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Mémoire de Maîtrise en médecine

Primary aldosteronism: The role of plasma free metanephrines as a lateralization marker in adrenal vein sampling and its concordance with CT-scan.

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Abstract

Background:

Primary aldosteronism (PA) is a common cause of secondary hypertension found in 5 to 10% of the hypertensive patients. The diagnostic of PA is important because it is associated with adverse cardiovascular outcomes and may be cured with surgery. The principal forms of PA are the adrenal adenoma (unilateral) and the hyperplasia of adrenal glands (bilateral). Adrenal vein sampling (AVS) is considered the gold standard to distinguish the unilateral from the bilateral form of PA. Compared to computed tomography scanners (CT-scan), AVS is often discordant. This discordance could be secondary to a lack of sensitivity of cortisol, the marker used to assess lateralization. Free metanephrines (fMN), which are continuously released by the adrenal gland could be a potential alternative. We hypothesized that the discordance with CT-scans would be lower when fMN were used as marker of lateralization.

Objective:

To compare the concordance of adrenal angio-CT with AVS using cortisol (control marker) and free metanephrine (new marker) as AVS lateralization markers.

Methods:

This study was prospective and monocentric. Patients with PA who had both a CT-scan and a bilaterally selective AVS and were included in the analysis. A Fisher exact test was used to compare the two methods (AVS and CT-san) with each marker. A Cohen's kappa coefficient was then used to compare the level of agreement.

Results:

A total of 101 participants (42 women/49 men) were included in the Study. Using a cut-off level of 3 for lateralization, the levels of agreement of CT-scan with AVS using fMN was 0.301 ± 0.072 compared to 0.272 ± 0.070 with AVS using cortisol. Using a cut-off level of 5 for lateralization, the levels of agreement of CT-scan with AVS using fMN was 0.247 ± 0.066 compared to 0.195 ± 0.064 with AVS using cortisol. The best agreement between AVS using PCC and PFMC is when the less stringent lateralization index is used (3 vs 5).

Conclusion:

The use of plasma free metanephrine concentration as a maker for lateralization only marginally improved the concordance of AVS compard to CT-scan. It confirms that the decision to surgically or pharmacologically treat patient with hypertension should no rely solely on imagery. More studies are needed to determine the utility of fMN in the interpretation of AVS lateralization.

Keywords: Primary aldosteronism, Cortisol, Free metanephrine, Adrenal vein sampling, Computed tomography, secondary hypertension.

Table of contents

Abstract 2

Table of contents 3

Introduction 4

Methodology 6

- Imagery 6
  - Adrenal vein sampling protocol 6
  - Adrenal CT protocol 7
  - Images analysis 7
- Hormones 7
- Statistics 8

Results 9

- Concordance between CT and AVS using cortisol as marker of lateralization 11
- Concordance between CT and AVS using free metanephrines as marker of lateralization 13
- Concordance between AVS using cortisol as marker of lateralization and AVS using free metanephrines as marker of lateralization 15
- Agreement 17

Discussion 18

- Limitations 18
- Results generalization 19

Conclusion 20

References 21

Introduction

Primary aldosteronism (PA) is common cause of secondary hypertension. PA is found in 5 to 10% of the hypertensive patients. (1) (2) (3). Its prevalence increases to 20% in patients with resistant hypertension.(4) The diagnostic of PA is important because it is associated with adverse cardiovascular outcomes and may be cured with surgery.(5)

Several clinical situations are associated with PA and warrant a diagnostic procedure. These situations are listed below:

- In case of unexplained hypokalemia. (6)
- When an arterial hypertension is resistant in standard treatment. (6)
- In case of early arterial hypertension (<30 years old) or early stroke (<50 y.o.). (6)
- If there is an history of early stroke (<50 y.o.) in a first degree relative of a young and hypertense patient. (6)
- If early target-organ damage is present, disproportionate to blood pressure (BP) value.(6)
- Adrenal incidentaloma

The confirmation of the diagnostic of PA is obtained with the ratio [Aldosterone]/[Plasma Renin Activity] . A universal cut-off value does not exist and depends on the laboratory and the test used. The cut-off value at Lausanne University hospital is > 416 pg/ml by ng/ml/h. (7) (8)

The principal forms of PA are the adrenal adenoma (unilateral) and the hyperplasia of adrenal glands (bilateral). (1) (9) (10) The therapeutic management of these 2 forms can be different depending of the aldosterone secretion, that can be lateralized or not. When hyperproduction of aldosterone is unilateral, patient can be treated and cured by surgery. In the case where the secretion is bilateral, pharmacological treatment with mineralocorticoid receptors antagonists is preferred.

Adrenal vein sampling (AVS) is still considered the gold standard to distinguish the unilateral from the bilateral form of PA. (1) (11) (12) (13) (14) (15)

So far, the biochemical markers used in AVS to define lateralization are the aldosterone and the cortisol. (1) (14) (16) However, the cortisol is a stress-induced hormone which increase during the AVS procedure and can modify the lateralization index. (16) (17) Recently, the free metanephrines (fMN) have shown to be better than cortisol for selectivity when AVS is performed without coysntropin stimulation. (18) The selectivity means the validation of the correct positioning of the catheter in the adrenal vein. However, to the best of our knowledge, this marker has never been tested as a marker of lateralization.

