Primary aldosteronism

Conn

- 1954, Dr Jerome W. Conn described the index patient with PA
  - a young woman who presented with intractable muscle spasms and tetany due to severe hypokalemia and hypertension

Introduction

- HTN is one of the most prevalent diseases worldwide, with a recent estimate in the United States reporting that 30.9% of Americans have the disorder
- only 50% are controlled with a blood pressure (BP) of <140/90
- PA has emerged as the most common form of endocrine HTN

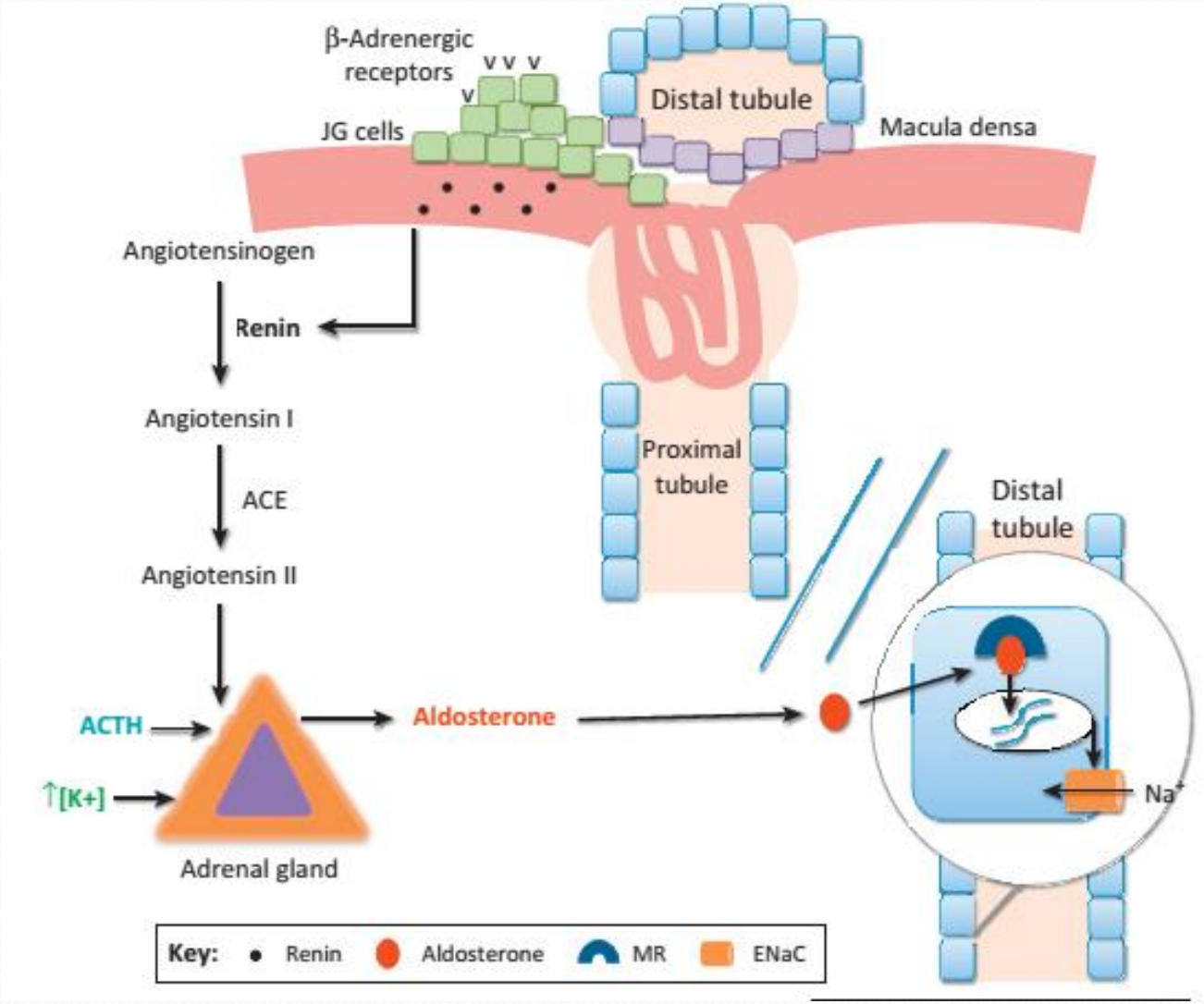
Prevalence study

- 1125 patients with hypertension were successfully screened
- 11.2% diagnosed with PA
  - aldosterone-producing adenomas (APAs): 42.8%
    - 52% were normokalemic
  - bilateral adrenal hyperplasia (BAH): 57.2 %
    - 83.1% were normokalemic
      - *Rossi, G.P. et al. (2006) J. Am. Coll. Cardiol. 48, 2293–2300*
- the presence of hypokalemia in a hypertensive patient should prompt clinical suspicion of PA, it need not be present.

