another indication than hypertension were also excluded from the analysis.

2.2. Clinical Data. At baseline, patients' sex, height, weight, the time of diagnosis of hypertension, their antihypertensive medication, their family history, and the presence or absence of diabetes at the start of ARA treatment were collected from patient files. Their electrocardiograms (ECGs), when not taken longer than one year before start of treatment, were scored for the presence of left ventricular hypertrophy (LVH) according to the Sokolow-Lyon criteria. The presence or absence of PA was based on the clinical judgement by their physician.

At baseline, at first followup (i.e., the first followup visit that BP was measured after start of ARA treatment), and at the end of followup (i.e., the date that ARA treatment was permanently discontinued or the last visit before the end of data collection), the following parameters were recorded: BP, serum sodium, potassium, urea, creatinine, uric acid, glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and hemoglobin and hematocrit, and plasma renin and aldosterone levels, where available.

BP measurements were taken in triplicate at an interval of five minutes with a semiautomatic BP measuring device after a rest of five minutes in sitting position. The mean of these measurements was used in the analysis.

Biochemical measurements were taken on the visit day or the nearest previous moment.

Plasma renin concentrations (PRCs) were assessed using an immunoradiometric assay (Renin III, Cisbio, Gif-sur-Yvette, France). Plasma aldosterone concentrations (PACs) were measured with a radioimmunoassay (Coat-a Count, Diagnostics Product Corporation, LA, CA, USA). Hyperkalemia was defined as serum potassium levels exceeding 5.5 mmol/L.

2.3. Data Analysis. Statistical analyses were performed in SPSS 17.0 for Windows.

Main effects at first followup and end of followup were calculated. Furthermore, to assess the long-term efficacy of treatment, patients were stratified based on the duration of followup into the following categories: <1 year, 1–5 years, and >5 years followup.

Values are expressed as mean ± SD, or as median and range when not normally distributed. Medication use was quantified by adding up the total number of different drugs, as well as by assessing the defined daily doses (DDDs) per drug and for total drug use according to the World Health Organization Anatomical Therapeutic Chemical (ATC) index [27]. Differences within subjects were tested using paired Student's t-tests for two groups and one-way analysis of variance (ANOVA) for repeated measurements for more groups. Between-subjects differences were tested with unpaired t-tests for two groups and one-way ANOVA for more groups. For values that were abnormally distributed, nonparametric tests were used (Mann-Whitney U test and Wilcoxon Signed Ranks test). Differences in proportions were tested with a chi-square test.

Patients with PA were excluded for regression analysis. A univariate linear regression analysis was performed to identify potential determinants of the BP response. Significant parameters were subsequently tested in a multivariate linear regression analysis. This model was further adjusted for age and sex.

3. Results

3.1. Study Population. A total of 175 patients were prescribed an ARA during the study period. Fifty-two patients were excluded: 39 because of insufficient data, 5 because our

Table 1: Baseline characteristics of the study population.

	Total	EH	PA	*P*-value
Number	123	102	21	
Age (years)	56.6 ± 10.7	56.7 ± 11.2	56.5 ± 8.2	.959
Male (%)	60.1	56.9	76.2	.099
BMI (kg/m^2)	29.4 ± 5.0	29.3 ± 5.0	30.1 ± 5.2	.537
SBP (mmHg)	159.7 ± 19.1	158.4 ± 18.3	166.0 ± 21.7	.094
DBP (mmHg)	93.3 ± 12.2	92.7 ± 12.5	96.0 ± 10.8	.268
Time since diagnosis (years)	10.0 (0–50)	10.0 (0–50)	7.5 (1.0–34)	.319
Age at diagnosis (years)	42.0 ± 13.0	41.5 ± 13.3	44.7 ± 11.4	.335
Nr. of antihypertensives	3 (2–6)	3 (2–6)	3 (2–5)	.071
DDD	5.0 (1.25–13.0)	5.0 (1.25–13.0)	3.7 (1.5–10.0)	.117
DM (%)	22.8	23.2	21.1	.842
LVH (%)	28.5	26.5	38.1	.125
Family history of HT	52.0	53.9	42.9	.355
Serum sodium (mmol/L)	141.5 ± 2.7	141.2 ± 2.8	143.0 ± 2.14	.008
Serum potassium (mmol/L)	3.9 ± 0.6	4.0 ± 0.6	3.4 ± 0.5	<.001
Serum creatinine (μmol/L)	83.8 ± 20.1	83.8 ± 21.1	84.1 ± 14.4	.959
Serum uric acid (mmol/L)	0.36 ± 0.08	0.37 ± 0.08	0.34 ± 0.08	.134
Hemoglobin (mmol/L)	8.9 ± 0.82	8.8 ± 0.8	9.5 ± 0.6	.001
Hematocrit (%)	0.42 ± 0.04	41.3 ± 3.6	45.3 ± 2.1	.003
Cholesterol (mmol/L)	5.31 ± 0.96	5.27 ± 0.97	5.55 ± 0.90	.345
HDL (mmol/L)	1.35 ± 0.42	1.37 ± 0.41	1.26 ± 0.44	.347
LDL (mmol/L)	3.37 ± 1.02	3.41 ± 1.02	3.16 ± 1.03	.407
Glucose (mmol/L)	5.5 ± 1.6	5.5 ± 1.6	5.5 ± 1.8	.943
ACR (g/mol)	2.19 (0.95–12.4)	2.19 (0.15–453.8)	1.96 (0.37–592.0)	.518
PAC (pmol/L)	282.5 (2.8–4172)	224.4 (2.8–4172)	548.5 (199–2282)	$P < .001$
PRC (mU/L)	13.9 (1.0–4374)	19.8 (1.0–4374)	5.8 (1.8–18.9)	$P < .001$
ARR (pmol/mU)	19.4 (0.3–1087)	9.5 (0.3–781)	82.7 (17.4–1087)	$P < .001$

(EH: essential hypertension; PA: primary aldosteronism; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; DDD: defined daily dose; DM: diabetes mellitus; LVH: left ventricular hypertrophy; HT: hypertension; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ACR: urinary albumin-to-creatinine ratio; PAC: plasma aldosterone concentration; PRC: plasma renin concentration; ARR: aldosterone-to-renin ratio).

criteria for difficult-to-treat hypertension were not met, 3 because of questionable treatment adherence, 2 because of a followup duration less than a month, 1 because baseline BP measurement was not performed with a semi-automatic BP measuring device, and 1 because an ARA was prescribed because of another indication than hypertension. In total, 123 patients were included in the analysis with a mean age of 56.6 ± 10.7 years. The median duration between diagnosis and start of ARA treatment was 10 years (range 0–50 years). The median number of different antihypertensive agents was 3 (total DDD 5.0). Twenty-three percent of patients had DM, and 29 percent had LVH. Twenty-one patients were diagnosed as having PA by their physician. The baseline characteristics of all patients and of the EH and PA subgroups are shown in Table 1. Serum potassium levels were lower in patients with PA than with EH (3.4 mmol/L versus 4.0 mmol/L in EH, $P < .001$). Serum sodium levels were higher in patients with PA than with EH (143 versus 141 mmol/L, $P < .001$).

As expected, PRC was lower in PA than in EH patients (5.8 versus 19.8 mU/L, $P < .001$). PAC and ARR were higher in PA patients (548.5 versus 224.4 pmol/L ($P < .001$) for PAC, and 82.7 versus 9.5 pmol/mU ($P < .001$) for ARR).

Values of haemoglobin and hematocrit were also higher in PA than in EH patients.

3.2. Treatment. Ninety-four patients started on spironolactone treatment with a median dose of 50 mg daily (range 12.5–100 mg). Twenty-nine patients started on eplerenone with a median dose of 50 mg (range 25–50 mg). Total starting DDD of ARA was 0.67 (range 0.17–1.33). At the end of followup 91 patients were on spironolactone with a median dose of 25 mg (range 12.5–100 mg) and 32 patients on eplerenone (median dose 50 mg, range 25–100 mg). Median ARA DDD at end of followup was 0.67 (range 0.17–2.00). Median treatment duration at first followup was 8 weeks (range 1–66 weeks). The median treatment duration at end of followup was 25 months (range 1–144 months).

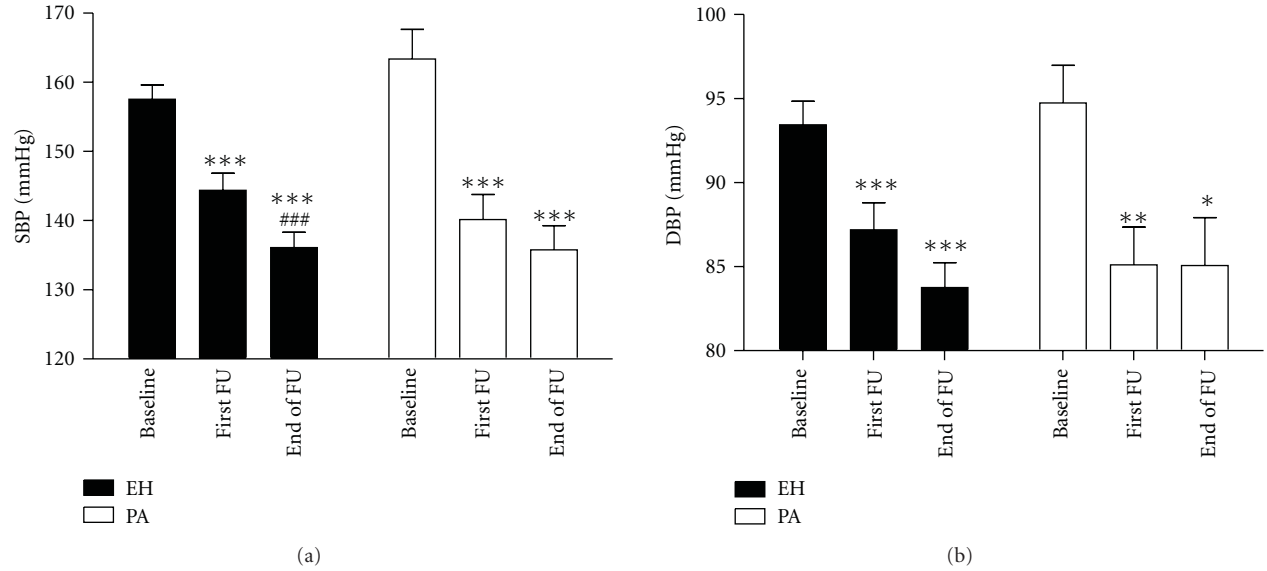

Figure 1: Systolic (SBP) and diastolic (DBP) blood pressure before start with an aldosterone-receptor antagonist (baseline), at first followup (FU), and at the end of FU in patients with essential hypertension (EH) and primary aldosteronism (PA). Overall trend was tested with one-way ANOVA for repeated measurements ($P < .001$ for all groups, except for DBP in the PA group ($P = .001$)). Indicated significance levels are for differences between groups after adjustment for multiple comparisons (*compared to baseline; $^{\#}$compared to first FU).

