Adrenal venous sampling (AVS) is considered the most reliable currently available means of differentiating unilateral from bilateral forms of primary aldosteronism (PA), and thereby guiding appropriate management (usually unilateral adrenalectomy for unilateral forms and medication with drugs that antagonize aldosterone action for bilateral forms). This is a critical step in the diagnostic workup of PA because (1) blood pressure responses to unilateral adrenalectomy in patients with unilateral forms are far superior to those in patients with bilateral forms in which, in one study of highly selected patients, a hypertension cure rate of only 15% was seen and was primarily restricted to those with mild hypertension preoperatively (compared with reported cure rates of 50%–80% for patients with unilateral PA) and (2) at least in terms of ongoing antihypertensive medication requirements and quality of life, clinical responses to unilateral adrenalectomy in patients with unilateral PA are also superior to those in patients with bilateral PA treated medically.

In this edition of Hypertension, Lethielleux et al present a retrospective analysis of AVS results from 537 procedures performed in a single center in Paris on patients with PA, in which they compared rates of (1) cannulation success, as assessed by adrenal/peripheral venous cortisol gradients and of (2) lateralization, assessed by comparison of right and left adrenal venous (plus or minus peripheral venous) aldosterone/cortisol ratios, when variably defined according to 4 different sets of diagnostic criteria in current use (in Padua, Turin, Paris, and Brisbane) plus 1 advocated in a recent consensus statement. These sets of criteria varied in stringency, Padua being the most liberal and Brisbane the most strict. Overall, the success rates for cannulation were relatively high (≥80% even with the strictest criteria), which probably was primarily a reflection of the expertise of the group (especially the radiologist) and the fact that the procedure was restricted to the 1 operator in that center. The main findings of the study were that rates of both cannulation success and lateralization were substantially higher, and reproducibility of subtype diagnosis poorer when multiple adrenal venous collections were made during the 1 procedure, when the less stringent diagnostic criteria were applied compared with the more stringent.

Although not unexpected, these findings have important consequences. First, if cannulation is considered unsuccessful, the AVS results are likely to be considered inconclusive with regards to lateralization, and the therapeutic options at that point will usually be restricted to either repeating AVS or accepting an unresolved subtype diagnosis and commencing empirical medical treatment for PA. Conversely, if cannulation has been considered successful by less stringent criteria, then the AVS results are likely to be accepted and a management decision (which could include surgery) made without repeating the study. Second, a higher rate of lateralization because of less stringent lateralization criteria will lead to a higher rate of adrenalectomy which, for at least some patients who would not have lateralized using more stringent criteria, may not result in significant clinical benefit. This is a potentially serious issue because adrenalectomy is not without risk and, unlike medical management for PA, cannot be reversed. Because the center using the least stringent criterion for cannulation success also uses the least stringent for lateralization, it is possible that a significant minority of patients worked up at that center have undergone surgery that, according to other groups, would not have been considered the optimal treatment approach based on the presence, by their more stringent criteria, of either failed AVS or bilateral PA. In agreement with this premise is the reported lower cure rates (30%) among operated patients diagnosed as having aldosterone-producing adenoma using permissive criteria, which is about half the rate reported by groups with more stringent criteria. The fact that the criteria with least stringency also showed the lowest reproducibility of subtype diagnosis (unilateral versus bilateral PA) among different samples collected during the same AVS procedure supports the notion that they are less reliable than those with greater stringency.

The findings of Lethielleux et al confirm and extend those of a smaller previous study by Mulatero et al that compared 3 (Padua, Turin, and Brisbane) of the 5 sets of criteria listed above but was restricted to patients who had undergone a second AVS procedure on the basis of failed cannulation (according to their more stringent criteria) during the first, thereby permitting assessment of reproducibility of subtype diagnosis between the 2 procedures. Once again, apparent cannulation success and lateralization rates were higher but reproducibility...
(between the first and second studies) poor with the least stringent, Padua criteria. In a study by Monticone et al.33 use of more stringent criteria (eg, adrenal/peripheral venous cortisol gradients of >3.0 basally and >4.0 postcorticotropin stimulation) for cannulation proved critical for optimizing pre-versus postcorticotropin diagnostic reproducibility. Similarly, Ceral et al.34 reported gradients of ≥3.0 to be associated with optimal rates of reproducibility in lateralization diagnosis (determined by comparing results among multiple samples collected during the same AVS procedure and using those with cortisol gradients of ≥10 as the reference samples) when AVS was performed during corticotropin infusion.

One of the major challenges to studies (including those described above) attempting to assess and validate approaches to distinguishing unilateral from bilateral PA has been the lack of a robust “gold standard” for diagnosing aldosterone-producing adenoma. The blood pressure response to surgery, for example, may be incomplete if the patient is studied too soon after adrenalectomy or has other causes of residual hypertension. The response to surgery of plasma aldosterone plus or minus renin levels and the ARR is better, but still imperfect because cutoff criteria are arbitrary to some extent, and the ARR is associated with false-positives and false-negatives. Demonstration of an adenoma in surgically removed adrenals does not prove it was actually producing aldosterone and reliance on this would have the potential to misclassify unilateral PA because of micronodular hyperplasia as bilateral PA. Recent studies have reported on the use of immunohistochemical staining of resected adrenals in an attempt to confirm aldosterone-producing adenoma removal.5–17 with some success, but additional studies are required to validate and refine this approach. Our own approach is to repeat suppression testing postoperatively,18 but our currently favored method (fludrocortisone suppression testing) is time consuming, cumbersome, and expensive to perform and therefore not popular elsewhere. Having found conventional recumbent saline suppression testing to lack sensitivity for confirming autonomous aldosterone secretion, we have recently reported on the superior performance of saline suppression testing performed in the seated position (in which plasma aldosterone levels are often higher),19 which may prove to be a reliable and much more convenient approach to fludrocortisone suppression testing when assessing patients both preoperatively for the presence of PA, and, more importantly in the current context of validating AVS and other approaches to subtype differentiation, postoperatively to determine whether true biochemical cure of PA has been achieved.

In the meantime, AVS, although imperfect, is still the best we have in terms of distinguishing unilateral from bilateral PA preoperatively and should, therefore, remain the preferred approach for all patients with confirmed PA who are otherwise reasonable candidates for adrenal surgery. Studies such as the ones discussed above6,12–14 are helping to shape AVS diagnostic criteria toward more reliable subtype outcomes, and cannulation success rates across centers are showing substantial improvements with increasing experience and expertise (aided by limiting the number of proceduralists at each institution to 1 or 2).20,21 and with the introduction of measures such as computed tomography-guided localization of adrenal veins22,23 and point-of-care cortisol assays24,25 to confirm whether cannulation has been achieved at the time of the procedure, as well as more accurate and reproducible mass spectrometric methods of measuring aldosterone.26 Hence, although there is certainly room for improvement, these exciting developments are helping to address this need and secure a bright and enduring future for AVS.

Disclosures

None.

References


Adrenal Venous Sampling for Differentiating Unilateral From Bilateral Primary Aldosteronism: Still the Best, but Could Be Better
Michael Stowasser

Hypertension. 2015;65:704-706; originally published online February 2, 2015; doi: 10.1161/HYPERTENSIONAHA.115.04930
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/65/4/704

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/