Types of PA

- BAH: most common two-thirds of cases
- APA: 1/3
- Unilateral hyperplasia, adrenocortical carcinoma (ACC), and ectopic aldosterone production: rare
- Genetic causes: familial hyperaldosteronism types 1, 2, and 3

Molecular physiology



ACE, angiotensin-converting enzyme;

ACTH,adrenocorticotrophic hormone;

ENaC, epithelium sodium channel;

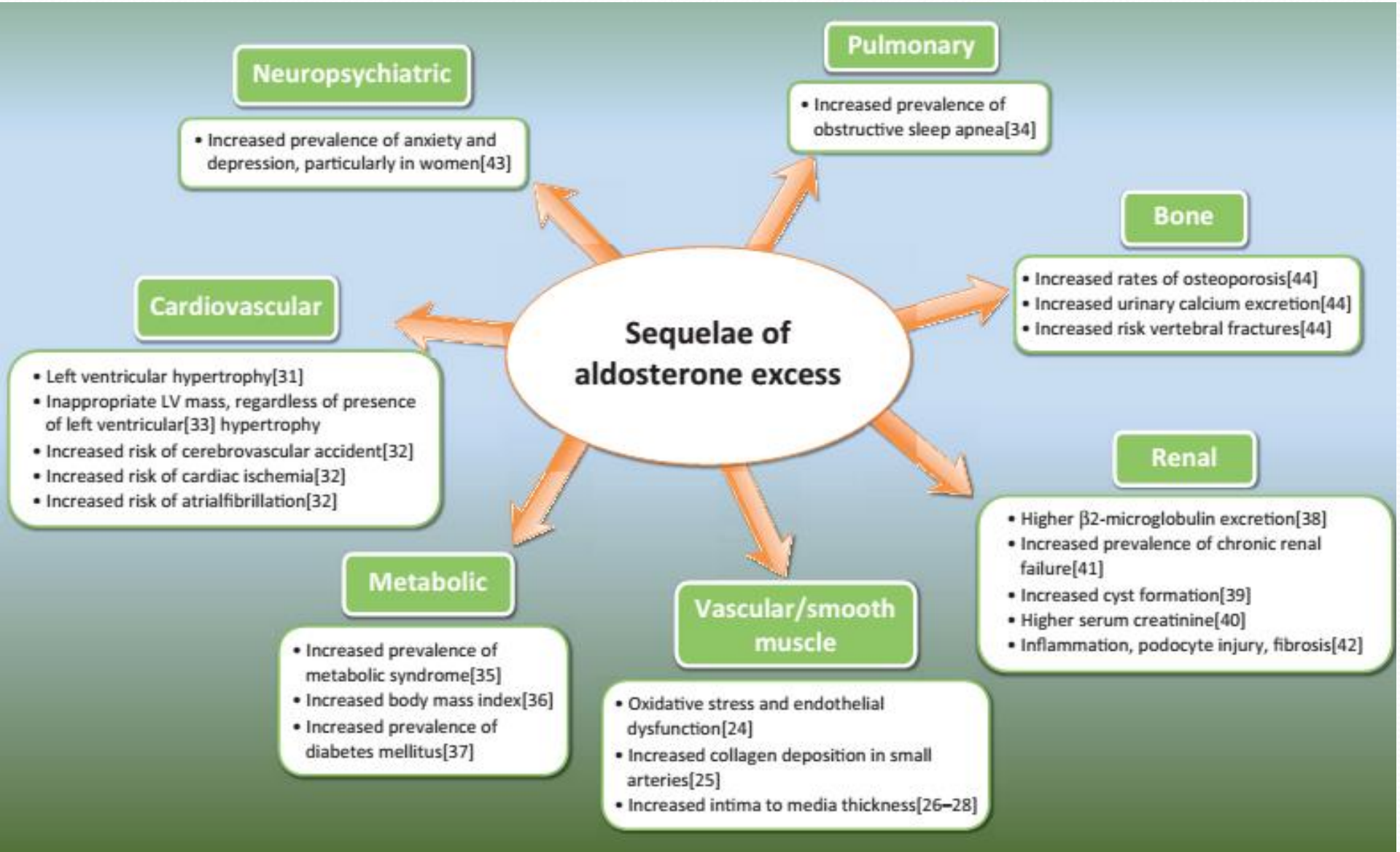
JG cells, juxtaglomerular cells;

MR, mineralocorticoid receptor.