Radiologic imagery with CT-scans or magnetic resonance imaging are also used as diagnostic tool in the workup of PA. However the discordance with AVS is high. (1) (19) (20) (21) (22) (23) (11) If therapeutic decision was based on imagery and not AVS, surgery would be performed for a bilateral problem in 14.6% of the patients, pharmacological treatment would

be proposed for a unilateral hypersecretion in 19.1% of the patients and finally adrenalectomy contralateral to hypersecretion would be performed in 3.9% of the patients.(1) These potential misdiagnoses are caused by inaccuracy of the diagnosis methods, and the consequences for the patient are potentially important.

In the figure 1, the usual management for the diagnosis and investigation of PA is described.

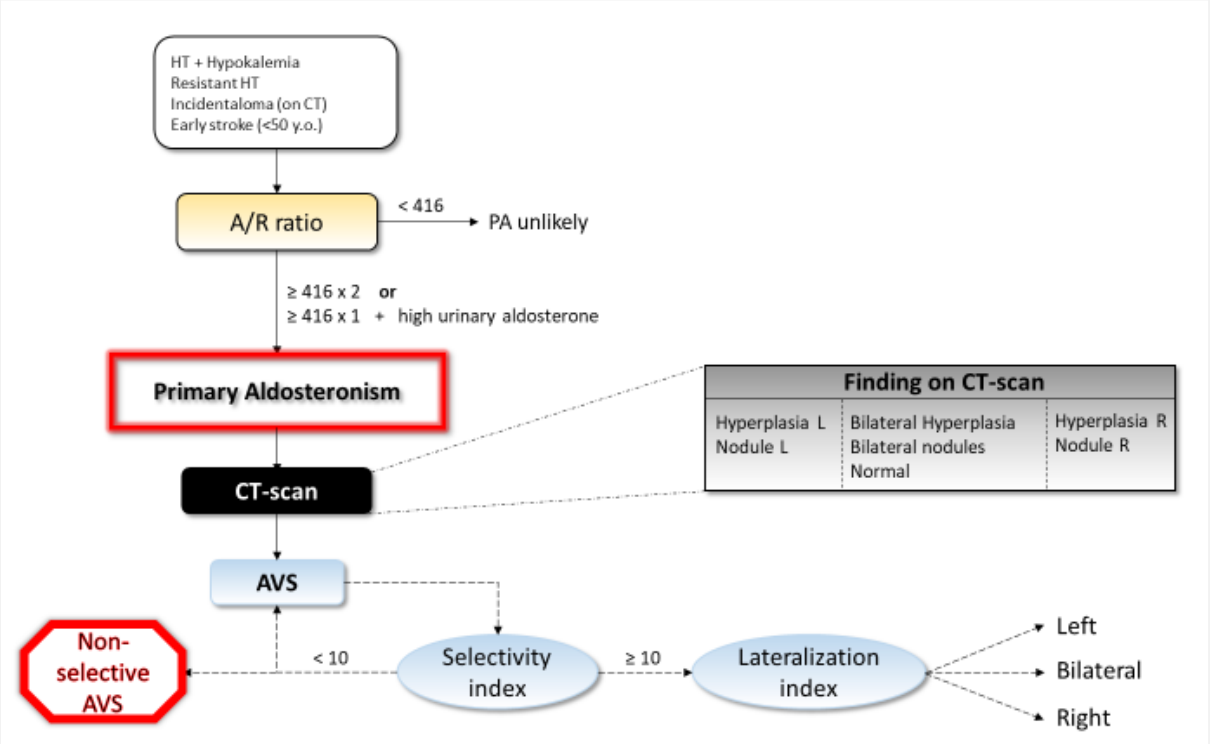

Figure 1: Algorithm of the diagnostic approach of primary aldosteronism. HT = Hypertension, CT = Ct-scan, AVS = Adrenal Vein Sampling, L = Left, R = Right. A/R Ratio = [Distal Aldosterone]/Plasma renin activity. Selectivity index = [Free metanephrines]$_{\text{adrenal vein}}$/[Free metanephrines]$_{\text{distal inferior cava vein}}$ *Lateralization index =* [Aldosterone/Cortisol]$_{\text{ipsilateral}}$/[Aldosterone/Cortisol]$_{\text{contralateral}}$ *and* [Aldosterone/Free metanephrines]$_{\text{ipsilateral}}$/[Aldosterone/Free metanephrines]$_{\text{contralateral}}$

In this study, the hypothesis was that with a more sensitive and specific marker than cortisol such as fMN, the concordance of the AVS with the CT-scan would be better. The primary objective of the study was to compare the concordance of adrenal angio-CT with AVS using cortisol (control marker) and free metanephrine (new marker) as adrenal vein lateralization markers.