Table 2: Changes in biochemical parameters at first followup and end of followup after start of treatment with an aldosterone-receptor antagonist for patients with essential hypertension (EH) and primary aldosteronism (PA). (Values were tested with one-way ANOVA for repeated measurements. Indicated P values are for differences between baseline and first followup (a), first and last followup (b), and baseline and last followup (c) after Bonferroni adjustment; n represents the number of patients with measurements at all three time points).

		n	Baseline	P value[a]	First FU	P value[b]	End of FU	P value[c]
EH	Serum sodium (mmol/L)	66	141.2 ± 2.7	1.000	140.9 ± 3.0	.927	141.3 ± 3.2	1.000
	Serum potassium (mmol/L)	80	4.0 ± 0.6	<.001	4.4 ± 0.6	1.000	4.4 ± 0.5	<.001
	Serum creatinine (μmol/L)	78	84.6 ± 20.8	<.001	90.8 ± 24.7	.355	93.6 ± 26.2	<.001
PA	Serum sodium (mmol/L)	17	142.9 ± 2.1	.015	141.0 ± 3.4	.103	142.7 ± 3.4	1.000
	Serum potassium (mmol/L)	19	3.4 ± 0.5	<.001	4.3 ± 0.5	1.000	4.3 ± 0.5	<.001
	Serum creatinine (μmol/L)	18	85.7 ± 14.1	.011	96.1 ± 22.6	1.000	95.7 ± 19.6	.169

3.3. Main Effects of ARA Treatment. The BP levels at first followup and at the end of followup are shown in Figure 1. In EH patients, BP decreased by 13 ± 1.8 mmHg systolically and 6.2 ± 1.0 mmHg diastolically at first followup, and by 21 ± 2.1 and 9.7 ± 1.4 mmHg at the end of followup. In PA patients, SBP had decreased by 23 ± 4.8 mmHg and DBP by 9.6 ± 2.5 mmHg at first followup and by 28 ± 4.9 and 9.7 ± 3.1 mmHg at the end of followup. Changes in BP were not significantly different for EH and PA patients at both time points, although a trend existed towards a larger SBP decrease at first followup in the PA group ($P = .063$).

Serum potassium and creatinine levels increased significantly after start of ARA treatment for both EH and PA patients. Furthermore, in PA patients, serum sodium was significantly lower at first followup compared to baseline (Table 2).

At baseline, PA and EH patients used a median number of 3 antihypertensive drugs (range 2–6). At the end of followup, the number of drugs had increased to 4 (range 1 to 7, $P < .001$). However, when expressed in DDD, the total amount of antihypertensive drugs remained unchanged (5 DDD at baseline versus 4.5 at end of followup, $P = .459$). Also in the EH subgroup, the number of antihypertensive drugs increased from 3 to 4 ($P < .001$), with a nonsignificant decrease in DDD (5 DDD at baseline against 4.6 at end of followup, $P = .663$). In PA patients, there was no significant change in number of antihypertensive drugs (3 versus 3, $P = .317$) or DDD (3.66 versus 3.83, $P = .407$).

3.4. Stratification to Followup Duration. Because of the wide variation in followup duration and to better assess the long-term efficacy of ARA treatment, patients were stratified according to their treatment followup. The following categories were formed: 0-1 year, 1–5 years, and >5 years. Number of patients in these categories were 33, 49, and

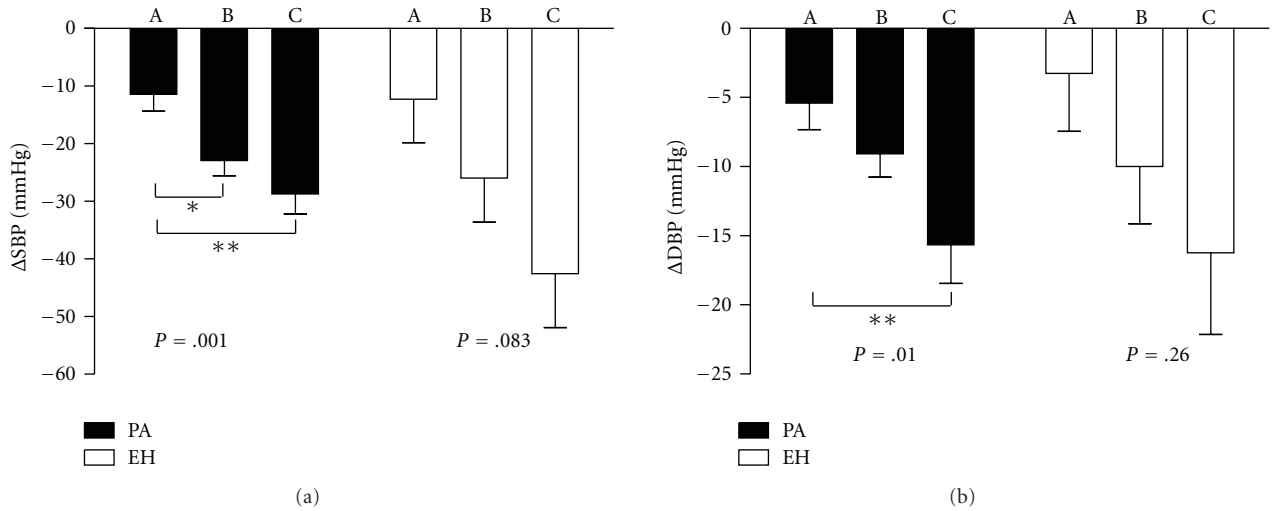

Figure 2: Changes in systolic (SBP) and diastolic (DBP) blood pressure at the end of followup compared to baseline for three categories of followup duration (A < 1 year; B 1–5 years; C > 5 years). *P* values are for trend tested with one-way ANOVA; indicated significance levels are for differences between groups after adjustment for multiple comparisons. (EH: essential hypertension; PA: primary aldosteronism).

20, respectively, for EH patients, and 5, 8, and 8 for PA patients. In Figure 2, blood pressure reduction is shown for the three categories of followup duration. In EH patients larger responses were seen with longer followup duration ($P = .001$ for ΔSBP and $P = .01$ for ΔDBP with one-way ANOVA). In PA patients, a similar trend was seen. The overall trends were not different for EH and PA patients ($P = .467$ for ΔSBP and $P = .907$ for ΔDBP at two-way ANOVA).

To investigate whether the reduction in BP was merely a result of a greater number of antihypertensive drugs than a specific effect of ARA treatment, baseline and end-of-followup BP is shown in relation to medication use for EH (Figure 3) and PA (Figure 4). The proportion of total DDD that consisted of ARA treatment is separately indicated. These figures show that at longer followup, BP further decreased, while the total DDD remained unchanged. In EH patients, the percentage of total DDD consisting of an ARA significantly increased from 9.1% to 14.2% ($P < .001$) in the 1–5-year followup group. In PA patients, the relative contribution of ARA to total DDD increased from 14.9% to 22.4% in the 1–5-year followup group ($P = .050$) and from 14.9% to 31.9% in the >5 years followup group ($P = .018$).

3.5. Predictors for the Blood Pressure Response. The main clinical parameters were tested for their potential association with SBP as well as DBP response at first and last followup by univariate regression analysis (with the change in BP being negative). Table 3 shows the beta coefficients of all parameters that were significantly associated with BP change in any of the four groups, as well as those considered relevant based on earlier reports. At first followup, the sodium/potassium ratio as well as followup duration were significantly associated with ΔSBP. The ARR was significantly associated with ΔDBP, yet with a very small and probably irrelevant regression coefficient considering the range in ARR. Interestingly, haemoglobin and hematocrit levels, total cholesterol, and LDL levels were negatively associated with blood pressure change at univariate analysis for ΔSBP, and the latter two also for ΔDBP.

At last followup, the change in BP was significantly correlated with baseline BP, urinary albumin-to-creatinine ratio (ACR), LVH, followup duration, and, for DBP, the ARR.

To identify independent predictors for BP response, the variables significantly associated in the univariate analyses were included in a multivariate linear regression analysis. In addition, the model was adjusted for age and sex. The regression coefficients and significance levels are shown in Table 4. Unfortunately, hemoglobin, hematocrit, total cholesterol, LDL, LVH, and the ARR could not be included in the analysis because numbers were too small to maintain sufficient statistical power.

At first followup, only baseline SBP seemed to be an independent predictor (borderline significant) for ΔSBP. For ΔDBP, there were no independent predictors for the response. At the end of followup, higher baseline BP and longer FU duration were independently associated with the change in BP.

3.6. Adverse Events. ARA treatment was in general well tolerated. In total, 13 adverse events were reported. Five cases of gynaecomastia were reported with spironolactone use resulting in a switch to eplerenone in 1 patient. Two cases of hyperkalemia were seen, and in two patients, a clinically relevant decrease in renal function was observed. Two patients (one on eplerenone and one on spironolactone) reported general discomfort and headache, and one patient experienced gastrointestinal discomfort, although this was probably already present before start of spironolactone. In 1 patient, the nature of the adverse event was not further specified.