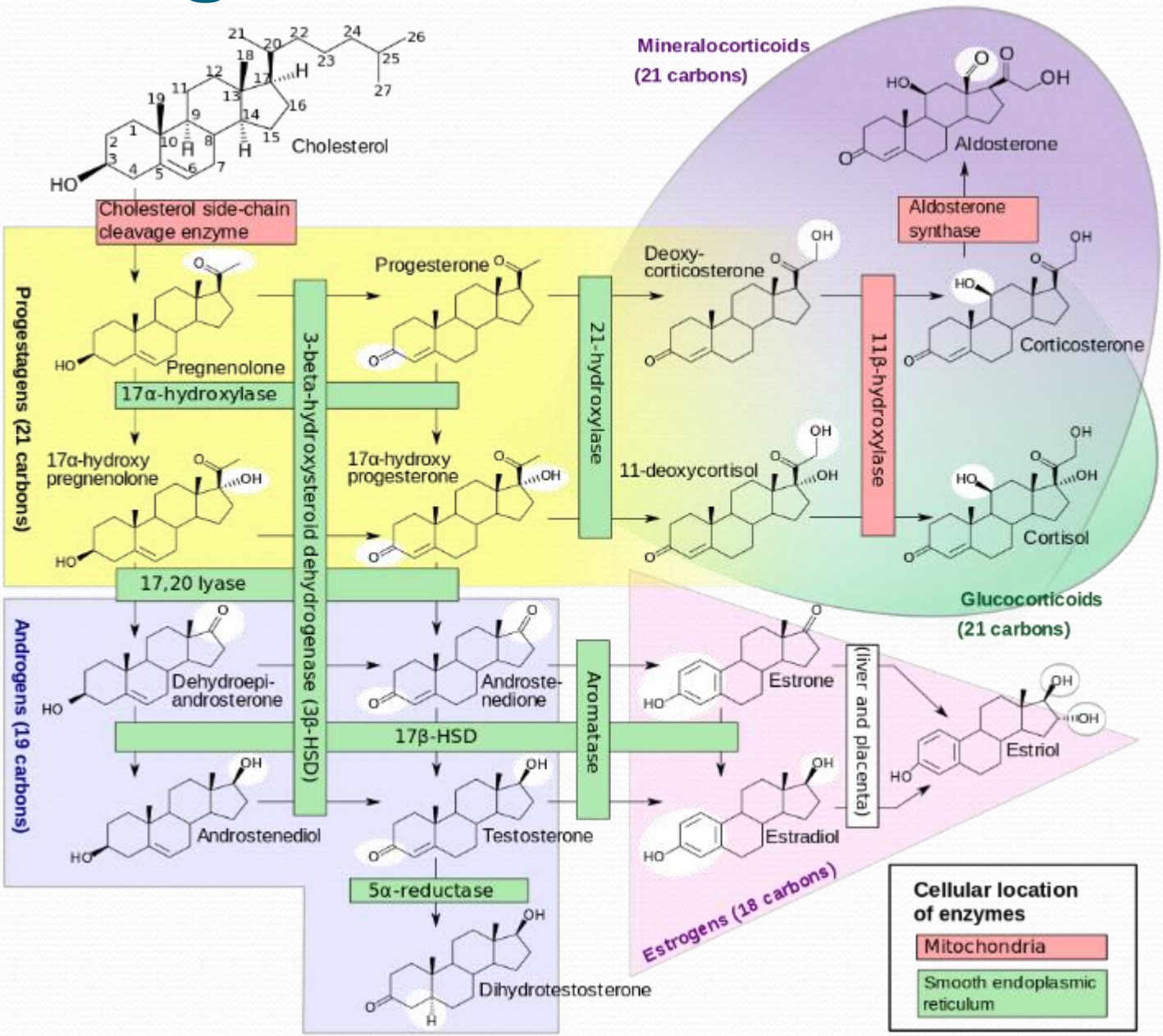
Cytoplasmic mineralocorticoid receptor (MR)

