Figure 1. Major discoveries in PA. The upper part of the panel represents clinical advances, in particular discoveries of new clinical forms of the disease and publications of guidelines for its management. The lower part represents major genetic discoveries in the field. APA, aldosterone-producing adenoma; FH, familial hyperaldosteronism.

Maria-Christina Zennaro - maria-christina.zennaro@inserm.fr

LEARNING THE ROPES

Other Endocrine Causes of Secondary Hypertension

PETER W DE LEEUW

Dept. of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

DOI: 10.30824/2010-11

Although primary hyperaldosteronism undoubtedly is the most frequent endocrine-related cause of hypertension, there are several other endocrine disturbances that may lead to an elevated blood pressure. Adrenal abnormalities such as Cushing's syndrome and pheochromocytoma are probably the most well-known, but diseases of the pituitary gland (acromegaly), the thyroid and the parathyroids may cause hypertension as well.

Adrenal corticoid hypertension (Cushing's syndrome)

Cushing's syndrome is characterized by glucocorticoid excess. The overproduction of cortisol produces a number of clinical features of which hypertension is one. Recent data suggest that hypertension is present in more than 75% of patients with Cushing's syndrome and quite often even is the presenting symptom^{1,2}. Typically, the nocturnal blood pressure dip is blunted or absent in patients with Cushing's syndrome. The

pathogenesis of hypertension in this condition is still incompletely understood but involves a variety of mechanisms, including retention of sodium and water due to mineralocorticoid receptor activation in the kidney, enhanced sensitivity to the action of angiotensin II (levels of which are usually low) as well as other vasoconstrictors and vascular remodeling. In addition, cytokines and several other mediators may contribute to the development of cardiovascular complications³.

Hypercortisolism may stem from autonomous adrenal production or from excessive stimulation by ACTH. Whenever Cushing's syndrome is suspected on clinical grounds, at least two of three available tests should be applied for screening. These are: measurement of 24-hour urinary excretion of free cortisol, determination of nighttime cortisol in saliva and the overnight dexamethasone suppression test⁴. Once overproduction of steroid hormones has been established, imaging studies should follow to localize the abnormality. There is little doubt that CT and magnetic resonance imaging (MRI) are the most suitable methods for detecting adrenal masses. Even small lesions can be picked up this way. One should realize, though, that these modern imaging techniques may also discover other (variant) types of abnormalities. It remains necessary, therefore, to match the images with the results of (dynamic) hormonal testing. Determination of plasma ACTH, if necessary, to be completed with functional tests and selective venous sampling, is necessary to differentiate between pituitary, adrenal and ectopic sources of hypercortisolism. Again, CT and/or MRI are useful for localization of extra-adrenal abnormalities.

Minimally invasive surgery is the treatment of choice, but hypertension may persist after removal of the lesion. All types of antihypertensive agents can be used for treating hypertension before and after surgery. There is some indication that cortisol-lowering medical treatment can also lower blood pressure⁵ but this needs to be substantiated further.

Apparent mineralocorticoid excess

Apparent mineralocorticoid excess is an extremely rare autosomal recessive abnormality that causes a form of hypertension in which primarily mineralocorticoid mechanisms are involved. Due

to an absolute or a relative lack of the enzyme 11- β hydroxysteroid dehydrogenase (11- β OHSD) type 2, the conversion of cortisol into the inactive cortisone at the level of the mineralocorticoid receptor in the distal renal tubules does not work properly. As a result, cortisol which is present in far greater concentrations than aldosterone competitively displaces aldosterone from its receptor. Low-renin hypertension due to sodium retention and hypokalemia ensue. In the urine, one will find an increased ratio of cortisol metabolites over cortisone metabolites. Probably, mineralocorticoid receptor antagonists are the best choice for treating the hypertension although convincing studies in this regard are lacking.

Other forms of steroid excess

Increased production of deoxycorticosterone (DOC) occurs primarily in congenital adrenal hyperplasia, where deficiency of either 11 β -hydroxylase or 17 α -hydroxylase impairs cortisol production. DOC-producing tumours and primary cortisol resistance are also associated with elevated DOC concentrations, but these conditions are rare. Due to its agonistic activity on the mineralocorticoid receptor, DOC causes a form of low-renin, low-aldosterone hypertension with hypokalemia. Except for the abnormalities at physical examination, one finds increased levels of DOC and adrenal androgens in 11 β -hydroxylase deficiency but low levels of androgens in 17 α -hydroxylase deficiency. In addition, 11-DOC is high in the former, while corticosterone and 18-hydroxycorticosterone are high in the latter. Table 1 summarizes the most important laboratory features, which may help in the initial work-up of patients with a suspected adrenal form of hypertension.

In cases of DOC excess, glucocorticoid replacement therapy will ameliorate clinical symptomatology.

Pheochromocytoma

Although pheochromocytoma may be found accidentally, in most cases there will be symptoms related to catecholamine excess. The prevalence of pheochromocytoma is low: less than 1% of the hypertensive population. When the diagnosis is suspected, the initial biochemical testing should include measurements of

plasma free metanephrines, preferably after 30 minutes of recumbency, or urinary fractionated metanephrines when a plasma assay is not available⁶. Repeat testing is recommended when initial test results are negative but clinical suspicion is high. Importantly, elevations of plasma metanephrines may also be false-positive, particularly in patients using tricyclic antidepressants or phenoxybenzamine⁷. Occasionally, and particularly with borderline elevations of metanephrines, one has to turn to the clonidine suppression test. Normally, plasma levels of normetanephrine or norepinephrine fall by about half but failure to do so strongly suggests the presence of a pheochromocytoma.

