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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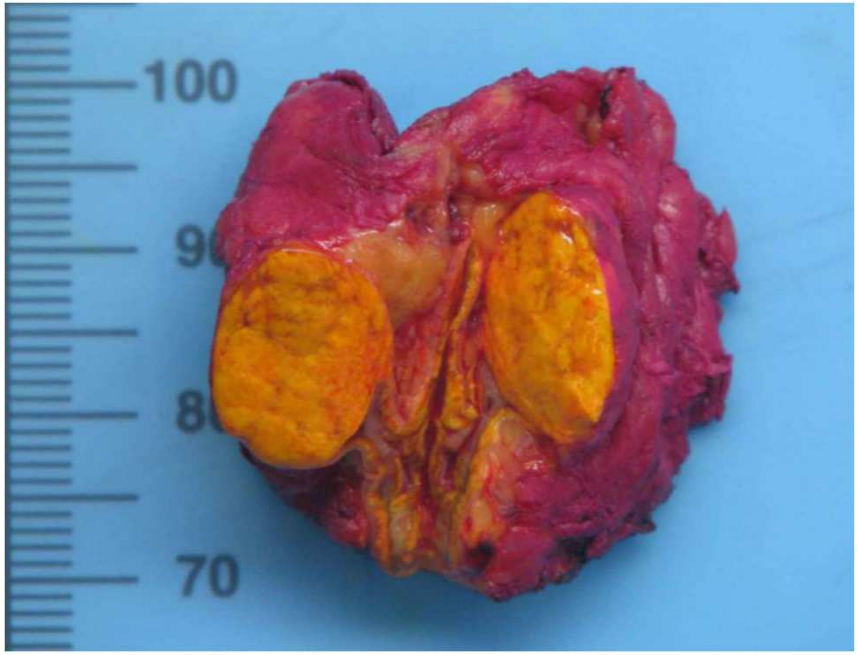
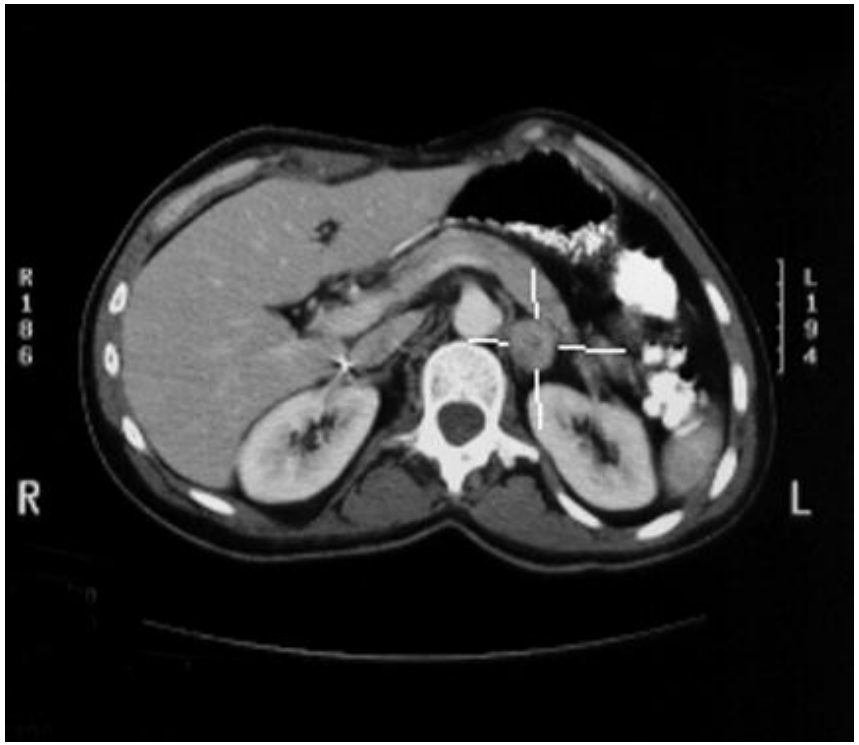
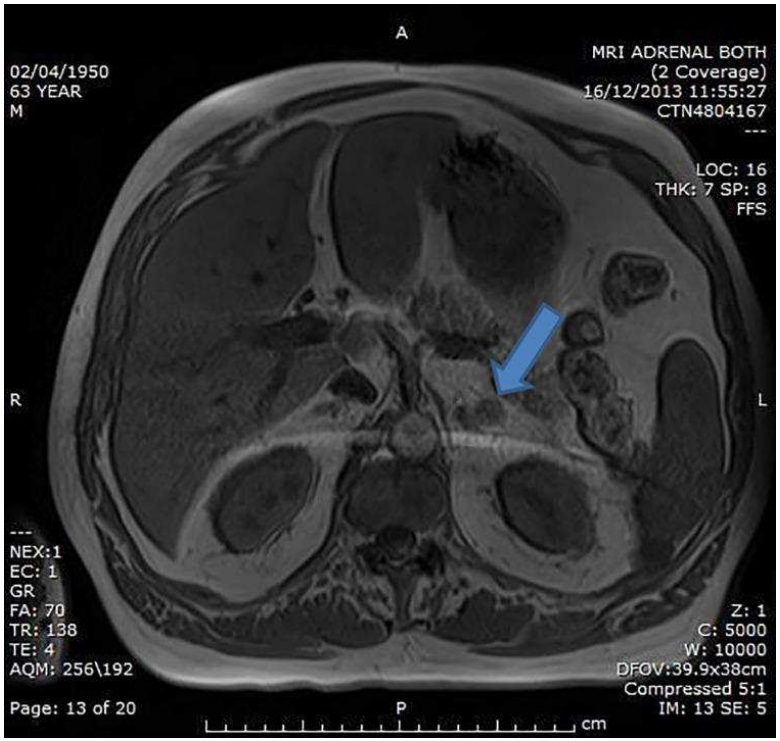
Background

