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ORIGINAL ARTICLE **CME**

Management of Primary Aldosteronism: Should Adrenal Gland Computed Tomography be Replaced by Adrenal Venous Sampling?

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ABSTRACT

Objectives: *To evaluate the accuracy of computed tomography (CT) in the management of primary aldosteronism by comparing the concordance between CT and adrenal venous sampling (AVS), and the feasibility of AVS as a standard component in the diagnostic workup.*

Methods: *From January 2009 to December 2012, 44 instances of AVS performed in 39 patients in Kwong Wah Hospital, Hong Kong were reviewed. All these patients had undergone CT of the adrenal glands before AVS. CT findings, and aldosterone and cortisol profiles of the left adrenal vein, right adrenal vein, and inferior vena cava during AVS were compared. Successful cannulation was defined by achieving an adrenal vein to the inferior vena cava cortisol level ratio of higher than 1.1. The positive predictive value of CT and concordance between CT and AVS were calculated. The pathology reports of patients who underwent adrenalectomy were reviewed.*

Result: *AVS was successful in 35 (90%) of the patients on the first attempt, and concordance between CT and AVS was observed in 23 (59%) patients. CT yielded a positive predictive value of 73% and 44% in unilateral disease and bilateral disease, respectively. A total of 27 patients with unilateral disease underwent adrenalectomy. Pathology confirmed cortical adenoma in all specimens.*

Conclusion: *CT is not an accurate tool for the management of primary aldosteronism, especially in bilateral disease. AVS as a standard procedure in the workup is feasible but depends on proper technique and radiologists with adequate experience.*

Key Words: *Adrenal glands; Adrenalectomy; Hyperaldosteronism; Predictive value of tests; Tomography, X-ray computed*

中文摘要

原發性醛固酮增多症的診斷：應否讓腎上腺靜脈取樣代替其電腦斷層掃描？

林卓恆、仇鴻烈、趙修軒、曹慶恩、柳洵、呂振英

目的：藉着比較電腦斷層掃描（CT）及腎上腺靜脈取樣（AVS）的結果是否達一致性來評估CT診斷原發性醛固酮增多症的準確性，並探討AVS作為診斷檢查中作為標準項目的可行性。

方法：回顧研究2009年1月至2012年12月期間，於香港廣華醫院的39名病人中完成的44例AVS。所有患者在進行AVS之前均已接受腎上腺CT掃描。把CT檢查結果與經AVS獲得的左腎上腺靜脈、右腎上

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腺靜脈和下腔靜脈的醛固酮及皮質醇水平作比較。如果腎上腺靜脈與下腔靜脈的皮質醇水平比值高於1.1，即代表插管成功。然後計算CT的陽性預測值，以及CT和AVS之間的一致性。並回顧接受腎上腺切除術的患者的病理報告。

結果：35例（90%）患者的AVS一次成功，23例（59%）可觀察到CT和AVS的結果一致。CT在單側和雙側腎上腺病變中的陽性預測值分別為73%和44%。總計27例單側發病患者接受腎上腺切除術，所有標本經病理學證實為皮質腺瘤。

結論：CT並非原發性醛固酮增多症的準確診斷工具，尤其是雙側腎上腺病變的檢查。AVS可作為診斷檢查的標準流程，但依賴於合適的技術和經驗充足的放射科醫生。

INTRODUCTION

Hypertension is a common disease affecting middle-aged subjects, and is increasingly encountered, especially in developed countries.[1] Primary aldosteronism is one of the secondary causes of hypertension. Historically, it was thought to be an uncommon cause of hypertension, with a prevalence of <1% among hypertensive patients.[2] However, since the early 1990s, there has been growing evidence suggesting that 10 to 15% of individuals with hypertension fulfil the biochemical criteria of primary aldosteronism.[3-6]

Numerous biochemical tests and imaging techniques are used in the workup of such patients, but they are indirect and inaccurate. In particular, the sensitivity and specificity of computed tomography (CT) is poor,[7] and it fails to identify patients who could benefit from surgery. More importantly, patients may undergo unnecessary and potentially futile surgery, when clinical decisions are based on CT findings alone. This study therefore set out to evaluate (i) the accuracy of CT in the management of primary aldosteronism by comparing the concordance between CT and adrenal venous sampling (AVS) and (ii) the feasibility of AVS as a standard component in the diagnostic workup.

