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ORIGINAL PAPER

The aldosterone to renin ratio in the evaluation of patients with incidentally detected adrenal masses

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Abstract Incidentally discovered adrenal masses are diagnosed with increasing frequency, especially among patients with hypertension. Thus, a reliable screening test for primary hyperaldosteronism (PA) is essential to avoid unnecessary diagnostic procedures to this population. The aim of the present study is the evaluation of aldosterone to renin ratio (ARR), using plasma renin concentration, in the diagnostic algorithm of patients with adrenal incidentaloma. A total of 123 individuals were studied: 17 patients with proven PA (age 55.5 ± 1.4 years), 27 patients with nonfunctioning adrenal incidentaloma (age 60.3 ± 1.8 years, 14 hypertensives and 13 normotensives) and 79 control subjects (age 58.7 ± 1.4 years, 27 hypertensives and 52 normotensives). A receiver operating characteristic (ROC) analysis disclosed that an ARR ≥32 combines a sensitivity of 100% with a specificity of 96.2% for the diagnosis of PA. No difference in ARR between hypertensive and normotensive individuals harbouring an adrenal incidentaloma and hypertensive and normotensive controls was found. Patients with adrenal incidentalomas with subtle glucocorticoid hypersecretion demonstrated similar ARR compared to patients with normal cortisol secretion. In conclusion, ARR is reliable for the exclusion of PA in patients with adrenal incidentalomas. Furthermore, subtle aldosterone hypersecretion, as indicated by increased ARR, in patients with adrenal incidentalomas is not associated with the presence of hypertension or subtle glucocorticoid hypersecretion.

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Introduction

Incidentally discovered adrenal masses (adrenal incidentalomas) are defined as accidentally discovered, clinically silent adrenal lesions present on abdominal imaging that has been performed for reasons other than suspected adrenal disease [1]. Due to the increased use of imaging for diagnostic purposes adrenal incidentalomas have become a growing clinical problem [1]. The prevalence of adrenal incidentaloma approaches 3% in middle age, and increases to as much as 10% in the elderly [2]. Although most adrenocortical masses are nonfunctioning adenomas, 5–47% produce cortisol and 1.6–3.3% mineralocorticoids [3–5]. In clinical practice, it is essential to separate the incidentalomas that need intervention, i.e. hormone secreting and malignant tumours, from the majority of incidentalomas that are benign, non-hyperfunctioning lesions and that can be left untreated. Available evidence suggests that a dexamethasone suppression test [5–7] and determination of fractionated urinary or plasma metanephrines [1, 2, 5] should be performed for the diagnosis of glucocorticoid secreting adenomas and pheochromocytomas respectively.

The serum aldosterone/plasma renin ratio is a useful screening tool for the diagnosis of disorders of autonomous mineralocorticoid hypersecretion [8, 9]. However, several questions about the sensitivity and the specificity of this test have been raised [10]. An abnormal high ratio may be present in patients with low plasma renin concentration, despite normal aldosterone levels [11]. Also, the diurnal and postural variation of aldosterone secretion, and a

variety of drugs (diuretics, b-blockers), can lead to different ratio readings [12, 13]. Finally, in most published series [4, 14–16] plasma renin activity (PRA) and not plasma renin has been measured. PRA is based on the measurement of angiotensin I generated from angiotensinogen during in vitro incubation with plasma renin, a method influenced by many conditions such as hepatic or cardiac disease, drugs such as estrogens, processing of plasma samples, incubation time, pH [17, 18] and thus this assay is very difficult to be standardized.

Our study was therefore designed to assess the value of aldosterone to renin ratio (ARR), using plasma renin measurements, in the evaluation of secretory profile of adrenal incidentalomas.

Subjects and methods

Subjects

We studied 44 patients (29 females, 15 males) who presented with adrenal incidentaloma in our endocrine clinic during the last 2 years. Inclusion criteria for these patients were: (1) adrenal mass discovered by a CT scan of the abdomen; (2) imaging features of the mass typical for adrenal adenoma (homogenous, smoothly marginated) (3) tumour size <5 cm, to minimize the possibility of malignancy; (4) negative biochemical screening for pheochromocytoma or Cushing's syndrome; (5) no medication known to interfere with endocrine function. Patients were advised to discontinue diuretics and spironolactone for 6 weeks, and beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers for 2 weeks prior to the evaluation. If antihypertensives could not be stopped completely, the above medications were replaced with calcium channel blockers or central-acting (moxonidine) antihypertensives.