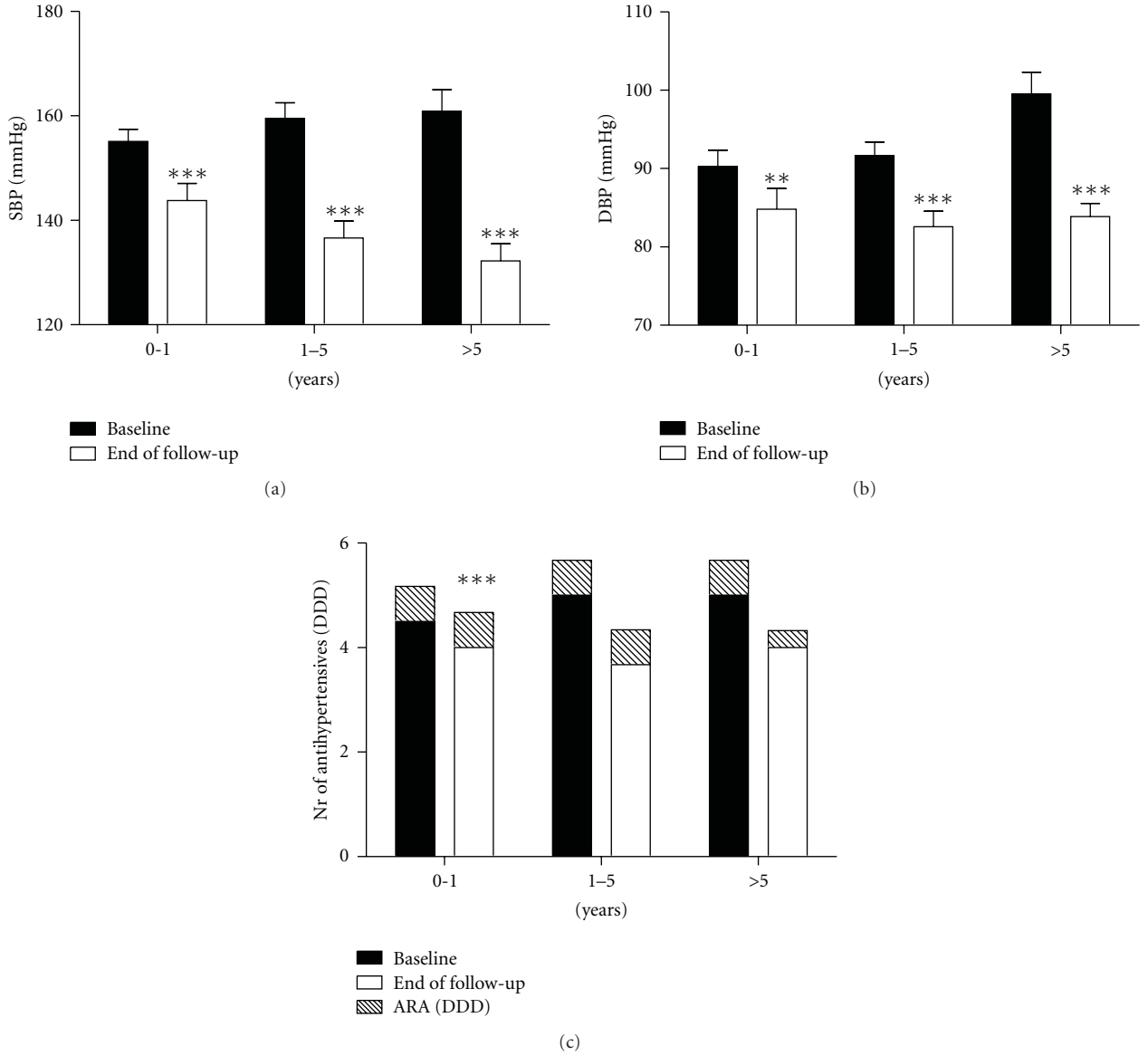

Figure 3: Systolic (SBP) (a), diastolic (DBP) (b) blood pressure and medication use (defined daily dose, DDD) (c) at baseline and end of followup after stratification for followup duration for patients with essential hypertension (Figure 3) and primary aldosteronism (Figure 4). Indicated in (c) is the DDD for the aldosterone-receptor antagonist (ARA). For baseline, this is added up to total DDD; at the end of followup, this is part of the total DDD since ARA was started at baseline. Differences were tested with paired t-test for SBP and DBP and Wilcoxon Signed Ranks test for DDD (DDD without ARA at baseline versus DDD including ARA at the end of followup).

4. Discussion

This study shows that the addition of aldosterone-receptor antagonists (ARAs) in patients with difficult-to-treat hypertension was highly effective in reducing SBP as well as DBP. This effect was already present at short-term followup (median followup 8 weeks) and persisted in the long run with a median followup of 25 months. The BP reduction in EH and PA patients was comparable, and in both groups ARA treatment resulted in a small rise in serum potassium and creatinine levels.

To assess whether the BP-lowering effect was still present after prolonged treatment, patients were stratified according to their duration of followup. We observed larger BP reductions with increasing followup, which was highly significant in EH patients. In the subgroup that had a followup of more than 5 years, SBP was 29 mmHg and DBP 16 mmHg lower than at baseline. In PA, a similar trend was seen although this failed to reach statistical significance, probably because of the small number of patients in each subgroup. Also in the multivariate regression analysis we observed a strong correlation between treatment duration and decrease in BP. Although it is appealing to conclude that a longer treatment duration leads to better BP control for instance by reversing target organ damage, a more likely explanation is some form of effect-bias implicating that patients with a better response

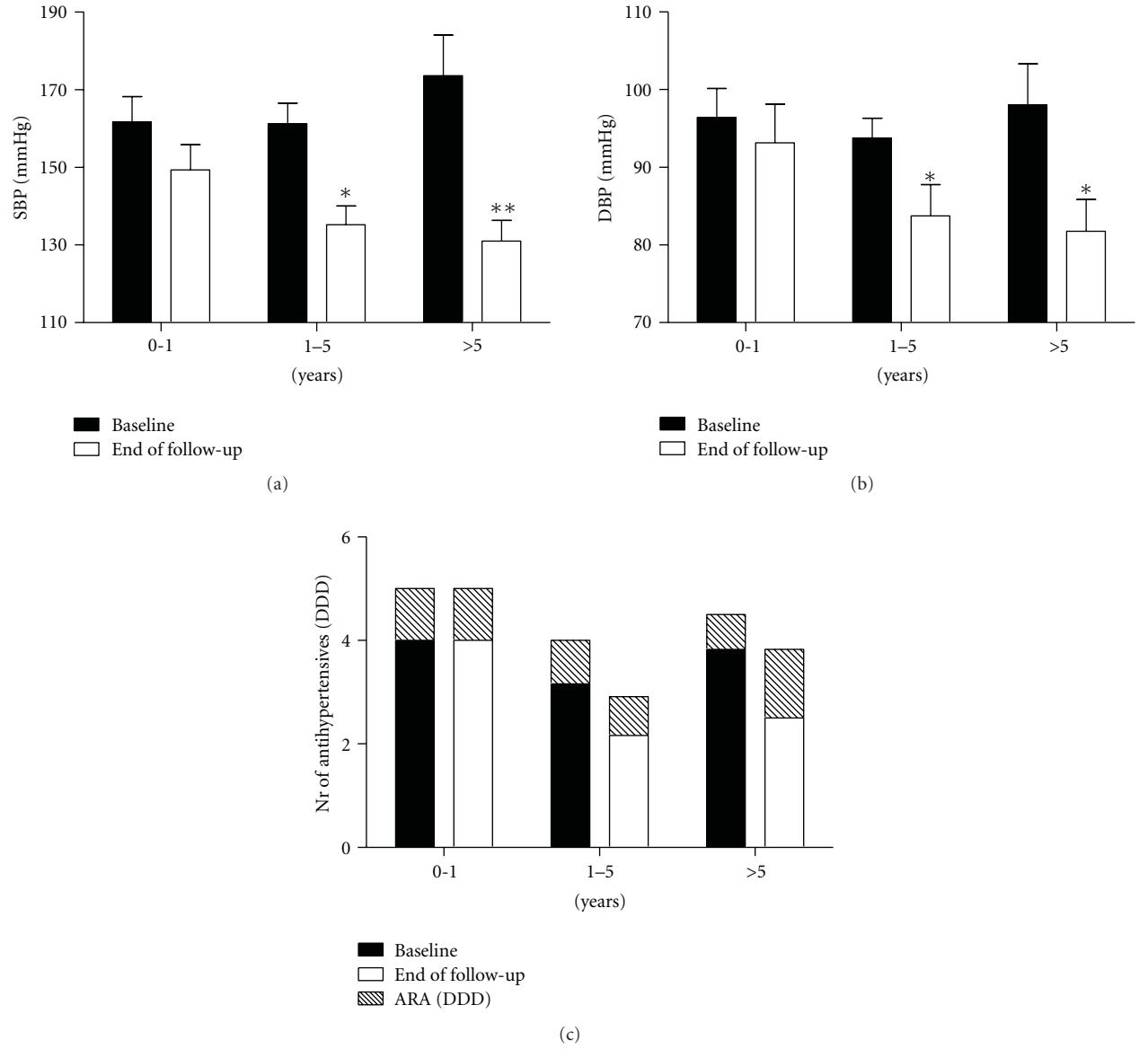

Figure 4: Systolic (SBP) (a), diastolic (DBP) (b) blood pressure and medication use (defined daily dose, DDD) (c) at baseline and end of followup after stratification for followup duration for patients with essential hypertension (Figure 3) and primary aldosteronism (Figure 4). Indicated in (c) is the DDD for the aldosterone-receptor antagonist (ARA). For baseline, this is added up to total DDD; at the end of followup, this is part of the total DDD since ARA was started at baseline. Differences were tested with paired t-test for SBP and DBP and Wilcoxon Signed Ranks test for DDD (DDD without ARA at baseline versus DDD including ARA at the end of followup).

are more likely to receive ARA treatment for a longer period. Whether prolonged treatment leads to a better BP control requires a long-term prospective study.

Another explanation for the favourable long-term BP response could be an optimalisation of the antihypertensive medication or merely the fact that the total amount of medication increased over time. To investigate this further, BP values at baseline and at end of followup were shown in relation to total medication use. Although BP decreased considerably over the study period, the total amount of DDD remained virtually the same. The relative contribution of ARA treatment to total DDD increased over time. The possibility that the improved BP reduction during long-term followup is due to an increase in total amount of antihypertensive medication can therefore be excluded.

The BP responses in this study were of similar magnitude as those observed in other retrospective or open-label studies concerning add-on ARA treatment [17–21, 23]. Interestingly, in two prospective trials, BP reductions were considerably smaller than in the aforementioned studies. Saha et al. [24] studied the effect of spironolactone in black hypertensive patients with uncontrolled BP despite the use of at least a diuretic and a calcium-channel-blocker in a randomized, placebo-controlled manner and reported a reduction of 7.3 mmHg in SBP and 3.3 mmHg in DBP. In a recent study, De Souza et al. [22] assessed the effect of open-label

Table 3: Outcomes of a univariate linear regression analysis with the changes in systolic and diastolic blood pressure at first and last followup compared to baseline (ΔSBP1, ΔDBP1, ΔSBP2, and ΔDBP2, resp.) as dependent variables. Included in the table are all independent variables with a significant β-coefficient in one of the ΔBP categories or those assumed to be relevant based on the literature. Also shown are the numbers (n) available for the individual analyses.

	ΔSBP1			ΔDBP1			ΔSBP2			ΔDBP2		
Independent variable	β	n	P value	β	n	P value	β	n	P value	β	n	P value
Age (years)	−0.750	83	.660	0.030	83	.758	-0.013	102	.937	0.043	102	.689
Sex (1 = female, 2 = male)	4.199	83	.260	3.477	83	.101	-4.737	102	.207	−2.789	102	.251
DM	−5.684	78	.202	−0.746	78	.770	−5.896	95	.181	−0.206	95	.943
LVH	2.948	63	.526	2.875	63	.276	−9.461	76	**.031**	−2.897	76	.343
SBP_0 (mmHg)	0.170	83	.083	0.000	83	.994	−0.388	102	**<.001**	−0.034	102	.608
DBP_0 (mmHg)	0.080	83	.572	−0.118	83	.143	−0.378	102	**.010**	−0.407	102	**<.001**
Na^+(mmol/L)	−0.742	78	.280	−0.825	78	**.032**	0.600	95	.393	−0.028	95	.951
K^+(mmol/L)	4.206	83	.162	0.341	83	.844	0.017	102	.996	−0.344	102	.867
Na^+/K^+	−0.663	78	**.038**	−0.174	78	.343	−0.123	95	.723	0.035	95	.876
Hb (mmol/L)	6.79	52	**.023**	2.632	52	.125	−1.837	59	.576	−1.329	59	.529
Ht (%)	162.2	30	.084	56.75	30	.259	−19.98	35	.831	−23.75	35	.707
TC (mmol/L)	5.374	61	**.025**	2.609	61	**.044**	−1.555	79	.480	−1.136	79	.424
HDL (mmol/L)	4.880	64	.311	3.639	64	.162	0.283	81	.956	2.826	81	.387
LDL (mmol/L)	5.127	60	**.004**	2.111	60	**.031**	0.585	78	.784	−0.291	78	.832
ACR (g/mol)	0.031	40	.518	0.041	40	.170	0.078	45	**.036**	0.049	45	**.028**
FU duration (weeks)	−0.371	83	**.018**	−0.150	83	.098	−0.039	102	**.001**	−0.028	102	**<.001**
Total DDD	0.503	83	.539	0.348	83	.458	−0.649	102	.435	−0.250	102	.642
DDD ARA	5.446	83	.360	6.501	83	.054	−1.130	102	.847	1.799	102	.634
PAC (pmol/L)	0.001	46	.788	0.003	46	.149	0.002	55	.621	0.004	55	.117
PRC (mU/L)	0.002	47	.553	0.002	47	.325	0.004	56	.392	0.003	56	.225
ARR (pmol/mU)	−0.034	46	.094	0.027	46	**.020**	−0.027	55	.289	0.033	55	**.029**

(DM: diabetes mellitus; LVH: left ventricular hypertrophy; Na^+: sodium; K^+: potassium; Hb: hemoglobin; Ht: hematocrit; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ACR: urinary albumin-to-creatinine ratio; FU: followup; DDD: defined daily dose; ARA: aldosterone-receptor antagonist; PAC: plasma aldosterone concentration; PRC: plasma renin concentration; ARR: aldosterone-to-renin ratio).

