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Secondary hypertension as a cause of treatment resistance

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ABSTRACT

In secondary hypertension, elevated blood pressure is caused by a known and/or potentially treatable underlying disease. Although the prevalence of secondary hypertension depends on the patient population and the thoroughness of applied diagnostic approaches, arterial hypertension is classified in 90 to 95% as primary in nature. In young patients, individuals without a family history of hypertension, late onset of hypertension or worsening of a previous well-controlled hypertension as well as in patients who have a difficult to treat hypertension, the prevalence of secondary hypertension is significantly higher. Because the identification and the specific therapy of secondary hypertension may result in normalisation or improvement of elevated blood pressure in many cases, a targeted diagnostics is of great importance.

KEY MESSAGES

- The prevalence of secondary hypertension is 5-10% of hypertensive patients (lower in the whole population, higher in patients with therapy-resistant hypertension).
- Patient history, physical examination, and laboratory results are very important to patients with suspected secondary hypertension to identify. After a preliminary screening, the assignment is made recommended for specialist medical clarification.
- Think about secondary hypertension In young patients, individuals without a family history of hypertension, late onset of hypertension or worsening of a previous well-controlled hypertension as well as in patients who have a difficult to treat hypertension.

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Introduction

Arterial hypertension is a major cardiovascular risk factor that affects between 10% and 40% of the general population in an age- and population-dependent manner.

Depending on the population, in up to 5% of individuals, an underlying cause of hypertension may be found defining secondary hypertension. The incidence of secondary hypertension differs widely among different patient populations [1,2].

As secondary hypertension has potentially correctable causes, diagnosing this type of hypertension is of particular clinical importance. Thus, whenever the diagnosis of arterial hypertension is confirmed according to current guidelines [3], as a general approach, an initial assessment (i.e. history, physical examination, and basic laboratory testing) to exclude or suspect possible secondary causes of high blood pressure should take place (Table 1).

Basic diagnostics in hypertension including medical history, physical examination, blood analysis, urine status and abdominal sonography usually allow for a initial suspicion of the most common secondary forms of hypertension. Further, special examinations are available for completing the diagnosis, which are best performed in specialised centre (Table 1) [3].

Secondary hypertension is classified according to its aetiology into different subgroups. A distinction is made between renal (renoparenchymal and renovascular) and endocrine hypertension (primary aldosteronism, Cushing's syndrome or disease, pheochromocytoma and thyroid/parathyroid disease).

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Table 1. Signs and symptoms suggesting specific causes of secondary hypertension. Reproduced from Ref. [1].

Signs and symptoms	Possible diagnosis	Diagnostic tests
Different BP (≥20/10 mmHg) between upper–lower extremities and/or between right–left arm; delayed femoral pulsations; interscapular ejection murmur; rib notching on chest X-ray	Coarctation of the aorta	Echocardiography, X-ray, thorax MRI
Peripheral oedema; pallor; loss of muscle mass	Renal parenchymal disease	Creatinine, ultrasound of the kidney
Abdominal bruits; peripheral vascular disease	Renal artery stenosis	Duplex, or computed tomography, or MRI, or angiography
Fatigue; constipation; polyuria, polydipsia, muscle weakness	Primary aldosteronism	Aldosterone–renin ratio
Weight gain; impotence; fatigue; psychological changes; polydipsia and polyuria, obesity, hirsutism, skin atrophy, striae rubrae, muscle weakness, osteopenia	Cushing's Syndrome	24 h urinary cortisol; dexamethasone testing
Headache; palpitations; flushing; anxiety; paroxysmal hypertension; pounding; headache; perspiration; palpitations; pallor	Phaeochromocytoma	Plasma or 24 h urinary metanephrines; 24 h urinary catecholamine
Hyperthyroidism: palpitations, weight loss, anxiety, heat intolerance; tachycardia, atrial fibrillation; accentuated heart sounds; exophthalmos	Thyroid disease	TSH, free T3 free T4
Hypothyroidism: weight gain, fatigue, obstipation, bradycardia; muscle weakness; myxoedema		
Snoring, daytime sleepiness; morning headache, irritability; increase in neck circumference; obesity; peripheral oedema	Obstructive sleep apnoea	Screening questionnaire; polysomnography

BP: blood pressure; MRI: magnetic resonance imaging; T3: tri- iodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone.

Table 2. Selected drugs that may elevate blood pressure. Reproduced from Ref. [1].

