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Editorial

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

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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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