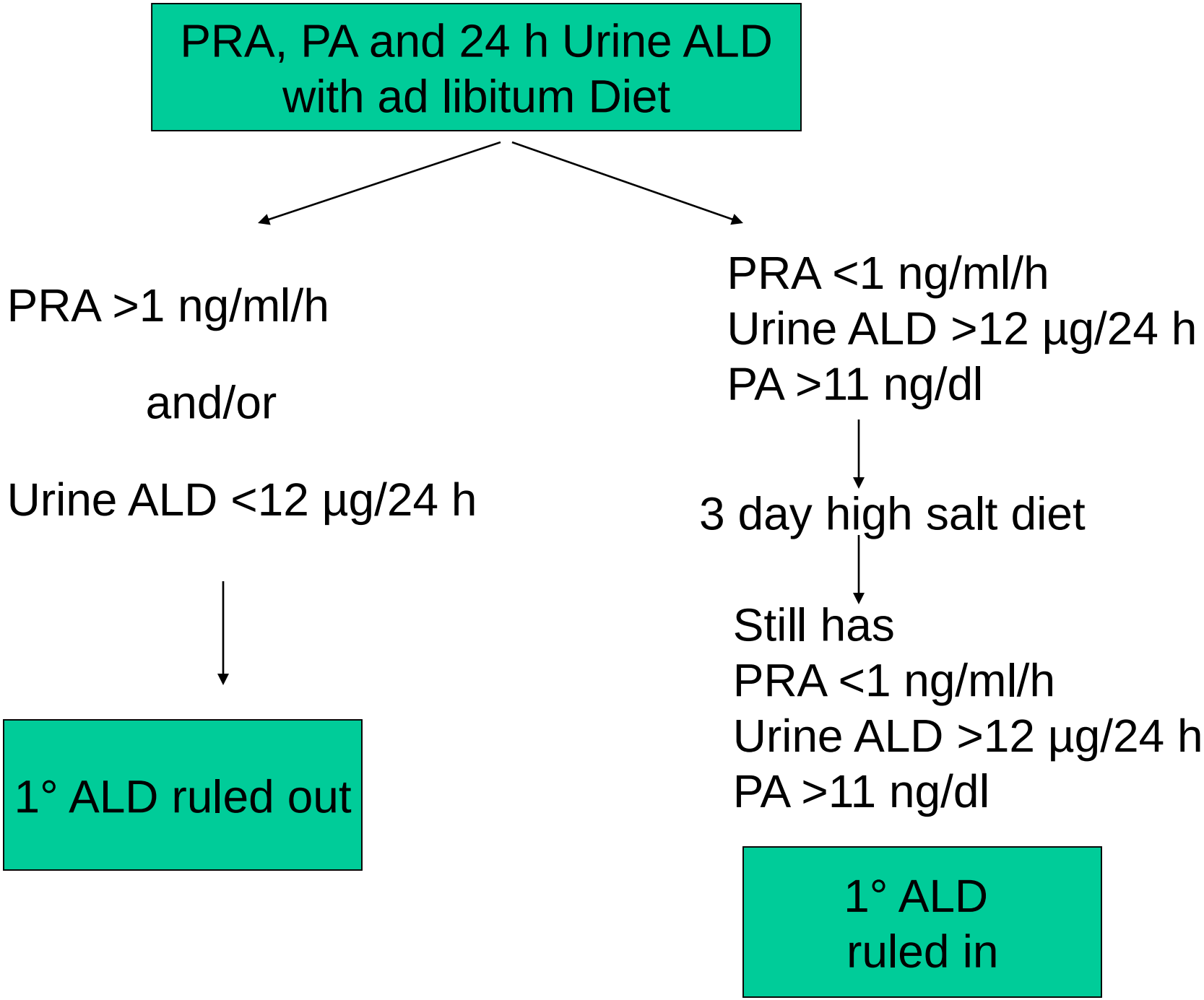
Hypertensive patients that taught me all I know

Friedrich C. Luft

#1

37 year-old woman with fairly severe hypertension

- Family history, negative
- Receives HCTZ, Amlodipine, & Valsartan
- Physical exam including fundi unremarkable
- Urine status +1 Protein
- Na 142, K 3.5, Cl 102, HCO_3 27 (mmol/l), $PaCO_2$ 41 mm Hg, pH 7.42
- Creatinine 88 µmol/l
- What now?

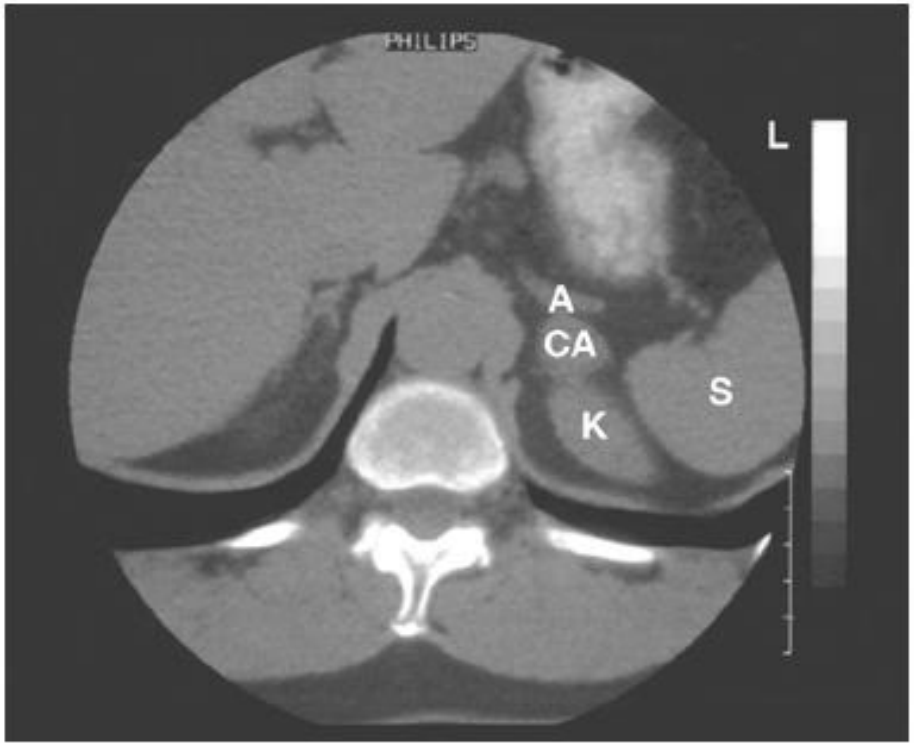

PRA, PA and 24 h Urine ALD with ad libitum Diet
PRA >1 ng/ml/h
and/or
Urine ALD <12 µg/24 h
1° ALD ruled out
PRA <1 ng/ml/h
Urine ALD >12 µg/24 h
PA >11 ng/dl
3 day high salt diet
Still has
PRA <1 ng/ml/h
Urine ALD >12 µg/24 h
PA >11 ng/dl
1° ALD ruled in

A/R ratio was 41.6

With new CT Scanner
Sensitivity >80 %

„Chemical shift“
MRI probably better

131-6-β-iodomethyl Nor-cholesterol (NP-59)
Scintigraphy available for adenomas <10 mm
Must take 7 days DEX



Benign Tumors are hypodense

HU <10
(Air: -1000,
Fat: -100
Water 0,
Bone +1000
Contrast +300)
Godfrey Hounsfield

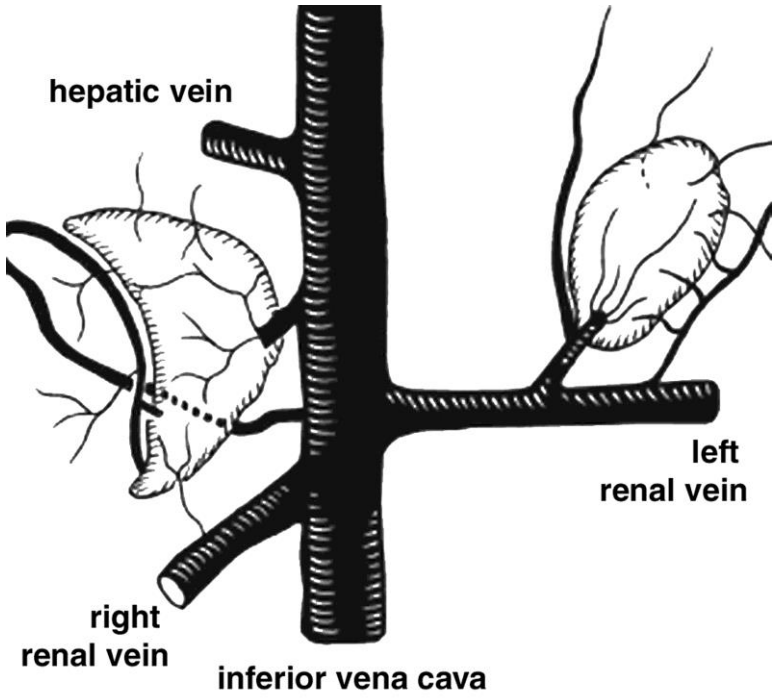
S=spleen, K=kidney, CA=Conns Adenoma, A=adrenal

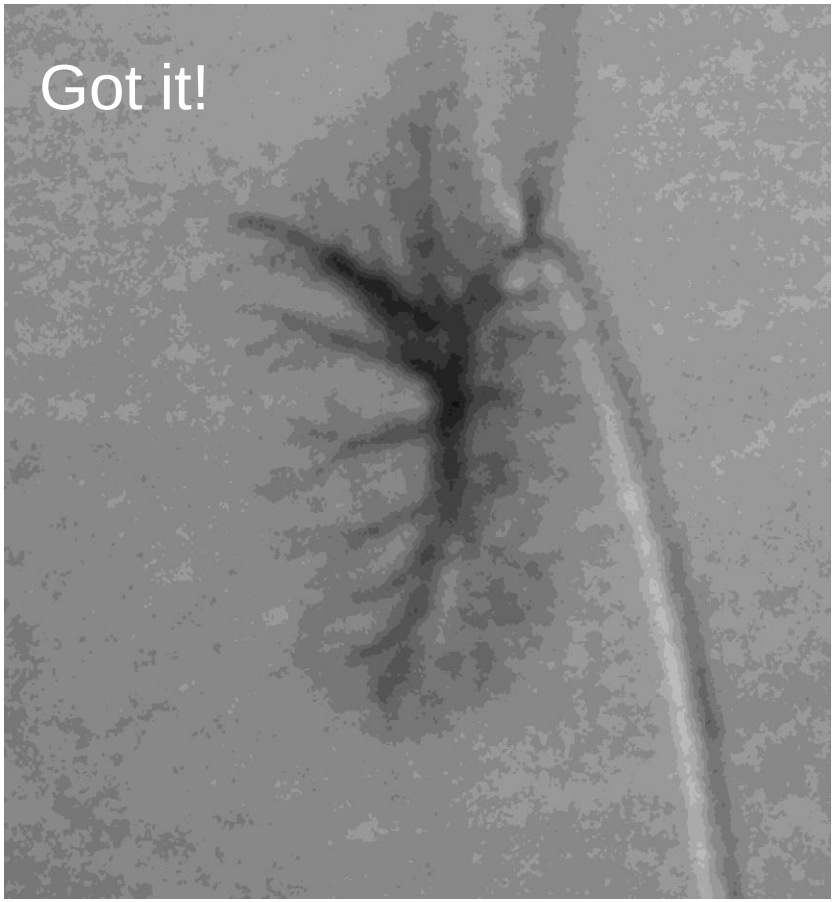
Adrenal vein sampling (AVS)

- Separate adenoma from hyperplasia
- ACTH infusion should be done concomitantly to AVS
- Cortisol in AVS and peripheral blood
- Bilateral samples about 50% successful
- But, Dr. S. Ito reported 95% success rate at this meeting last year (Radiology 2016)