Drugs class	Common examples
Oestrogen	Oral contraceptive
Herbal	Ephedra, Ginseng, ma Huang
Illicit	Amphetamines, Cocaine
Non-steroidal Anti-Inflammatory	Cyclooxygenase-2 inhibitors, ibuprofen, naproxene
Psychiatric	Buspirone, carbamazepine, clozapine, fluoxetine, lithium, tricyclic antidepressant
Steroid	Methylprednisolone, prednisone
Sympathomimetic	Decongestants, diet pills

Moreover, secondary hypertension can be caused by sleep-disordered breathing, aortic coarctation and other congenital conditions, be pregnancy-associated, induced by excessive alcohol consumption, hypervolemia, substances abuse or use of certain drugs, all of which may increase blood pressure (Table 2).

Secondary hypertension as a cause of difficult to treat hypertension

Despite the existence of evidence-based guidelines blood pressure (BP) control (BP < 140/90 mm Hg) is poor even in a treated hypertensive population. The lack of control remains an important issue because a clinically relevant reduction in cardiovascular events cannot be achieved without a reduction of BP to the target level [3]. Accordingly, the [4]current trends with a continued worsening of BP control in hypertensive patients is worrying and new strategies to improve BP control are urgently needed [4].

Difficult-to-control hypertension - defined, as uncontrolled hypertension on three antihypertensive medications including a diuretic - is becoming an increasingly common problem.

Besides factors such as older age, therapy adherence, technical issues related to blood pressure measurement and obesity, causes of secondary hypertension should be excluded before the diagnosis of treatment resistance can be confirmed.

The sympathetic nervous [5,6] and renin–angiotensin–aldosterone systems [7] regulate blood pressure, fluid volume, and the vascular response to injury and inflammation. Derangement of these systems is often found in patients with therapy-resistant hypertension and secondary hypertension [2]. In the clinical setting of difficult-to-control hypertension other factors such as socioeconomic factors, noise exposure and other environmental factors/exposures should be carefully evaluated.

Common causes of secondary hypertension

Kidney and renal artery diseases

The kidneys play a central role in blood pressure regulation. Arterial hypertension can lead to kidney damage, while renal and renal artery diseases can contribute to an increase in blood pressure.

Possible secondary forms of renal hypertension include glomerular kidney disease (e.g. glomerulonephritis) and tubulointerstitial processes (e.g. polycystic kidney disease) or microvascular kidney damage and renovascular hypertension [1].

The diagnosis of a renal form of hypertension is supported by clinical evidence and/or typical laboratory findings such as the presence of microalbuminuria or proteinuria (albumin creatinine ratio (ACR) in spot urine), increased creatinine value or reduced glomerular filtration rate and imaging abnormalities of kidney and/or the renal vessels [1,3].

Renal artery stenosis may be suspected as a cause of hypertension in younger individuals, mainly females with fibromuscular dysplasia, without a family history of arterial hypertension or in elderly patients presenting with hypertensive crises, flash pulmonary edoema (commonly in the context of bilateral renal artery stenoses, or of unclear progressive deterioration of renal function. The prevalence of the different aetiology of renal artery stenosis varies according to age and cardiovascular risk factor but it is reported that atherosclerotic renal artery stenosis account for 60–90% and fibromuscular dysplasia for 10-30% of the cases [8].

The screening examination of choice for renovascular hypertension is Doppler sonography, followed, if needed, by computed tomography, magnetic resonance imaging or catheter-based angiography.

Aetiologically, fibromuscular dysplasia, which typically affects young women needs to be distinguished from atherosclerotic artery stenosis, which is more common in older patients [1]. Fibromuscular dysplasia resembles a non-atherosclerotic, non-inflammatory vascular wall disease, involving renal, iliac, subclavian and carotid arteries. The changes in the renal arteries are typically found in the distal sections of the renal artery with 'string-of-beads' features, but also in the segmental arteries with characteristic pearl necklace-like arterial wall changes.

Atherosclerotic renal artery stenosis is common in elderly patients with cardiovascular risk factors (dyslipidemia, diabetes or tobacco use) or atherosclerotic lesions in other vessels (peripheral arterial occlusive disease and coronary or cerebrovascular disease). In contrast to fibromuscular dysplasia, the atherosclerotic lesions are typically in the proximal segments of the renal arteries.

Angioplasty is a safe modality to treat fibromuscular dysplasia and leads to the reduction of short and long-term complications [9].

Concerning atherosclerotic renal artery stenosis, the currently available data suggest that angioplasty or stenting in patients with treatment-resistant hypertension or presenting hemodynamically relevant renal artery stenosis (> 80% or with a gradient > 24 mmHg) or bilateral renal artery stenosis [10–12].

However, the debate about which groups of patients are most likely to benefit from an intervention is still ongoing.