- Location: renal distal tubule, colon, salivary glands, vasculature, and in non-epithelial tissues such as the heart, adipose tissue, and hippocampus
- Effect on tissue: oxidative stress with endothelial dysfunction and increased deposition of collagen within arterial walls, leading to increased arterial stiffness, result in left ventricular remodeling with hypertrophy, increase the risk of cardiovascular events
- Others obstructive sleep apnea, insulin resistance, and the metabolic syndrome and renal disease

Multi-system effects of aldosterone excess



Steroidogenesis



CYP11B1 vs. CYP11B2

- There are two distinct 11β-hydroxylase genes in man, CYP11B1 and CYP11B2
  - CYP11B1: high levels in normal adrenals and Cushing's syn.
  - CYP11B2: low levels in normal adrenals, but higher in PA

Genetics of PA

- FH 1: a recombination of the genes encoding the cytochrome P450 enzymes CYP11B1 (11bhydroxylase) and CYP11B2 (aldosterone synthase), resulting in a chimeric gene with overproduction of aldosterone
  - The ACTH-dependent promoter region from a CYP11B1 gene coupled to CYP11B2 enables suppression of gene expression with dexamethasone.
- FH 2: Diagnosis of FH 2 requires two or more involved family members and the exclusion of FH 1
- FH3: a mutation in the gene KCNJ5 which encodes a component of the Kir 3.4 potassium channel. Somatic (acquired) KCNJ5 in 34–65% of sporadic mutations in APAs

Genetic type testing

- FH-I: confirmed PA earlier than 20 years of age and in those who have a family history of PA or strokes at a young age (<40 years)
- FH-III: very young patients with PA, suggest testing for germline mutations in *KCNJ5* causing familial hyperaldosteronism type 3

