# Controlling the Hormonal Basis of Hypertension

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May 2019

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# Disclosure Information

- Debbie Cohen, MD has no financial conflicts of interest to disclose relevant to this activity.

# Objectives

1. Discuss the hormonal basis of hypertension
2. Describe how cathecholamine excess, hyperaldosteronism and hyperthyroidism can affect hypertension
3. Identify signs and symptoms in patients for whom hormone control may benefit blood pressure control

# Case 1

- 63 y.o. female who presents for evaluation of HTN pre-operatively
- Scheduled for thyroidectomy - multiple thyroid nodules
- Diagnosed with hypertension in 2005 at age 50, and has been on medication since that time
- BP from EMR show SBP in range of 160-170 mm Hg
- Office BP 168/88 mm Hg
- Home BP labile and often very high
- Has occasional symptoms of palpitations and sweating and BP very high on these occasions

# Case 1

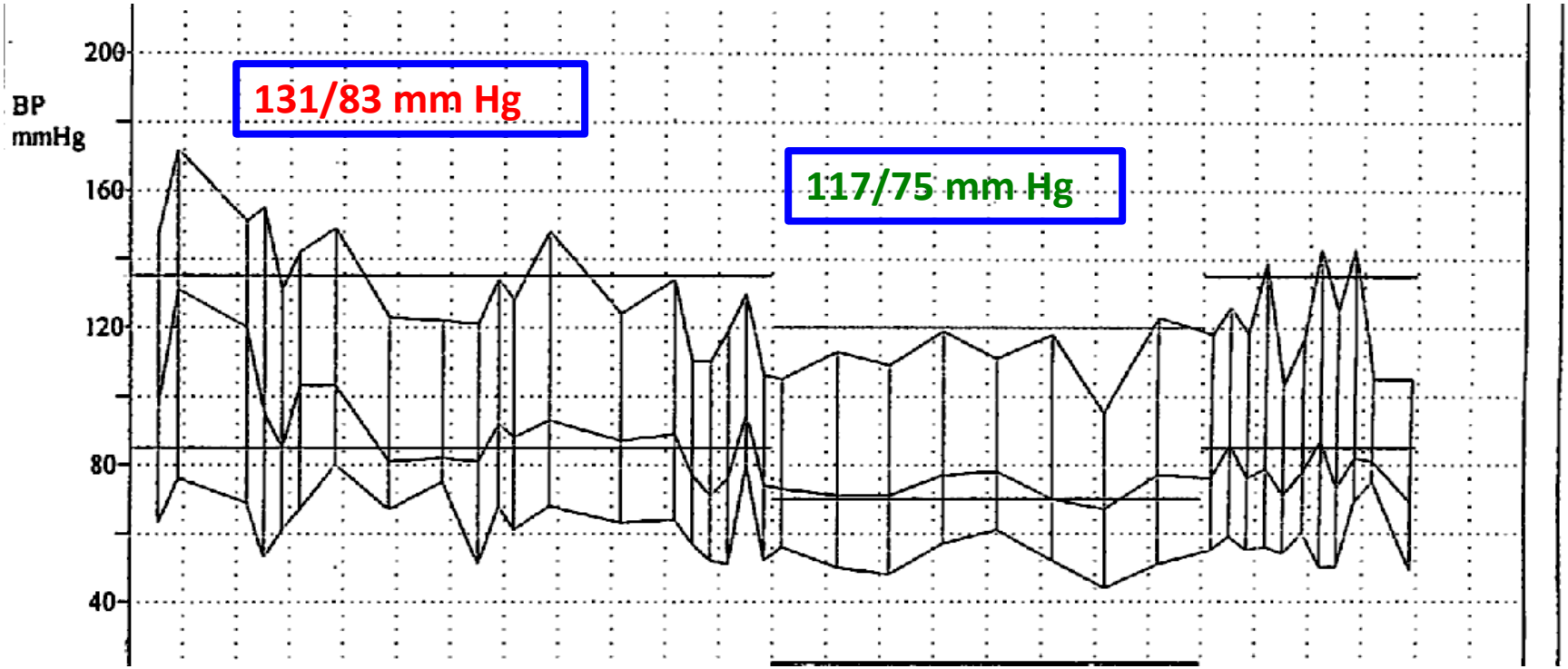
- Cannot tolerate beta blockers, had a dry mouth with lisinopril
- Current meds: amlodipine 5 mg BID, losartan/HCTZ100–25 mg daily
- She does follow a low-salt diet, she walks 2 miles per day and does weight training and spinning
- She was taking Advil PM for sleeping but stopped this about 2 months ago

What is the most appropriate next step in management ?

- 1. Add clonidine 0.1 mg bid
- 2. 24 hour ABPM
- 3. Check plasma metanephrines
- 4. Echo
- 5. Add hydralazine 50 mg tid

# ABPM

**Average BP = 125/60 mm Hg**



# Results

- Echo: no LVH, normal EF
- Plasma metanephrines normal
- Renin – 2.7, aldosterone = 10.7

# Management

- White coat effect with pseudopheochromocytoma type symptoms
- Changed to triple combination therapy – olmesartan/amlodipine/HCTZ 40/10/25
- Added low dose SSRI for lability
- One month later patient reported improvement in symptoms with less BP lability
- These patients generally respond well to agents active on the SNS (catapres patch) and low dose SSRIs

# Case 2

- 22 yo white female with recurrent streptococcal tonsilitis
- Admitted electively for tonsillectomy
- No prior medical or surgical history except for migraine headaches
- The tonsillectomy was aborted because she had surge in blood pressure at the time of anesthesia induction (110/70 mmHg –> 200/136 mmHg)

# Case 2: 22 yo F

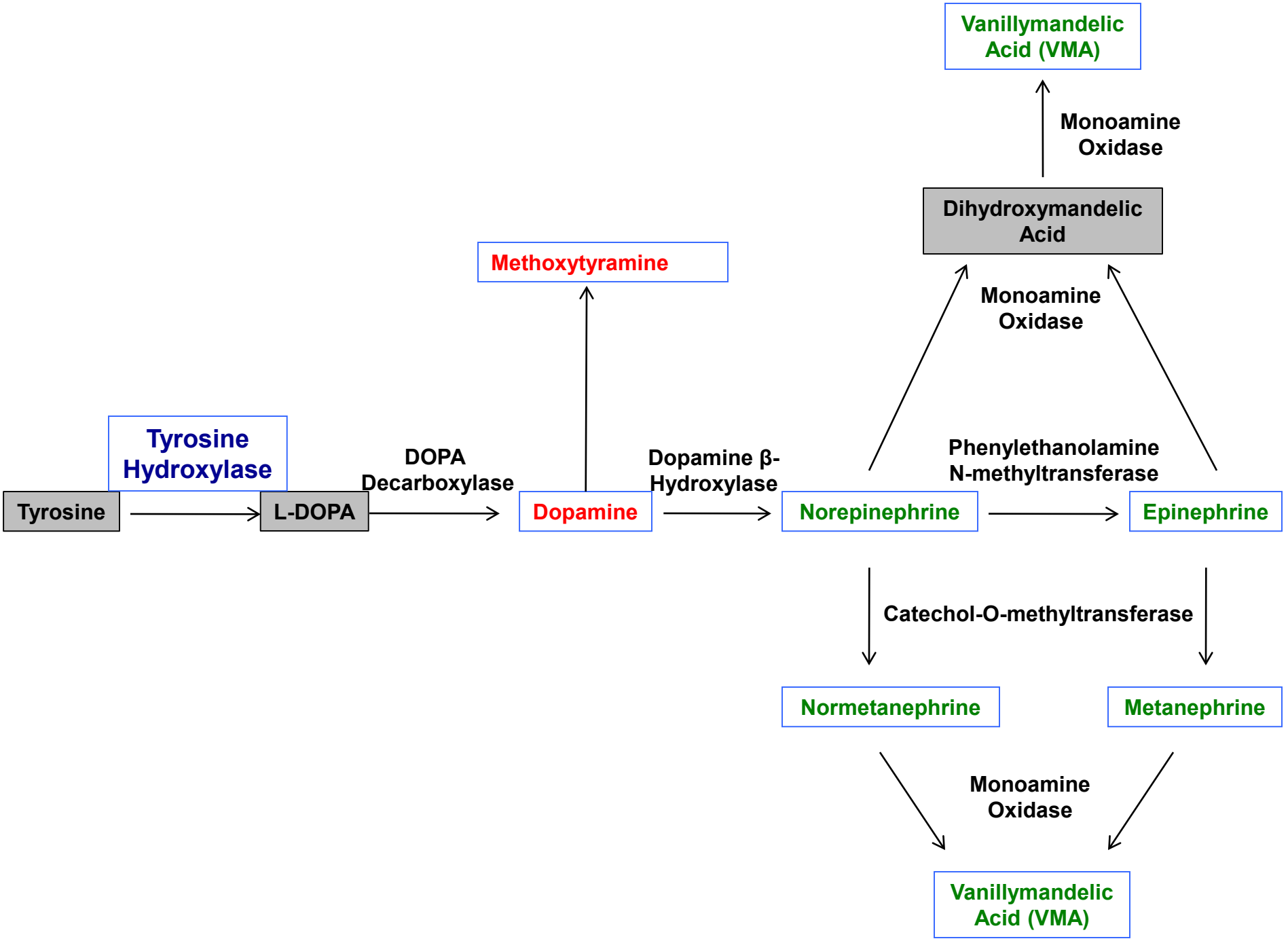
- The echo is normal
- The stress test was negative for ischemia. The 12 lead EKG in particular (pre-op) showed only sinus arrhythmia
- She also is on an oral contraceptive tablet.

# Case 2: 22 yo F

- BMI = 24
- Fundi are fine.
- BP is the same in both arms, but 130/94 mmHg and her heart rate is 96 beats/minute.
- Routine labs are normal (glucose, potassium, creatinine).

# Case 2: 22 yo F

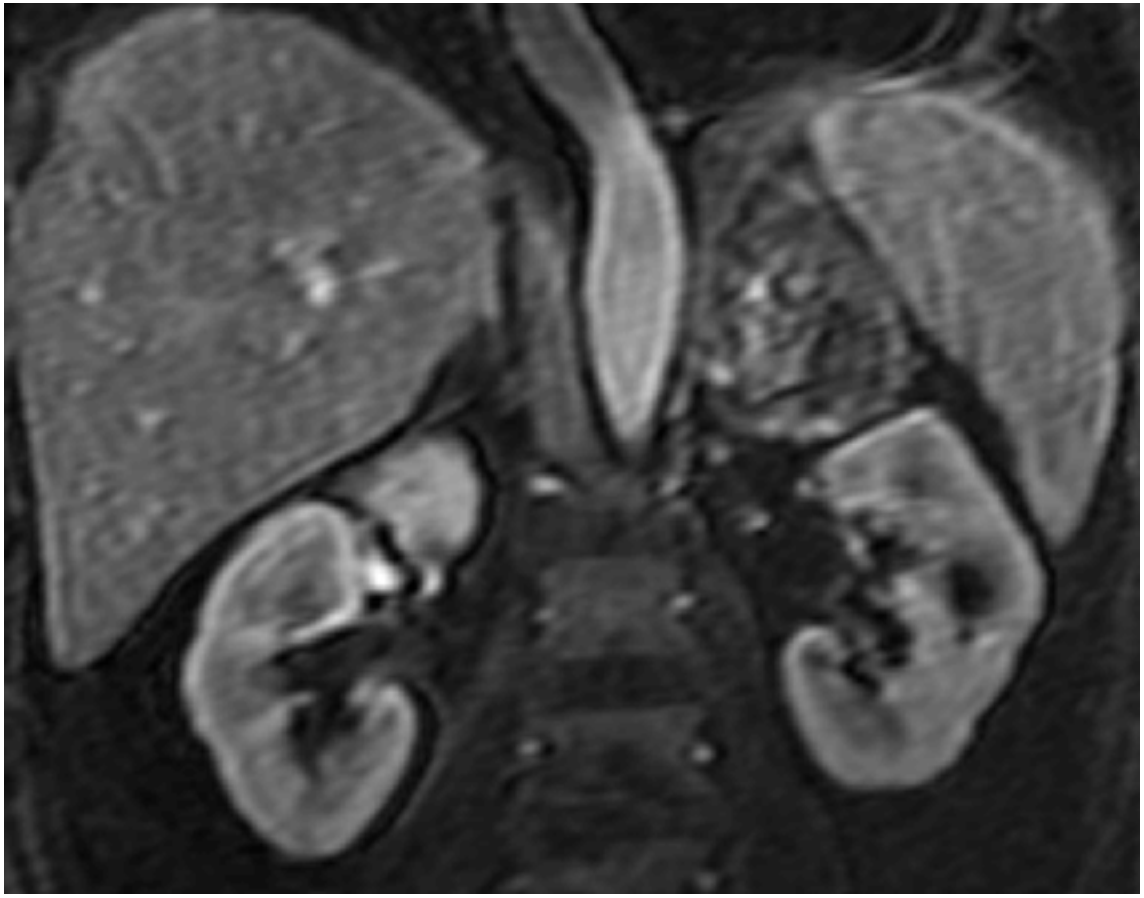
- Plasma renin activity 3.1 ng/ml/hr (0.5-3.5)
- Serum aldosterone  16 ng/dl
- Plasma metanephrine 4.54 pg/mL (<0.8)


Vanillymandelic Acid (VMA)
Monoamine Oxidase
Dihydroxymandelic Acid
Methoxytyramine
Monoamine Oxidase
Tyrosine Hydroxylase
DOPA Decarboxylase
Dopamine β-Hydroxylase
Phenylethanolamine N-methyltransferase
Tyrosine
L-DOPA
Dopamine
Norepinephrine
Epinephrine
Catechol-O-methyltransferase
Normetanephrine
Metanephrine
Monoamine Oxidase
Vanillymandelic Acid (VMA)

# Biochemical Testing

| | Hereditary | Spontaneous |
|---|---|---|
| | sensitivity/specificity | sensitivity/specificity |
| Plasma Met | 97/96 | 99/82 |
| Plasma Cat | 69/89 | 92/72 |
| Urine Met | 96/82 | 97/45 |
| Urine Cat | 79/96 | 91/75 |
| Total Urine Met | 60/97 | 88/89 |
| VMA | 46/99 | 77/86 |

# MRI upper abdomen



Surgery is consulted What is most appropriate pre-operative treatment for her BP ?

