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The where, who and how of adrenal vein sampling in Australia and New Zealand

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Abstract

Introduction: Primary aldosteronism (PA) causes 10–15% of cases of hypertension, and it is increasingly recognised as being under-diagnosed. An interventional radiology procedure, adrenal vein sampling (AVS), is a necessary and important diagnostic procedure for complete workup of PA. There is an anticipated increase in demand for AVS as detection of PA improves. This study aims to describe the current landscape of AVS in Australia and New Zealand (NZ).

Methods: Two surveys exploring AVS methodology and performance were conducted of (i) Endocrinology Unit Heads and (ii) interventional radiologists who perform AVS, at public hospitals with Endocrinology Units across Australia and NZ.

Results: Responses were received from 48/53 Endocrinology Unit Heads (91%) and 35 radiologists from 26 sites (87% of AVS sites). AVS was provided at 28/48 Endocrinology sites (58%) across Australia and NZ. In Australia, sites were concentrated in Victoria, New South Wales and Queensland with none in the Northern Territory; in NZ, sites were more evenly distributed across the North and South Islands. AVS was performed by 1–2 dedicated radiologists at 24 sites, 2–3 radiologists at two sites and a rotating roster of radiologists at two sites. Responses to both surveys revealed significant variation in AVS methodology and interpretation of AVS results.

Conclusion: There is significant heterogeneity in the availability of AVS, the procedural details and the interpretation of results across Australia and NZ, which potentially impacts the quality of patient care and ability to scale up AVS capacity to meet increasing demand.

Key words: adrenal vein sampling; endocrine hypertension; interventional radiology; primary aldosteronism; venous sampling.

Introduction

Primary aldosteronism (PA) is the most common endocrine cause of hypertension. The diagnostic process for PA involves three stages: screening, confirmation and subtyping, with the latter needed to determine whether one or both adrenal glands are affected. PA is surgically curable if caused by the unilateral subtype, while bilateral PA is managed medically. Adrenal vein sampling (AVS) is the recommended method for subtyping[1] to inform curative adrenalectomy or avoid unnecessary adrenalectomy. However, AVS is technically challenging and time-consuming, and success rates can vary widely.[2,3] Furthermore, the optimal methods of performing and interpreting

AVS are still being debated, leading to heterogeneity in performance of the procedure.[2,4] It is unclear if strategies reported to improve AVS success, including having dedicated radiologists and using point-of-care cortisol assays,[5–7] are routinely implemented.

The need to understand how AVS is performed and interpreted is important in consideration of the anticipated increase in demand for this procedure. Hypertension affects 34% and 31% of adults in Australia[8] and New Zealand (NZ),[9] respectively, where the combined population is 30.5 million (25.4 and 5.1 million).[10,11] While PA was previously considered rare and diagnosed in less than 0.1% of people with hypertension,[12] recent research indicated a prevalence of 14% in people with newly diagnosed hypertension.[13] Anecdotal evidence suggests limited AVS availability with heterogeneous test protocols and long waiting lists in both countries, but there are no current data on AVS availability and conduct in Australia and NZ.

Hence, we sought to evaluate the 'where, who and how' of AVS in Australia and NZ in preparation for future harmonisation and upscaling of the procedure.

Methods

Surveys of Endocrinology Unit Heads and interventional radiologists who perform AVS were prospectively conducted from March to November 2022.

Survey distribution

Heads of Endocrine Units at all Australian and NZ public hospitals providing an Endocrinology Training program through The Royal Australasian College of Physicians were invited to complete a survey by email. Hospital names were requested to prevent multiple participation. The sites identified as providing AVS were contacted to identify the interventional radiologists performing AVS. All interventional radiologists performing AVS were invited by email to complete a survey exploring AVS methodology and perceptions on barriers to AVS access. Consent was implied by agreement to undertake the voluntary survey.

Survey questions

Both surveys comprised closed questions and free-text responses (Appendices S1 and S2). AVS methodology explored included simultaneous or sequential blood sample collection from each adrenal gland, use of adrenocorticotrophic hormone (ACTH) stimulation and use of point-of-care rapid cortisol assays to evaluate the precision of adrenal vein cannulation. Adrenal vein cannulation success is determined by calculating the selectivity index (SI), defined as the ratio of cortisol in the adrenal vein to the peripheral vein. Subtype of PA (unilateral or bilateral) is determined by the lateralisation index (LI), which is calculated by dividing the aldosterone to cortisol ratio in the dominant adrenal vein by the nondominant adrenal vein.

