

Screening for primary aldosteronism in an argentinian population: a multicenter prospective study

Mariela Leal Reyna¹, Reynaldo M. Gómez², Susana N. Lupi³, Susana H. Belli⁴, Cecilia A. Fenili⁵, Marcela S. Martínez⁶, Gabriela F. Ruibal⁷, María A Rossi², Raúl A Chervin², Dora Cornaló⁸, Liliana N. Contreras⁹, Liliana Costa¹⁰, María T. Nofal¹¹, Sergio A. Damilano⁵, Ester M. Pardes³

¹ Complejo Médico Churrucavísca, Ciudad Autónoma de Buenos Aires, Argentina
² Hospital de Clínicas José de San Martín, Ciudad Autónoma de Buenos Aires, Argentina
³ Hospital JM. Ramos Mejía, Ciudad Autónoma de Buenos Aires, Argentina
⁴ Hospital C. Durand, Ciudad Autónoma de Buenos Aires, Argentina
⁵ Laboratorio Bioanalítica, Ciudad Autónoma de Buenos Aires, Argentina
⁶ Hospital C. Milstein, Ciudad Autónoma de Buenos Aires, Argentina
⁷ Hospital T. Alvarez, Ciudad Autónoma de Buenos Aires, Argentina
⁸ Hospital B. Rivadavia, Ciudad Autónoma de Buenos Aires, Argentina
⁹ Instituto de Investigaciones Médicas Dr. A. Lanari, Ciudad Autónoma de Buenos Aires, Argentina
¹⁰ Hospital A. Posadas (Provincia de Buenos Aires), Argentina
¹¹ Clínica Bazterrica, Ciudad Autónoma de Buenos Aires, Argentina

ABSTRACT

Objectives: Primary aldosteronism (PA) is characterized by the autonomous overproduction of aldosterone. Its prevalence has increased since the use of the aldosterone (ALD)/plasma renin activity (PRA) ratio (ARR). The objective of this study is to determine ARR and ARC (ALD/plasma renin concentration ratio) cut-off values (COV) and their diagnostic concordance (DC%) in the screening for PA in an Argentinian population. Design: multicenter prospective study. **Subjects and methods:** We studied 353 subjects (104 controls and 249 hypertensive patients). Serum aldosterone, PRA and ARR were determined. In 220 randomly selected subjects, 160 hypertensive patients and 60 controls, plasma renin concentration (PRC) was simultaneously measured and ARC was determined. **Results:** According to the 95th percentile of controls, we determined a COV of 36 for ARR and 2.39 for ARC, with ALD \geq 15 ng/dL. In 31/249 hypertensive patients, ARR was \geq 36. PA diagnosis was established in 8/31 patients (23/31 patients did not complete confirmatory tests). DC% between ARR and ARC was calculated. A significant correlation between ARR and ARC ($r = 0.742$; $p < 0.0001$) was found only with PRA $>$ 0.3 ng/mL/h and PRC $>$ 5 pg/mL. DC% for ARR and ARC above or below 36 and 2.39 was 79.1%, respectively. **Conclusion:** This first Argentinian multicenter study determined a COV of 36 for ARR and 2.39 for ARC. Applying an ARR \geq 36 in the hypertensive group, we confirmed PA in a higher percentage of patients than the previously reported one in our population. As for ARC, further studies are needed for its clinical application, since DC% is acceptable only for medium range renin values. Arch Endocrinol Metab. 2015;59(5):441-7

Keywords

Aldosterone/plasma renin ratio; primary aldosteronism; essential hypertension; screening; multicenter study

Correspondence to:

Ester Matilde Pardes
 División Endocrinología,
 Hospital JM Ramos Mejía
 General Urquiza, 609
 Ciudad Autónoma de Buenos Aires
 (1221), Argentina
 epard2003@yahoo.com.ar

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INTRODUCTION

Primary aldosteronism (PA) described by Jerome Conn in 1955 (1) is a relatively common curable cause of hypertension (HT). Since Hiramatsu and cols. reported that the aldosterone (ALD)/plasma renin activity (PRA) ratio (ARR) showed a higher sensitivity for detecting PA (2), various research groups applied ARR to detect PA in essential hypertensive patients, independently of the potassium levels. Thus, PA prevalence increased to a mean of 7.8% -higher than the 1% historically reported one in hypokalemic hypertensive patients (3). Furthermore, recent studies have reported the ALD/plasma renin concentration (PRC) ratio as an alternative method of screening (4,5).