- 1. Labetalol 200 mg bid
- 2. Amlodipine 10 mg daily
- 3. Hydralazine 50 mg tid
- 4. Doxazosin 2 mg bid
- 5. Phenoxybenzamine 10 mg bid

# Should you add a beta-blocker

- 1. yes
- 2. no
- 3. maybe

# Case 2: 22 yo F

- Surgery is undertaken and pathologic diagnosis confirmed. The next step should be?
- 1. Genetics consultation
- 2. Repeat relevant blood test within 5 days of surgery
- 3. No further evaluation, see in office in 2 weeks
- 4. Repeat abdominal imaging in 1 month

Ann Surg Oncol
DOI 10.1245/s10434-013-2944-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – ENDOCRINE TUMORS

# Doing Away with the Rule of 10 %

**Sarah C. Oltmann, MD and Herbert Chen, MD**

Department of Surgery, Section of Endocrine Surgery, University of Wisconsin, Madison, WI

Pheochromocytomas (PCC) and paragangliomas (PGL) are rare tumors that require definitive surgical resection for management. Depending on the location of the tumor, the patient may present to any number of surgical specialists, including endocrine surgery, urology, surgical oncology, thoracic surgery, otolaryngology, and general surgery.

The setting of this study is in a medical genetics clinic associated with a dedicated neuroendocrine tumor center, where all patients with PCC or PGL are at least offered referral to the medical genetics clinic.[4] Because only 14 (10 %) of the initial 139 patients within the study cohort

# Pheochromocytoma

- 80% of lesions are found in the adrenal gland
- 15-20% extra-adrenal (paragangliomas)
- 10% bilateral
- 5% malignant arising from adrenal gland
- 33% malignant if extra-adrenal
- 40 % genetic in origin

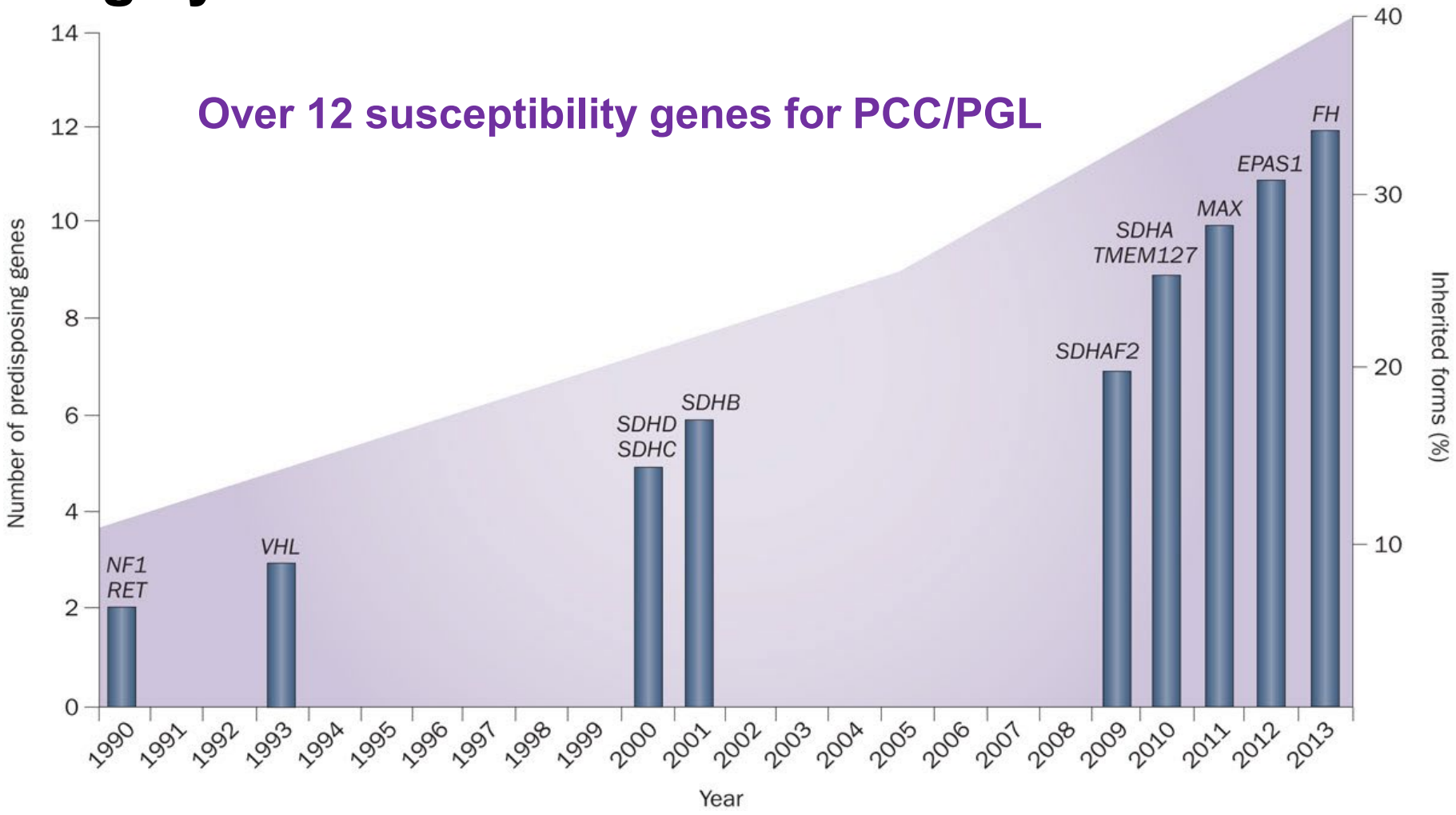
# Mutation Detection Rates

## Overall mutation detection rate: 41%

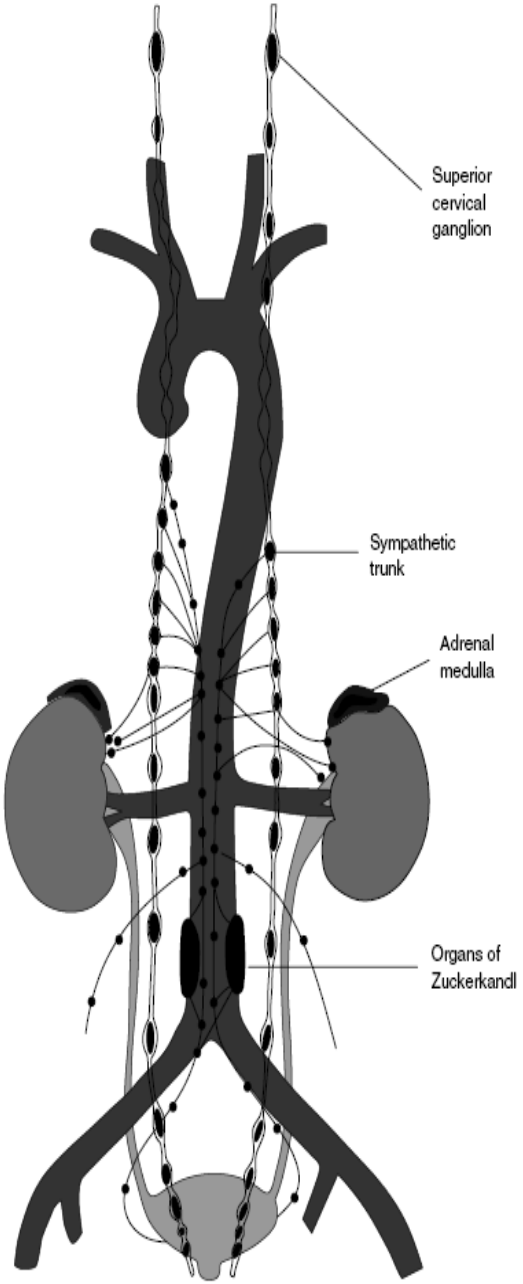
| Subgroup | Mutation Detection Rate |
|---|---|
| PCC | 29% |
| PGL | 47% |
| Positive FHX | 90% |
| Negative FHX | 23% |

**Inherited mutations in pheochromocytoma and paraganglioma: why all patients should be offered genetic testing.** Fishbein L, Merrill S, Fraker DL, Cohen DL, Nathanson KL. Ann Surg Oncol. 2013 May;20(5):1444-50.