METHODS

From January 2009 to December 2012, all patients who underwent AVS in Kwong Wah Hospital in Hong Kong were reviewed. They had all undergone CT of the adrenal glands before AVS. Their CT findings, as well as aldosterone and cortisol level profiles in the left adrenal vein, right adrenal vein, and inferior vena cava (IVC) based on AVS were compared. Successful cannulation was defined if the ratio of the cortisol level in the adrenal vein relative to the IVC exceeded 1.1.[8] The Endocrine Society guidelines suggest that a cortisol-corrected aldosterone ratio of >2 from the high side to the low side (in the absence of cosyntropin use) indicates unilateral disease. When cosyntropin was infused during the AVS procedure, a lateralisation ratio of >4 indicated unilateral disease and <3 was consistent with bilateral hypersecretion. Alternatively, unilateral hypersecretion could be concluded when the ratio of the cortisol-corrected aldosterone ratios between the affected gland and a peripheral vein (usually the IVC) exceeded 2.5 in the setting of suppressed aldosterone secretion from the contralateral gland.[9] The positive predictive value of CT and concordance between CT and AVS were calculated. The pathology reports of patients who underwent adrenalectomy were reviewed.

RESULTS

A total of 44 instances of AVS were performed in 39 patients during study period. AVS was successful in 35 (90%) of the patients on the first attempt; three underwent a second AVS due to unsuccessful venous cannulation. One patient proceeded to surgery despite failed first AVS because of indirect evidence supporting contralateral suppression. Also two patients who had surgery underwent repeat AVS, as the first AVS resulted in a large discrepancy with CT findings.

Based on AVS, there were 27 patients with suspected unilateral aldosterone-producing adenomas (APAs) and 12 with bilateral hypersecretion. On CT, 26 patients had unilateral nodules, 9 had bilateral disease, and 4 appeared normal. Concordance between CT and AVS was observed in 23 (59%) of the 39 patients. Patients who had discordant results were treated according to the AVS findings; eight underwent surgery. The blood pressure of two of these patients normalised without any antihypertensive medication, and one still warranted multiple antihypertensive drugs to control the blood pressure. Regarding the remaining 5 patients, they were deemed to require fewer antihypertensive drugs and / or lower dosages. All of them had normal potassium levels.

In the 27 patients having APAs (AVS proven), 19 had concordant CT findings and 8 had discordant findings. Among the latter, five had bilateral adrenal nodules, two had normal CTs, and paradoxically one had a contralateral nodule (Figure 1).

Figure 1. Computed tomography shows left adrenal nodule (arrow).

Figure 2. Computed tomography shows right adrenal nodule (arrow).

In the 12 patients with bilateral hypersecretion (AVS proven), concordance was even lower — four had concordant findings, and eight had discordant findings. Among the latter, six showed a unilateral lesion (Figure 2) and two had normal CTs.

CT had a positive predictive value of 73% and 44% in unilateral disease and bilateral disease, respectively (Table 1). 27 patients with unilateral disease underwent adrenalectomy. Pathology confirmed the presence of a cortical adenoma in all patients.

DISCUSSION

There is growing evidence that primary aldosteronism is more common than previously considered, ranging from 10% to 15%.[3-6] Evidently, it is even more prevalent (up to 20%) in patients with resistant hypertension.[10] Such patients are usually refractory to medical treatment and surgical treatment offers the only chance of cure or disease control.

Treatment strategies differ for unilateral and bilateral disease. APAs are treated with open or laparoscopic adrenalectomy, whereas bilateral adrenal hypersecretion involves medical therapy. Numerous biochemical tests and imaging techniques are used in the workup of these conditions but are indirect and inaccurate. AVS is the only direct and functional investigation that provides reliable information to identify cases suitable for surgical treatment, and is able to lateralise the surgical procedure.

More importantly, AVS can save the patient from unnecessary and potentially futile surgery. In our series, one patient with a unilateral adrenal nodule on CT exhibited paradoxical AVS findings (Figure 1, Table 2). Based on CT findings alone, this patient could well have undergone potentially futile surgery to resect the non-functioning nodule leaving the functional micronodule behind. Moreover, there were also six patients with

Table 1. Comparison of imaging results and adrenal venous sampling.

CT result	AVS result			
	Right	Left	Bilateral	CT PPV
Right	7	0	3	19/26 (73%)
Left	1	12	3	-
Bilateral	3	2	4	4/9 (44%)
NAD	2	0	2	-
Concordance	(Right) 7/13 (54%); (left) 12/14 (86%); (total) 19/27 (70%)		4/12 (33.3%)	-

Abbreviations: AVS = adrenal venous sampling; CT = computed tomography; NAD = no abnormality detected; PPV = positive predictive value.

unilateral adrenal nodules revealed by CT, but with AVS indicating bilateral hypersecretion (Figure 2, Table 3). These patients might have undergone unnecessary surgery with treatment decisions based solely on CT findings.