Methodology

The data are taken from a prospective registry from the Lausanne University hospital with patients diagnosed with PA who are referred for AVS. Inclusion criteria included two ratio [aldosterone]/[plasma renin activity] ≥ 416 or a high ratio with increased urinary aldosterone >10 ug/24h) , age >18 years, a signed informed consent, a CT-scan and a bilaterally successful AVS selectivity index for fMN on both sides. All the anti-hypertensive drugs except the alpha-blocker doxazosine or calcium channel blockers were suspended 2 weeks before the AVS. Spironolactone was suspended 6 weeks before the AVS.

Imagery

Adrenal vein sampling protocol

A single interventional radiologist with more than 35 years of experience performed all procedures in a hybrid interventional operating room equipped with a 128 slices CT Philips Ingenuity (Philips Systems, Cleveland, USA) and C-Arm Philips Veradius Unity (Philips Systems, Cleveland, USA). Each patient was placed lying on the table of the CT scan. After rigorous asepsis and surgical field placement, a common right femoral 6F access was introduced using Seldinger technique, under local anesthesia and with US guidance. Under fluoroscopy, the radiologist catheterized and obtained blood samples, first from the distal vena cava (just under the openings of hepatic veins), secondly from the proximal vena cava (under the ostia of renal veins), then from the left adrenal vein after passing through the left renal vein and finally from the right renal vein directly draining into the vena cava. The position of the tip of the catheter was always confirmed by gently injecting contrast media to show retrograde adrenal parenchymography for both sides. For the right side, a small helical CT acquisition was also always conducted to prove the placement of the catheter in the right adrenal vein. When the operator had difficulties to locate the adrenal veins, additional CT acquisitions were performed. The procedure was realized in an outpatient setting.

Sometimes, when it was difficult to reach the adrenal vein, the radiologists took 2 samples. The sample with the best selectivity was used.

In order to determine the success of the AVS, we needed to use a maker of selectivity. The marker for that was the free metanephrine, and an AVS was considered successful when the concentration ratio $[\text{Free metanephrines}]_{\text{adrenal vein}}/[\text{Free metanephrines}]_{\text{distal inferior cava vein}}$ was ≥ 10 (24). The selectivity index had to be reached on both sides to prove the bilateral success of the procedure.

The lateralization is defined by the following equations:
$[\text{Aldosterone/Cortisol}]_{\text{dominant}}/[\text{Aldosterone/Cortisol}]_{\text{non dominant}}$ and
$[\text{Aldosterone/Free metanephrines}]_{\text{dominant}}[\text{Aldosterone/Free metanephrines}]_{\text{non dominant}}$

In the systematic review of Kempers, different cut-offs are used ranging from 2 to 5. (1) We used 3 and 5 as index of lateralization.

Adrenal CT protocol

All periprocedural CT were obtained on the same 128 slides CT scan Philips Ingenuity. Imaging parameters for unenhanced CT were as follows: slice thickness, 2.5/2 mm; tube voltage, 120 kVp and DFOV, 50.7x44cm. Images were sent and stored on our institutional PACS.

Images analysis

Each CT-scan was first read by a junior radiologist and then reviewed by a radiologist with an experience of 5 years in urogenital and abdominal imaging using Vue Carestream PACS 12.1.5.1046 (Carestream Health, Rochester, NY, USA) with reformatting in the three orthogonal planes. The radiologist was unaware of the underlying cause, biological analysis or other clinical information or patient history.

Normal adrenal anatomy was defined by the normal values reported by Vincent and al. (25) We categorized adrenal anomalies as hyperplasia or nodules. Nodule was defined as a discrete and measurable mass, individualizable in at least two orthogonal reformat sections. Hyperplasia was defined as a diffuse thickened adrenal, with adrenal limb measuring more than 5 mm or the body more than 10 mm, without discrete nodular component. We then classified each patient as “normal”, “left sided anomaly”, “right sided anomaly” or “bilateral anomalies”.

Hormones

Plasma renin activity (PRA) and plasma aldosterone were measured with commercial radioimmunometric assays, (RENCTK (Angiotensin I) RIA, DiaSorin, Saluggia, Italy and ALDO RIACTR Kit, Cisbio Bioassays, Codolet, France, respectively). Serum cortisol levels were measured with FPIA (fluorescence polarisation immunoassay) on an AxSYM instrument (Abbott Diagnostics. Lake Forest, Illinois, USA). Free and total metanephrines were measured using ultra high performance liquid chromatography-tandem mass spectrometry. (26)

Statistics

The software STATA (version 14.2) was used for statistics.

Continuous variables are presented as means and standard deviation except for non-normally distributed data presented as medians with interquartile ranges. Categorical variables are presented as numbers (percentage). A chi-square test was used for categorical data to compare men and women. A student's t-test was used for normally distributed data and a Wilcoxon rank sum test was used for non-normally distributed continuous data.

A Fisher exact test was used to compare AVS (cortisol or free metanephrine) with CT scan. The concordance between each diagnostic method was been calculated using the Cohen's Kappa coefficient, which gives a more accurate definition of the agreement.

Statistical significance was considered for two-sided tests with a p-value <0.05.

