artigo original

The Syndromes of Low-Renin Hypertension: "Separating the Wheat From the Chaff"

Claudio E. Kater
Edward G. Biglieri

Adrenal and Hypertension Unit, Division of Endocrinology, Department of Medicine, Universidade Federal de São Paulo – UNIFESP (CEK), São Paulo, SP; University of California San Francisco – UCSF (EGB), San Francisco, California, USA

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ABSTRACT

Primary aldosteronism (PA) is characterized by hypertension and suppressed renin activity with or without hypokalemia and comprises the aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia or idiopatic hyperaldosteronism (IHA). In recent series employing the aldosterone (aldo, ng/dL):renin (ng/mL·h) ratio (ARR) for screening, prevalence of PA among hypertensives soars to 8-20%; current predominance of IHA (>80%) over APA suggests the inclusion of former low-renin essential hypertensives (LREH), in whom plasma aldo can be reduced by suppressive maneuvers. We evaluated the test characteristics of the ARR obtained retrospectively from 127 patients with PA (81 APA; 46 IHA) and 55 with EH (30 LREH; 25 NREH) studied from 1975 to 1990. Using the combined ROC-defined cutoffs of 27 for the ARR and 12ng/dL for aldo, we obtained 89.8% sensitivity (Ss) and 98.2% specificity (Sp) in discriminating PA from EH: all APA and 72% of the IHA patients had values above these limits, but only one (3%) with LREH. Among the 46 IHA patients, 10 (21.7%) had ARR <27, four of whom with aldo <12ng/dL, virtually indistinguishable from LREH. Use of higher cutoff values (ARR≥ 100; aldo ≥20) may attain 84%Ss and 82.6%Sp in separating APA from IHA. Because IHA and LREH ("the chaff") may be spectrum stages from the same disease, definite discrimination between these entities seems immaterial. However, precise identification of the APA ("the wheat") is critical, since it is the only surgically curable form of PA. Thus, while patients who may harbor an APA must be thoroughly investigated and surgically treated, non-tumoral disease (IHA and LREH) may be best treated with an aldo-receptor antagonist that will also prevent the aldo-mediated inflammatory effects involved in myocardial fibrosis and abnormal cardiac remodeling. **(Arq Bras Endocrinol Metab 2004;48/5:674-681)**

Keywords: Low-renin hypertension; Primary aldosteronism; Aldosterone-producing adenoma; Idiopathic hyperaldosteronism; Aldosterone; Aldosterone:renin ratio

RESUMO

Hiperaldosteronismo primário (HAP) é caracterizado por hipertensão com renina baixa, com ou sem hipocalemia, compreendendo o adenoma produtor de aldosterona (APA) e a hiperplasia adrenal bilateral ou HA idiopático (HAI). Em séries recentes usando a relação aldosterona (aldo, ng/dL):renina (ng/mL·h) (RAR) para rastreamento, a prevalência de HAP atinge 8-20% dos hipertensos; a predominância atual do HAI (>80%) sobre APA sugere a inclusão de hipertensos essenciais com renina baixa (HERB), nos quais aldo pode ser suprimida por expansão de volume. Avaliamos as características do teste RAR, obtido retrospectivamente de 127 pacientes com HAP (81 APA; 46 HAI) e 55 com hipertensão essencial (30 HERB; 25 com renina normal, HERN) estudados de 1975 a 1990. Usando a combinação de *cutoffs* de 27 para RAR e de 12ng/dL para aldo, obtivemos sensibilidade (S) de 89,8% e especificidade (E) de 98,2% na separação entre HAP e HE: todos os APA

e 72% dos HAI (mas apenas um [3%] HERB) tinham valores acima destes limites. Dentre os 46 HAI, 10 (21,7%) tinham RAR <27 e destes, 4 tinham aldo <12ng/dL, virtualmente indistingüíveis dos HERB. Valores mais elevados de *cutoff* (RAR≥ 100; aldo ≥ 20) permitem 84% de S e 82,6% de E na separação entre APA e HAI. Como HAI e HERB ("o joio") devem ser estágios do espectro de uma mesma doença, parece irrelevante a separação dessas entidades. Entretanto, identificação precisa do APA ("o trigo") é fundamental, por ser a única forma de HAP curável cirurgicamente. Assim, enquanto a suspeita de um APA precisa ser criteriosamente investigada e tratada cirurgicamente, pacientes com doença não tumoral (HAI e HERB) podem ser tratados com antagonistas do receptor de aldo, que também previnem os efeitos inflamatórios envolvidos no processo de fibrose e remodelação anormal do miocárdio. **(Arq Bras Endocrinol Metab 2004;48/5:674-681)**