Survey development and administration

Survey questions were developed by the study team comprising endocrinologists, interventional radiologists and a chemical pathologist. REDCap (Research Electronic Data Capture) was used for survey design, management and dissemination.[14] Study data were collected and managed using the REDCap electronic data capture tool.[14] Pretesting was performed by investigators to refine the survey questions and delivery.

Ethics

This study was approved by the local institutional Human Research Ethics Committee (RES-22-0000-169L).

Statistical analysis

Categorical variables were summarised using frequency tables, presenting subject counts and percentages. Continuous variables were expressed as medians and interquartile ranges (25th and 75th percentiles). Analyses were performed using SPSS® Statistics for Macintosh, version 26 (IBM®, Armonk, NY, USA).

Results

Survey participants

Of 53 Endocrinology Unit Heads contacted, 48 responded (91%) (Table 1). Of the five sites that did not respond, inquiry with their hospitals identified that two provided AVS, and their radiologists provided a survey response. Responses were received from 38 radiologists from 27 sites (90% of sites providing AVS) (Table 1).

Selection of patients for AVS

Most endocrinology sites reported having a formal local protocol for the diagnostic workup of PA (36 of 47 responses, 77%). The threshold for an abnormal aldosterone-to-renin ratio (ARR) reported by the Unit Heads was >70 pmol/L:mU/L at 26 sites (26/46 responses, 57%), >50 pmol/L:mU/L at 10 sites (10/46, 22%), >55 pmol/L:mU/L at two sites and >30.5 pmol/L:mU/L at three sites (all in NZ). Confirmatory testing was by saline suppression test at all sites, performed supine at 39 sites (81%) and seated at 9 sites.

AVS provision

AVS availability was confirmed at 30/53 (57%) endocrinology sites across Australia and NZ (28 identified from the 48 survey responses, and two identified by direct

Table 1. Survey responses

State	Population [25] million	Endocrine Training Sites (n = 53) n	Endocrinology Unit Head Responses (n = 48) n (%)	Sites offering AVS† (n = 30) n	AVS Radiologist Responses (n = 35) n (%)	AVS site per population site/million
Victoria	6.59	10	9 (18.8)	6	7 (20.0)	1.10
New South Wales	8.13	17	15 (31.3)	8	7 (20.0)	1.02
Queensland	5.30	8	7 (14.6)	4	7 (20.0)	1.33
Tasmania	0.57	2	2 (4.2)	1	1 (2.9)	0.57
Northern Territory	0.25	1	1 (2.1)	0	0	0
South Australia	1.82	4	4 (8.3)	2	3 (8.6)	0.91
Western Australia	2.77	3	3 (6.3)	1	3 (8.6)	2.77
Australian Capital Territory	0.46	1	1 (2.1)	1	1 (2.9)	0.46
New Zealand	5.12	7	6 (12.5)	7	6 (17.1)	0.73

†Endocrinology Unit Head responses for 28, and Radiologist response only for 2.

hospital contact). In Australia, this was concentrated in the more populous states, Victoria, New South Wales and Queensland. One AVS centre was identified in Tasmania, Western Australia and the Australian Capital Territory, and none in the Northern Territory (Table 1).

Ten or less procedures per year were performed by 43–44% of sites in 2018, 2019 and 2021, and 52% of sites in 2020. Over 50 procedures per year were conducted at one site in 2018, 2020 and 2021, and two sites in 2019. For the 20 sites who responded and did not offer AVS, 16 referred to another centre within the state, three referred to various centres depending on the waiting lists, and one referred to an interstate centre due to their higher success rates.

Endocrinology Unit Heads reported AVS provision by 1–2 dedicated radiologists at 24 sites, 2–4 dedicated radiologists at two sites and by the on-call radiologist at two sites. Most radiologists reported having at least two radiologists performing AVS at their site (15/37 had two, 10 had three, 1 had four, and 2 had five), while nine reported being the sole AVS radiologist at their site. The waiting time for AVS, which reflects the time between referral and completion of the procedure, was reported by most radiologists to be over 1 month (30/38), with nine (24%) reporting waiting times of over 3 months. The median number of staff involved with each procedure was 5 (IQR 5–6, range 3–7), comprising a mix of radiologist, radiology fellow, radiographer, nurse, chemical pathologist, endocrinology registrar, phlebotomist and scientist.

