Secondary hypertension: etiology and mechanism of disease

Hypertension afflicts up to 65 million adults in the USA. Although most cases of hypertension are without an underlying cause (i.e., primary hypertension), secondary causes of hypertension should be investigated due to the potential for cure. This article discusses the common causes of secondary hypertension. Furthermore, the etiology, mechanism of blood pressure elevation and treatment are discussed. Through an understanding of the mechanism, diagnosis and treatment of secondary hypertension, physicians can positively influence the associated long-term morbidity and mortality.

KEYWORDS: mineralcorticoid excess syndromes, obstructive sleep apnea, pheochromocytoma, renal artery stenosis, renovascular hypertension, secondary hypertension

Jeffrey H Freihage, Aravinda Nanjundappa & Robert S Dieter†

†Author for correspondence: Loyola University Medical Center, Maywood, IL 60153, USA
Tel.: +1 708 216 4466
Fax: +1 708 216 8795
rdieter@lumc.edu

Hypertension is estimated to affect up to 65 million adults in the USA, and is the most common primary diagnosis at clinic visits [1,2] . Due to the rising incidence of obesity and an aging population, the number of patients with hypertension is expected to increase. Importantly, elevated blood pressure can be effectively treated and lead to a reduction in the incidence of heart failure, stroke and myocardial infarction [3]. The evaluation of patients with hypertension includes identifying other disease conditions that either cause or contribute to elevation in blood pressure. The purpose of this article is to discuss causes of secondary hypertension, along with appropriate diagnostic testing, and the mechanism of blood pressure elevation in these conditions.

Although the vast majority (over 90%) of patients with hypertension have primary hypertension, that is, hypertension without an identifiable cause, an attempt to detect secondary causes of hypertension is important due to the potential for cure with appropriate treatment. **Box 1** lists conditions associated with secondary hypertension. A thorough medical history and physical examination can often provide clues as to the presence of secondary causes of hypertension. A review of medications, both prescribed and over the counter, is important, as many medications can lead to blood pressure elevation and must not be overlooked.

Renal hypertension

Hypertension of renal origin can be due to either chronic renal insufficiency (CRI) of any etiology, or renal artery stenosis (RAS). CRI leads to elevation in blood pressure due to inability of the diseased kidney to excrete sodium and water, resulting in volume expansion. Renovascular hypertension usually refers to RAS, caused either by atherosclerotic disease or fibromuscular dysplasia (FMD). RAS leads to elevated blood pressure as a result of low perfusion pressure to the affected kidney, with resultant activation of the renin–angiotensin–aldosterone axis. Atherosclerotic RAS, accounting for approximately 90% of cases of RAS, is a progressive disease affecting the proximal third of the main renal artery, and is usually found in patients with coronary artery disease and classic risk factors for atherosclerosis. On the other hand, FMD, accounting for the remaining 10% of cases of RAS, affects women between the age of 15 and 50 years, and involves the middle two-thirds of the main renal artery. **Box 2** lists the situations in which RAS should specifically be investigated. While most experts agree that balloon angioplasty with bail-out stenting is the optimal treatment strategy for patients with hypertension due to FMD, considerable debate exists between cardiovascular experts and nephrologists as to the appropriate indications for revascularization in patients with atherosclerotic RAS. Much of the controversy is due to the lack of a perfect tool for the assessment of the contribution of a renal artery obstruction to any individual's hypertension. Furthermore, discrepancies exist in the literature as to the efficacy of revascularization for improvement in blood pressure control and preservation of renal function. Currently, accepted indications for renal revascularization in the setting of atherosclerotic RAS are listed in **Box 3** [4,5].

part of Future Medicine fsg

Box 1. Causes of secondary hypertension.

- Chronic renal insufficiency
- Renal artery stenosis
- Coarctation of the aorta
- Mineralcorticoid excess syndromes
- Cushing's syndrome
- Hypothyroid
- Hyperthyroid
- Hyperparathyroidism
- Obstructive sleep apnea
- Pheochromocytoma and paraganglioma

Mineralcorticoid excess syndromes

Mineralcorticoid excess syndromes are recognized to contribute to elevations in blood pressure due to increased sodium and water retention by the kidney. Most cases (approximately two-thirds) of mineralcorticoid excess syndromes are attributable to primary aldosteronism (Conn's syndrome). The other cases of mineralcorticoid hypertension are largely due to bilateral adrenal hyperplasia and adrenal carcinomas (glucocorticoid-suppressible hyperaldosteronism). Screening for mineralcorticoid excess syndromes should be considered in patients with unprovoked hypokalemia, hypokalemia due to diuretics but not correctable with replacement therapy, a family history of hyperaldosteronism, and the presence of an adrenal mass on imaging. As the optimal method of establishing the diagnosis of primary aldosteronism and other causes of mineralcorticoid excess is complicated and controversial, biochemical testing with follow-up imaging, and possibly adrenal vein blood sampling, is best directed by specialists [6].