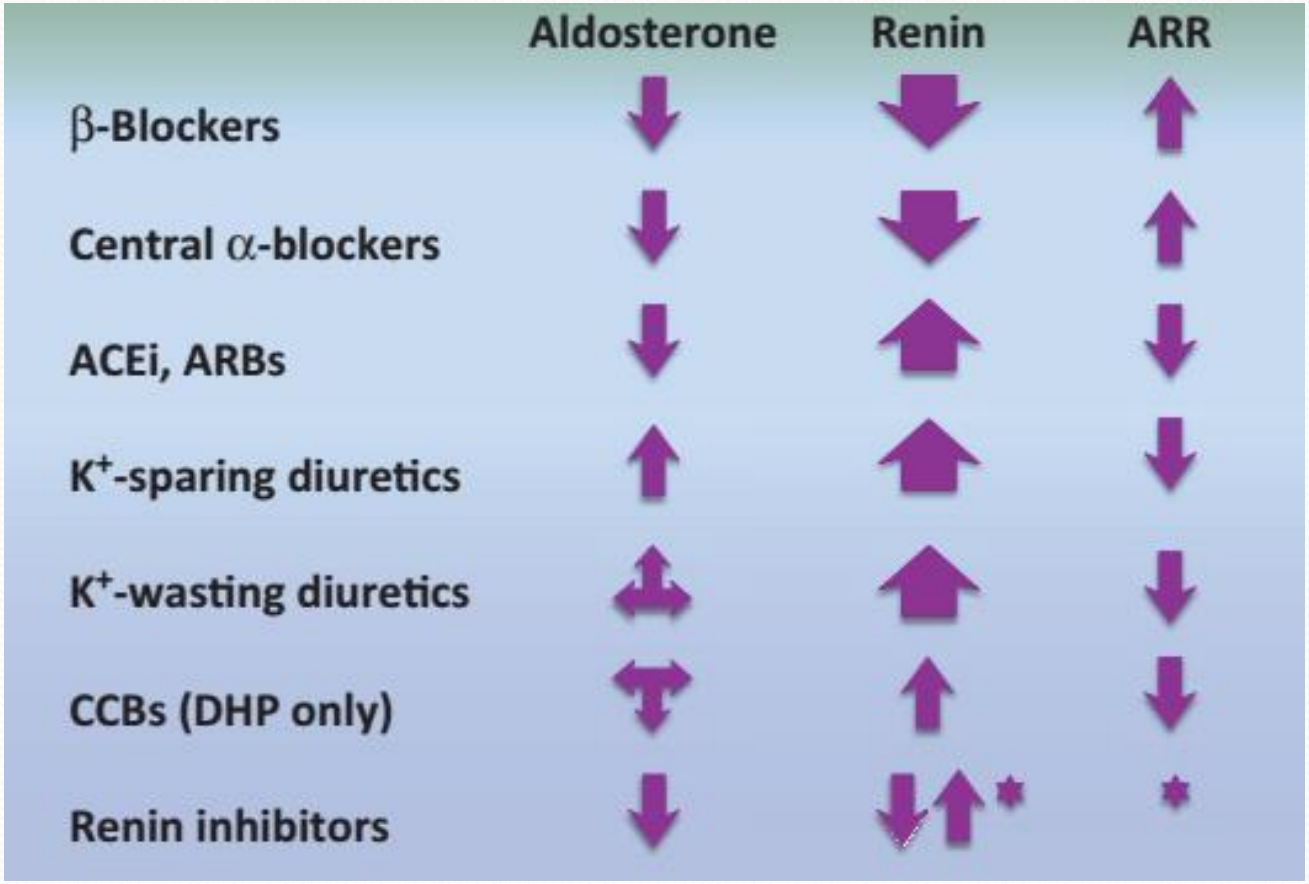
Diagnosis of PA: Screening

- sustained BP above 150/100 on each of three measurements
- resistant HTN
  - (BP > 140/90) resistant to three conventional antihypertensive drugs (including a diuretic)
  - controlled BP (140/90) on four or more antihypertensive drugs
- HTN and spontaneous or diuretic-induced hypokalemia
- HTN with a family history of early-onset disease
- HTN with an adrenal incidentaloma
- HTN and sleep apnea
- HTN and a family history of early onset hypertension or cerebrovascular accident at a young age (<40 years)
- all hypertensive first-degree relatives of patients with PA

Diagnosis of PA: Screening

- The aldosterone/renin ratio (ARR) has the highest sensitivity and specificity.
- Positive screening test: Both an ARR >35 ng/dL per ng/mL/h (Taiwan)
  - it is possible to derive meaningful information from the ARR on most anti-hypertensive agents with the exception of the MR receptor antagonists (spironolactone and eplerenone).
  - MR antagonist requires a 6 week washout.
  - transitioned to regimens, peripheral alpha-adrenergic antagonists (prazosin, doxazosin, or terazosin), hydralazine, or nondihydropyridine calcium channel blockers (verapamil and diltiazem)

Expected effect of anti-hypertensive agents on (ARR)



ACEi, angiotensin-converting enzyme inhibitor;

ARB, angiotensinrecepto r blocker;

CCB, calcium-channel blockers;

DHP, dihydropyridine (Norvasc, plendil, adalat..)

Diagnosis of PA: Confirmation

- oral sodium loading, saline infusion, fludrocortisone suppression, or captopril challenge tests, but there is no consensus on the optimal test