Table 4: Multivariate linear regression analysis for the change in systolic and diastolic blood pressure at first and last followup (ΔSBP1, ΔDBP1, ΔSBP2, and ΔDBP2).

	ΔSBP1			ΔDBP1			ΔSBP2			ΔDBP2		
	β	SEM	P value	β	SEM	P value	β	SEM	P value	β	SEM	P value
Age (years)	0.015	0.203	.941	−0.026	0.117	.824	0.070	0.191	.716	−0.200	0.122	.104
Sex (1=female, 2 = male)	2.669	3.990	.506	3.387	2.291	.144	−5.776	3.799	.132	−1.125	2.429	.644
SBP_0 (mmHg)	−0.223	0.121	.069	0.011	0.069	.874	−0.335	0.119	**.006**	0.133	0.076	.085
DBP_0 (mmHg)	0.122	0.198	.541	−0.162	0.113	.157	−0.051	0.205	.803	−0.485	0.131	**<.001**
FU-duration (weeks)	−0.251	0.160	.121	−0.099	0.092	.283	−0.031	0.013	**.016**	−0.018	0.008	**.030**
Na^+(mmol/L)	−0.273	0.799	.734	−0.704	0.459	.129	0.607	0.760	.427	−0.011	0.486	.982
K^+(mmol/L)	−12.162	11.925	.311	−5.051	6.846	.463	−16.925	12.363	.175	−3.339	7.905	.674
Na^+/K^+	−1.770	1.304	.179	−0.554	0.748	.461	−1.810	1.356	.185	−0.292	0.867	.737

(SBP_0: baseline systolic blood pressure; DBP_0: baseline diastolic blood pressure; FU: followup; Na^+: serum sodium concentration; K^+: serum potassium concentration).

spironolactone treatment in resistant hypertension with 24-hour ambulatory BP measurements, thereby eliminating a white-coat effect and at least in part also a placebo effect. In their study, SBP was reduced by 16 mmHg and DBP by 9 mmHg.

The longest followup in all mentioned studies was 15 months. Whether the effect persists over a longer period had not yet been reported. With all the limitations of a retrospective design, our study is the first to show that the BP lowering effect of add-on ARA treatment is profound and persistent even after years of treatment.

Earlier publications have focused on identifying clinical and biochemical predictors for the BP response to ARA treatment. Several studies have shown that neither plasma renin concentration or activity, nor aldosterone or the ARR are good predictors for this response [5, 9, 17, 22, 26], although this may only hold for patients on multidrug regimens [25] related to the interfering effects of many antihypertensives on renin and aldosterone levels [28]. Low serum potassium levels have consistently been shown to be associated with a better response [19, 21, 22, 25]. Other factors potentially related to a better BP response are higher waist circumference, lower aortic pulse wave velocity [22], the absence of DM [23], and a lower baseline HDL cholesterol [21]. In a univariate linear regression analysis, we could not confirm the predictive value of the serum potassium level for BP response. However, the sodium/potassium ratio (as a potential indicator for aldosterone excess) showed a significant correlation with SBP decrease at short followup at univariate analysis. In a multivariate analysis, only higher baseline BP and longer followup duration independently predicted BP response in the long run. Potential explanations for this have been discussed earlier in this section. In our univariate analysis, also haemoglobin, total cholesterol, and LDL for short-term followup and left ventricular hypertrophy and urinary albumin-to-creatinine ratio for long-term followup were identified as potential predictors. Unfortunately, because of too many missing values, these variables were not included in the multivariate analysis to maintain enough statistical power. However, these parameters are important candidates for further studies on determinants of BP lowering by ARAs. Plasma renin and aldosterone levels were not associated with BP response, as has been reported earlier. In our univariate analysis, the ARR was weakly, yet significantly, associated with change in DBP. Considering the median ARR of 9.5 pmol/mU in this patient group, a beta coefficient of 0.027 is probably of little relevance. Also the number of patients with ARR available at baseline was too small to include in the multivariate analysis.

The mechanism that underlies the BP-lowering effect of add-on ARA treatment is most likely induction of natriuresis and diuresis although extrarenal effects of aldosterone blockade may also be of importance, such as a reduction in sympathetic tone and modulation of vascular tone, and in the long run a reduction in vascular stiffness may also play a role (reviewed in [29]). The clinical relevance of these extrarenal mechanisms is unknown. A cross-over trial in patients with low-renin hypertension, an elevated ARR, and a previous favourable BP response to spironolactone showed that even in this selected population, high-dose thiazide diuretic treatment was as effective as 100 mg of spironolactone, strongly suggesting that natriuresis is the most important mode of action [30]. This also underscores the relevance of dietary salt reduction in resistant hypertension as has been shown elsewhere [31]. In general, ARA treatment was well tolerated and side effects were rare. In 13 patients, side effects were reported (10.6%), most of them presenting with gynaecomastia or hyperkalemia. The occurrence of sex hormone-related side effects with spironolactone is dose dependent [32], and in many cases, these side effects can be prevented by using lower doses. When this is also not tolerated, treatment with eplerenone, being a more specific ARA with virtually no sex hormone-related actions in therapeutic doses, can be considered.

Risk factors for hyperkalemia are advanced age, diabetes mellitus, higher baseline potassium levels [33], and advanced stage 3 nephropathy [34]. The presence of renal function impairment and concomitant use of other diuretics predisposes to the development of renal failure [33]. Frequent monitoring of serum potassium and renal function is warranted in these patients.

Our study has several limitations, the most significant one being its retrospective nature. Because of this, there is an important heterogeneity in patients, treatment, and followup. To properly assess the long-term efficacy of ARA treatment taking into account the large differences in followup, stratification to followup duration was made. This makes the analysis prone to bias with overrepresentation of patients with a good response in the group of prolonged followup. It would have been more ideal to collect patient data at several time points during the followup period, but clinical information in the written files was not always present. Furthermore, biochemical parameters, especially haemoglobin and cholesterol (including HDL and LDL) at baseline, were only available for a limited number of patients, thereby limiting their usefulness for multivariate analysis because of lack of statistical power. Also renin and aldosterone levels were only available for a subset of patients.

This study shows that long-term treatment including an ARA leads to a persistent BP reduction. Whether this is attributable to the ARA itself or to better treatment in general is an important point of consideration. As shown, BP reduction was not accompanied by an increase in total amount of antihypertensive drugs, thereby making a specific effect of the intervention with an ARA more likely. Last, the distinction between patients with EH and PA was solely based on a clinical diagnosis by the patient's physician. A formal confirmation test for PA was only performed in a proportion of the patients labelled with the diagnosis PA. The recent guidelines for the diagnosis and treatment of PA made by the Endocrine Society advise to perform a confirmation test in patients with an ARR of approximately 91 pmol/mU [35]. From the ranges in ARR reported in Table 1, it could be deduced that some of the EH patients actually had PA and that some of the PA patients had been misdiagnosed. However, considering the substantial differences in renin, aldosterone, and potassium levels between our EH and PA patients, we think that the diagnosis was correct in most of the patients.

With all limitations, our results are in favour of a profound and long-term BP lowering effect of ARA treatment in difficult-to-treat hypertension. To assess the magnitude of the response more accurately, a randomized, placebo-controlled trial is needed. With all evidence available, ARAs at moderate dosages are a welcome treatment option in patients with difficult-to-treat or resistant hypertension.

Abbreviations

ACR: Urinary albumin-to-creatinine ratio
ANOVA: Analysis of variance
ARA: Aldosterone-receptor antagonist
ARR: Aldosterone-to-renin ratio
BP: Blood pressure
DBP: Diastolic blood pressure
DDD: Defined daily dose
DM: Diabetes mellitus
ECG: Electrocardiogram
EH: Essential hypertension
HDL: High-density lipoprotein
LDL: Low-density lipoprotein
LVH: Left ventricular hypertrophy
PA: Primary aldosteronism
PAC: Plasma aldosterone concentration
PRC: Plasma renin concentration
RAAS: Renin-angiotensin-aldosterone system
SBP: Systolic blood pressure.

Acknowledgment

P. M. Jansen is financially supported by the Dutch Kidney Foundation (Grant no. C05.2151).

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 196518, 8 pages
doi:10.4061/2011/196518

Review Article

Renal Sympathetic Denervation for the Treatment of Difficult-to-Control or Resistant Hypertension

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Received 1 October 2010; Revised 22 December 2010; Accepted 19 January 2011

Academic Editor: Alan Gradman

Hypertension represents a major health problem with an appalling annual toll. Despite the plethora of antihypertensive drugs, hypertension remains resistant in a considerable number of patients, thus creating the need for alternative strategies, including interventional approaches. Recently, catheter-based renal sympathetic denervation has been shown to be fairly safe and effective in patients with resistant hypertension. Pathophysiology of kidney function, interaction and crosstalk between the kidney and the brain, justifies the use of renal sympathetic denervation in the treatment of hypertension. Data from older studies have shown that sympathectomy has effectively lowered blood pressure and prolonged life expectancy of hypertensive patients, but at considerable cost. Renal sympathetic denervation is devoid of the adverse effects of surgical sympathectomy, due to its localized nature, is minimally invasive, and provides short procedural and recovery times. This paper outlines the pathophysiological background for renal sympathetic denervation, describes the past and the present of this interventional approach, and considers several future potential applications.

1. Introduction

Resistant hypertension is defined as uncontrolled blood pressure despite the use of optimal doses of three antihypertensive agents, of which one is a diuretic [1–4]. Using this definition prevalence of resistant hypertension can be as high as 30% in some regions, but prevalence of true resistant hypertension is most likely around 5% in organized referral centers [2–4]. Although several factors contribute to "resistant hypertension" (poor patient adherence, physician inertia, inappropriate drug combinations or inadequate dosing, drug-interaction, and secondary causes), the fact is that a small percentage of hypertensive patients remain with unacceptably high blood pressure levels. It has been shown that a majority of patients with resistant hypertension and no identifiable secondary causes have activated sympathetic nervous system and increased sympathetic outflow (Figure 1). The high prevalence of hypertension in the general population renders this small percentage of patients significant, in terms of actual patient numbers. The above, combined with several limitations of drug therapy (cost, adverse effects, polypharmacy, etc.), create the need for other therapeutic options, such as devices and interventions.

