Why invasive testing?

- Resolve diagnostic uncertainty **when imaging/biochemistry are inconclusive.**
- **Localize hormone source** (e.g., unilateral aldosterone secretion, pituitary ACTH).
- **Guide definitive therapy** (surgery vs medical management).

Strongly invasive tests

HYPERCORTISOLISM

Bilateral Inferior Petrosal Sinus Sampling (BIPSS/IPSS) — differentiates pituitary vs ectopic ACTH

PRIMARY HYPERALDOSTERONISM

Adrenal Venous Sampling (AVS) — gold standard for subtyping primary aldosteronism

POLYURIA/POLYDIPSIA

Water deprivation test

Saline infusion

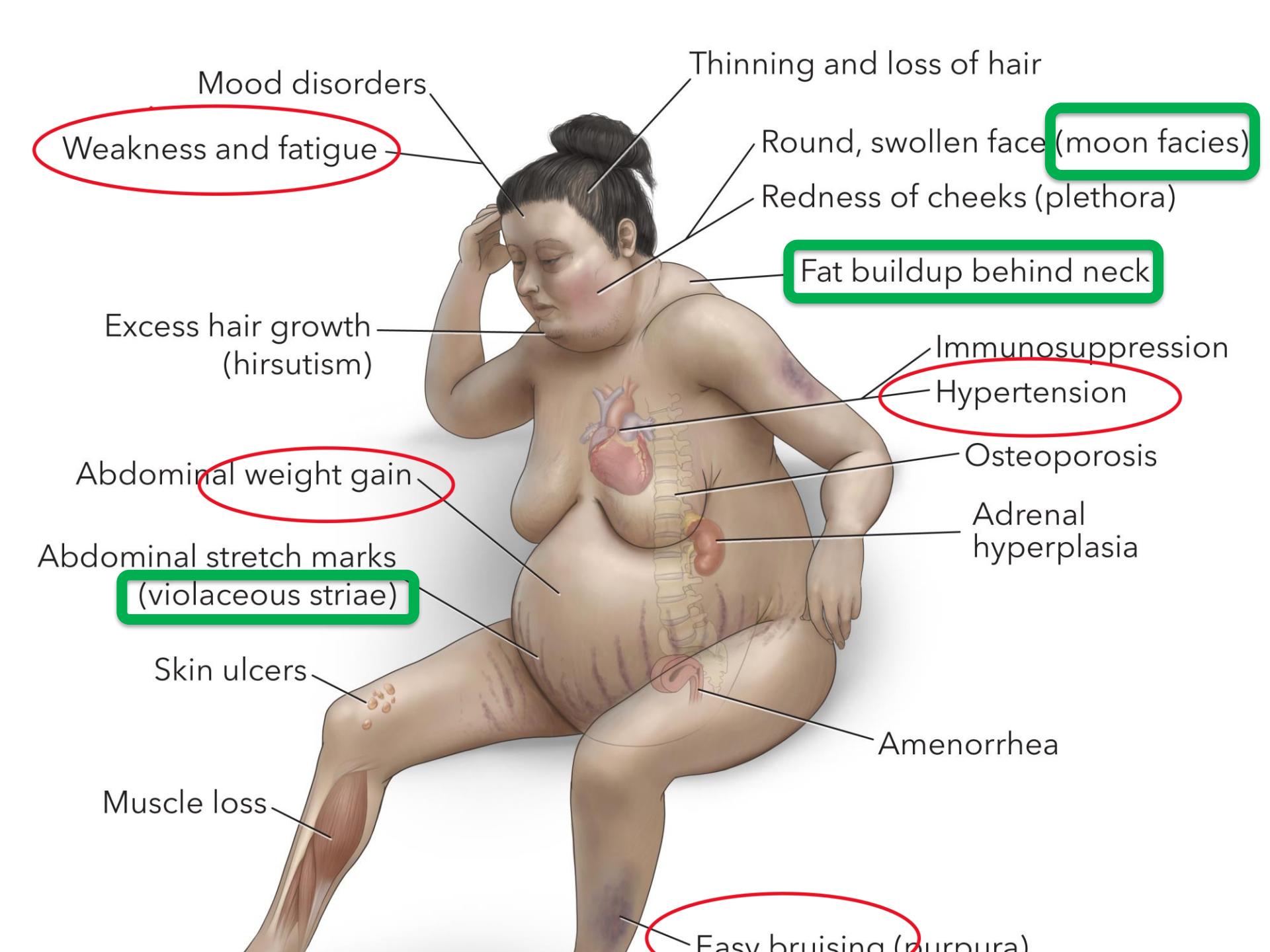
Investigation of Hypercortisolism

Diagnostic Approach and Clinical Insights

Step 1: Excluding Pseudo-Cushing's

- EXOGENOUS cortisol
- MIMICS: alcoholism, depression, obesity, pregnancy

Approach: repeat testing after treating underlying condition


Mood disorders
Thinning and loss of hair
Weakness and fatigue
Round, swollen face (moon facies)
Redness of cheeks (plethora)
Fat buildup behind neck
Excess hair growth (hirsutism)
Immunosuppression
Hypertension
Osteoporosis
Abdominal weight gain
Adrenal hyperplasia
Abdominal stretch marks (violaceous striae)
Skin ulcers
Amenorrhea
Muscle loss
Easy bruising (purpura)

Background

- Hypercortisolism = excess cortisol production
- Causes: ACTH-dependent (pituitary adenoma, ectopic ACTH)
- Causes: ACTH-independent (adrenal adenoma, carcinoma, hyperplasia)
- Diagnosis requires biochemical confirmation before imaging

Step 2: Confirming Hypercortisolism

Initial screening tests (need ≥2 abnormal results):

- 24-hour urinary free cortisol – elevated
- Late-night salivary cortisol
- 1 mg overnight dexamethasone suppression test – failure to suppress < 1,8 µg/dl