	Protocol	Interpretation	Clinical Pearls
Intravenous saline load	• Infusion of 2 L of 0.9% normal saline over 2 h while the patient remains in the recumbent position. • Infusion should being in the morning, and the patient should lie recumbent for 1 h before the infusion. • Renin, PAC, cortisol and potassium levels are drawn pre- and post-infusion.	• PAC >10 ng/dL post-infusion is highly suggestive of PA. • PAC <5 ng/dL is less likely to be consistent with PA. • PAC between 5 and 10 ng/dL is indeterminate and may represent PA or low-renin hypertension.	• Potassium supplementation is required for patients with hypokalemia, but during the test potassium does not tend to vary significantly. • Should not be performed in patients with uncontrolled HTN, congestive heart failure, or arrhythmias.
Oral salt load	• Goal sodium intake is >6 g/day for 3 days with diet and sodium chloride tabs. • Patient performs 24 h urine collection starting on day 3 for sodium and aldosterone.	• 24 h urinary aldosterone excretion >12 μg/day consistent with PA. • 24 h urinary sodium 200 mEq/24 h indicates adequate intake.	• Potassium supplementation and daily potassium measurements are required for patients with hypokalemia. • Should not be performed in patients with uncontrolled HTN, congestive heart failure, or arrhythmias. • False negatives in renal insufficiency. • There is laboratory variability in measurement.
Captopril challenge test	• Patient is administered 25–50 mg of oral captopril after sitting or standing for 1 h. • PAC, renin, cortisol levels are measured before captopril administration and 1–2 h after.	• PAC is suppressed by 30% or more if PA is not present. • ARR is greater than 30–50, PAC remains elevated (>8.5 ng/dL or greater), and renin remains suppressed in PA.	• High false positive/false negative rate. • Results may be variable, particularly in BAH, where there are reports of PAC suppression. • Safer in patients at risk of volume overload.
Fludro-cortisone suppression test	• Patients receive 0.1 mg of fludrocortisones every 6 h for 4 days. • Potassium supplements are also administered four times daily, serum potassium is measured four times daily to maintain values of >4.0 mmol/L. • High-sodium diet plus sodium chloride tabs are administered. • On the morning of day 4, plasma cortisol is measured at 7 or 8 a.m. and 10 a.m., and PAC and renin are measured at 10 a.m., with the patient in the seated position.	• PAC >6 ng/dL confirms PA provided that • Renin is suppressed to <1 ng/mL/h (<8.4 mU/L). • Plasma potassium is normal. • 10 a.m. cortisol is lower than 7–8 a.m. cortisol to exclude an ACTH effect.	• Requires inpatient admission for monitoring. • Potassium supplementation and daily potassium measurements required for patients with hypokalemia. • Should not be performed in patients with uncontrolled HTN, congestive heart failure or arrhythmias. • False negatives in renal insufficiency. • There is laboratory variability in measurement.

No need for Confirmation

- Spontaneous hypokalemia,
- & plasma renin below detection levels
- & PAC > 20 ng/dL (550 pmol/L)

Diagnosis of PA: CT

- the primary role of CT is to the exclude the presence of ACC (adrenocortical carcinoma)
- also useful in defining the adrenal anatomy and localizing the adrenal veins
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Diagnosis of PA: AVS

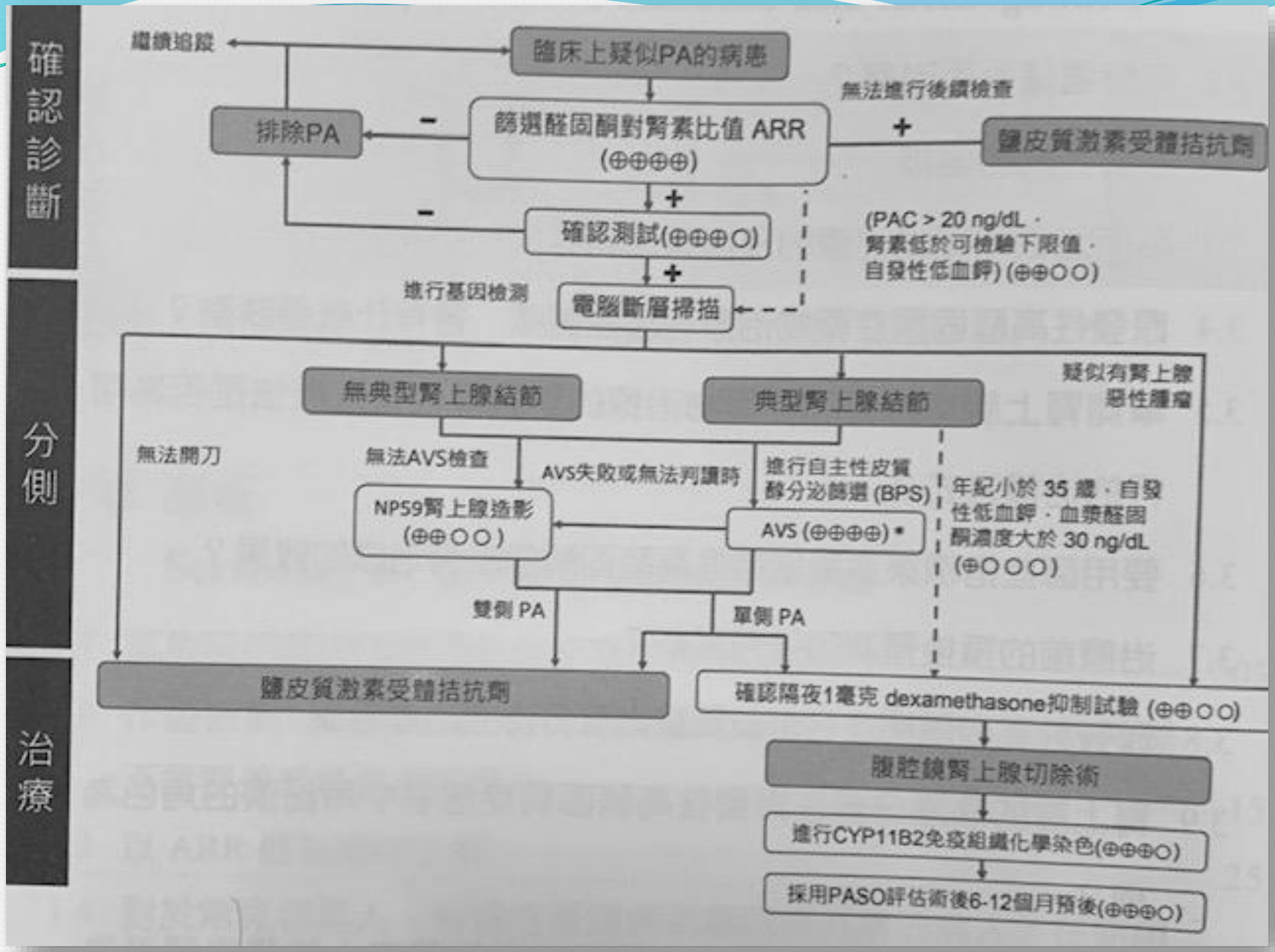
- AVS should be performed in all patients with established PA in whom surgical adrenalectomy is being considered.
- Adequate cannulation of the adrenal veins : peripheral cortisol:adrenal cortisol ratio of 2-3:1
  - Unilateral: A ratio of PAC/cortisol from the high side to PAC/cortisol from the low side greater than 2:1 (no continuous cosyntropin stimulation)
  -