We performed a prospective multicenter study in order to determine firstly the cut-off value (COV) for ARR in our population as a screening test for PA in hypertensive patients, regardless of the potassium le-

vel (6). Additionally, in a randomly selected subgroup, PRC was simultaneously measured. The aim of this paper is to present our results, to determine the ALD/PRC ratio (ARC) and to compare ARR and ARC in order to assess the possible clinical application of ARC by calculating the diagnostic concordance (DC%) between both ratios.

SUBJECTS AND METHODS

We performed a prospective multicenter study at the Adrenal Department of the Argentine Society of Endocrinology and Metabolism, comprising 10 hospitals of Buenos Aires. Four hundred and forty subjects of both sexes were recruited in a three-year period. Eighty-seven subjects were excluded due to heart, liver or kidney failure, chronic neuropathy, Cushing's syndrome, glucocorticoid therapy, hyperthyroidism, untreated

hypothyroidism, hypercalcemia, diabetes mellitus, secondary HT, hormone replacement therapy or missing data. The remaining 353 subjects were divided into two groups: 1) Controls: 104 subjects (68 females and 36 males), aged 16 to 77 years old, with blood pressure (BP) measurements \leq 139/85 mmHg and no first-degree family history of HT. 2) Hypertensive group: 249 patients (193 females and 56 males), aged 17 to 76 years old, with BP measurements \geq 140/90 mmHg.

In both groups, the following data was obtained: waist circumference, weight, height, body mass index (BMI) and sitting BP, which was measured on three different days. Serum levels of sodium, potassium, calcium, urea, creatinine, cholesterol, LDL-C, HDL-C, triglycerides, ALD and PRA were determined. Waist circumference less than 102 cm in males and 88 cm in females was considered normal. Hypokalemia was defined as serum potassium concentration $<$ 3.5 mEq/l.

PRC was simultaneously measured in a subgroup of 220 randomly selected subjects, 60 controls (52 females and 8 males) and 160 hypertensive patients (111 females and 49 males).

Approval was obtained from each hospital ethical committee. Informed consent was obtained from all subjects.

Preanalytical conditions

Preanalytical conditions were unified and samples were processed in a single laboratory.

Prior to performing baseline sample collection, unrestricted sodium diet was indicated for seven days and potassium was added if needed. Treatments that strongly interfere with the renin-angiotensin system were not allowed; the washout period was 15 days for beta-adrenergic blockers, angiotensin II receptor blockers (ARBs) and diuretics and 6 weeks for spironolactone. α -adrenergic blockers, angiotensin converting enzyme inhibitors (ACE-I) and calcium channel blockers (CCBs) were allowed.

Fasting blood samples were drawn from subjects seated for 15 minutes and after at least 2 hours of upright posture between 8.00 and 9.00 AM. Serum samples were used for ALD and PRC and clinical chemistry determination while Na₂-EDTA treated plasma samples, obtained by centrifugation at 4°C and intended for PRA measurement, were immediately frozen at -20°C until assayed. Each aliquot was thawed once. In all cases, lipemic and/or hemolyzed samples were excluded.

Assay methods and measurements

ALD was measured by a solid-phase RIA (DPC), with a functional sensitivity of 2 ng/dL (20 pg/mL) and intra- and interassay precision of 5.4% and 15.7%, respectively. Reference range for an ambulatory individual on a normal sodium diet and in an upright position: 4-30 ng/dL (40-300 pg/mL).

PRA was measured by a solid-phase RIA (DIA SO-RIN) that measures angiotensin I (AT I) generated *in vitro*, as described by Sealey (7), with an analytical sensitivity of 0.018 ng AT/tube, and an intra- and interassay precision of 10%.

PRC was measured by a solid-phase IRMA DSL (Diagnostic Systems Laboratories) with an analytical and functional sensitivity of 0.36 and 5.0 pg/mL, respectively, and an intra- and interassay precision of 10%. This method has been standardized against the second reference standard IRP 68/356.

The upper limit of the reference range in ambulatory subjects on a normal sodium diet and in an upright position is 3.3 ng/mL/h for ARP and 65 pg/mL for PRC.