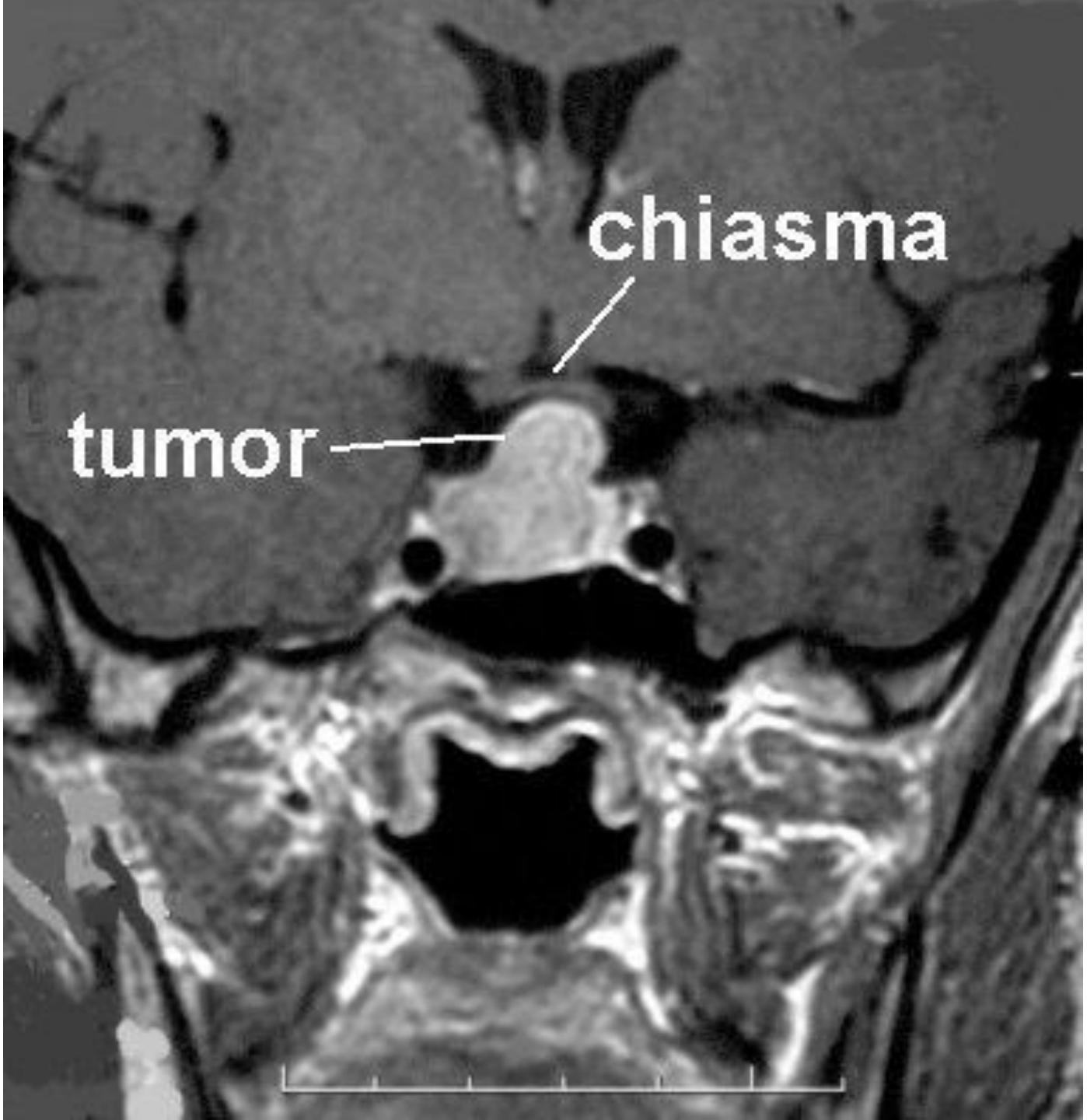
Step 3: Determine ACTH Dependence

Measure plasma ACTH:

- Low/undetectable → ACTH-independent (adrenal cause)
- Normal/high → ACTH-dependent (pituitary or ectopic)

Step 4: Localizing the Source

- ACTH-independent (low ACTH): CT/MRI of adrenal glands
- ACTH-dependent (high ACTH): pituitary MRI
- **If pituitary MRI negative/uncertain** → Inferior petrosal sinus sampling (IPSS)
- Ectopic suspicion → chest/abdominal imaging

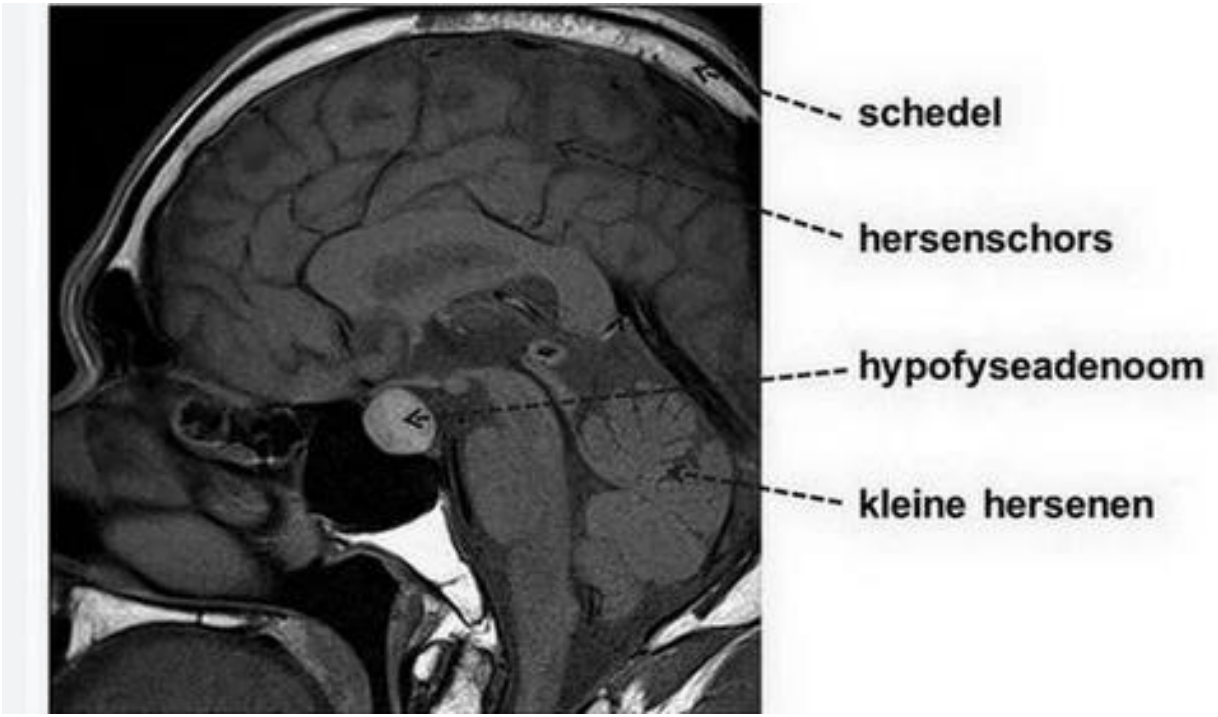

chiasma
tumor

Indication for IPSS

- High ACTH + high cortisol
- Pituitary MRI often non-conclusive (10–50% microadenomas invisible)

