0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(3):1045–1050

doi: 10.1210/jc.2003-031337

EXTENSIVE PERSONAL EXPERIENCE

Increased Diagnosis of Primary Aldosteronism, Including Surgically Correctable Forms, in Centers from Five Continents

PAOLO MULATERO, MICHAEL STOWASSER, KEH-CHUAN LOH, CARLOS E. FARDELLA, RICHARD D. GORDON, LORENA MOSSO, CELSO E. GOMEZ-SANCHEZ, FRANCO VEGLIO, AND WILLIAM F. YOUNG, JR.

Hypertension Unit (P.M., F.V.), Department of Medicine and Experimental Oncology, University of Torino, 10133 Torino, Italy; Hypertension Unit (M.S., R.D.G.), Department of Medicine, University of Queensland, Princess Alexandra and Greenslopes Hospitals, Brisbane, Australia 4212; Endocrine Unit (K.-C. L.), Tan Tock Seng Hospital, Singapore, Republic of Singapore 308433; Department of Endocrinology (C.E.F., L.M.), Faculty of Medicine, P. Universidad Catòlica de Chile, 114D Santiago, Chile; Division of Endocrinology (C.E.G.-S.), University of Mississippi Medical Center, Jackson, Mississippi 39216; and Division of Endocrinology, Metabolism, Nutrition, and Internal Medicine (W.F.Y.), Mayo Clinic, Rochester, Minnesota 55905

Primary aldosteronism (PA) is a common form of endocrine hypertension previously believed to account for less than 1% of hypertensive patients. Hypokalemia was considered a prerequisite for pursuing diagnostic tests for PA. Recent studies applying the plasma aldosterone/plasma renin activity ratio (ARR) as a screening test have reported a higher prevalence. This study is a retrospective evaluation of the diagnosis of PA from clinical centers in five continents before and after the widespread use of the ARR as a screening test. The application of this strategy to a greater number of hypertensives led to a 5- to 15-fold increase in the identification of patients affected by PA. Only a small proportion of patients (between 9 and 37%) were hypokalemic. The annual detection rate of aldosterone-producing adenoma (APA) increased in all centers (by 1.3–6.3 times) after the wide application of ARR. Aldosterone-producing adenomas constituted a much higher proportion of patients with PA in the four centers that employed adrenal venous sampling (28–50%) than in the center that did not (9%). In conclusion, the wide use of the ARR as a screening test in hypertensive patients led to a marked increase in the detection rate of PA. (*J Clin Endocrinol Metab* 89: 1045–1050, 2004)

PRIMARY ALDOSTERONISM (PA) is a common form of endocrine hypertension in which aldosterone production is inappropriate and at least partially autonomous of the renin-angiotensin system. PA was previously believed to account for less than 1% of hypertensive patients. In addition, hypokalemia was considered a prerequisite for pursuing diagnostic tests for PA (1, 2). However, recent studies applying the plasma aldosterone/plasma renin activity (PRA) ratio (ARR) as a screening test among both hypokalemic and normokaliemic hypertensives have reported a much higher prevalence of this disease, with PA accounting for up to 12% of hypertensive patients and most patients being normokaliemic (3–7). Therefore, PA could be the most common identifiable, specifically treatable and potentially curable form of hypertension. It has been suggested that it is only worthwhile to perform diagnostic workup for PA in hypokalemic patients in the belief that the great majority of patients with normokaliemic PA have bilateral adrenal hyperplasia (BAH) rather than aldosterone-producing adenoma (APA) and are therefore rarely surgically curable (8).

This study is a retrospective evaluation of the diagnosis of PA from clinical centers in different continents before and after the widespread use of the ARR as a screening test for the diagnosis of PA. In particular, we sought to determine whether changing the PA screening strategy resulted in an increased detection of PA, including surgically treatable forms. Because most of the controversy regarding use of the ARR as a diagnostic test for PA has centered on the failure to follow-up with confirmatory testing (9), we focused on strategies for confirming PA and identifying the subtypes.

Patients and Methods

We asked five participating medical centers (Torino, Italy; Rochester, MN; Brisbane, Australia; Singapore, Republic of Singapore; and Santiago, Chile) to provide data on the number of patients diagnosed with PA before and after the widespread use of ARR as a screening test. Only patients in whom the PA was confirmed by an aldosterone suppression test [oral sodium or iv saline load or fludrocortisone suppression test (FST)] were included.