AVS techniques and outcomes

Both surveys revealed significant variation in AVS methodology, including timing of adrenal vein cannulation and sample collection, ACTH administration and point-of-care cortisol assay use (Table 2). The most common methods reported were sequential sampling (79% of sites), use of ACTH stimulation before AVS (50%), sampling without use of the rapid cortisol assay (54%), and measurement of aldosterone and cortisol by immunoassay (74% for aldosterone, 89% for cortisol).

Table 2. AVS methodology as reported by radiologists

			n	%
AVS cannulation (n = 38)	Sequential		27	71.1
	Simultaneous		8	21.1
	Variable		3	7.9
Use of ACTH stimulation (n = 37)	Yes – before AVS		12	32.4
	Yes – during AVS with collection of pre- and post-ACTH samples		11	29.7
	No – not used at all		4	10.8
	Variable		10	27.0
Use of point-of-care rapid cortisol assay (n = 38)	Yes – always		19	50.0
	Yes – most of the time		3	7.9
	Yes – sometimes		2	5.3
	Yes – occasionally		2	5.3
	No		12	31.6
Personnel collecting and labelling samples during AVS (n = 37)	Nurse		18	48.6
	Chemical pathologist		10	27.0
	Other (n = 9)	Endocrine nurse and/or registrar	6	16.2
		Nurse or chemical pathologist	1	2.7
		Phlebotomist	1	2.7
		Scientist from endocrine laboratory	1	2.7

The radiologists reported that 95% of cases (median) required less than 2 h to complete and 5% required 2–4 h. Only four radiologists reported a small percentage of their cases lasted over 4 h. Most radiologists performed between 5 and 20 procedures per year from 2019 to 2021 (Fig. 1). Complications were reported by 13 radiologists, 11 due to adrenal haemorrhage and the remainder due to a groin haematoma. The median self-reported success rate for adrenal vein cannulation as determined

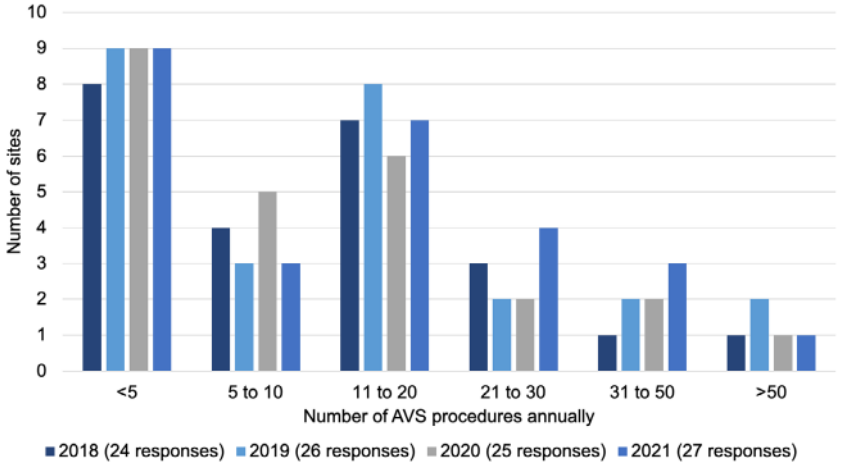

Fig. 1. Number of AVS procedures performed at each site per year from 2018 to 2021 (reported by Unit Heads).

by intraprocedural venography was 85% (IQR 75–95) for the right, 100% (IQR 98–100) for the left and 90% (IQR 76–96) for bilateral cannulation. Endocrinology Unit Heads reported success of adrenal vein cannulation as 50–100% (mean 80%, median 75%), with greater success in centres with dedicated radiologists and higher volume. Radiologists recommended that 20 procedures were required to acquire proficiency (median response).