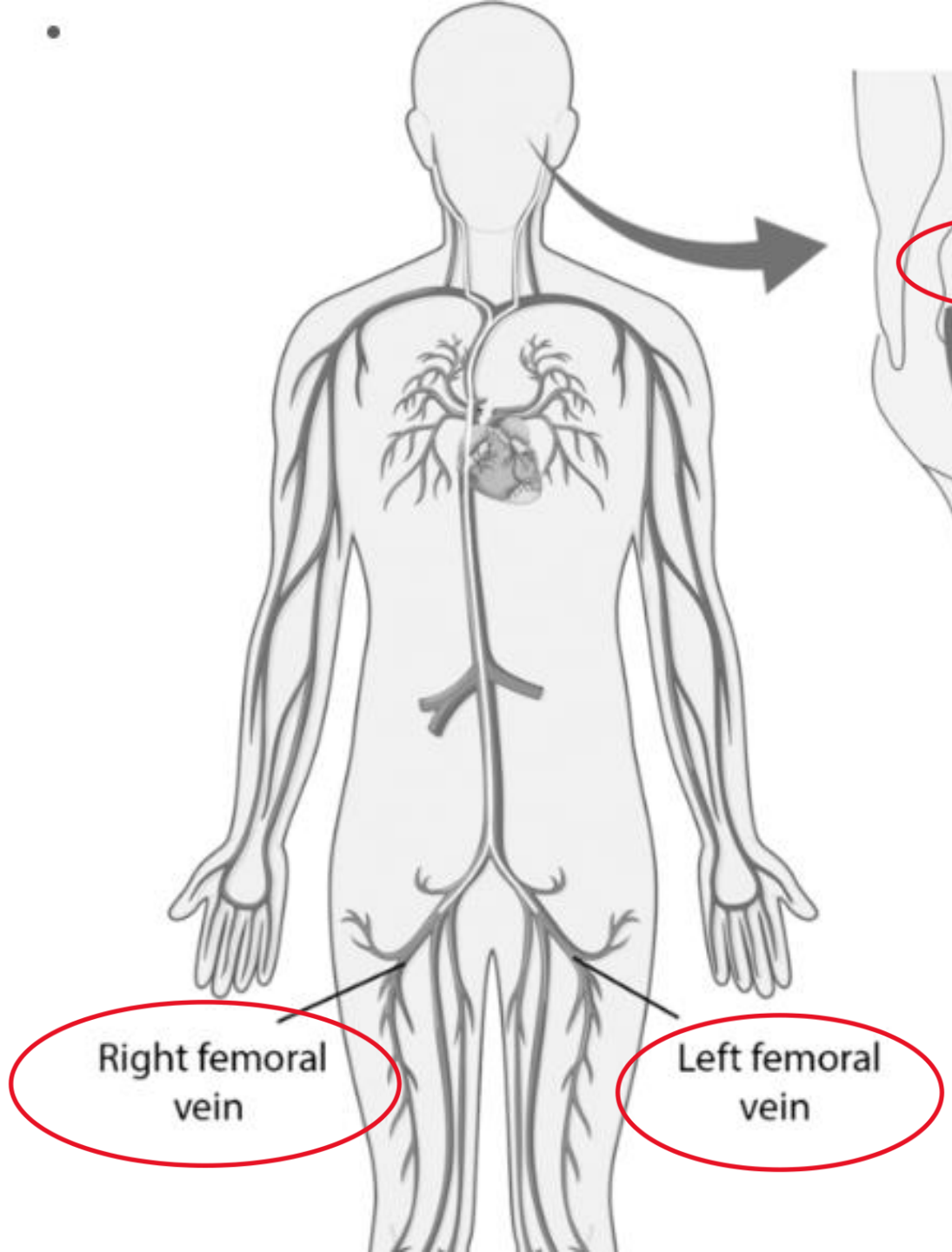
Differential Diagnosis

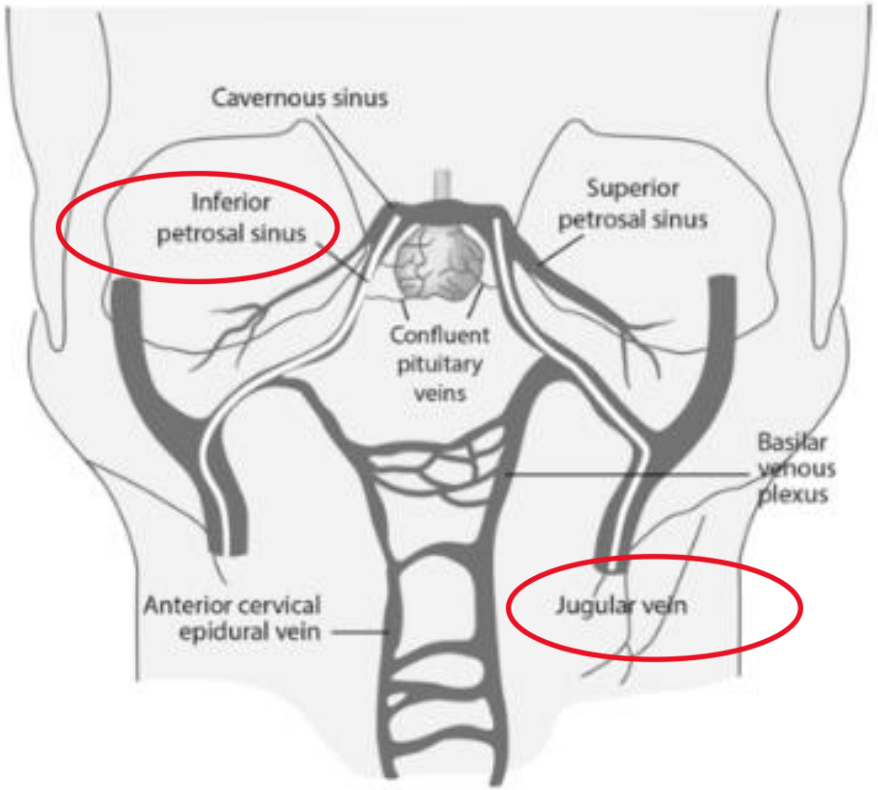
- Pituitary adenoma (Cushing's disease): most common cause
- Often not visible on MRI
- Ectopic ACTH tumors: small-cell lung carcinoma, carcinoids, pheochromocytomas


schedel
hersenschors
hypofyseadenoom
kleine hersenen

IPSS Procedure: Catheterization

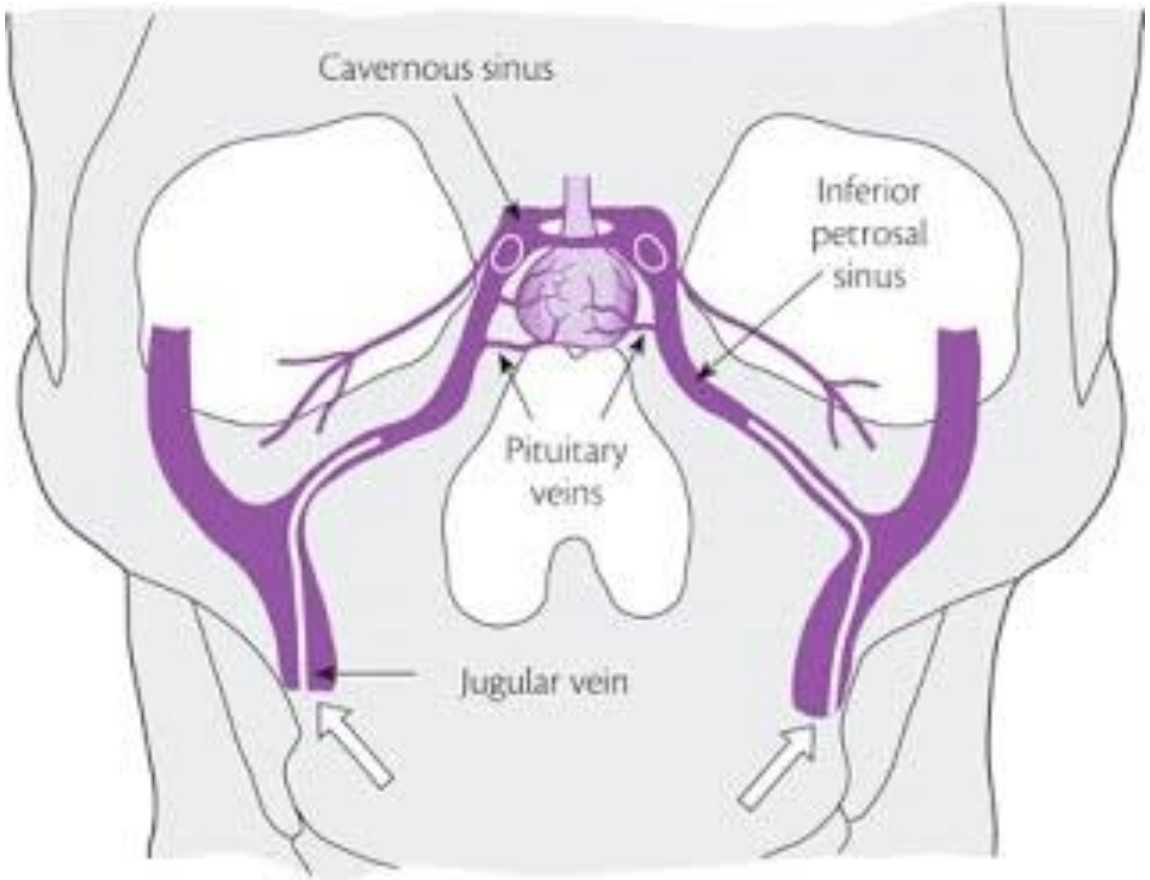
- Catheter insertion via femoral vein
- Advance into both inferior petrosal sinuses
- Precise positioning for accurate sampling