Harvey et al. Surgery 2006

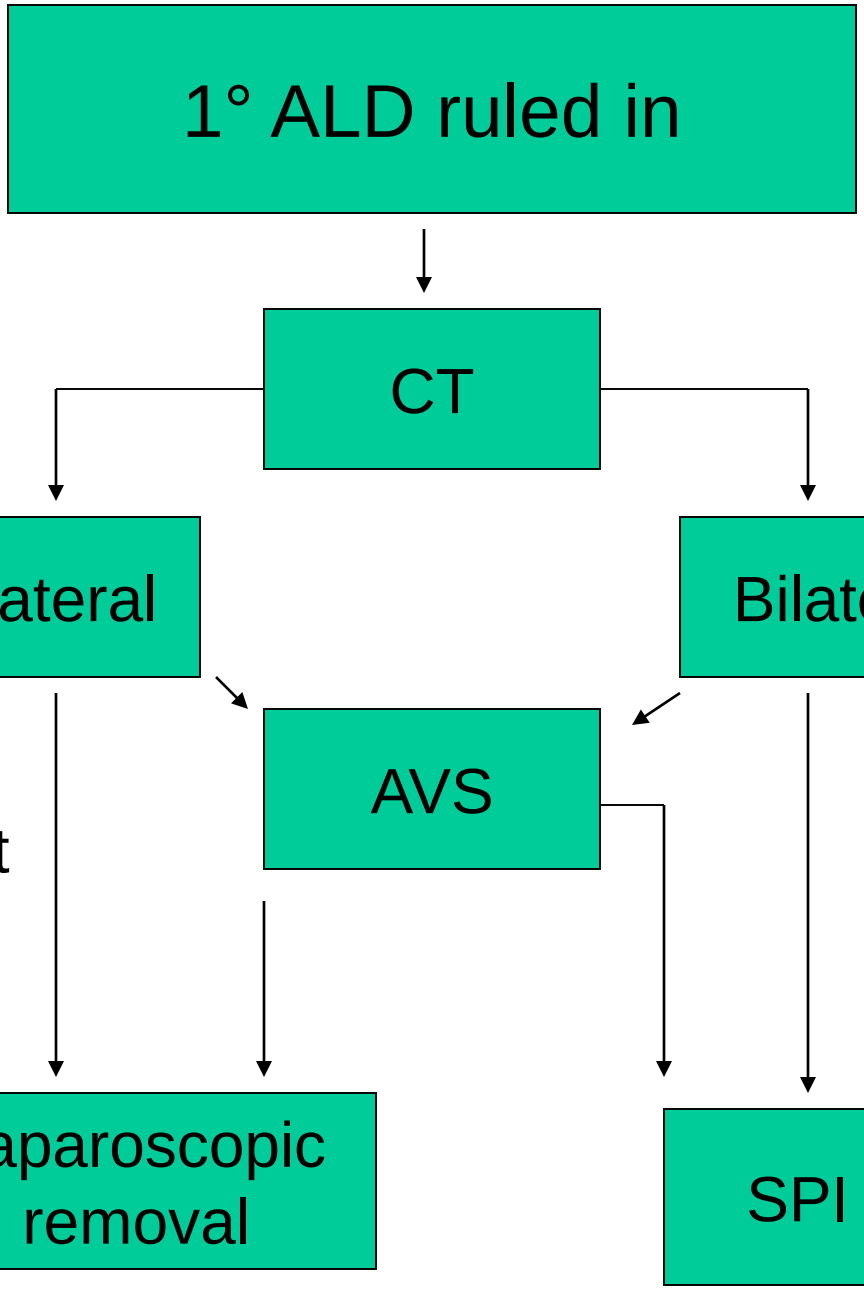
Why is AVS difficult? Left side empties into renal vein. The right empties into vena cava at acute angle





Daunt N. Radiographics 2005

(Queensland Australia)



AVS not necessary
<40 years old
<10 HU
(Air -1000,
Water about 0,
Bone +1000,
Contrast +300)

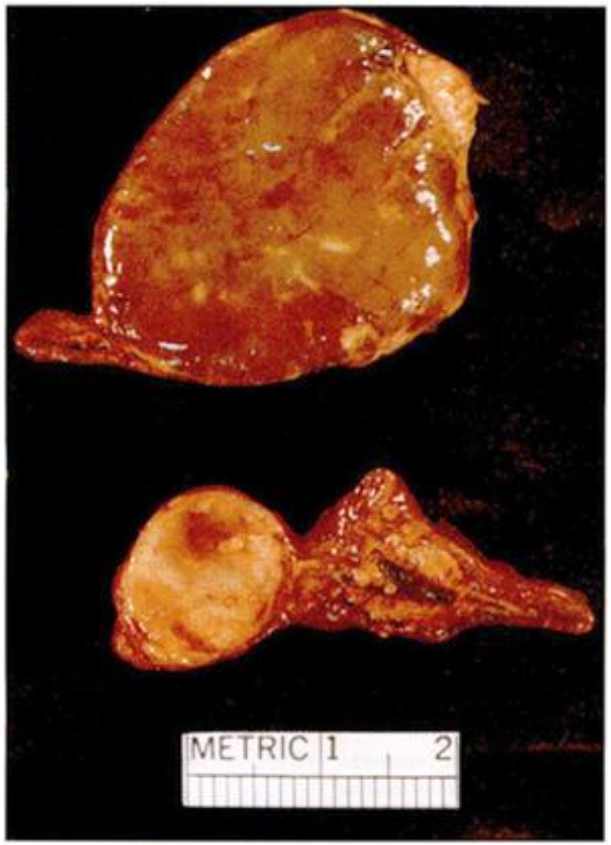
But, others are better and report even segmental success.

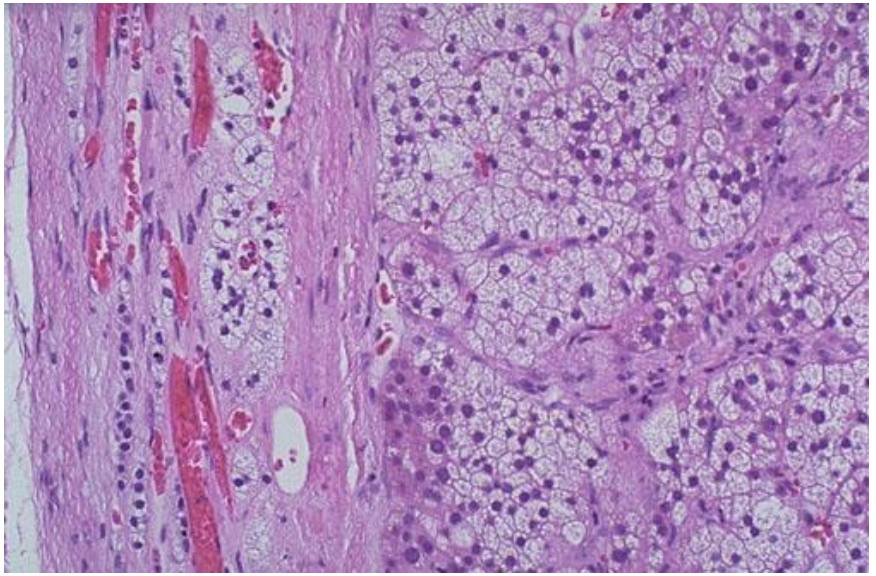
AVS not necessary in patients not wanting surgery

Mattsson and Young. Nat Clin Pract 2005
Santani et al. Radiology 2016

Ald 25 ng/dl; PRA 0.6 ng/ml/h; after salt diet, Urine Ald 19 µg/24 h;

Yellow fatty tumor





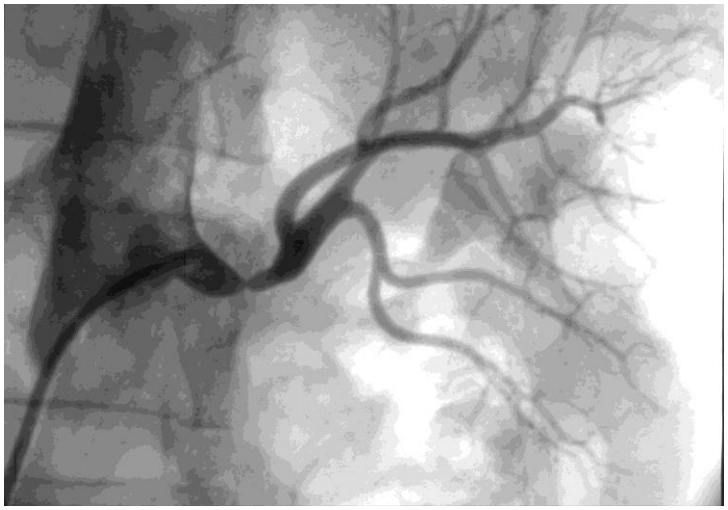
Gain-of-function mutations in the inward rectifier potassium channel KCNJ5 (Kir3.4) is present in ≈40% of APAs. Also CACNA1D, ATP1A1, and ATP2B3

#2

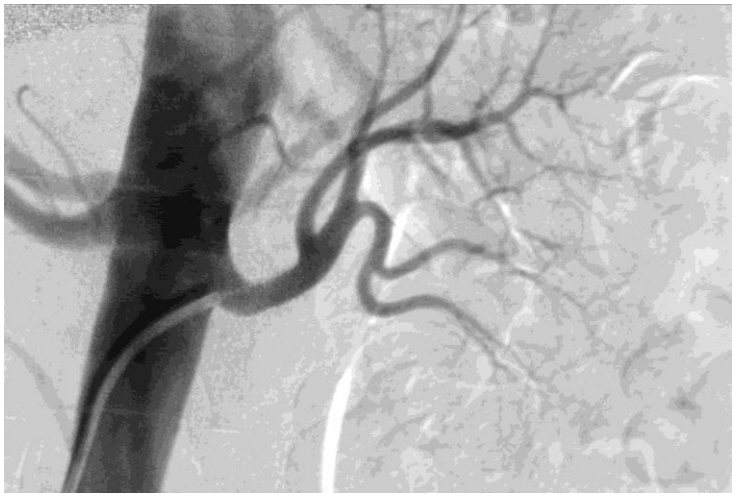
55 year-old woman, heavy smoker

- Resistant hypertension >10 years
- Family history, smoking and cardiovascular disease
- Physical examination Keith and Wagner Gr II eye grounds
- Duplex: renal arteray stenosis left
- Resistive Index (after Jörg Radermacher) <0.8

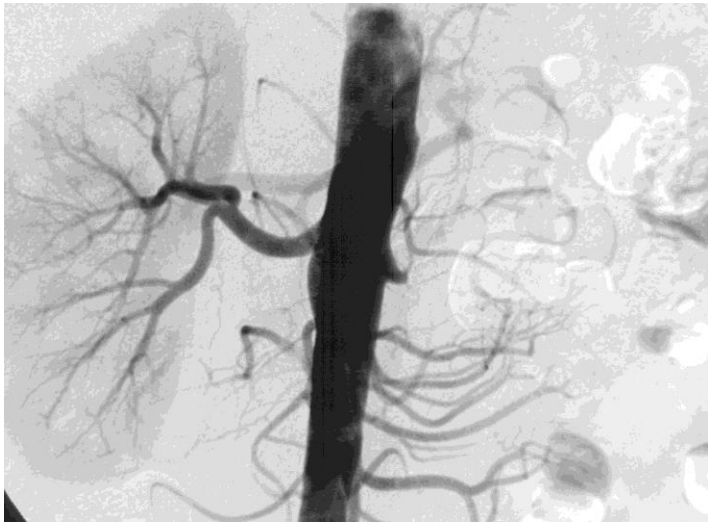
Selective angiography left



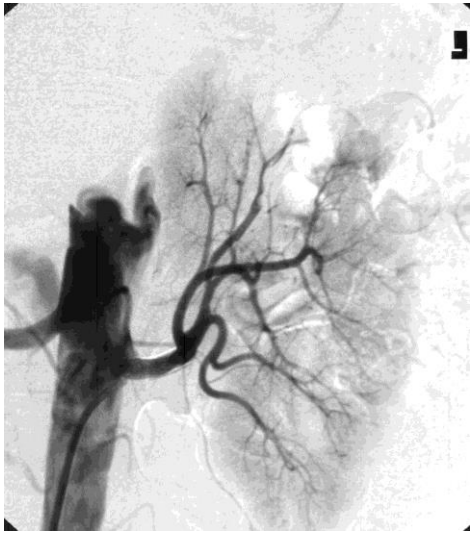
Stent placed without incident
(Gradient from 30 to 0 mm Hg)



Next morning, pain and Cr increase



Much effort and abciximab



We conclude:

„Shit happens“
The kidney was eventually lost

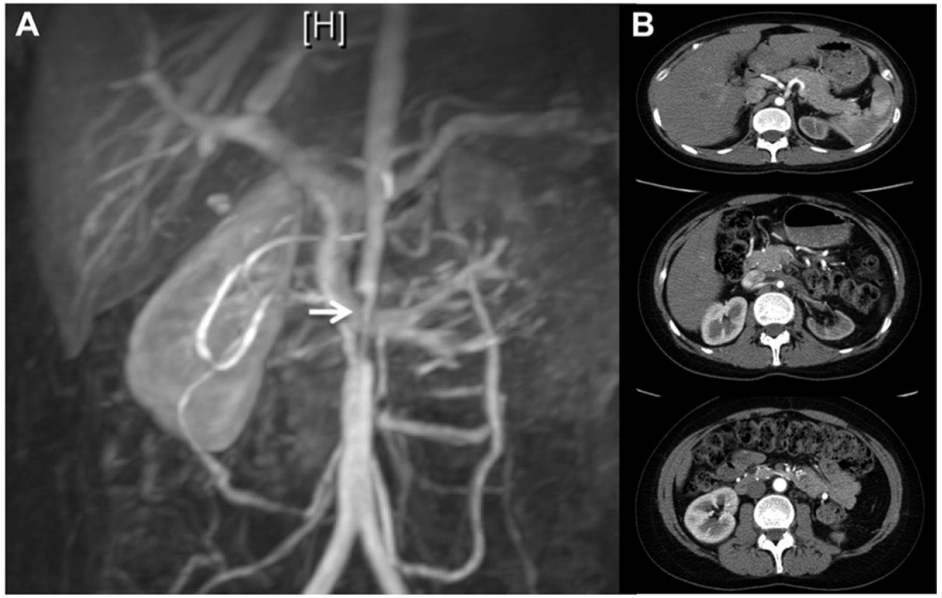
Luft FC, Gross CM. Heart. 2007.

