The Adrenal Vein Sampling International Study (AVIS) for Identifying the Major Subtypes of Primary Aldosteronism

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Context: In patients who seek surgical cure of primary aldosteronism (PA), The Endocrine Society Guidelines recommend the use of adrenal vein sampling (AVS), which is invasive, technically challenging, difficult to interpret, and commonly held to be risky.

Objective: The aim of this study was to determine the complication rate of AVS and the ways in which it is performed and interpreted at major referral centers.

Design and Settings: The Adrenal Vein Sampling International Study is an observational, retrospective, multicenter study conducted at major referral centers for endocrine hypertension worldwide.

Participants: Eligible centers were identified from those that had published on PA and/or AVS in the last decade.

Main Outcome Measure: The protocols, interpretation, and costs of AVS were measured, as well as the rate of adrenal vein rupture and the rate of use of AVS.

Results: Twenty of 24 eligible centers from Asia, Australia, North America, and Europe participated and provided information on 2604 AVS studies over a 6-yr period. The percentage of PA patients systematically submitted to AVS was 77% (median; 19–100%, range). Thirteen of the 20 centers used sequential catheterization, and seven used bilaterally simultaneous catheterization; cosyntropin stimulation was used in 11 centers. The overall rate of adrenal vein rupture was 0.61%. It correlated directly with the number of AVS performed at a particular center ($P = 0.002$) and inversely with the number of AVS performed by each radiologist ($P = 0.007$).

Conclusions: Despite carrying a minimal risk of adrenal vein rupture and at variance with the guidelines, AVS is not used systematically at major referral centers worldwide. These findings represent an argument for defining guidelines for this clinically important but technically demanding procedure. (***J Clin Endocrinol Metab*** **97: 1606–1614, 2012)**

Primary aldosteronism (PA) is a syndrome caused by excess aldosterone secretion, which leads to arterial hypertension and also, in a proportion of patients, to hypokalemia. In large studies, PA is the most common curable form of hypertension in patients referred to specialized centers (with or without drug-resistant hypertension), where it was found in over 11% of patients (1, 2). PA can also be common in general practice because an elevated

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Abbreviations: APA, Aldosterone-producing adenoma; AVS, adrenal vein sampling; CT, computed tomography; PA, primary aldosteronism; ROC, receiver operator characteristic.

aldosterone-to-renin ratio was reported to involve one of three hypertensive individuals randomly selected from the general population (3). Because PA patients are at increased risk of target organ damage and cardiorenal complications (4, 5), their early identification is crucial for preventing such complications and for reversing preexisting cardiovascular damage by specific therapy (6, 7).

Fundamental to selecting the most appropriate treatment is the distinction between PA deriving from bilateral aldosterone excess (predominantly from bilateral adrenal hyperplasia, also referred to as idiopathic hyperaldosteronism) and that due to unilateral overproduction of the hormone [predominantly aldosterone-producing adenoma (APA)]. Although lifelong medical treatment is usually required in the former, adrenalectomy can cure PA and arterial hypertension in the latter (8).

To distinguish between these causes, The Endocrine Society Guidelines advocate the use of adrenal vein sampling (AVS), which has been applied to identification of PA subtypes at many centers after its first introduction by Masoni (9) in 1957 (9–13). This procedure is generally regarded as invasive and carrying a risk of adrenal vein rupture (14). It is also held to be technically demanding, which may explain the high rate (69.5%) of failure, defined as a selectivity index (see *Materials and Methods*) of less than 2.0, recently found in the German Conn's Registry (14–16). These views, however, are mainly based on anecdotal experience and/or retrospective observational studies (17). In addition, both the performance of AVS and the interpretation of its results are generally regarded as challenging (18–20), mainly due to the lack of accepted criteria to define selectivity of adrenal vein catheterization and lateralization of aldosterone excess. For these reasons and the recognized lack of reliability of alternative methods [such as computed tomography (CT) and biochemical tests] for distinguishing unilateral from bilateral disease (21), many patients with PA still undergo adrenalectomy without prior demonstration of lateralized aldosterone excess. This practice can lead to unnecessary adrenalectomy and/or removal of the wrong adrenal in a substantial proportion of cases, as recently shown (22, 23). The Adrenal Vein Sampling International Study (AVIS) was planned to determine the percentage of PA patients selected for adrenalectomy based on AVS and the rate of adrenal vein rupture at major referral centers worldwide. The ways in which AVS is performed and interpreted were also examined. The AVIS was registered at www.clinicaltrials.gov, where details of the methodology and the aims of the study can be found. We herein report on the results of stage I, the main aims of which were to establish the safety and usage rate of AVS worldwide (Table 1).

