Adrenal Vein Sampling: A Critical Tool for Subtyping Primary Aldosteronism

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Disclosures
- No conflicts of interest relevant to this presentation

Outline
- Definitions
- Patient selection and preparation
- Technique
- Controversies
- Assessment of successful catheterization
- Interpretation of results and assessment of successful lateralization

Primary Aldosteronism
- Most common adrenal hypersecretory disease, characterized by excess aldosterone secretion
- Physiology of aldosterone excess
  - Hypertension
  - Hypokalemia
  - Metabolic alkalosis
- Prevalence of 5-10% in unselected hypertensive patients

Sampling for Lateralization
- Is over-secretion unilateral or bilateral?
  - Unilateral hypersecretion nearly always from an aldosterone-producing adenoma (APA) → Unilateral adrenalectomy
  - Bilateral hypersecretion nearly always from bilateral idiopathic hyperplasia (IHA) → Medical management with MR blockade


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AVS is Underutilized!

- Technically challenging, risky, invasive
- Lack of accepted standards for performance of AVS
- Lack of established criteria for interpretation of results
- Failure rates are unacceptably high!

Evaluation of the German Conn’s Registry

- Retrospective Data Analysis
  - 230 of 569 patients with PA underwent AVS in 5 participating centers between 1990-2007
  - Selectivity index ≥ 2.0 denoted successful adrenal vein catheterization
    • 61/200 patients (30.5%) successfully catheterized on both sides
    • In 42.5%, AVS selective only on the left
    • 33/200 patients (16.5%), AVS unsuccessful on BOTH sides

German Conn’s Registry

| Table: Conn’s German Registry
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<td>PAC/PRA</td>
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| PAC/PRA >32 (sensitivity 100%, specificity 61% for APA)1
| APAs associated with more severe hypokalemia (≤ 3.0 mEq/L) and higher plasma levels of aldosterone (≥ 25 ng/dL) compared to IHA

Patient Selection for AVS

- Laboratory analysis
  - Plasma Aldosterone Concentration to Plasma Renin ratio (PAC/PRA)
    • Normal PAC/PRA is 4-10
    • In primary aldosteronism PAC/PRA is ~30-50
    - PAC/PRA >32 (sensitivity 100%, specificity 61% for APA)1
  - APAs associated with more severe hypokalemia (≤ 3.0 mEq/L) and higher plasma levels of aldosterone (≥ 25 ng/dL) compared to IHA


Patient Preparation

- Optimally performed in the morning
- Supine position for 1 hour prior to AVS
- Correct hypokalemia, if present
- Careful adjustment of antihypertensive agents before and during AVS
- MR antagonists or amiloride stopped for at least 4 weeks before AVS
- Pre-AVS contrast-enhanced CT

AVS influences the management in as many as 35.7% of patients who would otherwise have been treated incorrectly based on results of CT or other modalities!1

AVS Technique

- Transfemoral access
- Single femoral vein access → *sequential AVS*
- Dual femoral vein access → *simultaneous AVS*
- Sampling order: 1) Right adrenal vein 2) Left adrenal vein 3) Infrarenal IVC
  - Minimize time between sample collection

AVS: Technique

- ± Heparin bolus prior to adrenal vein selection (70-100 U/kg)
- Catheter selection
  - Right adrenal vein → Cobra 2, Mikaelsson, Simmons-1, RDC
  - Left adrenal vein → Simmons-2, Simmons-3
  - Extra sidehole on catheter to permit blood aspiration without adrenal vein collapse*

*Extra sidehole on catheter to permit blood aspiration without adrenal vein collapse*
Right Adrenal Vein

Inferior Accessory HV

Right adrenal vein

Sample Processing
- 8 mL aliquots of blood are aspirated sequentially from each adrenal vein and the infrarenal IVC
  - Right side sampled first as it is technically most challenging to cannulate
- Each 8 mL sample is divided between sampling vials (i.e. 4 mL in each vial) and sent for rapid cortisol assay and aldosterone
- If each selectivity index (SI) ≥ 3, AVS successful

AVS: Results Interpretation
- Selectivity Index (SI) = Adrenal vein:peripheral vein cortisol ratio
- Successful catheterization of the adrenal vein is reflected in a selectivity index ≥ 3*
- Lateralization Index (LI) = Ipsilateral A/C: Contralateral A/C ratio
- LI ≥ 4.0 denotes unilateral APA
- LI ≤ 2.0 denotes IHA
- LI 2.0-4.0 borderline

*When cosyntropin is used; SI ≥ 2 reflects consensus threshold when cosyntropin is not used
Pharmacological Stimulation with Cosyntropin
- Most adenomas are partially ACTH-sensitive
- Rationale:
  - Minimize stress-induced fluctuations in aldosterone secretion during sequential (non-simultaneous) AVS
  - Maximize cortisol gradient between adrenal vein and the IVC (mixed venous blood)
  - Maximize aldosterone secretion from a unilateral adenoma

Cosyntropin Stimulation
- Continuous cosyntropin infusion (50 µg/h) started at least 30 minutes before sampling
- Single 250µg bolus during AVS

Bilaterally Simultaneous or Sequential Catheterization?
- Pulsatile secretion of aldosterone can generate time-related variability in hormone concentrations
- Consensus guidelines:
  - If cosyntropin stimulation is used, sequential technique is acceptable but higher SI and LI thresholds are indicated
  - If no cosyntropin stimulation is used, bilateral simultaneous technique should be performed

Safety and Management of Complications
- In experienced hands, AVS is safe with very low complication rate
- Adrenal vein rupture rate 0.61% in AVIS Phase I
  - Dissection
  - Infarction
  - Intraglandular/periadrenal hematoma
  - Vessel thrombosis

Summary
- Despite its widespread use for almost two decades, AVS is not performed in a standardized fashion, even at major referral centers worldwide
- We likely overestimate our own success at bilateral selective sampling
- Numerous techniques and protocols exist to improve the likelihood of successful bilateral selection
- Further work is needed to arrive at threshold limits for selectivity and lateralization indices

Consensus Threshold Values (for identifying lateralization):
- Without cosyntropin: LI≥2.0 in combination with SI≥2.0
- With cosyntropin: LI≥4.0 in combination with SI≥3.0