We also compiled data on the percentage of patients with hypoka-

Abbreviations: APA, Aldosterone-producing adenoma; ARR, plasma aldosterone/PRA ratio; AVS, adrenal venous sampling; BAH, bilateral adrenal hyperplasia; CT, computed tomography; FH-II, familial hyperaldosteronism type II; FST, fludrocortisone suppression test; GRA, glucocorticoid-remediable aldosteronism; PA, primary aldosteronism; PRA, plasma renin activity.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

lemia and the prevalence of the two major subtypes of PA (BAH and APA). Additional data included the number of patients screened for glucocorticoid-remediable aldosteronism (GRA) and the other familial form of PA not treatable with glucocorticoids [familial hyperaldosteronism type II (FH-II)]; the cut-off levels for which an ARR was considered positive; the lower limit of detection for PRA assay; the type and cut-off level for the confirmatory test; the technique used for adrenal imaging; and the criteria for determining whether to perform adrenal venous sampling (AVS). When available, reliability of posture and/or angiotensin II infusion testing in differentiating subtypes of PA was provided. Because the selection criteria varied slightly among the centers, the different diagnostic criteria are presented separately.

Torino, Italy

During the years 1988–1993, only patients with a high suspicion for PA, such as those with spontaneous or diuretic-induced hypokalemia or hypertension and an adrenal mass, were further examined for PA. From 1994 to 2002 the ARR was progressively used to study almost all patients with blood pressure more than 160/100 mm Hg. The cut-off level considered to be a positive ARR was 40 (ng/dl/ng·ml^{-1}·h^{-1}) (4000 pmol/liter·ng·liter^{-1}·sec^{-1}) together with aldosterone level greater than 15 ng/dl (416 pmol/liter). The confirmatory test was an iv saline load (2 liters of 0.9% NaCl infused over 4 h), which was considered positive if posttest aldosterone levels were greater than 5 ng/dl (138.7 pmol/liter) (10). The lower limit of detection for the PRA assay was 0.1 ng/ml^{-1}·h^{-1}(0.028 ng/liter^{-1}·sec^{-1}). A computed tomography (CT) scan with fine cuts (2.5–3 mm) of the adrenal was used as the imaging technique. Adrenal vein cannulation was considered successful if the adrenal vein/inferior vena cava cortisol gradient was at least 2; lateralization was considered when the aldosterone/cortisol ratio from one adrenal was at least 4 times the ratio from the other adrenal gland. The posture test was performed by measuring plasma aldosterone at 0800 h after an overnight recumbency and after 2 h of standing; a greater than 50% increase in aldosterone levels over basal was considered a positive test result. Finally, all patients with PA were screened for GRA using a long-PCR technique.

Rochester, Minnesota

Between 1955 and 1985, patients were screened for PA when they presented with hypokalemic hypertension. After 1985 the ARR was widely used, although not with all hypertensive patients. The cut-off level for a positive ARR was greater than 20 (ng/dl/ng·ml^{-1}·h^{-1}) (2000 pmol/liter/ng·liter^{-1}sec^{-1}) together with an aldosterone level greater than 15 ng/dl (416 pmol/liter). The confirmatory test was an oral sodium load for 3–4 d and was considered positive if posttest 24-h urinary aldosterone excretion was greater than 12 μg/d (33.3 nmol/d) with concomitant urinary sodium excretion greater than 200 mEq per 24 h. The lower limit of detection for the PRA assay was 0.6 ng/ml^{-1}·h^{-1} (0.17 ng/liter^{-1}·sec^{-1}) A CT scan with fine cuts (2.5–3 mm) of the adrenal glands was the usual imaging technique. Adrenal vein cannulation was considered successful if the adrenal vein/inferior vena cava cortisol gradient was at least 5; lateralization was considered when aldosterone/cortisol ratio from one adrenal was at least 4 times the ratio from the contralateral adrenal gland. A minority of the patients diagnosed with PA were screened for GRA. Indications for performing AVS included patients with resistant hypertension, spontaneous hypokalemia, plasma aldosterone concentration more than 25 ng/dl (693.5 pmol/liter), patients older than 40 yr (regardless of CT findings), nondiagnostic CT in patients younger than 40 yr, and patients desiring a surgical cure for their PA.

Brisbane, Australia

Within the Greenslopes Hospital Hypertension Unit, during the years from 1971 to 1991, hypertensive patients were considered candidates for PA when they presented with hypokalemia, low renin levels, or having an incidentally discovered adrenal mass. From 1990, stage 3 or resistant hypertension was added to the list. During 1991, the unit adopted the policy to screen all hypertensive patients for PA by ARR testing, using a positive cut-off level of 30 (ng/dl/ng·ml^{-1}·h^{-1}) (3000 pmol/liter/ng·liter^{-1}·sec^{-1}). The confirmatory test was the FST, in which upright plasma aldosterone levels were measured at 1000 h after 4 d of administration of fludrocortisone acetate (0.1 mg every 6 h) and sodium chloride supplementation (slow-release sodium chloride, 30 mmol thrice daily), and with patients consuming sufficient dietary salt to achieve a urinary excretion rate of 3 mmol/kg^{-1}·d^{-1}. The FST was considered positive if the posttest upright (1000 h) aldosterone levels were more than 6 ng/dl (166.4 pmol/liter), provided concomitant PRA levels were less than 1.0 ng/ml^{-1}·h^{-1} (0.28 ng/liter^{-1}·sec^{-1}), potassium levels were normal, and plasma cortisol on d 4 was no higher at 1000 h than at 0700 h. The lower limit of detection for the PRA assay was 0.1 ng/ml^{-1}·h^{-1} (0.028 ng/liter^{-1}·sec^{-1}). A CT scan with fine cuts (2.5–3 mm) of the adrenal was the imaging technique. Adrenal vein cannulation, performed in all patients with positive FST (unless found to have GRA by genetic testing) was considered successful if the adrenal vein/inferior vena cava cortisol gradient was at least 3. AVS was considered to show lateralization when adrenal venous aldosterone/cortisol ratio was at least 2 times peripheral on one side and no higher than peripheral on the other side. The posture test was performed measuring plasma aldosterone at 0800 h after overnight recumbency and after 2 h of upright posture. An increase in aldosterone levels of at least 50% over basal was considered a positive test result. Angiotensin II infusion (2 ng/kg·min for 60 min) was performed after overnight recumbency with the patient recumbent throughout the test. The test was considered positive if aldosterone increased by at least 50% above basal. Approximately 1000 patients (including all with PA) were screened for GRA.