# Pheochromocytomas and Paragangliomas are Highly Heritable




Favier et al. Nat Rev Cancer 2014

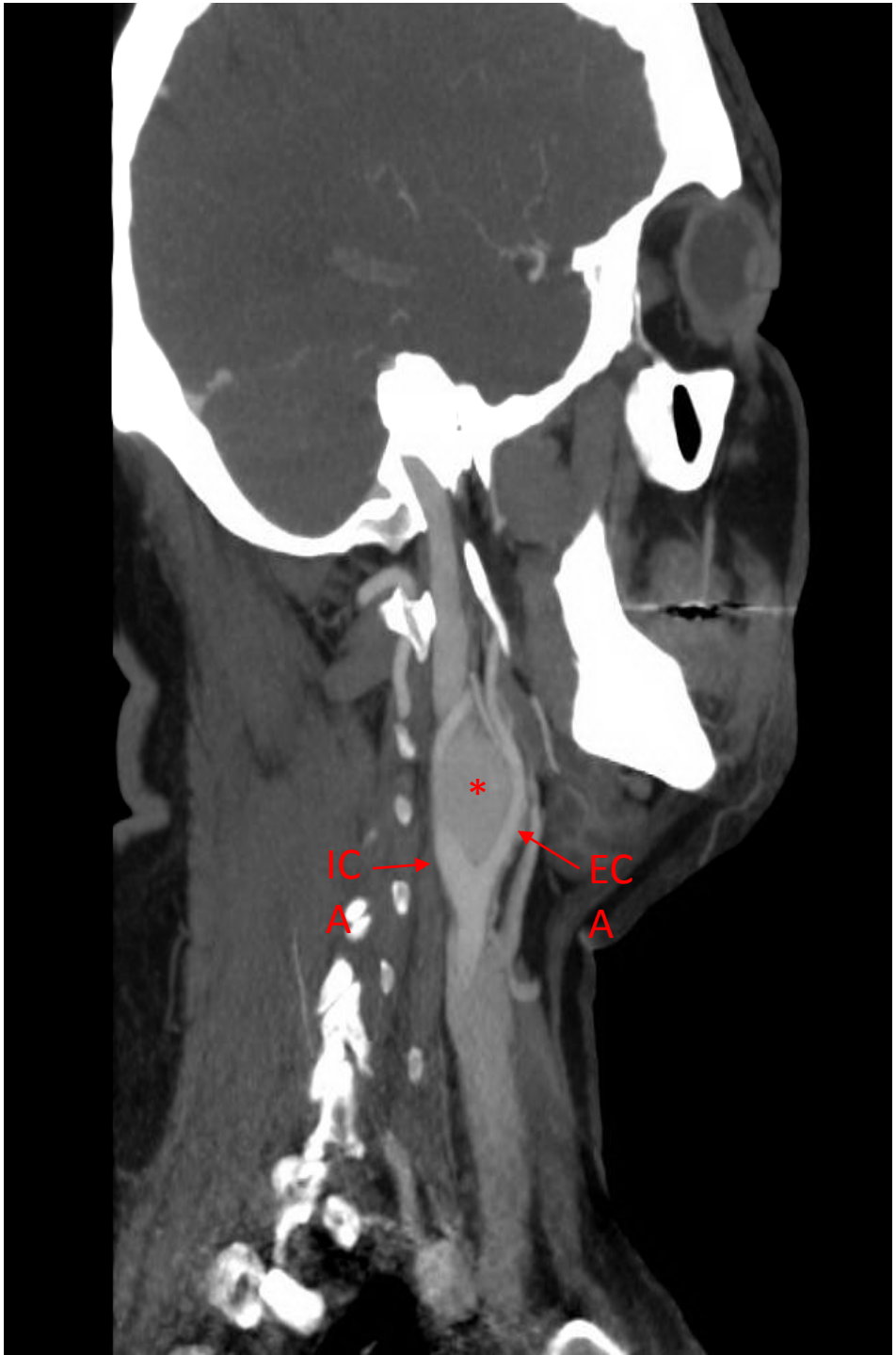



**Head and neck paragangliomas (HNPGL)**

**Adrenal medulla tumors = pheochromocytomas (PCC)**

**Tumors at other sites = paragangliomas (PGL)**

Petri et al British Journal of Surgery 2009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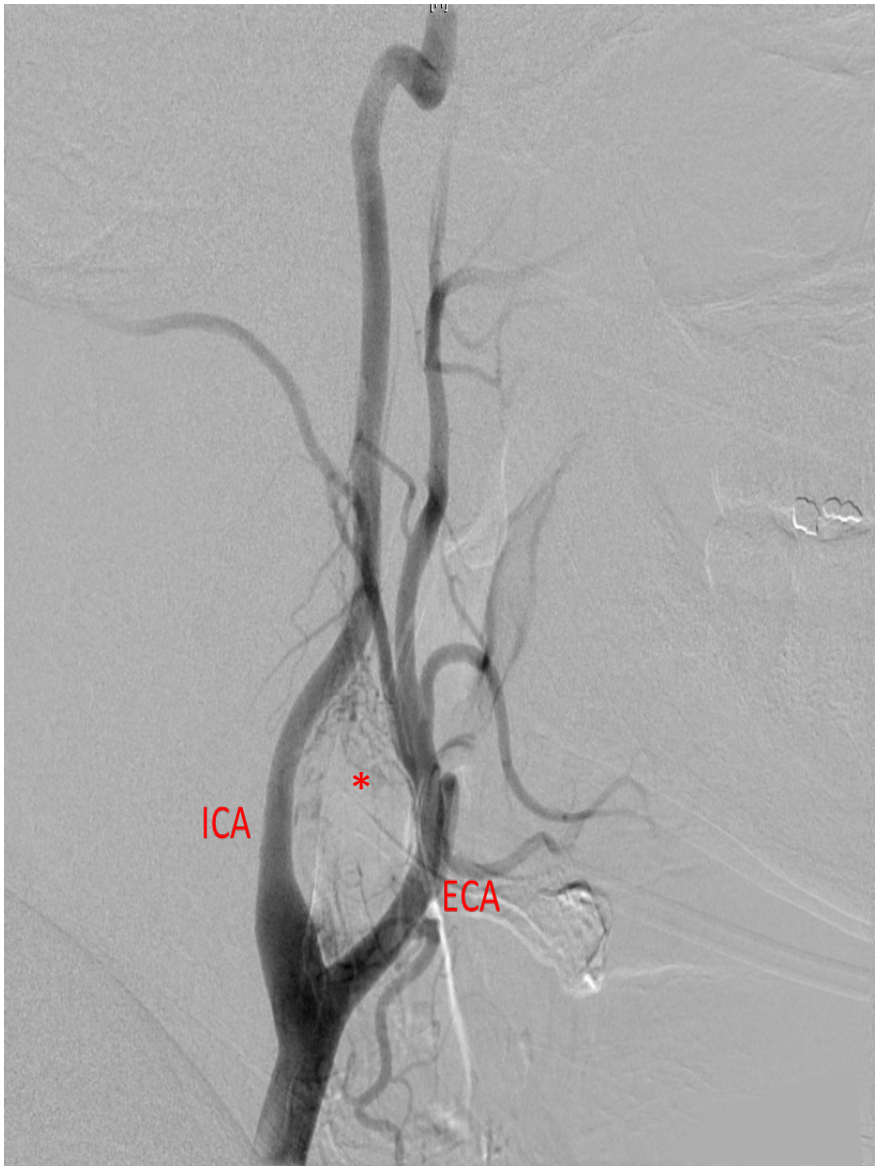
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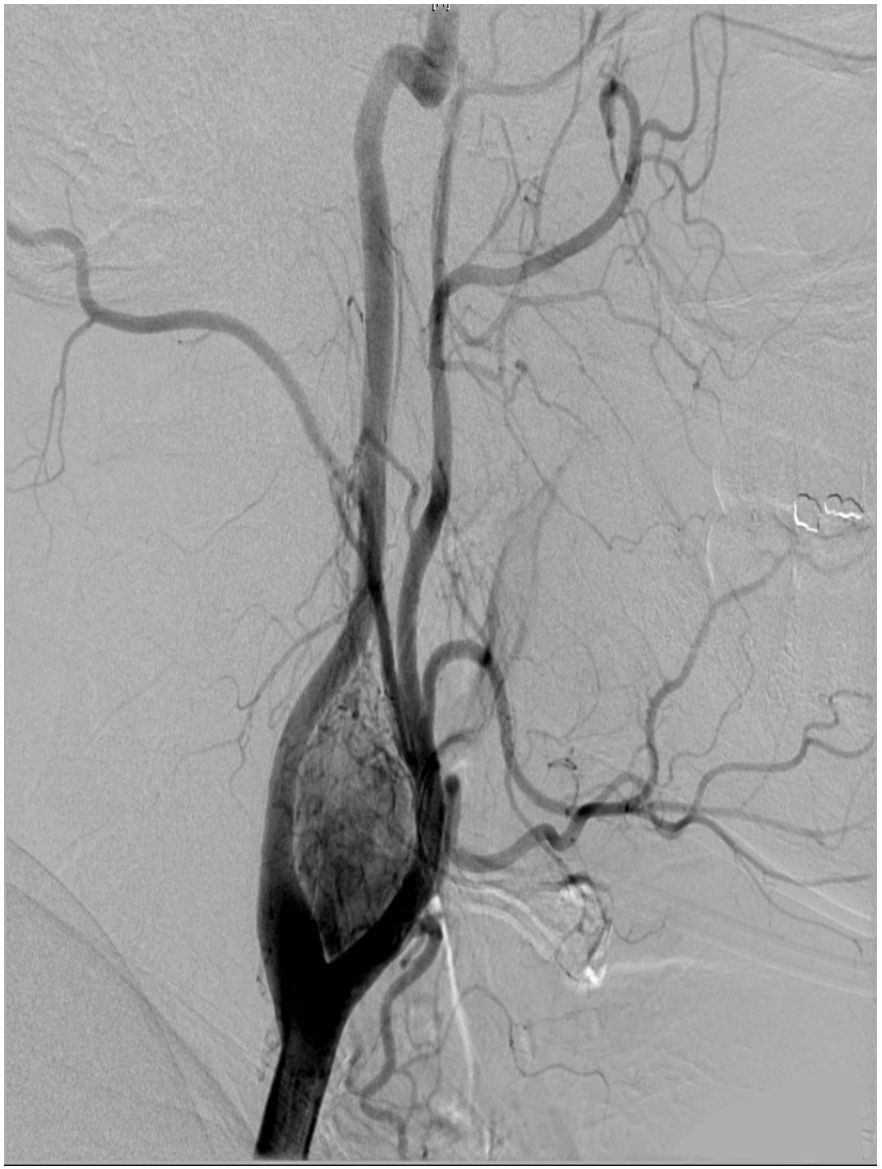
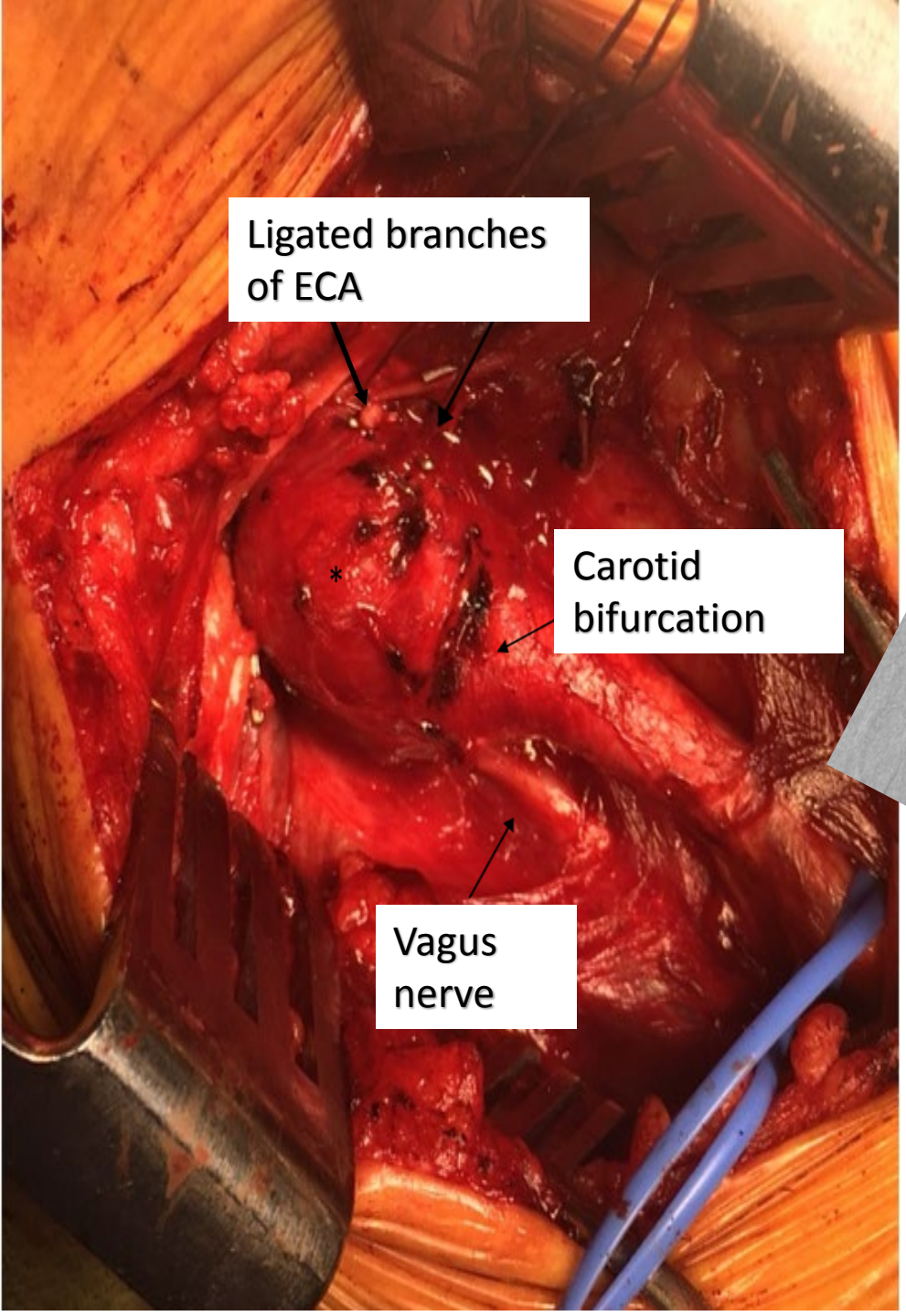
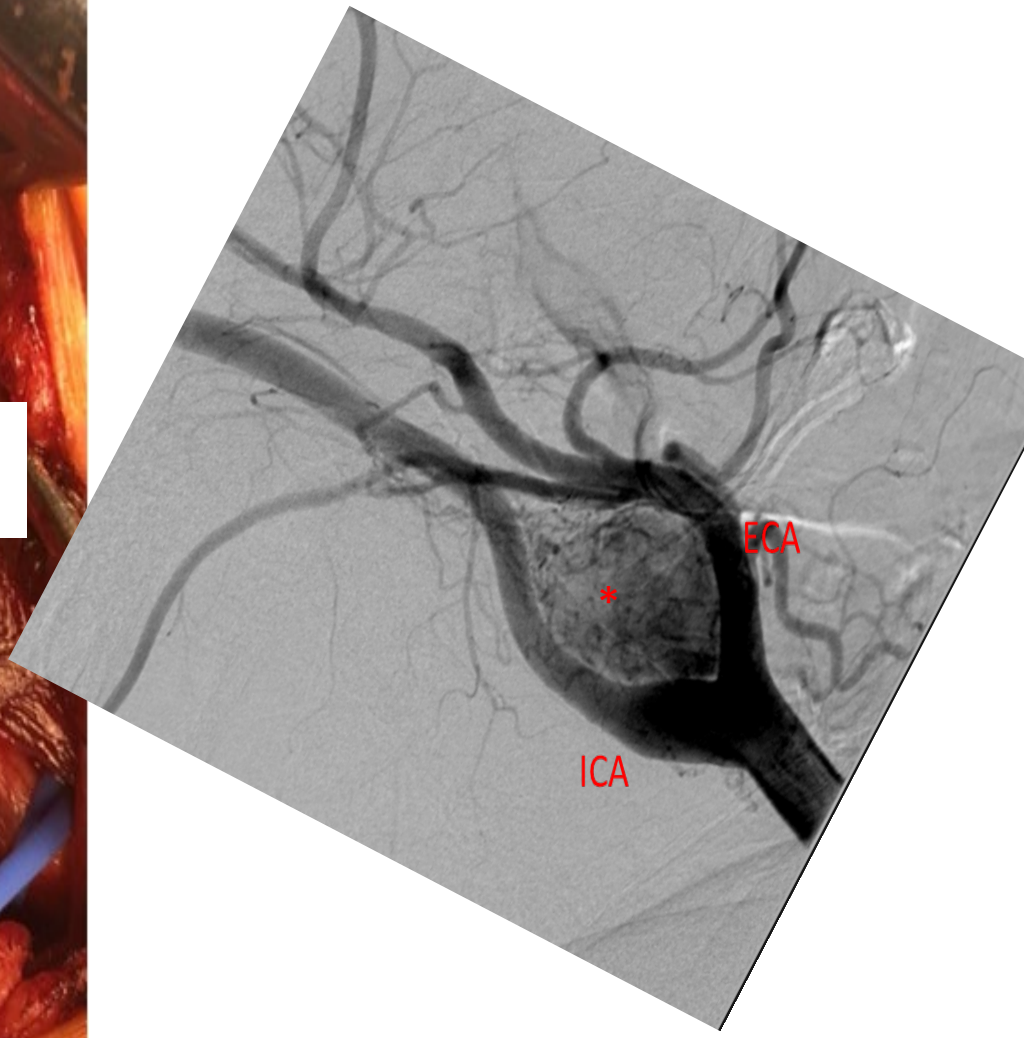
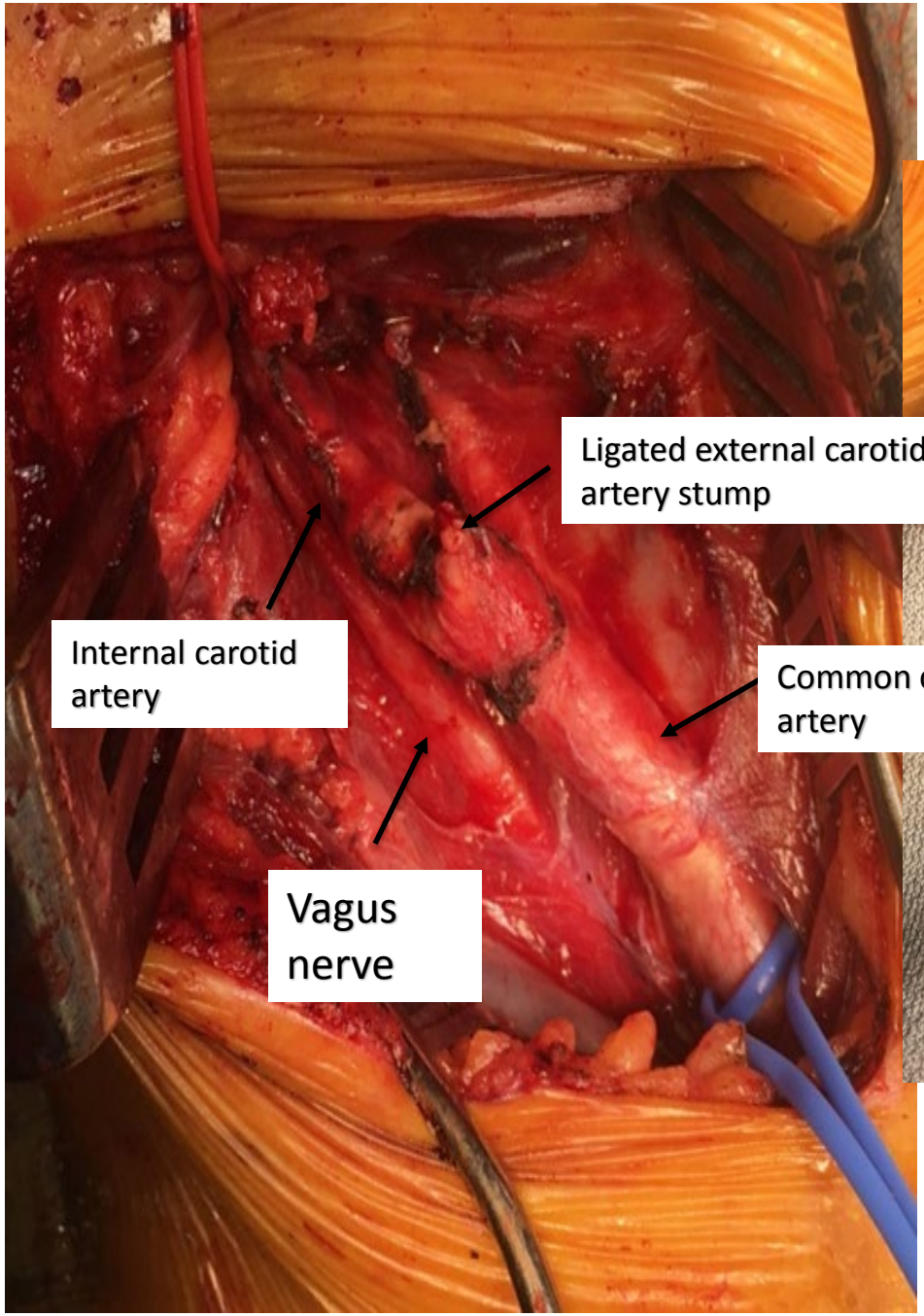
ICA
ECA