All patients underwent standard evaluation under ambulatory conditions, for hormonal hypersecretion according to a defined protocol. This included a combination of serum aldosterone and plasma renin measurements (blood sampling at 0900 h after overnight fast) to determine aldosterone to renin ratio (ARR), a saline suppression test, and a standard low dose dexamethasone suppression test (LDDST). For the saline suppression test, patients attended the clinical investigation unit on the day of testing at approximately 0900 h. Blood was sampled after 30 min and again after infusion of 2 l of normal saline over 4 h. Adequate suppression was defined as a decrease in postsaline aldosterone level to less than 50 pg/ml [19]. For the LDDST dexamathasone 0.5 mg was administered orally every 6 h for 2 days and serum cortisol was measured at 08:00, 48 h after the first dose [20]. Adequate suppression was defined by cortisol levels post LDDST of 2.5 μg/dl [2, 6, 7], while patients not fulfilling this criterion were diagnosed as having subtle autonomous glucocorticoid hypersecretion (SAGH).

After this evaluation, the patients were classified into two groups. Seventeen patients, nine men and eight women, mean age 55.5 ± 1.4 years, were diagnosed with primary hyperaldosteronism (PA) based on the following criteria: (1) hypertension (as defined by repeated systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least 90 mmHg; (2) repeatedly low renin in the presence of high normal or elevated aldosterone; (3) positive confirmatory test (failed suppression of serum aldosterone after saline infusion); (4) response to surgery or spironolactone treatment (improvement of blood pressure—when BP decreased to 140/90 mmHg or less); (5) histological confirmation of diagnosis in all patients (n = 10) who underwent unilateral adrenalectomy. Twenty seven patients, (six men, 21 women, mean age 60.3 ± 1.8 years), had nonfunctional adrenal incidentalomas. In this group, 14 patients were hypertensive and 13 were normotensive.

The control group consisted of 79 individuals (12 men, 67 women, mean age 58.7 ± 1.4 years) with normal imaging of the adrenal glands on abdominal ultrasound or CT performed for reasons other than suspected adrenal disease. Twenty seven members of this group were hypertensive and the other 52 were normotensive. If antihypertensives could not be stopped completely in the hypertensive individuals, they were replaced with calcium channel blockers or central-acting antihypertensives. None of the participants had confounding conditions such as congestive heart failure, hepatic cirrhosis, nephrotic syndrome, renal impairment or other secondary causes of hypertension. Blood samples were drawn from these individuals for serum aldosterone and plasma renin at 0900 h after an overnight fast, to determine the aldosterone to renin ratio (ARR).

The study is consistent with the principles of the Declaration of Helsinki, was approved by the Ethical Committee of our institution, and written informed consent was obtained from all individuals.

Hormone measurements

Serum aldosterone concentration was measured using a commercial RIA kit (Diagnostic Systems Laboratories, Inc, Webster TX, USA), with a normal range of 29.4–161.5 pg/ml in the supine position, and 38.1–313 pg/ml in the upright position. Assay sensitivity was 21.2 pg/ml. The intrassay coefficient of variation was 3.3%, 4.5% and 3.9% at an aldosterone concentration of 66 pg/ml, 118.7 pg/ml and 494.5 pg/ml respectively.

Plasma renin was measured in EDTA-plasma using a commercial IRMA kit (Diagnostic Systems Laboratories, Inc, Webster TX, USA), with a normal range of 3.0–33 μU/ml in the supine position, and of 5.0–50.0 μU/ml in the upright position. The assay sensitivity was <0.7 μU/ml and the intraassay coefficient of variation of 1.63%, 1.31% and 0.92% at a renin concentration of 9.8 μU/ml 99.5 μU/ml and 254 μU/ml respectively. The aldosterone to renin (ARR) ratio was expressed as the value of serum aldosterone (pg/ml) divided by plasma renin (μU/ml).

Serum cortisol was measured by an automated chemiluminescence system (ACS:180 cortisol assay, Bayer Tarrytown, NY, USA) with a sensitivity of 0.19 μg/dl and intraassay coefficient of variation of 8.0%, 6.4% and 9.2% at a cortisol concentration of 5.4, 14.8, and 31.7 μg/dl respectively.

Statistics

Group data are presented as the mean ± SEM. Comparisons between the three groups were performed with one way ANOVA on the ranks followed by Dunn's test for comparisons between means. Analysis for differences between hypertensive and non-hypertensive patients and patients with SAGH or not was performed by Mann Whitney rank sum test.