Cushing's syndrome

Cushing's syndrome, glucocorticoid excess syndrome, is another cause of secondary hypertension. Although Cushing's syndrome may be suspected based on physical examination signs and symptoms, laboratory confirmation demonstrating hypercortisolism is required to establish the diagnosis and cause of the syndrome. The mechanism by which cortisol excess leads to elevation in blood pressure is unclear [7]. However, recent studies have demonstrated that cortisol-induced blood pressure elevation is more complicated than simply renal sodium retention [8].

Box 2. Situation in which renal artery stenosis should be investigated.

- Onset of hypertension ≤30 years or ≥55 years
- Malignant, accelerated or resistant hypertension
- Unexplained renal dysfunction
- Development of azotemia with an ACE inhibitor or ARB medication
- Unexplained size discrepancy of ≥1.5 cm between kidneys
- Flash pulmonary edema (usually bilateral RAS)
- Refractory angina
- Unexplained congestive heart failure
- Multivessel coronary artery disease

ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; RAS: Renal artery stenosis.

Pheochromocytoma & paraganglioma

Pheochromocytoma and paraganglioma are tumors of chromaffin cell origin that produce symptoms of headache, palpitations and diaphoresis, along with elevation in blood pressure, due to the release of catecholamines. Circulating levels of catecholamines, along with elevated sympathetic nervous system activity, contribute to persistent elevations in blood pressure due to increased peripheral vascular tone and impairment in endothelium-dependent and -independent vasodilatation [9,10]. Establishment of the diagnosis of a pheochromocytoma consists of measuring 24-h urinary excretion of total or fractionated metanephrines and catecholamines. Once biochemical testing has confirmed the elevation in catecholamine levels, localization of the tumor with a CT scan, MRI, iodine 131- or iodine 123-labeled metaiodobenzylguanidine (MIBG) or PET scan should be performed prior to surgical resection [11].

Coarctation of the aorta

Coarctation of the aorta should be specifically investigated via upper and lower extremity blood pressure measurements in all hypertensive patients. Most experts agree that surgical correction should be performed in infancy and early childhood [12]. However, many adult patients also benefit by becoming normotensive after coarctation repair during adulthood [13].

Hyperthyroidism & hypothyroidism

Hyperthyroidism and hypothyroidism have both been recognized as causes of secondary hypertension. Hyperthyroidism can lead to isolated secondary hypertension by alterations in systemic vascular resistance and increases in heart rate and cardiac output [14]. In hypothyroidism, hypertension, predominantly diastolic, can occur in up to 50% of patients. The mechanism of hypertension is related to increased systemic vascular resistance and changes in aortic wall stiffness, which can become fixed if treatment of the hypothyroid state is not initiated early in the disease course [15].

Box 3. Indications for renal artery revascularization in a patient with RAS.

- Failure of medical therapy despite full doses of ≥3 drugs, including a diuretic
- Compelling need for ACE inhibition/angiotensin blockade with angiotensin-dependent GFR
- Recent rise in serum creatinine
- Loss of GFR during antihypertensive therapy (e.g., with ACE inhibition/ARB therapy)
- Circulatory congestion, recurrent 'flash' pulmonary edema
- Refractory congestive heart failure with bilateral renal arterial stenosis

ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; GFR: Glomerular filtration rate; RAS: Renal artery stenosis.

Hyperparathyroidism

The contribution of hyperparathyroidism to elevation in blood pressure has been well recognized. However, the exact mechanism is undefined, but most likely relates to hypercalcemia (vasoconstriction) and hypercalcemia's contribution to renal insufficiency (renal parenchymal damage). Importantly, in patients with primary hyperparathyroidism, hypertensive patients have a higher mortality relative to normotensive patients. However, the yearly death risk after surgery in patients with hypertension decreases by double relative to that of the normotensive patient, implying that elevated blood pressure is a major source of increased cardiovascular mortality in patients with hyperparathyroidism [16].

Obstructive sleep apnea

The number of patients with obstructive sleep apnea (OSA) and hypertension is extremely high, ranging from 35 to 70% [17]. Hypertension in patients with OSA is thought to be related to sympathetic activation, oxidative stress and endothelial dysfunction. Treatment of OSA with either weight loss or continuous positive airway pressure has been shown to improve blood pressure control.

