Primary hyperaldosteronism and adrenal incidentaloma: an argument for physiologic testing before adrenalectomy

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Objective: To determine the frequency of nonfunctioning adrenal masses in patients with primary hyperaldosteronism.

Design: A case series.

Setting: A tertiary care hypertension clinic.

Patients: Twenty-seven consecutive patients with primary hyperaldosteronism.

Measurements: Blood pressure, serum electrolytes, supine and upright plasma renin, cortisol and aldosterone levels, selective adrenal vein aldosterone and cortisol levels, adrenal computed tomography (CT) scans and pathology reports.

Results: There was considerable overlap in the clinical features and laboratory investigations for patients with unilateral aldosteronoma and those with bilateral adrenal hyperplasia. Of the 27 patients who had confirmed primary hyperaldosteronism investigated at this centre, 25 had a definitive diagnosis assigned on the basis of postural stimulation tests, adrenal CT scans, and bilateral adrenal vein sampling, surgery or a combination of test results. Of this group, 18 had adrenal masses visualized on CT. However, only 13 of these 18 patients had an adrenal aldosteronoma subsequently proven by selective adrenal vein sampling or surgery, or both; the other 5 patients were found to have bilateral adrenal hyperplasia with nonfunctioning adrenal masses. CT had a sensitivity of 100% for the diagnosis of aldosteronoma, but the specificity was only 58% and the positive predictive value was only 72%. The likelihood ratio for the diagnosis of aldosteronoma in patients with primary hyperaldosteronism and an adrenal mass on CT was only 2.4.

Conclusion: Given the poor specificity of CT in patients with primary aldosteronism, full biochemical and physiologic testing should be done before adrenalectomy in patients with suspected adrenal aldosteronoma.

Objectif : Déterminer la fréquence de masses surrénales non fonctionnelles chez des patients atteints d'aldosteronisme primaire.

Conception : Série de cas.

Contexte : Clinique de soins tertiaires sur l'hypertension.

Patients : Vingt-sept patients consécutifs atteints d'aldosteronisme primaire.

Mesures : Tension artérielle, électrolytes sériques, niveaux de rénine, de cortisole et d'aldostérone en position couchée et assise, niveaux sélectifs de cortisol et d'aldostérone dans la veine surrénale, scanographies (CT) des surrénales et rapports de pathologie.

Résultats : Il y a eu énormément de chevauchement dans les caractéristiques cliniques et les examens de laboratoire de patients atteints d'un aldosteronome unilatéral et de ceux atteints d'hyperplasie surrénale bilatérale. Des 27 patients présentant un aldosteronisme primaire confirmé qui ont été examinés à ce centre, 25 ont reçu un diagnostic définitif sur la base de tests de stimulation orthostatique, de scanographies des

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surrénales, d'un prélèvement veineux bilatéral des surrénales, d'une chirurgie ou d'une combinaison de résultats de tests. De ce groupe, 18 ont montré à la scanographie des masses surrénales. Cependant, seulement 13 de ces 18 patients avaient un aldosteronome surrénal qui a par la suite été confirmé par un prélèvement veineux sélectif des surrénales ou par chirurgie, ou les deux; chez les cinq autres patients, on a découvert une hyperplasie surrénale bilatérale sans masses surrénales non fonctionnelles. La scanographie a affiché une sensibilité de 100 % pour le diagnostic de l'aldosteronome, cependant la spécificité n'a atteint que 58 % et la valeur prédictive positive, seulement 72 %. Le rapport de vraisemblance de diagnostic d'aldosteronome chez des patients atteints d'aldosteronisme primaire et d'une masse surrénale à la scanographie n'a été que de 2.4.

CONCLUSION : Compte tenu de la piètre spécificité de la scanographie chez les patients atteints d'aldosteronisme primaire, il y aurait lieu d'effectuer des tests biochimiques et physiologiques complets avant de procéder à une adrénalectomie chez des patients chez qui l'on soupçonne un aldosteronome surrénal.