Descritores: Hipertensão com renina baixa; Hiperaldosteronismo primário; Adenoma produtor de aldosterona; Hiperaldosteronismo idiopático; Aldosterona; Relação aldosterona:renina

THE SYNDROME OF PRIMARY aldosteronism (PA) is characterized by "autonomous" or angiotensin-independent aldosterone excess resulting in suppressed levels of plasma renin activity (PRA). Increased aldosterone activation of the mineralocorticoid hormone (MCH) receptor in the distal kidney tubule produces sodium and fluid retention, volume expansion, renin suppression, and potassium wasting (1). However, a distinctive feature of PA, hypokalemia is seldom observed in current series (2). In contrast with other florid syndromes of steroid excess (cortisol, androgens), the clinical picture of PA is pale, confined to hypertension in presence of renal potassium wasting and, only occasionally, hypokalemia. Thus, except for some resistance to conventional medical therapy (3-5) the clinical picture of PA may not be distinct from essential hypertension.

The archetype of PA is the aldosterone-producing adrenal adenoma (APA), the first identifiable cause of the syndrome reported in the mid 50's by J. Conn. Bilateral adrenal hyperplasia (also called non-tumorous and idiopathic hyperaldosteronism [IHA]) was recognized a few years later in several patients submitted to surgery in the search for an APA. Ever since, APA and IHA are considered the main subtypes of PA. Because of their large biochemical, pathologic, therapeutic and prognostic differences, APA and IHA are not universally regarded as part of the same syndrome (6-14). Instead, IHA may well be considered an extreme of the spectrum of low-renin "essential hypertension" (LREH) in which plasma or urinary aldosterone levels are somewhat resistant to suppression.

Until 15 years ago, PA was considered a rare cause of secondary hypertension (less than 1% of the hypertensive population) with the APA and IHA subtypes responding for approximately 80% and 20% of the cases, respectively (15). Suspicion and identification of PA among patients with hypertension was based mostly on the presence of hypokalemia and further demonstration of reduced PRA with elevated and non-suppressible plasma and urinary aldosterone levels. Lately, with the use of the aldosterone:renin ratio (ARR) for screening, the prevalence of PA has soared to a surprising 8 to 20% of the hypertensive population (16-23), being considered the most frequent cause of secondary hypertension (24).

Since the unilateral disease (APA) is the sole form of surgically correctable PA, patients who may harbor an APA must be carefully scrutinized and lateralization must be thoroughly pursued with appropriate adrenal imaging (CT) and adrenal vein sampling for aldosterone measurements (25,26). On the other hand, since IHA is not amenable to surgery, it may not be specifically distinguished from LREH for treatment purposes.

Because the ARR (in presence of elevated plasma aldosterone concentration [PAC]) seems to be at present the most convenient test to screen for PA among hypertensives, we examined in this paper the best cutoff points for these parameters in a significant population of previously diagnosed patients with PA and essential hypertension, in an attempt to separate PA from EH and, especially, APA ("the wheat") from IHA ("the chaff") in prospective screening.

MATERIAL AND METHODS

We reviewed the hospital charts from 182 patients admitted for studies in the General Clinical Research Center at the San Francisco General Hospital Medical Center (UCSF) or the University Hospital at the Federal University of São Paulo (UNIFESP) from 1975 to 1990. This 15-year period was chosen because at that time hypokalemia was virtually mandatory for the diagnosis of PA, whereas the aldosterone:renin ratio (ARR) was not systematically used for screening. Computerized tomography (CT) and adrenal vein sampling (AVS) for aldosterone measurements were already available to confirm the presence

Table 1. Mean±SE [and range] of plasma potassium (K^+), aldosterone (PAC), renin activity (PRA), aldosterone:renin ratio (ARR) and corrected (c)ARR (PRA ≤0.2ng/mL·h corrected for 0.2) in patients with "primary aldosteronism" (due to an APA - aldosterone-producing adenoma and IHA - idiopathic hyperaldosteronism) and "essential hypertension" (with low [LREH] and normal [NREH] renin levels; <1 and 1 ng/mL-h, respectively).