TABLE 1. Aims of the AVIS study: phase 1

1. How many adrenal vein ruptures occurred during the AVS?
2. What is the percentage of PA patients in whom AVS is performed?
3. How many AVS studies have been performed yearly from 2005 to 2010 at each center?
4. How many centers use bilaterally simultaneous and how many use sequential AVS catheterization?
5. How many radiologists perform AVS at each center?
6. How many centers use an ACTH (cosyntropin) stimulation during AVS?
7. How many centers calculate the selectivity index, the lateralization index, and the contralateral suppression index, and what is the minimum cutoff used?
8. Are the AVS studies that are not bilaterally selective used for diagnosis?
9. What is the cost of AVS for the National Health System, or insurance, and for patients?

Materials and Methods

Study selection criteria

Eligible centers were identified from those that had published in English on PA and/or AVS in the last decade following the PICO strategy (P, population = adults with PA; I, intervention = AVS; C, comparator = simultaneous AVS *vs.* sequential catheterization technique, use of cosyntropin testing *vs.* nonstimulated condition, use of bilaterally *vs.* unilaterally selective AVS results, use of absolute hormonal data *vs.* selectivity and lateralization indices; and O, outcome = the ways AVS was performed and interpreted, adrenal vein rupture) (24). Suitable studies were identified by computer-assisted database searches (PubMed database, U.S. National Library of Medicine) using the

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key words aldosterone, primary aldosteronism (PA), endocrine hypertension, adrenal vein sampling, and the Boolean operator "AND"; scanning of reference lists; hand-searching of relevant journals; correspondence with authors of relevant reports and meeting presentations; and consultation with experts in the field. After identification of the centers, the only inclusion criterion was the lead investigator's agreement to participate in data collection. The only exclusion criterion was unwillingness of the lead investigator to participate in the study.

Data collection

Data were collected in a predefined form and stored securely and anonymously on a server protected by firewalls and passwords at the coordinating center. Information on categorical variables was systematically recoded to ensure comparability among studies. Data obtained from each participating study were checked for internal consistency and for outliers. Any queries that arose were clarified directly with the lead investigator of each center, before harmonization to a standard format. The content of the data was unchanged by this process.

Definitions

The selectivity index, which is used to assess the selectivity of the adrenal catheterization based on the step-up of plasma cortisol between the adrenal vein and the inferior vena cava, was defined as the ratio of cortisol in each adrenal vein and in the infrarenal inferior vena cava. The lateralization index, which is used to establish whether a lateralized aldosterone excess exists, was defined as the ratio of aldosterone to cortisol on the dominant side, *e.g.* the side with higher aldosterone secretion, over aldosterone to cortisol on the nondominant side, *e.g.* the side with lower aldosterone secretion. The contralateral suppression index was defined as the ratio of aldosterone over cortisol of each side and aldosterone over cortisol of the infrarenal inferior vena cava. This index is used to determine whether the aldosterone concentration in the adrenal vein blood is, or is not, higher than expected based on the peripheral arterial level of the hormone.

Adrenal vein rupture was defined as lumbar pain occurring during or after AVS plus fluoroscopic evidence of adrenal gland and/or retroperitoneal hemorrhage. Postprocedure imaging (*e.g.* ultrasound, CT, or magnetic resonance imaging) was performed to document this complication whenever clinically required as judged by the lead investigator of each participating center.

Statistical analyses

Data collection ended mid-November 2010, and some centers provided their data earlier than the deadline. Thus, to avoid underestimating the AVS number for 2010, this number was calculated by adding the figure of the months with complete information to that projected for the missing months. The latter was calculated by multiplying the average monthly rate of AVS observed at each center during the first 6 months of 2010 by the number (and fraction) of months for which information was missing.

Statistical analysis was performed by SPSS for Mac (version 18.0; SPSS Inc., Chicago, IL), GraphPad (GraphPad Software, Inc., San Diego, CA), and the MedCalc (MedCalc Software, Mariakerke, Belgium) software. Stepwise regression analysis (backward, Wald) with a p-in = 0.05 and p-out = 0.10 was used to identify the predictors (number of AVS performed by each radiologist, number of AVS performed by each center, use of cosyntropin stimulation, use of bilateral simultaneous *vs.* sequential AVS technique) of adrenal vein rupture.

