Pitfalls in adrenal vein sampling interpretation

Pièges dans l’interprétation d’un cathétérisme selectif des veines surrénaliennes chez les patients avec hyperaldostéronisme primaire

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Primary aldosteronism (PA) is one of the most common form of secondary hypertension (5-15%). It is potentially curable when aldosterone secretion is lateralized.
When primary aldosteronism is diagnosed, is standard radiologic imaging sufficient to perform an adrenalectomy?
Frequency of non functional adrenal tumors increases with age

Adrenal vein sampling vs radiologic imaging

- 472 studies, 38 analyzed (950 patients)

Results

• Discordance between CT/IRM avec AVS: 37.8% (359/950)
• Inappropriate adrenal surgery: 14.6% (bilateral secretion)
• Inappropriate exclusion of adrenalectomy: 19.1% (unilateral secretion)
• Adrenalectomy on the wrong side: 3.9%

Key questions to be asked before adrenal vein sampling

1. Is the patient seeking long-term cure of hypertension and hypokalemia with adrenalectomy?
   - YES
   - NO

2. Is adrenalectomy indicated (size, tumor) or is adrenalectomy out of question (surgery risk, HF-I or FH-III)?
   - YES
   - NO

3. Does the patient accept a 20-50% risk of having the wrong adrenal gland removed?
   - YES
   - NO

4. Inform the patient of the possibility of unsuccessful AVS and of a 0.5% risk of complication
   - NO

5. Perform AVS
   - AVS not necessary
What is adrenal vein sampling (AVS)?

- Adrenal venous sampling (AVS) is the gold standard method for determining unilateral or bilateral aldosterone oversecretion.
- AVS is a technically difficult procedure and correct positioning of the catheter (selectivity) is crucial for interpretation.
Angiography during AVS
Anatomic variant of the right adrenal vein

In most of the cases, the principal adrenal vein on the right opens in the IVC and the principal adrenal vein on the left opens in the left renal vein

- 5% variations on the right (4 of 88 cases)
- 6% variations on the left (5 of 88 cases)


Courtesy of Dr Doenz, Département de radiologie CHUV
The Selectivity Index

- Plasma Cortisol Concentration (PCC)
- $\text{PCC}_{\text{side}}/\text{PCC}_{\text{IVC}}$
- Values greater than the cutoff confirm that the blood sample was obtained from the adrenal vein
### Table 1  Features of various AVS interpretation rules

<table>
<thead>
<tr>
<th>Component</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>No biochemical assessment of catheter positioning</td>
<td>N/A</td>
</tr>
<tr>
<td>Primary confirmation of correct adrenal catheter placement with adrenal:IVC cortisol ratios</td>
<td>Cortisol_affected:Cortisol_IVC 2:1 or 3:1 or 4:1 or 5:1</td>
</tr>
<tr>
<td>No ACTH infusion</td>
<td>N/A</td>
</tr>
<tr>
<td>Bolus or continuous ACTH infusion</td>
<td>15-min post 250 ug ACTH bolus or 25 ug Cosyntropin IV 30 min prior to sampling</td>
</tr>
<tr>
<td>Pre- and post-ACTH infusion data collection</td>
<td>N/A</td>
</tr>
<tr>
<td>Lateralization defined by R:L normalized aldosterone ratio</td>
<td>Aldosterone/cortisol_affected:aldosterone/cortisol_unaffected 2:1 or 3:1 or 4:1 or 5:1</td>
</tr>
<tr>
<td>Lateralization defined by suppression of contralateral (uninvolved) normalized aldosterone ratio vs. IVC</td>
<td>Aldosterone/cortisol_unaffected:aldosterone/cortisol_IVC 1.0 or &lt;1.0</td>
</tr>
<tr>
<td>Lateralization defined by R:L absolute aldosterone levels</td>
<td>Aldosterone_affected:aldosterone_unaffected &gt; 10</td>
</tr>
<tr>
<td>Lateralization defined by combinations of above</td>
<td></td>
</tr>
</tbody>
</table>

Kline et al., Int Urol Nephrol (2008) 40:1035–1043
The Selectivity Index

AVS studies that are not bilaterally successful should not be used to establish lateralization

- Use of increasingly restrictive cutoffs markedly decreases the number of AVS studies that are bilaterally selective.
- The cutoff value for the SI should be ≥2.0 under unstimulated conditions.
- The cutoff value for the SI should be ≥3.0 during cosyntropin stimulation.

*Hypertension*. 2014;63:151-160
What is the best way to perform AVS?