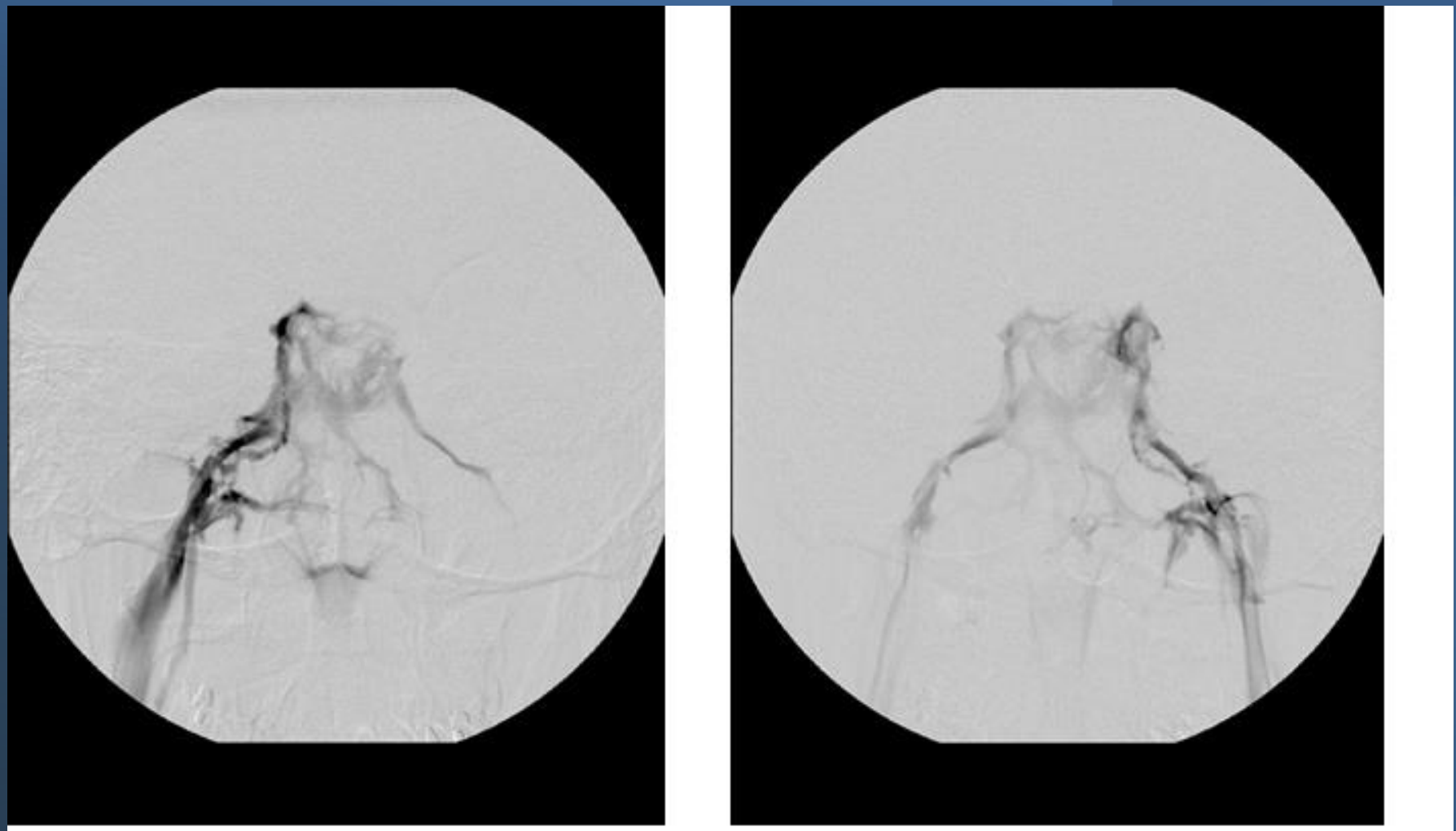

Right femoral vein
Left femoral vein


Cavernous sinus
Inferior petrosal sinus
Superior petrosal sinus
Confluent pituitary veins
Basilar venous plexus
Anterior cervical epidural vein
Jugular vein

Blood Sampling Protocol

- Baseline samples from sinuses + peripheral vein
- Stimulation with CRH or desmopressin
- Timed samples at 2, 5, 10, 15 minutes
- Improves diagnostic sensitivity


Cavernous sinus
Inferior petrosal sinus
Pituitary veins
Jugular vein



Injections of Right and Left Inferior Petrosal Sinuses

Interpretation of IPSS Results

- Compare central vs peripheral ACTH levels
- Baseline ratio > 2.0 → pituitary source
- Stimulated ratio > 3.0 → pituitary source

Lateralization and Localization

- Inter-petrosal ratio determines side of adenoma
- Ratio > 1.4 suggests adenoma side

Risks and Complications

- Catheter-related: vessel injury, thrombosis
- Contrast-related: allergy, kidney dysfunction
- Neurological risks: stroke, bleeding (rare)

Sinus petrosus sampling Prolactine

Basaal 1 (0 min)

Prolactine: Perifere vene	29.5	µg/L
Prolactine: IPS rechts	106.0	µg/L
PRL gradiënt: IPS rechts	3.59	
Prolactine: IPS links	176.0	µg/L
PRL gradiënt: IPS links	5.97	

Centraal/perifeer prolactine > 1,8 à 2,0

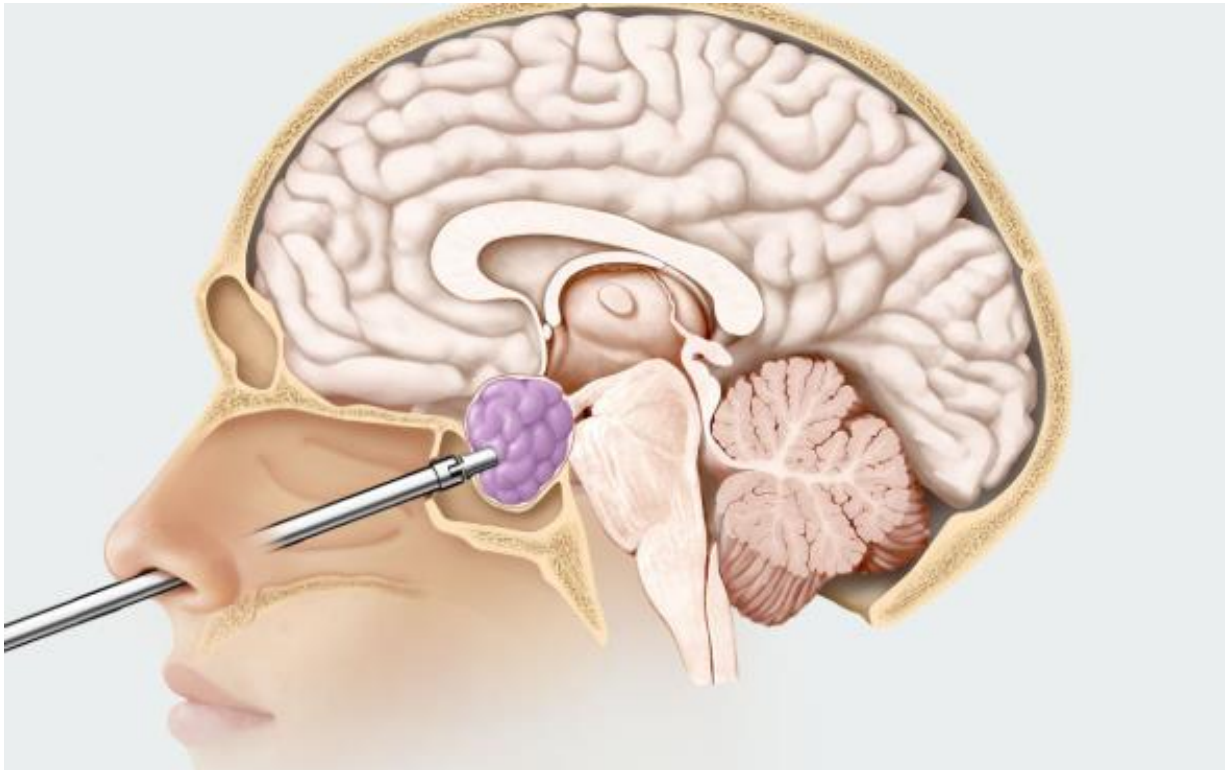
Sinus petrosus sampling ACTH		
Basaal 1 (0 min)		
ACTH: Perifere vene	67.8	ng/L
ACTH: IPS rechts	276.0	ng/L
ACTH: gradiënt: IPS rechts	4.07	
ACTH: IPS links	584.0	ng/L
ACTH: gradiënt: IPS links	8.61	
Basaal 2 (na 3 min)		
ACTH: Perifere vene	69.5	ng/L
ACTH: IPS rechts	447.0	ng/L
ACTH: gradiënt: IPS rechts	6.43	
ACTH: IPS links	582.0	ng/L
ACTH: gradiënt: IPS links	8.37	

Injectie CRH 1 µg/kg IV op tijdstip 0		
5 min post CRH		
ACTH: Perifere vene	114.0	ng/L
ACTH: IPS rechts	1350.0	ng/L
ACTH: gradiënt: IPS rechts	11.84	
ACTH: IPS links	1033.0	ng/L
ACTH: gradiënt: IPS links	9.06	
10 min post CRH		
ACTH: Perifere vene	121.0	ng/L
ACTH: IPS rechts	689.0	ng/L
ACTH: gradiënt: IPS rechts	5.69	
ACTH: IPS links	382.0	ng/L
ACTH: gradiënt: IPS links	3.16	