Receiver operating characteristic (ROC) curves were constructed to examine the diagnostic accuracy of serum aldosterone, plasma renin and ARR—that is the ability of these parameters to discriminate between patients with PA or not. Sensitivity (true positive rate) against 1-specificity (false positive rate) was plotted at each level, and the area under the curve was computed by the nonparametric Wilcoxon statistic [21]. Area under the curve represents the probability of correctly identifying patients with primary hyperaldosteronism. The statistical analysis, the area under the curve (AUC) for the receiver-operating-characteristics (ROC) curves and the cutoff values were performed using the SPSS for Windows statistical package (version 10.0; SPSS, Inc., Chicago, IL). Two-tailed *P*-values <0.05 were considered significant.

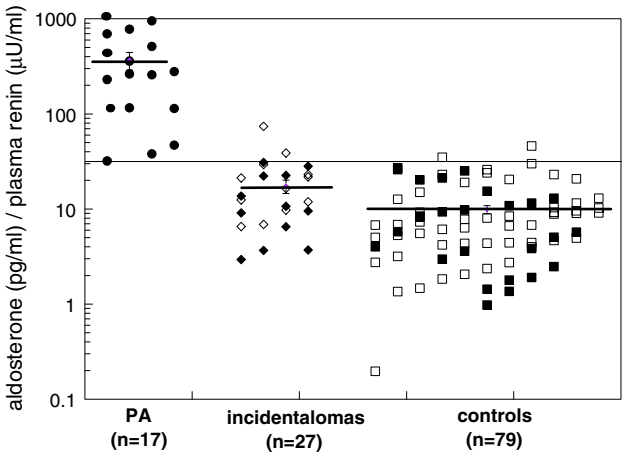

Fig. 1 Individual data of the ARR in the three groups The solid horizontal lines indicate mean value of ARR of each group. The dashed horizontal lines indicate the cutoff value of ARR for the diagnosis of PA

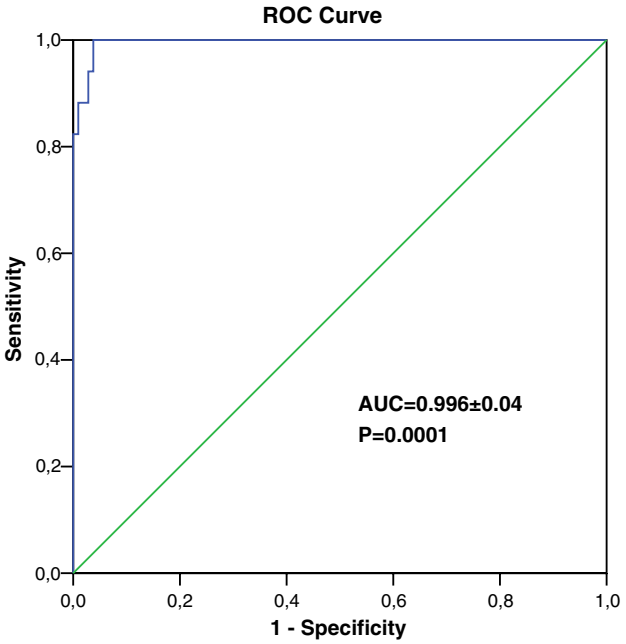

Fig. 2 ROC curve of the ARR in the diagnosis of PA. AUC = area under the curve

Results

Specificity and sensitivity of ARR as a marker of autonomous aldosterone hypersecretion

As expected, ARR was significantly higher in patients with PA compared to patients with nonfunctional incidentalomas and controls (366.53 ± 78.2 vs 17.3 ± 2.9 and 9.88 ± 0.98 pg/ml per μU/ml respectively). However as shown in Fig 1, individual ARR values were somewhat overlapping between the three groups and thus we proceed to ROC analysis to define the ARR value that best discriminated the patients with PA.