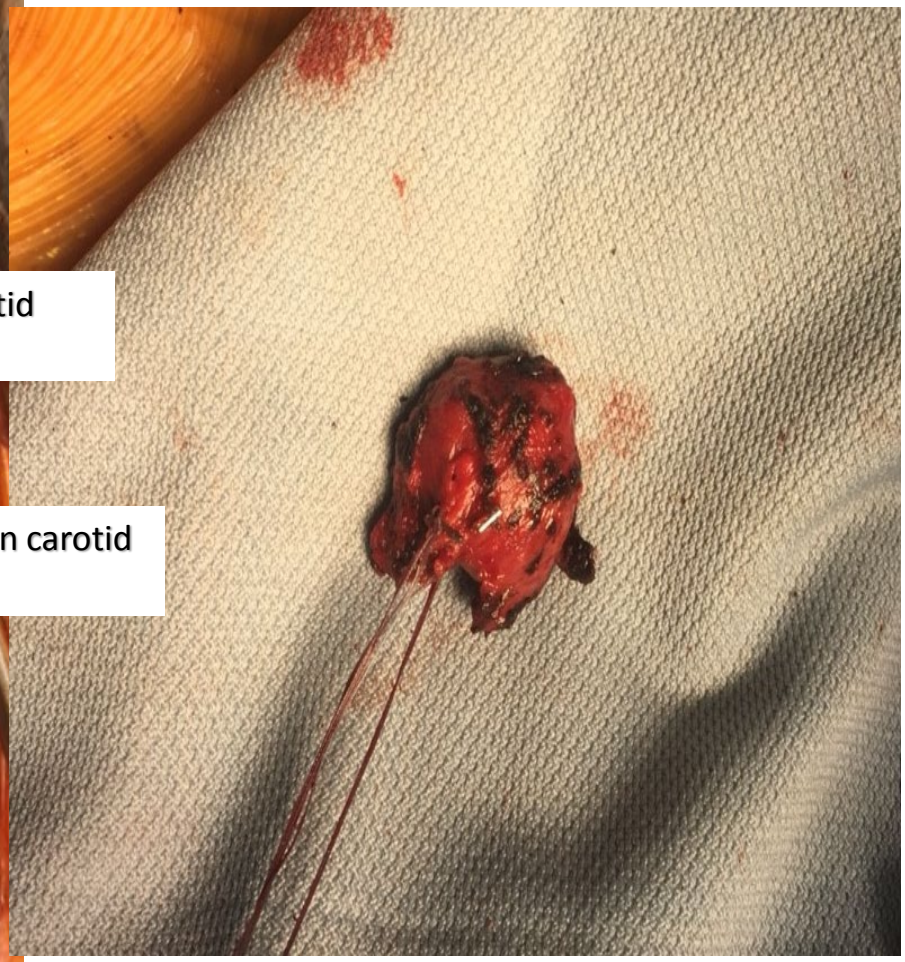



Ligated branches of ECA
Carotid bifurcation
Vagus nerve
*

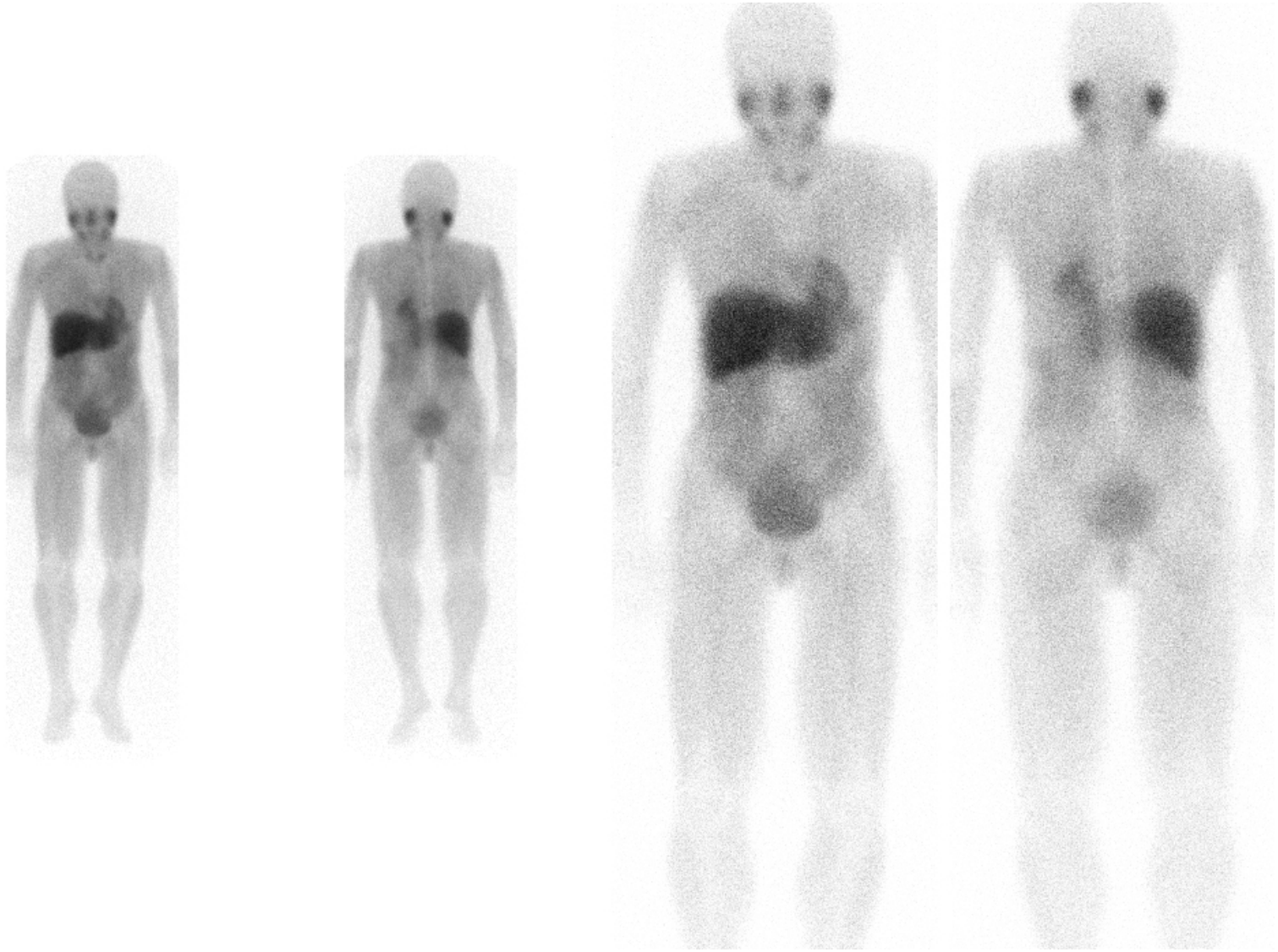

ECA
*
ICA

# Post resection

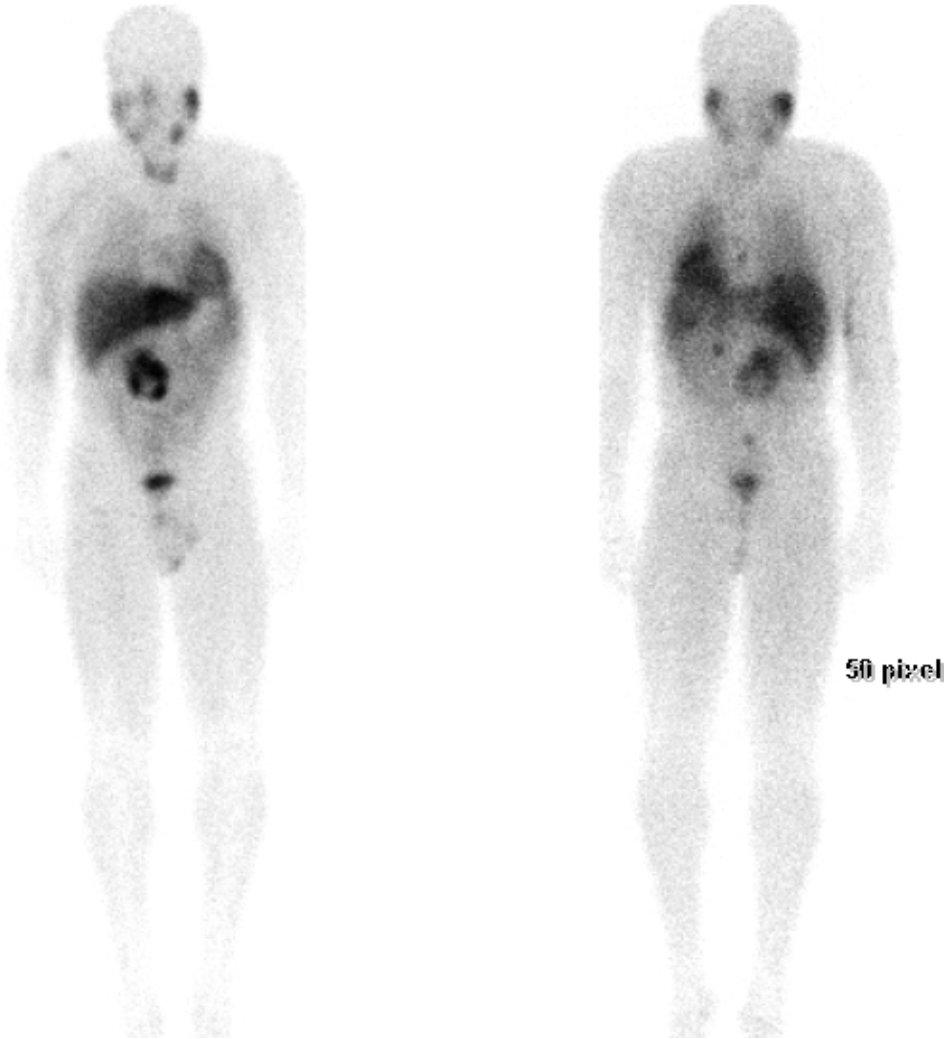


# Normal I-123 MIBG



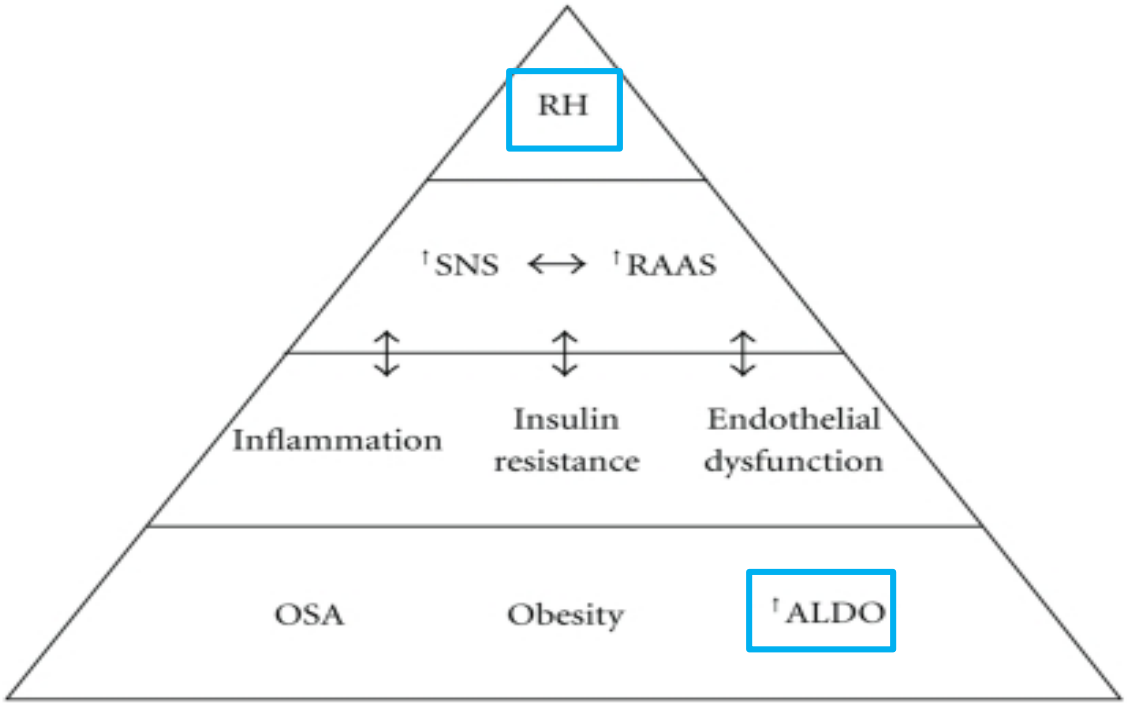
# Abnormal I-123 MIBG: metastatic paraganglioma



# Summary

- Catecholamine excess/pseudopheochromocytoma requires treatment with antihypertensives acting on SNS, antianxiety and anti-depressants with psychotherapeutic interventions
- Plasma metanephrines best screening test to detect pheo
- There are more inherited germline mutations in pheo/PGL than any other tumor type
- Need to keep a high clinical suspicion to avoid missing pheo diagnosis

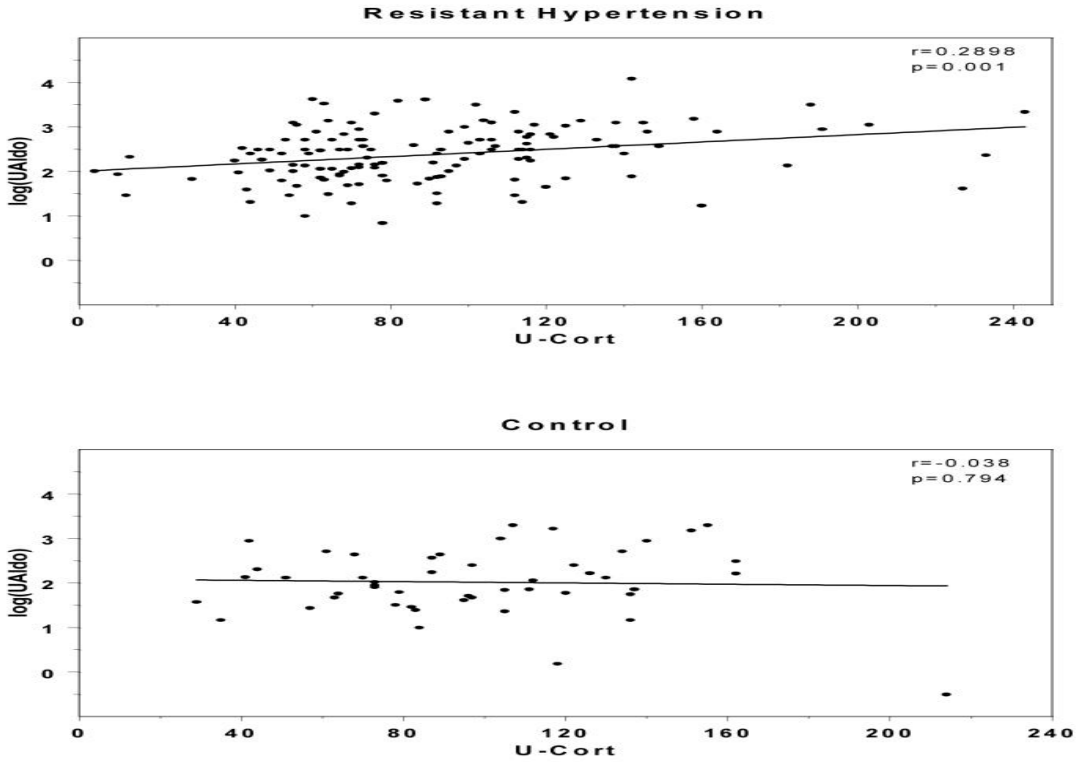
# Resistant HTN and aldosterone excess




A proposed pathophysiologic pathway for the activation of SNS and the development of RH. Obesity, OSA and aldosterone excess are covering a great area of the mosaic of the phenotype of RH and are correlated with increased SNS activity, via multiple mechanisms. ↑ALDO: Aldosterone excess, OSA: Obstructive sleep apnea, ↑RAAS: Renin-Angiotensin-Aldosterone System activation, RH: Resistant hypertension, ↑SNS: Sympathetic nervous system hyperactivity.