The ARR [ALD (ng/dL)/PRA (ng/mL/hour)] and the ARC [ALD (ng/dL)/PRC (pg/mL)] were calculated in hypertensive patients, ARR values were considered suspicious for PA only with ALD \geq 15 ng/dL, in agreement with other authors (8,9).

Fludrocortisone suppression tests (FST) or saline infusion tests (SIT) were used to confirm PA, according to each participating center. In the FST, ALD was measured at baseline and at 10.00 AM on the fifth day after administration of fludrocortisone (0.1 mg every 6 hours for four days on an unrestricted sodium diet) and in the SIT, ALD was measured after a 4-hour infusion of two liters of saline solution (0.9%). PA was confirmed with ALD levels above 6 ng/dL in the FST (10) and above 7 ng/dL in the SIT (11). In all PA patients, adrenal computed tomography was obtained, and in two of them (1 adenoma and 1 hyperplasia) adrenal venous catheterization was performed (9).

Diagnostic concordance assessment (DC%)

Since PRC measures renin mass concentration and PRA estimates renin enzymatic activity and their results are expressed in different units, both values cannot be directly compared. Therefore, we calculated the DC% in order to determine if the results obtained by both methods (ARR and ARC) are comparable or provide,

at least, the same diagnostic information. DC% is the percentage obtained from adding the concordant results below (A) and above (B) the COV for ARR and ARC, respectively, divided by the total number of results (concordant and discordant) multiplied by 100:

$$DC\% = \{(A+B) / \text{total } N^{\circ} \text{ of results}\} \times 100.$$

Statistical analyses

Normality of variables was analyzed with the Shapiro-Wilks test. Comparisons were made by the non-parametric Wilcoxon test. Differences between control subjects, essential hypertensive patients and PA hypertensive patients were compared by a non-parametric variance analysis using the Kruskal Wallis test; for post-hoc comparisons, the Conover method was used. The relationship between variables was analyzed using the non-parametric Spearman coefficient of correlation (ρ) and its corresponding test to determine whether the correlation is significantly different from zero. Significance was set at $p < 0.05$.

In order to calculate the cut-off values for ARR and ARC, the Collings and Hamilton method and/or the determination of the 95th percentile were used.

RESULTS

Control subjects had a mean age lower than hypertensive patients (45.2 ± 13.8 vs. 51 ± 13.6); however, the median (47 vs. 53 years) and the range (16-77 vs. 17-76 years) were similar. Both BMI and waist circumference were significantly higher in hypertensive subjects than in controls ($p < 0.0001$). Hypertensive subjects had a significantly higher serum concentration of creatinine ($p = 0.0001$), total cholesterol ($p = 0.0165$), LDL-C ($p = 0.0344$) and triglycerides ($p < 0.0001$), while the HDL-C concentration was significantly lower ($p = 0.0078$). They also had a higher prevalence of metabolic syndrome according to the National Cholesterol Education Program-Adult Treatment Panel III (ATP III) (12). No significant differences were found in blood sodium, glucose or potassium levels (Table 1).

ALD concentrations were similar in both groups, while PRA was significantly lower in hypertensive patients ($p = 0.0036$). Consequently, higher values of ARR were found in hypertensive patients, a finding that reached statistical significance ($p = 0.0002$).

Since the ARR variable did not show a normal distribution, the cut-off value according to the 95th per-

centile was 36.15. If the 95th percentile is calculated by estimating the empirical distribution function using Collings and Hamilton's method, the COV was 35.79. According to both results, the COV for ARR was set at 36 (Figure 1).

Table 1. Clinical and biochemical characteristics of control subjects and hypertensive patients