Arteriosclerotic renal artery stenosis is common

- 5 % all US hypertensive patients
  - 4 000 000 cases in the US; even more in EU
- Autopsy prevalence is age-related
  - 5 % <64 years, 20 % 70 years, 40 % >75 years
- 10-40 % coronary artery stenosis patients
  - (J Am Soc Nephrol, Am J Cardiol, and others)
- 40 % of patients with peripheral vascular disease
  - (Ann Vasc Surg)
- CORAL and ASTRAL have decreased our zealousness to treat these patients

#3 21 year-old architecture student of Turkish ancestry. She presented with a subarachnoid hemorrhage that was „coiled“ and she was sent to us.

- BP 130/70 right, 130/60 left, 120/60 right, 120/70 left (legs) under 3-step medications
- Hb 11, CRP 0.3 (mg/dl) Electrolytes OK, Crea 1.2 mg/dl, PRA und ALD OK, Antibody panel negative.

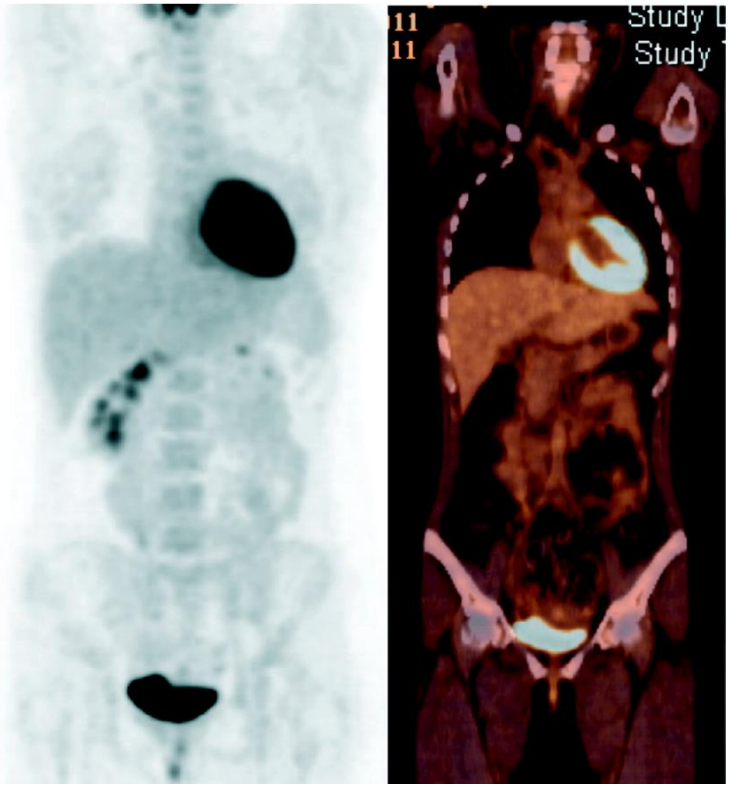


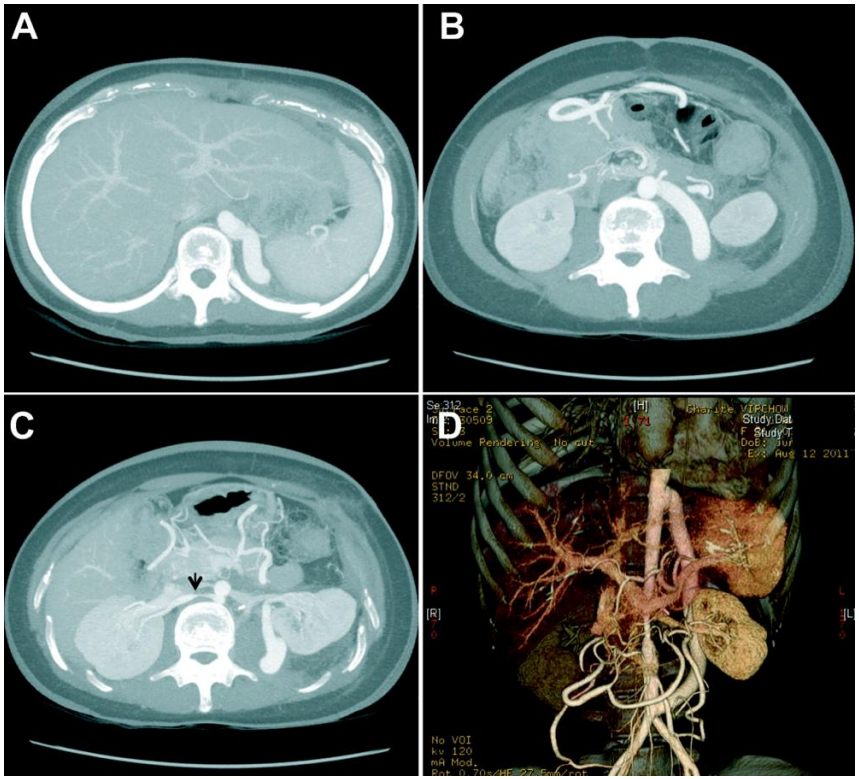
1. <40 years,
2. Bruit,
3. Focal stenosis in abdominal aorta
4. Left kidney shows up „late“

Surgeon friends: “Oh, no problem, we will bypass the stenosis and revascularize these kidneys

We got a bypass but the kidneys were not fixed (right lost).

Nucleotide uptake (left) and PET-CT (right) show no active inflammation.





Upper (A) and lower (B) anastomes between aorta and prosthesis. Right renal artery stenosis (arrow C). Between aorta und vessel prosthesis there is a renal artery stenosis with arrow (C). The prosthesis and “right kidney gone” are displayed (D).

Kettritz, Luft. Hypertension 2012

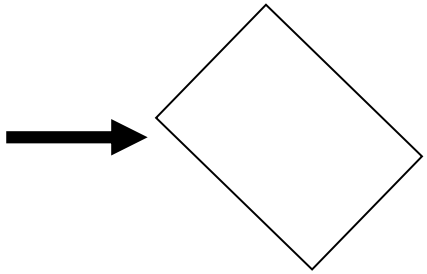
#4 52 year-old man because of paroxysmal headache, tachycardia, sweating episodes

- All this stuff is going on for about 5 years
- BP 140/90 but occasionally 212/114 mm Hg
- Numerous work-ups for pheochromocytoma were unrevealing
- MRI abdomen negative
- We put him on a tilt table and he passed out

Who needs pheochromocytoma „screening“

- Episodic „attacks“
- Resistant hypertensive persons (25!)
- Family history of these and others (MEN2, VHL, NF-I, SDH)
- Incidentaloma workup
- BP problems during anesthesia
- BP elevations in young persons
- BP elevations causing cardiomyopathy
- Pressure, Pain, Perspiration, Palpitation, Pallor
- 10 % Extra-adrenal, 10 % in children, 10 % multiple, 10 % recurrence, 10 % malignant, >10 % genetic, 10 % incidentaloma

^{123}I-Meta-iodobenzylguanidine (MIBG) Scinti, CT, MRI, CT head, neck, Somatostatin receptor Scinti, PET etc.



Birkenfeld et al.
Am J Med 2004

Cluster 1 mutations are involved with the pseudo hypoxic pathway. These mutations comprised of *PHD2, VHL, SDHx, IDH, HIF2A, MDH2* and fumarate hydratase (*FH)* mutated *PCC/PGL.* Cluster 2 mutations are associated with abnormal activation of kinase signaling pathways and included mutations of *RET, NF1, KIF1Bβ, MAX and TMEM127.* In addition, *VHL, SDHx* (cluster 1 genes) and *RET, NF1* (cluster 2 genes) germline mutations are involved in the neuronal precursor cell pathway in the pathogeneses of PCC/PGL. Also, *GDNF, H-ras, K-ras, GNAS, CDKN2A (p16), p53, BAP1, BRCA1&2, ATRX* and *KMT2D* mutations have roles in the development of PCC/PGLs.
Overall, known genetic mutations account for the pathogenesis of approximately 60% of PCC/PGLs.
(Pheochromocytoma-paraganglioma = PCC/PGL)

#5 The patient was a 51 year-old sculptor who had immigrated to Germany from the Czech republic. He came to the emergency department because of progressive dyspnea and chest discomfort over 3 days.

The patient had no stigmata of Cushing's syndrome; aside from the fact that he had psyciatric symtomatolgy that we missed completely.

BP 240/120 mm Hg; HRwas irregularly irregular at 120 bpm. We learned about difficult-to-treat hypertension, atrial fibillation, and coronaries that were „OK". He was cardioverted.

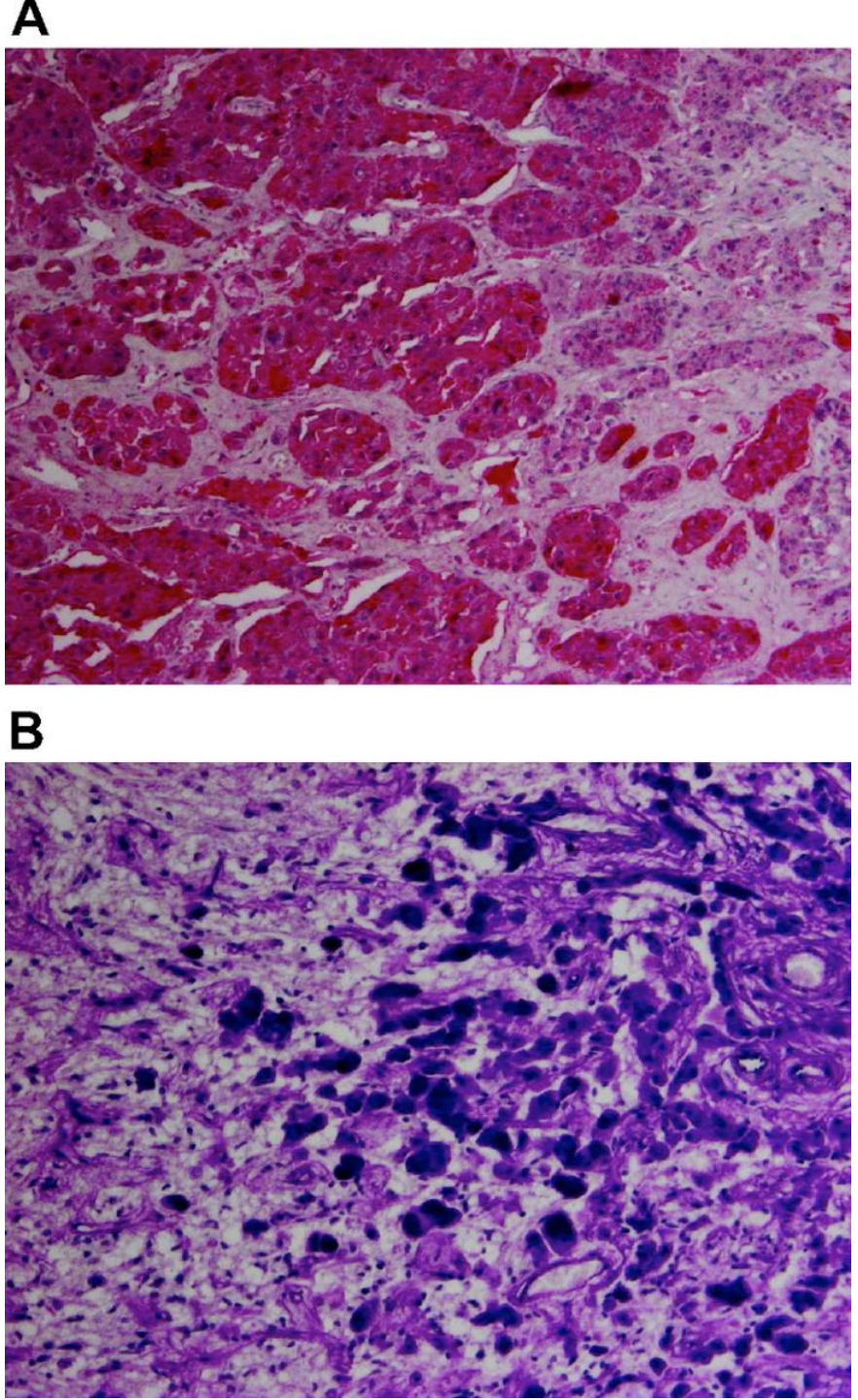
Na 142, K 2.7, Cl 99, HCO3 31 (mmol/L). pH 7.53, PaCO2 38 and PaO2 121 (mm Hg room air). Hb 16.7, HCT 51 vol%. TTKG 14.