Singapore, Republic of Singapore

From 1990 to 1994, screening for PA was considered when hypertensive patients presented with hypokalemia or adrenal mass. From 1995, ARR was extensively used as the screening test and was applied to most of the hypertensive patients referred to the unit. The cut-off level for positive ARR was 20 (ng/dl/ng·ml^{-1}·h^{-1}) (2000 pmol/liter/ng·liter^{-1}·sec^{-1}) together with a plasma aldosterone level greater than 15 ng/dl (416 pmol/liter). The confirmatory test was an iv saline load (2 liters of 0.9% NaCl infused in 4 h), which was considered positive if posttest aldosterone levels were greater than 10 ng/dl (277.4 pmol/liter). The lower limit of detection for the PRA assay was 0.66 ng/ml^{-1}·h^{-1} (0.18 ng/liter^{-1}·sec^{-1}). A spiral CT scan of the adrenal was the imaging technique. Adrenal vein cannulation was considered successful if the adrenal vein/inferior vena cava cortisol gradient was at least 5 and was considered to show lateralization when the aldosterone/cortisol ratio in one adrenal vein was at least 5 times the ratio in the other adrenal vein. None of the patients were screened for GRA.

Santiago, Chile

During the years 1996–1999, hypertensive patients were screened for PA when presenting with hypokalemia. From 2000, the ARR was extensively used as a screening test and was applied to all hypertensive patients referred to the unit. The cut-off level for a positive ARR was 25 (ng/dl/ng·ml^{-1}·h^{-1}) (2500 pmol/liter/ng·liter^{-1}·sec^{-1}). The confirmatory test was the FST, performed by measuring upright plasma aldosterone levels at 1000 h after 4 d of administration of fludrocortisone acetate (0.1 mg every 6 h) during a high-sodium diet and sodium supplementation (slow-release sodium chloride, 30 mmol thrice daily). It was considered positive if posttest aldosterone levels were greater than 5 ng/dl (138.7 pmol/liter) with concomitant PRA less than 1.0 ng/ml^{-1}·h^{-1} (0.28 ng/liter^{-1}·sec^{-1}), normal potassium levels, and cortisol on d 4 that were lower at 1000 h than at 0700 h. The lower limit of detection for the PRA assay was 0.3 ng/ml^{-1}·h^{-1}(0.08 ng/liter^{-1}·sec^{-1}). A CT scan of the adrenals was the imaging technique. AVS was not performed in any of the patients. Twenty-seven patients with PA were screened for GRA.

Hormone assays were performed in each group as previously published (3, 5, 6, 11, 12). GRA has been investigated by long-PCR amplification of the chimeric gene as previously described (13, 14).

Results

Torino, Italy

In the period 1988–1993, 2237 patients were seen in the unit, 40 of whom had confirmed PA (1.8%, 6.7 cases/yr) (Fig.

1). Of the confirmed cases, 28 (70%; 4.7/yr) had an APA, and 12 (30%; 2/yr) had BAH. Thirty-six (90%) were hypokalemic (Fig. 2). In the period 1994–2002, 7343 patients were referred to the unit. Five hundred eighty-seven (8%, 65.2 cases/yr) had confirmed PA. One hundred seventy (30%; 18.9/yr) had an APA; 417 were diagnosed as having BAH (70%; 46.3/yr). The prevalence of APA could have been slightly higher because 40% of patients with no evidence of adrenal mass and at low risk for APA, as defined elsewhere (15), did not undergo AVS. Only 146 (24.9%) were hypokalemic (Figs. 1–3). Twenty-one patients from one family were affected by GRA. Five patients from two different families were diagnosed with FH-II. The posture test was performed in 212 patients with BAH and in 153 patients with APA: 168 patients with BAH (79.2%) and 46 with APA (30.1%) displayed a positive result on the posture stimulation test.