Primary hyperaldosteronism is an uncommon but important condition characterized by hypertension, potassium and magnesium wasting, metabolic alkalosis and suppression of the renin–angiotensin axis.[1] The diagnosis of primary hyperaldosteronism is established by the demonstration of elevated plasma or urinary aldosterone levels in conjunction with suppressed plasma renin activity. After confirmation of primary hyperaldosteronism, the work-up focuses on distinguishing between unilateral aldosterone-producing adenoma (APA), which is cured by adrenalectomy in 70% to 75% of patients, or bilateral adrenal hyperplasia (BAH), which is treated medically.[2–5]

The methods of distinguishing APA from BAH (and their reported accuracies) include: adrenal CT (70% to 75%), the aldosterone postural stimulation test (72% to 85%), 18-hydroxycorticosterone assay (80% to 82%), NP-59 adrenal iodoscintigraphy (70% to 90%), and selective adrenal vein sampling (90% to 95%).[2,5–10] The standard work-up of patients with primary aldosteronism stresses the role of adrenal CT as the initial investigation of choice, and many authors advocate adrenalectomy when the CT reveals an APA.[2–4,11–18] This algorithm is based on the assumption that CT can accurately distinguish BAH from APA. However, Doppman and associates[19] have demonstrated that the diagnosis of hyperplasia by CT is unreliable. We hypothesize that, given the often macronodular nature of BAH and the prevalence of incidental adrenal masses (reported to be between 1% and 10%),[20–24] the diagnosis of aldosteronoma with CT scans may also be unreliable. To test our hypothesis, we reviewed the diagnostic procedures carried out for all patients with primary aldosteronism seen at the University of Alberta Hospital over the past 5 years.

METHOD

This study was a single-observer, retrospective chart review of all patients with primary hyperaldosteronism who were investigated at a tertiary care hypertension clinic between 1990 and 1995. Primary hyperaldosteronism was accepted as the diagnosis if there was evidence of suppressed plasma renin (less than 3.5 ng/L) in conjunction with aldosterone excess (urinary aldosterone more than 39 nmol/d on an adequate salt intake as indicated by urinary sodium level greater than 120 mmol/d). Although standard protocols were used for all of the investigations, the choice of tests in each case was left to the discretion of the 3 attending physicians. Similarly, the decision to proceed to adrenalectomy or to manage the patient medically was made on an individual basis.

Investigations

All patients had assays of their serum potassium, aldosterone and renin; 24 patients had their 24-hour urinary aldosterone measured. In our laboratory, plasma renin concentration was measured with the use of a commercially available reagent kit (Sanofi Diagnostics Pasteur Inc., Chaska, Minn.) and the normal ranges were 3.5 to 14.5 ng/L (supine) and 3.5 to 29 ng/L (upright). The urine and serum aldosterone levels were assayed with the use of a commercially available coated tube radioimmunoassay (Diagnostic Products Corp., Los Angeles, Calif.), with normal ranges of 28 to 444 pmol/L (supine) and 110 to 860 pmol/L (upright). All patients had CT of the adrenal glands, done on a GE Hispeed machine with nonionic contrast medium. All scans were read by a qualified radiologist who was blinded to the details of each case. Lesions that were seen on the CT scan were diagnosed as aldosteronomas if they were unilateral, discrete and of low attenuation in the presence of a normal contralateral gland (Fig. 1).

The aldosterone postural stimulation test (PST), which was done in 24 patients, was carried out by collecting plasma aldosterone, cortisol and renin samples from patients at 08:00 (before arising) and at 12:00 (after 4 hours of ambulation). The PST was defined as positive if there was evidence of autonomous aldosterone secretion (suggestive of APA) in that the upright plasma aldosterone level was equal to

or less than that measured in the supine position. A negative PST (suggestive of BAH) was defined by an increase in the aldosterone levels with upright posture (after subtracting the percent cortisol increase).[25]

Fifteen patients underwent bilateral adrenal vein sampling (BAVS) according to the protocol described below:

(1) Medications were withdrawn before testing as follows: diuretics 4 weeks before testing (6 weeks for spironolactone), sympatholytics 1 week before, and angiotensin-converting enzyme inhibitors at least 3 days before investigation. Five days before testing, patients were started on a high-salt diet.

(2) An intravenous infusion of 50 µg/h adrenocorticotropin hormone (ACTH) was started approximately 1 hour before the procedure.

(3) Selective adrenal vein sampling percutaneously through a femoral vein catheter, and the cortisol and aldosterone levels were measured from the infrarenal inferior vena cava (IVC) and the right and left adrenal veins. The ACTH infusion was stopped after the procedure.