Results

Recruitment of centers

After preliminary identification of eligible centers, 20 of 24 invited centers from Asia, Australia, North America, and Europe agreed to participate (Table 2). Of the remaining centers, two declined and two did not respond to the invitation (Fig. 1). Data collection began on May 15, 2010, and ended on November 15, 2010.

Number of AVS performed

When the database was locked, information on 2604 AVS studies at 20 centers over a 6-yr period from 2005 and 2010 was collected. The average total number of AVS performed over the 6 yr at each center was 130.2 (SEM = 24.4), which corresponds to the average number of AVS per year per center shown in Fig. 2. The number of AVS performed yearly at each center showed a trend toward increasing use over time.

Rate of performance of AVS and use of stimulation tests

AVS was not offered to all patients eligible for adrenalectomy: the percentage of patients with confirmed PA in whom AVS was performed was 77% (median) but ranged widely between 19 and 100%. Moreover, whereas most centers provided detailed explanation of the procedures to the patients, an experienced hypertension nurse accompanied the patient to the hemodynamic room and remained throughout the procedure only at one center. Thus, no systematic use of strategies to minimize the stress related to AVS emerged, although the procedure induces a stress reaction and raises cortisol and aldosterone secretion. This was recently well documented in a study where the AVS samples were obtained twice, *e.g.* when starting AVS and again 15 min later (25).

Almost two thirds (13 of 20) of the centers reported using sequential catheterization technique (cannulation of the adrenal veins one at a time), whereas the remaining seven used bilateral simultaneous cannulation of both adrenal veins (26). There were no differences in the rate of adrenal vein rupture between the centers using either catheterization technique.

In terms of dynamic testing, 11 of 20 centers performed AVS with ACTH stimulation, and the rest without any stimulation. Use of ACTH was not more common among centers that used sequential catheterization.

TABLE 2. List of participating centers

Center	City	State, Country	Principal investigator/investigators
Università degli studi di Padova, DIMED	Padova	Italy	G. P. Rossi, M. Barisa, D. Miotto, T. M. Seccia, A. C. Pessina
Hospital of The University of Pennsylvania	Philadelphia	Pennsylvania, United States	S. Trerotola, D. Cohen
Yokohama Rosai Hospital	Yokohama City	Kanagawa, Japan	T. Nishikawa, M. Omura
Foothills Medical Centre, University of Calgary	Calgary	Canada	G. Kline
General Faculty Hospital, Prague	Prague	Czech Republic	J. Widimsky Jr.
University of Paris, Hopital Européen Georges Pompidou	Paris	France	P. F. Plouin, L. Amar
University of Texas Southwestern Medical Center	Dallas	Texas, United States	R. J. Auchus
Tohoku University Hospital	Sendai	Miyagi, Japan	F. Satoh
Heinrich Heine Universität Düsseldorf	Düsseldorf	Germany	L. C. Rump, O. Vonend
National Taiwan University Hospital	Taipei	Taiwan	K. D. Wu, V. Wu
National Hospital Organization, Kyoto Medical Center	Kyoto	Japan	M. Naruse
Medical College of Wisconsin	Menomonee Falls	Wisconsin, United States	S. B. Magill
Centre Hospitalier de l'Université de Montreal	Montreal	Quebec, Canada	A. Lacroix, E. Therasse
Medizinische Klinik Innenstadt	Munich	Germany	M. Reincke, C. Degenhart, E. Fischer
Charité Campus Mitte	Berlin	Germany	M. Quinkler
University Hospital Wuerzburg	Wuerzburg	Germany	B. Allolio, R. Kickuth, K. Lang
Endocrine Hypertension Research Centre, University of Queensland School of Medicine, Greenslopes Hospital	Brisbane	Queensland, Australia	M. Stowasser, R. Gordon, E. Pimenta
Tokyo Women's Medical University	Tokyo	Japan	A. Tanabe
Radboud University Nijmegen Medical Center	Nijmegen	The Netherlands	J. Deinum, L. Schultze Kool
Dipartimento di Medicina Interna e Specialità Mediche, Medicina 2	Reggio Emilia	Italy	E. Rossi