Endocrine causes of hypertension

Elevated blood pressure resulting from endocrine disorders (endocrine hypertension) accounts for a relevant proportion of cases of secondary hypertension. Although some features may be clinically suggestive, many cases of endocrine hypertension remain uncovered until specifically worked up. A majority of cases result from primary aldosteronism. Other rare conditions include rare forms of congenital adrenal hyperplasia, Liddle syndrome, phaeochromocytomas, Cushing's syndrome, acromegaly, thyroid diseases, primary hyperparathyroidism, and iatrogenic hormone manipulation.

Primary aldosteronism

Primary aldosteronism is the most common form of secondary hypertension in adults with an estimated prevalence of around 10% in referral centres and 4% in a primary care setting. In a significant proportion of patients who are resistant to combined antihypertensive medical treatment (i.e. between 11% and 20%), primary aldosteronism was identified as the underlying cause [13].

Initially, primary aldosteronism was described by Conn in 1955 as autonomous production of aldosterone by a tumour of the adrenal cortex and the secondary suppression of renin with the development of hypertension with hypokalemic alkalosis [14].

Conn also recognised that normokalaemic forms of the syndrome exist which masquerade as essential hypertension. Consequently, normokalaemic primary aldosteronism is often overlooked. It is of note that hypokalaemia is found in 9–37% of all cases of primary hyperaldosteronism with a predominance in patients with aldosterone-producing adenoma [15].

The advent of a simple screening test, the aldosterone–renin ratio, led to better recognition of such patients. Given the detrimental cardiovascular adverse effects of aldosterone excess that are in part independent of high blood pressure [16], early detection of primary aldosteronism has an important impact on clinical outcome and survival. It is important to underlined that patients with primary hyperaldosteronism have significantly higher cardiovascular mortality compared to patients with essential hypertension – even when controlled for blood pressure [17].

The two predominant causes of autonomous aldosterone secretion are aldosterone-producing adenomas, treated commonly by unilateral adrenalectomy, and bilateral adrenal hyperplasia, currently managed by chronic mineralocorticoid antagonist therapy (i.e. spironolactone, eplerenone). Despite progress in the management of primary aldosteronism, critical issues related to diagnosis, subtype differentiation, and treatment of not surgically correctable forms still persist. To date, the definitive

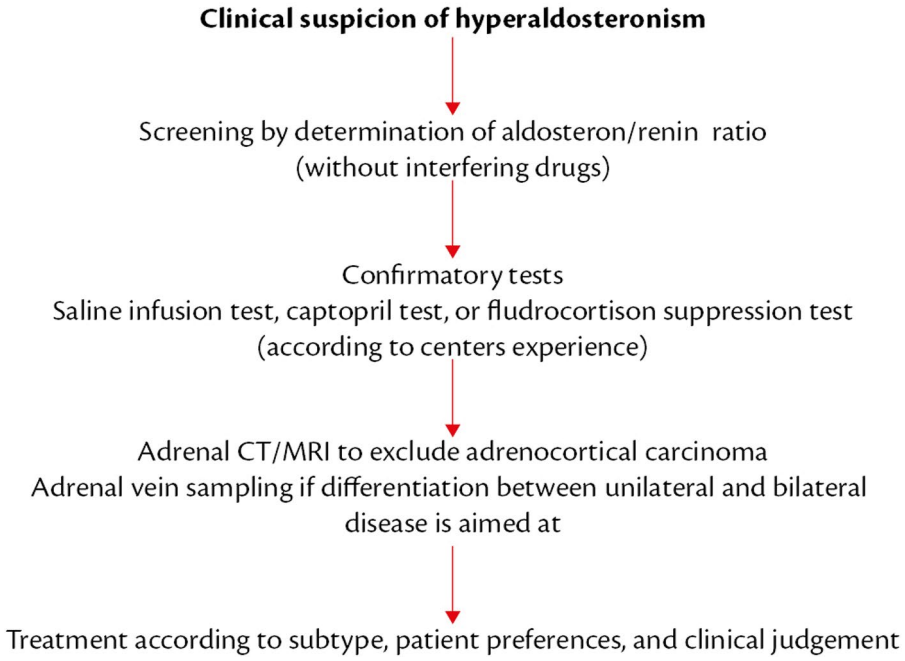

Figure 1. Flow chart diagnosis of hyperaldosteronism. Modified from Ref [1].

diagnosis of primary aldosteronism is a multistep procedure requiring expert knowledge (Figure 1) [18,19].

For example, while adrenal venous sampling is recommended to assess whether aldosterone hypersecretion is lateralised in patients with primary aldosteronism, this procedure is invasive, poorly standardised, and not widely available [20].