The cortisol levels in each locale were measured to ensure correct catheter placement (the cortisol levels should be greater in the adrenal veins than in the IVC). Adrenal vein catheterization was considered successful if both adrenal vein cortisol levels were greater than those measured in the IVC. When neither level was greater than the IVC levels, the results were considered uninterpretable (defined as "unsuccessful" in the Results section); when only the left adrenal vein was successfully cannulated, the aldosterone:cortisol (A:C) ratio in the left adrenal vein was compared with that in the IVC to localize the lesion by inference. To correct for dilution of adrenal venous samples by blood from the IVC or inferior phrenic vein, the A:C ratio was calculated for both adrenal veins and the IVC. When both adrenal veins were successfully cannulated, we interpreted lateralization of aldosterone secretion as follows: a 5-fold difference between the A:C ratios of the ipsilateral and contralateral adrenal veins was considered to be definitive evidence of an APA, a 3-fold difference was considered to be suggestive of an APA, and a less than 3-fold difference was considered to be definitive evidence for BAH.[19,26]

The records from follow-up visits were reviewed to collect data on blood pressure, plasma potassium levels and symptomatology. For the purposes of this article, the diagnosis of APA was accepted if there was supportive histopathology and a consistent clinical course (blood pressure and potassium normalized postoperatively), or definitive BAVS results, or a positive PST with either a positive CT scan or suggestive BAVS results. The diagnosis of BAH was accepted if there was supportive histopathology and a consistent clinical course (blood pressure and potassium did not normalize postoperatively), or definitive BAVS results, or a negative PST with either a negative CT scan or suggestive BAVS results.

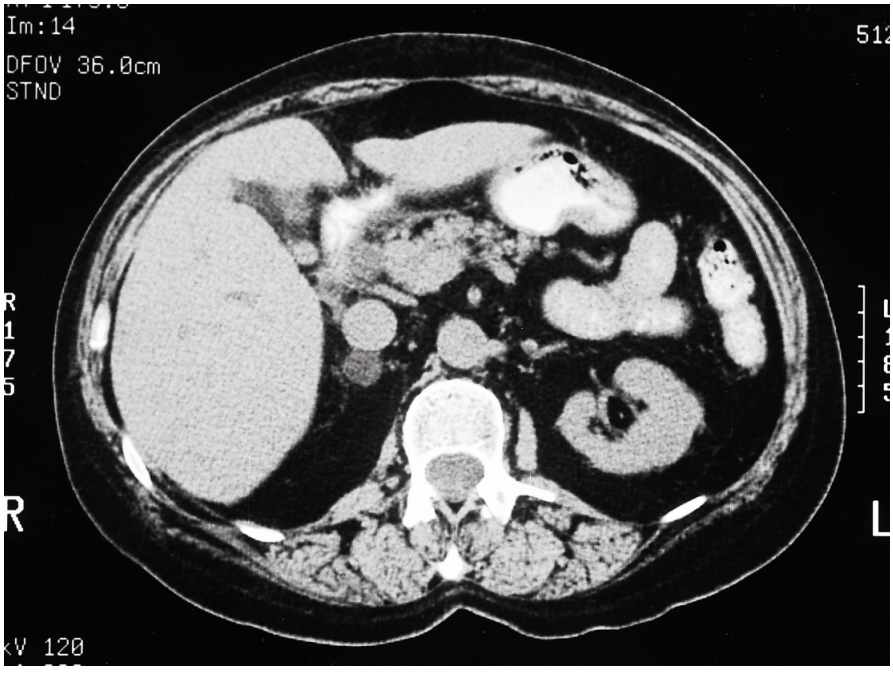

FIG. 1. Adrenal CT scan from a patient (no. 27) demonstrating a 2-cm mass in the right adrenal gland thought to be typical of an aldosteronoma.

RESULTS

This current series represents the most recent 27 cases (16 men, 11 women) of confirmed primary hyperaldosteronism investigated at this centre. The patients ranged in age from 31 to 72 years. Fourteen patients underwent adrenalectomy for presumed APA: the diagnosis was confirmed in 12 (all were normotensive and normokalemic in follow-up), but 2 patients (nos. 14 and 15) were found to have nodular hyperplasia and continued to demonstrate features of hyperaldosteronism postoperatively, requiring treatment with potassium-sparing diuretics and antihypertensive drugs. On the basis of the investigations outlined in Tables I and II, APA was diagnosed in 13 patients (nos. 1 to 13) (12 were confirmed surgically; patient 13 refused BAVS or