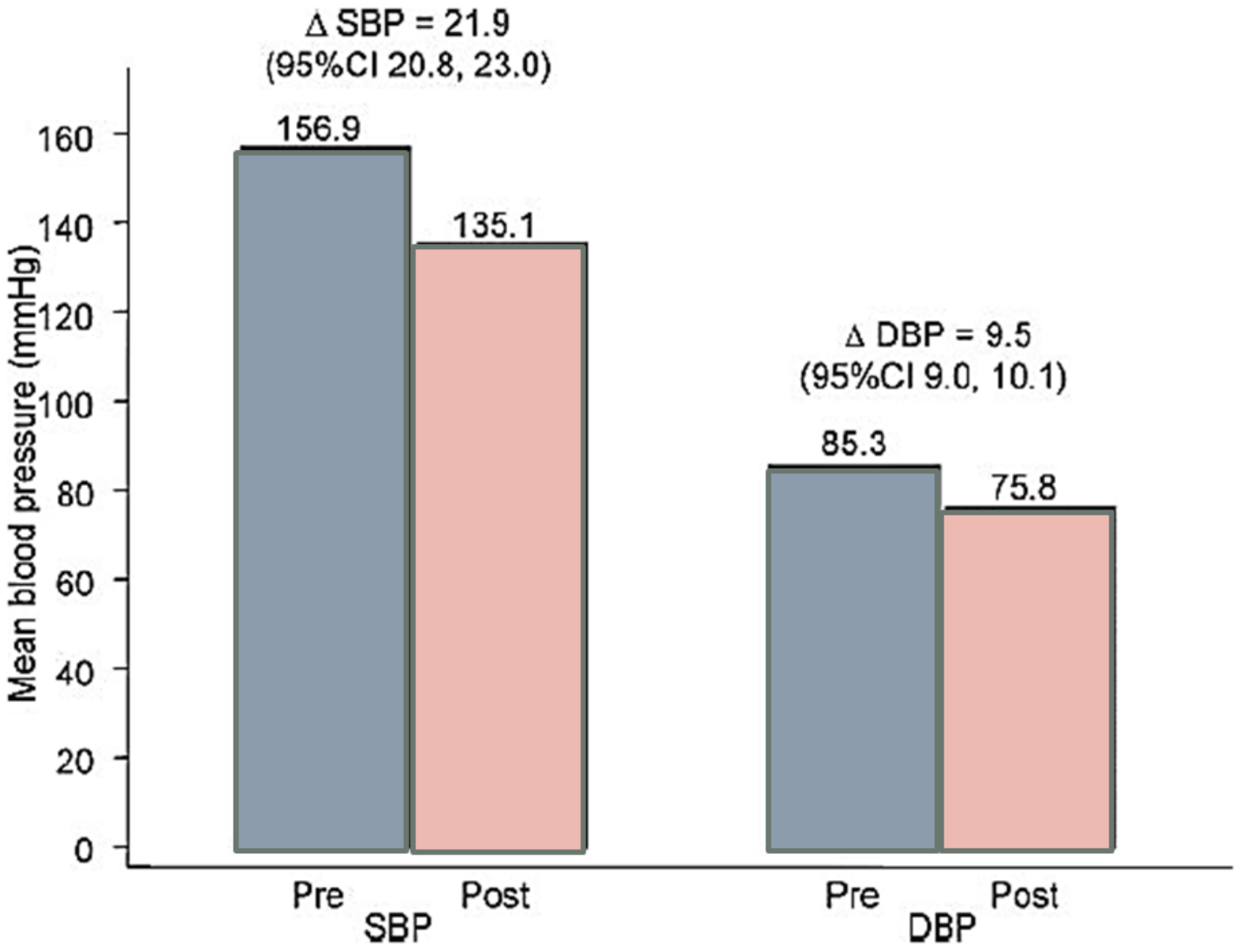
Tsioufis C, Kordalis A, Flessas D, Anastasopoulos I, Tsiachris D, Papademetriou V, Stefanadis C.
Int J Hypertens. 2011 Jan 20;2011:642416

# Aldosterone Excess and Resistant Hypertension



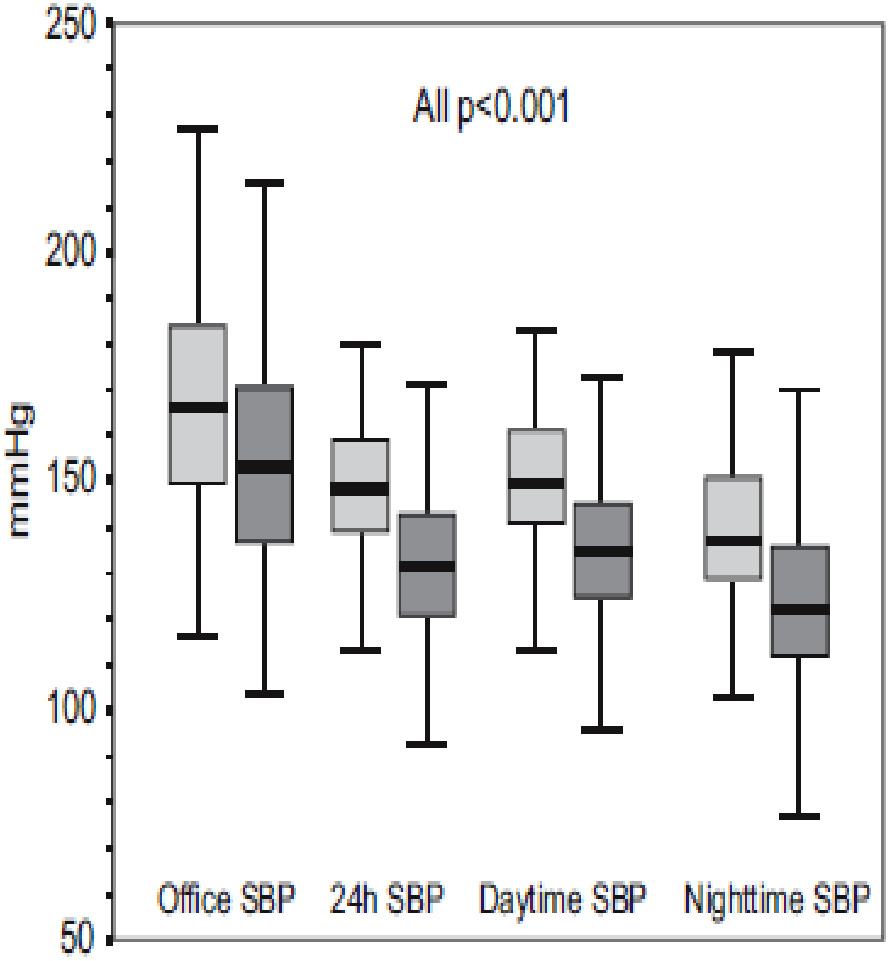

Correlation between 24-hour urinary aldosterone (reference range 2 to 16 µg/24-hr) and urinary cortisol (reference range 56 to 286 µg /24-hr) among patients with resistant hypertension (top panel) and controls (bottom panel).
Krishna K Gaddam, et al. Arch Intern Med. Arch Intern Med; 2008, 168(11):1159-1164.

# MRA as 4th Line Agent




Chapman N. Hypertens. 2007;49:839-845

# Efficacy of Spironolactone Therapy in Patients With True Resistant Hypertension




175 patients true resistant hypertension spironolactone in doses of 25 to 100 mg/d.

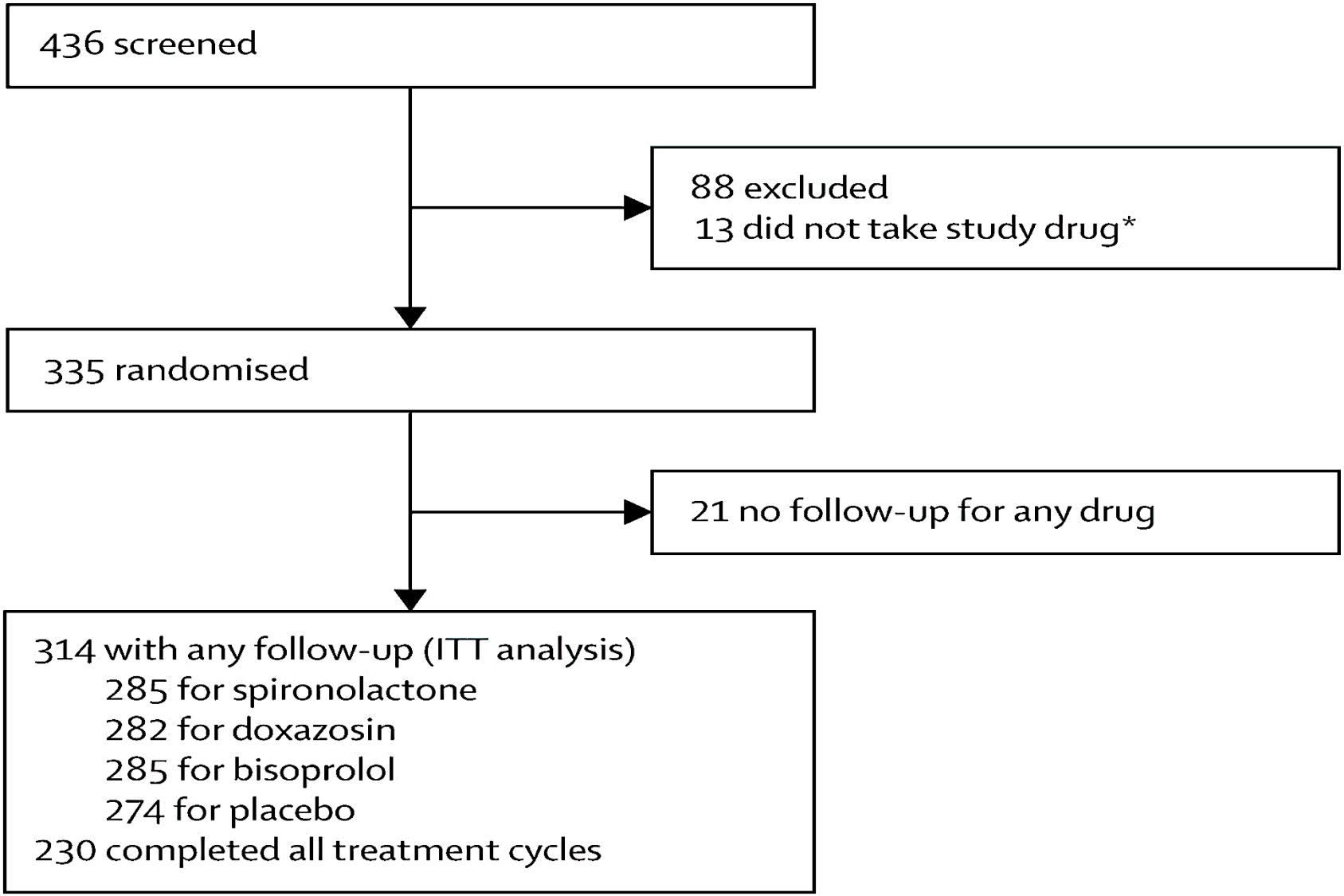
mean reductions of 16 and 9 mm Hg, in 24-hour systolic and diastolic blood pressures

**Efficacy of spironolactone therapy in patients with true resistant hypertension. de Souza F1, Muxfeldt E, Fiszman R, Salles G.**

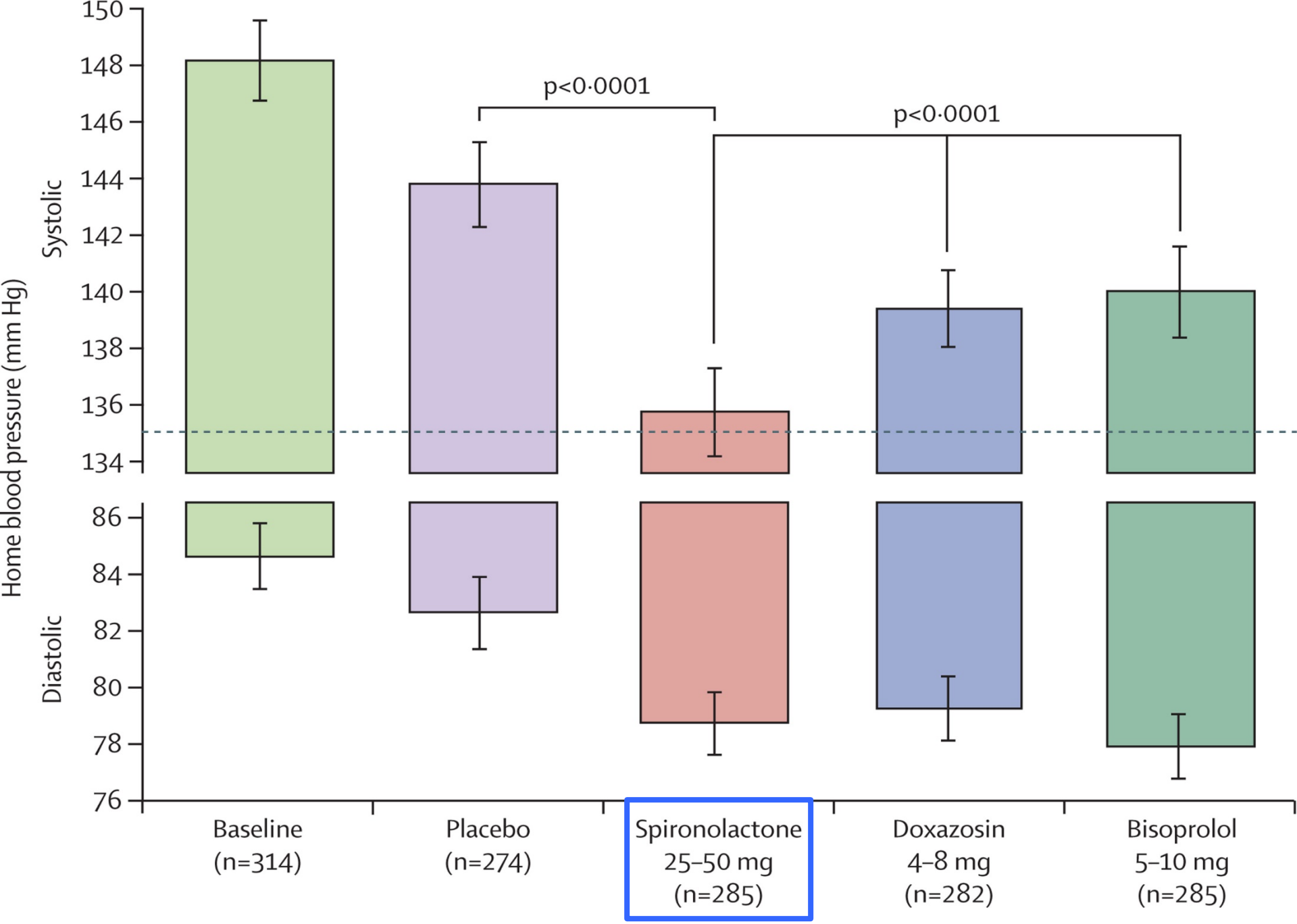
(***Hypertension***. **2010;55:147-152.**)

**Increased response to spironolactone with increased abdominal obesity** and increased lower arterial stiffness

# PATHWAY-2 Study: Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension: a randomised, double-blind, crossover trial




Williams B, et.al. Lancet 2Williams B, et.al. Lancet 2015;386 (10008):2059-2068.