Overall, compared with its importance as the major secondary cause of hypertension, the currently available tools for diagnosis and treatment of primary aldosteronism are quite inefficient. These shortcomings relate in part to the heterogeneity of Conn's syndrome. In epidemiological terms, there appears to be a continuous spectrum from low renin hypertension, normokalaemic Conn's syndrome to hypokalaemic primary aldosteronism that makes cut-offs used for screening somewhat arbitrary. Likewise, based on histopathology of adrenal tissues resected during adrenalectomy, heterogeneity exists at multiple levels as aldosterone excess may be caused by micro- or macronodular hyperplasia or by a typical adrenal adenoma; the adjacent adrenal cortex may be atrophic, diffuse hyperplastic, or nodular hyperplastic [21].

In appreciation of the overall high prevalence and the complexity of the endocrine work-up, current guidelines support a relatively broad screening policy as well as a liberal treatment trial with mineralocorticoid receptor antagonists despite incomplete differential diagnosis [19]. Candidates with a particular high cure rate following a surgical procedure are females, younger patients, and those with a short history of hypertension. Therefore, in these patients, completion of the complete diagnostic procedure should be aimed for.

Cushing's syndrome

Endogenous hypercortisolism, also termed Cushing's syndrome, is characterised by typical clinical signs/symptoms that in its overt form are usually not missed. The diagnosis of Cushing's syndrome involves hormonal assessments, including a non-suppressible serum cortisol after application of 1 mg of dexamethasone overnight, the elevation of urinary free cortisol in a 24 h urine collection, or demonstration of a flattened circadian cortisol rhythm indicated by elevated (salivary) midnight cortisol levels. The localisation (i.e. central vs adrenal) is guided by the assessment of baseline adrenocorticotropic hormone levels. Further differential diagnosis will likely require other functional tests (such as high-dose dexamethasone suppression test and corticotropin-releasing hormone stimulation testing), targeted imaging procedures, and sometimes invasive procedures such as sinus petrosus venous sampling [22,23].

While glucocorticoid excess does play a role in blood pressure regulation, arterial hypertension is only rarely the leading clinical feature in patients with

Cushing's syndrome. Considering the rarity of the condition, it is, therefore, prudent to restrict screening procedures in hypertensive patients to those suggested by current guidelines [24,25]:

- Patients with unusual features for age (e.g. osteoporosis, hypertension).
- Patients with multiple and progressive features [25], particularly those that are more
- predictive of Cushing's syndrome such as between others facial plethora, Striae or proximal myopathy [24].
- Children with decreasing height percentile and increasing weight.
- Patients with adrenal incidentaloma compatible with adenoma.

Recent evidence suggests that also subtle forms of endogenous hypercortisolism - as often encountered in patients with adrenal incidentalomas – is associated with a relevant cardiovascular disease burden including arterial hypertension [26].

Phaeochromocytoma

Tumours secreting excessive amounts of catecholamines are termed 'phaeochromocytomas' or 'paraganglioma' in accordance with their anatomical location.

Lesions producing excess catecholamines may be located in the adrenal glands (phaeochromocytomas, around 90% of the diagnosis) or in sympathetic ganglia, which are present along the entire sympathetic chain (paragangliomas or extra-adrenal phaeochromocytomas, around 10%). Although the sympathetic chain extends throughout the body, most secreting extra-adrenal phaeochromocytomas are located in the abdomen; less common locations for these lesions include the neck, chest, and urinary bladder. The majority of head and neck paraganglioma are not hormonally active.

Both phaeochromocytoma and paraganglioma are uncommon tumours that account for less than 0.1% of all hypertensive cases [1]. The clinical presentation of phaeochromocytomas is quite variable, ranging from severe, causing emergencies and sudden death, to those cases with minimal or no symptoms. In the latter, the diagnosis is often initiated following abdominal imaging with an incidental finding of an adrenal tumour. Commonly described symptoms are headache, flushing, palpitations, anxiety, chest pain, dyspnoea, abdominal pain, diarrhoea, blurred vision, dizziness, weakness and fatigue, anorexia and weight loss, polyuria, and polydipsia; clinical signs include arterial hypertension (stable or hypertensive crisis), tachycardia, orthostatic hypotension, and heart failure [27].

Phaeochromocytoma and paraganglioma have a strong genetic background and in more than 30% of cases, mutations in one of many identified susceptibility genes can be identified. Therefore, genetic testing has been advocated for in all affected patients. The diagnosis of a pheochromocytoma requires confirmation of inappropriate catecholamine production. This is achieved by measurement of normetanephrine, metanephrines, and methoxytyramine in plasma and/or 24h urine, which provides high sensitivity and specificity [27].