On the analysis of the coordinate points of the ROC curve, ARR presented the best discriminatory ability for the diagnosis of PA (Fig. 2, AUC = 0.996, *P* = 0.000, 95% CI 0.988–1.003), compared to serum aldosterone (AUC = 0.928 (*P* = 0.000), 95% CI 0.873–0.984) and plasma renin levels (AUC = 0.951 (*P* = 0.000), 95% CI 0.912–0.991). A cutoff of ARR value of ≥32 combines a sensitivity of

Table 1 Coordinates of the ROC curve

ARR	Sensitivity	1—Specificity
5.054	1.000	.717
10.025	1.000	.377
12.176	1.000	.311
12.573	1.000	.302
12.846	1.000	.292
15.232	1.000	.245
15.947	1.000	.236
20.393	1.000	.208
20.691	1.000	.198
25.706	1.000	.104
26.375	1.000	.094
26.828	1.000	.085
28.649	1.000	.075
30.667	1.000	.066
31.272	1.000	.057
31.446	1.000	.047
31.756	1.000	.038
32.711	.941	.038
35.776	.941	.028
38.496	.882	.028
42.444	.882	.019
46.627	.882	.009
60.802	.824	009
90.900	.824	000
110.753	.765	000
115.475	.706	000
173.448	.647	000
244.057	.588	000

The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values

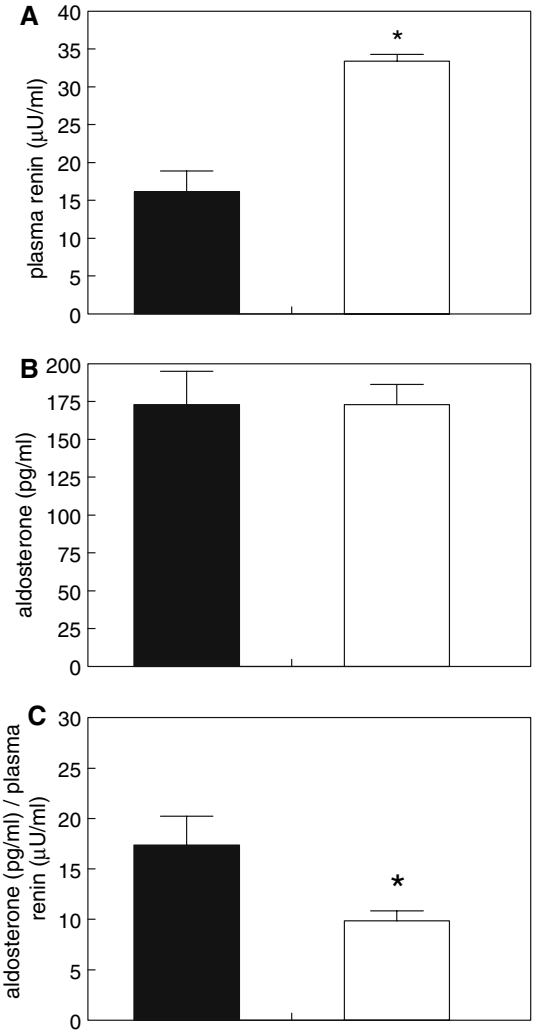

Fig. 3 Comparison of renin, aldosterone and ARR ratio between patients with incidentalomas (■) and controls (□)

100% with a specificity of 96.2% for the diagnosis (Table 1). Using this cutoff the negative predictive value was 100%, the positive predictive value 81% and the diagnostic accuracy 96.8%. All patients with PA fulfilled this criterion, and 102 of the remaining 106 subjects (96.2%) were below this ratio. Thus, four subjects (3.7%), two with incidentaloma and two controls, were falsely classified as having PA (Fig 1). Raising the ARR cutoff value to 75 improved the specificity to 100.0% at the cost of a loss of sensitivity to 82.4%, so all subjects with incidentalomas and controls (n = 106) and also three of the 17 of patients with PA (17.6%), were below this ratio, therefore falsely classified as non PA.

An aldosterone cutoff value of ≥180 pg/ml combines a sensitivity of 100% with a specificity of 65.1% for the diagnosis of PA. However, the combination of two criteria, i.e. an ARR ≥32 plus an aldosterone level ≥180 pg/ml, improves the diagnostic accuracy without compromising sensitivity, (diagnostic accuracy 99.2%, sensitivity 100%, specificity 99.1%, false positive rate 0.9%, false negative rate 0%, negative predictive value 100%, positive predictive value 94.4%). Thus, all patients with PA fulfilled this criterion, and only one subject of the control group was falsely classified as having PA.

