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## Review Article

# Common Secondary Causes of Resistant Hypertension and Rational for Treatment

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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 rationale 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.

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
(viii) Erythropoietin
(ix) Herbal supplements
(x) VEGF inhibitors

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.

## 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<sub>2</sub> and I<sub>2</sub>) [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 cyclooxygenase 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. Naproxenod 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.

## 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 through 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

TABLE 3: Endocrine causes of secondary hypertension.

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

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 non-invasive methods remains tricky. Although several methods are used for the detection of RAS (duplex ultrasound, renal scintigraphy, and 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 rationale 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 methyl dopa) 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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