Results

Of the 122 participants who had an AVS, 101 had a successful bilateral catheterization (Figure 2).

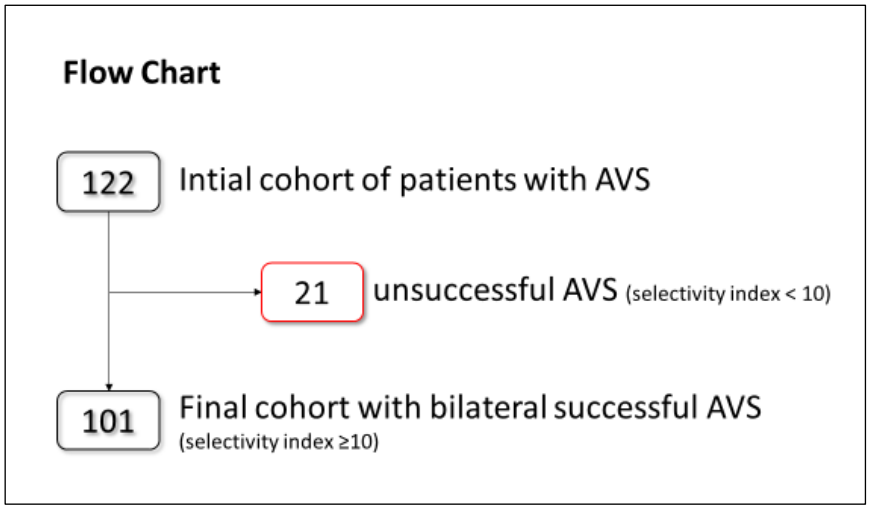

Figure 2: Flow chart of the study. AVS = Adrenal vein sampling.

The baseline characteristics are shown in table 1. Men had lower potassium and higher peripheral value of aldosterone. BMI was marginally higher (p=0.0504) in men.

Baseline characteristics:

	Male	Female	p value	All	n (M/F)
Age, years	50.5 ± 10.2	47.5 ± 10.1	0.1465	49.3 ± 10.2	101 (59/42)
BMI, kg/m^2	29.9 (27.4-33.6)	27.9 (23.6-33.7)	0.0504	29.1 (26.4-30.1)	101 (59/42)
SBP, mmHg	151.6 ± 15.7	151.1 ± 20.4	0.8853	151.4 ± 17.7	95 (55/40)
DBP, mmHg	92.0 ± 13.0	92.8 ± 12.0	0.7654	92.3 ± 12.5	95 (55/40)
K, mmol/l	3.4 ± 0.5	3.7 ± 0.5	0.0189	3.5 ± 0.5	101 (59/42)
Creatinine, mmol/l	82 (72-100)	62 (53-68)	0.0000	72 (62-92)	101 (59/42)
PRA dist, ng/ml/h	0.08 (0.08-0.14)	0.08 (0.08-0.30)	0.5678	0.08 (0.08-0.20)	101 (59/42)
Aldo dist, pg/ml	159 (110-260)	114 (84-199)	0.0353	140 (93-229)	101 (59/42)
RAR	694.5 (384-1145)	475 (255-955)	0.0745	635.2 (315-1015)	101 (55/42)
Cortisol dist, nmol/l	295 (249-395)	306 (255-440)	0.3262	297 (249-416)	101 (59/42)
Meta libre dist, nM	0.11 (0.09-0.15)	0.11 (0.08-0.13)	0.5274	0.11 (0.08-0.14)	101 (59/42)

Table 1: Dist = In the ICV distal, during the AVS. Prox = In the ICV proximal, during the AVS.. Data are means ± SD or medians with interquartile ranges when not normally distributed (25%-75%). ***BMI*** *= Body Mass Index,* ***SBP*** *= Systolic Blood Pressure,* ***DBP*** *= Diastolic Blood Pressure,* ***PRA*** *= Plasma Renin Activity,* ***RAR*** *= Renin/Aldosterone Ratio,* ***Meta*** *= Free Metanephrines*

Most of the CT-scans were without abnormalities (Figure 3). Left nodules were more frequents than right nodules. Hyperplasia and bilateral nodules were rare.