- Primary aldosteronism (PA) is one of the most common form of secondary hypertension (5-15%)
- It is potentially curable when aldosterone secretion is lateralized

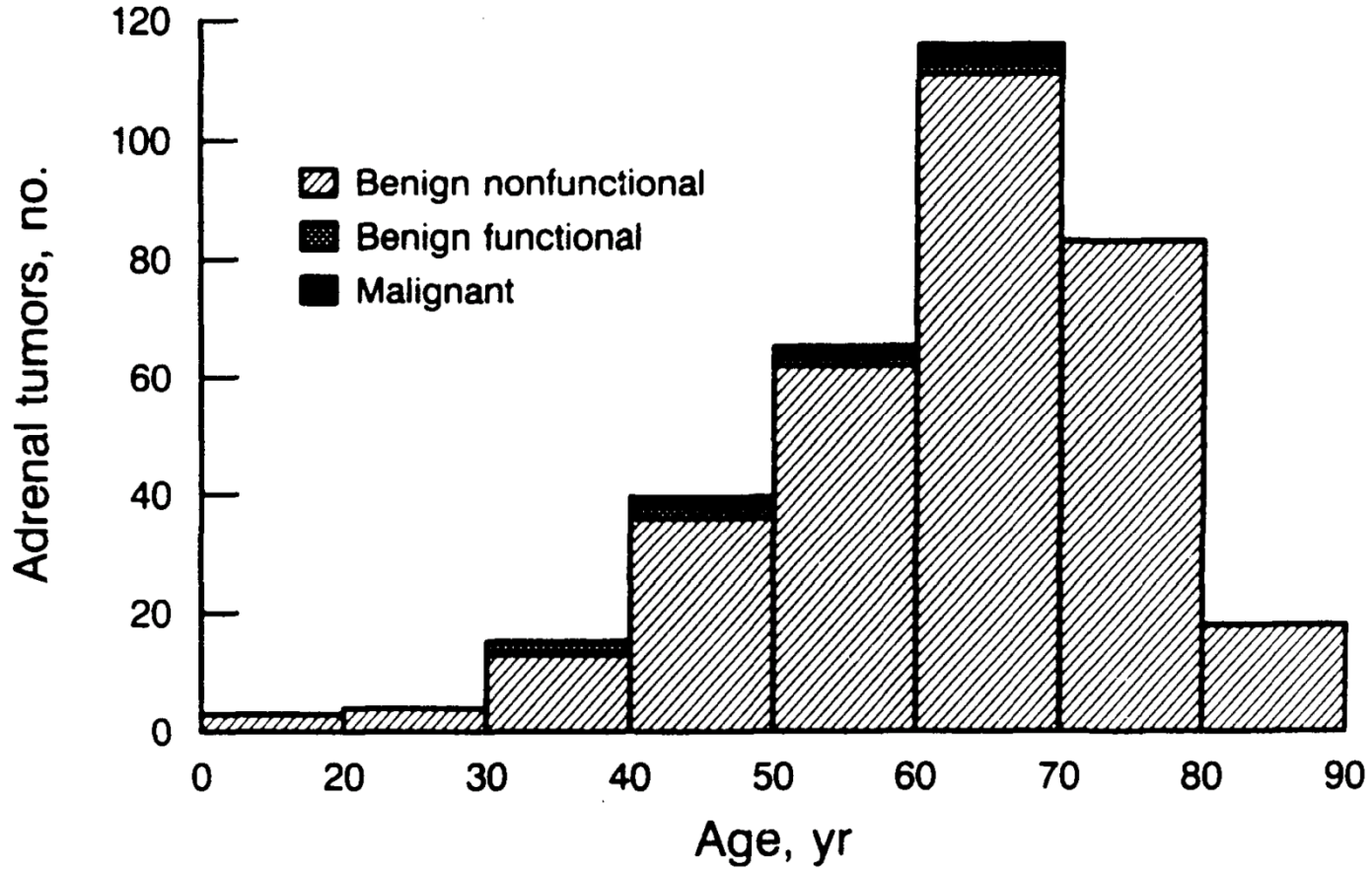


When primary aldosteronism is diagnosed, is standard radiologic imaging sufficient to perform an adrenalectomy?