Despite the availability of multiple medications, control rates are still very low worldwide. Although progress has been made in the USA and other countries, control rates remain around 50% in the US and much lower in the rest of the world. The present situation is reminiscent of the 40s and 50s when therapeutic options for hypertension were limited and radical sympathectomy became popular among hypertension experts. The beneficial effects of pharmacologic therapy shown first by the Veteran Administration study group [5, 6] and later confirmed by many other trials made pharmacologic therapy the preferred and only option for the treatment of hypertension.

Surgical sympathectomy was driven to total obscurity primarily due to serious adverse effects. It should be noted, however, that sympathectomy was the first attempt to

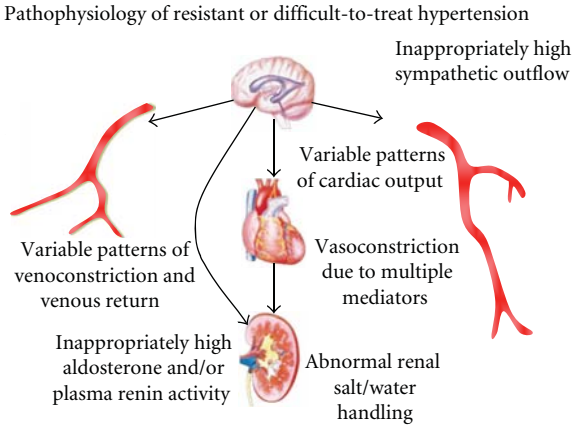


Figure 1: Demonstrates pathophysiology of resistant hypertension. Increased sympathetic outflow is a fundamental abnormality in most patients.

effectively confront malignant hypertension and its consequences through an interventional approach [7–12]. Indeed several studies have shown sympathectomy to be very effective in reducing blood pressure, and results were maintained in the long term (Figure 2). Recently another innovative approach has been used to decrease sympathetic outflow using an implantable device (Rheos) to electrically stimulate the carotid baroreceptors. Early results have shown adequate blood pressure and heart rate reduction (Figure 3), and feasibility studies have shown promising long-term results [13, 14]. However long-term randomized data are still pending.

Selective renal sympathetic denervation (RSD) [15] is the latest and perhaps the most interesting approach used recently in an attempt to interrupt the influence of the sympathetic nervous system on the kidney and systemic hemodynamics.

The sympathetic innervation of the kidney is implicated in the pathogenesis of hypertension through effects on rennin secretion, increased plasma rennin activity that leads to sodium and water retention, and reduction of renal blood flow (RBF) [16, 17]. Complete bilateral renal denervation decreases the level of blood pressure in several experimental models, such as spontaneously hypertensive rats, DOCA hypertensive rats, two-kidney one-clip rats, obesity-induced hypertensive dogs, and aortic coarctation dogs [16].

In this paper we will briefly summarize the role of renal sympathetic innervation on blood pressure regulation and discuss the past and the present of RSD in the treatment of arterial hypertension.

2. Renal Sympathetic Innervations

2.1. Efferent Sympathetic Fibers. The sympathetic innervation of the kidney is achieved through a dense network of postganglionic neurons that innervate the kidney [18, 19]. The axons of preganglionic neurons exit the thoracic and lumbar sympathetic trunk and reach the pre- and paravertebralsympathetic ganglia. Renal preganglionic nerves run alongside the renal artery and enter the hilus of the kidney. Thereafter, they divide into smaller nerve bundles following the blood vessels and penetrate the cortical and juxtamedullary areas (Figure 5). Renal sympathetic nerve activation enhances noradrenalin production for nerve endings and noradrenalin spillover [20–22], while interruption of renal sympathetic fibers results in a marked decrease of noradrenalin spillover (up to 95% [16]). When renal sympathetic nerves are activated, b_1 adrenergic receptors enhance rennin secretion and a1 receptor activation results in increased sodium and fluid reabsorption, renal vasoconstriction, and decrease in renal blood flow.

2.2. Afferent Renal Sympathetic Innervation. Afferent renal sympathetic nerves originate mostly from the renal pelvic wall [23–25]. Mechanoreceptors respond to stretch and chemoreceptors detect renal ischemia [16, 26]. The cell bodies of renal afferent nerves lie in the ipsilateral dorsal root ganglia (T6-L4). From there, ascending signals travel to the renal cardiovascular centers in the CNS. Afferent renal nerve activation promotes vasopressin and oxytocin release from the neuro-hypophysis[51]. Prior renal denervation of the stimulated kidney, however, attenuates these effects, suggesting that complete renal denervation effectively inhibits ascending afferent stimuli. Overall afferent sympathetic fibers may have important contribution in regulation of systemic vascular resistance and blood pressure control. Figures 5 and 6 depict schematically the sympathetic innervations of the kidney and the pathophysiologic role of efferent and afferent fibers.

3. Renal Sympathetic Denervation (RSD)

3.1. Historical Perspective. Partial sympathectomy was attempted more than 40 years ago in patients with malignant hypertension. Malignant hypertension was a devastating disease with a five-year mortality rate of almost 100% [27], thus interventional approaches have been tested for its treatment given the lack of effective drug therapy. Sympathectomy was mainly applied in patients with severe or malignant hypertension, as well as in patients with cardiovascular deterioration despite of relatively good blood pressure reduction by other means [7–12]. After the introduction of antihypertensive drugs, sympathectomy was reserved for patients who failed to respond to antihypertensive therapy or could not tolerate it.

Total sympathectomy was impractical and poorly tolerated by most patients. It had to include the abdominal organs in order to be effective, and it was thus termed splanchnicectomy. Sympathectomy was performed either in one or two stages, required a prolonged hospital stay (2–4 weeks) and a long recovery period (1-2 months) and more importantly a skilled surgeon to perform it. It was thus performed only in a few selected centres in the USA (Boston, Michigan, Cleveland, Rochester, Miami, and California) and in Europe. Pioneers with significant contribution in this field include Page, Craig, Peet, Isberg, Smithwick, Allen, and Adson.

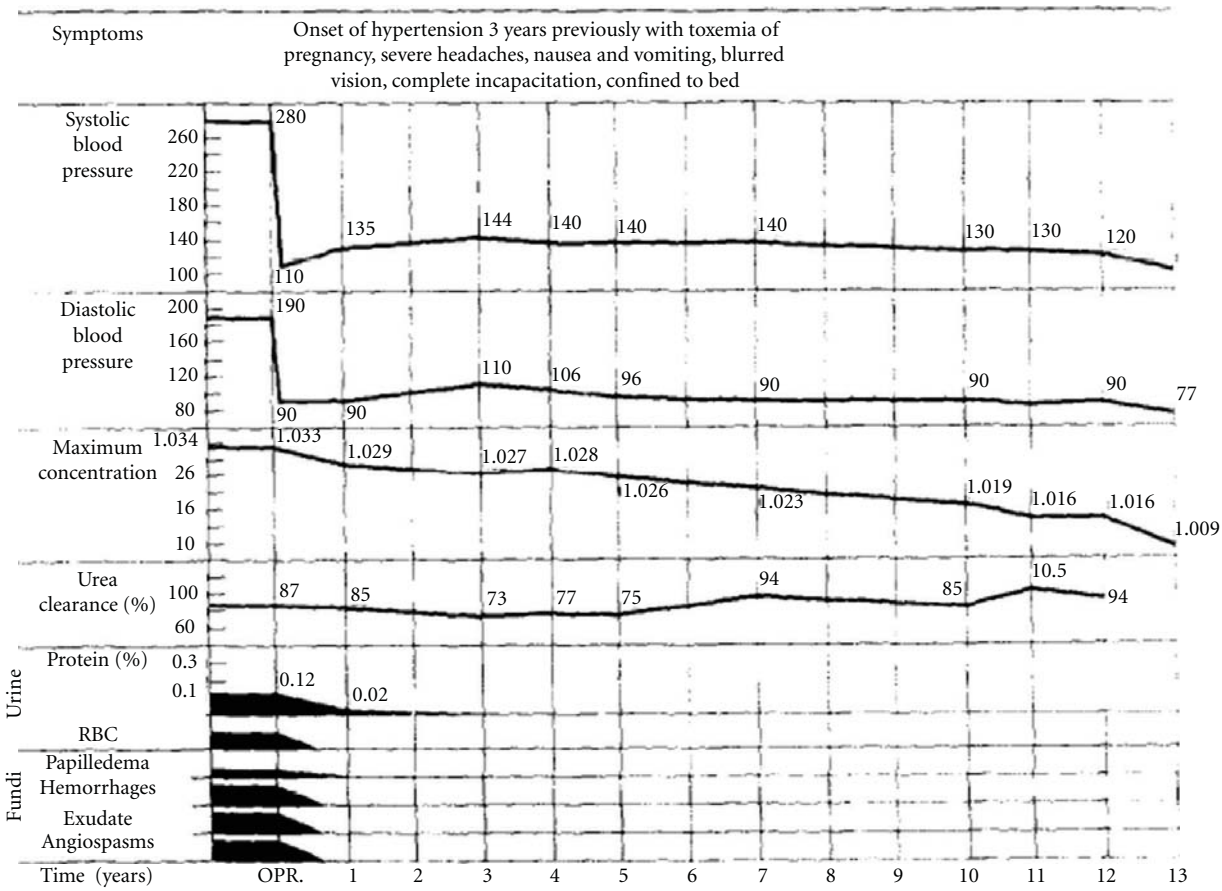


Figure 2: Long-term blood pressure control following surgical sympathectomy.

Ability to personalize and control the therapy

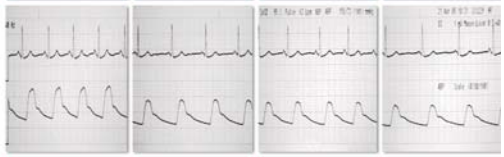
	Control	1 volt	2 volts	3 volts
				
Heart rate (bpm)	71	56	58	50
Blood pressure (mmHg)	210/96	168/73	156/72	144/66

Figure 3: Blood pressure and heart rate reduction using baroreceptor stimulation therapy (BST) from 1 to 3 volts. Note that acutely blood pressure was reduced from 210/96 to 144/66 and heart rate from 71 to 50 beats per minute.

Radiofrequency ablation of sympathetic fibers

Figure 4: Sympathetic fibers, both efferent and afferent, are found in the adventitia of renal arteries. These fibers can be ablated using specialized catheters that deliver radiofrequency energy.

Sympathectomy proved to be effective in reducing blood pressure immediately postoperatively, and the results were maintained in the long term in most patients. Sympathectomy was associated with improved survival in the long run. Notably, in a large observational study of more than 2,000 patients (1,506 splanchnicectomy), survival rates were more than doubled in patients undergoing sympathectomy, and the benefits were evident in all stages of hypertension [28]. A satisfactory blood pressure response was observed in about half of the patients that underwent splanchnicectomy.