Screening is recommended in patients with typical signs and symptoms, in those with a family history or earlier diagnosis of a phaeochromocytoma or paraganglioma, and in all patients with an adrenal incidentaloma. Similar to the situation for Cushing's syndrome, the low pre-test probability renders a general screening of the hypertensive population inappropriate.

Thyroid and parathyroid diseases

Deregulation of the thyroid and parathyroid function are reversible causes of secondary hypertension [28]. Thyroid disorders induce several haemodynamic changes leading to elevated blood pressure as a consequence of their interaction with endothelial function, vascular reactivity, renal haemodynamics, and renin–angiotensin system. However, in thyroid disorders, the regulation of blood pressure and the development and maintenance of variable forms of arterial hypertension are different [29]. Hyperthyroidism results in an increased endothelium-dependent responsiveness secondary to the shear stress induced by the hyperdynamic circulation and contributes to reduce vascular resistance. Conversely, hypothyroidism is accompanied by a marked decrease in sensitivity to sympathetic agonists with an increase in peripheral vascular resistance and arterial stiffness. Increased blood pressure due to thyroid disorders is usually reversible with the achievement of euthyroidism, but in some cases, the pharmacological treatment for blood pressure control is required. In hyperthyroidism, beta-blockers are the first-choice treatment to control blood pressure, but when they are contraindicated or not tolerated, angiotensin-converting enzyme inhibitors or calcium channel blockers are recommended. Hypothyroidism is a typical low-renin hypertension responding particularly well to calcium antagonists and diuretics; indeed, in hypothyroidism a low-sodium diet seems to improve blood pressure control further [1].

Sporadic primary hyperparathyroidism is an endocrine disorder usually characterised by persistent fasting hypercalcaemia attributable to autonomous overproduction of parathyroid hormone by parathyroid adenoma or hyperplasia (hypercalcaemic primary hyperparathyroidism).70 However, a proportion of patients with primary hyperparathyroidism (20%) show normal total and ionised serum calcium levels in the presence of persistently elevated parathyroid hormone concentrations [30]. Primary hyperparathyroidism is associated with an increased risk of arterial hypertension [30]. Recent investigations have reported high blood pressure in 40–65% of patients with primary hyperparathyroidism [31]. Despite variations in published data due to different patient selection criteria, the prevalence of hypertension in patients with primary hyperparathyroidism is higher than in the general population regardless of age [31]. However, elevated parathyroid hormone levels have also been reported in a subgroup of patients with primary (essential) hypertension. Proposed mechanisms linking hypertension and primary hyperparathyroidism include abnormalities in major endocrine pressor factors, such as the sympathetic nervous system and/or the renin– angiotensin–aldosterone axis, dysfunction or structural changes of resistance vessels documented either by an altered vasodilatory response, and/or an enhanced vascular constriction to pressor hormones.

Other causes of secondary arterial hypertension

Non-Adherence to the antihypertensive therapy

Adherence to antihypertensive therapy is critical to achieving adequate blood pressure control [32]. Of note, 30–50% of hypertensive patients do not take their drugs as prescribed and physicians often underestimate this issue, particularly in their own patients. Non-adherence has important public health implications and, moreover, it results in increased morbidity and mortality rates [33].

The causes of poor adherence are both patient and therapy related. Reducing the number of drugs that need to be taken daily by prescribing fixed-dose combination drugs and regular visits[34] as well as biochemical screening[35] have been shown to improve adherence.

Currently, multiple, different direct and indirect methods to measure therapeutic adherence are available, but in clinical practice there is no cost-effective and simple tool. Therapeutic drug monitoring, characterised by drug (or metabolite) concentration measurement in body fluids (blood or urine), is a cost-effective direct method to assess therapeutic adherence [35].

Despite some limitations, therapeutic drug monitoring may decrease health costs, by reducing the number of visits and by identifying those patients who would undergo unnecessary further diagnostic and/or interventional procedures and would rather need more intensive counselling. Moreover, therapeutic drug monitoring is useful to identify patients with true resistant hypertension, rather than those with poor compliance. Other possibilities include urine testing with fluorescent drugs, pill counting, among others [36].

Sleep-disordered breathing

Obstructive sleep-disordered breathing is characterised by recurrent episodes of partial or complete upper airway obstruction during sleep[37] Indeed, obstructive sleep-disordered breathing is accepted as an important independent risk factor for cardiovascular diseases in general, and in particular for hypertension. It is an important part of both the European and American guidelines as an identifiable and treatable cause of secondary hypertension [3]. Moderate or severe obstructive sleep-disordered breathing can be detected in a third or more of patients with primary hypertension and in up to 80% of individuals with drug-resistant hypertension [37].