Frequency of non functional adrenal tumors increases with age



Kloos R et al. Endo. Reviews.1995

Adrenal vein sampling vs radiologic imaging

Annals of Internal Medicine | REVIEW

Systematic Review: Diagnostic Procedures to Differentiate Unilateral From Bilateral Adrenal Abnormality in Primary Aldosteronism

Marlies J.E. Kempers, MD, PhD; Jacques W.M. Lenders, MD, PhD; Lieke van Outheusden, MSc; Gert Jan van der Wilt, PhD; Leo J. Schultze Kool, MD, PhD; Ad R.M.M. Hermus, MD, PhD; and Jaap Deinum, MD, PhD

- 472 studies, 38 analyzed (950 patients)

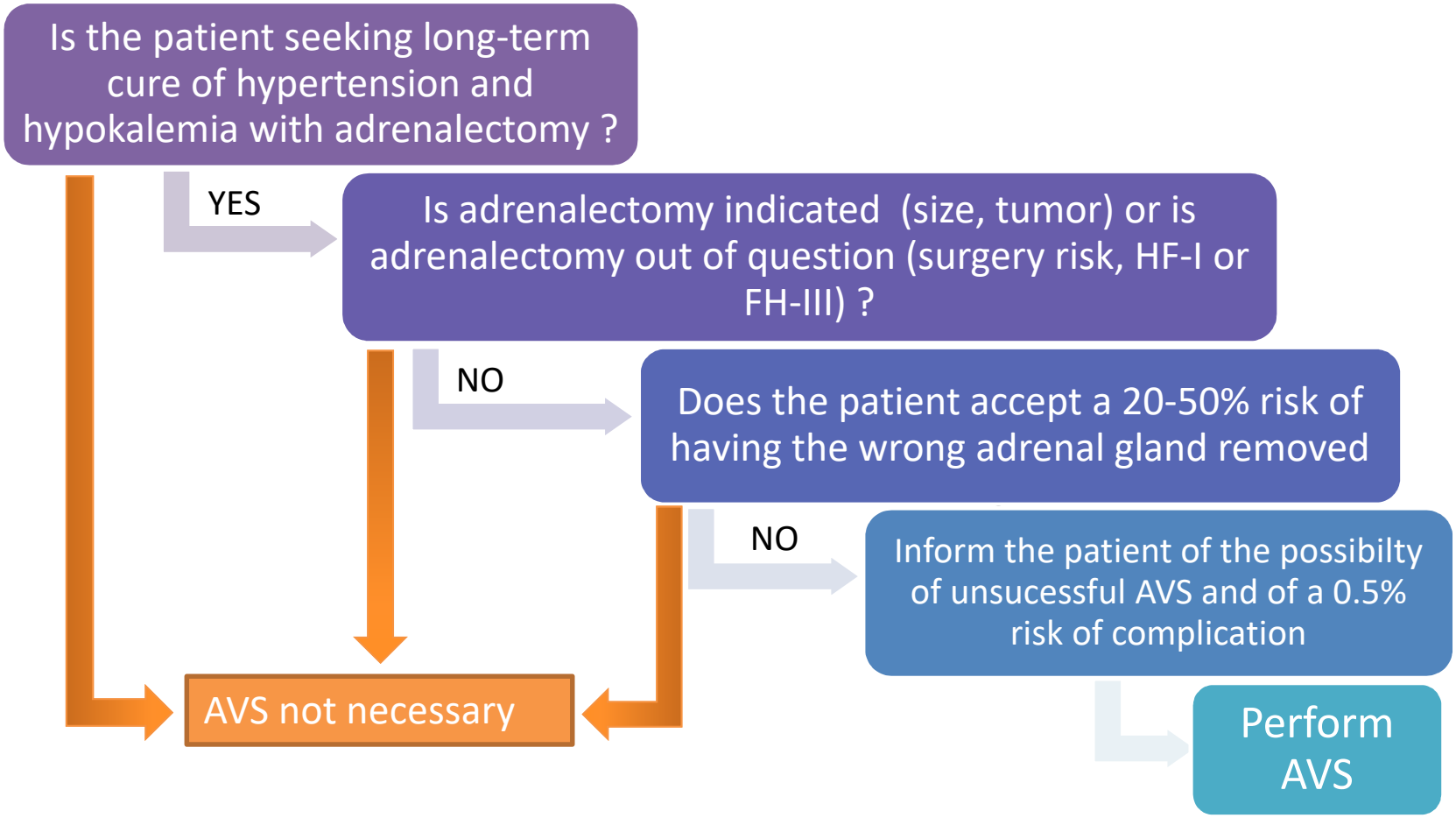
Kempers et al., *Ann Intern Med.* 2009;151:329-337