Group	n (F/M)	Age (years)	K+ (meq/L)	PAC (ng/dL)	PRA (ng/mL·h)	ARR (ng/dL:ng/mL·h)	cARR (ng/dL:ng/mL·h)
Primary Aldosteronism							
APA	81 (57/24)	37±11 [21-57]	2.9±0.5 [2.0-3.8]	53.6±44.7 [12.7-338]	0.2±0.2 [0.1-0.8]	373±459 [43-3380]	231±224 [43-1690]
IHA	46 (23/23)	43±12 [12-66]	3.2±0.5 [1.9-3.8]	18.9±12.8 [7.5-88.9]	0.3±0.2 [0.1-1.0]	82.5±81.5 [14.8-445]	67.8±67.3 [14.8-445]
Essential Hypertension							
LREH	30 (20/10)	36±10 [15-64]	4.0±0.2 [3.4-4.6]	8.0±3.6 [4.3-17.9]	0.5±0.2 [0.2-0.9]	18.1±9.5 [5.1-47]	18.1±9.5 [5.1-47]
NREH	25 (08/17)	32±9 [19-55]	4.1±0.3 [3.7-4.6]	8.7±2.0 [4.1-13.1]	1.7±0.7 [1.0-3.4]	5.5±1.9 [2.7-9.4]	5.5±1.9 [2.7-9.4]

of an APA. From these, 127 patients were found to have PA, including 81 with an APA (57F/24M, 21 to 57y, median 33] and 46 with IHA due to bilateral adrenal hyperplasia [23F/23M, 13 to 66y, median 41]. The remaining 55 patients had been labeled as essential hypertensives, 30 with the low renin variant (LREH; 20F/10M, 15 to 64y, median 35) and 25 with normal renin levels (NREH; 8F/17M, 19 to 55y, median 30). All patients were investigated during hospital admission and after equilibration for a period of 3 to 5 days on a metabolic diet containing approximately 2meq Na and 1meq K per kg of BW per day.

PA was documented by the presence of hypertension, hypokalemia (in 95% of the cases) or low-normal plasma potassium levels (3.4-3.7meq/L), suppressed PRA and normal to elevated PAC and/or urinary aldosterone levels, that did not suppress in response to either a saline infusion test ($2^{1/2}$L NaCl 0.9% IV for 4h) (27) or administration of DOC acetate (10mg IM every 12h for 3 days) (28). A bonafide APA was excised from every one of the 81 patients whose previous adrenal CT scans showed a clear-cut unilateral adrenal lesion and whose PAC did not increase (in 90% of cases) in response to a 2-4h upright postural stimulation test (29). Diagnosis of IHA was entertained in 46 patients whose PAC increased significantly (at least 30% above baseline) after postural stimulation (in 95% of cases) and in whom a solitary adrenal mass could not be identified on repeated adrenal CT scans. Selective AVS for PAC determination was performed in a few patients whose previous tests were unrevealing.

After exclusion of other causes of secondary hypertension by standard evaluation, a diagnosis of essential hypertension was decided in 55 patients whose normal to slightly increased PAC and/or urinary aldosterone levels were promptly reduced by more than 50% in response to suppressive maneuvers; 30 of them had "low" PRA levels (arbitrarily considered as <1 ng/mL·h on the study conditions) and were considered LREH, whereas the remaining 25 had normal PRA (≥1 ng/mL·h), being classified as NREH.

Individual ARR was calculated from record data since this ratio was not systematically being used at that time to screen for PA. In every patient the ARR was determined by dividing their simultaneously obtained PAC and PRA values after standing for 2-4hs while equilibrated on the ward metabolic diet and free from any possible interfering medication. To avoid inaccurate interpretation of the ARR, all PRA values ≤0.2ng/mL·h (detection limit: 0.1ng/mL·h) were subsequently round up to 0.2 ng/mL·h and a new "corrected" ARR (cARR) was calculated.