It is difficult to tease out confounding variables and to infer a direct causal relationship between obstructive sleep apnoea and hypertension. Nevertheless, a large body of evidence suggests a link, after adjusting for confounders. Importantly, treating obstructive sleep-disordered breathing may improve hypertension and may translate into an improved CV risk profile and patient outcomes. Obstructive sleep-disordered breathing is seen in 70% of patients with resistant hypertension, but only in 38% of those with controlled hypertension.95 The mechanisms by which obstructive sleep-disordered breathing is thought to elicit hypertension include sympathetic activation), endothelial dysfunction, increased endothelin release, reduced nitric oxide production, and systemic inflammation [1].

A sustained effect of obstructive sleep-disordered breathing on muscle sympathetic nerve activity has been documented during wakefulness in subjects with normal and impaired left ventricular systolic function. Of note, Grassi and colleagues[38] recorded daytime muscle sympathetic nerve activity in four otherwise similar lean and obese cohorts with and without severe obstructive sleep- disordered breathing (Apnoea–Hypopnea Index averaging at least 40 events per hour). Muscle sympathetic nerve activity burst

incidence was significantly greater in lean and in obese subjects with obstructive sleep- disordered breathing as compared to controls, indicating that these neural disturbances are not due to confounding effects of obesity. They also documented significantly greater daytime muscle sympathetic nerve activity in individuals characterised as having 'non-dipping' or 'reverse dipping' nocturnal ambulatory blood pressures, a clue to the presence of obstructive sleep apnoea, compared with individuals who are normotensive during the day and night.

Of note is the fact that an increased incidence of hypertension has also been associated with restless legs syndrome and reduced sleep duration, independently of the presence of obstructive sleep-disordered breathing. Furthermore, obstructive sleep-disordered breathing has also been linked to diabetes, metabolic syndrome, heart failure, arrhythmia, depression, and erectile dysfunction.

In patients with obstructive sleep-disordered breathing, several meta-analyses and randomised trials demonstrate improved blood pressure control with the use of positive airway pressure (continuous or bi-level). A meta-analysis of 32 randomised trials pooled 1948 patients and showed a mean net reduction in blood pressure of 2.5 mmHg. Including studies involving patients with resistant hypertension and obstructive sleep apnoea and measuring blood pressure changes by ambulatory blood pressure monitoring only, Iftikhar and colleagues[39] found a mean change in 24 h systolic blood pressure of −7.21 mmHg and in 24 h diastolic blood pressure of −4.99 mmHg. Blood pressure-lowering effects are especially evident in those with more severe obstructive sleep-disordered breathing. Even a modest blood pressure reduction is of relevance at the population level when considered in the context of the 10/5 mmHg reduction in systolic/diastolic blood pressure, which may reduce the risk of stroke, major cardiovascular events, and death between 20% to 25%. Randomised trials suggest that treatment of obstructive sleep-disordered breathing with mandibular devices can also lower blood pressure [40].

Whether other beneficial effects of obstructive sleep-disordered breathing therapy, such as attenuation of nocturnal hypoxaemia, sympathetic activation, and systemic inflammation, confer further benefits beyond blood pressure reduction remains to be determined. Currently, no class of antihypertensive drugs is best suited to treat hypertension related to obstructive sleep-disordered breathing. Aldosterone antagonists may be beneficial in those with resistant hypertension and obstructive sleep-disordered breathing, but randomised data are at the present time not available. Aldosterone has emerged as a key factor linking obstructive sleep-disordered breathing, dietary sodium intake, renal sympathetic activation, fluid retention, and hypertension. Any fluid retention resulting from increased renal- and aldosterone-mediated sodium retention will shift fluids at night from the legs to the neck. The resultant peripharyngeal oedema and increase in neck circumference will increase upper airway resistance and the severity of obstructive sleep-disordered breathing and in turn, leads to an increase in blood pressure [1].

A recent meta-analysis suggests renal denervation may prove to be beneficial as an adjunct for patients with obstructive sleep-disordered breathing and hypertension (see the contribution of F. Mafoud et al. in this issue) [41]. Efferent renal sympathetic nerve stimulation elicits increases in renin release from juxtaglomerular cells, renal sodium and water reabsorption, and renal vascular resistance. Thus, if obstructive sleep-disordered breathing activates efferent renal sympathetic nerve discharge in parallel with muscle sympathetic nerve activity, this could increase blood pressure acutely *via* sympathetically mediated vasoconstriction and sustain hypertension chronically by engaging sodium and water retention in addition to entraining and resetting the sympathetic nervous system [1].