Lateralisation: right > left

Current status / importance in 2025:

- It remains the **gold standard** in challenging cases of ACTH-dependent Cushing’s where imaging is negative or equivocal, or biochemical tests are ambiguous.
- It is ***not* required**:
  - if the clinical/biochemical picture is clear
  - imaging shows a big pituitary adenoma
- Limitations remain:
  - It is invasive
  - technically demanding (requires experienced interventional radiology),
  - has some risks
  - anatomical variation may lead to false negatives
- Recent publications continue to show its utility



Conclusion

- Gold standard
- High sensitivity and specificity
- Essential when MRI is inconclusive

Investigation of Hyperaldosteronism

Diagnostic approach, screening, confirmatory tests, and subtype classification

WHY PA MATTERS

- PA = renin-independent aldosterone excess
- Prevalence: 5–10% of hypertensive patients
- Associated with:
  - → Cardiovascular morbidity
  - → Renal damage
  - → Metabolic complications
- Often missed → diagnosis changes management dramatically

1. Clinical Suspicion

- Resistant hypertension (≥3 drugs)
- Hypokalaemia (spontaneous or diuretic-induced)
- Hypertension with adrenal incidentaloma
- Early onset hypertension (<40 years)
- Hypertension with sleep apnea
- Family history of early hypertension or stroke

2. Initial Biochemical Screening

- Test: Aldosterone-to-Renin Ratio (ARR)
  - PAC > 15 ng/dL with suppressed renin → suspicious
  - Renin: suppressed
  - ARR > 20–30 (unit dependent)

- Pre-test requirements:
  - Correct hypokalaemia
  - Liberalize sodium intake
  - (Stop interfering drugs: MR antagonists, diuretics, ACEi, ARBs, β-blockers)

3. Confirmatory Testing

- Saline Infusion Test: PAC > 10 ng/dL → PA confirmed
- Oral Sodium Loading Test: 24h urinary aldosterone > 12 µg → PA confirmed
- (Fludrocortisone Suppression Test: PAC > 6 ng/dL → PA confirmed)
- (Captopril Challenge: PAC fails to suppress, ARR remains high)

4. Subtype Classification

Adrenal CT Scan:

- exclude carcinoma
- identify adenoma
- hyperplasia

Adrenal Venous Sampling (AVS):

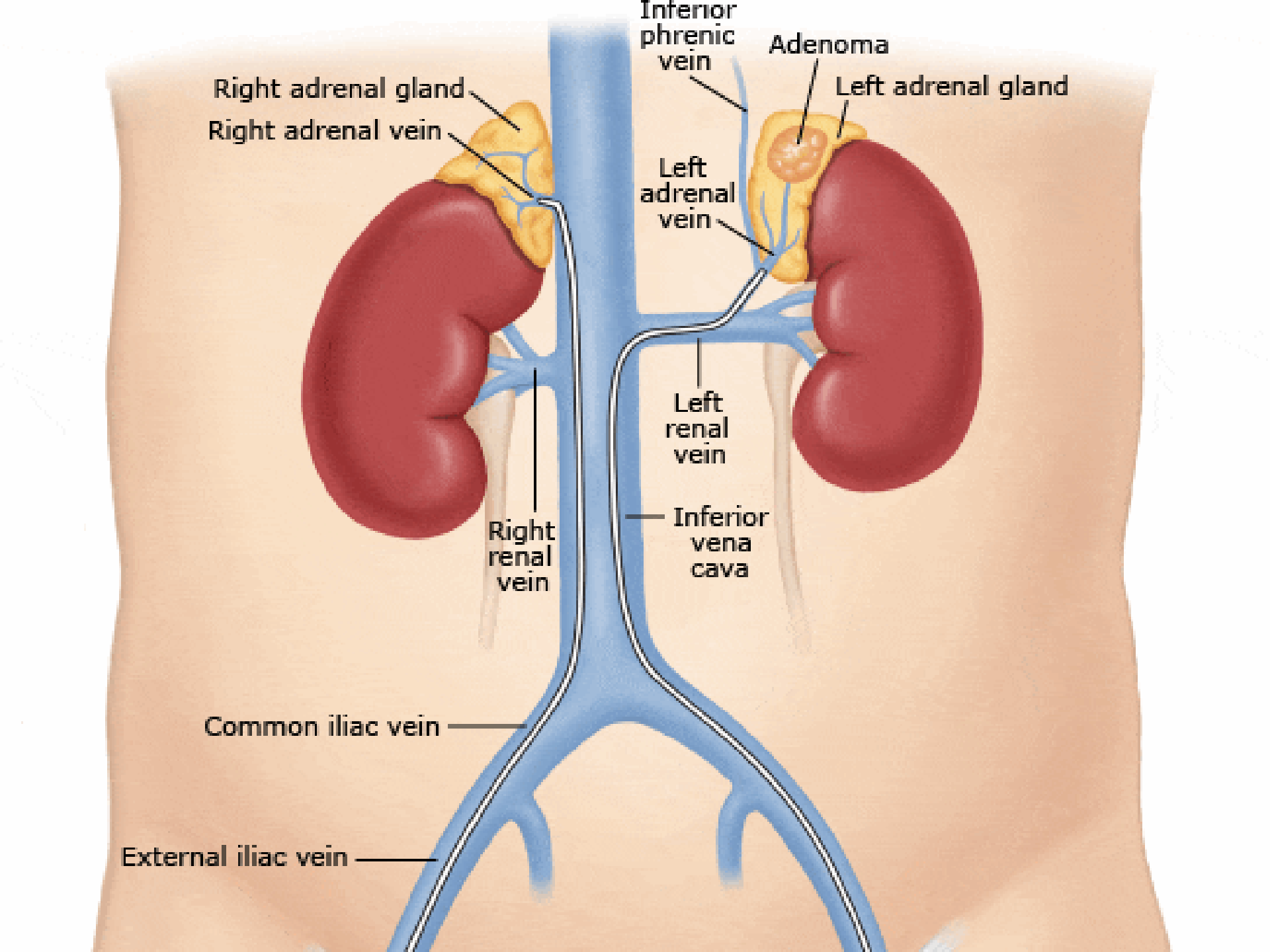
- gold standard for lateralization
- lateralization index >4:1 → unilateral
- <3:1 → bilateral disease