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%

Kempers et al., *Ann Intern Med.* 2009;151:329-337

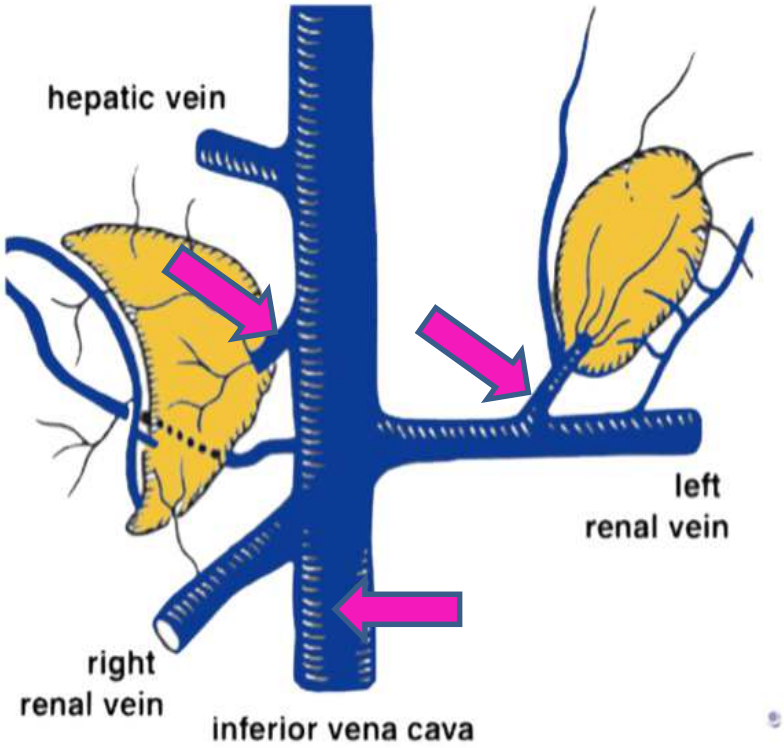
Key questions to be asked before adrenal vein sampling



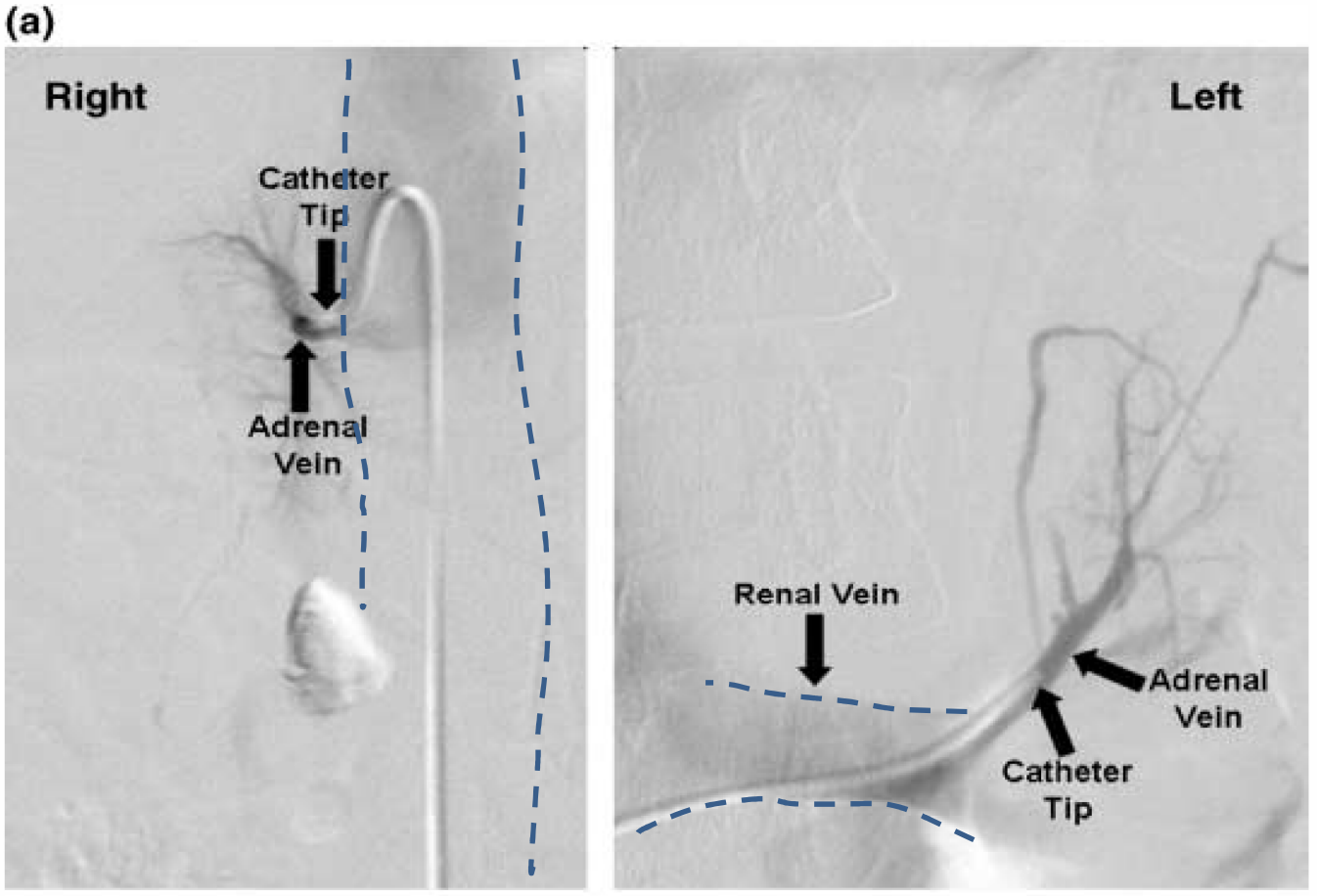
Rossi et al. Hypertension. **2014;63:151-**