Although AVS is clinically important for the management of aldosteronism, it is not commonly performed. A multicentre study showed that only around a median of 77% (range, 19-100%) of patients were referred for AVS.[11] This was attributable to the relatively high failure rate of the procedure. The rate of successful bilateral cannulation is very variable, ranging from 29% to 74% in one multicentre study.[12] In our series, we achieved a success rate of 89%, after adjustment for the adrenal to IVC cortisol level ratio. Using the ratio of >2 advocated in the multicentre study, our success rate became 86%.

Techniques for Successful Adrenal Venous Sampling

Patient Preparation

All our cases were performed by three interventional radiologists, each with more than 10 years' experience. AVS is a procedure with high technical demands, especially on the right side. The corresponding vein is short and small making it difficult to cannulate and withdraw blood. As mentioned in many articles, a preprocedural CT can demonstrate the anatomy and position of the right adrenal vein to facilitate planning.[13] In our experience, however, it is not always useful because the position of right adrenal vein varies during angiography due to the patient's respiration. A Synacthen bolus injection (250 μg) followed by 250 μg in 250 ml normal saline continuously infused at 300 ml/h was given as a stimulant when our patients were called to the angio-suite.

Table 2. Adrenal venous sampling showing hypersecretion from the right with suppression on the left side in a patient.

	Right	Left	Inferior vena cava
Aldosterone (A)	98 800	3690	1291
Cortisol (C)	15 584	3496	550
A/C ratio	6.34	1.06	2.35

Table 3. Adrenal venous sampling showing bilateral hypersecretion in a patient.

	Right	Left	Inferior vena cava
Aldosterone (A)	18 866	14 646	1093
Cortisol (C)	6508	5014	598
A/C ratio	2.9	2.92	1.82

Right Adrenal Vein Cannulation

The right adrenal vein usually enters the IVC at the lateral posterior aspect above the upper pole of right kidney at around the level of T12. According to the literature, in 10% of cases, the right adrenal vein drains into posterior aspect of one of the hepatic veins. However in our series, no such case was observed. We used a number of catheters including C1, C2, S1, and SHK to cannulate the right adrenal vein. Most commonly we used C2 with side holes. We used C1 if the calibre of the IVC was small. When the engagement of the catheter was unstable, a reverse curve catheter would be used. When we used other catheters, we created side holes at the catheter tip with a 22G hypodermic needle, which was safe; no foreign body embolism due to broken catheter tip was encountered. There are many mimickers of the right adrenal vein (accessory hepatic vein, caudate vein, and right hepatic vein; Figures 3-5). It is vital to recognise these, lest a wrong sample is collected. Presence of emissary veins which course laterally, medially, or inferiorly favours successful right adrenal vein cannulation (Figure 6).

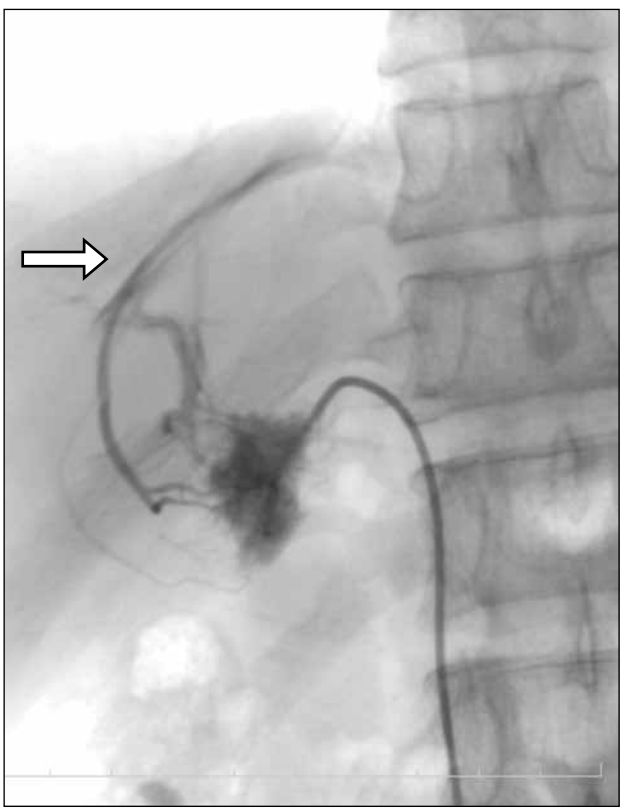

Figure 3. Accessory hepatic vein with a superior course (arrow).