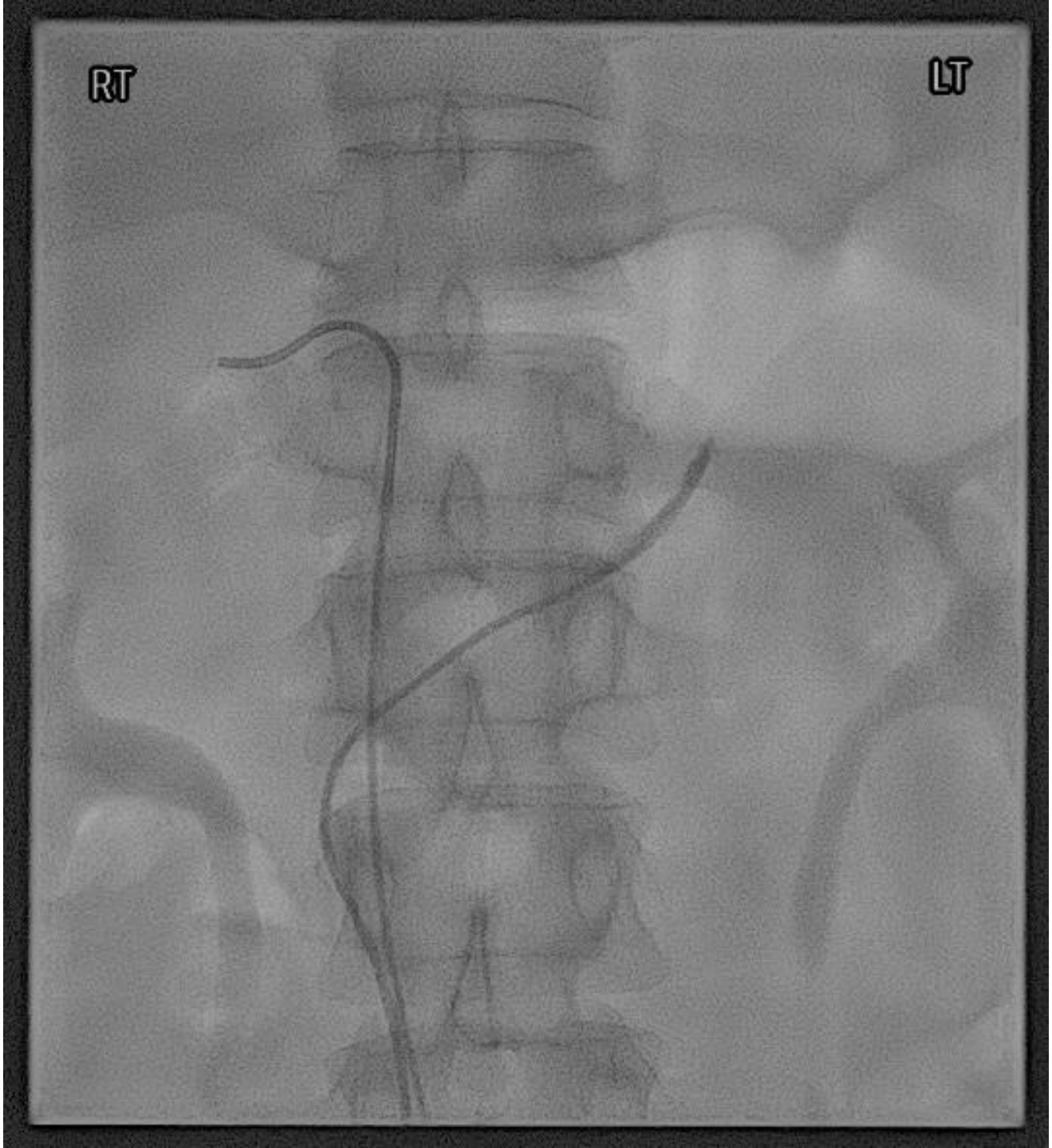
Adrenal Venous Sampling (AVS)

- Indication: confirm unilateral aldosterone production prior to adrenalectomy.
- Technically demanding; success depends on experienced interventional radiology.

What is AVS?

- Adrenal Venous Sampling (AVS) is the gold standard to distinguish unilateral from bilateral aldosterone excess.
- Blood is sampled from:
  - Left adrenal vein
  - Right adrenal vein
  - Peripheral vein (IVC)
- Hormones measured: Cortisol and Aldosterone.


Inferior phrenic vein
Adenoma
Left adrenal gland
Right adrenal gland
Right adrenal vein
Left adrenal vein
Left renal vein
Inferior vena cava
Right renal vein
Common iliac vein
External iliac vein


RT
LT


LEFT

Worked Example 1: Raw Lab Values

Sample	Cortisol	Aldosterone
Left AV	80 µg/dL	3600 ng/dL
Right AV	30 µg/dL	30 ng/dL
Peripheral (IVC)	10 µg/dL	30 ng/dL

Step 1 — Selectivity Index (SI)

Formula: SI = Cortisol_adrenal / Cortisol_peripheral

Purpose: Confirms correct catheter placement (adequate adrenal sampling).

Cutoffs:

- Unstimulated: SI ≥ 2
- ACTH-stimulated: SI ≥ 5

Selectivity Index Calculations

Left SI = 80 / 10 = 8 (adequate)

Right SI = 30 / 10 = 3 (adequate)

Both ≥ 2 → valid samples.

Step 2 - Lateralization Index (LI)

LI = (A/C dominant) ÷ (A/C non-dominant)

Left A/C = 3600 / 80 = 45
Right A/C = 30 / 30 = 1

= 45 ÷ 1 = 45

Interpretation: LI ≫ 4 → strong unilateral (left) aldosterone hypersecretion.

Aldosterone/Cortisol Ratios

Left A/C = 3600 / 80 = 45

Right A/C = 30 / 30 = 1

Step 3: Contralateral Suppression Index (CSI)

Formula:
CSI = (A/C)nondominant / (A/C)peripheral

Values:
- Right A/C = 30/30= 1
- Peripheral A/C = 30/10 = 3
- CSI = 1 ÷ 3 = **0.33**

Interpretation:
CSI < 0.5 → **contralateral suppression** → supports unilateral disease.

Illustration: Fraction 1/3 = 0.33 with “suppressed” right adrenal.

Worked Example 2: Raw Lab Values

Sample	Cortisol	Aldosterone
Left AV	220 µg/dL	5400 ng/dL
Right AV	730 µg/dL	6000 ng/dL
Peripheral (IVC)	16 µg/dL	340 ng/dL

Step 1 — Selectivity Index (SI)

Formula: SI = Cortisol_adrenal / Cortisol_peripheral

Purpose: Confirms correct catheter placement (adequate adrenal sampling).

Cutoffs:

- Unstimulated: SI ≥ 2
- ACTH-stimulated: SI ≥ 5

Selectivity Index Calculations

Left SI = 220 / 16 = 14 (adequate)

Right SI = 730 / 16 = 46 (adequate)

Both ≥ 2 → valid samples.

Step 2 - Lateralization Index (LI)

LI = (A/C dominant) ÷ (A/C non-dominant)

Left A/C = 5400 / 220 = 25
Right A/C = 6000 / 730 = 8

= 25 ÷ 8 = 3,1

Interpretation: LI < 4 → inconclusive, but dominant left

Step 3 — Aldosterone/Cortisol Ratios

Left A/C = 5400 / 220 = 25

Right A/C = 6000 / 730 = 8

Step 3: Contralateral Suppression Index (CSI)

Formula:
CSI = (A/C)nondominant / (A/C)peripheral

Values:
- Right A/C = 8/21= 8
- Peripheral A/C = 21
- CSI = 8 ÷ 21 = **0.38**

Interpretation:
CSI < 0.5 → **contralateral suppression** → supports unilateral disease.

Illustration: Fraction 8/21 = 0.38 with “suppressed” right adrenal.

- *2024: Resultaten bijniervenesampling discordant met beeldvorming, met een lateralisatie-index ten voordele van LINKS en veel lagere aldosteron-cortisolratio rechts dan perifeer (gemiddelde suppressie-index rechts 0.38).*
- *Surrenalectomie links op basis van resultaat bijniervenesampling. Postoperatief geen duidelijke val van het plasma-aldosteron.*
- *Vermoedelijk geen remissie; histologisch ook geen evidentie voor een kleine conntumor. Herstarten van Aldactone.*

- *2025: Electieve resectie bijniernodulus rechts - postoperatief laag aldosteron. Aldactone gestopt.*

AVS — Practical points & pitfalls

- Patient prep: medication adjustments (MRAs usually withheld when possible), correct potassium.
- Catheterization challenges: right adrenal vein is small; use experienced operators.
- Interpretation: lateralization index, contralateral suppression ratios; standardization improves yield.