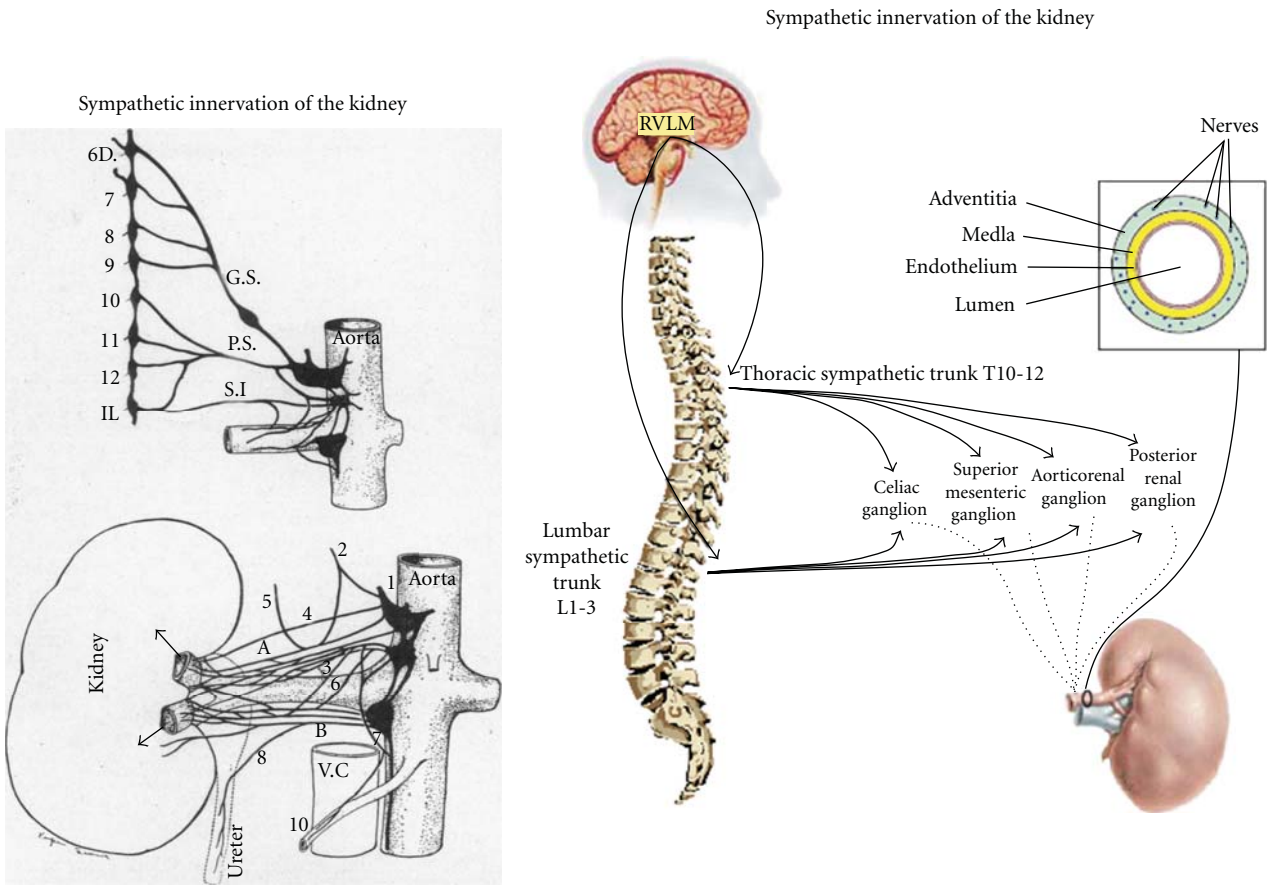


Figure 5: Schematic representation of sympathetic innervations of the kidney.

The two major limitations of splanchnicectomy were the required surgical expertise and the frequent adverse events occurring with this procedure. Adverse events were common, annoying, some of them serious, and included orthostatic hypotension, orthostatic tachycardia, palpitations, breathlessness, anhidrosis, cold hands, intestinal disturbances, loss of ejaculation, sexual dysfunction, thoracic duct injuries, and atelectasis. The advent of effective antihypertensive therapy made surgical sympathectomy unattractive and undesirable for most patients.

4. Current Use of Renal Sympathetic Denervation (RSD)

Renal sympathetic denervation presents a major improvement with several significant advantages over the radical sympathectomy that was performed five decades ago. It is a localized procedure, minimally invasive, and has no systematic side effects, and the procedural and recovery times are very short (see Figure 4). The technique was pioneered by Sobotka, Krum, and others who performed the first study of catheter-based RSD [14]. The study included 50 patients with resistant hypertension, with 45 of them fulfilling eligibility anatomical criteria. Renal sympathetic ablation was achieved using a radiofrequency ablation catheter inserted through the femoral artery and selectively engaging the renal artery bilaterally (Symplicity, Ardian Inc., Palo Alto, Calif, USA). This proof-of-principle trial was carried out in patients with resistant hypertension (i.e., systolic blood pressure ≥ 160 mmHg on three or more antihypertensive medications, including a diuretic). The primary objective of the study was safety and efficacy. The primary endpoint was change in office blood pressure at 1, 3, 6, 9, and 12 months after the procedure. Renal angiography was done before, immediately after, and 14–30 days after procedure, and magnetic resonance angiogram 6 months after the procedure in some patients. The efficacy of RSD was confirmed in a subgroup of 10 patients by the use of noradrenaline spillover technique. Renal sympathetic ablation resulted in impressive blood pressure reductions that were maintained during the 12-month follow-up period (Figure 7). Five patients that were ineligible for the study due to anatomical reasons were used as controls; blood pressure in these patients gradually increased during the follow-up period.

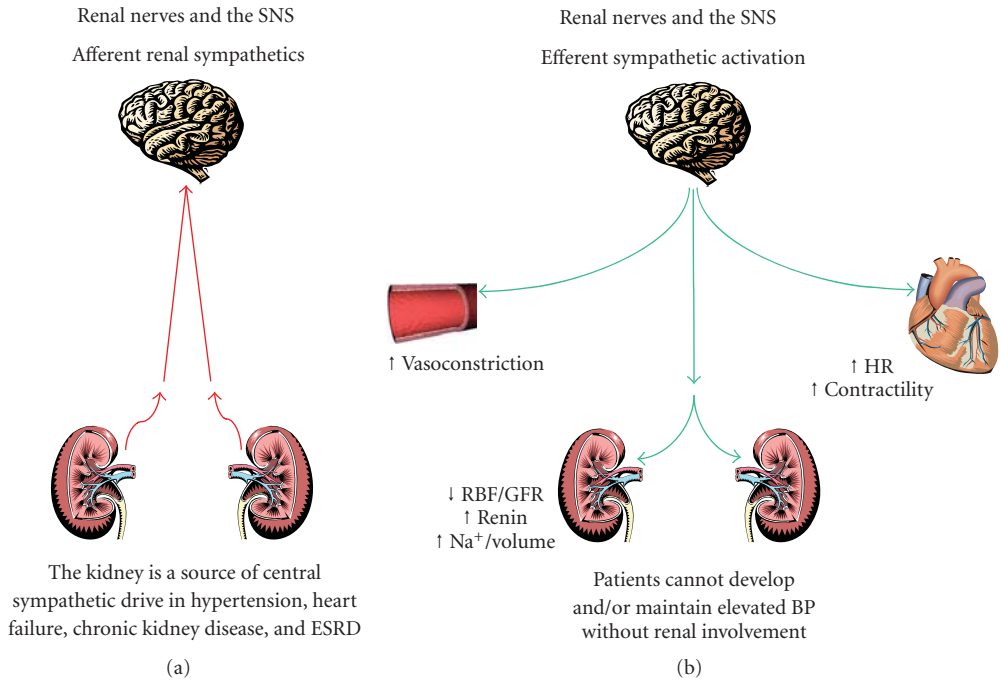


Figure 6: Afferent and efferent sympathetic innervations of the kidney.

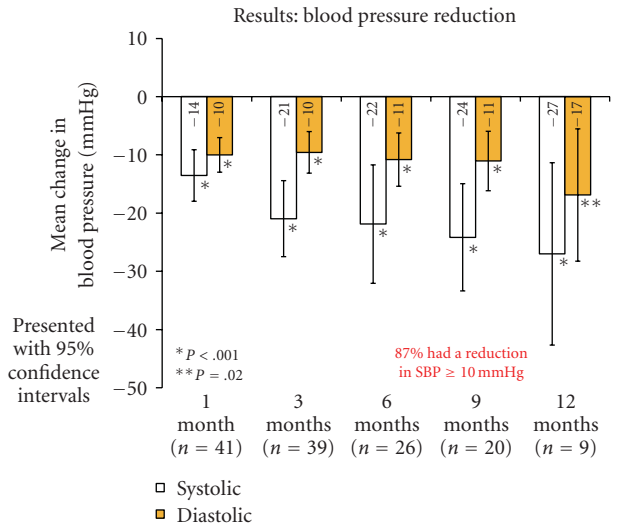


Figure 7: Blood pressure response following bilateral renal sympathetic denervation using a radiofrequency ablation catheter.

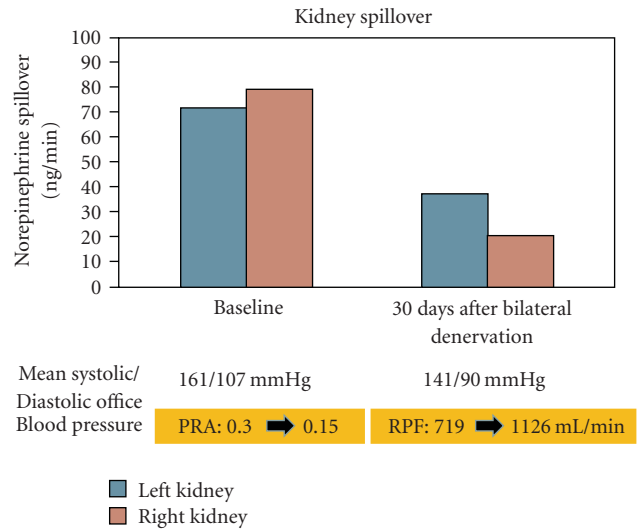


Figure 8: Noradrenalin spillover of both the right and the left kidneys at baseline and 30 days after sympathetic renal denervation.

This proof-of-concept study opens new avenues in the treatment of resistant hypertension. The study provided the first evidence that catheter-based ablation of renal sympathetic fibers is safe and effective. Only two adverse effects occurred (one renal artery dissection and one femoral artery pseudoaneurysm). These were complications related to the percutaneous technique and not to radiofrequency ablation. Postprocedural anatomic adverse events were evaluated by renal angiography at one month in 18 patients and renal magnetic resonance angiography (MRA) at six months in 14 patients. The study is important because it demonstrates for the first time in humans that RSD can reduce blood pressure in a safe way and results are sustained in the long term. In fact follow-up data in an expanded group of patients ($N = 153$) indicate that blood pressure lowering is maintained for >2 years after the procedure with favorable target organ consequences.