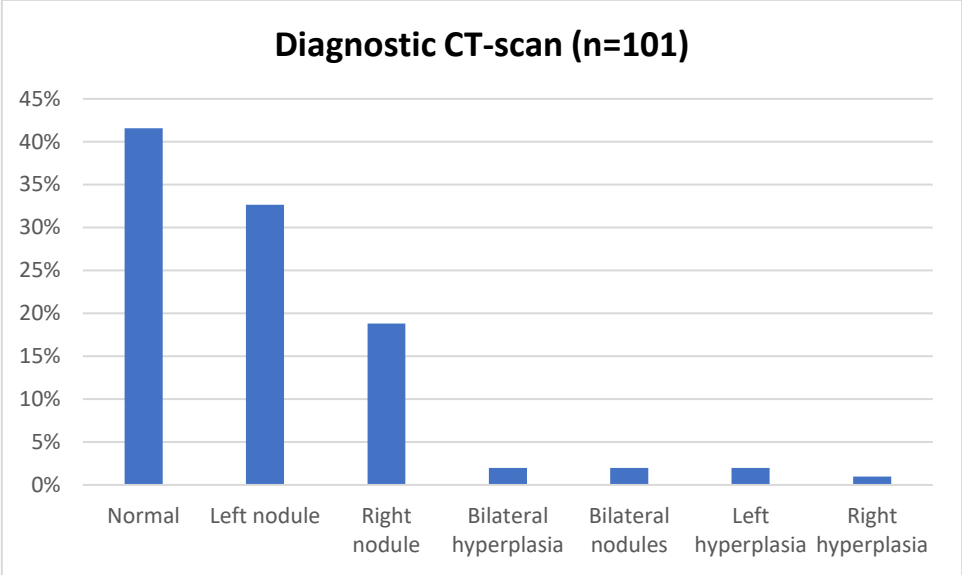

Figure 3: This table shows the CT-scan diagnostic made by the radiologists for the 101 patients with bilaterally successful AVS.

Concordance between CT and AVS using cortisol as marker of lateralization

When a cut-off value of 5 was used, the overall concordance was 52.4 % (53/101) (table 2) with a significant difference between the two diagnostic tests (fisher exact = 0.002). When no or bilateral abnormalities were found on CT, the concordance was 84.7 % (39/46). When a left abnormality was described on CT, only 22.9 % (8/35) of AVS found a left lateralization of PA. When a right abnormality was described, 30 % (6/20) of the AVS found a lateralization. When the kappa test was used the agreement was 52.48 % with a kappa of 0.1948 +/- 0.0635 (p: 0.0011, table 2). The Kappa test tells us that our hypothesis is better than if it was randomly distributed. A Kappa of 0.1948 indicates a "slight" agreement, according to the characterization of Kappa coefficient defined by Landis and Koch. (27)

Lateralization diagnostic CT and AVS using Cortisol, details

Cut off for lateralization is 5/0.2

	CT scan			
	no/bilat abnormality	Left abnormality	Right abnormality	**Total AVS:**
AVS				
No lateralized AVS	**39** 38.6%	26 25.7%	10 9.9%	75 74.3%
Left lateralized AVS	2 2.0%	**8** 7.9%	4 4.0%	14 13.8%
Right lateralized AVS	5 5.0%	1 1.0%	**6** 5.9%	12 11.9%
Total CT:	46 45.5%	35 34.7%	20 19.8%	101 100%

Fisher's exact = 0.002

Cohen's Kappa coefficient CT / AVS with Cortisol Cut-off: 5/0.2

Agreement	Expected agreement	Kappa	Std. Err.	Z	Prob>Z
52.48%	40.98%	0.1948	0.0635	3.07	0.0011

*Table 2: AVS = Adrenal Vein Sampling, CT = Compluted Tomography. The **pink** compartments show the concordant diagnostics between CT and AVS.*

When a cut-off value of 3 was used, the overall concordance was 55.4% (56/101) (table 3) with a significant difference between the two diagnostic tests (fisher exact 0.002). When no or bilateral abnormalities were found, the concordance was 76.1% (35/46). When a left abnormality was described, 40% (14/35) AVS found a left lateralization of PA. When a right abnormality was described 35% (7/20) was described. When the kappa test was used the agreement was 54.45% with a kappa of 0.2715 +/- 0.0701, p: 0.0001 (Table 3). The Kappa test tells us that our hypothesis is better than if it was randomly distributed. A Kappa of 0.2715 indicates a "fair" agreement, according to the characterization of Kappa coefficient defined by Landis and Koch.

Lateralization diagnostic CT and AVS using Cortisol, details

Cut off for lateralization is 3/0.33

	CT scan			
	No/bilat abnormality	Left abnormality	Right abnormality	**Total AVS:**
AVS				
No lateralized AVS	**35** 34.7%	18 17.8%	9 8.9%	62 61.4%
Left lateralized AVS	4 4.0%	**14** 13.9%	4 4.0%	22 21.8%
Right lateralized AVS	7 6.9%	3 3.0%	**7** 6.9%	17 16.8%
Total CT:	46 45.5%	35 34.7%	20 19.8%	101 100%

Fisher's exact = 0.002

Cohen's Kappa coefficient CT / AVS with Cortisol Cut-off: 3/0.33

Agreement	Expected agreement	Kappa	Std. Err.	Z	Prob>Z
55.45%	38.84%	0.2715	0.0701	3.88	0.0001

*Table 3: AVS = Adrenal Vein Sampling, CT = Computed tomography. The **pink** compartments show the concordant diagnostics between CT and AVS.*

Concordance between CT and AVS using free metanephrines as marker of lateralization

When a cut-off value of 5 was used, the overall concordance was 55.4 % (56/101) (table 4) with a significant difference between the two diagnostic tests (fisher exact = 0.001). When no or bilateral abnormalities were found on CT, the concordance was 82.6 % (38/46). When a left abnormality was described on CT, 37.1 % (13/35) of AVS found a left lateralization of PA. When a right abnormality was described, 25 % (5/20) of AVS found the same. When the kappa test was used the agreement was 55.45 % with a kappa of 0.2474 +/- 0.0664, p: 0.0001 (table 4). A Kappa of 0.2474 indicates a "fair" agreement, according to the characterization of Kappa coefficient defined by Landis and Koch.