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 positionning of the catheter (selectivity) is crucial for interpretation



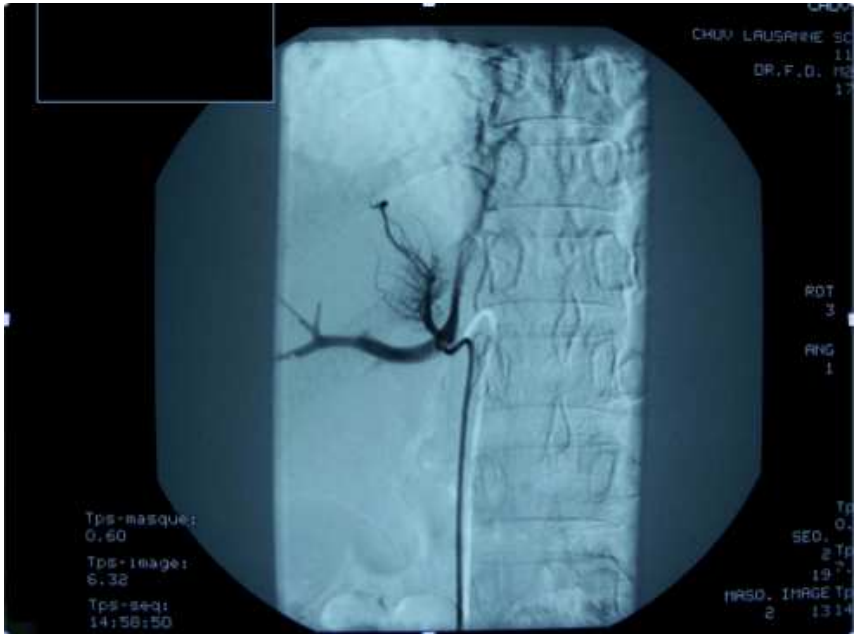
Angiography during AVS



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)