surgery), BAH was diagnosed in 12 patients (nos. 14 to 25), and 2 patients (nos. 26 and 27) were considered to have primary hyperaldosteronism of indeterminate etiology. Patient 26 had a 1.8-cm low-attenuating nodule in the left adrenal gland and adrenal vein sampling results suggestive (but not diagnostic) of APA; however, his postural stimulation test was negative. His clinical signs were easily corrected with low doses of amiloride (5 mg twice daily) and enalapril (2.5 mg twice daily), and he remained normotensive and normokalemic after 2 years of follow-up. Patient 27 had a 2-cm low-attenuating nodule in the right adrenal gland and a negative postural stimulation test. BAVS was uninterpretable, as neither adrenal vein was successfully cannulated. She has been successfully treated with medical therapy alone (spironolactone 50 mg daily and verapamil SR 240 mg twice daily) for 4 years.

While on the high-salt diet (300 mmol/d), 11 of the 13 patients with adenoma had hypokalemia (mean serum potassium 3.1 mmol/L), and 8 of the 12 patients with hyperplasia were hypokalemic (mean serum potas-

Table I

Investigations in 27 Patients With Primary Hyperaldosteronism

Patient no.	Age/sex	Plasma potassium, mmol/L*	Plasma aldosterone, pmol/L*	Plasma renin, ng/L*	Postural stimulation test†	CT scan diagnosis	Venous sampling diagnosis‡	Surgical results
1	31/F	3.3	1690	0.1	Positive	Adenoma (L)	Not done	Adenoma (L)
2	56/F	3.5	961	1.5	Positive	Adenoma (L)	Unsuccessful	Adenoma (L)
3	57/F	3.2	1738	2.5	Not done	Adenoma (L)	Not done	Adenoma (L)
4	37/F	2.8	1810	2.8	Positive	Adenoma (L)	Adenoma (L)	Adenoma (L)
5	59/M	3.2	460	3.8	Positive	Adenoma (L)	**Hyperplasia**	Adenoma (L)
6	67/M	2.5	976	0.2	Negative	Adenoma (L)	**Adenoma (L)**	Adenoma (L)
7	55/M	2.6	1950	0.1	Negative	Adenoma (R)	Not done	Adenoma (R)
8	44/F	3.4	1450	0.1	Positive	Adenoma (L)	Not done	Adenoma (L)
9	54/M	2.6	1590	1.5	Positive	Adenoma (R)	Not done	Adenoma (R)
10	56/M	3.5	766	3.0	Positive	Adenoma (L)	**Adenoma (L)**	Adenoma (L)
11	47/M	3.7	1130	3.0	Negative	Adenoma (L)	Adenoma (L)	Adenoma (L)
12	56/M	3.6	3450	1.5	Positive	Adenoma (L)	Not done	Adenoma (L)
13	72/F	2.1	2420	1.5	Positive	Adenoma (L)	Not done	Not done
14	49/M	3.2	728	0.5	Negative	Adenoma (L)	**Adenoma (L)**	Hyperplasia
15	59/F	3.0	610	3.0	Not done	Adenoma (L)	Not done	Hyperplasia
16	49/F	3.2	829	1.2	Negative	Hyperplasia	**Hyperplasia**	Not done
17	55/M	3.2	529	0.13	Negative	Adenoma (R)	**Hyperplasia**	Not done
18	39/M	4.1	642	0.62	Negative	Adenoma (L)	**Hyperplasia**	Not done
19	61/F	2.8	637	1.5	Negative	Hyperplasia	Not done	Not done
20	69/M	3.0	1220	1.5	Positive	Adenoma (L)	**Hyperplasia**	Not done
21	37/M	3.8	562	5.0	Negative	Hyperplasia	**Hyperplasia**	Not done
22	61/F	3.8	518	1.5	Negative	Hyperplasia	Unsuccessful	Not done
23	38/M	3.9	441	0.3	Not done	Hyperplasia	Not done	Not done
24	43/M	3.0	789	3.0	Negative	Hyperplasia	Not done	Not done
25	61/M	3.2	510	1.5	Negative	Hyperplasia	Not done	Not done
26	57/M	2.8	2230	3.5	Negative	Adenoma (L)	Adenoma (L)	Not done
27	61/F	3.2	1240	0.7	Negative	Adenoma (R)	Unsuccessful	Not done