The best diagnostic cutoff points for both the cARR and PAC that could discriminate PA from essential hypertension (highest sensitivity and specificity, or the largest area under the curve) were determined by analyzing a ROC (receiver operator characteristics) curve where sensitivity was plotted against specificity (1-specificity) for every value of each parameter, from 100% specificity to 100% sensitivity.

Based on the data obtained, a diagram was constructed where individual cARR were plotted against the respective PAC on a semi-logarithmic scale. We also used distinctive combination of cutoff points for cARR and PAC to assess sensitivity, specificity and the positive predictive value in an attempt to discriminate APA from IHA.

RESULTS

Table 1 presents the mean (±SE) and range for age, plasma K^+, aldosterone (PAC), renin, and the ARR (raw and corrected) for the 4 groups of hypertensive patients:

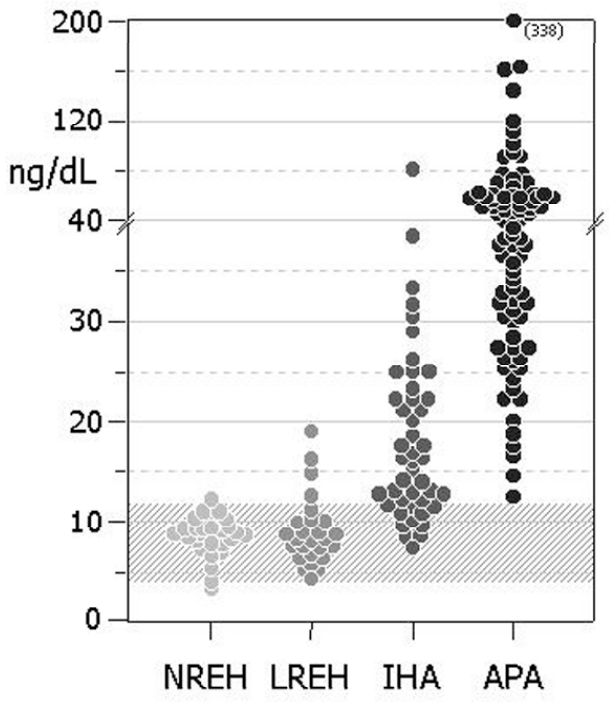

Figure 1. Individual baseline plasma aldosterone concentration in patients with "primary aldosteronism" (aldosterone-producing adenomas [APA, n=81] and idiopathic hyperaldosteronism [IHA, n=46]) or "essential hypertension" (low- [LREH, n= 30] and normal-renin [NREH, n=25]).

APA, IHA, LREH and NREH. Mean plasma K^+ was significantly reduced in APA and IHA, and PRA also in LREH (albeit not suppressed), whereas PAC was significantly increased in APA and IHA (53.6±44.7 and 18.9±12.8ng/dL, respectively) but not in LR or NREH (8.0±3.6 and 8.7±2.0ng/dL, respectively). Mean cARR was significantly increased in APA (231±224, and above 40 in all patients) and in IHA (67.8±67.3, but below 20 in 4 [8.7%] patients); among patients with EH, cARR was below 20 in 19/30 (63.3%) with LREH, and below 10 in all with NREH.

Figure 1 discloses the individual values of PAC in all 4 groups. Although patients with an APA had the highest individual values (≥30ng/dL in 77%, and ≥ 40ng/dL in 50%), some with IHA also had values in the upper range (≥ 30ng/dL in 11%, and ≥40ng/dL in one [2%] patient). However, a considerable overlap is observed in the slightly elevated range (from 12 to 20ng/dL) among patients with APA, IHA and LREH.

Figure 2 depicts the two ROC curves built for the cARR and PAC when subjects were separated according to the presence of PA (APA and IHA) or not (LREH and NREH). The best cutoff points obtained were: 27 (ng/dL:ng/mL·h) for the cARR (93% sensitivity; 96.5% specificity) and 12 ng/dL for PAC (94.5% sensitivity; 93.5% specificity).