Conclusion:

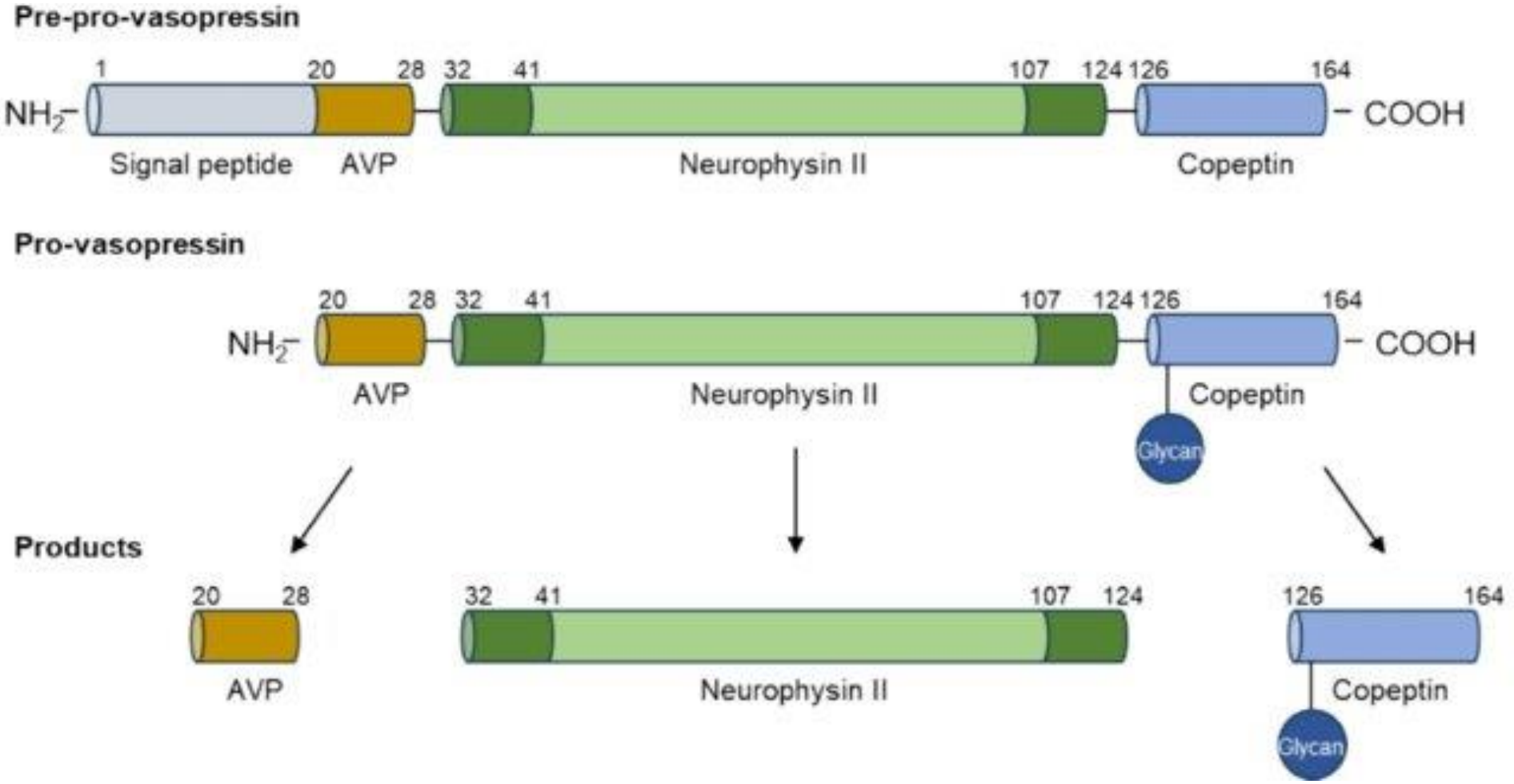
AVS remains **very important** in the diagnostic workup of primary aldosteronism, especially when the result will change management (i.e., surgery vs medical). It is *not obsolete*, but its implementation requires expertise, and patient selection is key.

Investigation of Polyuria-Polydipsia Syndrome

Diagnostic Approach and Clinical Insights

Principle of Copeptin Measurement

- Copeptin is the C-terminal peptide of the AVP prohormone.
- Secreted in equimolar amounts with AVP from the posterior pituitary.
- Copeptin is stable in plasma, making it a reliable AVP surrogate.
- Provides superior diagnostic accuracy to the water deprivation test.


Pre-pro-vasopressin
1
20
28
32
41
107
124
126
164
NH2–
– COOH
Signal peptide
AVP
Neurophysin II
Copeptin
Pro-vasopressin
20
28
32
41
107
124
126
164
NH2–
– COOH
AVP
Neurophysin II
Copeptin
Glycan
Products
20
28
AVP
32
41
107
124
Neurophysin II
126
164
Copeptin
Glycan

Indications for Test

- Polyuria >3 L/24h without osmotic cause.
- Early morning urine osmolality <750 mOsm/kg.
- Differentiation between Central DI, Nephrogenic DI, and Primary Polydipsia.
- NOT hyponatremia or SIADH

Contraindications

- Children.
- Cardiac failure.
- Seizure history.
- Significant cerebrovascular disease.
- Severe uncontrolled hypertension.

Required Equipment

- BP monitor/sphygmomanometer.
- Infusion pump with IV sets and cannulae.
- 3% saline (500–1000 mL) and 5% glucose (500 mL).
- Scales for patient weight.
- Yellow-top (serum) tubes x7 (no need for ice).

Procedure Overview

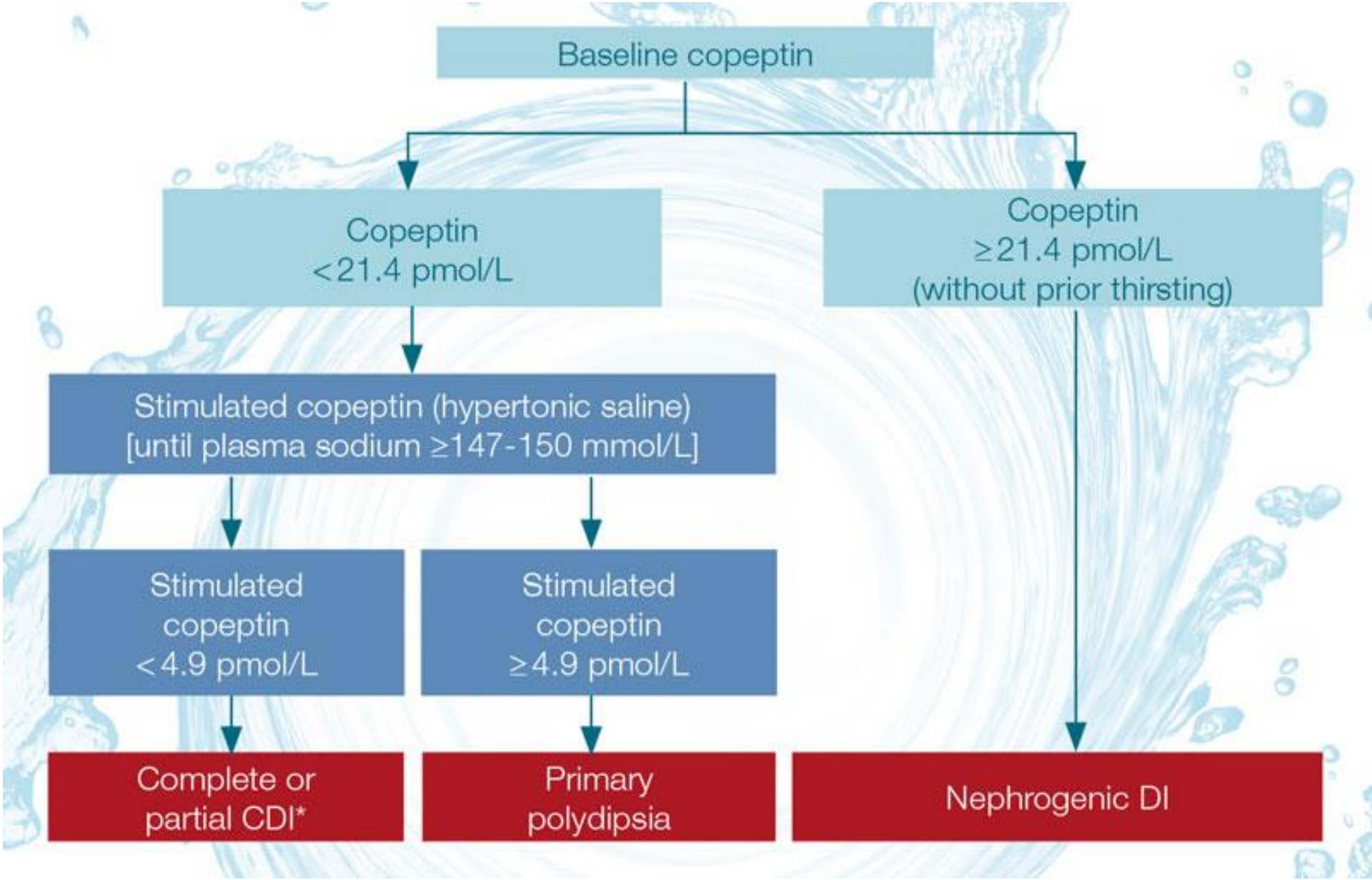
- Keep patient supine; measure BP and weight hourly.
- Insert cannulae into both arms (one for infusion, one for sampling).
- Administer 250 mL 3% saline bolus over 20 minutes.
- Infuse 3% saline at 0.15 mL/kg/min.
- Take sodium samples every 30 minutes; stop if Na >150 mmol/L.