Diagnosis of PA: AVS

- AVS has greater sensitivity and specificity than CT
- Limitations:
  - lack of standardization and cost
  - variable failure rates from 2 to 60%
  - complication rates ranging from 0.2 to 13%

Cases no need AVS

- (< age 35) with spontaneous hypokalemia,
- marked aldosterone excess,
- and unilateral adrenal lesions with radiological features consistent with a cortical adenoma on adrenal CT scan


確認診斷
分側
治療
繼續追蹤
臨床上疑似PA的病患
無法進行後續檢查
排除PA
篩選醛固酮對腎素比值 ARR
(⊕⊕⊕⊕)
鹽皮質激素受體拮抗劑
確認測試(⊕⊕⊕○)
(PAC > 20 ng/dL ·
腎素低於可檢驗下限值 ·
自發性低血鉀) (⊕⊕○○)
進行基因檢測
電腦斷層掃描
無典型腎上腺結節
典型腎上腺結節
疑似有腎上腺惡性腫瘤
無法開刀
無法AVS檢查
AVS失敗或無法判讀時
進行自主性皮質醇分泌篩選 (BPS)
NP59腎上腺造影
(⊕⊕○○)
AVS (⊕⊕⊕⊕)*
年紀小於 35 歲 · 自發性低血鉀 · 血漿醛固酮濃度大於 30 ng/dL
(⊕○○○)
雙側 PA
單側 PA
鹽皮質激素受體拮抗劑
確認隔夜1毫克 dexamethasone抑制試驗 (⊕⊕○○)
腹腔鏡腎上腺切除術
進行CYP11B2免疫組織化學染色(⊕⊕⊕○)
採用PASO評估術後6-12個月預後(⊕⊕⊕○)

Treatment outcome of PA

- all-cause mortality in patients with PA after initiation of treatment was not significantly different from that of control patients with treated HTN
  - *Reincke, M. et al. (2012) the German Conn's registry. Hypertension 60,618–624*
- although cardiovascular complications are more prevalent in patients with PA than in patients with essential HTN, this increased risk is reversed by eliminating the effects of elevated aldosterone with adrenalectomy or with MR antagonists
  - *Catena, C. et al. (2008) Arch. Intern. Med. 168, 80–85*
- Long-term studies of renal outcomes have shown significantly decreased rate of decline in GFR and improvement in albuminuria
- Improvements in the metabolic complications of PA, such as plasma glucose control

