Primary aldosteronism (PA) is much more common than previously thought, possibly accounting for 5%–10% of hypertension cases (1, 2). Importantly, specific treatment of PA not only cures or improves the hypertension but also leads to amelioration of the excess cardiovascular damage and morbidity seen in these patients, compared with other forms of hypertension (1, 2). Consequently, recently published guidelines have recommended wider screening for PA via testing for the plasma aldosterone/renin ratio, in an effort to maximize the detection of patients who may then benefit from optimal, specific management (4).

Once diagnosed, it is important to determine the subtype of PA, because the optimal treatment differs for each form. When PA is confined to a single adrenal gland (as in aldosterone-producing adenoma), unilateral adrenalectomy usually cures and virtually always improves the hypertension, with an accompanying improved quality of life. Bilateral forms, however, are more likely to respond to drugs—such as spironolactone, eplerenone, or amiloride—that antagonize aldosterone action. In most current series, unilateral forms make up approximately 30% of patients with PA, and bilateral forms make up the remaining 70% (2, 4).

Computed tomography (CT) and other imaging modalities lack adequate sensitivity for identifying unilateral PA, because many aldosterone-producing adenomas are small (<1 cm) or the gland may only be mildly hyperplastic (2). Furthermore, CT may be frankly misleading by demonstrating unilateral nonfunctioning nodules in patients with bilateral PA or by showing nodules that are contralateral to the affected adrenal in unilateral PA (2). Owing to this diagnostic uncertainty, the only reliable way to differentiate unilateral from bilateral PA is by adrenal venous sampling (AVS), which seeks to estimate and evaluate each adrenal’s aldosterone production separately (2, 4). The value of AVS is maximized when confounding factors that could complicate the interpretation of results are controlled for or at least taken into account. Within our center, potentially interfering medications (including diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and dihydropyridine calcium channel blockers) are withdrawn for several weeks (when possible) before initial testing of the aldosterone/renin ratio and are avoided until the diagnostic workup for PA (including AVS) has been completed. Hypertension control is maintained with other drugs (including slow-release verapamil with or without hydralazine, and including prazosin or doxazosin) that are renin and aldosterone neutral. If renin is rendered “unsuppressed” by drugs such as diuretics, there is a risk that it could lead to stimulation, via angiotensin II, of aldosterone production by the contralateral, otherwise suppressed adrenal gland in patients with an aldosterone-producing adenoma. That could lead to a loss of lateralization on AVS. Similarly, patients are encouraged to follow a liberalized salt diet to avoid the potential of dietary sodium restriction to stimulate renin and aldosterone. Patients are given detailed information sheets regarding AVS and are instructed in relaxation techniques by trained allied health personnel in an attempt to minimize the effects of stress on steroid production. Changes in posture can alter aldosterone concentrations in patients with angiotensin II–responsive varieties of PA. This possibility is avoided by performing AVS in the morning after overnight recumbency, a strategy that also takes advantage of the effect of high early morning endogenous adrenocorticotropic hormone (ACTH) concentrations on aldosterone production (2).

Great skill is required to successfully cannulate the adrenal veins, especially the right one, which is smaller and shorter than the left and usually empties into the inferior vena cava rather than the renal vein. Cannulation success can be judged by examining the concentration ratio of adrenal cortisol to peripheral venous cortisol. Within our center, ratios ≥3.0 are taken to indicate adequate sampling; samples demonstrating ratios <2.0 are always excluded from further consider-
ation. According to these criteria, the success rate for cannulation of the right adrenal vein at Greenslopes Hospital has remained ≥90% since 1999 (2). The keys to this success rate have included: (a) restricting the procedure to a small number of radiologists highly experienced in this technique; (b) maintaining a high throughput (at least 15–20 procedures per year), (c) performing a fine-cut adrenal CT evaluation with intravenous contrast before AVS to identify both the right adrenal vein at its point of entry into the inferior vena cava and the vertebral level on the corresponding “scout” film, which can then be used to direct catheter placement; (d) asking the radiologist to obtain multiple samples from each side; and (e) maintaining a close liaison between the treating physicians and radiologists to permit feedback on performance (2). Other investigators have reported higher success rates when AVS is performed with ACTH stimulation, which is also used as a means of minimizing fluctuations in steroid production during the procedure and ensuring that sampling is not undertaken during a relatively “quiescent” phase (5).