*Collected after 3 days on a high-salt (300 mmol/d) diet
†Defined as positive if the upright plasma aldosterone was equal to or less than the supine plasma aldosterone (suggestive of autonomous aldosterone hypersecretion)
‡Results in bold type are considered definitive; results in regular type are considered suggestive (see Method for definitions).
L = left, R = right

sium 3.4 mmol/L). The supine plasma renin levels were suppressed in 12 (92%) of those with aldosteronoma and 11 (92%) of those with bilateral hyperplasia. Plasma aldosterone levels were elevated in all patients in both groups. The urinary aldosterone levels were elevated in 92% of the patients in whom the test was done, with no difference between the 2 groups (data not shown). The postural stimulation test was positive in 9 (75%) of the aldosteronoma group and in only 1 of the 10 hyperplasia patients in whom it was carried out.

Although all 13 patients with aldosteronoma had a visible adrenal mass on the CT scan, 5 of the 12 patients (nos. 14, 15, 17, 18 and 20) with BAH (proven by selective adrenal vein sampling or surgery) also had a visible adrenal mass. In the absence of evidence for corticosteroid excess or pheochromocytoma, these 5 patients were thought to have bilateral adrenal hyperplasia and either a hyperplastic macronodule or an adrenal incidentaloma.

Satisfactory improvement in blood pressure control was noted for all 12 patients with APA who underwent adrenalectomy. On the other hand, satisfactory blood pressure control (defined as diastolic blood pressure less than 90 mm Hg) and normokalemia were achieved medically in patient 14 (with amiloride and nifedipine), patient 15 (amiloride, nifedipine and atenolol), patients 17 and 18 (spironolactone and verapamil), and patient 20 (amiloride and nifedipine). The only significant operative complication (unrecognized laceration of the left renal artery, eventually necessitating nephrectomy) occurred in patient 15.

Excluding the 2 patients (nos. 26 and 27) with indeterminate etiology, the prevalence of APA was 52%. The sensitivity (and specificity) of the various investigations for the diagnosis of APA were: 100% (58%) for CT, 80% (83%) for BAVS and 75% (90%) for the postural stimulation test (PST). Positive predictive values for APA ranged from 72% with CT to 90% with PST; negative predictive values varied from 75% with PST to 100% with CT. Likelihood ratios for a positive test result were 2.4 with CT, 4.7 with BAVS, and 7.5 with PST; likelihood ratios for a negative test result were 0 with CT, 0.24 with BAVS, and 0.28 with PST.

Discussion

In summary, a definitive etiology was established in 25 of the 27 patients with biochemically proven hyperaldosteronism who were referred to this tertiary care hypertension clinic. Various investigations were used to confirm the etiologies, including PST, adrenal CT, BAVS and surgery. Although our study is retrospective, we analysed a consecutive series of patients referred

Table II

Results of Adrenal Vein Sampling

	Aldosterone levels, pmol/L			Cortisol levels, mmol/L			Aldosterone:cortisol ratio		
Patient no.	IVC	RAV	LAV	IVC	RAV	LAV	IVC	RAV	LAV
2	325	385	638	234	212	228	1.4	1.8	2.8
4	2 000	2 140	112 000	639	614	11 100	3.1	3.5	10.1
5	1 620	1 520	33 000	1 210	913	13 700	1.3	1.7	2.4
6	2 800	9 450	33 000	1 320	21 900	13 500	2.1	0.4	2.4
10	403	369	3 300	383	279	508	1.1	1.3	6.5
11	2 190	1 990	124 000	797	812	14 200	2.7	2.5	8.7
14	4 390	46 500	117 300	1 520	62 300	22 800	2.9	0.7	5.1
16	860	753	3 500	735	391	1 660	1.1	1.9	2.1
17	921	986	998	322	292	738	2.9	3.4	1.4
18	1 770	74 000	116 000	490	29 450	21 450	3.6	2.5	5.4
20	2 446	2 397	36 850	768	1 150	20 800	3.2	2.1	1.8
21	1 598	1 729	35 499	812	884	10 500	2.0	2.0	3.4
22	1 360	270	1 040	667	609	615	2.0	0.4	1.7
26	1 230	123 000	127 000	167	2 960	922	7.4	41.6	137.7
27	168	255	134	703	586	570	0.2	0.4	0.2