Treatment of PA: BAH

- MR antagonists spironolactone and eplerenone (Inspra)
- BAH are generally less responsive to monotherapy with MR antagonists than patients with APA, and typically require additional anti-hypertensive agent

Spironolactone

- initial MR antagonist of choice
- antagonistic properties at the androgen receptor and agonistic properties at the progesterone receptor
  - painful gynecomastia, erectile dysfunction, decreased libido in men
  - menstrual irregularity in women

Eplerenone

- selective MR antagonist
- lacks the progesterone-stimulatory and anti-androgen properties of spironolactone that result in its side effects
- anti-hypertensive effect of spironolactone was significantly greater than that of eplerenone

Unilateral laparoscopic adrenalectomy

- Treatment of choice for most patients with unilateral APAs
- Rates of cure: (defined as BP <140/90) range from 30 to 60%
- improves BP and serum potassium levels in nearly 100% of patients
- Factors associated with resolution or improvement of BP
  - less than one first-degree relative with HTN
  - using two or less antihypertensive medications preoperatively
  - age less than 50 years
  - HTN less than 5 years
  - presence of increased serum creatinine
  - presence of hypokalemia
  - High urinary aldosterone secretion
  - positive pre-operative response to spironolactone

Adrenalectomy vs.medical management

- side-effects of MR antagonists
- more cost-effective
- long-term retrospective cohort demonstrated control of HTN in approximately 70% of patients with APA managed with MR antagonist
- 40 patients with BAH who underwent unilateral adrenalectomy reported HTN cure in 15% of patients.
  - *Sukor, N. et al. (2009) J. Clin. Endocrinol. Metab. 94, 2437–2445*
- recent study comparing patients with APAs treated surgically and patients with BAH managed medically illustrated superior cardiovascular outcomes with adrenalectomy after 2.5 years
  - *Bernini, G. et al. (2012 J. Endocrinol. Invest. 35, 274–280*

Original Definitions for Cure (18)	Current Definitions for Cure	PASO International Consensus Definitions for Cure of Primary Aldosteronism (24)	
Criteria applied to: Group 1 and Group 2	Criteria applied to: Group 2	Criteria applied to: Group 2	
Criteria	Criteria	Criteria	
Cure	Cure	Biochemical success	
1) Normokalemia not requiring potassium supplementation at the time of the postoperative visit AND 2) Stable or decreased mean arterial blood pressure OR systolic pressure less than 140 WITH 3) Same OR a reduced number of antihypertensive medications taken on a daily basis. (Neither the medication dose nor a change in class of antihypertensive medication was considered in the assessment of the medication regimen.)	1) Normokalemia not requiring supplemental potassium at the time of the postoperative visit 2) Normal PAC; 3) PRA >1ng/mL/h; AND 4) No requirement for blood pressure medication OR a decrease in WHO ATC/DDD Index greater than 0.5.	Complete	Normokalemia AND normalization of ARR OR suppression of aldosterone with a confirmatory test when ARR is elevated
		Partial	Normokalemia AND elevated ARR and one or both of the following: 1) >50% decrease in baseline plasma aldosterone level 2) Abnormal but improved post-surgery confirmatory result[c]
	Benefit	Missing	Persistent hypokalemia (if present pre-surgery) AND/OR elevated ARR AND/OR failure to suppress aldosterone with confirmatory test
Failure	If not entirely cured, benefit from surgery is defined as: 1) PRA >1 ng/mL/h AND 2) PAC decreased by greater than 50% compared to the pre-operative value OR 3) WHO ATC/DDD Index falls by greater than 0.5.	Clinical success	
Hypokalemia OR Increase in antihypertensive medications OR Increase in blood pressure		Complete	Normal BP, no antihypertensive medications
	Failure	Partial	Reduction[a] or unchanged[b] BP AND less medication OR reduction in BP with same amount of medication
	None of the components under cure or benefit are met.	Missing	Unchanged[b] or increased[a] blood pressure levels and/or the same or an increased amount of antihypertensive medications

Co-secreting tumor

Co-secreting adernal adenoma

- Prevalence of PA with subclinical Cushing's syndrome:up to 21%
  - *Endocrine Journal* 2011, **58** (7), 543-551
- Impact the post-surgical management: Adrenal insufficiency
  - Späth, Martin, et al. *European Journal of Endocrinology* 164.4 (2011): 447-455.