Within the past year, 3 reports (from Italy, the US, and Germany) have reported on the use of intraprocedural cortisol measurement (IPCM), which permits on-the-spot clarification as to whether the adrenal veins have been successfully cannulated (6–8). Initial samples are immediately forwarded to the pathology department for cortisol assay, the results of which are then returned to the radiologist while the patient is still in the radiology department. If these results indicate successful cannulation, AVS is terminated at that point. If not, sampling is repeated via the same femoral catheter sheath, which was left in place after the first attempt. This process is sometimes repeated several times. By all reports, IPCM has been associated with improvements in cannulation success rates (defined as an adrenal/peripheral venous cortisol gradient of either ≥5.0 when ACTH stimulation is used or ≥2.0 when it is not), which have ranged among centers from 54% to 81% before IPCM to 84% to 93% after IPCM (6–8). Importantly, cannulation was successful after repeat sample collection in 4 of the 6 patients in whom initial results showed failed cannulation in the Italian cohort (n = 25), 3 of 6 patients in the US cohort (n = 28), and 14 of 21 patients in the German cohort (n = 46) (6–8). This process prevents the considerable time and costs associated with having to repeat the entire AVS procedure.

A drawback of IPCM is the delay during AVS due to sample transport to and from the pathology department, centrifugation, dilution (when required), and assay. For the 3 reports described above, the mean delay ranged from 20 min to 40 min (6–8). A previous report from the US described an even longer delay (1–2 h) (9). For centers with the longest delay, patients were maintained in the radiology recovery room (with femoral sheaths left in place) to free up the radiology suite for other procedures. Presumably, the longer the sheaths are left in situ, the greater the risk of such complications as bleeding, thrombosis, and infection. At centers with shorter delays, the patient was kept in the radiology suite, and in the German study the patient underwent cannulation of the left adrenal vein while the results from the right side were undergoing IPCM (8). In the original IPCM study reported in 2000 by Woods and coworkers (10), this delay was greatly reduced through the use of a portable analyzer that could be operated within the radiology department, thereby reducing the transport time to virtually zero. Furthermore, the analyzer required only 50 μL of serum, which meant very short centrifugation times and the ability to provide a cortisol concentration in just a few minutes. We successfully used this system for several years in our own center until we were forced to abandon it, because maintenance items for the analyzer were no longer being manufactured. Dilution was rarely required to demonstrate successful cannulation, because the upper limit of reliable measurement with the assay was 1500 nmol/L. Provided that recumbent peripheral concentrations did not exceed 500 nmol/L (which was rarely the case in our experience), an adrenal venous concentration greater than the upper limit of the assay met our criteria for cannulation success. Mengozzi and colleagues in Torino, Italy, reported on a similar rapid IPCM method in 2007, and it is still in use there (11).

Assessment of lateralization requires calculating the aldosterone/cortisol ratio, which corrects for the dilution of adrenal blood by nonadrenal venous blood. According to the criteria used in our center, if the aldosterone/cortisol ratio on one side is at least 2 times greater than the simultaneous peripheral venous ratio, and the aldosterone/cortisol ratio on the other side is no higher than peripheral venous ratio, the study is considered to show lateralization, indicating that unilateral adrenalectomy should cure or improve the hypertension (2). Unlike in IPCM, assessment of lateralization requires that both aldosterone and cortisol be measured precisely (and not just above a certain interval). Because steroid values in adrenal venous samples are so high, dilution is usually required to obtain a precise concentration. Small errors in sample dilution may have major effects on results. Perhaps even more critical is the reliability of the assays used. Not only are the concentrations of aldosterone and cortisol very high in adrenal venous blood, but so are the concentrations of other steroids (including precursors and metabolites), with the potential for assay cross-reactivity. We recently reported on the use of a new, rapid-throughput
method that uses HPLC and tandem mass spectrometry. This method is capable of measuring both steroids simultaneously with high degrees of reliability and reproducibility (12). Studies are currently under way to compare results obtained with this method with those obtained by conventional assay approaches.

With PA now being sought at greater rates than ever before and with the demand for AVS increasing, urgent measures are required to improve AVS success rates and reliability in centers still experiencing suboptimal results. Although the level of expertise and experience of the proceduralist and a close liaison with the treating team are probably of foremost importance in this respect, the use of such approaches as pre-AVS CT localization of the adrenal veins, IPCM, and highly reliable assay techniques are additional interventions that can assist in achieving these important goals.

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