Lateralization diagnostic CT and AVS using Free Metanephrines, details

Cut off for lateralization is 5/0.2

	CT scan			
	No/bilat abnormality	Left abnormality	Right abnormality	**Total AVS:**
AVS				
No lateralized AVS	**38** 37.6%	21 20.8%	13 12.9%	72 71.3%
Left lateralized AVS	3 3.0%	**13** 12.9%	2 2.0%	18 17.8%
Right lateralized AVS	5 5.0%	1 1.0%	**5** 5.0%	11 10.9%
Total CT:	46 45.5%	35 34.7%	20 19.8%	101 100%

Fisher's exact = 0.001

Cohen's Kappa coefficient Cut-off: 5/0.2

Agreement	Expected agreement	Kappa	Std. Err.	Z	Prob>Z
55.45%	40.80%	0.2474	0.0664	3.73	0.0001

*Table 4: AVS = Adrenal Vein Sampling, CT = Computed tomography. The **pink** compartments show the concordant diagnostics between CT and AVS.*

When a cut-off value of 3 was used, the overall concordance was 56.4% (57/101) (table 5) with a significant difference between the two diagnostic tests (fisher exact 0.000). When no or bilateral abnormalities were found, the concordance was 69.6% (32/46). When a left abnormality was described, 51.4% (18/35) AVS found a left lateralization of PA. When a right abnormality was described 35% (7/20) was described. When the kappa test was used the agreement was 56.44% with a kappa of 0.3014 +/- 0.0715, p: 0.0000 (Table 5). A Kappa of 0.3014 indicates a "fair" agreement, according to the characterization of Kappa coefficient defined by Landis and Koch.

Lateralization diagnostic CT and AVS using Free Metanphrines, details

Cut off for lateralization is 3/0.33

	CT scan			
	No/bilat abnormality	Left abnormality	Right abnormality	**Total AVS:**
AVS				
No lateralized AVS	**32** 31.7%	14 13.9%	9 8.9%	55 54.5%
Left lateralized AVS	4 4.0%	**18** 17.8%	4 4.0%	26 25.7%
Right lateralized AVS	10 9.9%	3 3.0%	**7** 6.9%	20 19.8%
Total CT:	46 45.5	35 34.7%	20 19.8%	101 100%

Fisher's exact = 0.000

Cohen's Kappa coefficient Cut-off: 3/0.33

Agreement	Expected agreement	Kappa	Std. Err.	Z	Prob>Z
56.44%	37.64%	0.3014	0.0715	4.22	0

*Table 5: AVS = Adrenal Vein Sampling, CT = Computed tomography. The **pink** compartments show the concordant diagnostics between CT and AVS.*

Concordance between AVS using cortisol as marker of lateralization and AVS using free metanephrines as marker of lateralization

When a cut-off value of 5 was used, the overall concordance was 81.2 % (82/101) (table 6) with a significant difference between the two diagnostic tests (fisher exact = 0.000). When no or bilateral abnormalities were found with AVS using cortisol as a marker, the concordance was 85.3 % (64/75) with the AVS using fMN. When a left abnormality was described with AVS using cortisol, 71.4 % (10/14) of AVS using fMN found the same. When a right abnormality was described by AVS using cortisol, 33.3 % (8/12) of AVS using fMN found the same. When the kappa test was used the agreement was 81.19 % with a kappa of 0.5655 +/- 0.0753, p: 0.0000 (table 6). A kappa score of 0.5655 is defined as "moderate".

Lateralization diagnostic AVS using Cortisol and AVS using Free Meta, details

Cut off for lateralization is 5/0.2

	AVS Meta			
	No lateralized AVS	Left lateralized AVS	Right lateralized AVS	**Total AVS Cort:**
AVS Cort				
No lateralized AVS	**64** 63.4%	8 7.9%	3 3.0%	75 74.3%
Left lateralized AVS	4 4.0%	**10** 9.9%	0 0%	14 13.9%
Right lateralized AVS	4 4.0%	0 0.00%	**8** 7.9%	12 11.9%
Total AVS Meta:	72 71.3%	18 17.8%	11 10.9%	101 100%

Fisher's exact = 0.000

Cohen's Kappa coefficient Cut-off: 5/0.2

Agreement	Expected agreement	Kappa	Std. Err.	Z	Prob>Z
81.19%	56.70%	0.5655	0.0753	7.51	0

*Table 6: AVS = Adrenal Vein Sampling, CT = Computed tomography. Meta = Free metanephrines, Cort = Cortisol. The **pink** compartments show the concordant diagnostics between AVS with cortisol and AVS with fMN.*

When a cut-off value of 3 was used, the overall concordance was 78.2% (79/101) (table 7) with a significant difference between the two diagnostic tests (fisher exact 0.000). When no or bilateral abnormalities were found, the concordance was 87.3% (48/55). When a left abnormality was described, 69.2% (18/26) AVS found a left lateralization of PA. When a right abnormality was described 65% (13/20) was described. When the kappa test was used the agreement was 78.22% with a kappa of 0.6220 +/- 0.0727, p: 0.0000 (table 7). A kappa score of 0.6220 is defined as "substantial".