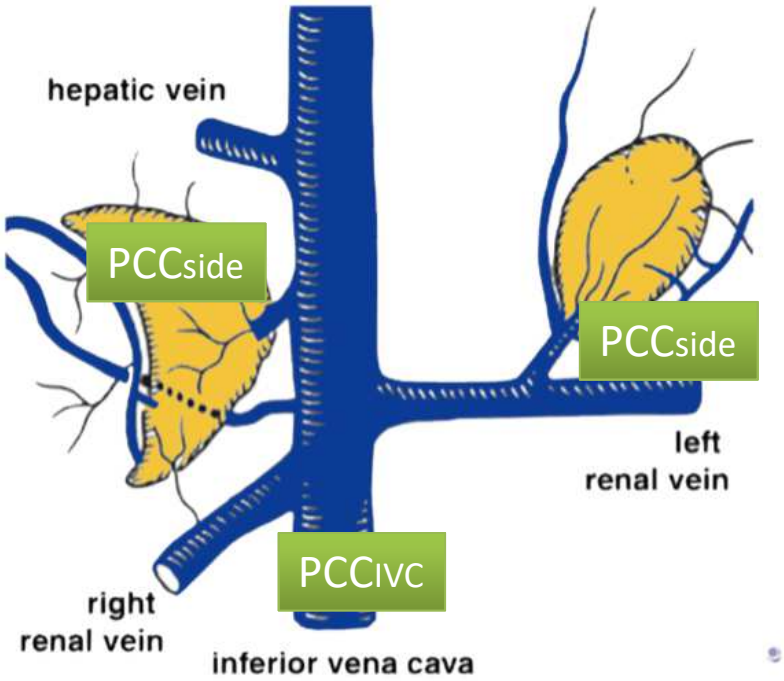


Courtesy of Dr Doenz, Département de radiologie CHUV

Sebe et al. Surg Radiol Anat (2002) 24:222-225

The Selectivity Index

- Plasma Cortisol Concentration (PCC)
- PCC_{side}/PCC_{IVC}
- Values greater than the cutoff confirm that the blood sample was obtained from the adrenal vein



Cut-off values for determining the selectivity and lateralisation indexes

Table 1 Features of various AVS interpretation rules

Component	Examples
No biochemical assessment of catheter positioning	N/A
Primary confirmation of correct adrenal catheter placement with adrenal:IVC cortisol ratios	$Cortisol_{adrenal}$:$Cortisol_{IVC}$
	2:1 or 3:1 or 4:1 or 5:1
No ACTH infusion	N/A
Bolus or continuous ACTH infusion	15-min post 250 ug ACTH bolus or 25 ug Cosyntropin IV 30 min prior to sampling
Pre- and post-ACTH infusion data collection	N/A
Lateralization defined by R:L normalized aldosterone ratio	Aldosterone/$cortisol_{affected}$:aldosterone/$cortisol_{unaffected}$
	2:1 or 3:1 or 4:1 or 5:1
Lateralization defined by suppression of contralateral (uninvolved) normalized aldo vs. IVC	Aldosterone/$cortisol_{unaffected}$:aldosterone/$cortisol_{IVC}$
	1.0 or <1.0
Lateralization defined by R:L absolute aldosterone levels	$Aldosterone_{affected}$:$aldosterone_{unaffected}$
	> 10
Lateralization defined by combinations of above	

Selectivity index

Lateralization index

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

The Selectivity Index

AVS studies that are not bilaterally successful should no 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

Catheterization	Advantage	Disadvantage
Sequential	Easier for the radiologist	Pulsatile secretion = chance of creating time-related artifical gradients
Bilaterally simultaneous	Minimises effect of pulsatile secretion	AVT, duration of procedure

Unstimulated vs Pre-stimulated

Catheterization	Advantage	Disadvantage
Pre-stimulated (ACTH)	Increases selectivity, decreases effect of pulsatile secretion	May lower diagnostic accuracy (missing aldosterone lateralization)
Unstimulated	Easier procedure	Decreases selectivity

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

Tanja Dekkers, Jaap Deinum, Leo J. Schultzekool, Dirk Blondin, Oliver Vonend, Ad R.R.M. Hermus, Mirko Peitzsch, Lars C. Rump, Gerald Antoch, Fred C.G.J. Sweep, Stefan R. Bornstein, Jacques W.M. Lenders, Holger S. Willenberg, Graeme Eisenhofer

Dekkers T et al. *Hypertension. 2013;62(6):1152-1157.*

Why would plasma metanephrine be a more reliable candidate?

	Cortisol	Metanephrine
Production	60-70% from adrenal	>90% from adrenal (<10% from circulating epinephrine)
Secretion	Pulsatile	Continuous
Half-life	Long (~ 100 minutes)	Short (~ 3-5 min)
Concentration in adrenal blood/systemic blood	Variable (15-30)	High (~ 80-100)
Concentration modification to stress	++++	+