**Williams B, et.al. Lancet 2015;386 (10008):2059-2068**

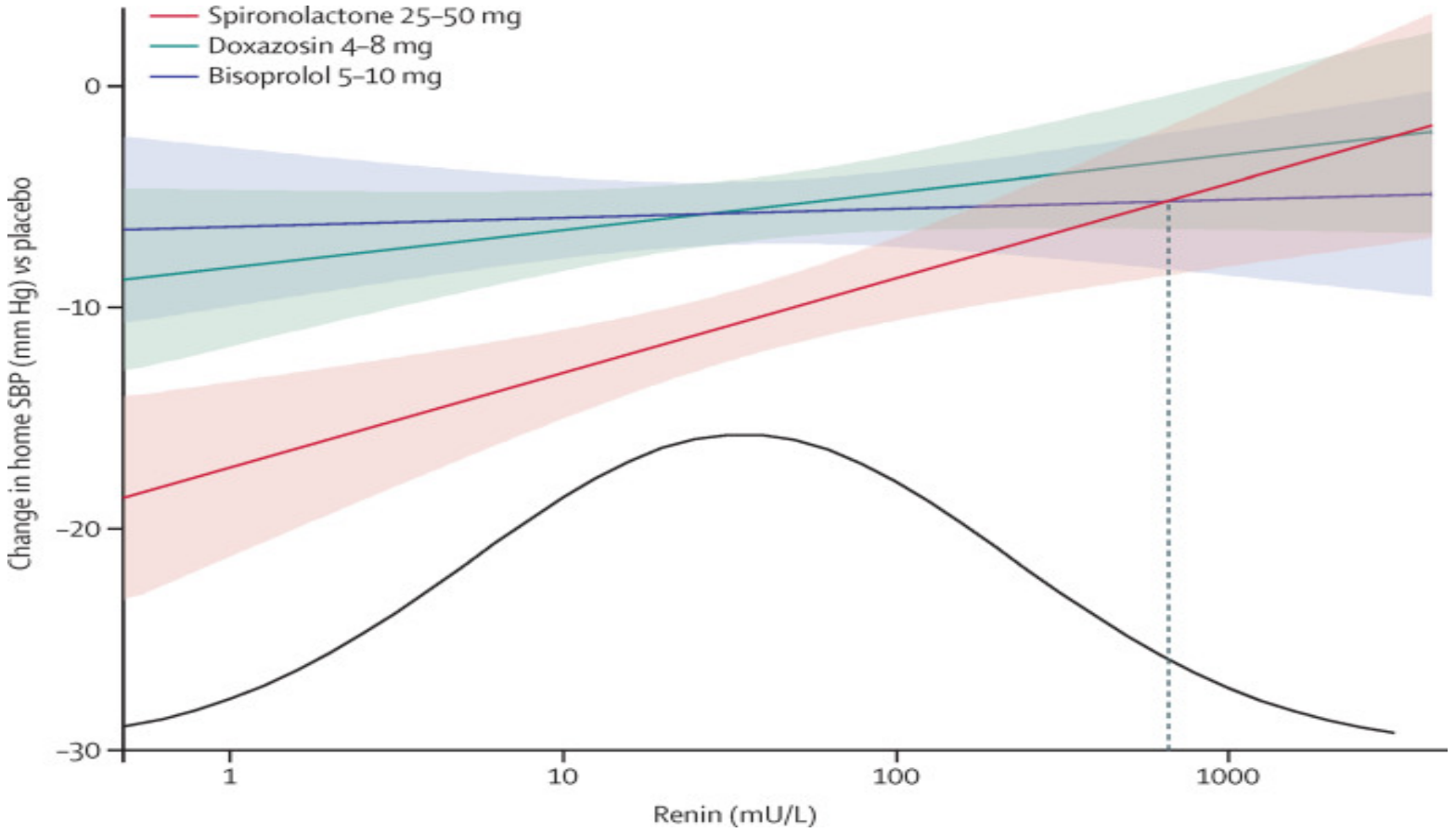



**Figure : Blood pressure response versus renin regression (90% CI) of placebo corrected change in home systolic blood pressure versus renin for spironolactone (r2=0·037, p=0·003), doxazosin (r2=0·007, p=0·183), and bisoprolol (r2=0·0004, p=0·750).**

**Williams B, et.al. Lancet 2015;386 (10008):2059-2068**

# Case 3

- 54 y.o. male who presented for evaluation of severe uncontrolled hypertension
- Had massive CVA at age 38 resulting in left hemiplegia
- Required 7 medications
- BMI 28, BP -168/98 mm Hg, HR = 88 /min
- Left hemiplegia

# Case 3

7/15/2015

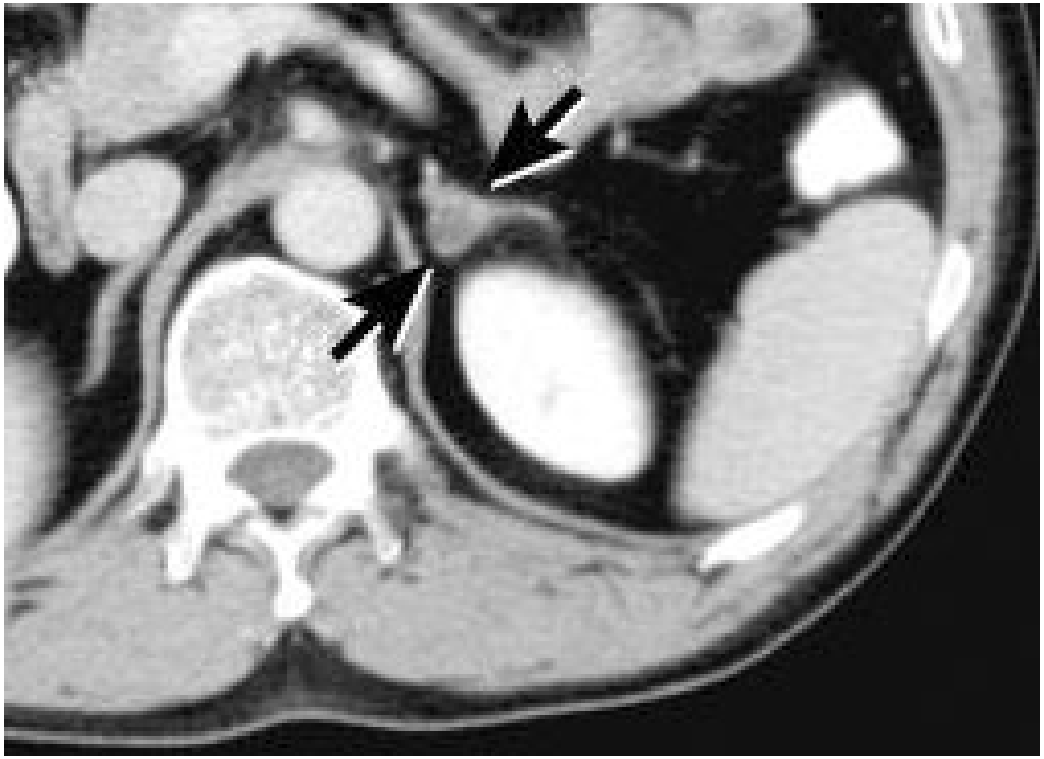
- Creat = 1.78, K = 3.3, Ca = 9.7, iPTH = 145
- Albumin = 4.1
- Renin = 0.2, Aldosterone = 21
- Urine prot/creat ratio = 1.6 g
- Plasma metanephrines - normal

# Case 3

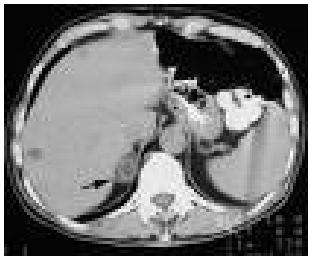
**CTA abdomen 8/24/15:**

- **5 x 4 cm left adrenal mass demonstrated enhancement consistent with adenoma**, mild atheromatous changes in the aorta and branch vessels but **no evidence for renal artery stenosis**, findings consistent with bilateral cortical renal cysts

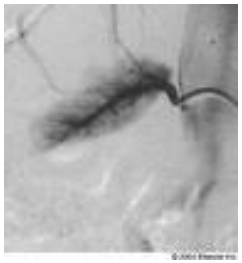
**A 1.4 mm nodule in the medial limb of the right adrenal gland that measures < 10 HU on precontrast images and shows > 50% washout on delayed images is in keeping with an adrenal adenoma.**



IMAGING



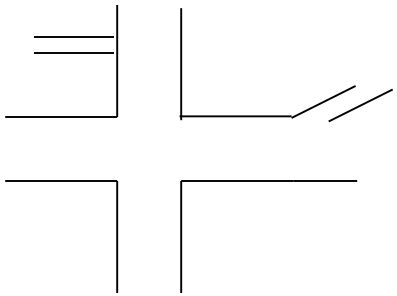
SAMPLING



Lateralization index (LI) =
ipsilateral A/C ratio [ng/dL/mcg/dL]
over contralateral A/C ratio: 21/0.5 = 42

MAPPING

**RIGHT**
A: 19560
C: 931



**LEFT**
A: 348
C: 738

**IVC**
A: 114
C: 44

Selectivity index (SI) = ratio of cortisol level in each adrenal vein compared with IVC.
Right 931/44 = 21
Left 738/44 = 17

Right A/C Ratio = 21
Left A/C Ratio = 0.5
IVC A/C Ratio = 2.6

| Sample | Aldosterone ng/dL | Cortisol ug/dL | Ratio | LI |
|---|---|---|---|---|
| **Right adrenal** | 758.0 | 605.9 | 1.3 | |
| **Left adrenal** | 4000.0 | 404.9 | 9.9 | **7.9** |
| **IVC** | 198.0 | 43.5 | 4.6 | |

# Case 3

**Pathology: 9/16:**

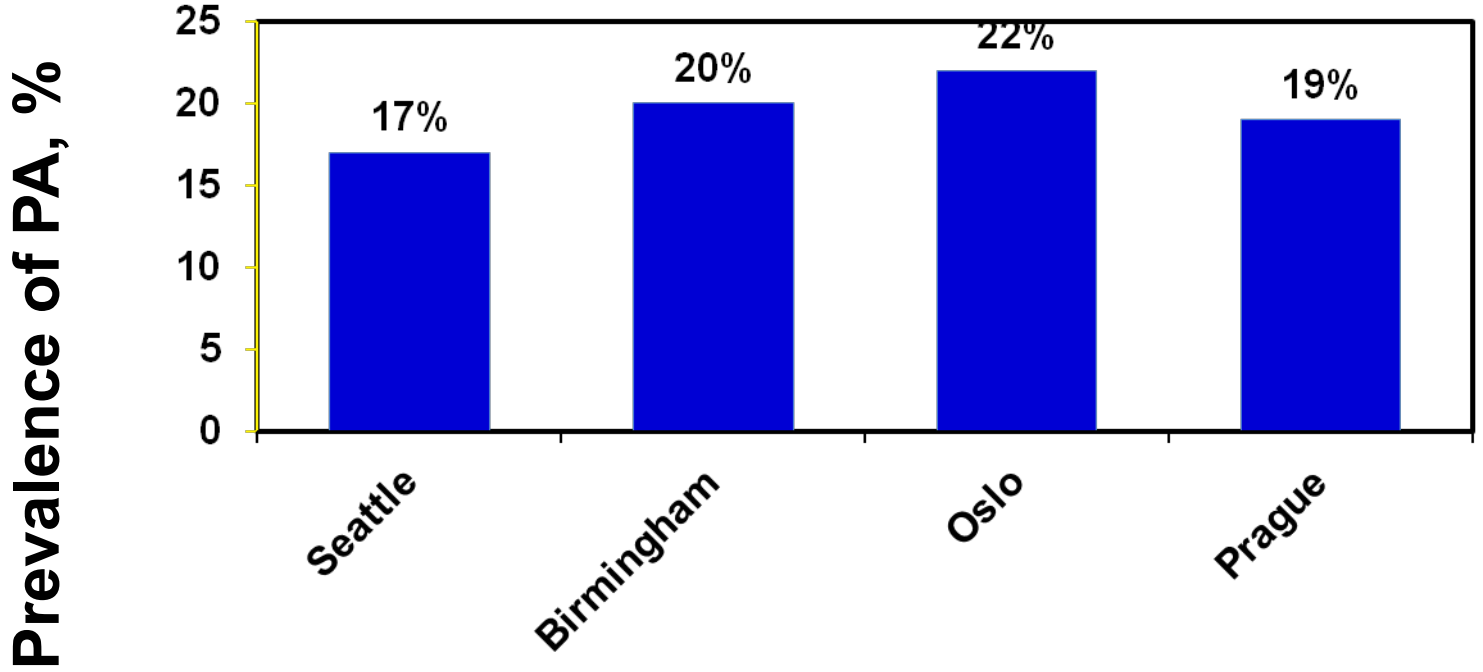
- Final Diagnosis: 1. Adrenal gland, left, 46.8 g, adrenalectomy: - Two synchronous adrenal cortical adenomas (clinically aldosteronoma), 4.2 cm and 1.6 cm, completely excised.