Lateralization diagnostic AVS using Cortisol and AVS using Free Meta, details

Cut off for lateralization is 3/0.33

	AVS Meta			
	No lateralized AVS	Left lateralized AVS	Right lateralized AVS	**Total AVS Cort:**
AVS Cort				
No lateralized AVS	**48** 47.5%	7 6.9%	7 6.9%	62 61.4%
Left lateralized AVS	4 4.0%	**18** 17.8%	0 0%	22 21.8%
Right lateralized AVS	3 3.0%	1 1.0%	**13** 12.9%	17 16.8%
Total AVS Meta:	55 54.5%	26 25.7%	20 19.8%	101 100%

Fisher's exact = 0.000

Cohen's Kappa coefficient Cut-off: 3/0.33

Agreement	Expected agreement	Kappa	Std. Err.	Z	Prob>Z
78.22%	42.37%	0.622	0.0727	8.56	0

*Table 7: AVS = Adrenal Vein Sampling, CT = Computed tomography. Meta = Free metanephrines, Cort = Cortisol. The **pink** compartments show the concordant diagnostics between AVS with cortisol and AVS with fMN.*

Agreement

The Kappa score's significance described by Landis and Koch (27) is reported in this table:

κ	<0	0.0-0.20	0.21-0.40	0.41-0.60	0.61-0.80	0.81-1.00
Significance	No agreement	Slight	fair	moderate	substantial	Almost perfect

The levels of agreement of each test is shown in figure 4. The agreement is low when CT is compared to AVS whether Plasma Cortisol Concentration (PCC) or Plasma Free Metanephrine Concentration (PFMC) are use. The agreement is high between AVS with PCC or PFMC although not perfect. The levels of agreements were slightly better using a lateralization cut-off of 3 than 5.