AVS result interpretation

Interpretation of AVS results was performed by a dedicated endocrinologist at 6/27 sites, multidisciplinary team at 14/22 sites and variably at the remaining sites, by either a chemical pathologist, ward service consultant, hypertension specialist, renal physician or dual-trained chemical pathologist/endocrinologist. Cut-offs for selectivity index (SI) and lateralisation index (LI) also varied, with the most commonly used cut-offs being SI > 2 without ACTH (13/17) or SI > 3 after ACTH (15/25) for adrenal vein cannulation success; LI > 2 or >4 without ACTH (7/22 each) and LI > 4 with ACTH (21/25) for lateralisation of aldosterone excess (Table 3).

Perceived barriers and enablers of AVS provision

Key issues limiting AVS provision, as identified by Endocrinology Unit Heads, were the lack of interventional radiology expertise and low success rates due to the low volume of procedures and the limited number of dedicated interventional radiologists. It was proposed that designated centres should perform AVS rather than it being undertaken by all. Most radiologists highlighted the importance of a dedicated AVS interventional radiologist for achieving a high technical success rate. Both groups observed increased rates of cannulation success with point-of-care cortisol assays. Radiologist-reported barriers to performing AVS were inadequate hospital resources including supporting staff, the time requirement of AVS diverting attention from other procedures and lack of financial incentive. The multidisciplinary interaction involved in PA subtyping was stated to enhance the appeal of AVS as compared to other interventional procedures.

Table 3. AVS interpretation as reported by Endocrinology Unit Heads

			n	%
Selectivity index (SI) cut-off to indicate successful cannulation (ratio of adrenal-to-peripheral vein cortisol concentration)	Without ACTH stimulation (*n* = 25)	SI > 4	1	4
		SI > 3	3	12
		SI > 2	13	52
		N/A	8	32
	With ACTH stimulation (*n* = 25)	SI > 4	3	12
		SI > 3	15	60
		SI > 2	4	16
		SI > 5	1	4
		Other	2	8
Lateralisation index (LI) cut-off to indicate lateralisation of aldosterone excess (aldosterone to cortisol ratio in the dominant adrenal vein divided by that in the nondominant adrenal vein)	Without ACTH stimulation (*n* = 26)	LI > 4	7	27
		LI > 3	3	12
		LI > 2	7	27
		N/A	8	31
		Other: LI > 2.5 + contralateral suppression	1	4
	With ACTH stimulation (*n* = 25)	LI > 4	21	84
		LI > 3	2	8
		LI > 2	1	4
		Unsure	1	4
Laboratory methods (*n* = 27)	Cortisol measurement	Immunoassay	24	89
		LCMS/MS	3	11
	Aldosterone measurement	Immunoassay	20	74
		LCMS/MS	7	26

ACTH, adrenocorticotropic hormone; LCMS/MS, liquid chromatography with tandem mass spectrometry; LI, lateralisation index; N/A, not applicable; SI, selectivity index.

The proposal of a streamlined nation-wide protocol was welcomed by the majority of radiologists on the basis that it would allow consistent interpretation and comparison of results, streamline training and collaboration, reduce confusion among referring doctors and achieve more predictable patient outcomes. Equivocal responses to the role of a protocol were explained by opinions that existing practices were adequate to achieve good outcomes and that varying access to resources (e.g. point-of-care assays) would impact protocol adherence.

Proposed methods to improve access and interest in AVS included formal training, better remuneration for radiologists, a multidisciplinary team approach, standardisation of the procedure, formation of an interest group and education of hospital management to increase support for staffing and resources.

Discussion

This study describes the current landscape of AVS in Australia and NZ, and has identified marked heterogeneity in AVS provision and methodology. In Australia, AVS availability relative to population was comparable in most states, but there was complete absence of AVS services in the Northern Territory. In NZ, AVS sites were evenly distributed across the country, but availability relative to population was comparable to Australian states (Table 1). With AVS services provided by 0.46–2.77 sites per million population and the majority of sites performing <20 AVS per year (Fig. 1), there is an apparent need to increase capacity to adequately cater for the 14% of hypertensive individuals who may have PA that requires subtyping. One major barrier to AVS provision identified in this study relates to the AVS resources needed to facilitate higher case volume. The financial aspect of AVS provision is a barrier given the costs of suitable facilities, staffing and point-of-care testing kits. Additionally, the current lack of a Medicare Benefits Schedule item for AVS in Australia means the time and effort invested in the procedure is not well remunerated for the radiologist or the hospital. These represent important targets for intervention in future implementation strategies.