Conclusion

Secondary cause of hypertension is more frequent in patients with difficult-to-treat hypertension than in a general population of hypertensive patients. An early diagnosis leads to better control of blood pressure and has a positive impact on the reduction of cardiovascular risk.

Disclosure statement

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References

[1] Sudano I, Beuschlein F, Lüscher TF, et al. Secondary causes of hypertension. In : A.J. Camm editor The ESC textbook of cardiovascular medicine. (3 edn), . 2018. p. 1–10. Oxford, UK: Publisher Oxford University Press.

[2] Rimoldi SF, Scherrer U, Messerli FH. Secondary arterial hypertension: when, who, and how to screen? Eur Heart J. 2014;35(19):1245–1254. doi: 10.1093/eurheartj/eht534.
[3] Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–3104. doi: 10.1093/eurheartj/ehy339.
[4] Muntner P, Miles MA, Jaeger BC, et al. Blood pressure control among US adults, 2009 to 2012 through 2017 to 2020. Hypertension. 2022;79(9):1971–1980. doi: 10.1161/HYPERTENSIONAHA.122.19222.
[5] Grassi G, Mark A, Esler M. The sympathetic nervous system alterations in human hypertension. Circ Res. 2015;116(6):976–990. doi: 10.1161/CIRCRESAHA.116.303604.
[6] Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. Eur Heart J. 2012;33(9):1058–1066. doi: 10.1093/eurheartj/ehs041.
[7] Yang T, Xu C. Physiology and pathophysiology of the intrarenal Renin-Angiotensin system: an update. J Am Soc Nephrol. 2017;28(4):1040–1049. doi: 10.1681/ASN.2016070734.
[8] Safian RD, Textor SC. Renal-artery stenosis. N Engl J Med. 2001;344(6):431–442. doi: 10.1056/NEJM200102083440607.
[9] Patel SM, Li J, Parikh SA. Renal artery stenosis: optimal therapy and indications for revascularization. Curr Cardiol Rep. 2015;17(9):623. doi: 10.1007/s11886-015-0623-7.
[10] Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med. 2014;370(1):13–22. doi: 10.1056/NEJMoa1310753.
[11] Jenks S, Yeoh SE, Conway BR. Balloon angioplasty, with and without stenting, versus medical therapy for hypertensive patients with renal artery stenosis. Cochrane Database Syst Rev. 2014;2014(12):CD002944.
[12] Prince M, Tafur JD, White CJ. When and how should we revascularize patients with atherosclerotic renal artery stenosis? JACC Cardiovasc Interv. 2019;12(6):505–517. doi: 10.1016/j.jcin.2018.10.023.
[13] Arlt W. A detour guide to the endocrine society clinical practice guideline on case detection, diagnosis and treatment of patients with primary aldosteronism. Eur J Endocrinol. 2010;162(3):435–438. doi: 10.1530/EJE-09-0869.
[14] Conn JW, Louis LH. Primary aldosteronism: a new clinical entity. Trans Assoc Am Physicians. 1955;68:215–231; discussion, 231-3.
[15] Gruber S, Beuschlein F. Hypokalemia and the prevalence of primary aldosteronism. Horm Metab Res. 2020;52(6):347–356. doi: 10.1055/a-1134-4980.
[16] Reincke M, Fischer E, Gerum S, et al. Observational study mortality in treated primary aldosteronism: the German conn's registry. Hypertension. 2012;60(3):618–624. doi: 10.1161/HYPERTENSIONAHA.112.197111.
[17] Meng Z, Dai Z, Huang K, et al. Long-term mortality for patients of primary aldosteronism compared With essential hypertension: a systematic review and meta-analysis. Front Endocrinol. 2020;11:121. doi: 10.3389/fendo.2020.00121.
[18] Mulatero P, Monticone S, Burrello J, et al. Guidelines for primary aldosteronism: uptake by primary care physicians in Europe. J Hypertens. 2016;34(11):2253–2257. doi: 10.1097/HJH.0000000000001088.
[19] Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(5):1889–1916. doi: 10.1210/jc.2015-4061.
[20] Mulatero P, Bertello C, Sukor N, et al. Impact of different diagnostic criteria during adrenal vein sampling on reproducibility of subtype diagnosis in patients with primary aldosteronism. Hypertension. 2010;55(3):667–673. doi: 10.1161/HYPERTENSIONAHA.109.146613.
[21] Schieda N, Siegelman ES. Update on CT and MRI of adrenal nodules. AJR Am J Roentgenol. 2017;208(6):1206–1217. doi: 10.2214/AJR.16.17758.
[22] Loriaux DL. Diagnosis and differential diagnosis of cushing's syndrome. N Engl J Med. 2017;377(2):e3.
[23] Pappachan JM, Hariman C, Edavalath M, et al. Cushing's syndrome: a practical approach to diagnosis and differential diagnoses. J Clin Pathol. 2017;70(4):350–359. doi: 10.1136/jclinpath-2016-203933.
[24] Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of cushing's syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(5):1526–1540. doi: 10.1210/jc.2008-0125.
[25] Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of cushing's disease: a guideline update. Lancet Diabetes Endocrinol. 2021;9(12):847–875. doi: 10.1016/S2213-8587(21)00235-7.
[26] Prete A, Subramanian A, Bancos I, et al. Cardiometabolic disease burden and steroid excretion in benign adrenal tumors: a cross-sectional multicenter study. Ann Intern Med. 2022;175(3):325–334. doi: 10.7326/M21-1737.
[27] Lenders JWM, Duh Q-Y, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915–1942. doi: 10.1210/jc.2014-1498.
[28] Mazza A, Beltramello G, Armigliato M, et al. Arterial hypertension and thyroid disorders: what is important to know in clinical practice? Ann Endocrinol. 2011;72(4):296–303. doi: 10.1016/j.ando.2011.05.004.
[29] Streeten DH, Anderson GH, Howland T, et al. Effects of thyroid function on blood pressure. Recognition of hypothyroid hypertension. Hypertension. 1988;11(1):78–83. doi: 10.1161/01.hyp.11.1.78.
[30] Fraser WD. Hyperparathyroidism. Lancet. 2009;374(9684):145–158. doi: 10.1016/S0140-6736(09)60507-9.