Variable	Controls n = 104	Hypertensives n = 249	P
Age (years)	45.18 ± 13.78	51.0 ± 13.6	0.0001
Weight (kg)	65.68 ± 16.13	78.0 ± 17.3	< 0.0001
Height (m)	1.61 ± 0.08	1.61 ± 0.09	NS
BMI (weight/height ²)	25.25 ± 5.19	29.9 ± 6.0	< 0.0001
Waist (cm)	83.63 ± 15.32	95.2 ± 15.7	< 0.0001
SBP (mmHg)	114.53 ± 11.16	152.5 ± 19.1	< 0.0001
DBP (mmHg)	73.05 ± 8.03	93.8 ± 11.7	< 0.0001
Creatinine (mg%)	0.82 ± 0.13	0.91 ± 0.19	0.0001
Potassium (mEq/l)	4.26 ± 0.37	4.21 ± 0.49	NS
Sodium (mEq/l)	139.97 ± 3.23	140.8 ± 2.9	NS
Cholesterol (mg%)	202.44 ± 33.86	214.2 ± 39.6	0.0165
HDL cholesterol (mg%)	55.11 ± 12.94	51.2 ± 12.15	0.0078
Triglycerides (mg/dL)	106.33 ± 41.57	143.8 ± 73.2	< 0.0001
LDL cholesterol (mg%)	126.79 ± 30.82	135.9 ± 36.6	0.0344
Blood calcium (mg%)	9.34 ± 0.43	9.33 ± 0.61	NS
Blood glucose (mg%)	92.81 ± 11.56	96.7 ± 8.1	NS
ALD (ng/dL)	16.23 ± 8.78	19.03 ± 14.91	NS
PRA (ng/mL/h)	1.84 ± 1.27	1.54 ± 1.38	0.0036
ARR	12.96 ± 10.23	29.9 ± 59.7	0.0002

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; ALD: aldosterone; ARP: plasma renin activity; ARR: aldosterone/plasma renin activity ratio; NS: not significant. To convert aldosterone from ng/dL to pmol/l, multiply by 27.7. Values are expressed as mean ± standard deviation.

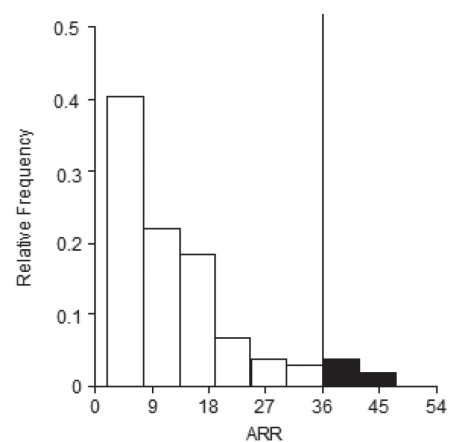


Figure 1. Histogram of aldosterone/plasma renin activity (ARR) values in the 104 controls. The line represents the 95th percentile corresponding to a value of 36.

In 12.45% of hypertensive patients (31/249), the ARR was ≥ 36 with ALD levels ≥ 15 ng/dL. In 8 subjects (4 males and 4 females) confirmation tests were performed, and PA was diagnosed in all cases. The range of post-suppression ALD levels was 12-25 ng/dL. Seven patients had aldosterone-producing adenomas (APA) and the remaining one had idiopathic hyperplasia. Compared to all other hypertensive subjects, PA patients showed higher ALD and ARR values ($p = 0.001$) and significantly lower potassium concentrations ($p = 0.001$). In the PA patients, 7/8 had kalemia < 3.5 mEq/l and 1/8, 3.7 mEq/l (Table 2).

Table 2. Serum concentration of ALD, PRA, ARR and blood potassium in hypertensive patients with primary aldosteronism (PA) and without PA (non-PA)

Variable	non- PA n = 241	PA n=8	p
ALD ng/dL	17.6 \pm 10.07	61.2 \pm 47.9	0.001
PRA ng/mL/h	1.58 \pm 1.38	0.34 \pm 0.33	0.001
ARR	22.3 \pm 26.44	258 \pm 202	0.001
Blood potassium (mEq/l)	4.25 \pm 0.41	2.94 \pm 0.72	0.001

ALD: serum aldosterone; PRA: plasma renin activity; ARR: aldosterone/plasma renin activity ratio. To convert aldosterone from ng/dL to pmol/l, multiply by 27.7. Results are expressed as mean \pm standard deviation.

PA was confirmed in 3.2% of our hypertensive patients but, since the confirmatory diagnostic evaluation could not be completed in the remaining 23 patients with ARR ≥ 36 , the actual prevalence rate cannot be accurately established.

No correlation was found between the severity of HT and ARR either in the hypertensive group as a whole or in the PA patients. Likewise, no correlation was found between ARR levels and systolic and diastolic blood pressure (SBP and DBP, respectively) using the Spearman coefficient of correlation.