Number of radiologists performing AVS and rate of complications

The total number of radiologists who performed AVS at the 20 centers was 51 (range, 1 to 7; median, 2). The number of ruptures of an adrenal vein during or after AVS was 16, corresponding to an overall rate of 0.61%. In all cases, this complication resolved with conservative treatment, and there were no deaths. The rate differed significantly among centers: at one center, for instance, it was 10-fold higher than the average rate recorded by all others. Adrenal vein rupture fell to 0.51% on exclusion of this outlier. Regression analysis showed that adrenal vein rupture was predicted by the number of AVS performed by each radiologist ($\beta = -0.683$; $P = 0.007$) and the number of AVS performed per center ($\beta = 0.831$; $P = 0.002$), but

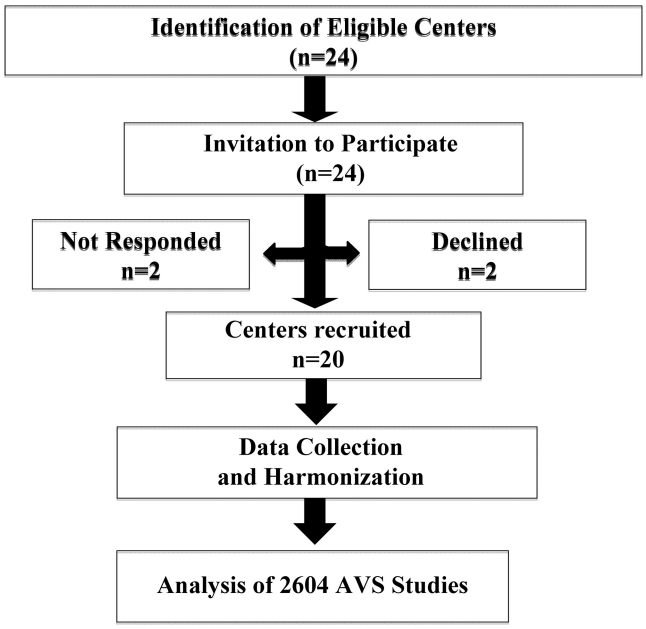

FIG. 1. Flow chart of the AVIS.

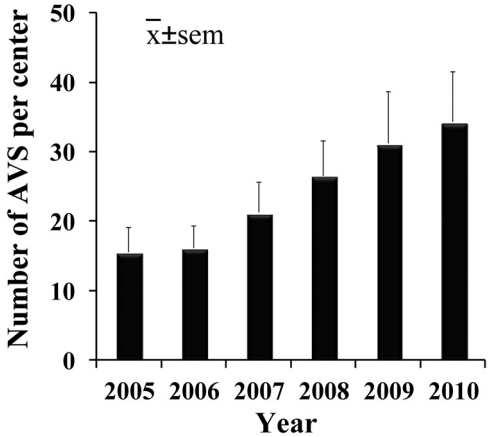

FIG. 2. The histogram shows the average number of AVS performed for each center yearly.

not by use of ACTH stimulation, bilateral simultaneous *vs.* sequential AVS technique, or by the continent on which the performing center was located. A regression model with these two predictors ($F = 7.72$; $P = 0.005$) accounted for 40% of adrenal vein ruptures.

Use of bilaterally *vs.* unilaterally selective AVS results

AVS is aimed at obtaining adrenal venous blood, and therefore its results are interpreted based on the assumption that selective blood samples have been obtained from each side. Notwithstanding this, eight centers used bilaterally selective studies for diagnosis, whereas the majority (12 of 20) used unilaterally selective studies when bilateral results were unavailable. Use of a unilateral study is based on the assumption that if the patient has unequivocal evidence of PA and one side is suppressed (by volume expansion and high blood pressure) then the excess aldosterone should come from the contralateral side. This might be important because it can allow diagnosis even when the right adrenal vein cannot be successfully catheterized; unfortunately, it is largely theoretical and yet unsupported by specific studies.

Interpretation of AVS results

Wide variations in the way results are used and interpreted across centers were evident: one center used absolute hormonal values instead of selectivity and lateralization indices, whereas another center calculated only the lateralization index even for nonselective studies.