Although these results were impressive, the study created several concerns and many questions were left to be explored: There was no proper control group, since the study was

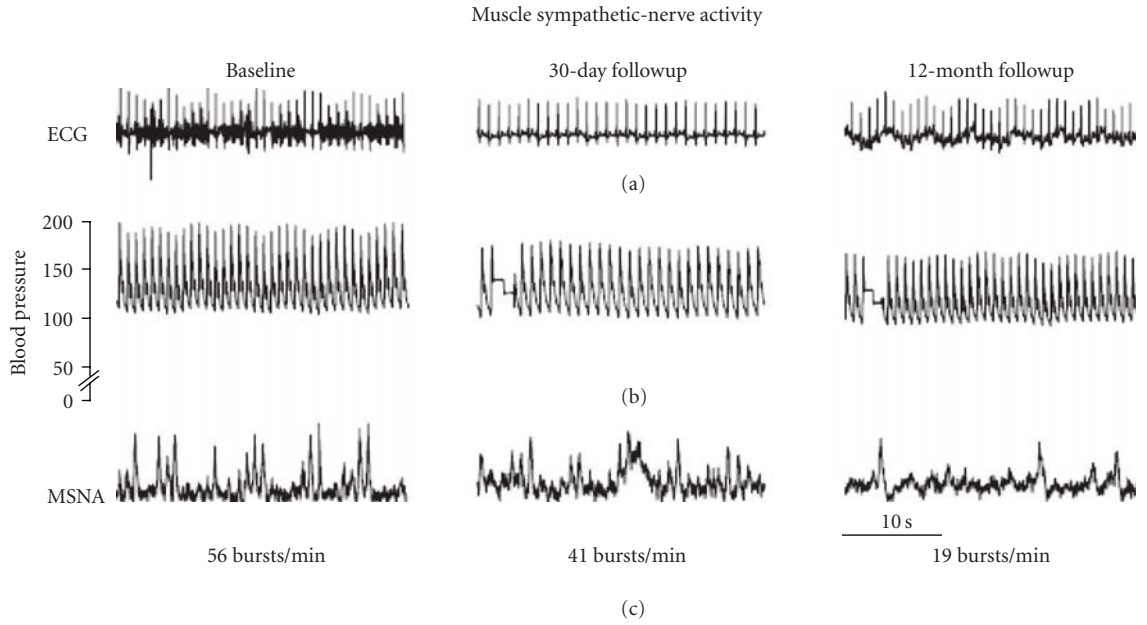


Figure 9: Results of microneurography before and after renal nerve ablation. Panel (a) shows the results of bilateral renal denervation, as assessed by the radiotracer dilution method, at baseline and 30 days after the procedure. After ablation, decreases in renal norepinephrine spillover were observed in both kidneys (48% in the left kidney and 75% in the right kidney), indicating substantial modulation of renal sympathetic efferent nerve activity after the procedure. Simultaneously, a marked reduction in whole-body sympathetic nerve activity was apparent, with a decrease in whole-body norepinephrine spillover of 42% (b). Panel (c) shows a reduction in muscle sympathetic-nerve activity (MSNA), as assessed in the peroneal nerve on microneurography, after bilateral renal nerve ablation, which highlights the possibility that inhibition of afferent renal-nerve activity may contribute to the reduction in central sympathetic drive.

not randomized or placebo (sham-operation) controlled. A proper workup of resistant hypertensives was not performed prior to randomization, in order to exclude patients with white coat hypertension, poor adherence, secondary forms or hypertension, or other correctable types of resistant hypertension. Furthermore, predictors of blood pressure response have not been identified, generating unavoidable concerns when it comes to an interventional approach.

Another major concern with the radiofrequency-induced renal sympathetic nerve ablation was the potential for development of suitable substrate for renal artery stenosis due to intimal injury. Tissue damage and fibrosis have been observed with radiofrequency ablation in other areas of the body (i.e., left atrium for atrial fibrillation, tumor ablation, etc.). it is important to note, however, that the energy delivered in other conditions is much higher compared to the one required for RSD, thus rendering RSD potentially harmless. Credence to this argument comes from the findings of Krum et al. [14, 15]. They reported that no signs of renal artery stenosis were observed during the six-month follow-up period, using magnetic resonance angiography, and no evidence of renal artery stenosis was found in the expanded group of patients with >2 year follow-up.

Further insights into mechanisms of hypertension control through RSD were published in a recent case report of a 59-year old patient with long-standing uncontrolled hypertension on a multidrug regimen [29]. In this case, baseline renal nor-epinephrine spillover from both the left and right kidneys, was approximately three times the normal level, indicating increased renal sympathetic neuronal efferent activity. Bilateral renal sympathetic nerve ablation resulted in marked reduction of blood pressure and decrease of norepinephrine spillover by 48% from the left kidney and 75% from the right kidney (Figure 8). This reduction in renal norepinephrine spillover was associated with a 57% increase in renal plasma flow. Whole-body norepinephrine spillover was reduced by 42%, providing evidence of afferent renal nerve interruption resulting in decreased central sympathetic outflow. Furthermore, muscle sympathetic nerve activity, assessed by microneurography, decreased toward normal levels at 30 days and 12 months after renal denervation (Figure 9).

Recently a second catheter-based RSD study—the Simplicity HTN-2 [30] study—was published confirming the initial results in a controlled sample. In this multicentre, prospective, randomised trial, patients with a baseline systolic blood pressure of 160 mmHg or more (≥150 mmHg for patients with type 2 diabetes) were randomly assigned to renal denervation with previous treatment or to maintaining previous treatment alone (control group). The primary endpoint was change in seated systolic blood pressure at 6 months. Out of 190 patients screened for eligibility, 106 were randomized to renal denervation ($n = 52$) or control ($n = 54$) groups. Office-based blood pressure measurements in the renal denervation group decreased by 32/12 mmHg (baseline of 178/96 mmHg, $P < .0001$), whereas they did not differ from baseline in the control group (change of 1/0 mmHg (21/10), baseline of 178/97 mmHg, $P = .77$

systolic and $P = .83$ diastolic). Between-group differences in blood pressure at 6 months were 33/11 mmHg ($P < .0001$). At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 18 (35%) of 51 controls ($P < .0001$). No serious procedure-related or device-related complications were noted, and occurrence of adverse events did not differ between groups. Results of this study are reassuring and take the concept one step further. Nonetheless concerns about long-term safety and efficacy still remain.

5. The Future of RSD

Certainly results of these two studies employing catheter-based SRD open new avenues for the treatment of patients with resistant or difficult-to-control hypertension. Future research needs to investigate whether RSD can be applied in milder forms of hypertension, for noncompliant patients, patients intolerant to medication, and in several other conditions, such as hypertension with left ventricular hypertrophy (LVH), congestive heart failure, and chronic kidney disease.

6. Conclusions

Resistant hypertension represents a significant challenge in everyday clinical practice. Catheter-based RSD represents an innovative new technique to effectively reduce blood pressure in these patients. The pathophysiology of hypertension supports the use of RSD in the treatment of many patients with essential hypertension.

A vast amount of evidence suggests beneficial effects of sympathectomy on life expectancy in patients with severe or malignant hypertension and in the prevention of cardiovascular complications in patients with milder forms of hypertension.

RSD will significantly enrich the therapeutic armamentarium for hypertension treatment and control. Indeed if RSD proves to have long-lasting beneficial effects, patients would have a choice between interventional therapy or cure of hypertension and lifelong drug therapy with associated expense and potential side effects. It may be far fetched, but, RSD may become in the future a viable alternative to lifelong drug therapy.

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SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 964394, 5 pages
doi:10.4061/2011/964394

Review Article

Carotid Baroreceptor Stimulation for the Treatment of Resistant Hypertension

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Received 2 October 2010; Accepted 28 February 2011

Academic Editor: Henry Punzi

Interventional activation of the carotid baroreflex has been an appealing idea for the management of resistant hypertension for several decades, yet its clinical application remained elusive and a goal for the future. It is only recently that the profound understanding of the complex anatomy and pathophysiology of the circuit, combined with the accumulation of relevant experimental and clinical data both in animals and in humans, has allowed the development of a more effective and well-promising approach. Indeed, current data support a sustained over a transient reduction of blood pressure through the resetting of baroreceptors, and technical deficits have been minimized with a subsequent recession of adverse events. In addition, clinical outcomes from the application of a new implantable device (Rheos) that induces carotid baroreceptor stimulation point towards a safe and effective blood pressure reduction, but longer experience is needed before its integration in the everyday clinical practice. While accumulating evidence indicates that carotid baroreceptor stimulation exerts its benefits beyond blood pressure reduction, further research is necessary to assess the spectrum of beneficial effects and evaluate potential hazards, before the extraction of secure conclusions.

1. Introduction

Arterial hypertension represents a major public health problem around the word. Currently, more than one billion people are thought to have hypertension worldwide and the number is estimated to exceed 1.5 billion by 2025 [1]. The advent of antihypertensive therapy has provided drugs that effectively lower blood pressure and contributed significantly to the reduction of cardiovascular events [2]. The rates of awareness, treatment, and control of hypertension have been constantly increased over the last decades; they remain, however, far from optimal [3], underlining the need for the implementation of more effective approaches.

Antihypertensive drugs belong to different categories, exerting their actions through different mechanisms that are sometimes complimentary. It has been shown, however, that despite the proper use of several antihypertensive agents, blood pressure remains uncontrolled in a small percentage of hypertensive patients (5%–15%). This subgroup has been called over the years as suffering from refractory, difficult to control, or resistant hypertension (lately). Although the percentage of this subgroup does not seem significant, the actual number of resistant hypertensives is estimated to be very large due to the high prevalence of hypertension in the general population. Therefore, the need for alternative approaches has been widely recognized over the last several years. This is the reason why the interventional management of hypertension, which has been used at the mid of the 20th century and abandoned thereafter, has rekindled and gained intense scientific interest. In particular, carotid baroreceptor stimulation and renal sympathetic denervation have been tested during the last decade for the treatment of resistant hypertension with promising preliminary results.

The carotid baroreflex represents a significant element of blood pressure homeostasis. Carotid baroreceptors sense the intra-arterial blood pressure and modulate the sympathetic tone towards the opposite direction that is, high blood pressure results in reduced sympathetic tone through baroreceptor activation, while enhanced sympathetic tone compensates for low blood pressure. For a long period of time, the carotid baroreflex has been considered as a short-term buffering system, regulating the abrupt transient fluctuations of blood pressure around a "constant set-point", while its role in the long-term regulation of blood pressure has been significantly questioned. Recent experimental and clinical data however challenge this long-standing belief, and strongly suggest the ability of the carotid baroreflex to exert long-term effects on blood pressure; therefore, the interventional activation of the carotid baroreflex has revived for the management of resistant hypertension.