Figure 4. Draining vein of caudate lobe sometimes mimics right adrenal vein.

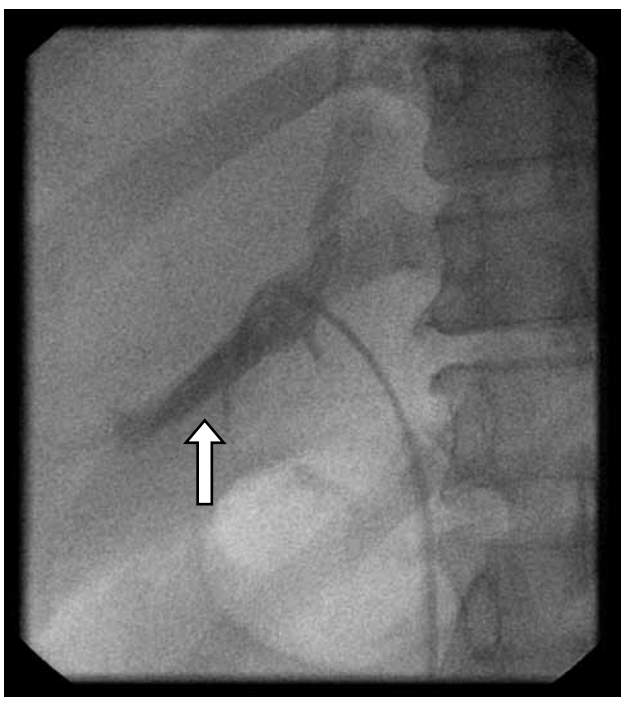

Figure 5. Cannulation of the right hepatic vein (arrow).

Sometimes, direct visualisation of an adrenal adenoma also aids confirmation of successful cannulation (Figure 7).

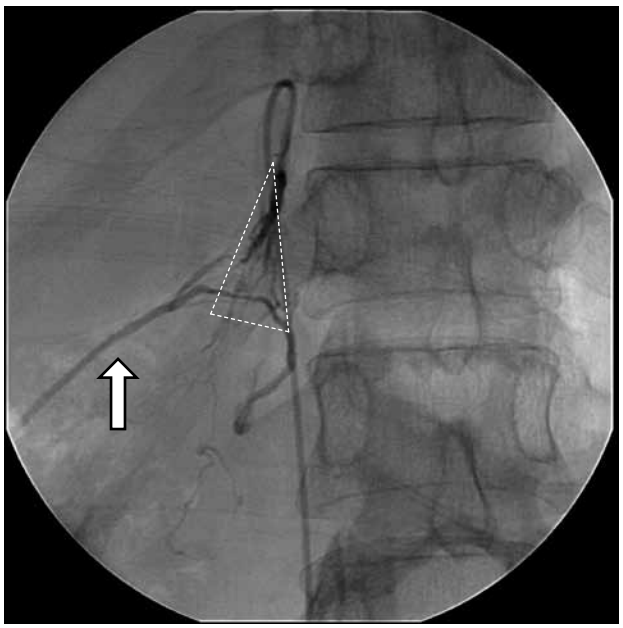

Figure 6. Successful cannulation of right adrenal vein with a communicating vein inferolaterally (arrow). Also note triangular-shaped configuration of the vessels.