- BP = 112/62 mm Hg

Meds:

- Amlodipine 10 mg daily, Labetalol 400 mg tablet twice daily and Ramipril 20 mg twice daily

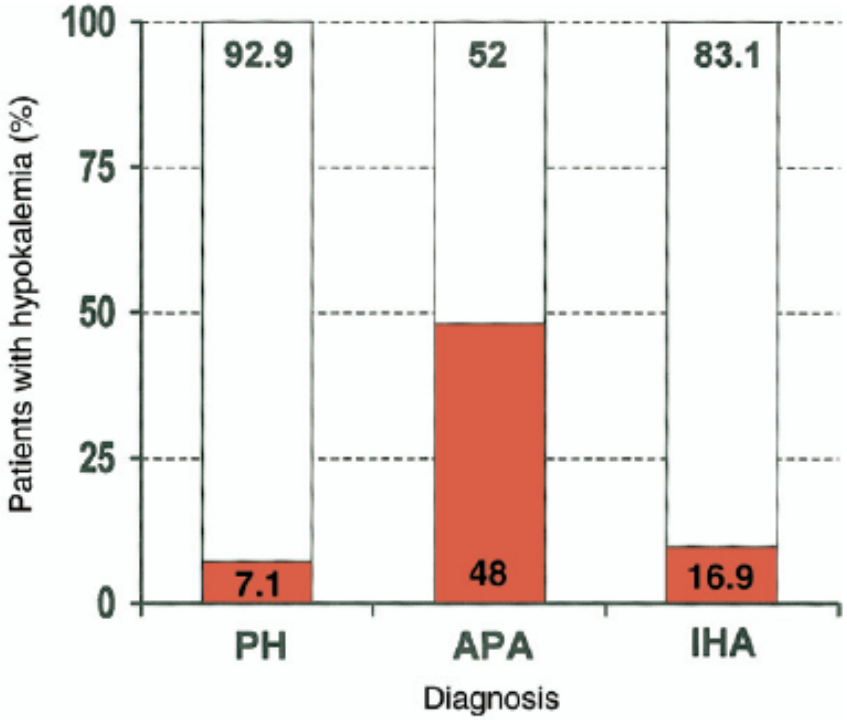
# Prevalence of Primary Aldosteronism in Subjects With Resistant Hypertension

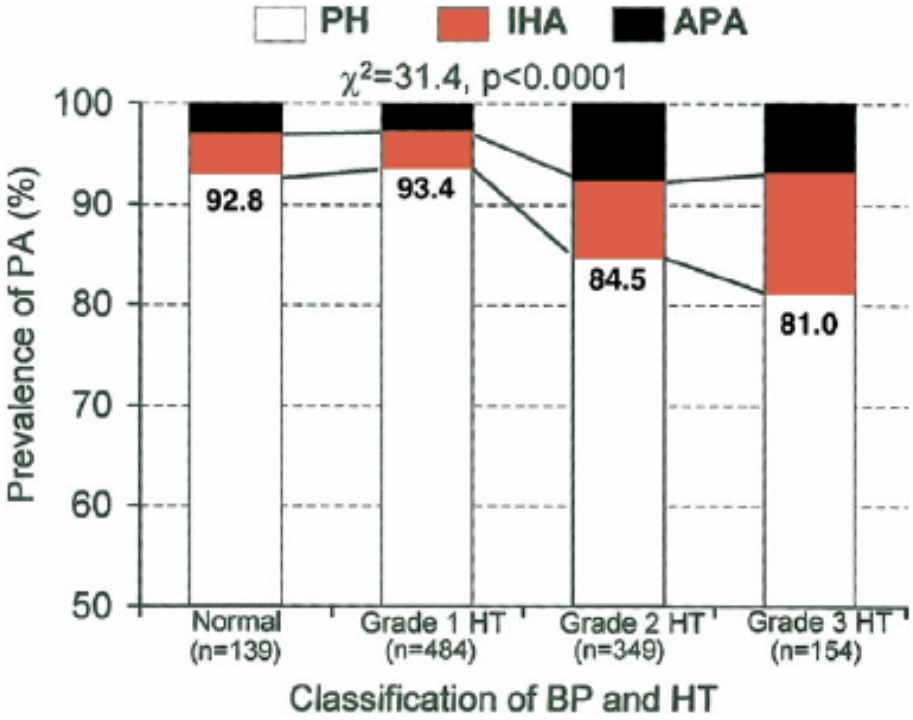



PA = Primary aldosteronism


1. Gallay BJ, et al. *Am J Kidney Dis*. 2001;37:699-705.
2. Calhoun DA, et al. *Hypertension*. 2002;40:892-896.
3. Eide IK, et al. *J Hypertens*. 2004;22:2217-2226.
4. Strauch B, et al. *J Hum Hypertens*. 2003;17

# PAPY Study

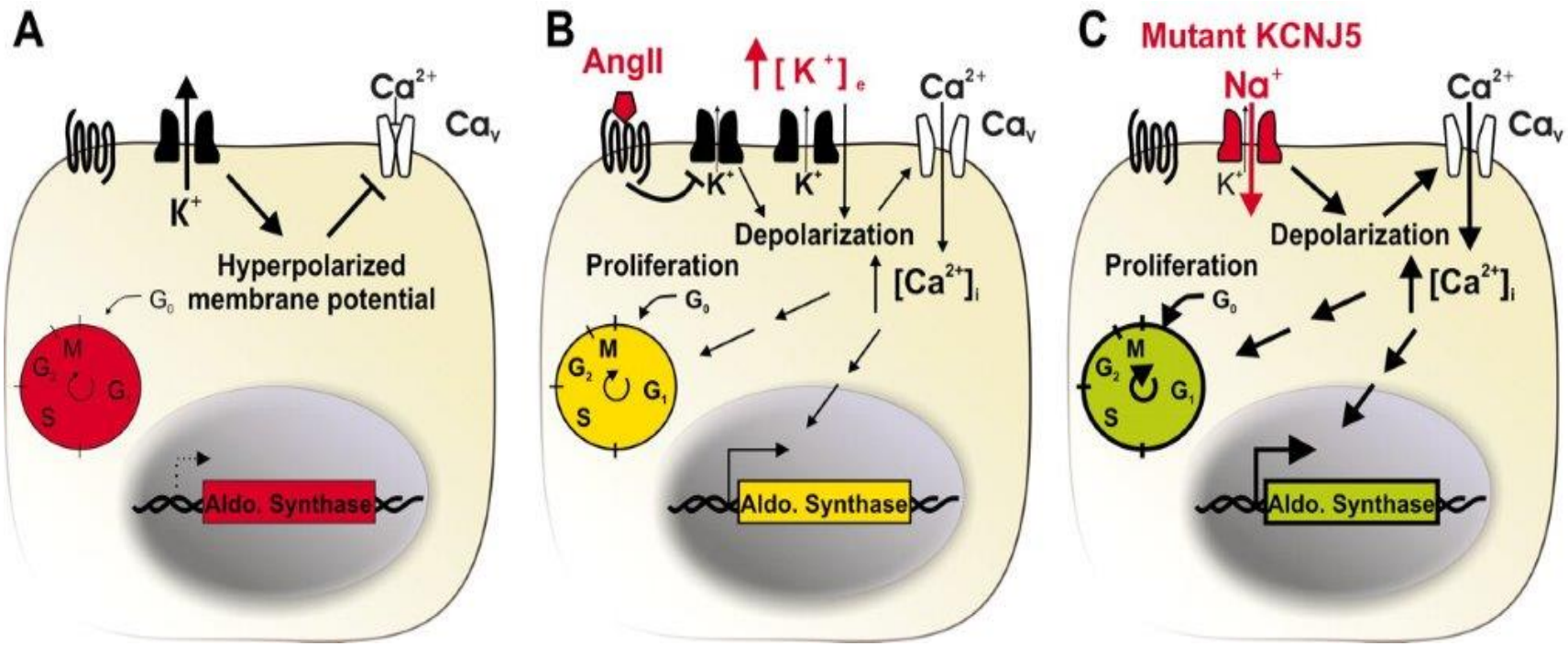



**Rossi JACC 2006;48:2293-2300**

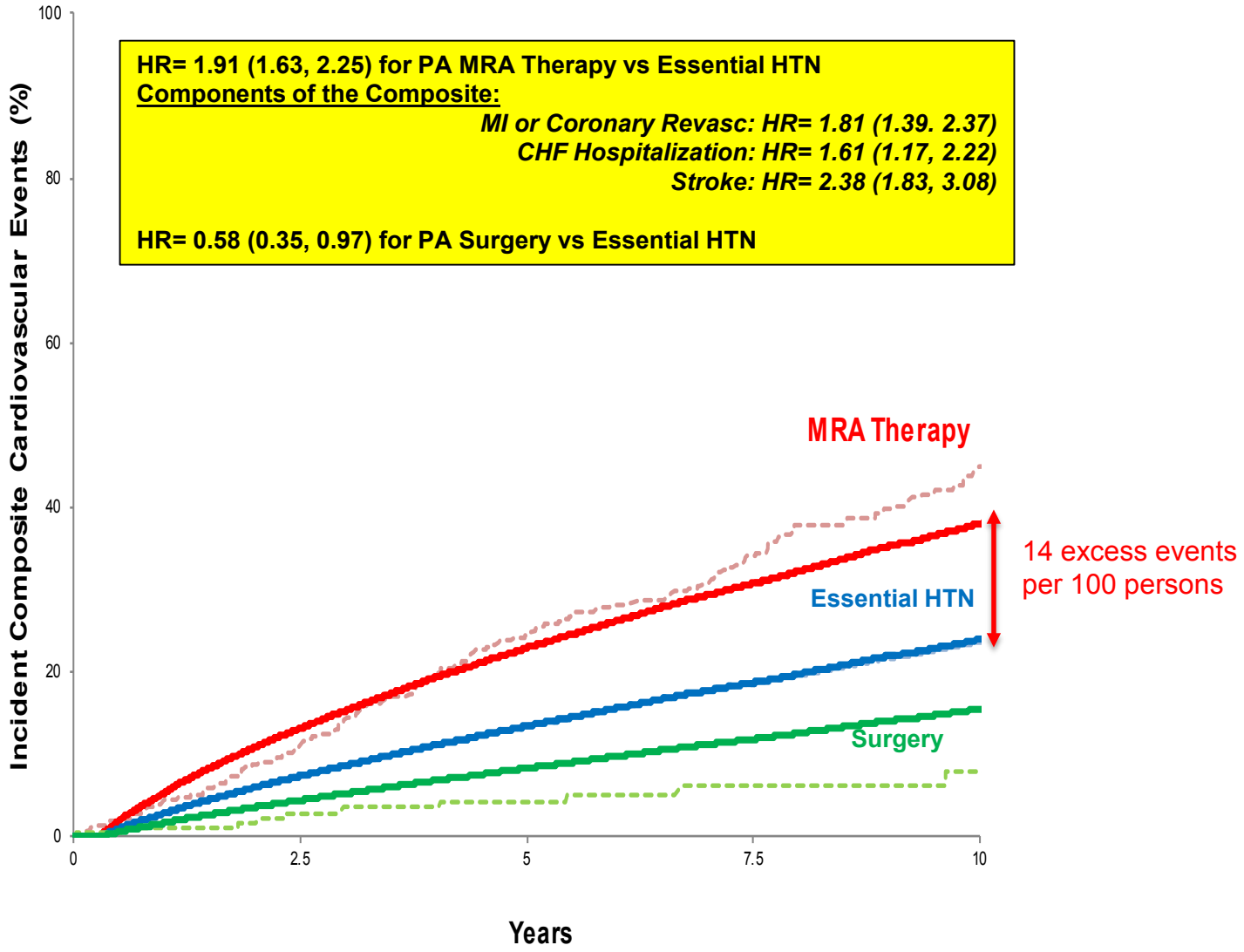
**The Management of Primary Aldosteronism: Case Detection, Diagnosis and Treatment: Endocrine Society Practice Guidelines. Funder JW, et al. J Clin Endocrinol Metab. 2016**

# Mutation in Potassium Channel KCNJ5



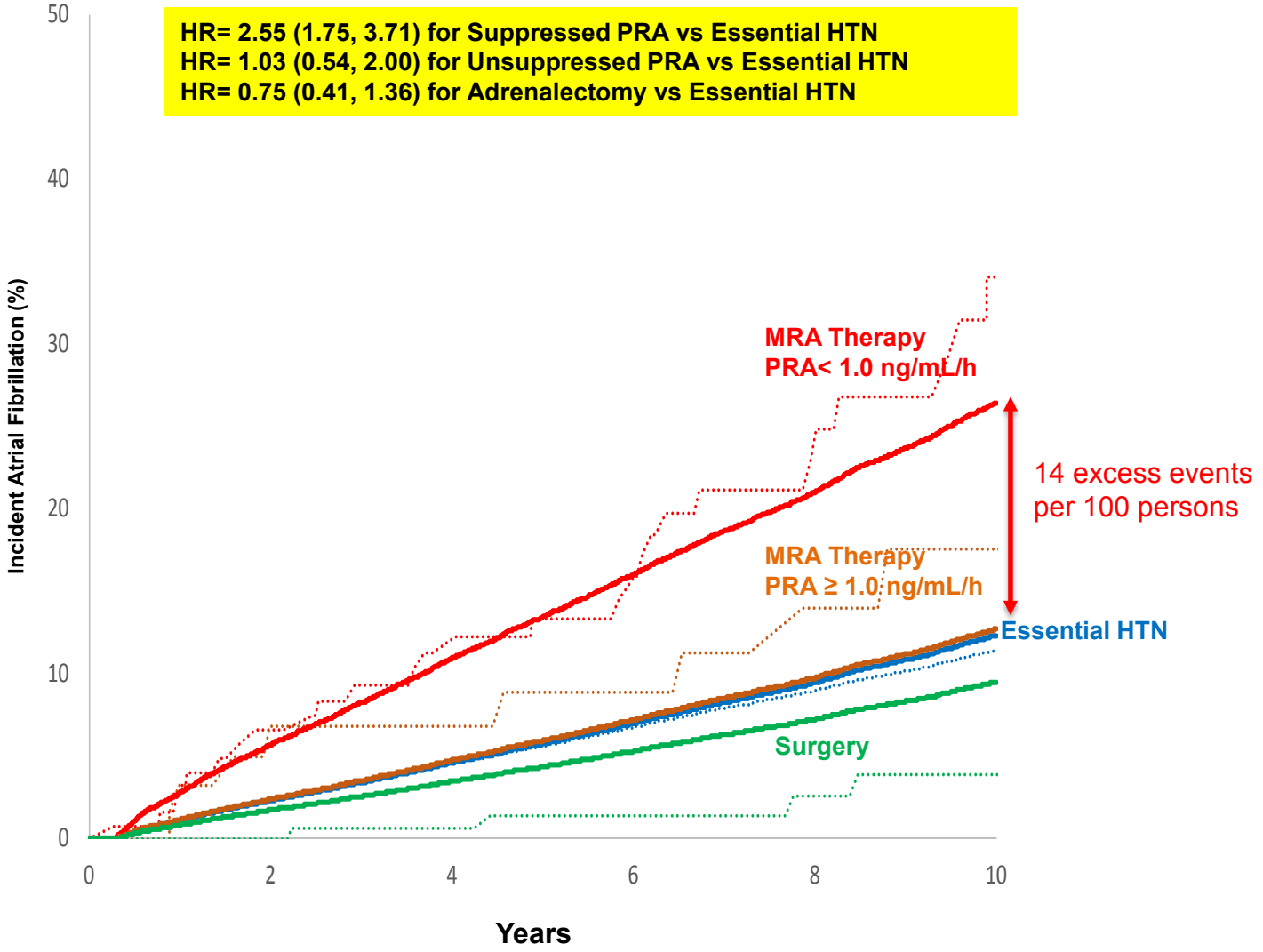

Proposed mechanism underlying aldosterone-producing adenoma and Mendelian aldosteronism. (**A**) Adrenal glomerulosa cells have a high resting $K^+$ conductance, which produces a highly negative membrane potential (*2*). (**B**) Membrane depolarization by either **elevation of extracellular $K^+$ or closure of $K^+$ channels by angiotensin II activates voltage-gated $Ca^{2+}$ channels**, increasing intracellular $Ca^{2+}$ levels (*1*). This provides signals for increased expression of enzymes required for aldosterone biosynthesis, such as aldosterone synthase, and for increased cell proliferation. (**C**) Channels containing KCNJ5 with G151R, T158A, or L168R mutations conduct $Na^+$, resulting in $Na^+$ entry, chronic depolarization, constitutive aldosterone production, and cell proliferation.