This paper aims to present available data on the role of the carotid baroreflex in the treatment of resistant hypertension by: (a) delineating the anatomy, physiology, and pathophysiology of the baroreflex arc, (b) presenting the experience with carotid nerve activation that was used in the 60s for the treatment of severe hypertension and other cardiovascular diseases, and (c) by critically evaluating recent experimental and clinical data with carotid baroreceptor stimulation using the Rheos device.

2. Anatomy, Physiology, and Pathophysiology of the Carotid Baroreflex

The carotid baroreflex circuit represents the main part of the arterial baroreflex system. Although peripheral baroreceptors can be found in the aortic arch, the heart, and the pulmonary vessels, a vast amount of evidence points towards the pivotal role of the carotid baroreceptors on blood pressure buffering. Carotid baroreceptors are stretch-sensitive mechanosensors, located at the right and left carotid sinus. They sense the distention of the carotid wall and transmit signals to the brain stem via the glossopharyngeal nerve. The nucleus tractus solitaris (NTS) that lies in the dorsal medulla represents the "reception center" of afferent signals from arterial baroreceptors. Signals are then neurotransmitted to the caudal ventrolateral medulla (CVLM), which represents the "conversion center", since it converts the excitatory signals from peripheral baroreceptors to inhibitory signals that sequentially travel to the rostral ventrolateral medulla (RVLM). The latter represents the "coordinating center" since sympathoexcitatory neurons travel from here towards all over the body regulating the sympathetic tone.

Actually, the baroreflex circuit is much more complicated than the afore-mentioned brief description. Anatomical crossovers, intersections, and bypasses exist, while a great variety of peptides are used as neurotransmitters with either inhibiting or activating properties. Moreover, data from anatomical, pharmacological, and electrophysiological studies are sometimes conflicting, mainly due to the sophisticated and demanding techniques that are used for these studies, thus rendering methodological problems unavoidable. However, a detailed description of the carotid baroreflex is beyond the scope of the current paper. Therefore, it can be summarized that, irrespective of the exact nature of the baroreflex circuit, the net result of baroreceptor activation is a subsequent suppression of the sympathetic tone.

The functional evaluation of the carotid baroreflex has been mainly based on suppression studies through carotid denervation. A large amount of animal studies with carotid denervation in different species provided essential information regarding the role of carotid baroreceptors in the regulation of blood pressure, especially during the long term. Older studies have mainly pointed towards a transient increase of blood pressure following baroreceptor denervation that was not sustained during longer followup periods, despite some opposite findings that have been reported [4–10]. A limited role of carotid baroreflex in the long-term regulation of blood pressure was further established by the landmark study of McCubbin, which described the phenomenon of "baroreceptor resetting" [11]. The response to the carotid baroreflex is blunted in hypertensive animals suggesting a resetting of the carotid baroreceptors towards the prevailing pressure, which is actually very rapid and takes place within minutes [12]. However, several concerns can be raised regarding the denervation studies as well as the level of baroreceptor resetting that have been recently reviewed [13]. Indeed, recent animal studies suggest a significant role of the carotid baroreflex even in the long-term blood pressure regulation, by using different, more sophisticated, methodological approaches that better resemble clinical conditions [14–20].

Data in humans exist as well, although limited, and derive from denervation studies reporting the effects of iatrogenic damage of carotid sinus during various procedures (carotid body tumour surgery, carotid paraganglioma excision, carotid endarterectomy, and head and neck radiotherapy). The majority of these studies failed to find a persistent elevation of blood pressure, despite acute transient increases of blood pressure levels and enhanced blood pressure variability [21–25]; however, opposite studies can be found as well, reporting long-lasting blood pressure elevations following carotid baroreceptor denervation [26–28]. The above-mentioned controversial findings may be attributed to the retrospective nature of the studies that has not permitted for appropriate study designs.

3. Carotid Nerve Activation—Experimental and Clinical Data

Carotid baroreflex activation for the treatment of resistant hypertension does not represent a new idea. The pursuit of blood pressure reduction through the continuous baroreflex activation has flourished during the 50s and 60s. Several devices have been invented for the exogenous electrical stimulation of the carotid nerves. The principal idea was that an external generator transmitted signals to an implanted receiver through an antenna coil, and the signals subsequently travelled to electrodes that were placed in contact with the carotid sinus nerves. The concept was based on

the assumption that the continuous carotid nerve signalling would be sensed by the central nervous system as a constant rise in blood pressure, leading to sympathetic attenuation and subsequent blood pressure reduction. This concept created a lot of enthusiasm, and initial experimental studies have been shortly thereafter followed by clinical studies. This is not surprising, given the limited armamentarium for the therapeutic management of severe hypertension at that time.

Animal studies with carotid nerve activation uncovered significant blood pressure reduction, which was not only transient but was maintained during the one-year followup study period [29, 30]. The observation that electrical carotid nerve activation acutely decreases blood pressure in humans [31] encouraged the application of these devices in patients with resistant hypertension. Several case series from specialized clinics in North America have been published during the 60s [32–37]. The results showed a consistent blood pressure reduction in the majority of patients that was evident rapidly and lasted during prolonged followup periods, up to twelve years. The enthusiasm regarding this efficacious method however subsided rather rapidly, due to the excessive incidence of adverse events and the severe technical disadvantages of the devices.

4. Carotid Baroreceptor Stimulation—Experimental and Clinical Data

Recent advances in technology seem to overcome many of the prior technological problems with the devices, thus rekindling the scientific interest and rendering carotid baroreflex activation an appealing field of research. A small, US-based, pharmaceutical company (CVRx Inc, Minneapolis, Minn) has developed an implantable device (Rheos) for the electrical stimulation of carotid baroreceptors. In brief, a pulse generator that resembles a pacemaker is implanted in the right infraclavicular space and connects to two electrode leads that are placed in the perivascular space of the two carotid sinuses (Figure 1). The generator communicates with an external computer system that is capable of programming the baroreceptor activation in a noninvasive way. The procedure requires an experienced team of surgeons, anaesthesiologists, hypertension specialists, and technicians for the proper placement of the electrodes, the efficacy testing, and the overall success. The properties of the Rheos device along with the advancements in the surgical and anesthesiology field seem to address a lot of previous concerns; adverse events are not encountered as frequently as with the old devices and are mostly of less severity.

The Rheos device has been extensively tested in animals, reflecting current stringent requirements by regulatory authorities worldwide. Carotid baroreceptor stimulation was effective in reducing blood pressure of conscious normotensive dogs [38] and in obesity-induced hypertension [39]. On the other hand, blood pressure reduction was significantly attenuated, but not abolished, in angiotensin II-induced hypertension [40], suggesting that the overactivation of the renin-angiotensin system may partially overcome the effects of the carotid baroreceptor stimulation. The clinical significance of this finding and the answer to the subsequent question, whether drugs inhibiting the renin-angiotensin axis are essential in patients undergoing carotid baroreceptor stimulation for the maintenance of blood pressure reduction, remain to be clarified. Another puzzling finding comes from the study of carotid baroreceptor stimulation before and after bilateral renal denervation [41]. Blood pressure reduction with the Rheos device was unaltered by renal denervation, casting doubts on the role of renal innervation in mediating the effects of the carotid baroreflex on blood pressure regulation. However, further studies in hypertensive animals need to be performed to uncover the role of renal denervation in this experimental setting. It has to be noted, however, that in all the afore-mentioned animal studies [38–41], the blood pressure reduction was accompanied by a significant decrease in plasma noradrenaline levels, indicating that the suppression of the sympathetic tone mediates the effects of carotid baroreceptor stimulation on blood pressure.

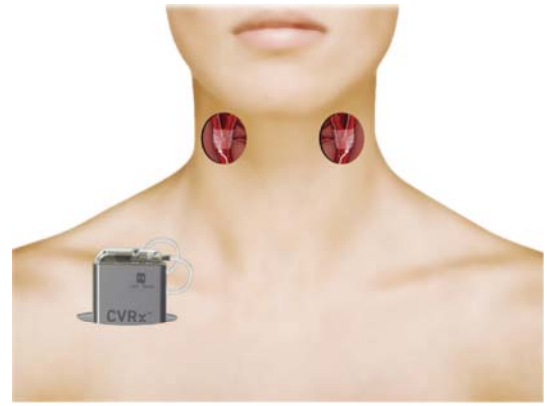

Figure 1: Schematic representation of the Rheos device for carotid baroreceptor stimulation.

Studies in humans have confirmed the efficacy of this interventional approach, which was observed in animals. Acute blood pressure reduction was noted by using the Rheos device during elective carotid surgery [42]. Several case reports in patients with resistant hypertension have shown the clinical utility and long-lasting reductions in blood pressure with carotid baroreceptor stimulation, setting the basis for proof-of-concept, properly designed, clinical trials [43–45]. The device based therapy of hypertension (DEBuT-HT) trial in 45 patients with resistant hypertension revealed a significant reduction in both systolic and diastolic blood pressure, which was evident from the beginning of the study and was maintained thereafter [46]. The 3-year efficacy was recently presented verifying the long-lasting effects of carotid baropacing. Recruitment for a large randomized study has been completed and results are still pending. Preliminary information suggests that some patients may not respond as well, and a more careful selection process may need to be implemented.

Available data suggest a beneficial effect of carotid baroreceptor stimulation on the reversal of left ventricular hypertrophy. Moreover, additional desirable effects on cardiac

structure and function have been observed, including attenuated mitral A-valve velocity and reduced left atrial dimensions. Whether these pilot findings would be of major clinical importance remain to be further investigated. Another important aspect relates to the effects of carotid baroreceptor stimulation on renal function. Available data suggests that carotid baropacing does not impair the renal function of patients with resistant hypertension, even during prolonged followup periods. Two recent studies enlighten the mechanisms via which carotid baroreceptor stimulation achieves blood pressure reduction [47, 48]. Similar to findings from animal studies, it was shown that baroreceptor stimulation was accompanied by attenuation of sympathetic activity, assessed by muscle sympathetic nerve activity [47] or by analysis of heart rate variability [48]. Regarding safety, recent data indicate that the Rheos device can be safely used in patients with pacemakers [49]. In addition, it has been shown that the chronic stimulation of the carotid baroreceptors does not cause injury, remodelling, or stenosis of the carotid arteries [50].

It has to be noted that some technical issues need to be resolved, and several clinical aspects need to be clarified, before the wide application of this interventional technique in everyday clinical practice [13]. However, the latest concerns regarding the efficacy of the device underline the need for careful evaluation of every emerging therapeutic approach to fulfill the two fundamental requirements: safety and efficacy.

5. Conclusions

The carotid baroreflex represents an essential component of blood pressure regulation. The activation of the carotid baroreflex results in the attenuation of the sympathetic tone and subsequent blood pressure reduction. Carotid nerve activation has been used in the past for the treatment of severe hypertension, but its use has been abandoned due to adverse events and several technical disadvantages. Recent technological advances have permitted the development of a new device (Rheos) that electrically stimulates carotid baroreceptors and seems to overcome prior technical problems. Available experimental and clinical data point towards adequate efficacy with acceptable safety of this device although some concerns have been raised lately. Therefore, further studies are needed to clarify the place of carotid baroreceptor stimulation in the management of patients with resistant hypertension.

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