Variation in AVS methodology was reported by both Endocrinology Unit Heads and radiologists and may contribute to the range of AVS success rates across centres. This included timing of adrenal vein cannulation and blood sample collection, use of ACTH administration and use of point-of-care cortisol assays, all of which have been described to affect AVS results.[15–18] In particular, the use of rapid cortisol assays has been shown to increase cannulation success,[15] while the use of ACTH during AVS has been recognised to improve cannulation success while reducing the rate of lateralisation, either due to masking of unilateral disease or unmasking of bilateral disease.[17,18] Furthermore, there were differences in the assessment of cannulation success and lateralisation such that AVS considered successful at one site may be considered unsuccessful at another, or disease considered unilateral at one site may be considered bilateral at another. A multicentre study involving sites in Asia, Australia, North America and Europe, as well as a more recent Spanish study, demonstrated similar variability across sites.[4,19] This lack of standardisation of AVS has implications not only for the outcome of the procedure itself but also for the accurate subtyping of PA and appropriate treatment.[20] Consensus statements on AVS have been published by international experts[21]; however, suboptimal quality and implementation of these guidelines have been acknowledged.[22] Identifying and documenting the inconsistencies in AVS performance and interpretation in Australia and NZ may provide a basis for the targeted development of harmonised guidelines to achieve reproducible outcomes.

Many survey respondents raised the issue of a negative cycle experienced by sites with low success rates and subsequent low referral rates leading to a reduced opportunity to improve AVS techniques. It is well described that focused expertise of dedicated interventional radiologists is an important factor for procedural success.[23] Experienced radiologists who responded to this survey suggested at least 20 procedures needed to be performed to achieve proficiency. A Swedish study of a tertiary referral centre serviced by a single interventional radiologist reported that satisfactory AVS success rates were achieved after 36 procedures and maintained by undertaking 27 procedures annually.[24] Limiting AVS to few specialised centres has the advantage of creating opportunity for dedicated radiologists to build experience and improve procedural success. However, this may limit access for patients in regional or rural locations, and this factor would need to be addressed in plans to increase AVS capacity.

Most survey responders supported the role of a unified protocol, with perceived benefits including standardisation of processes (including AVS training), reproducibility of results and consistency of patient care. At a minimum, new harmonised AVS guidelines would offer radiologists an outline of effective methodology based on existing evidence, which may facilitate training and upskilling to strengthen the AVS workforce. This would be especially useful in areas with fewer radiologists and therefore few opportunities for continued training and discussions regarding AVS methodology. Local access to AVS would translate to improved rates of PA diagnosis and subtyping; referrals to interstate providers require travel expenses and time off work, which would pose a barrier to timely subtyping and optimal treatment of PA.

This is the first study to evaluate current AVS practices in Australia and NZ. Survey response rates were high and almost all sites, which provide AVS contributed to the presented data. This study has not captured details of AVS services in the private healthcare setting or newer sites that may have been set up since survey

dissemination, though the former is likely to be minimal due to the lack of a Medicare Benefits Schedule rebate, at least in Australia. The nature of data collection by surveys is subjective and therefore vulnerable to biases that could not be accounted for. One source of potential bias is that those who responded may have greater interest in PA and therefore higher rates of procedural success. Cannulation success rates were self-reported but have not been validated with hospital data. This is reflected in the discrepancy in procedural success rates reported by the radiologists compared to the Unit Heads. This discrepancy may be due to variations in SI criteria to determine cannulation success between centres, whereas the radiologist's initial impression of success is the venogram confirming cannulation, especially in centres where the rapid cortisol assay is not used.

There is significant heterogeneity in the way AVS is conducted and interpreted around Australia and NZ, which potentially impacts the ability to scale up capacity to cater for an anticipated increasing need for AVS. These findings suggest a role for harmonisation of AVS methodology and interpretation to facilitate reproducible outcomes and consistent patient care. Documenting current AVS practices also provides benchmarks that allow for advocacy and measurement of future improvements in the availability and delivery of AVS.

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Data availability statement

Data generated or analysed during the study are available from the corresponding author by request.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1
Appendix S2