The evaluation of the hypertensive patient must include a search for identifiable, and thus, potentially curable, conditions. Often, a thorough history and physical exam with supplemental laboratory testing will give strong clues to the presence of an underlying disease process that is contributing to a patient's hypertensive state. Unfortunately, uncertainty exists as to the best diagnostic tools and optimal therapy for some of these conditions. Future research into the mechanism, diagnosis and treatment of secondary causes of hypertension will lead to better diagnostic tests and therapies that will improve the long-term morbidity and mortality associated with hypertension.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Hypertension is estimated to affect up to 65 million adults in the USA.
- An attempt to detect secondary causes of hypertension is important due to the potential for cure with appropriate treatment.
- A thorough medical history and physical examination can often give clues as to the presence of secondary causes of hypertension.
- Chronic renal insufficiency leads to elevation in blood pressure due to inability of the diseased kidney to excrete sodium and water, resulting in volume expansion.
- Renal artery stenosis leads to elevated blood pressure as a result of low perfusion pressure to the affected kidney, with resultant activation of the renin–angiotensin–aldosterone axis.
- Mineralcorticoid excess syndromes are recognized to contribute to elevations in blood pressure due to increased sodium and water retention by the kidney.
- Coarctation of the aorta should be specifically investigated via upper and lower extremity blood pressure measurements in all hypertensive patients.
- Hypertension in patients with obstructive sleep apnea is thought to be related to sympathetic activation, oxidative stress and endothelial dysfunction.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Field LA, Burt VL, Cutler JA *et al.*: The burden of adult hypertension in the United States 1999 to 2000: a rising tide. *Hypertension* 44, 398–404 (2004).

2 Cherry DK, Woodwell DA: National Ambulatory Medical Care Survey: 2000 summary. *Advance Data* 328, 1–32 (2002).

3 Neal B, MacMahon S, Chapman N: Effects of ACE inhibitors, calcium agonists, and other blood-pressure-lowering drugs. *Lancet* 356, 1955–1964 (2000).

▪ **Article comparing the efficacy of various classes of antihypertensive medications.**

4 White CJ: Catheter-based therapy for atherosclerotic renal artery stenosis. *Circulation* 113, 1464–1473 (2006).

▪ **Good review of evidence for the management of renal artery stenosis.**

5 Garovix VD, Textor SC: Renovascular hypertension and ischemic nephropathy. *Circulation* 112, 1362–1374 (2005).

6 Stewart PM: Mineralcorticoid hypertension. *Lancet* 353, 1341–1347 (1999).

▪ **Review of the mechanism, diagnosis and treatment of mineralcorticoid hypertension.**

7 Whitworth JA, Mangos GJ, Kelly JJ: Cushing, cortisol and cardiovascular disease. *Hypertension* 36, 912–916 (2000).

8 Whitworth JA, Kelly JJ: Evidence that high dose cortisol-induced Na^+ retention in man is not medicated by the mineralcorticoid receptor. *J. Endocrinol. Invest.* 18, 586–591 (1995).

9 Roman S: Pheochromocytoma and functional paraganglioma. *Curr. Opin. Oncol.* 16, 8–12 (2003).

10 Bravo EL, Tagle R: Pheochromocytoma: state of the art and future prospects. *Endocr. Rev.* 24, 539–553 (2003).

11 Lenders JW, Pacak K, Walther MM *et al.*: Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA* 287, 1427–1434 (2002).

▪ **Review of the various biochemical tests used to diagnose pheochromocytoma.**

12 Behl PR, Sante P, Blesousky A: Surgical treatment of isolated coarctation of the aorta: 18 years experience. *Thorax* 42, 309–314 (1987).

13 Ozkokeli M, Sensoz Y, Gunay R *et al.*: Blood pressure changes after aortic coarctation surgery performed in adulthood. *J. Card. Surg.* 20, 319–321 (2005).

▪ **Article discussing the utility of correction of aortic coarctation in the adult population.**

14 Prisant LM, Gujral JS, Mulloy AL: Hyperthyroidism: a secondary cause of isolated systolic hypertension. *J. Clin. Hypertens.* 8, 596–599 (2006).

15 Dernellis J, Panaretou M: Effects of thyroid replacement therapy on arterial blood pressure in patients with hypertension and hypothyroidism. *Am. Heart J.* 143, 718–724 (2002).

16 Hedback GM, Oden AS: Cardiovascular disease, hypertension and renal function in primary hyperparathyroidism. *J. Intern. Med.* 251, 476–483 (2002).

17 Drager LF, Bortolotto LA, Figueiredo AC *et al.*: Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. *Chest* 131, 1379–1386 (2007).

▪ **Article on the mechanism of hypertension in patients with obstructive sleep apnea.**