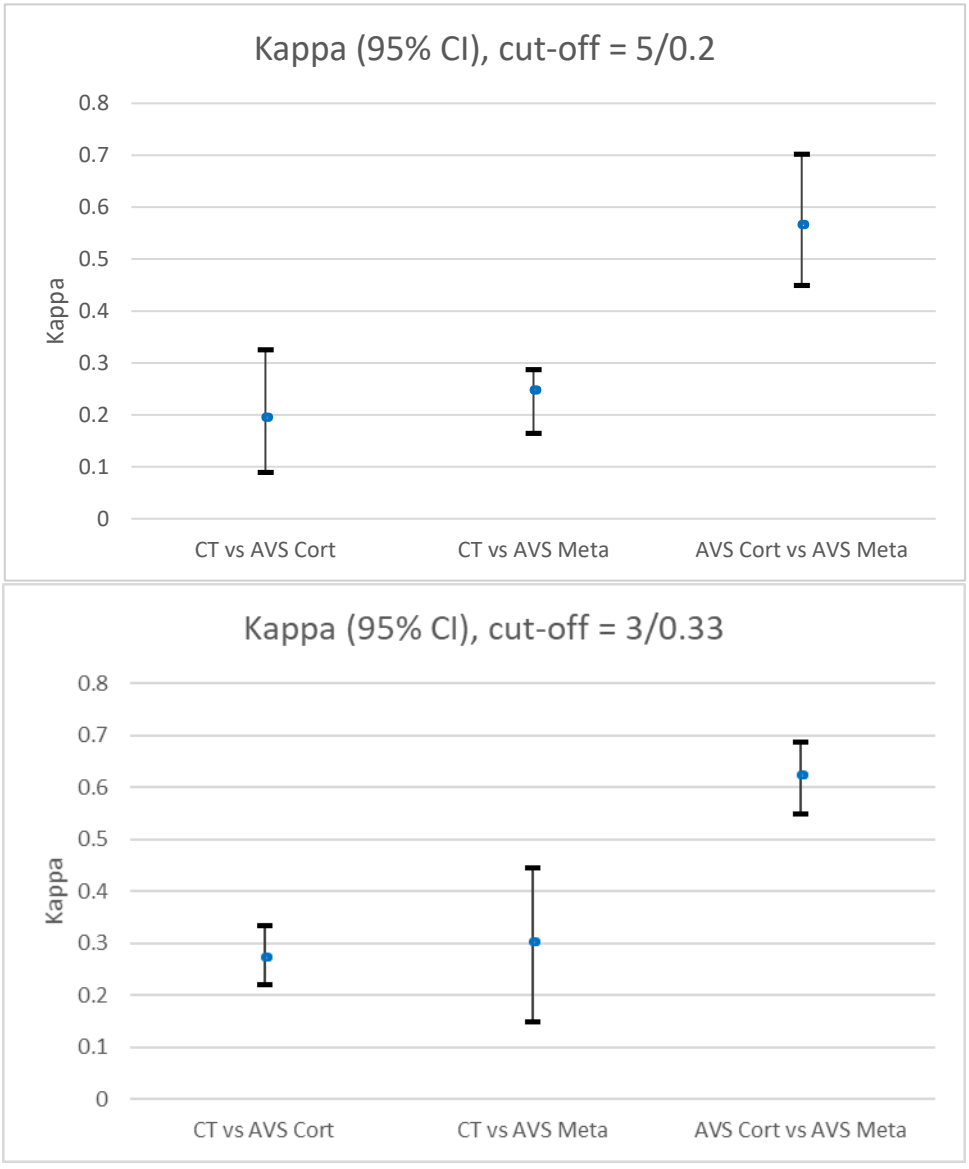

Figure 4: Data are Kappa with 95% confidence interval. CT = Computed tomography AVS Cort = Adrenal Vein Sampling using cortisol as a lateralization marker. AVS Meta = Adrenal Vein Sampling using free metanephrines as a lateralization marker.

Discussion

This study was the first to compare the agreement of AVS using PFMN as a marker of lateralization with angio-CT and to compare the agreement with PAC. Our analysis showed that the agreement of AVS using PFMC as a marker of lateralization instead of PCC only marginally increases the agreement between AVS and Ct-scan. Secondly, the best agreement between AVS using PCC and PFMC is when the less stringent lateralization index is used (3 vs 5).

Compared to in the systematic review of Kempers and al., from 2009, that showed a 62.2% concordance between CT/MRI and AVS with cortisol on 950 people, the concordance was even lower in our study ranging from 52 à 55% depending the cut-off used for diagnosis. (1)This difference may be secondary to the procedure used during AVS and the cut-offs used in the studies included in the systematic review. Recently, some researchers have questioned the utility of AVS in the therapeutic decision to operate patients with PA or not (15)(28). The possibility of surgically remove the wrong adrenal ranged from 1 to 7% in our study depending on the cut-offs used. It should alert physicians and patients about the possible consequences of performing an adrenalectomy on the contralateral side of the biological hypersecretion. More over the probability of performing an unnecessary adrenalectomy ranged from 23.8 to 35.6%.

<u>Limitations</u>

During the AVS, we didn't do cosyntropin stimulation, which could lower the sensitivity to detect correct bilateral selective AVS. (18) Several studies have highlighted the importance of cosyntropin stimulation to minimize the variability that could exist in the cortisol concentration during the collection of samples in the adrenal vein. (16–18) However, as FMPC was used to assess selectivity this limitation should not have affected the number of patients included in our study as shown by Dekkers and al.. (18)

Another potential bias could be the use of different cut-offs. The selective cut-off, $[\text{Free metanephrines}]_{\text{adrenal vein}}/[\text{Free metanephrines}]_{\text{distal inferior cava vein}}$ has been fixed to 10, following a recent report from our group. (24) But for an accurate lateralization index, which equations are $[\text{Aldosterone/Cortisol}]_{\text{dominant}}/[\text{Aldosterone/Cortisol}]_{\text{nondominant}}$ and $[\text{Aldosterone/Free metanephrines}]_{\text{dominant}}/[\text{Aldosterone/Free metanephrines}]_{\text{nondominant}}$, there is so far no validated cut-offs. As we can see it in the systematic review of Kempers and al., various articles used lateralization cut-offs going from 2 to 5. (1) In our analysis, we decided to compare 2 different cut-offs: 3 and 5, both for the cortisol and fMN in order to compare the results and the impact of the chosen cut-off on the concordance with the CT-scan.

By choosing the strict 5 cut-off we logically obtained less lateralization and more bilateral PA, but this strict cut off also limited the cases where CT and AVS diagnosed an opposite lateralization, as we can see it in the tables. And these are the cases that can be the cause of a wrong-side adrenalectomy, which is probably the worst situation that can occur in the

clinical management of this disease based on CT-scans. From this point of view, the 5/0.2 cut-off is probably more secure and less risky than the 3/0.33 for the patients. With this cut-off, more patients will be treated pharmacologically.

Results generalization

Our study shows that when PFMC is used as a marker of lateralization instead of cortisol, the concordance with the CT-scan is still quite low. These results confirm that the discordance between AVS and CT-scans is too high to rely solely on CT scan. CT scans may lead to misdiagnosis that could expose patients to unnecessary or even wrong sided adrenalectomy.

A definite answer of the utility of fMN in the lateralization diagnosis of PA cannot be given with our results. For that, we would have to compare the clinical outcome of the treatment following a diagnostic made with AVS using cortisol versus the clinical outcome of the treatment following a diagnostic made with AVS using fMN. Finally, validated cut-off values for lateralization are needed to help physicians correctly decide whether adrenalectomy should be performed or not.

Conclusion

The use of plasma free metanephrine concentration as a maker for lateralization in the AVS hasn’t shown an improvement in the concordance with CT-scan diagnosis, but confirms the inaccuracy of the CT-scan in the lateralization diagnosis of the PA.

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