In all patients diagnosed as having an APA by AVS, the diagnosis was confirmed pathologically after surgery. Sixty-five percent of patients who underwent surgery were cured, whereas 35% displayed a marked improvement in hypertension control.

Rochester, Minnesota

In the period 1955–1985, 248 patients were diagnosed as having PA (8 cases/yr). Sixty-eight percent of the patients had APA (5.4 detected per year) and 31% had BAH (2.5 detected per year); 98% of the patients were hypokalemic. In the period 1994–2000, 5479 patients were screened for PA. In one year (1999), of the 1112 patients screened, 120 were confirmed to have PA (10.8%); 34 patients (28%) had an APA; 86 patients (72%) had BAH; 37% were hypokalemic (Figs. 1–3). The true prevalence of APA was likely higher because more than 50% of PA patients with no evidence of an adrenal mass and at low risk for APA, as defined elsewhere (15), did not undergo AVS. No patients were identified with GRA, whereas seven were affected by FH-II. APA was confirmed on pathology in all patients diagnosed as having an APA by AVS and who subsequently underwent unilateral adrenal-

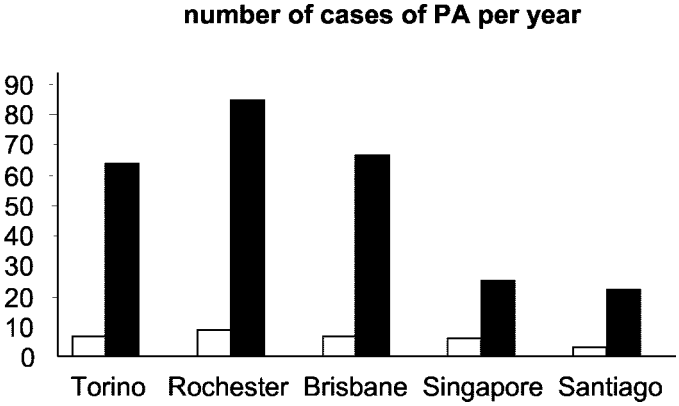

FIG. 1. Number of diagnosed cases of PA per year. Pre-ARR (*white columns*) signifies the period before adopting the strategy of screening most of the hypertensives referred to the center. Post-ARR (*black columns*) signifies the period after the widespread use of the ARR as a screening test. Torino: pre-ARR 1988–1993, post-ARR 1994–2002; Rochester: pre-ARR 1955–1985, post-ARR 1999; Brisbane: pre-ARR 1971–1991, post-ARR 1992–2002; Singapore: pre-ARR 1990–1994, post-ARR 1995–2001.

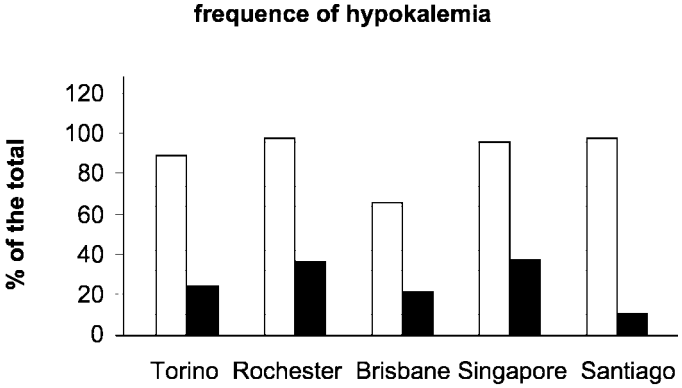

FIG. 2. Percentage of PA patients with hypokalemia. Pre-ARR (*white columns*) signifies the period before adopting the strategy of screening most of the hypertensives referred to the center. Post-ARR (*black columns*) signifies the period after the widespread use of the ARR as a screening test. Torino: pre-ARR 1988–1993, post-ARR 1994–2002; Rochester: pre-ARR 1955–1985, post-ARR 1999; Brisbane: pre-ARR 1971–1991, post-ARR 1992–2002; Singapore: pre-ARR 1990–1994, post-ARR 1995–2001

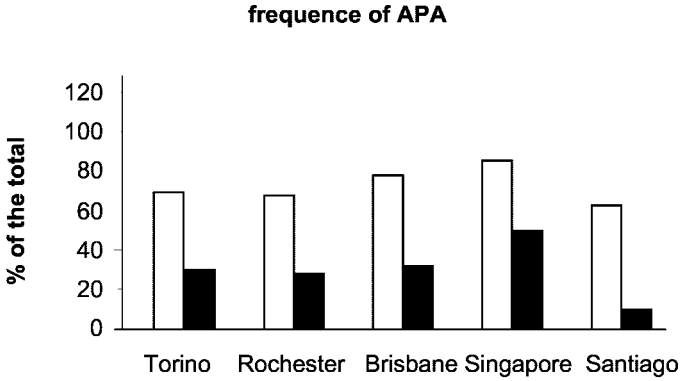

FIG. 3. Percentage of PA patients with APA. Pre-ARR (*white columns*) signifies the period before adopting the strategy of screening most of the hypertensives referred to the center. Post-ARR (*black columns*) signifies the period after the widespread use of the ARR as a screening test. Torino: pre-ARR 1988–1993, post-ARR 1994–2002; Rochester: pre-ARR 1955–1985, post-ARR 1999; Brisbane: pre-ARR 1971–1991, post-ARR 1992–2002; Singapore: pre-ARR 1990–1994, post-ARR 1995–2001