Subtle aldosterone hypersecretion in adrenal incidentalomas

We used the ARR as a tool to test the hypothesis of subtle aldosterone hypersecretion in patients with apparently nonfunctional adrenal incidentalomas. We found that patients with incidentalomas demonstrated significantly lower renin levels from controls (16.11 ± 2.8 and 33.3 ± 5.0 μU/ml respectively, P = 0.001, Fig. 3a) and

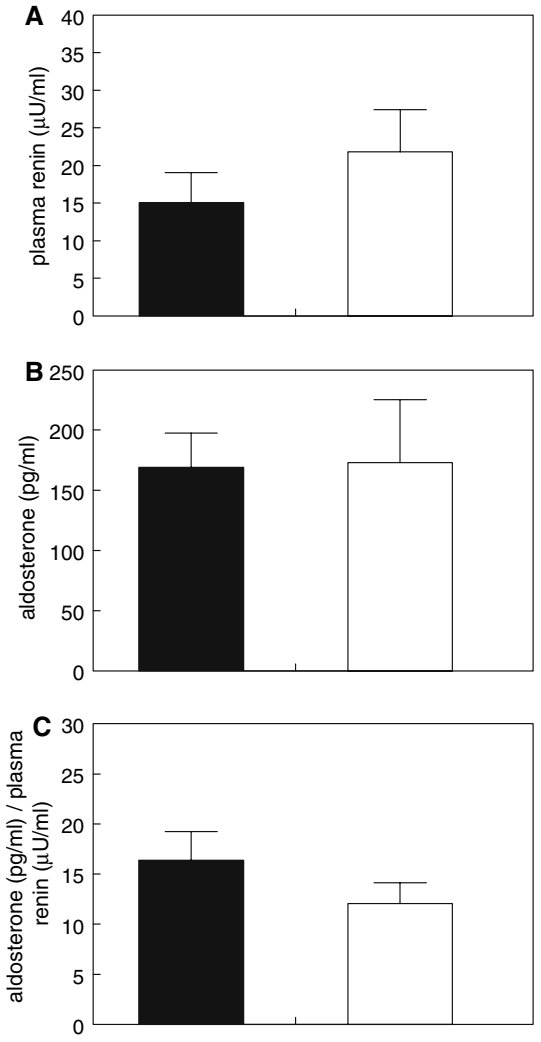

Fig. 4 Comparison of renin, aldosterone and ARR ratio between the two subgroups of patients with incidentalomas, with (■) or without (□). subtle autonomous glucocorticoid hypersecretion

higher ARR values (17.3 ± 2.9 and 9.88 ± 0.9 respectively $P = 0.002$, Fig. 3c). No differences of ARR between hypertensive and normotensive individuals neither in patients with incidentalomas nor in control individuals were noted (Fig 3b).

Subtle aldosterone hypersecretion in adrenal incidentalomas with SAGH

To examine the co-existence of subtle aldosterone hypersecretion and SAGH in patients with adrenal incidentaloma we divided patients with incidentalomas into two subgroups, according to the results of LDDST. Fifteen patients demonstrated an adequate suppression of cortisol levels (<2.5 μg/dl). Twelve patients failed to suppress (cortisol levels post LDDST >2.5 μg/dl) and were therefore diagnosed with SAGH. Statistical analysis disclosed no differences between the two subgroups in plasma renin levels, serum aldosterone and ARR (Fig. 4)

Discussion

With the extensive use of imaging techniques adrenal incidentalomas have become a common problem [1]. In response, validated and cost-effective tools are needed to exclude hormonal hypersecretion from the tumour and to avoid delays in diagnosis and therapeutic interventions.

In the present study, we have shown that ARR is a reliable screening tool to identify aldosterone hypersecretion in patients with adrenal incidentaloma evaluated in ambulatory conditions, after discontinuation of all antihypertensive medications except calcium channel blockers or central-acting antihypertensives. It has been shown that calcium channel blockers such as amlodipine, can be safely used if necessary to control blood pressure [5] as they result only in a very small percentage of false-negative diagnoses for PA by lowering ARR [22]. We calculated that a ARR value of ≥32 has a sensitivity of 100% with a specificity of 96.2% and a diagnostic accuracy 96.8% for PA. ARR presented superior discriminatory ability for the diagnosis of PA as compared with its two individuals determinants (i.e. to serum aldosterone and plasma renin levels).