PRA 26 ng/L, ALD 218 ng(L
ALD/R ratio 8.4, but ACTH was 22 (Normal 10 pmol/L)

Cortisol was 1750 (>500 nmol/L); urine 18.774 /<400 nmol/24 h).

We performed DEX suppression tests: After 2 mg Dex at bedtime, ACTH stayed at 36 pmol/L. After 8 h, the values were at 27.5 mmol/L.

We next planned inferior petrosal sinus ACTH sampling in conjunction with corticotropin releasing hormone (CRH) stimulation. We discussed the nature of, and reasons for, the test with the patient in detail, and written, informed consent was obtained. On the following morning of the planned procedure, the patient climbed out of his fourth floor hospital room window and leaped to the concrete below. He was killed instantly. The medical examiner's office was contacted after the patient's death was ascertained.



Gomori stain. A, ACTH immunohistochemistry staining of hyperplastic basophilic cells in adenohypophysis. B, Invasion of basophilic cells into the neurohypophysis. Periodic acid Schiff staining.

Cushing's disease – we missed it and the patient died. Singer et al. Hypertension 2008

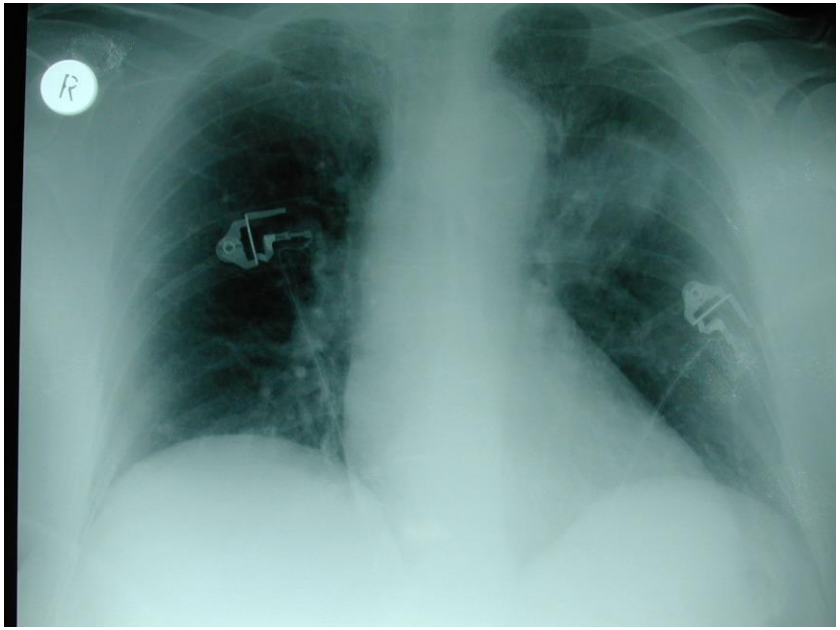
#6

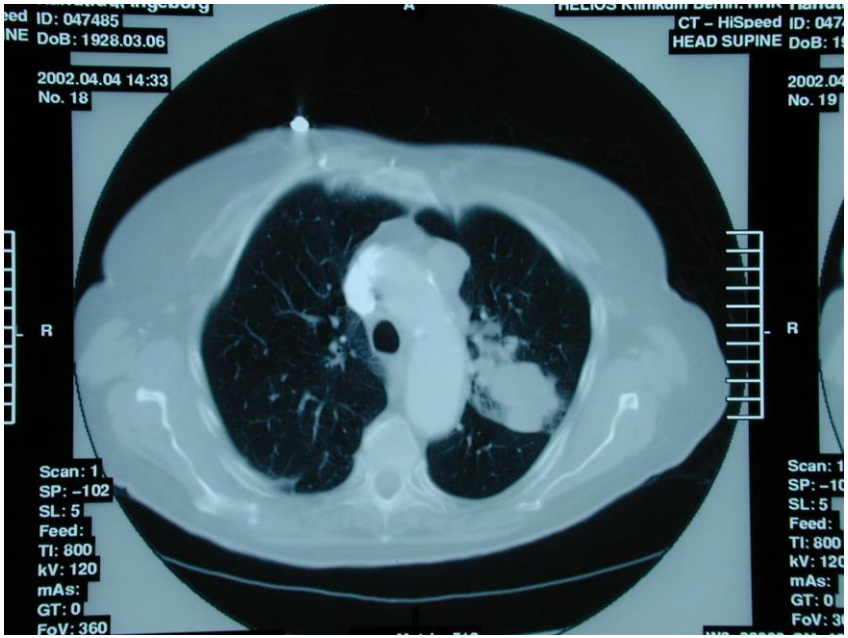
68 year-old woman with acute coronary syndrome; gets abciximab and LAD stent

- pH 7.52, $PaCO_2$ 43 mm Hg, PaO_2 82 mm Hg, Na 141, K 2.7, Cl 96, HCO_3 36 mmol/l
- Acid-base balance?
- UCl, UK, UNa, UOsm, TTKG?
- TTKG = (U/P K) ÷ (U/P Osm)
- UK was 36 mmol/l UOsm was 270
- TTKG was 14%. That means renal potassium loss

My ICU rounds next morning:

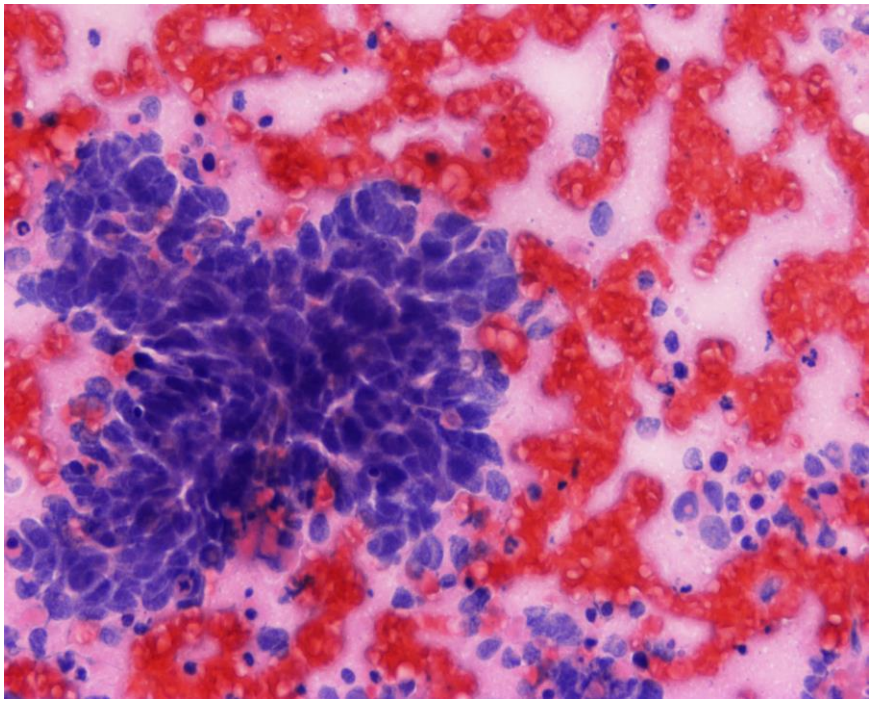
Chest xray and CT





Professional smoker, hypertension and HCTZ for 10 years, no Cushings stigmata

- PRA was low
- PA not elevated
- Cortisol 2000 nmol/l
- ACTH 90 pmol/l
- Dex no suppresion
- Biopsy was done



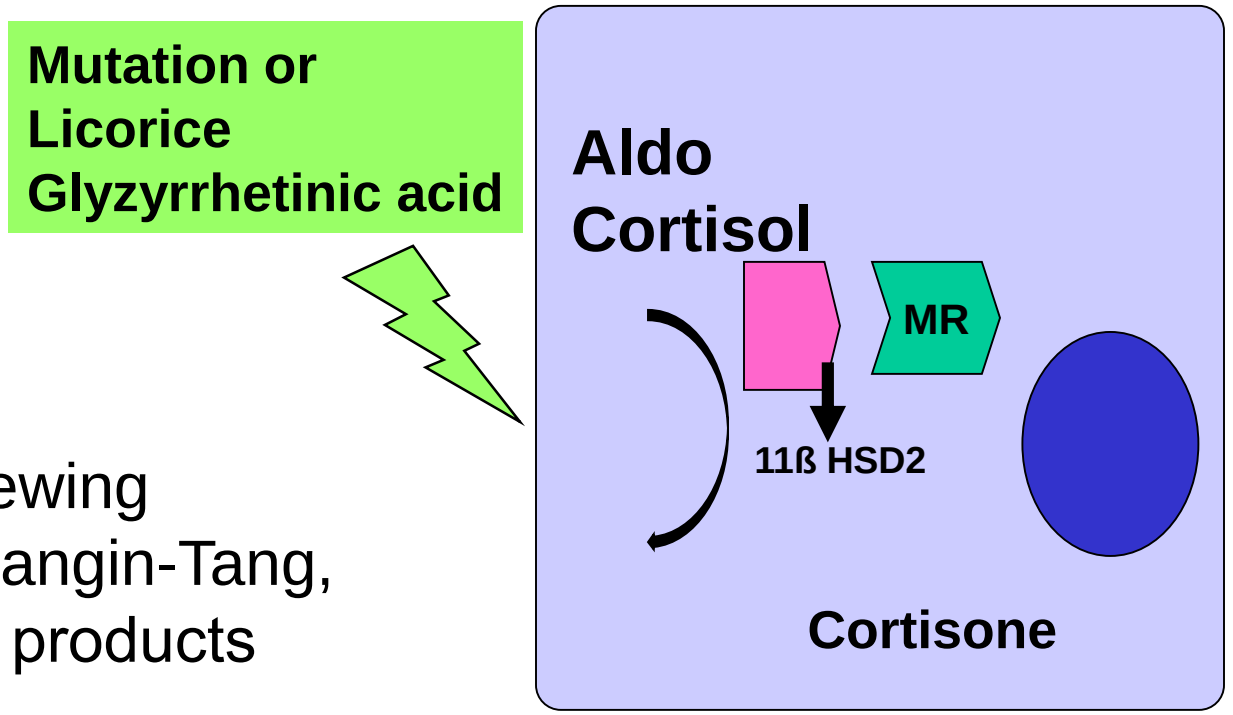
#7

38 year-old office worker; BP 250/110 mm Hg

- No family history of hypertension
- Physical examination normal
- Na 143, Cl 105, K 3,5, HCO_3 26 (mmol/l)
- PRA <1 ng/ml/h; PA low
- Triple combination did not help much
- We were all clueless
- So we sent her off to MRI