The cutoff values for selectivity and lateralization indices varied markedly among those centers that systematically used them. Figure 3 shows the proportion of centers using the different cutoffs for selectivity and lateralization indices under nonstimulated condition and with ACTH stimulation. Under nonstimulated condition, cutoffs were lower than during stimulated sampling for selectivity, but not for lateralization. In terms of the selectivity index, the majority of the centers used a cutoff of 2 under nonstimulated conditions and 3–5 under ACTH stimulation. For the lateralization index, most centers used 2–4 under nonstimulated conditions and 2.6–4 for ACTH stimulation. For the selection of the selectivity and lateralization index cutoffs, 67% of the centers relied on values reported in the literature; 11% reported selecting their cutoffs based on a formal assessment of diagnostic accuracy with receiver operator characteristic (ROC) curves alone, and a further 11% also used the Youden index. In 11% of the centers, the selection was made empirically with no formal analysis.

Use of unilaterally selective AVS results for diagnostic purposes would imply reliance on contralateral suppression, instead of a lateralization index. We therefore next examined how many centers used the former index and whether there was an association between use of unilateral selective AVS and contralateral suppression. We found that those centers that systematically relied on non-bilaterally selective AVS also used contralateral suppression more frequently than expected by chance ($X^2 = 5.90$; $P = 0.05$). In contrast, no significant correlation could be found between the use of ACTH stimulation and contralateral suppression.

Costs

The costs of AVS showed a wide variability among centers and countries, both for the patient and for the insurance or national health care system. The cost ranged from 80 to 10,532 € (corresponding to 14,218 USD) for health insurance systems and from 0 to 1357 € (1,832 USD) for the patient. In the U.S. centers, the average cost per center was 5806 USD, and the cost to patients was 435 USD. Overall in the centers from Europe, Australia, and Asia, the average cost per center was 1754 € and the cost to patients was 204 €.

Discussion

This study provides novel information on the way in which AVS is performed and interpreted at major referral centers around the world. The first important finding concerns the degree to which current practice follows The Endocrine Society guidelines: on average AVS was systematically performed on average in only 77% (range, 19 to 100%) of patients with confirmed PA. The rate ranged from a systematic use of AVS to a lowest figure of 19%. Such a low AVS rate might depend on several factors, including reliance on imaging tests, costs, and lack of expertise in AVS or surgery or comfort with using medical management alone. However, it is of concern in that adoption of an imaging-based strategy in the rest of the patients may well be suboptimal because it bears the risk of denying curative adrenalectomy in about 20% of patients, performing unnecessary adrenalectomy in 15–25%, and removing the wrong adrenal in almost 4%, as shown in the Mayo Clinic series and in a recent systematic review (22, 23). The low accuracy of CT alone for diagnosing APA was recently confirmed (27), although two retrospective studies claimed that an imaging-based strategy did not perform significantly worse than an AVS-based strategy for selecting the patients for surgery, at least when assessed in terms of blood pressure and correction of hypokalemia (12, 28).

The findings of this survey thus show that even at major referral centers treatment decisions for PA are not based

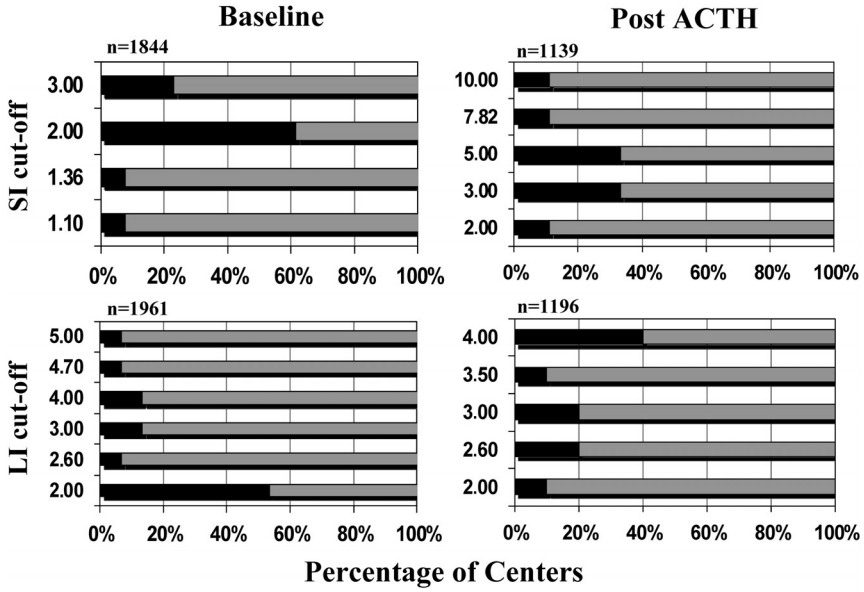

FIG. 3. The histograms illustrate the proportion of centers using the different cutoffs for the selectivity index (SI) and the lateralization index (LI) under unstimulated conditions (*left*) and during ACTH stimulation (*right*). n, Number of AVS studies available for each index.

on AVS in a substantial proportion of the PA patients. Accordingly, the lack of systematic use of AVS herein documented can have an impact on the physician's ability to make the correct diagnosis. Given that AVS is safe, as discussed below, other barriers against utilization of this test, such as costs, low technical success rate, or center preferences and reliance on medical management need to be understood and addressed to optimize patient care.