In the hypertensive group – with or without PA – no significant differences were found in BMI, waist circumference, SBP and DBP readings, plasma concentrations of HDL-C, LDL-C, triglycerides, cholesterol and glucose.

PRC subgroup

In this subgroup, neither PRA nor PRC showed significant differences between controls and HT. ALD levels were significantly higher in hypertensive patients than in controls (Table 3).

The analysis of the relationship between PRC and PRA, both in the whole group and in the subgroup of hypertensive patients (Spearman ρ), showed a significant

correlation between PRC and PRA only in the 143 patients with PRC values between 5 and 20 pg/mL ($p < 0.001$).

Table 3. Plasma concentration of ALD, PRA, PRC, ARR and ARC in control subjects and in hypertensive patients

Variable	Controls n = 60	Hypertensives n = 160	p
ALD (ng/dL)	14.36 \pm 8.70	19.69 \pm 17.27	0.007
PRA (ng/mL/h)	1.53 \pm 1.12	1.50 \pm 1.33	NS
PRC (pg/mL)	13.92 \pm 11.13	13.25 \pm 13.64	NS
ARR	14.43 \pm 12.50	29.45 \pm 57.39	0.018
ARC	1.39 \pm 1.31	2.28 \pm 3.10	0.001

ALD: aldosterone; PRA: plasma renin activity; PRC: plasma renin concentration; ARR: aldosterone/plasma renin activity ratio; ARC: aldosterone/plasma renin ratio; NS: not significant. To convert aldosterone from ng/dL to pmol/l, multiply by 27.7. Values are expressed as mean \pm standard deviation.

As the ARC variable did not show a normal distribution, the cut-off value according to the 95th percentile was 2.41 when it was directly calculated. If it is calculated by estimating the empirical distribution function using the method proposed above, the COV is 2.39.

In the 220 subjects evaluated, we found a significant correlation between ARR and ARC ($r = 0.742$; $p < 0.0001$) results, which was similar in the control group and in the hypertensive patients – which included 5/8 PA patients.

Even though ARR and ARC are not comparable in absolute values, the percentage of consistent results above or below 36 for ARR and 2.39 for ARC was 79.1%: $[(153+21)/220] \times 100$. Therefore, the DC% between the results of ratios is 79.1% (Figure 2).

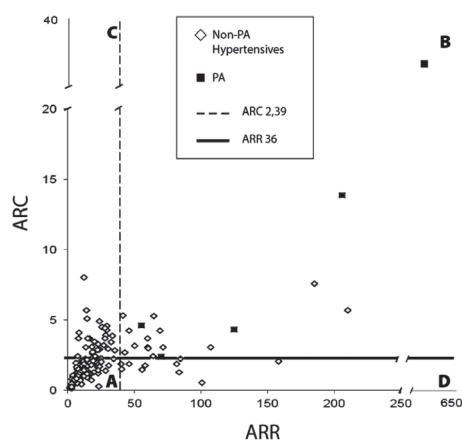


Figure 2. Diagnostic concordance between aldosterone/renin ratio (ARC) and aldosterone/plasma renin activity ratio (ARR). Results in primary aldosteronism (PA) hypertensive patients and non-PA hypertensive patients are shown. Areas A and B represent concordant results; areas C and D represent non-concordant results. (A) Results below the cut-off values (COV) by both methods. (B) Results above the COV by both methods. (C) Results below the COV for ARR and above the COV for ARC. (D) Results above the COV for ARR and below the COV for ARC.

If results are evaluated according to PRA and PRC ranges studied, discordance between ARR and ARC is greater in samples with PRA below 0.3 ng/mL/h and PRC below 5.0 pg/mL than in samples with medium to high levels (Table 4).

Table 4. DC% observed between ARR and ARC results in samples selected according to the levels of PRC or PRA

Selection criterion: ARR and ARC results obtained from samples with:	DC%
PRC < 5 pg/mL	68
PRC > 5 pg/mL	88
PRA < 0.3 ng/mL/h	59
PRA 0.3-3.3 ng/mL/h	86
PRA > 3.3 ng/mL/h	87

DC%: diagnostic concordance; ARR: aldosterone/plasma renin activity ratio; ARC: aldosterone/plasma renin ratio; PRC: plasma renin concentration; PRA: plasma renin activity.