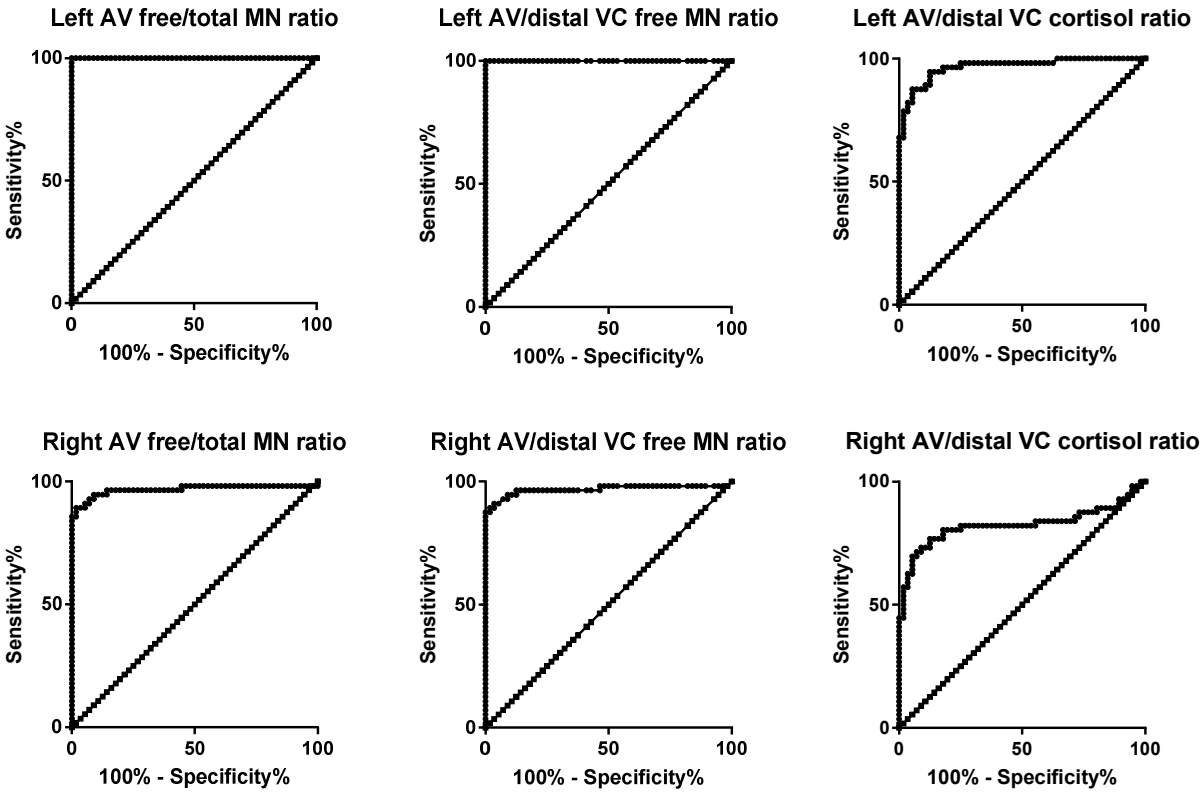
Success Rates of Selective AVS With and Without Cosyntropin Stimulation According to Cortisol-Derived and Metanephrine-Derived SI Cutoffs

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

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

Dekkers T et al. *Hypertension. 2013;62(6):1152-1157.*

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



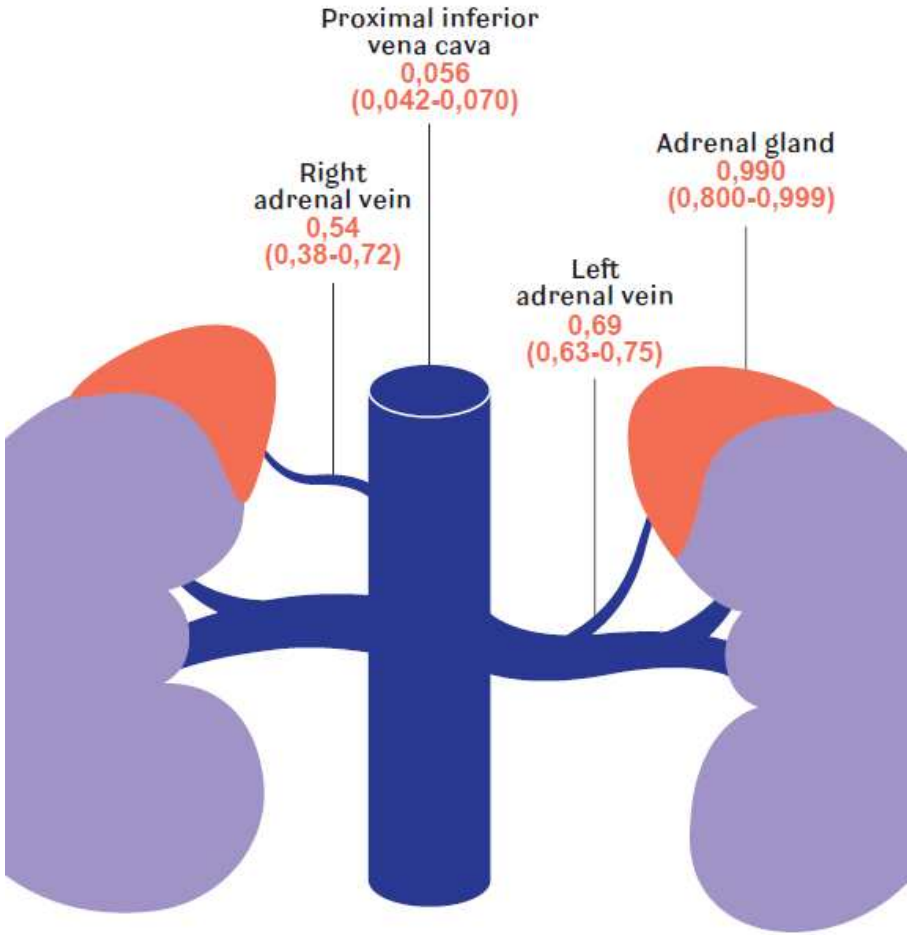
Christou F et al.ESH2017

Results: cut-off values for selectivity index (based on ROC curves)