ectomy. In the AVS era, unilateral adrenalectomy cured hypertension (blood pressure $< 140/90$ mm Hg without the aid of antihypertensive agents) in 31 of 93 patients (33%) (16). Of the patients with continuing hypertension, 61 of 62 (98%) demonstrated improved control of hypertension (defined as a decrease in blood pressure or fewer antihypertensive agents taken at follow-up).

Brisbane, Australia

In the period 1971–1991, 139 patients were diagnosed as having PA (6.6 cases/yr); 66.2% of the patients were hypokalemic. Of the 112 patients for whom a subtype was determined, three had GRA, 84 (75%; 4/yr) had an APA, one (0.9%) had an aldosterone-producing carcinoma, and 24 (21.4%; 1.1/yr) had BAH. After adopting the policy to screen all hypertensives by ARR (1992–2002), 721 (65.5 cases/yr) were diagnosed with PA, 21.7% of whom were hypokalemic. Of the 631 patients for whom a subtype was determined, 31

had GRA, 187 (29.6%; 17/yr) had an APA, three (0.5%) had an aldosterone-producing carcinoma, two (0.3%) had giant macronodular hyperplasia (with one lateralization on AVS), and 408 (64.6%; 37.1/yr) had BAH (Figs. 1–3). In total, 193 patients (30.6%) had a lateralizing form of PA and were therefore candidates for surgical correction by unilateral adrenalectomy. Approximately 1000 patients were screened for GRA; 34 patients from five families tested positive. Seventy-two patients from 29 families were diagnosed as having FH-II. Aldosterone was found to be responsive to upright posture in 112 of 227 (49.3%) patients with APA and in 331 of 427 (77.5%) patients with BAH. All 241 patients who were diagnosed preoperatively as having APA and who underwent surgery demonstrated a typical cortical adenoma (93%) or nodular hyperplasia (7%) on pathological examination of the removed adrenal. Fifty-five percent of operated patients were cured of hypertension and the remaining 45% showed improvement in hypertension control. Aldosterone was responsive to angiotensin II infusion in 108 of 175 (61.7%) patients with APA and in 231 of 289 (79.9%) patients with BAH.

Singapore, Republic of Singapore

In the period 1990–1994, approximately 2800 hypertensive patients were seen in the unit, 28 (1%, 5.6 cases/yr) of whom had a confirmed PA. Twenty-four (85.7%; 4.8/yr) had an APA, and four (14.3%; 0.8/yr) BAH. Twenty-seven were hypokalemic (96.4%). In the period 1995–2001, approximately 3850 hypertensive patients were referred to this unit. One hundred seventy-seven (4.6%, 25.3 cases/yr) had a confirmed PA. Eighty-eight (50%; 12.6/yr) had an APA, and 89 (50%; 12.7/yr) had BAH. The prevalence of PA could have been even higher if a cut-off less strict for the aldosterone levels after saline load (10 ng/dl, 277.4 pmol/liter) would have been chosen. Sixty-six (37.3%) were hypokalemic (Figs. 1–3). All patients diagnosed as having an APA by AVS had a pathological confirmation of the diagnosis after surgery. Forty percent of the patients who underwent surgery were cured, 55% displayed a marked improvement in hypertension control, and 5% displayed no significant changes in blood pressure levels.

Santiago, Chile

In the period 1996–1999, approximately 600 hypertensive patients were seen in the unit, of whom six (1%, 1.5/yr) had a confirmed PA. Five patients (83%; 1.25/yr) had an APA and one BAH. In the period 2000–2002, 914 were screened for PA: 66 (7.2%, 22/yr) were confirmed as having PA. Six patients (9.1%) were hypokalemic. Six (9.1%; 2/yr) had an APA, and 60 (88.9%; 20/yr) BAH (Figs. 1–3). The prevalence of APA could have been higher because AVS was not performed in any of the patients. Interestingly, after subdivision according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) VI into three different stages, depending on the severity of hypertension, the prevalence of PA was 2.2% in patients with hypertension stage 1, 8.9% in patients with stage 2, and 14.6% in patients with stage 3. Twenty-seven patients were screened for GRA and three tested positive. Ten of 11 patients with APA underwent adrenalectomy: pathological examination of the removed adrenal revealed a typical adenoma in each case. Seventy percent of patients who underwent surgery were cured, and 30% displayed a marked improvement in hypertension control.