All individual values of the cARR were plotted against the respective PAC in figure 3; the dashed cut-off lines identifies 4 quadrangles: the upper right panel (cARR≥27 and PAC≥12) defines the typical PA area (in which all APA and 72% of the IHA were located), whereas the lower left panel (cARR<27 and PAC<12) would exclude PA (except for 9% of IHA); the upper left (cARR ≥ 27 and PAC<12) and the lower right panels (cARR<27 and PAC≥12) encompass patients in whom the diagnosis of IHA (but not APA) is possible but less likely. However, 6.5% and 13% of the IHA patients lie in these areas, respectively.

Figure 4 discloses the percentage of patients encompassed from each category group (APA, IHA, LREH and NREH) according to the different combined cutoffs established for cARR and PAC. The combination of a cARR ≥100 and a PAC ≥ 20 has a positive predictive value of 89.5% in discriminating APA from IHA (with 84% sensitivity and 82.6% specificity).

DISCUSSION

PA is a common cause of secondary hypertension due to aldosterone excess in which specific treatment is available. PA has been diagnosed at increasing rates in the past 15 years (2,17,21), reaching in some reports a prevalence as high as 15-30% of the hypertensive population (2,21,30). Approximately 80% of the cases are due to non-tumorous disease (bilateral adrenal hyperplasia or IHA), rather than the prototypic form of PA, the unilateral APA (17). Thus, identification of those 20% of patients who may harbor an APA ("the wheat") will permit surgical removal of the affected gland with normalization of blood pressure and electrolyte abnormalities and reduction of mineralocorticoid (MCH) receptor-mediated cardiovascular damage (31). The remaining patients with low-renin hypertension ("the chaff"), regardless of their possible identification as IHA or LREH, will not benefit from surgery but instead from specific medical treatment with aldosterone receptor antagonists as spironolactone and eplerenone that will also reduce potential cardiovascular complications (32-34).

Until the late 80's, suspicion of PA was based solely on the presence of hypertension with hypokalemia (overt PA), which is only occasionally observed in present series (17,21). However, during the past 15 years, screening for PA has been largely based on the finding of an elevated plasma aldos-

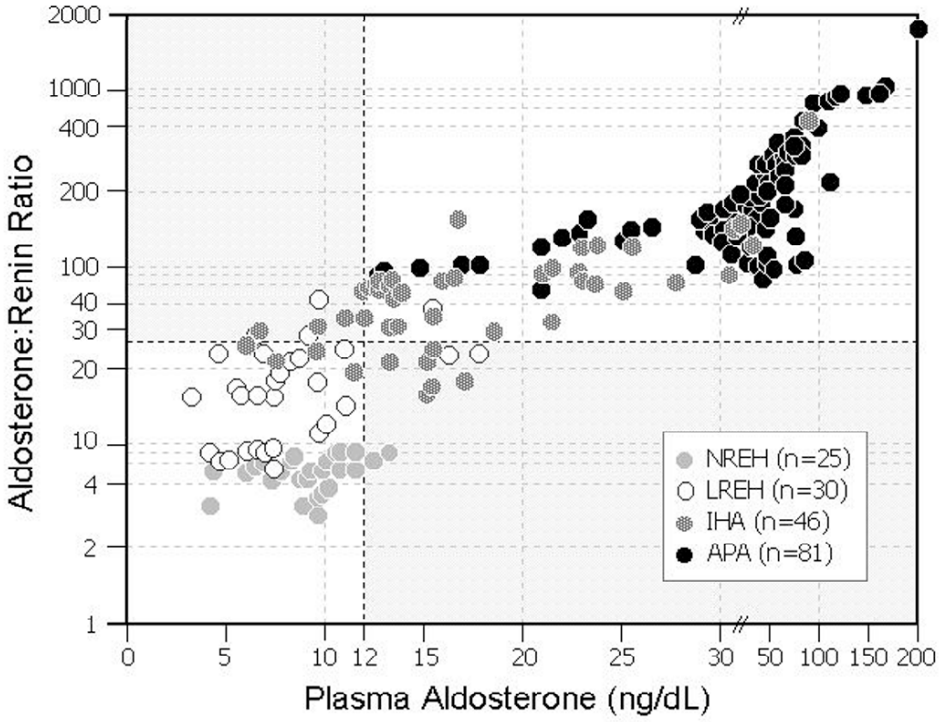

Figure 3. Scattered plot (on a semi-logarithmic scale) correlating plasma aldosterone: plasma renin activity ratio (ARR) with the corresponding plasma aldosterone concentration in patients with "primary aldosteronism" (APA and IHA) and with "essential hypertension" (LREH and NREH).