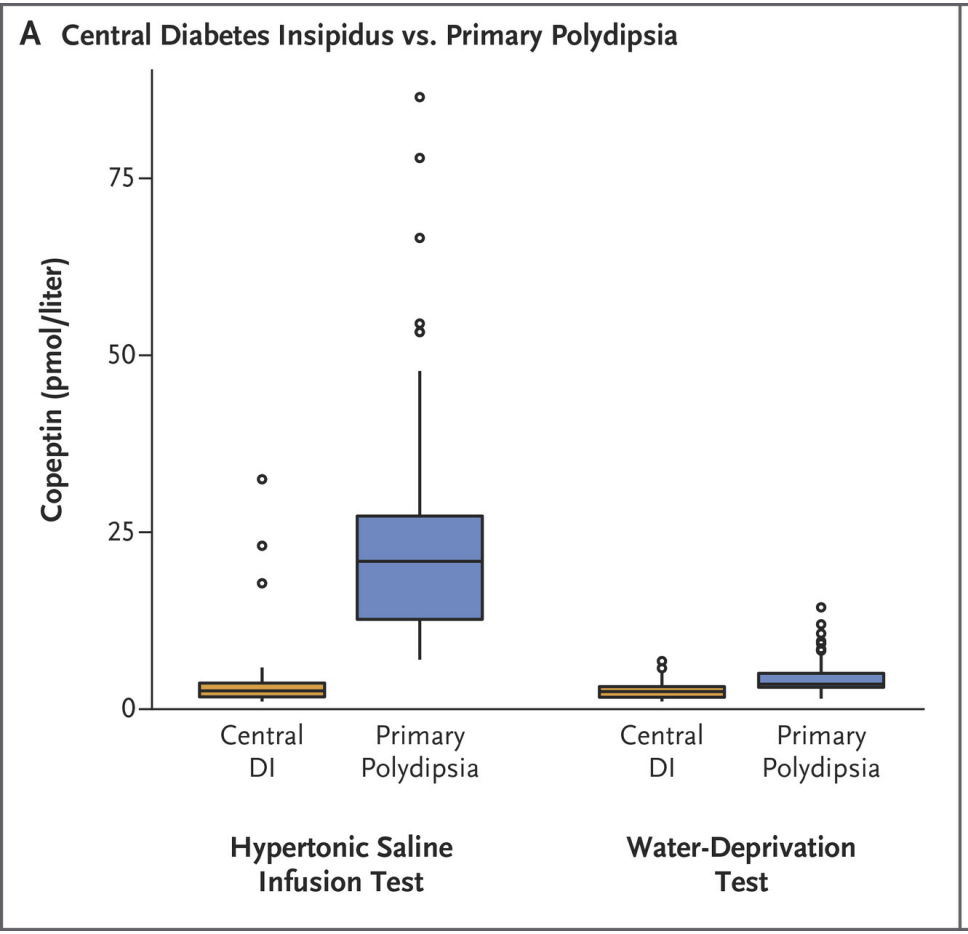
Sampling and Stopping Criteria

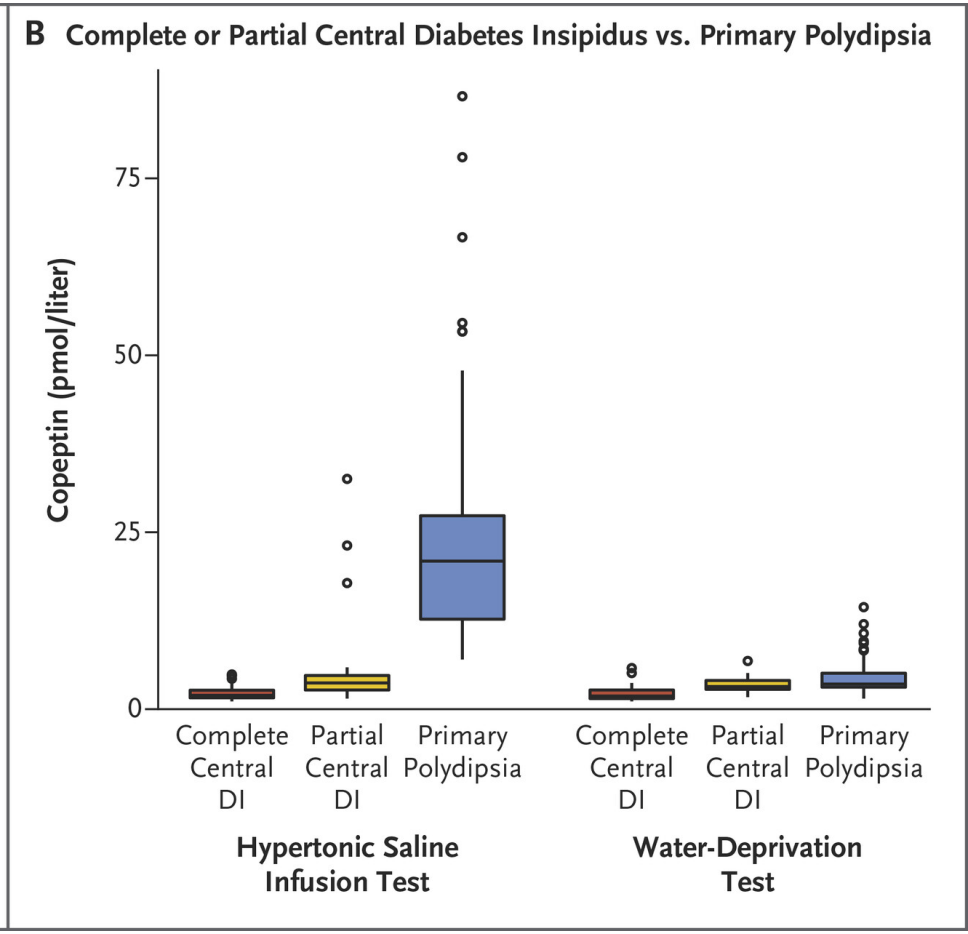
- Stop infusion when serum sodium exceeds 150 mmol/L.
- Take copeptin sample (yellow tube) and concurrent sodium measurement.
- Rehydrate with oral water (30 mL/kg) after stopping infusion.
- Recheck sodium 1 hour later.

Interpretation of Results

- Central DI: Copeptin <4.9 pmol/L (low AVP production).
- Nephrogenic DI: Copeptin >21.4 pmol/L (AVP resistance).
- Primary Polydipsia: Copeptin 4.9–21.4 pmol/L (normal AVP response).


Baseline copeptin
Copeptin
<21.4 pmol/L
Copeptin
≥21.4 pmol/L
(without prior thirsting)
Stimulated copeptin (hypertonic saline)
[until plasma sodium ≥147-150 mmol/L]
Stimulated
copeptin
<4.9 pmol/L
Stimulated
copeptin
≥4.9 pmol/L
Complete or
partial CDI*
Primary
polydipsia
Nephrogenic DI


A Central Diabetes Insipidus vs. Primary Polydipsia
Copeptin (pmol/liter)
75
50
25
0
Central DI
Primary Polydipsia
Central DI
Primary Polydipsia
Hypertonic Saline Infusion Test
Water-Deprivation Test


B Complete or Partial Central Diabetes Insipidus vs. Primary Polydipsia
Copeptin (pmol/liter)
75
50
25
0
Complete Central DI
Partial Central DI
Primary Polydipsia
Complete Central DI
Partial Central DI
Primary Polydipsia
Hypertonic Saline Infusion Test
Water-Deprivation Test

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Safety and Post-Test Care

- Monitor for headache, thirst, nausea, vertigo, malaise.
- Ensure adequate rehydration post-procedure.
- Document sodium trends and timing accurately.