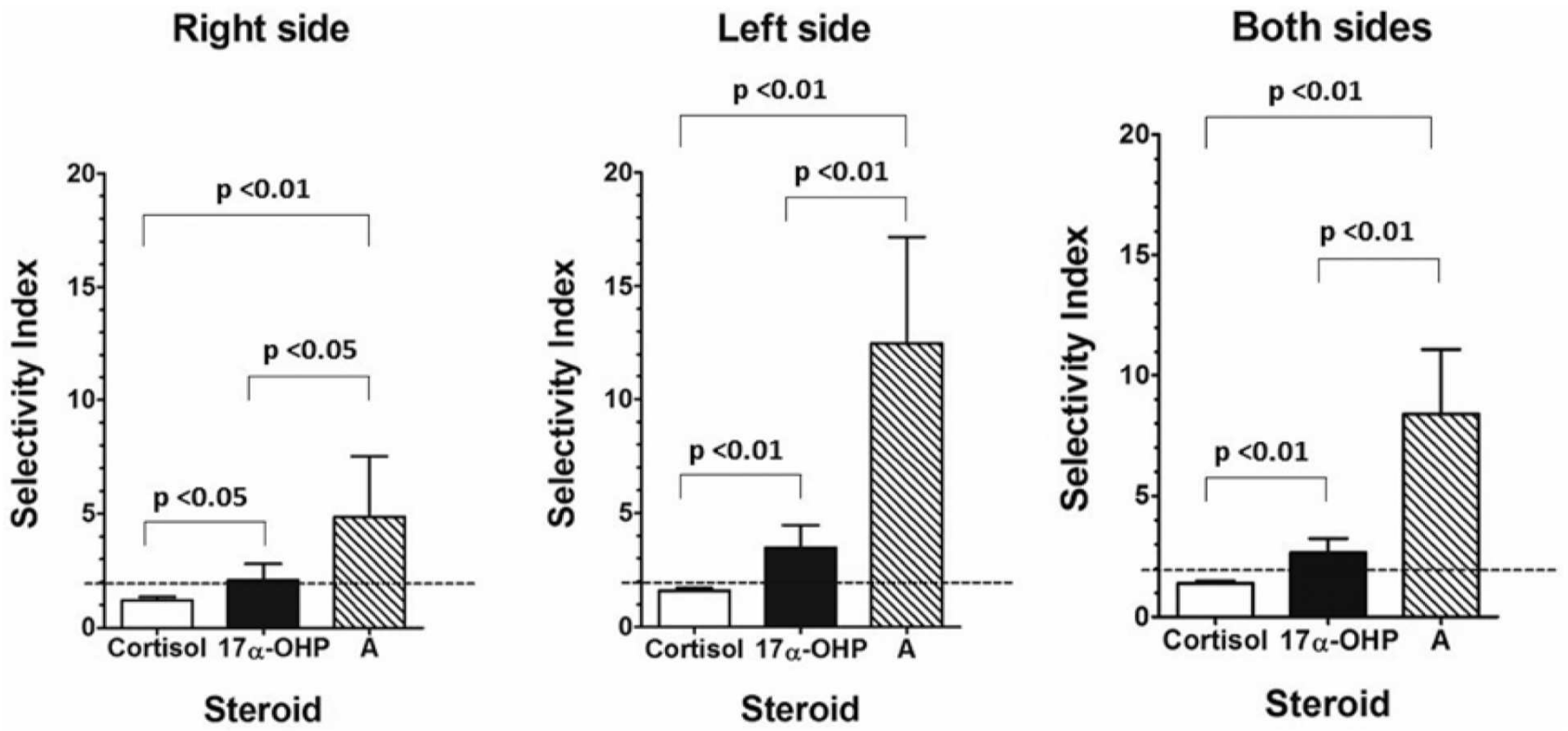
Parameter	Left adrenal selectivity index	Right adrenal selectivity index
Cortisol	>2.6	>2.5
Free metanephrine	>10	>9.9
Free-to-total metanephrine ratio	>0.31	>0.27

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_{side}/PCC_{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