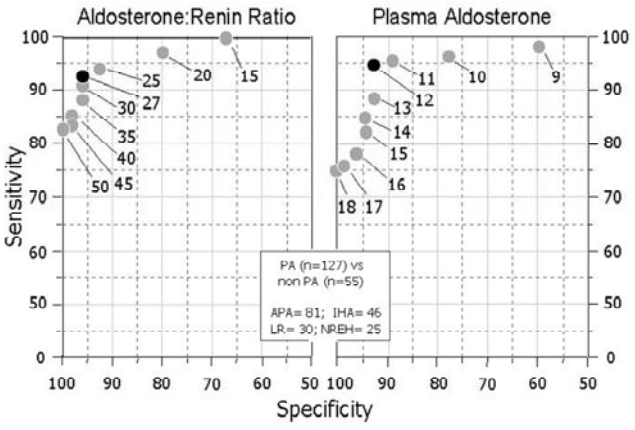

Figure 2. Receiver-operator characteristics (ROC) curves for plasma aldosterone: plasma renin activity ratios (ARR) and plasma aldosterone concentration obtained from 127 patients with "primary aldosteronism" (APA and IHA) and 55 with "essential hypertension" (LREH and NREH).

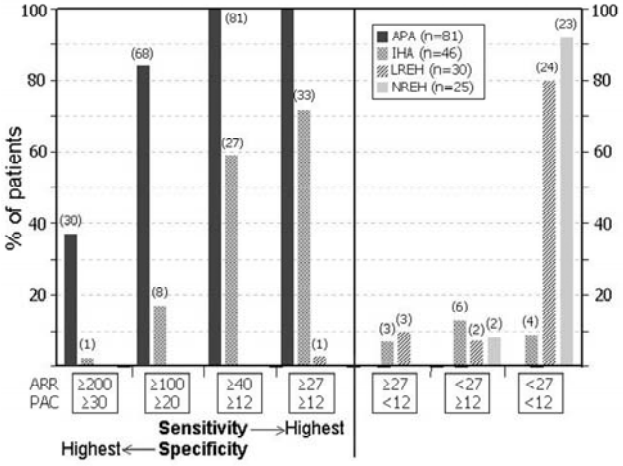

Figure 4. Percentage of patients with "primary aldosteronism" (APA and IHA) and "essential hypertension" (LREH and NREH) that fit the different restriction criteria for ARR and PAC.

terone-to-renin ratio (ARR) obtained in unrestricted or relatively controlled conditions (35-38), regardless of the presence of hypokalemia. As a consequence, yearly identification of patients with PA increased approximately 10 fold in several centers around the world (2,17) and it is also part of our recent experience.

When the highly sensitive ARR test replaces the specificity of hypokalemia in screening for PA, there may be a potential increase in the rate of false positive results, making it critical to decide on a test cutoff point that has high sensitivity without losing specificity. Confirmatory procedures are then necessary to establish a firm diagnosis of PA and to exclude false positives.

These maneuvers aim to characterize the autonomy of aldosterone secretion via acute or prolonged expansion of blood volume with saline infusion (27,39), fludrocortisone (2,17) or DOCA administration (2,28), together with a high sodium chloride intake. However, the diversity of tests and interpretation criteria (2,40) associated with different methodology for PRA (or direct renin) and aldosterone assays may be misleading. Although interpretation criteria for these tests include a fall by 50% or more, the level below which plasma or urinary aldosterone levels should be suppressed to attain a normal response has been arbitrarily set and varies widely from 5 to 15 ng/dL or µg/24h, respectively, producing non-comparable results, which may also be influenced by pre-test conditions such as patient's hydration status, sodium ingestion, posture, time of sampling, stress, and use of medications. In addition, reproducibility of these suppression tests has not been systematically investigated.

Therefore, a segment of the hypertensive population defined as non-aldosterone suppressors by one of these tests (and thus considered PA) may in fact represent somewhat resistant LREH. Conversely, a number of IHA patients may suppress aldosterone levels below the arbitrary limit and thus be considered LREH. This must have been the case in some of our "IHA" and "LREH" patients (figure 3).