Although the ARR is used from many years to screen hypertensive patients for PA, there is a wide range of diagnostic cutoff values, with varying sensitivity and specificity, probably due to protocols differing in terms of posture (upright or supine), discontinuation of the antihypertensive drugs and diet. Hiramatsu et al. [9] were the first to use ARR to screen for PA. They have reported that a cutoff ARR value of 40 offers a good discrimination between essential hypertension and PA [9]. Bernini et al. have studied 125 normokalemic patients with adrenal incidentalomas and 89 patients with essential hypertension, after discontinuation of antihypertensive treatment. They used an ARR cutoff of 112 (representing the 95% upper confidence limit of normal values) and they reported six false positives for PA [4]. In another study from Japan [14], a cutoff ARR of 35 was used and interestingly no differences in ARR were described between patients evaluated as outpatients under antihypertensives (except diuretics) and hospitalized patients without treatment (except Ca channel blockers). By contrast, other investigators demonstrated that ARR, although superior to aldosterone or plasma renin activity as diagnostic test for PA, is significantly affected by medication [23], posture and time of the day during sampling [16].

All but one of the above studies used plasma renin activity (PRA) determinations and not direct plasma renin levels to calculate ARR. PRA is based on the measurement of angiotensin I generated from angiotensinogen during in vitro incubation with plasma renin, a method influenced by many factors (decreased angiotensinogen levels in hepatic cirrhosis, type 1 diabetes mellitus, severe cardiac failure and increased angiotensinogen levels during estrogen treatment, which often leads to lower renin levels in order to keep PRA close to constant.) [17, 18], resulting in variability of results. Furthermore, direct plasma renin measurements show good inter-laboratory reproducibility, due to calibration against a WHO standard, while PRA determination is strongly influenced by the assay conditions (incubation time, pH and dilution methodology), leading to lack of standardization [24].

As already demonstrated [24], the aldosterone to PRA ratio is higher than the aldosterone to plasma renin ratio, and this may explain the higher than ours cutoff ARR values in all of the abovementioned studies. Another explanation for the lower ARR cutoff in our study is that all our patients had normal potassium levels, thus showing a mild form of PA [25], which today, has become the most common presentation of the disease [4, 26–28] making the differential diagnosis between PA and essential hypertension very challenging. We estimate that our data have an additional value as they propose a sensitive and specific tool to confront this diagnostic problem. In one of the very few studies using plasma renin levels that have been published, Schirpenbach et al. [29] reported good diagnostic accuracy for an ARR of >21, (but determined by the mean + SD of normotensive subjects and not by ROC analysis as in our study).

It has been suggested [8, 30] that due to low specificity a positive result by ARR has to be followed by a confirmatory test, *iv* saline suppression being the most widely used. Unger et al. [24] achieved better specificity by using a combination of ARR with a threshold value of 62 and plasma aldosterone >200 pg/ml, in patients with adrenal mass. The combined use of ARR and aldosterone levels as screening criteria has also been advocated by the last NIH conference on adrenal incidentalomas [1] and by others [8, 31]. Similarly to our study, Unger et al. [24] have measured plasma renin but the assay used had quite a lower normal range in upright position blood sampling (2.1–2.6 ng/l) than ours, and this may be responsible for the higher ARR cutoff levels in their study. Furthermore, their patients were on various antihypertensive medications, that may increase aldosterone levels [8, 23] and they did not exclude from their analysis patients harbouring pheochromocytoma and cortisol secreting adenoma [24]. Although in our cohort ARR specificity was very good (96.2%) for a cutoff of ARR >32, we improved specificity to 99.1%, by considering aldosterone levels >180 pg/ml, and thus we had only one false positive diagnosis of PA. However, as individuals in our control group did not undergo saline infusion testing, specificity may not be measured accurately in this study.

We also demonstrated that ARR values were statistically higher in patients harbouring an adrenal incidentaloma, compared to controls. It has been shown a higher prevalence of hypertension in patients with adrenal incidentaloma [32, 33] suggesting a possible pathogenetic link. Our finding may lead us to assume the presence of a slight degree of autonomously produced aldosterone from the adrenal incidentalomas. As no difference in ARR between patients with and without subclinical cortisol production from the adrenal mass was disclosed in our study, it seems that subtle hypersecretion of glucocorticoids and mineralocorticoids do not coexist in the same adrenal mass, indicating the different (monoclonal) origin of these tumours. However, few cases of adrenal tumours secreting both cortisol and aldosterone in patients with PA or Cushing's disease have been reported [34, 35].

In conclusion, we have shown that ARR is a reliable screening tool to identify autonomous aldosterone hypersecretion in patients with adrenal incidentaloma under ambulatory conditions and using calcium channel blockers or central-acting antihypertensives to control blood pressure if needed. A ARR <32 excludes the presence of PA, and thus no further evaluation of these patients is necessary.

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