[31] Schiffl H, Lang SM. Hypertension secondary to PHPT: cause or coincidence? Int J Endocrinol. 2011;2011: 974647. doi: 10.1155/2011/974647.

[32] Peacock E, Krousel-Wood M. Adherence to antihypertensive therapy. Med Clin North Am. 2017;101(1):229–245. doi: 10.1016/j.mcna.2016.08.005.

[33] Corrao G, Parodi A, Nicotra F, et al. Better compliance to antihypertensive medications reduces cardiovascular risk. J Hypertens. 2011;29(3):610–618. doi: 10.1097/HJH.0b013e328342ca97.

[34] Bangalore S, Ley L. Improving treatment adherence to antihypertensive therapy: the role of single-pill combinations. Expert Opin Pharmacother. 2012;13(3):345–355. doi: 10.1517/14656566.2012.652086.

[35] Gupta P, Patel P, Štrauch B, et al. Biochemical screening for nonadherence Is associated with blood pressure reduction and improvement in adherence. Hypertension. 2017;70(5):1042–1048. doi: 10.1161/HYPERTENSIONAHA.117.09631.

[36] Burnier M, Wuerzner G, Struijker-Boudier H, et al. Measuring, analyzing, and managing drug adherence in resistant hypertension. Hypertension. 2013;62(2):218–225. doi: 10.1161/HYPERTENSIONAHA.113.00687.

[37] Parati G, Lombardi C, Hedner J, et al. Position paper on the management of patients with obstructive sleep apnea and hypertension: joint recommendations by the european society of hypertension, by the European respiratory society and by the members of European COST (COoperation in scientific and technological research) ACTION B26 on obstructive sleep apnea. J Hypertens. 2012;30(4):633–646. doi: 10.1097/HJH.0b013e328350e53b.

[38] Grassi G, Seravalle G, Brambilla G, et al. Regional differences in sympathetic activation in lean and obese normotensive individuals with obstructive sleep apnoea. J Hypertens. 2014;32(2):383–388. doi: 10.1097/HJH.0000000000000034.

[39] Iftikhar IH, Valentine CW, Bittencourt LRA, et al. Effects of continuous positive airway pressure on blood pressure in patients with resistant hypertension and obstructive sleep apnea: a meta-analysis. J Hypertens. 2014;32(12):2341–2350; discussion 2350. doi: 10.1097/HJH.0000000000000372.

[40] Bratton DJ, Gaisl T, Wons AM, et al. CPAP vs mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: a systematic review and meta-analysis. JAMA. 2015;314(21):2280–2293. doi: 10.1001/jama.2015.16303.

[41] Shantha GP, Pancholy SB. Effect of renal sympathetic denervation on apnea-hypopnea index in patients with obstructive sleep apnea: a systematic review and meta-analysis. Sleep Breath. 2015;19(1):29–34. doi: 10.1007/s11325-014-0991-z.