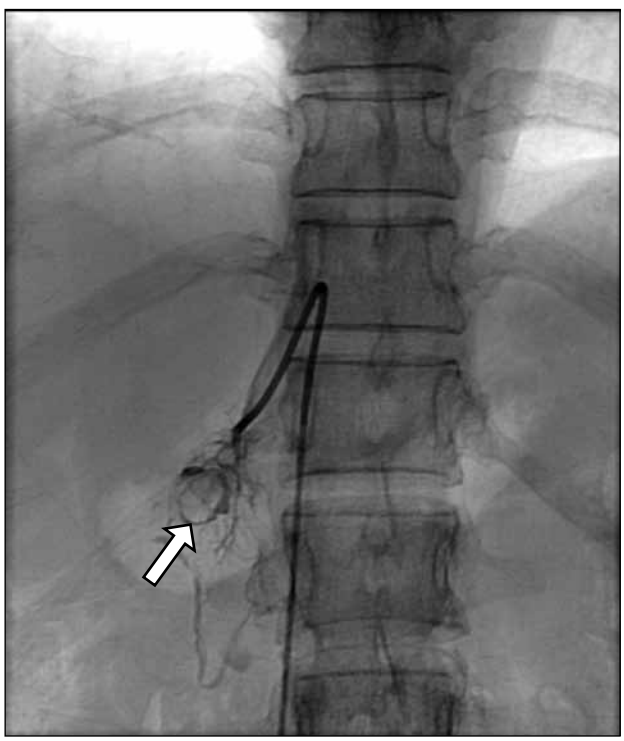

Figure 7. Angiogram can directly show an adenoma as a staining defect.

Left Adrenal Vein Cannulation

The anatomy of the left adrenal vein is fairly consistent. On the left we used an S2 catheter. By pulling the catheter from peripheral left renal vein, the tip flips upwards and engages the phrenicoadrenal trunk (Figure

8), where the venous sample is obtained. Further advancement into the left adrenal vein poses additional risks of wrong cannulation into the inferior phrenic vein or can cause vascular injury (Figure 9) from pushing; a reverse curve catheter may not be ideal for deep cannulation of the phrenicoadrenal trunk. Therefore superselective sampling of left adrenal vein is not advised.

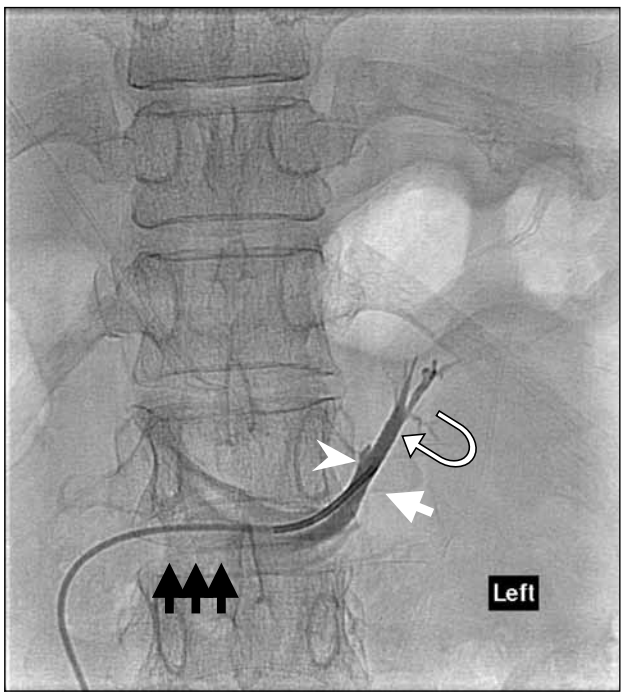

Figure 8. Cannulation of left phrenicoadrenal trunk (white arrow) with opacification of inferior phrenic vein (white arrowhead) and left adrenal vein (curved arrow) via the left renal vein (black arrows).

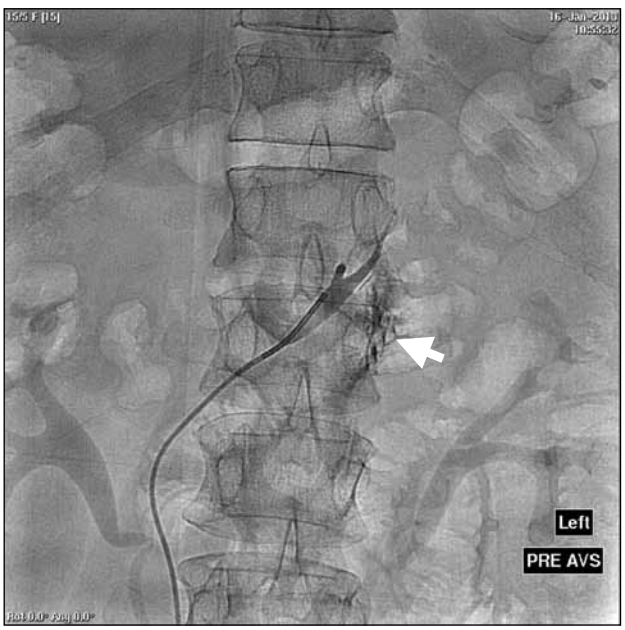

Figure 9. Contrast staining (arrow) at left renal vein due to small renal vein dissection on pushing the catheter.