Found these in her night table

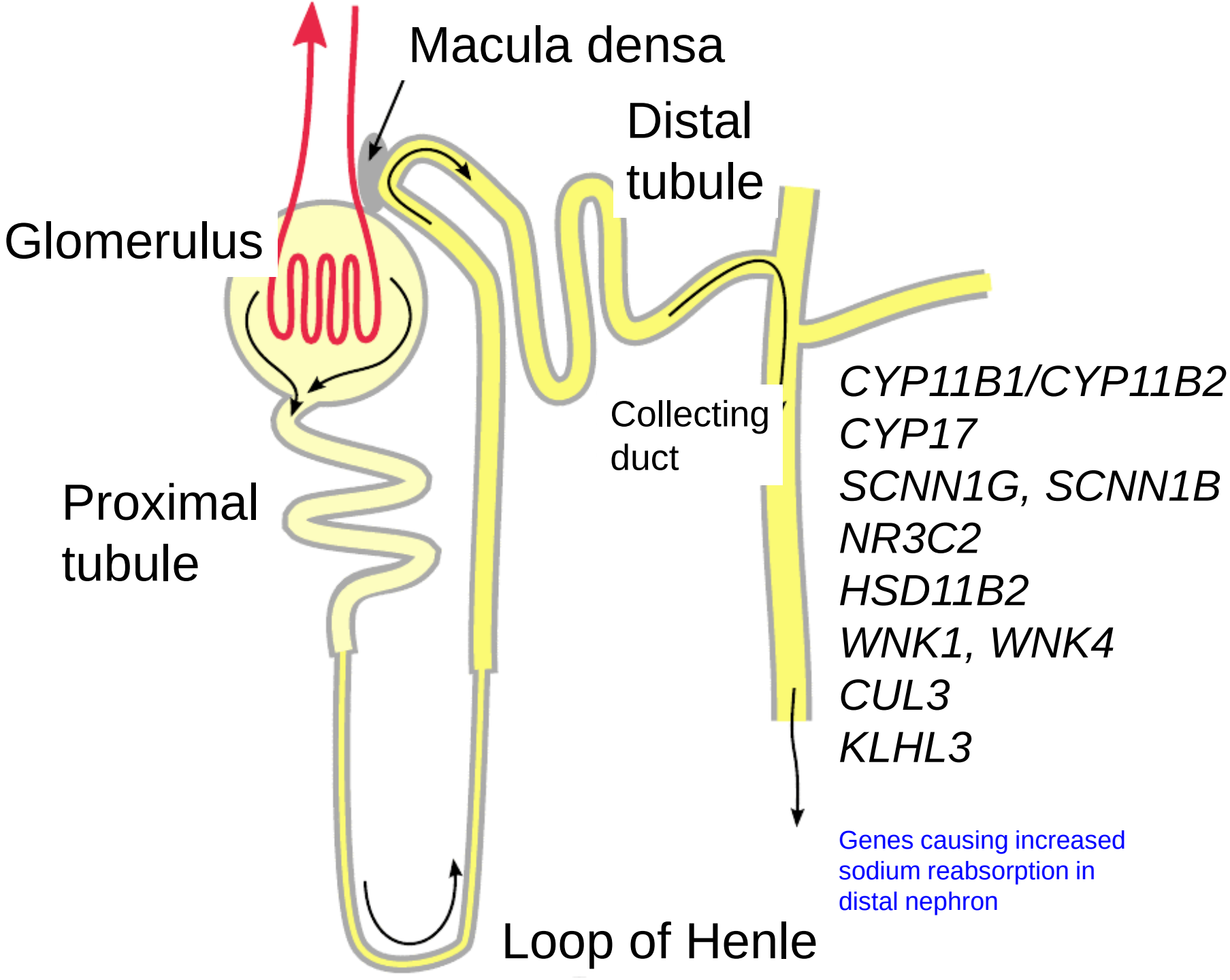
The 11-Beta hydroxysteroid dehydrogenase 2



Licorice, chewing tobacco, Huangin-Tang, other „herb“ products etc.

„Apparent mineralo-corticoid excess“

Woywodt et al. Postgrad Med J 2000

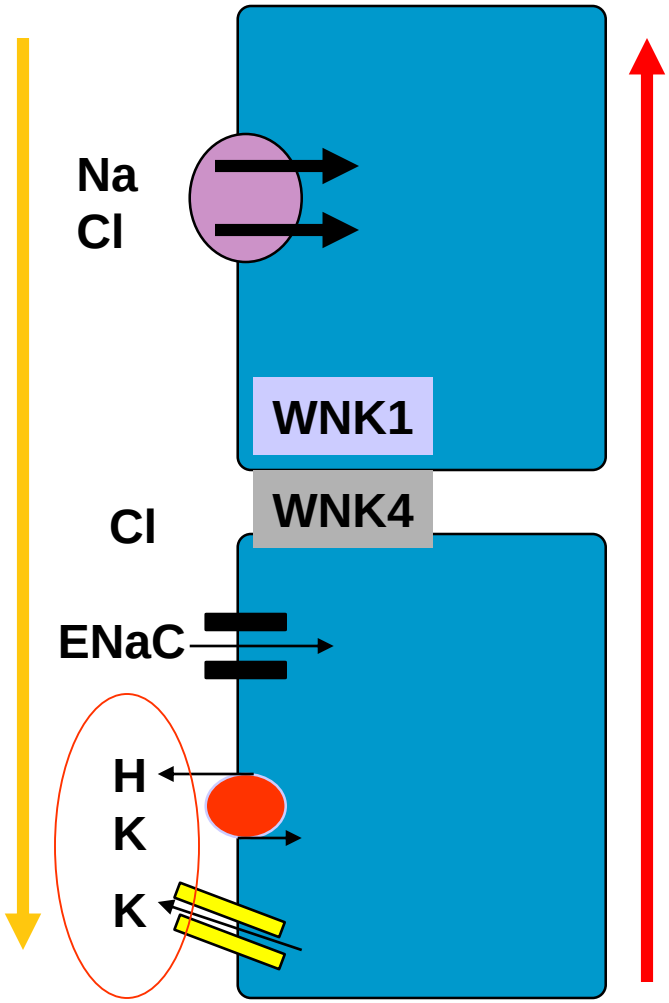

Macula densa
Distal tubule
Glomerulus
Collecting duct
Proximal tubule
CYP11B1/CYP11B2
CYP17
SCNN1G, SCNN1B
NR3C2
HSD11B2
WNK1, WNK4
CUL3
KLHL3
Genes causing increased sodium reabsorption in distal nephron
Loop of Henle

#8

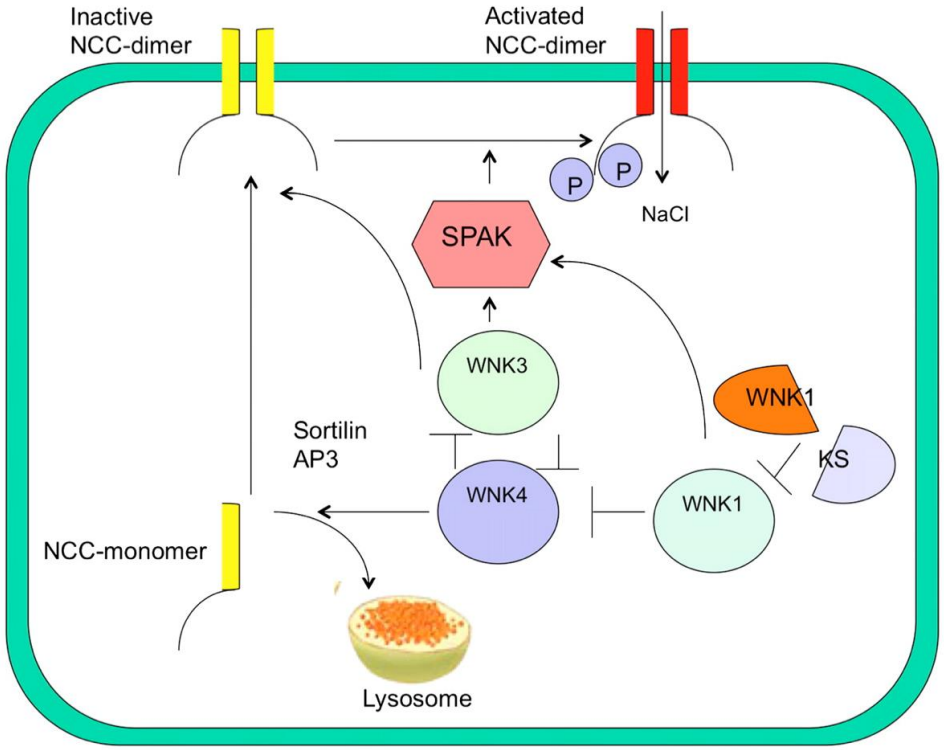
24 year-old woman with hypertension visits Berlin and faints. She is from a large family and half are hypertensive.

- pH 7.41, $PaCO_2$ 35, PaO_2 100 (mm Hg), Na 140, K 6.3, Cl 109 HCO_3 21 (mmol/l)
- Crea 80 µmol/l, UpH 5.3, UNa 53, UK 24, UOsm 450
- TTKG 3.6 (inappropriately low!)
- PRA <1 ng/ml/h; PA upper normal
- Mild metabolic acidosis without AG, but with hyperkalemia + hypertension
- What is going on here?

The „with-no-lysine“ kinases and pseudo-hypoaldosteronism type 2



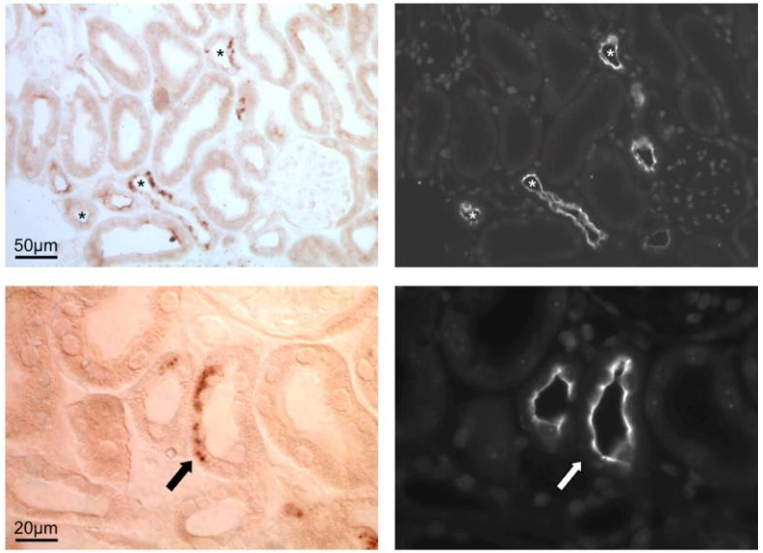
- The WNKs regulate sodium reabsorption via NaCl cotransporter (NCC) in DT.
- This is the HCTZ binding site.
- The NCC is upregulated;
- Volume expansion and hypertension.
- Little sodium left for ENaC
- Electrochemical gradient to excrete K+ and H+ is reduced
- Blocking NCC with HCTZ shuts all this off
- Condition also known as „Gordon“ syndrome



How do CNI cause high blood pressure?

Calcineurin is co-expressed with NCC. Tacrolimus stimulates NCC (also WNK3, WNK4 and SPAK). Tacrolimus induces salt sensitive hypertension. NCC knock-out mice to not respond to tacrolimus. (Hoorn et al. Nat Med 2011)

Hoorn et al. Nat Med 2011;17:1304-1309.



#9

45 year-old man, mild hyptertension treated with amlodipine. He also takes various Chinese herbs and is referred because of hypokalemia. His parents were first cousins.

120 mmol/day of potassium citrate (Kalinor-Brause) does not help. Diabetes, Turkish extraction, 169 cm, 81 kg, BP 139/90 mm Hg.

Na	140
Cl	96
K	2.81
Ca	2.41
Ph	1.04

Hb	15.3
Hct	42
Thrombo	323
Leuko	8.6

pH	7.48
pCO2	37 mmHg
pO2	92 mmHg
HCO3	27 mmol/l

Aldo (466 pmol/l) and Renin (43.2 ng/ml) slightly high
Cortisol 636 nmol/l, after Dexamethasone 27 nmol/l

$$TTKG = \frac{K_{Urine} \times Osm_{Plasma}}{K_{Plasma} \times Osm_{Urine}} = \frac{75 \times 297}{2.81 \times 763} = 10.4$$

ABPM: mean pressure: 134/85, dips well at night

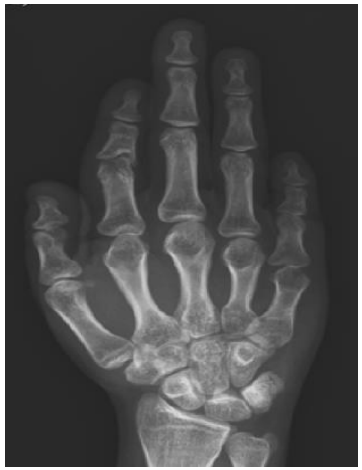
$Ca_{24\ h}$	0.51 mmol/d (2.5 – 8)
FeCa	0.07
$Mg_{24\ h}$	3.65 mmol/d (2.5 – 8)
FeMg	5.8

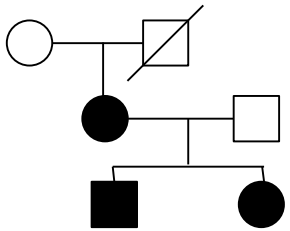
Genetic testing showed mutations in SLC12A3 gene that encodes NCC. Gitelman syndrome, oddly with HBP

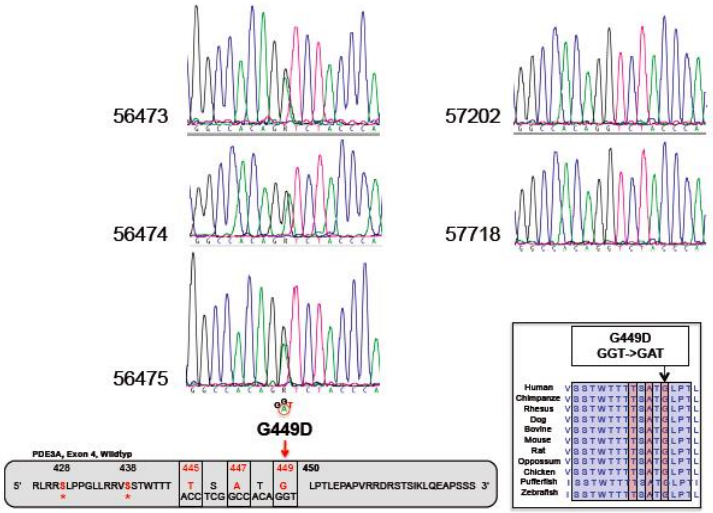
The message of our report is that genetic variance is not exclusive to those patients that we might expect to have the genetic disease. These mutations exist in the population at large and conceivably, our patient would have had malignant hypertension without this mutation. Elitok et al. Clin Kidney J 2012