A second major finding of this study is the minimal (0.61%) overall rate of adrenal vein rupture. Moreover, this rate was probably an overestimate in that one center reported a much higher rate than all the others. This anomaly reflected assignment at that center of radiologists in training and in rotation to perform the procedure, which might account for this unusual rate. The finding that the number of AVS performed by each radiologist is a strong predictor of adrenal vein rupture supports this: small numbers of procedures per operator are associated with a significantly increased rate of complications. Thus, these results disprove the concept that AVS *per se* is a risky procedure and do not contradict The Endocrine Society Practice Guidelines recommending that AVS should be offered to all PA patients who are candidates for adrenalectomy and seek a surgical resolution of PA (21).

The average number of AVS performed annually for each center was generally lower than 40 and ranged between 16 in 2005 and 34 in 2010 (Fig. 2). The number of radiologists performing the procedure at each center was low, on average 2.6. At only two centers were more than three radiologists (6, 7) performing AVS. It is likely that the low number of radiologists involved at each procedure, by promoting the development of enhanced expertise in those individuals, contributed to the low rate of complications.

AVS technique and stimulation test

An important result of this survey is the little uniformity in the way each center performed AVS and interpreted its data. Apparently, most centers appear to use their own guidelines and criteria.

Initially, AVS involved sequential catheterization—catheterization of one adrenal vein followed by the other adrenal vein. Aldosterone and cortisol are released in bursts from the adrenals, which can bias the results of AVS due to a difference in timing of blood sampling, but not if aldosterone is corrected for cortisol. To overcome this problem, the strategy of maximally stimulating hormone secretion with ACTH (cosyntropin) infusion was proposed in 1979 by Weinberger *et al.* (29). Simultaneous bilateral catheterization was first introduced in 1980 to minimize differences between the sides due to timing (10) and then was improved with the use of differently shaped catheters on each side (26). This technique might therefore be viewed as a means of obviating cosyntropin stimulation. Despite this, only seven of 20 centers reported adopting this technique, with the majority still relying on sequential catheterization with or without cosyntropin stimulation. Reasons for this may include the added technical difficulties inherent with attempting to successfully catheterize both adrenal veins at the same time.

Centers were almost equally divided between those using and not using cosyntropin stimulation. Because stimulation might appear to be necessary when the sequential catheterization is used, we hypothesized that the use of cosyntropin stimulation might be associated with sequential catheterization. This was not the case, in that sequential sampling was not more common at the centers that used the cosyntropin stimulation.

Clinical use and interpretation of AVS

A basic assumption underlying the appropriate diagnostic utility of AVS is obtaining adrenal vein blood with minimal dilution from extraadrenal sources (30). This means that the proper placement of the catheter into the adrenal vein should be verified. This is generally accomplished by measuring the cortisol step-up between blood from the infrarenal inferior vena cava and blood from each adrenal vein to thereby calculate the selectivity index (31).

Moreover, because the level of both cortisol and aldosterone in adrenal vein blood is highly dependent upon the proximity of the catheter tip to the adrenal cortex, it is necessary to correct aldosterone levels against those of cortisol when assessing lateralization. These reasons support using the selectivity index and the lateralization index for optimal benefit for patients undergoing AVS. Several centers did not use one or both indices; this was unexpected, and of concern in that it may lead to suboptimally informed clinical decisions.