# Risk for Incident Composite Cardiovascular



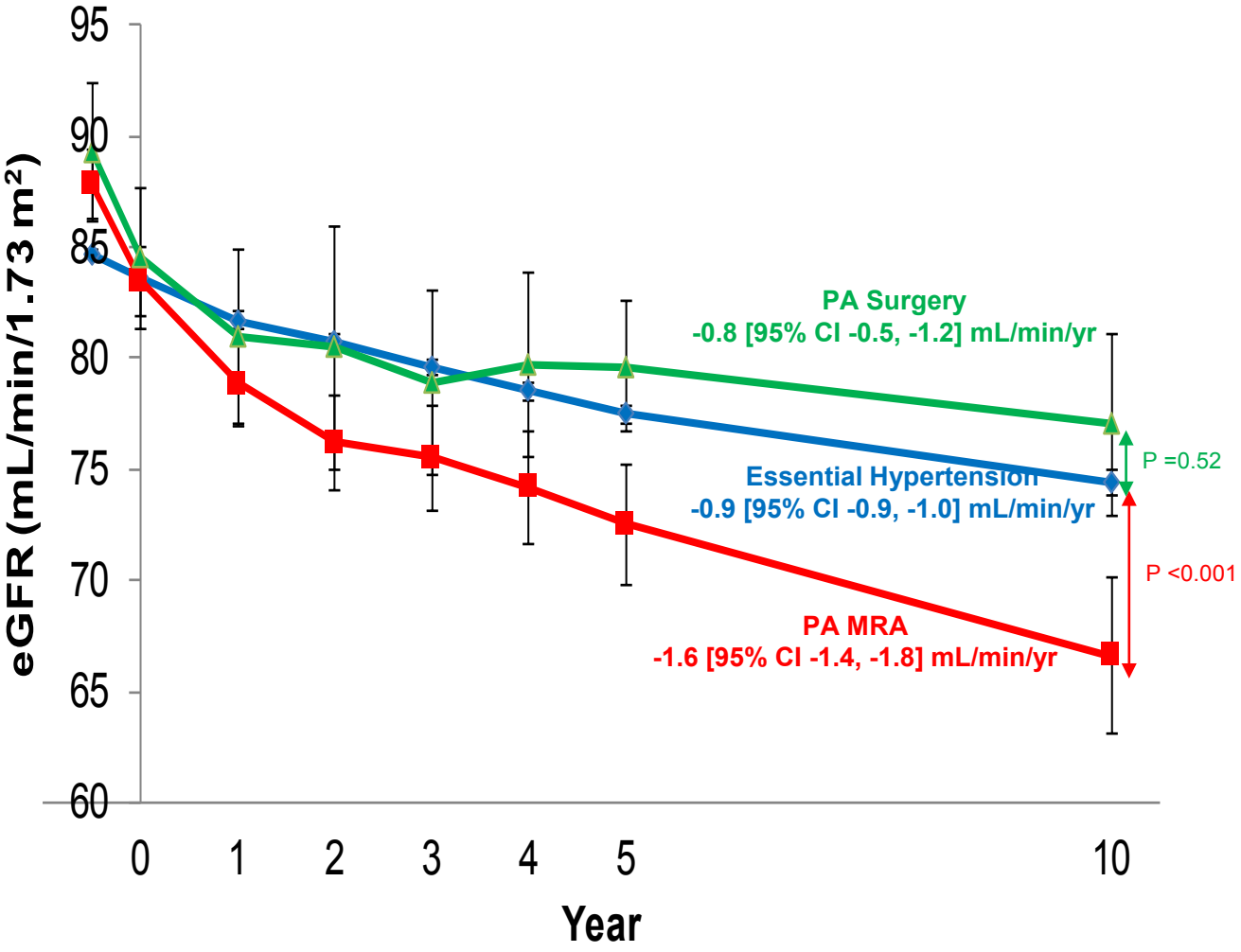

Hundemer et al, The Lancet D&E 2018

# Risk for Incident Atrial Fibrillation




Hundemer et al, *JAMA Cardiology* 2018

# Longitudinal eGFR Decline



# Why is Primary Aldosteronism important:

- Higher prevalence than previously thought
- PA patients have higher CV morbidity and mortality than age and sex matched patients with essential hypertension and the same degree of BP elevation
- **Treatment of PA with either MRA or unilateral adrenalectomy:**

- *resolves hypokalemia*
- *lowers BP*
- *reduces number of BP meds*
- *improves parameters of impaired cardiac and renal function*

Milliez P et al. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol. 2005;45:1243–1248.
Stowasser M et al. Evidence for abnormal left ventricular structure and unction in normotensive individuals with familial hyperaldosteronism type I. JCEM. 2005;90:5070–5076.

# Hyperthyroidism

- Hyperthyroidism increases SBP by decreasing SVR, increasing HR and CO
- Hyperthyroidism associated with atrial arrhythmias (especially AFib), pulmonary hypertension, LVH and heart failure
- Prevalence of HTN is greater among hyperthyroid patients than euthyroid patients
- Treatment of hyperthyroidism improves BP

# Hyperthyroidism

- Treatment of hyperthyroidism usually involves RAI, antithyroid drugs and beta-blockers (propranolol 120-160 mg per day or atenolol 50 mg per day)
- Treatment of hyperthyroidism is associated with a reduction in SBP, HR and CO
- If severe hyperthyroidism/thyroid storm – need intensive CV monitoring

# Hypothyroidism

- Hypothyroidism is associated with increases in NE and aldosterone with predominantly increase in DBP and decreased pulse pressure
- DBP may vary directly with serum TSH levels
- 20-40% of hypothyroid patients have hypertension, even though CO is reduced
- Usually have low renin hypertension and are salt sensitive
- Hypothyroidism is thought to have only a minor contribution to hypertension overall

# Hyperparathyroidism

- Primary hyperparathyroidism (PHPT) is associated with CVD, HTN, arrhythmias, LVH, diastolic dysfunction and vascular calcifications
- HTN is common in PHPT, even with mild disease
- Cause of HTN is unclear as BP does not improve with cure of PHPT except with MEN1/2
- Recent studies have shown inappropriately high aldosterone levels may partially explain the high prevalence of HTN in PHPT
- Increased arterial stiffness has been demonstrated with PHPT and the increase in arterial vessel stiffness may be related to the severity of hyperparathyroidism

# Hyperparathyroidism

- Single meta-analysis in PHPT - + effect of parathyroidectomy on LVMI, highest pre-op PTH levels were associated with the greatest improvements in LVMI
- Normocalcemic PHPT - CV risk factors are almost similar compared to hypercalcemic PHPT - strengthening the role of PTH in the cardiovascular involvement

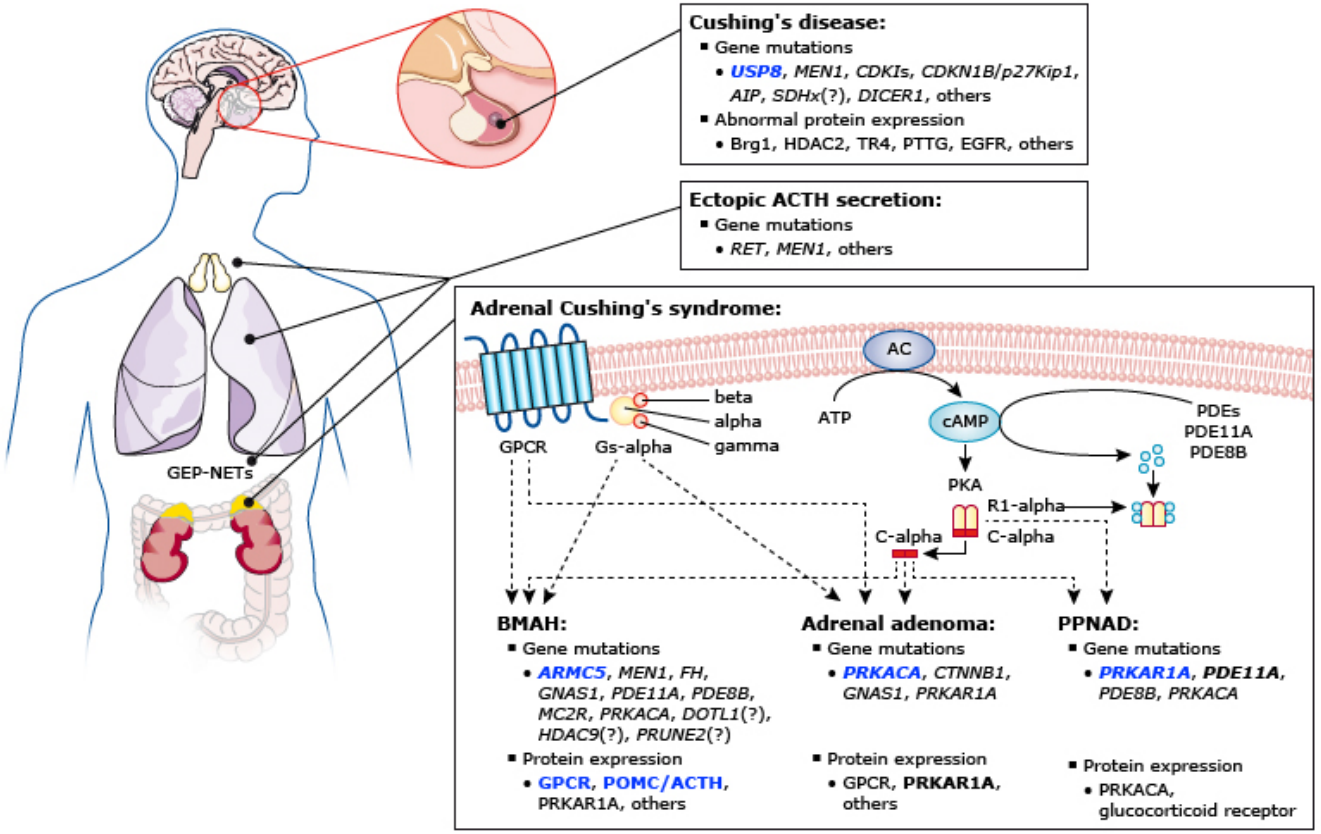
# Cushings

The pathogenesis of hypertension in Cushing's syndrome is multifactorial and not well understood

There appears to be:

- Increased peripheral vascular sensitivity to adrenergic agonists
- Increased hepatic production of angiotensinogen
- Activation of MRA receptors by cortisol (in patients with severe hypercortisolism - usually due to ectopic ACTH secretion)
- It is also possible that cortisol has a direct cardiotoxic effect

## Summary of genetic and molecular mechanisms implicated in Cushing's syndrome




For each cause, the various genetic mutations or abnormal protein expression believed to play a part in the pathophysiology are shown. The most frequent mechanisms are highlighted in blue characters; the well-characterized mechanisms are highlighted in bold characters, and other potential mechanisms are in normal characters; a question marks shows an unconfirmed association or genetic predisposition.

ACTH: corticotropin; AC: adenylate cyclase; GPCR: G-protein-coupled receptor; Gs-alpha: alpha subunit of Gs; ATP: adenosine triphosphate; cAMP: cyclic adenosine monophosphate; PDEs: phosphodiesterases; GEP-NETs: gastroenteropancreatic neuroendocrine tumors; PKA: protein kinase; R1-alpha: type 1-alpha regulatory subunit of PKA; C-alpha: catalytic subunit of PKA; BMAH: bilateral macronodular adrenal hyperplasia; PPNAD: primary pigmented nodular adrenocortical disease.

*From: Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. Lancet 2015; 386:913. Illustration used with the permission of Elsevier Inc. All rights reserved.*

# Cushings

- Treatment of hypertension does not differ from that of patients with primary hypertension
- Use of mineralocorticoid inhibitors (spironolactone) are effective in pts with high serum cortisol concentrations, especially with hypoK
- BP improves and may normalize with treatment of Cushings

# Cushings due ectopic ACTH

- Severe hypertension and hypokalemia are more prevalent in patients with ectopic ACTH
- High serum cortisol concentrations overwhelm the ability of the kidneys to convert cortisol to cortisone, resulting in activation of mineralocorticoid receptors
- Hypokalemia may also result from adrenal hypersecretion of mineralocorticoids, such as deoxycorticosterone and corticosterone
- The diagnosis of ectopic ACTH is characterized by markedly increased 24-hour urinary free cortisol excretion and elevated serum ACTH

## Frequency of causes of Cushing's syndrome

| Diagnosis | Percent of patients |
|---|---|
| **ACTH-dependent Cushing's syndrome** | |
| Cushing's disease | 68 |
| Ectopic ACTH syndrome | 12 |
| Ectopic CRH syndrome | <<1 |
| **ACTH-independent Cushing's syndrome** | |
| Adrenal adenoma | 10 |
| Adrenal carcinoma | 8 |
| Micronodular hyperplasia | <1 |
| Macronodular hyperplasia | <1 |
| **Pseudo-Cushing's syndrome** | |
| Major depressive disorder | 1 |
| Alcoholism | <<1 |

Relative prevalence of various causes of Cushing's syndrome in 630 patients (146 consecutive patients seen at Vanderbilt University Medical Center before 1993 and published reports describing 484 patients). The prevalence of pseudo-Cushing's syndrome depends upon the individual clinician's threshold of clinical suspicion; in our experience, it is very rare. The relative prevalence of various causes of Cushing's syndrome among children and adolescents may differ somewhat from that of adults. The ectopic ACTH syndrome, for example, is less common in children.

ACTH: corticotropin; CRH: corticotropin-releasing hormone.

- Questions ?

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