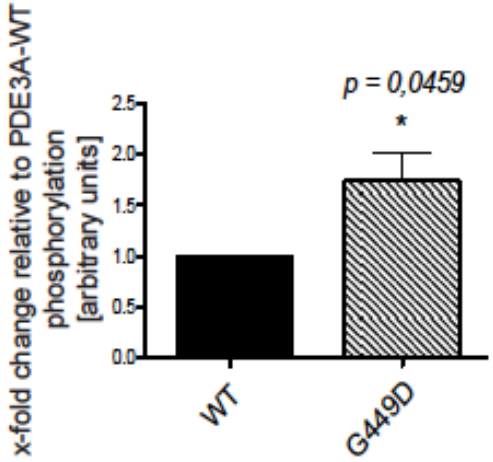
#10

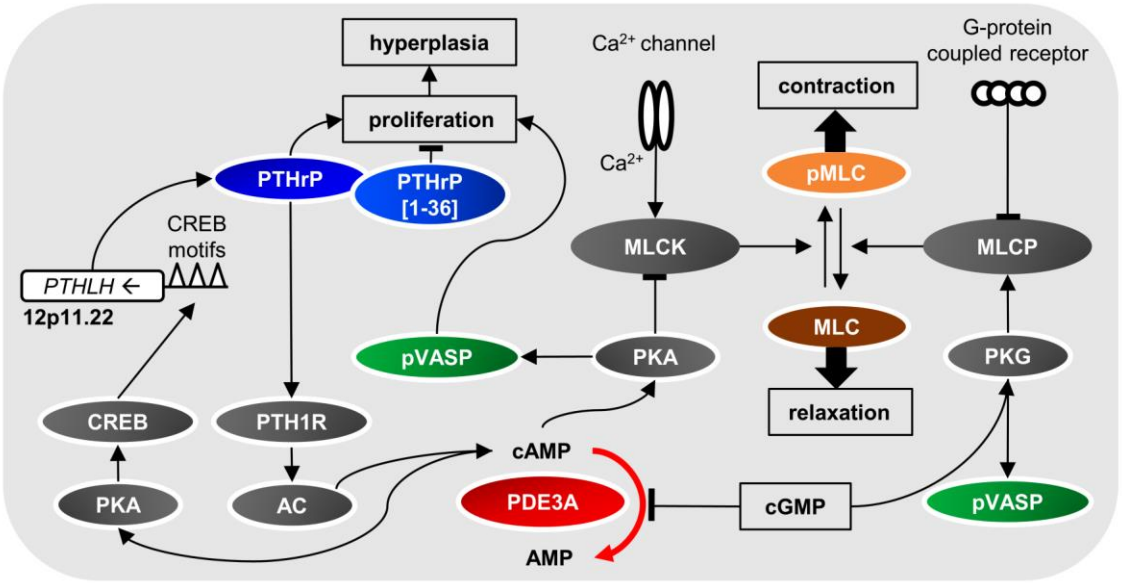
A 37 year-old ballet dancer with BP 185/120 and a TIA. Comes to her doctor and says: “I have HTNB (OMIM#)”





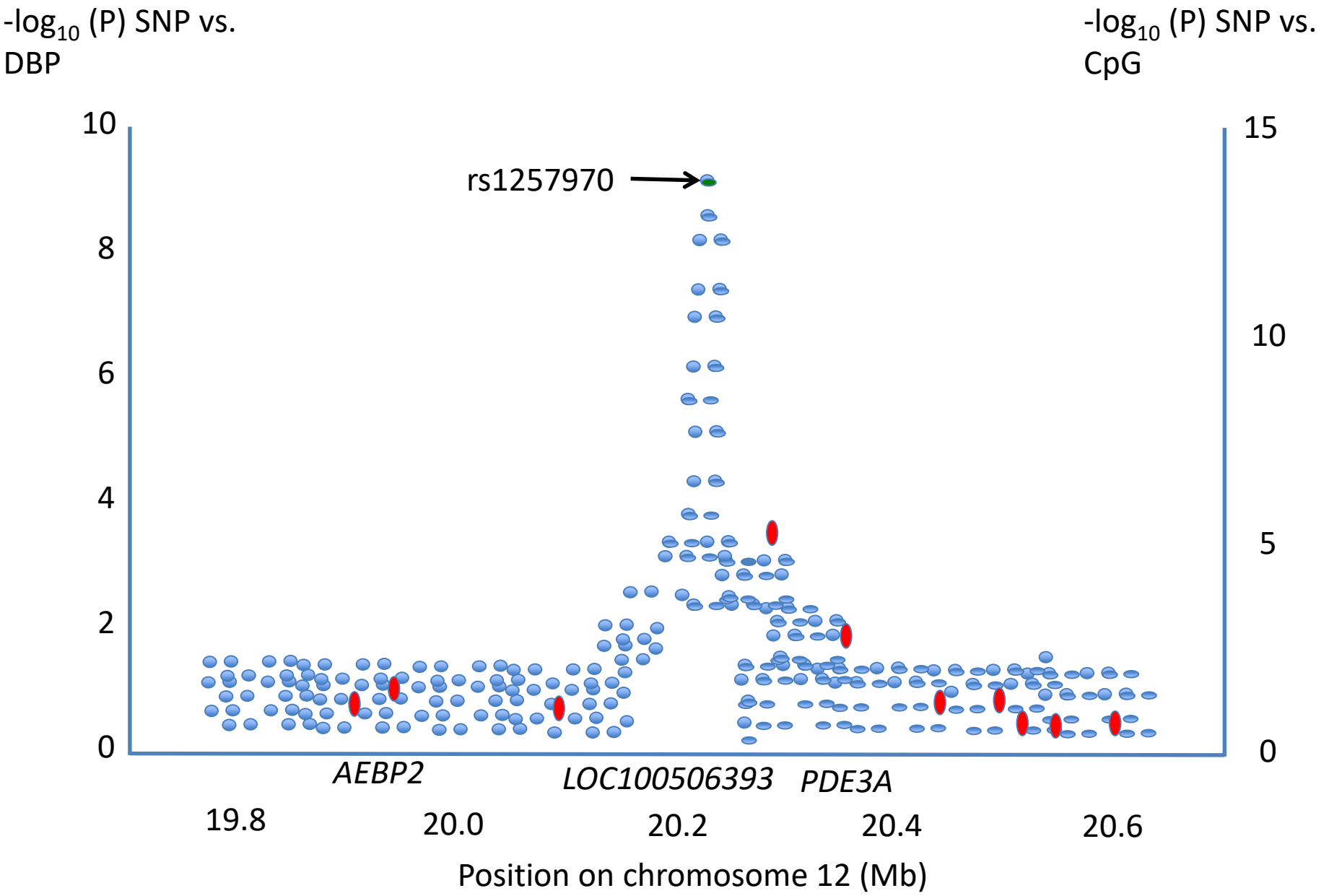






Maass et al.
Nat Genet 2015

Recent GWAS study maps essential hypertension to PDE3A

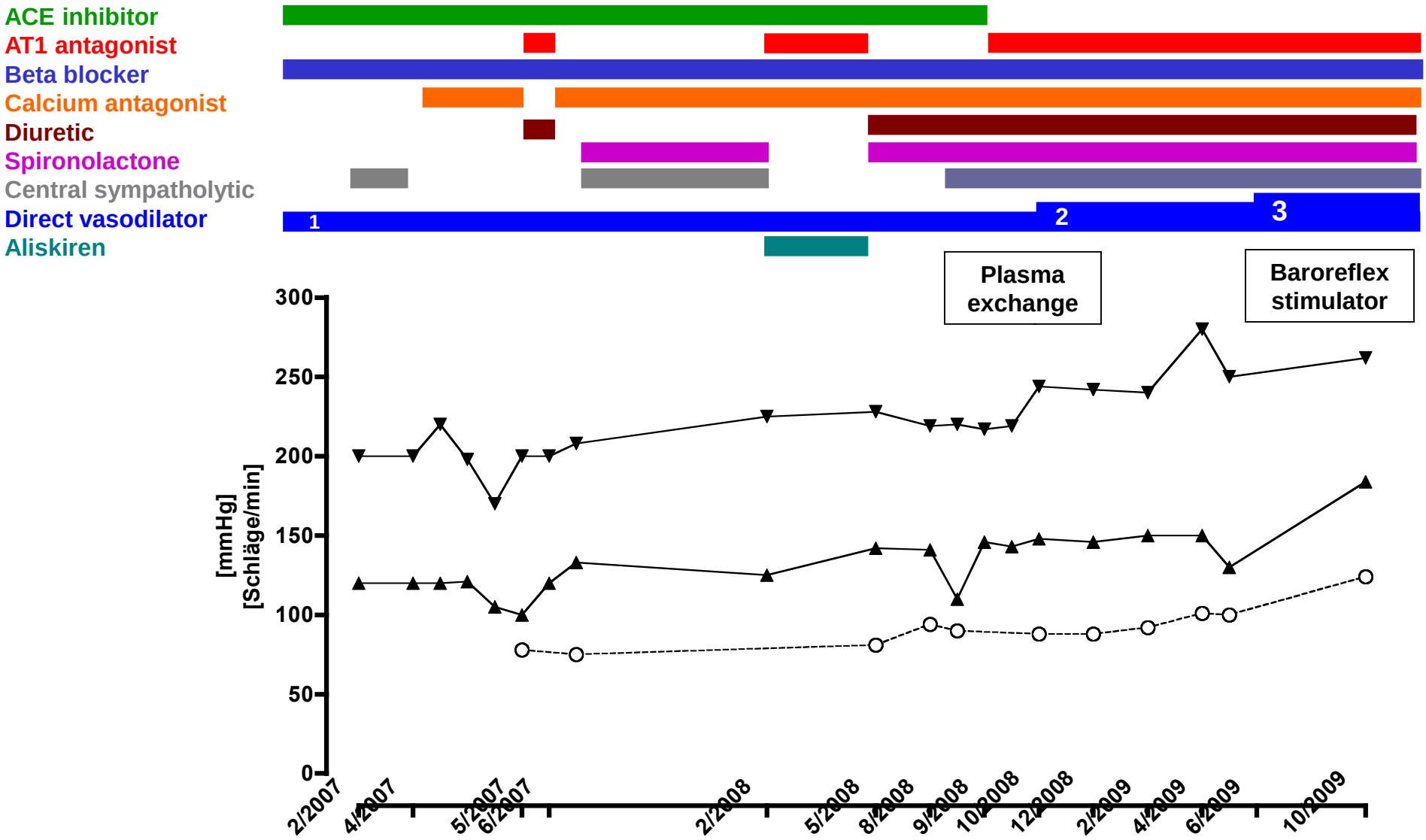


#11

49 year-old woman, 166 cm, BMI 18.5, 4 pregnancies, 4 healthy children, hypertensive since 1997, otherwise nothing