Discussion

This report highlights the impact that widespread use of the ARR on the rate of diagnosis of PA. This strategy of screening, and even more, the application of this strategy to a greater number of hypertensive patients, led to a 5- to 15-fold increase in the identification of patients affected by PA. The identification of these patients ensures a specific treatment for all of them and the possibility of a definitive cure of hypertension in the APA patients. The majority of the patients who were diagnosed using the wider screening strategy would not have had a correct diagnosis following the old criteria for the suspicion of PA. In fact, only a small proportion of patients (between 9 and 37%, depending on the center) were hypokalemic. The increased PA detection rate was surprisingly consistent after the more widespread use of the ARR in different continents, even though it was applied to patients of different ethnicity and different confirmatory tests were used.

It is important to emphasize that the importance of diagnosing PA is not just an issue of classification, in that hypertension in patients with APA can be cured or at least significantly ameliorated by unilateral adrenalectomy. Furthermore, although BAH patients might not benefit from surgery, the determination of the underlying cause of the increased blood pressure in these patients is fundamental for targeted pharmacotherapy. Increased aldosterone levels cause vascular and cardiac toxicity that is, in part, independent of the effect on blood pressure (17–24). Therefore, if BAH is left undiagnosed, many of these patients would be treated with antihypertensive drugs other than aldosterone receptor antagonists, and aldosterone-induced vascular toxicity may advance unabated. The Randomized Aldactone Evaluation Study (RALES) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) recently highlighted this issue in demonstrating benefits of aldosterone receptor antagonist treatments in terms of reduced morbidity and mortality that appeared to be at least partly independent of the effect on blood pressure levels (25, 26). The difficulty of distinguishing normal from abnormal, especially with variables that display a continuous distribution such as hormone levels, could have caused the inclusion of a small number of patients with other low-renin form of hypertension in the BAH group: this is not of major clinical importance because these patients may nonetheless benefit from therapy with spironolactone (27). Similarly, the supraphysiological salt load (with or without fludrocortisone), used by all groups to confirm the diagnosis of PA, might have caused aldosterone inhibition in patients with BAH that retain some negative feedback regulatory mechanism, resulting in a small underestimation of the actual prevalence.

A limitation of the present report is that, being retrospective, the criteria of screening and confirmation of PA were

different between the participating centers. This was in part due to the characteristics of the hormone assay in the single centers; however, the results were remarkably consistent despite the diverse locations of each center and indicate that it is not just hypokalemic hypertensive patients that should to be screened for PA. It is important to note that the increased diagnosis of PA was observed in every center in our study, independent of the cut-off used for the screening test and the type of confirmatory test. It has been argued that the use of wider screening strategies might result in significantly increased health expenditure resulting from the costs of performing ARR measurements, confirmatory tests, CT scans and AVS in a greater number of hypertensives. It should be remembered, however, that the great majority of patients who undergo ARR testing (which, taken alone, is relatively inexpensive) will test negative, and therefore will be excluded from having to undergo the more expensive confirmatory tests, CT and AVS. In a recent study on patients with APA, adrenalectomy was reported to be associated with a mean cost saving of $20,472 (United States) per patient when compared with the estimated cost of medical treatment over each patient's lifetime (28). Furthermore, this calculation did not include the potential costs associated with diagnosis and treatment of complications and time off work arising from long-term exposure to increased aldosterone levels and less adequately controlled hypertension in medically treated patients and, of course, did not take into account the improvement in the quality of the life consistently reported by patients who are surgically cured and able to cease antihypertensive medication therapy.

It has been reported that the determination of PRA levels can help toward optimizing antihypertensive therapy in individual patients with hypertension and thereby potentially reduce costs by decreasing the number of drugs required. In one study, the prescription of antihypertensive therapy based on the renin profile of the patient resulted in a mean reduction of 0.6 drugs (from 2.1 to 1.5) per patient, compared with a random prescription (29), which was in turn associated with reductions in cost (−20%) and side effects. Furthermore, this strategy allowed a diagnosis of secondary hypertension in 17.8% of patients, half of whom were patients with PA (29).

Recently investigators reporting on findings of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study concluded that diuretic therapy should be considered the first line treatment in hypertension (30). However, in the light of the findings of the current study, this approach would have the potential for placing significant numbers of patients with as-yet-undiagnosed normokaliemic PA at risk of hypokalemia.

A possible criticism of the present report is that the observed high prevalence of PA may be specific to the tertiary care centers and reflect the highly selected nature of patients referred to those centers. However, similar high prevalence rates have been reported in studies involving less selected patients (4, 5) and in a large group of hypertensive patients in which resistant hypertensives were excluded (7). Further, in the present study, the Chilean group demonstrated a high prevalence of PA in stage 2 hypertension (8.9%).

It should be emphasized that an increased ARR is not in itself a diagnosis and that careful suppression testing (for example, by FST or sodium loading) is required to definitively confirm or exclude the diagnosis of PA. In the current study, overdiagnosis of PA was avoided by only including patients in whom PA had been confirmed by one of these techniques.