The pulsatile pattern of secretion of cortisol and aldosterone can generate time-related variability in hormone concentrations in the adrenal vein blood:

- Cosyntropin stimulation and bilateral simultaneous sampling can minimize this time-related variability compared with sequential sampling without cosyntropin stimulation;
- Outcome data supporting one approach over the other are not available.
### Sequential vs Bilaterally simultaneous

<table>
<thead>
<tr>
<th>Catheterization</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential</td>
<td>Easier for the radiologist</td>
<td>Pulsatile secretion = chance of creating time-related artificial gradients</td>
</tr>
<tr>
<td>Bilaterally simultaneous</td>
<td>Minimises effect of pulsatile secretion</td>
<td>AVT, duration of procedure</td>
</tr>
</tbody>
</table>
## Unstimulated vs Pre-stimulated

<table>
<thead>
<tr>
<th>Catheterization</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-stimulated (ACTH)</td>
<td>Increases selectivity, decreases effect of pulsatile secretion</td>
<td>May lower diagnostic accuracy (missing aldosterone lateralization)</td>
</tr>
<tr>
<td>Unstimulated</td>
<td>Easier procedure</td>
<td>Decreases selectivity</td>
</tr>
</tbody>
</table>
Is cortisol the correct marker to use to assess selectivity?

The ideal marker:
- short half-life
- originates mostly from the adrenals
- continuous and stable secretion

Plasma Metanephrine and Adrenal Venous Sampling

Plasma Metanephrine for Assessing the Selectivity of Adrenal Venous Sampling


Why would plasma metanephrine be a more reliable candidate?

<table>
<thead>
<tr>
<th></th>
<th>Cortisol</th>
<th>Metanephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Production</strong></td>
<td>60-70% from adrenal</td>
<td>&gt;90% from adrenal (&lt;10% from circulating epinephrine)</td>
</tr>
<tr>
<td><strong>Secretion</strong></td>
<td>Pulsatile</td>
<td>Continuous</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>Long (~ 100 minutes)</td>
<td>Short (~ 3-5 min)</td>
</tr>
<tr>
<td><strong>Concentration in adrenal blood/systemic blood</strong></td>
<td>Variable (15-30)</td>
<td>High (~ 80-100)</td>
</tr>
<tr>
<td><strong>Concentration modification to stress</strong></td>
<td>++++</td>
<td>+</td>
</tr>
</tbody>
</table>
### Success Rates of Selective AVS With and Without Cosyntropin Stimulation According to Cortisol-Derived and Metanephrine-Derived SI Cutoffs

<table>
<thead>
<tr>
<th>AVS Procedures</th>
<th>No. (%) Based on Cortisol (Cutoff 3.0)</th>
<th>No. (%) Based on Cortisol (Cutoff 2.0)</th>
<th>No. (%) Based on Metanephrine (Cutoff 12.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosyntropin stimulated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAV</td>
<td>44/52 (85)</td>
<td>46/52 (89)</td>
<td>43/52 (83)</td>
</tr>
<tr>
<td>LAV</td>
<td>51/52 (98)</td>
<td>52/52 (100)</td>
<td>51/52 (98)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>43/52 (83)</td>
<td>46/52 (89)</td>
<td>43/52 (83)</td>
</tr>
<tr>
<td>Nonstimulated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAV</td>
<td>26/34 (76)</td>
<td>31/34 (91)*</td>
<td>32/34 (94)*</td>
</tr>
<tr>
<td>LAV</td>
<td>24/34 (71)†</td>
<td>29/34 (85)†*</td>
<td>33/34 (97)*</td>
</tr>
<tr>
<td>Bilateral</td>
<td>19/34 (56)†</td>
<td>27/34 (79)*</td>
<td>31/34 (91)*</td>
</tr>
</tbody>
</table>

AV indicates adrenal vein; AVS, AV sampling; LAV, left adrenal vein; and RAV, right adrenal vein.

*P<0.05 higher than corresponding success rates determined by a cortisol-derived cutoff of 3.0.
†P<0.05 lower than corresponding success rate in cosyntropin-stimulated samplings.

Using ROC curves to determine cutoff values for cortisol, free metanephrines and the fMN/tMN ratio

Christou F et al. ESH2017
Results: cut-off values for selectivity index (based on ROC curves)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Left adrenal selectivity index</th>
<th>Right adrenal selectivity index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>&gt;2.6</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>Free metanephrine</td>
<td>&gt;10</td>
<td>&gt;9.9</td>
</tr>
<tr>
<td>Free-to-total metanephrine ratio</td>
<td>&gt;0.31</td>
<td>&gt;0.27</td>
</tr>
</tbody>
</table>

Christou F et al. ESH2017
The use of the free-to-total metanephrines allows a cartography of venous sampling.
Androstenedione is another promising adrenal marker of selectivity.

73% rescue of AVS judged non selective with cortisol.

Ceolotto G. et al. Hypertension. 2017;70:342-346
Conclusion

- Adrenal vein sampling remains the gold standard method to determine lateralisation of aldosterone secretion
- There is no consensus yet on whether AVS should be sequential or bilaterally simultaneous
- There is no consensus yet on whether AVS should be unstimulated or stimulated
- AVS should be performed by an experienced team with standard operating procedures
- New adrenal marker of selectivity such as metanephrine or androstenedione are an important step forward in the simplification and the success of the procedure
What is the ideal marker of selectivity?

- Historically, cortisol has been used as a marker of selectivity
- Definition SI: ratio $PCC_{\text{side}} / PCC_{\text{ivc}} >$ threshold on both sides
- The ideal marker:
  - short half-life
  - originates mostly from the adrenals
  - continuous and stable secretion
Hypothesis:
Use of the Free-to-total metanephrine ratio cou