Finally, given that unilateral aldosterone excess would be expected to turn off aldosterone synthesis in (and secretion from) the contralateral adrenal gland, contralateral suppression has also been clinically used to lateralize PA (19). However, the adrenal gland of subjects receiving deoxycorticosterone and salt, *e.g.* placed in conditions that mimic PA and the adrenal cortex surrounding the APA (32), can continue to produce aldosterone (33). Although it was reported that plasma aldosterone concentrations are 129 ± 60 and 498 ± 84 ng/dl at 0 and 30 min after ACTH stimulation, respectively, in ten essential hypertensive patients (34), data on aldosterone plasma levels in adrenal veins or, more importantly, aldosterone/cortisol ratios and concurrent peripheral ratios of healthy volunteers subjected to similar conditions are lacking, presumably for ethical reasons. Thus, normal values of aldosterone production, and thereby the normal cutoff values, remain uncertain. Accordingly, the use of the contralateral suppression index remains empirically based. Despite all these considerations, contralateral suppression is being used in two thirds of the centers; in one center, demonstration of contralateral suppression was a *sine qua non* indication for adrenalectomy.

This study also showed that slightly less than one third of centers systematically used nonselective AVS for diagnostic purposes and that an additional six of the 20 occasionally used unilaterally selective studies, necessitating a finding of contralateral suppression. Those centers that systematically relied on non-bilaterally selective AVS also used contralateral suppression more frequently than expected by chance.

Establishing whether contralateral suppression could be used for diagnosing lateralization when only unilateral (usually left-sided) AVS is successful may thus be of major importance because it may justify using left-sided AVS results to diagnose lateralization to the right adrenal when bilaterally selective studies are not available. Catheterization of the left side is much easier than on the right, and it has a success rate close to 100%. Thus, demonstration of the diagnostic accuracy of contralateral suppression would allow results of more procedures to be clinically interpretable. Phase II of the AVIS will therefore formally investigate this important issue.

Cutoff values for AVS

This study documents a wide variability in the cutoff values used for selectivity, lateralization, and contralateral suppression, both under basal conditions and cosyntropin stimulation. This variability is due in large part to choices of the cutoff values that were experience-guided rather than based on formal assessment of diagnostic performance. Overall, the majority of the centers selected their cutoff values for both the selectivity index and the lateralization index from the literature, and only a minority based their selection on a formal assessment of diagnostic accuracy using ROC curve analysis alone (11%) or combined with the Youden index (11%). The latter is a single value that captures the performance of a diagnostic test and is defined as the point of the ROC curve farthest from the diagonal line. The only studies that have prospectively explored the performance of these indices under nonstimulated conditions to date support the choice of low values for both the selectivity and the lateralization index (13, 31), but a recent study on patients who required a repeated AVS because of failure on the first attempt would suggest the use of more stringent cutoffs for the selectivity index (35). The choice of higher cutoff values for lateralization adopted in many centers presumably identifies patients with an increased chance of cure but might exclude from adrenalectomy some patients who are curable. Upon completion of phase II of the AVIS, which will collate individual hormonal data and outcomes of therapy, we expect to have more precise information on optimal cutoff values for all indices and their applicability to clinical practice.

Costs of AVS

The lead investigator at many centers was surprisingly unaware of the cost of the procedure; only 12 of 20 were able to provide accurate information on costs for insurance and/or the patient. Cost varied widely between centers and countries, largely reflecting the wide variability in organization of health care system and the minimum level of care provided in different countries.

Conclusions

Despite the high prevalence of PA, and the fact that AVS is crucial for discriminating between its two major subtypes and therefore for selecting the most appropriate treatment, marked differences remain in the use of AVS even at major referral centers. This large study on data from 2604 AVS procedures documents the existence of a low complication rate and marked dissimi-

larities in the percentage of use, protocols, and interpretation and cost of AVS among the major referral centers around the world.

Importantly, overall the rate of major complications was minimal, between 0.51% and 0.61%, which demonstrates that although being generally regarded as a risky procedure, AVS is in truth safe in experienced hands. This observation therefore supports The Endocrine Society recommendation that AVS should be used in all patients with confirmed PA who are candidates for adrenalectomy and seek surgical cure. For a number of reasons, this recommendation does not appear yet to be generally applied, even at the major referral centers participating in this survey. Despite the introduction of the bilateral simultaneous catheterization technique by some centers, almost two thirds of the centers continue to use the sequential technique and perform catheterization during cosyntropin stimulation, whereas only a few centers use ACTH stimulation with bilateral simultaneous catheterization (36). Finally, some centers rely on measurement of absolute hormonal values rather than indices of selectivity, lateralization, and contralateral suppression. These findings represent a strong argument for defining guidelines for clinically important but technically demanding procedures as AVS, and for determining the diagnostic accuracy of the different indices for the identification of unilateral aldosterone secretion that will be assessed in phase II of the AVIS.

Acknowledgments

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