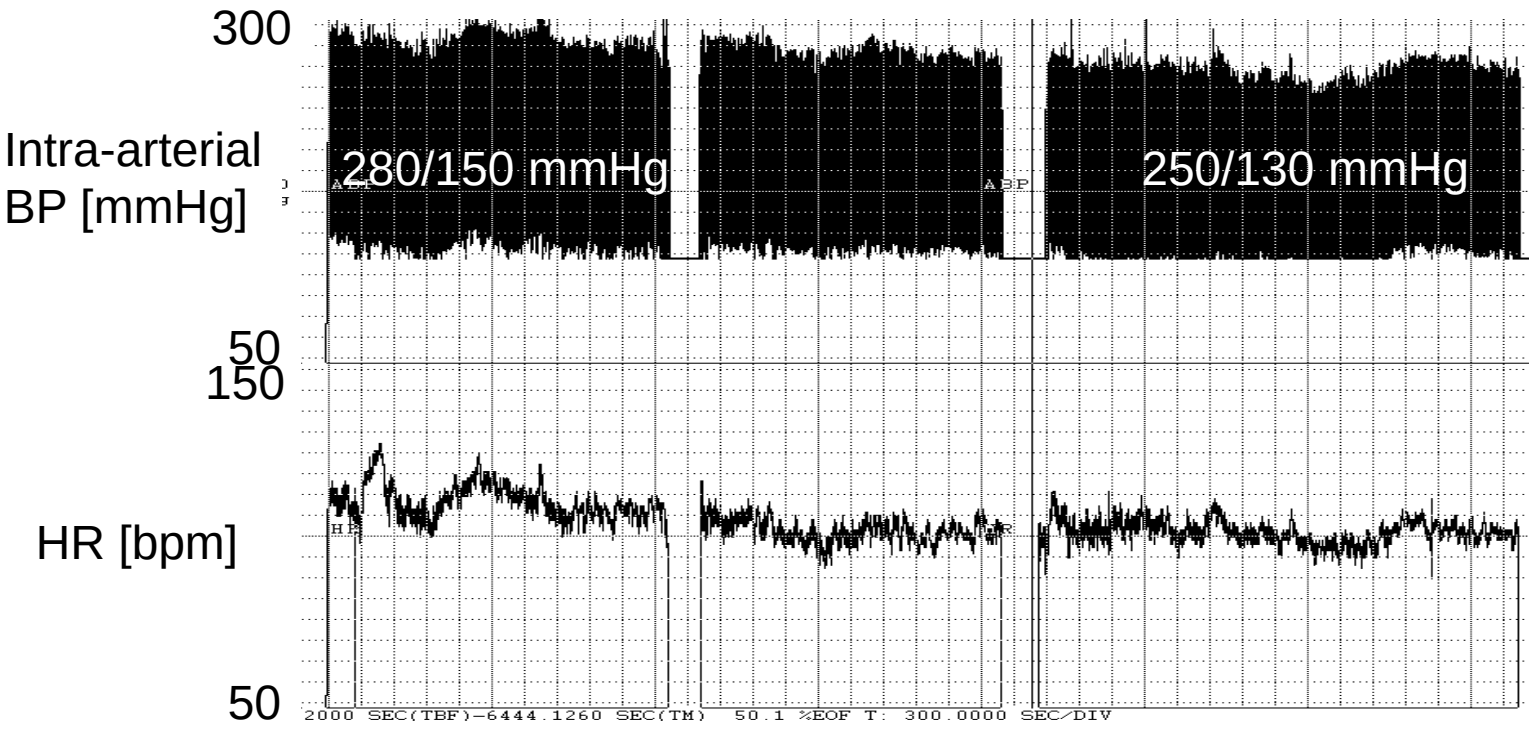
- Many metanephrines, aldosterones, cortisols, MR angios, Echos (mild LVH), Fundus 1°, ABGs OK, crea normal, no proteinuria, K 3.9 mmol/l, renin und aldo OK, 24-h UNaV 167 mmol/day, cMR Angio no NV contact, intra-arterial BP 280/130 mm Hg 2 h after observed medication ingestion
- Drug levels clonidine, amlodipine, bisoprolol, torasemidd, spironolactone therapeutic; candesartan, minoxidil and urapidil could not be measured
- Compliance was not the problem

BP and heart rate over 2 years of treatment



Observed ingestion, p.o.:
Bisoprolol 10 mg
Candesartan 32 mg
Clonidine 0.3 mg
Minoxidil 10 mg
Urapidil 90 mg
Torasemide 10 mg
Spironolactone 200 mg

Compliance?



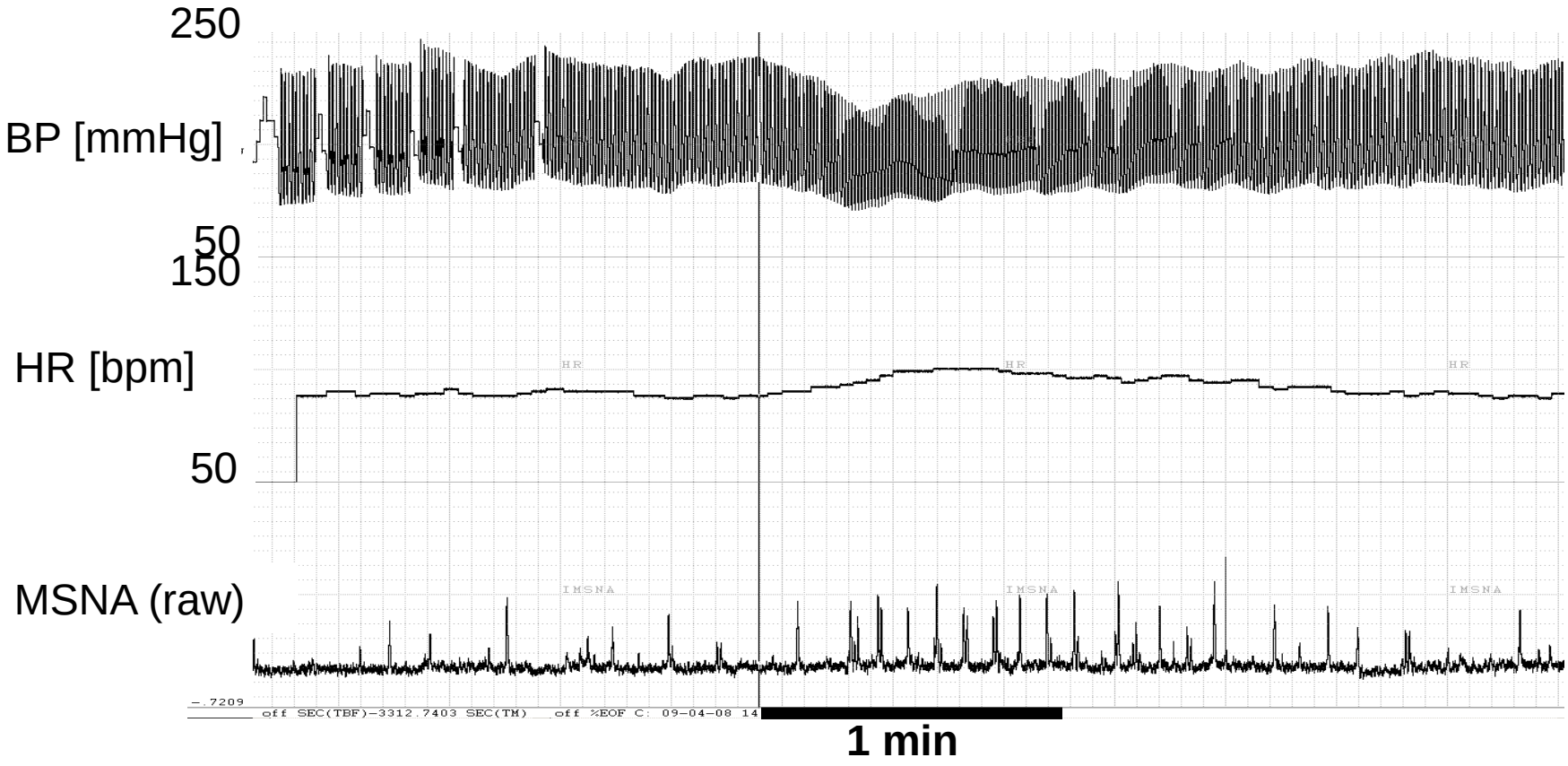
----------↑**Medikation**----------**1h**----------**2h**----------

Effect of morning medication dose on BP and heart rate (1 box = 5 min):

BP lowering ca. 30/20 mm Hg at 2.5 hours

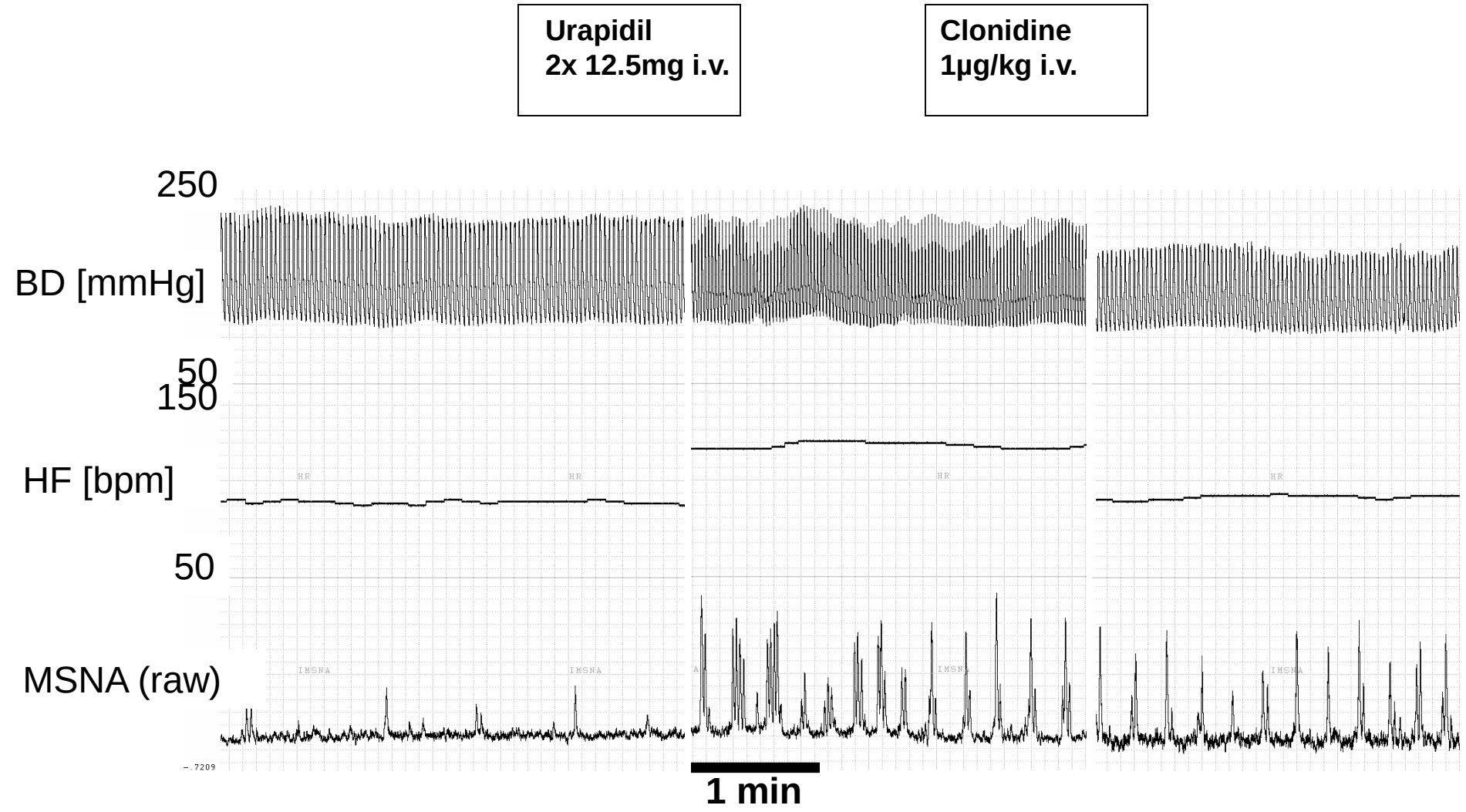
Sympathetic nerve activity

Nitroprussid
1.5 µg/kg i.v.



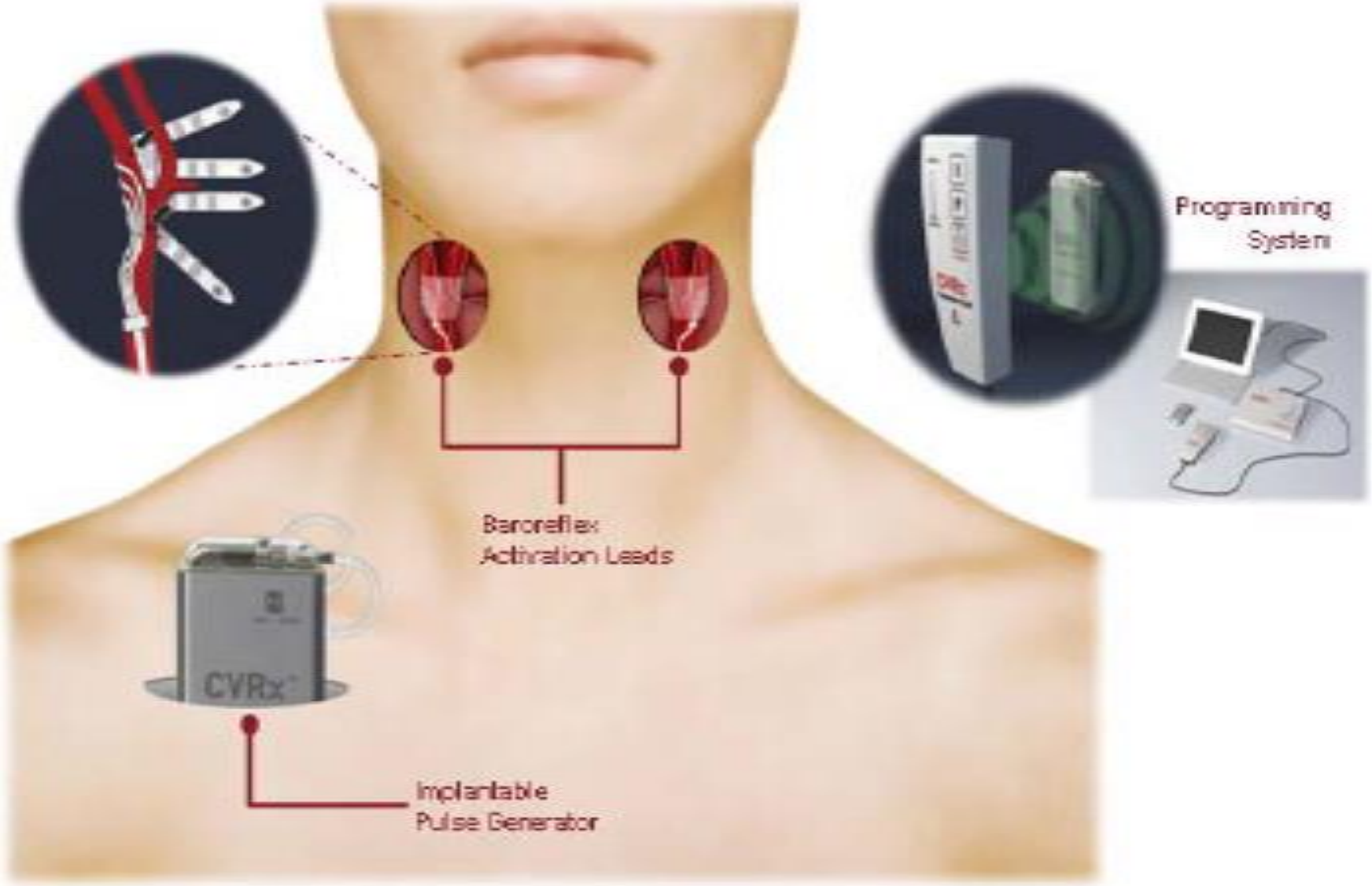
Increase in sympathetic activity reduces any effect on BP