Low renin levels are seen in approximately 20% of the hypertensive population worldwide. In these LREH patients, aldosterone is usually normal but inappropriately elevated for the renin level and this may pose a problem in the differential diagnosis with IHA, especially when aldosterone levels are increased. However, labeling LREH as IHA may not be important and implies only the addition or switch to aldosterone receptor antagonists (spironolactone or eplerenone) as a therapeutic strategy. This may in fact be appropriate and useful since the low-renin state may reflect increased MCH activity (not necessarily aldosterone excess) (41-45), that has been shown both in experimental animals and in man (34) to be deleterious to myocardial plasticity and function. On the other hand, misdiagnosing IHA as LREH would preclude such patients from specific treatment if an anti-MCH agent is not considered, leaving them overexposed to aldosterone excess.

Thus, if one agrees for therapeutic purposes that IHA and LREH may be stages of a disease continuum (the non-tumorous low-renin hypertension syndrome) (12,13,40,46,47) it seems conceivable that a MCH receptor antagonist should be considered at least as part of their treatment, regardless of he/she being diagnosed as IHA or LREH.

The search for an APA among the low-renin hypertensive patients with an increased ARR is critical (48). Using the combination of higher cutoff levels for both the ARR (≥100) and the PAC (≥20) would significantly increase the positive prediction for and APA among patients with the low renin hypertension syndrome. At present, missing an APA by current imaging techniques in an otherwise biochemically typical case would be extremely unusual. If it happens, selective adrenal vein sampling (AVS) is imperative (26). When lateralization is documented (with contralateral suppression of aldosterone production) the presence of an occult adenoma may be considered and the gland excised. Based on the present findings it must be emphasized that marked elevations of the ARR and PAC is typical of an APA, and an AVS is mandatory if adrenal imaging is negative. This must have been the case in 4 of our IHA patients which were clearly outliers in the ARR x PAC diagram (figure 3) and in whom an APA could have been missed by former less-accurate generation imaging techniques and in whom AVS was not performed. If there is no clear-cut lateralization the alternate diagnosis of "primary hyperplasia" must be entertained (49). Because "primary hyperplasia" (a subset of IHA that responds biochemically as an APA) also responds to surgical reduction of adrenal mass, subtotal adrenalectomy is indicated (49). Post-surgical treatment with anti-MCH may nevertheless be necessary to control blood pressure.

Easier than missing an adrenal lesion is the occasional finding of adrenal nodules in an otherwise biochemically typical IHA. Bilateral adrenal hyperplasia (IHA) may occasionally be associated with the presence of one or more small or large nodules. Although a multinodular adrenal hyperplasia will not impose any special care, the presence of a single or predominant larger nodule may be tempting for the surgeon. Different from the occasional APA that behaves biochemically as an IHA (angiotensin-responsive APA) and will certainly benefit from adrenalectomy, an otherwise typical IHA will not need surgery, even when a large nodule is present.

In summary, using the combined ROC-defined cutoff points of 27 for the ARR and 12ng/dL for PAC, we were able to discriminate patients with primary aldosteronism (APA and IHA) from those with essential hypertension (LREH and NREH) with 89.8% sensitivity and 98.2% specificity. Since patients with an APA ("the wheat") are the sole ones who will benefit from surgery, they could be identified (positive

predictive value of 90%) and separated from other causes (IHA and LREH, "the chaff") of the low-renin hypertension syndrome using a higher combined cut-off values for the ARR (≥100) and PAC (≥20). However, imaging procedures and adrenal vein sampling for aldosterone measurements must be used for confirmation. The remaining patients (IHA and LREH) may not need an accurate discrimination and should be treated with a MCH-receptor antagonist, either alone or in combination with additional therapy. However, one can anticipate that indiscriminate and widespread use of such agents will hamper the possibility of a definite diagnosis in previously undetected patients with an APA.

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Address correspondence to:

Claudio E. Kater
Laboratório de Esteróides
Disciplina de Endocrinologia, Depto. de Medicina
Universidade Federal de São Paulo - UNIFESP
Rua Pedro de Toledo, 781 – 13º. Andar
04039-032 São Paulo, SP
e.mail: kater@endocrino.epm.br