When there is biochemical evidence of a pheochromocytoma, CT scanning is the preferred method to localize the tumor. Given its suboptimal performance and the fact that the uptake of [¹²³I]-meta-iodobenzyl-guanidine (MIBG) may be decreased by several drugs, imaging with this agent should not be applied routinely.

Before the surgeon can remove a pheochromocytoma, preferably by laparoscopy, one must be sure that the patient has had adequate treatment with an alpha-blocking drug. Pheochromocytomas are usually benign and patients are cured after removal of the tumor. In case of malignant disease, however, long-term follow-up is necessary.

Acromegaly, thyroid and parathyroid disorders

Hypertension and its associated cardiovascular complications may occur in up to 60% of patients with acromegaly. In particular, diastolic pressure is elevated, and the nocturnal dip is often absent. In the pathogenesis of acromegaly-associated hypertension volume expansion plays a major role but several other factors, similar to those in Cushing's syndrome are also involved. All antihypertensive agents can be used to control the pressure but treatment of the primary abnormality improves blood pressure as well⁸.

Hypertension, mainly isolated systolic hypertension, is present in about 10% of patients with hyperthyroidism and is related to an excess of T₃ causing increased cardiac output, increased arterial stiffness and activation of several

neurohumoral systems⁹. Treatment should preferably include beta-blockers. Per contra, hypothyroidism is predominantly associated with a rise in diastolic pressure, a narrow pulse pressure and increased vascular resistance. It often disappears when the patient becomes euthyroid.

Finally, primary hyperparathyroidism has been identified as a cause of hypertension and cardiovascular complications with a prevalence of about 50%¹⁰. The mechanisms involved are not well understood but are likely related to increased cellular calcium influx and sensitization of the vascular wall to vasoconstrictor agents. Although parathyroidectomy may resolve the hypertension, there is insufficient information as to how often this occurs.

References

1. Stachowska B, Kuliczowska-Plaksej J, Kaluzny M, Grzegorzolka J, Jonczyk M, Bolanowski M. Etiology, baseline clinical profile and comorbidities of patients with Cushing's syndrome at a single endocrinological center. *Endocrine*. 2020 DOI: [10.1007/s12020-020-02468-1](https://doi.org/10.1007/s12020-020-02468-1)
2. Valassi E, Santos A, Yaneva M, Toth M, Strasburger CJ, Chanson P, et al. The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. *Eur J Endocrinol*. 2011;165(3):383-92. DOI: [10.1530/EJE-11-0272](https://doi.org/10.1530/EJE-11-0272)
3. Barbot M, Ceccato F, Scaroni C. The Pathophysiology and Treatment of Hypertension in Patients With Cushing's Syndrome. *Front Endocrinol (Lausanne)*. 2019;10:321. DOI: [10.3389/FENDO.2019.00321](https://doi.org/10.3389/FENDO.2019.00321)
4. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93(5):1526-40. DOI: [10.1210/JC.2008-0125](https://doi.org/10.1210/JC.2008-0125)
5. Colao A, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M, et al. A 12-month phase 3 study of pasireotide in Cushing's disease. *N Engl J Med*. 2012;366(10):914-24. DOI: [10.1056/NEJMOA1105743](https://doi.org/10.1056/NEJMOA1105743)
6. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(6):1915-42. DOI: [10.1210/JC.2014-1498](https://doi.org/10.1210/JC.2014-1498)

7. Eisenhofer G, Goldstein DS, Walther MM, Friberg P, Lenders JW, Keiser HR, et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. *J Clin Endocrinol Metab.* 2003;88(6):2656-66. DOI: [10.1210/JC.2002-030005](https://doi.org/10.1210/JC.2002-030005)

8. Ramos-Levi AM, Marazuela M. Bringing Cardiovascular Comorbidities in Acromegaly to an Update. How Should We Diagnose and Manage Them? *Front Endocrinol (Lausanne).* 2019;10:120. DOI: [10.3389/FENDO.2019.00120](https://doi.org/10.3389/FENDO.2019.00120)

9. Doubleday AR, Sippel RS. Hyperthyroidism. *Gland Surg.* 2020;9(1):124-35. DOI: [10.21037/gs.2019.11.01](https://doi.org/10.21037/gs.2019.11.01)

10. Pepe J, Cipriani C, Sonato C, Raimo O, Biamonte F, Minisola S. Cardiovascular manifestations of primary hyperparathyroidism: a narrative review. *Eur J Endocrinol.* 2017;177(6):R297-R308. DOI: [10.1530/EJE-17-0485](https://doi.org/10.1530/EJE-17-0485)

Table 1 : Laborarory Features Of Various Forms of Corticoid-Related Hypertensive Disorders

	Serum potassium	Renin	Aldosterone	Other biochemical features
Cushing's syndrome	Normal or low	Normal or low	Normal or low	Elevated cortisol
Apparent mineralocorticoid excess	Low	Low	Low	Increased urinary excretion of tetrahydrocortisol plus 5 α -tetrahydrocortisol, relative to that of tetrahydrocortisone
Deoxycorticosterone excess	Low	Low	Low	Increased plasma concentration of deoxycorticosterone; additional abnormalities depending on the nature of the defect

Peter W de Leeuw - p.deleeuw@maastrichtuniversity.nl

JOINT MEETING
ESH-ISH
2021 **ON-AIR**

April 11-14, 2021
www.hypertension2021.org

European Society of Hypertension

International Society of Hypertension

British and Irish Hypertension Society
Committed to preventing cardiovascular disease

#hypertension2021