Sympathic nerve activity



BP lowering with vasodilator occurs only after central blockade

Baroreflex-Stimulator



Baroreflex-Stimulator

Short-term hemodynamic effects

Nr.	ΔSBP	ΔDBP	ΔHR
1	–12	–5	–1
2	–7	–4	–3
3	+7	+2	–1
4	+1	–1	–1
5	–88	–32	–13
6	–22	–16	–4
7	–24	–9	0
8	–27	–15	–6
9	–54	–35	–10
10	–9	–1	–3
11	–35	–14	–14
12	–108	–45	+1

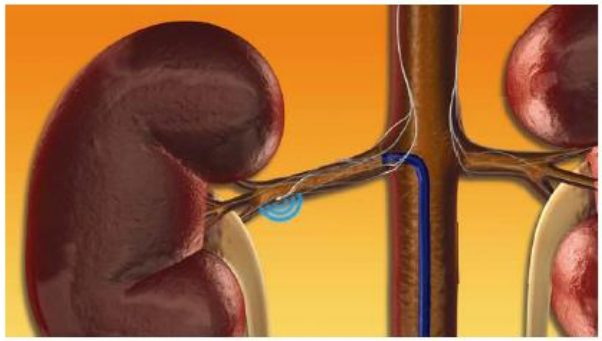
Heusser K et al., **Hypertension. 2010;55:619-626**

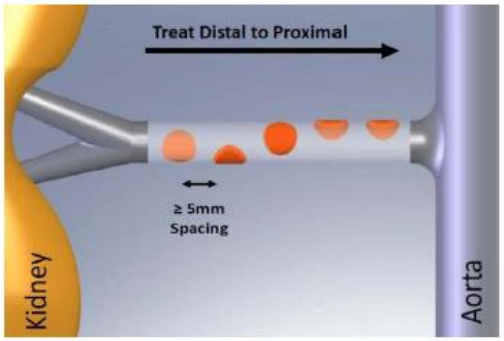
The acute effect looked impressive: 60 – 80 mmHg.

But after chronic usage the effect disappeared. Nine-drug regimen still ~~280 mm Hg~~.

Renal denervation to lower blood pressure was done:

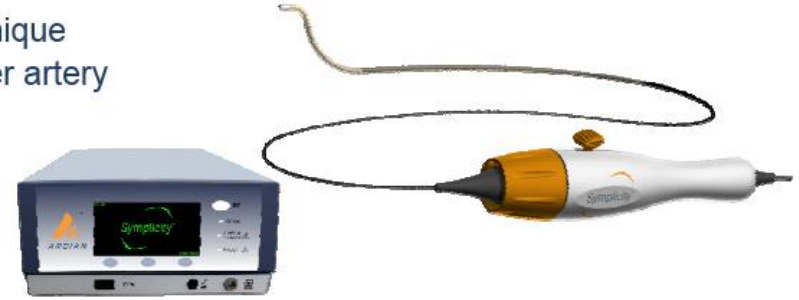
Renal Nerve Anatomy Allows a Catheter-Based Approach





Sympathetic nerves lie within and immediately adjacent to the renal artery wall.

- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms



To this point there is no positive result!

Last email from my friends:

•Zu Frau Hoffmann gibt´s leider keine guten Neuigkeiten:
•Auch nach HF-Ablation der renalen sympathischen Nervenfasern Anfang letzten Jahres ist der Blutdruck (unter 9-fach Medikation) unverändert hoch mit Werten zwischen 250 – 300 mmHg systolisch.
•Wir schicken sie nach Bristol für Hirnstimulation

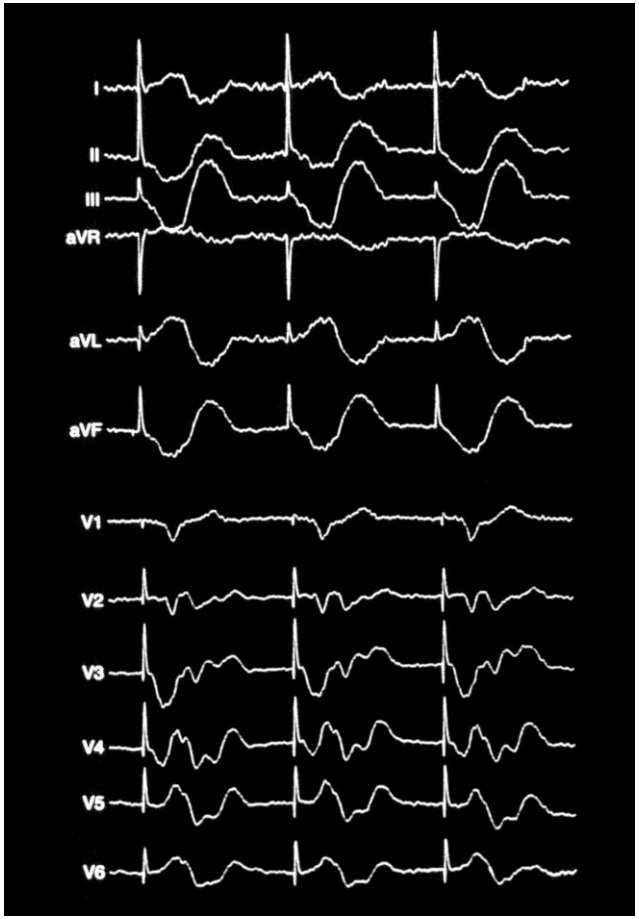
•Christoph Schroeder

Wir (ich bin) sind ratlos

#12

85 year-old with hypertension and diabetes is admitted because of all-round weakness.

- Crea 472 µmol/l
- pH 7.19
- $PaCO_2$ 20 mm Hg
- PaO_2 97 mm Hg
- HCO_3 4 mmol/l
- Na 136, Cl 100 mmol/l
- K 11 mmol/l
- UK 26, UOsm 277
- TTKG <3



Mechanisms of hyperkalemic type IV RTA

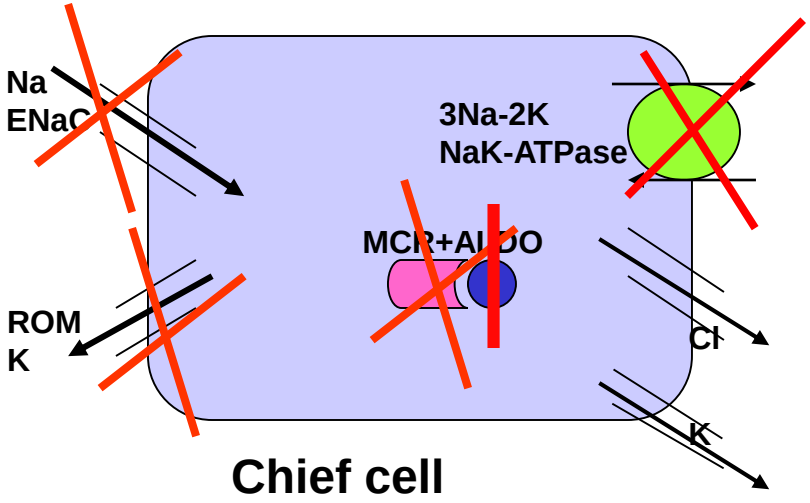
ENaC malfunction
insufficient electronegative gradient for K excretion

Low aldosterone levels, MR blockade or limited CCT function

Digitalis effects on Na-K-ATPase

Diminished NH_4^+
Elimination because of decreased Proximale production and decreased NH_3 capture

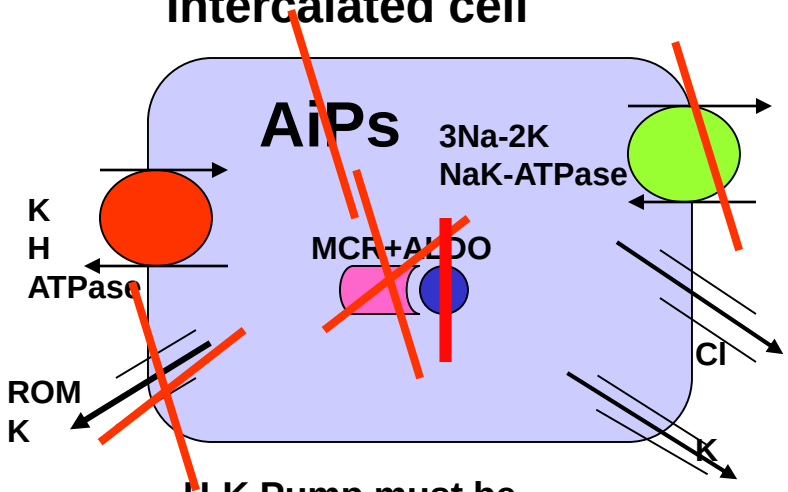
We need COX2 for renin and Ald release



Chief cell

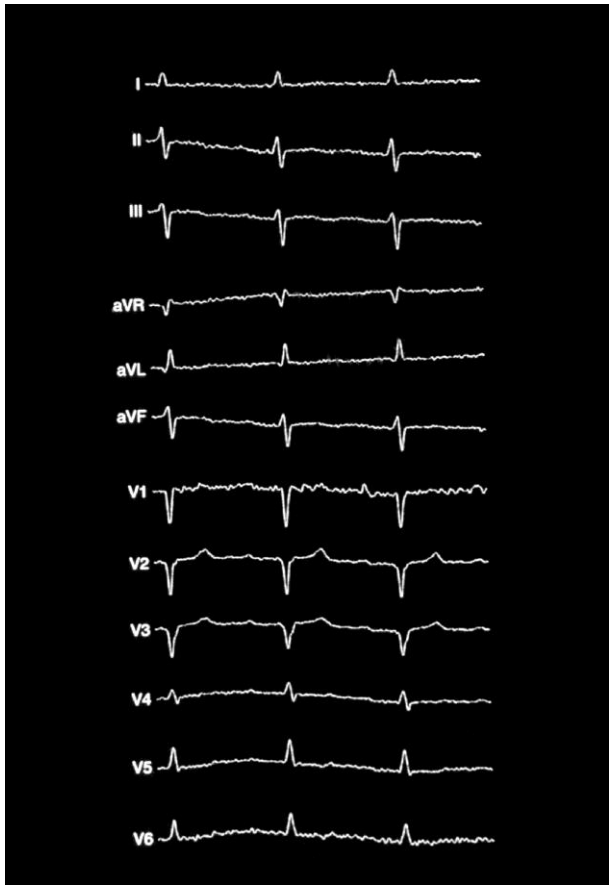
ENaC regulates H and K excretion; MR also

Intercalated cell



H-K Pump must be functional

How do we treat this?



Stop all meds

Intravenous calcium
Glucose+insulin
$NaHCO_3$
Dialysis

So what have we learned?

1. 1° Aldo – simple tests, good imaging
2. Renal artery stenosis, stay skeptical
3. Pheo, not limited to abdomen
4. Cushing's syndrome – difficult
5. Gitelman's with hypertension?
6. Vasculitis
7. Worthwhile knowing a few genes because of novel mechanisms!
8. Not all essential hypertension is easy
9. We cause hyperkalemia

Thank you!