Techniques for Blood Withdrawal

Even though the adrenal vein is successfully cannulated, sometimes it is difficult to withdraw sufficient blood because of its extremely small lumen. Some techniques may be helpful, which include using a small volume syringe (2.5 ml / 5 ml), using a catheter with side holes, and application of gentle intermittent pressure. In our series, we never used microcatheters. With proper technique and adequate experience, successful AVS is usually feasible.

Simultaneous Versus Sequential Cannulation

There is debate regarding whether sequential cannulation is less accurate than simultaneous cannulation. One study showed that there is no significant difference in the reliability of the results.[14] All our cases were performed sequentially, cannulating the right adrenal vein first followed by the left. This is because right adrenal venous cannulation is usually more difficult and more time-consuming and the left adrenal vein can be cannulated quickly without much difficulty. This helps to minimise the time difference between the collection of right and left adrenal venous samples.

Contrast or Drug Allergy

There is controversy concerning whether patients having contrast or drug allergy should proceed to AVS with steroid cover, as this may interfere directly or indirectly with cortisol levels. In our series, two patients with drug allergy received steroid cover prior to the procedure but this did not seem to affect the biochemical results.

CONCLUSION

The usefulness of AVS in lateralisation and guiding treatment is undeniable. It should be considered a standard procedure in the diagnostic workup for primary aldosteronism, so that patients can be spared from the risk of unnecessary surgery. CT is not sensitive to pick up functioning micronodules and is not capable of differentiating the functional state of any lesion. It can also cause diagnostic confusion, if there is discrepancy between CT and AVS results. These drawbacks make its role in diagnosis questionable, though it has got a role in preoperative planning. AVS, as a standard procedure in diagnostic workup, is feasible with proper technique

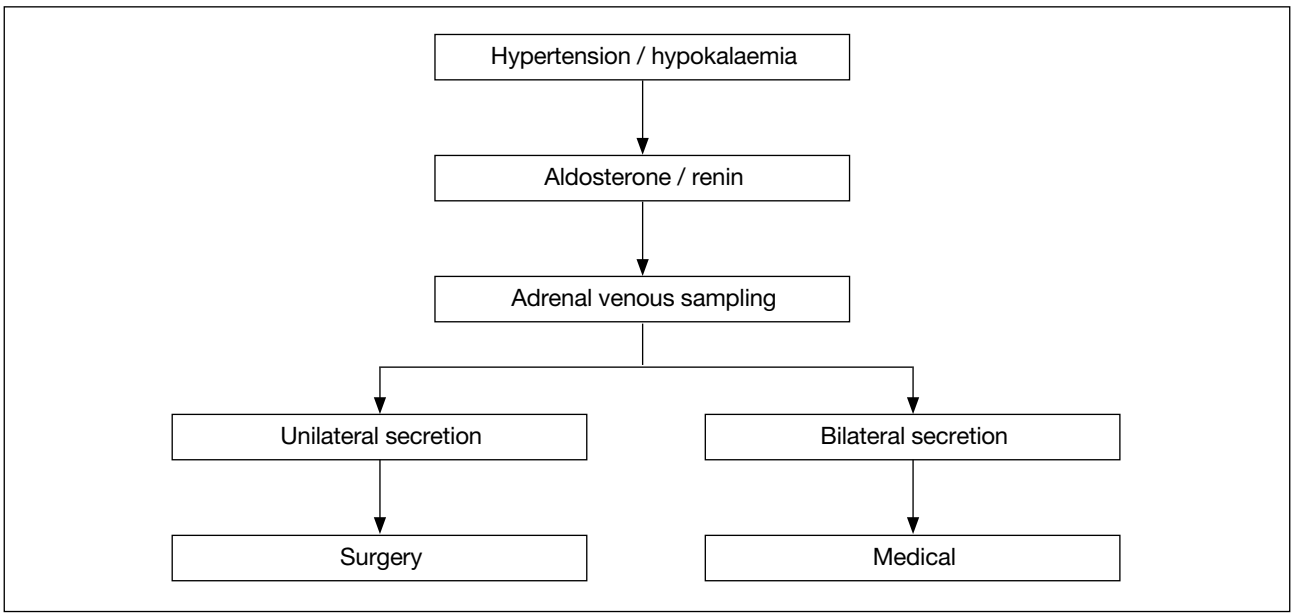

Figure 10. Algorithm in management of primary aldosteronism.

and adequately experienced staff. It should therefore be encouraged and advocated in the future (Figure 10).

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