This study found the most common form of PA to be BAH and not APA. However, the annual detection rate of patients with APA nevertheless increased in all centers (by 1.3–6.3 times) after the wide application of ARR testing. Furthermore, the prevalence of BAH could have been overestimated in centers that relied on imaging techniques or posture studies rather than AVS to detect APA because of the low sensitivity of imaging techniques for the detection of small APAs (<1 cm), and the inability of posture studies to differentiate BAH from angiotensin-responsive APA (31). In keeping with this, APAs constituted a much higher proportion of patients with PA in the four centers that employed AVS (28–50%) than in the single center that did not (9%). These findings argue for a critical role for AVS in the detection of APAs and support the findings of others (32–34) who have reported on the unreliability of imaging techniques and advocated AVS as being the only dependable means of differentiating medically and surgically treatable forms of PA. In patients who demonstrate a unilateral adrenal mass on imaging studies, AVS minimizes the risk of inappropriate surgery by determining whether aldosterone overproduction is confined to the corresponding gland: AVS allows the clinician to avoid removing an incidentaloma or a macronodule of hyperplasia in a patient in which these conditions are associated with BAH. Conversely, AVS allows the identification of microadenomas, which may be missed by imaging techniques and thus provide the opportunity of a cure to the patient.

Finally, we would like to emphasize that an early diagnosis of PA, by permitting early institution of specific medical or surgical treatment and thereby minimizing target organ damage due to exposure to high blood pressure and high aldosterone levels, will provide the best choice for an optimal therapeutic outcome, as evidenced by the findings of our group and others that resolution of hypertension after adrenalectomy is associated with younger age and shorter duration of hypertension (15, 16, 35, 36).

In conclusion, in this retrospective multicenter study, the wide use of the ARR as a screening test in hypertensive patients for the diagnosis of PA led to a marked increase in detection rate. When AVS was used for subtype differentiation, this was associated with a marked increase in the identification of patients with APA, thereby providing the opportunity for definitive surgical treatment and the possibility of disease-specific pharmacotherapy.

Acknowledgments

Received August 1, 2003. Accepted December 16, 2003.

Address all correspondence and requests for reprints to: Dr. Paolo Mulatero, Hypertension Unit, San Vito Hospital, Strada San Vito 34, 10133 Torino, Italy. E-mail: paolo.mulatero@libero.it.

References

1. **Kaplan NM** 1994 Clinical hypertension. 6th ed. Baltimore: Williams & Wilkins;389–408