IVC = inferior vena cava, RAV = right adrenal vein, LAV = left adrenal vein

to a tertiary care hypertension clinic with primary hyperaldosteronism, and our study population is comparable to that of other published series. Definite hypokalemia (serum potassium less than 3.5 mmol/L) was documented in 78% of our patients and 96% had serum potassium levels of less than 4.0 mmol/L. Like those described in previous reports,[2,17,18] our patients with APA exhibited more severe hypokalemia, higher plasma and urinary aldosterone levels, and lower plasma renin levels than those with BAH. However, there was a wide dispersal of values within both groups such that none of the screening laboratory tests accurately differentiated between BAH and APA. The most important finding from our study was that, in those patients for whom we could make definitive diagnosis, 5 of the 18 patients with lesions that were considered typical of aldosteronoma according to the CT scan were found to have BAH and a macronodule or nonfunctioning incidentaloma.

Our experience mirrors that of previous reports. Hambling and associates[17] found that 2 of their 6 patients with BAH had abnormal adrenal CT scans; Doppman and associates[19] reported that in 1 of their 2 patients with BAH an incorrect diagnosis of APA was made on the basis of the CT scan; and McLeod and colleagues[26] reported that 11 of the 32 patients with a preoperative diagnosis of APA at their centre actually had BAH on pathological examination. The high frequency with which incidental adrenal masses are detected in patients with primary aldosteronism is not surprising given their prevalence in the general population (1% to 8% in various series),[20–24,27–29] the lack of a clear definition distinguishing micro/macronodular hyperplasia and adenoma, and the fact that the adrenal glands of patients with BAH often exhibit focal micronodular hyperplasia.[30] As technology continues to improve and the sensitivity of CT for detecting masses increases, more misdiagnoses of APA can be expected in patients with hyperplastic glands (and further reductions in the specificity of CT). Similarly, higher-resolution CT scans may eventually lead to incorrect localization in those patients with a small APA in 1 gland and a larger incidentaloma or macronodule in the contralateral gland.

The success rate of adrenalectomy depends on the accurate lateralization of aldosterone hypersecretion.[10,18,26] Given the high false-positive rate with CT, we believe that physiologic testing should be done in all patients with primary hyperaldosteronism and an adrenal mass on the CT scan before the surgeon considers adrenalectomy. The aldosterone PST is noninvasive, easy to perform and requires only a minimum of nursing care. In our study population, 75% of the patients with APA and 90% of those with BAH were correctly classified by PST; this is consistent with the rates reported in the literature.[18] Although a negative PST is useful as it supports a diagnosis of BAH, a positive PST is of limited use as it only suggests the presence of APA but does not provide any information as to which adrenal gland contains the tumour. On the other hand, BAVS allows accurate determination of which gland is hypersecreting. However, the investigation is highly operator-dependent, and canalization of the adrenal veins can be difficult, with published failure rates of 20% to 25% (our failure rate was 21%). Although Bayliss, Edwards and Starer[31] reported a 5% frequency of major and minor complications with BAVS, the patients in their study underwent both adrenal vein catheterization and venography with large volumes of ionic contrast medium. As the majority of the complications were related to the contrast medium, it is reasonable to suppose that the risk of complications from BAVS in the 1990s is significantly lower, given that only minimal amounts of nonionic contrast material are now used. In our case series, 5 patients suffered hematomas at the site of femoral vein puncture; none of them required transfusion or hospital admission for control of the bleeding and no other complications were noted. Certainly, the risk–benefit ratio of BAVS appears favourable when one considers the risk of inappropriate adrenalectomy (or adrenalectomy on the wrong side) when treatment decisions are based solely on anatomic imaging, given the apparently high prevalence of adrenal incidentalomas or macronodules in patients with BAH. In centres where BAVS is not readily available, other techniques for functional localization (such as NP-59 adrenal iodoscintigraphy) may be more appropriate depending on local expertise and resource availability.

In summary, given the morbidity (and occasional mortality) associated with adrenalectomy,[32] we believe that the preoperative work-up of patients with primary hyperaldosteronism should emphasize tests of high specificity so that a misdiagnosis of APA is made in a minimum of patients. We believe that the poor specificity of CT limits its use as a localizing investigation in these patients. The use of physiologic tests such as the PST or BAVS in all patients with primary hyperaldosteronism would significantly enhance the information available to the clinician and reduce the chance of inappropriate adrenalectomy.

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