2. **Ganguly A** 1998 Primary aldosteronism. N Engl J Med 339:1828–1834
3. **Gordon RD, Ziesak MD, Tunny TJ, Stowasser M, Klemm SA** 1993 Evidence that primary aldosteronism may not be uncommon: 12% incidence among antihypertensive drug trial volunteers. Clin Exp Pharmacol Physiol 20:296–298
4. **Gordon RD, Stowasser M, Tunny TJ, Klemm SA, Rutherford JC** 1994 High incidence of primary aldosteronism in 199 patients referred with hypertension. Clin Exp Pharmacol Physiol 21:315–318
5. **Loh KC, Koay ES, Khaw MC, Emmanuel SC, Young Jr WF** 2000 Prevalence of primary aldosteronism among Asian hypertensive patients in Singapore. J Clin Endocrinol Metab 85:2854–2859
6. **Fardella CE, Mosso L, Gomez-Sanchez C, Cortes P, Soto J, Gomez L, Pinto M, Huete A, Oestreicher E, Foradori A, Montero J** 2000 Primary hyperaldosteronism in essential hypertensives: prevalence, biochemical profile, and molecular biology. J Clin Endocrinol Metab 85:1863–1867
7. **Mulatero P, Rabbia F, Milan A, Paglieri C, Morello F, Chiandussi L, Veglio F** 2002 Drug effects on aldosterone/plasma renin activity ratio in primary aldosteronism. Hypertension 40:897–902
8. **Kaplan NM** 2001 Cautions over the current epidemic of primary aldosteronism. Lancet 357:953–954
9. **Lim PO, Rodgers P, Cardale K, Watson AD, MacDonald TM** 1999 Potentially high prevalence of primary aldosteronism in a primary-care population. Lancet 353:40
10. **Holland OB, Brown H, Kuhnert L, Fairchild C, Risk M, Gomez-Sanchez CE** 1984 Further evaluation of saline infusion for the diagnosis of primary aldosteronism. Hypertension 6:717–723
11. **Young Jr WF, Stanson AW, Grant CS, Thompson GB, van Heerden JA** 1996 Primary aldosteronism: adrenal venous sampling. Surgery 120:913–919
12. **Mulatero P, Veglio F, Pilon C, Rabbia F, Zocchi C, Limone P, Boscaro M, Sonino N, Fallo F** 1998 Diagnosis of glucocorticoid-remediable aldosteronism in primary aldosteronism: aldosterone response to dexamethasone and long polymerase chain reaction for chimeric gene. J Clin Endocrinol Metab 83: 2573–2575
13. **Jonsson JR, Klemm SA, Tunny TJ, Stowasser M, Gordon RD** 1995 A new genetic test for familial hyperaldosteronism type I aids in the detection of curable hypertension. Biochem Biophys Res Commun 207:565–571
14. **Mulatero P, Curnow KM, Aupetit-Faisant B, Foekling M, Gomez-Sanchez C, Veglio F, Jeunemaitre X, Corvol P, Pascoe L** 1998 Recombinant CYP11B genes encode enzymes that can catalyze conversion of 11-deoxycortisol to cortisol, 18-hydroxycortisol, and 18-oxocortisol. J Clin Endocrinol Metab 83:3996–4001
15. **Young Jr WF** 2002 Primary aldosteronism: management issues. Ann NY Acad Sci 970:61–76
16. **Sawka AM, Young WF, Thompson GB, Grant CS, Farley DR, Leibson C, van Heerden JA** 2001 Primary aldosteronism: factors associated with normalization of blood pressure after surgery. Ann Intern Med 135:258–261
17. **Rocha R, Martin-Berger CL, Yang P, Scherrer R, Delyani J, McMahon E** 2002 Selective aldosterone blockade prevents angiotensin II/salt-induced vascular inflammation in the rat heart. Endocrinology 143:4828–4836
18. **Delcayre C, Swynghedauw B** 2002 Molecular mechanisms of myocardial remodeling. The role of aldosterone. J Mol Cell Cardiol 34:1577–1584
19. **Rocha R, Rudolph AE, Frierdich GE, Nachowiak DA, Kekec BK, Blomme EA, McMahon EG, Delyani JA** 2002 Aldosterone induces a vascular inflammatory phenotype in the rat heart. Am J Physiol Heart Circ Physiol 283: H1802–H1810
20. **Sun Y, Zhang J, Lu L, Chen SS, Quinn MT, Weber KT** 2002 Aldosterone-induced inflammation in the rat heart: role of oxidative stress. Am J Pathol 161:1773–1781
21. **Young M, Head G, Funder J** 1995 Determinants of cardiac fibrosis in experimental hypermineralocorticoid states. Am J Physiol 269:E657–E662
22. **Rocha R, Funder JW** 2002 The pathophysiology of aldosterone in the cardiovascular system. Ann NY Acad Sci 970:89–100
23. **Rossi GP, Sacchetto A, Pavan E, Palatini P, Graniero GR, Canali C, Pessina AC** 1997 Remodeling of the left ventricle in primary aldosteronism due to Conn's adenoma. Circulation 95:1471–1478
24. **Schmidt BM, Schmieder RE** 2003 Aldosterone-induced cardiac damage: focus on blood pressure independent effects. Am J Hypertens 16:80–86
25. **Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J** 1999 The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 341:709–717
26. **Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M** 2003 Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 348:1309–1321
27. **Laragh J** 2001 Abstract, closing summary, and table of contents for Laragh's 25 lessons in pathophysiology and 12 clinical pearls for treating hypertension. Am J Hypertens 14:1173–1177
28. **Sywak M, Pasieka JL** 2002 Long-term follow-up and cost benefit of adrenalectomy in patients with primary hyperaldosteronism. Br J Surg 89:1587–1593
29. **Blumenfeld JD, Laragh JH** 1998 Renin system analysis: a rational method for the diagnosis and treatment of the individual patient with hypertension. Am J Hypertens 11:894–896
30. **ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group** 2002 Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 288:2981–2997
31. **Gordon RD, Gomez-Sanchez CE, Hamlet SM, Tunny TJ, Klemm SA** 1987 Angiotensin-responsive aldosterone-producing adenoma masquerades as idiopathic hyperaldosteronism (IHA: adrenal hyperplasia) or low-renin essential hypertension. J Hypertens Suppl 5:S103–S106
32. **Magill SB, Raff H, Shaker JL, Brickner RC, Knechtges TE, Kehoe ME, Findling JW** 2001 Comparison of adrenal vein sampling and computed tomography in the differentiation of primary aldosteronism. J Clin Endocrinol Metab 86:1066–1071
33. **Young Jr WF** 1999 Primary aldosteronism: a common and curable form of hypertension. Cardiol Rev 7:207–214
34. **Stowasser M, Gordon RD, Rutherford JC, Nikwan NZ, Daunt N, Slater GJ** 2001 Diagnosis and management of primary aldosteronism. J Renin Angiotensin Aldosterone Syst 2:156–169
35. **Blumenfeld JD, Vaughan Jr ED** 1999 Diagnosis and treatment of primary aldosteronism. World J Urol 17:15–21
36. **Celen O, O'Brien MJ, Melby JC, Beazley RM** 1996 Factors influencing outcome of surgery for primary aldosteronism. Arch Surg 131:646–650

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.