DISCUSSION

In our control group, the cut-off value for ARR was set at 36. ARR may be significantly modified by a decrease in PRA levels, which does not necessarily imply the presence of autonomous ALD secretion; therefore many authors only take into account the ARR value when serum ALD levels exceed a specific concentration (8,9,13). Thus, we required an ALD concentration ≥ 15 ng/dL as a further requisite for applying ARR in our hypertensive patients. According to these criteria, the estimated PA prevalence would be 3.2%, but this percentage is most probably not representative of the true PA prevalence, since confirmatory tests could be performed only in 8/31 patients with ARR ≥ 36 . Unfortunately, 23/31 patients with ARR ≥ 36 did not return to perform these tests – despite being repeatedly called for this purpose. Nevertheless, the percentage we found in our study is still higher than the previously reported one (0.82%) in a population of Buenos Aires, where the screening for PA was based on the criteria of hypertension and hypokalemia (14).

ARR is widely used as a screening test for PA in hypertensive patients. However, its results may be modified by factors such as patient selection, sampling conditions, sample storage and processing, absence of standardized laboratory methods and variations in PRA and ALD due to geographical location and ethnicity (13-18) – leading to difficulties in establishing a universal cut-off value. Thus, published reports show a wide range of ARR cut-off levels – between 20 and 100, although most authors report values between 25 and 40 (3).

PA prevalence ranges from 0.7 to 27% with a mean of 7.8% (3). In agreement with our data, a multicenter study in 1236 unselected hypertensive patients found a prevalence of PA of 3.3% (19).

Although PA prevalence has been reported to increase according to HT severity (20,21), we have not observed a correlation between ARR and higher blood pressure in hypertensive subjects as a whole or in PA patients, in accordance with Bussolengo's findings (22).

In our hypertensive patients, we ensured an adequate sodium and potassium supply before sampling and appropriate washout periods from diuretics, beta-adrenergic blockers, ARBs and spironolactone. Treatment with ACE-I, α -adrenergic blockers and CCBs was allowed, as these drugs have little or no impact on the renin-angiotensin system (23). There is no agreement on this point among different authors. According to clinical practice guidelines, only drugs with minimal or no effects on plasma ALD levels, such as non-dihydropyridine CCBs, hydralazine and α -adrenergic blockers (prazosin, doxazosin, terazosin), can be used for the control of blood pressure during screening tests (24). Nevertheless, according to Young, the study is valid even under treatment with ACE-I and ARBs, since low renin levels in these conditions would increase the degree of suspicion of PA (9).

In our study, we observed an increased prevalence of metabolic syndrome in hypertensive patients as compared with controls, but in agreement with other reports (25), we found no differences between PA and essential hypertensive patients. Neither Fallo and cols. (26) nor Catena and cols. (27) found differences in the lipid profile between PA patients and those with essential hypertension, despite the higher prevalence of metabolic syndrome and insulin resistance in PA patients versus controls. Furthermore, ALD may exert a direct effect on insulin receptor function (28) and decrease insulin sensitivity in human adipocytes (29).

There was no correlation between age and ALD concentration or PRA either in controls or in hypertensive patients (data not shown). This is consistent with findings reported by other authors evaluating normotensive subjects (30) and hypertensive patients (31), but it differs from other author's reports (32), where both ALD and PRA were found to decrease with age.

In our study, eight PA cases were confirmed in 249 hypertensive patients. Unlike other studies, the 7 patients with APA had hypokalemia. This situation is usually associated with disturbances of internal milieu,

as reported in the PAPY study, where a higher prevalence of hypokalemia was shown in subjects with adenoma (48%) than in those with hyperplasia (17%) (21).

Regarding PRC determination, this methodology has many advantages over PRA (33,34): less demanding preanalytical conditions (serum *vs.* plasma), shorter incubation times and direct measurement of the renin molecule, which makes it more applicable to the clinical diagnostic laboratory and less operator-dependent, narrowing interlaboratory coefficients of variation. This method is calibrated against the WHO standard IRP 68/356 (NIBSC), which ensures traceability. Additionally, in recent years automated methodology for PRC measurement has been developed. The disadvantages include greater prorenin cryoactivation effects and less sensitivity when measuring low renin concentrations (35). Since PRC and ALD/renin ratio have been proposed for PA screening (4,5), we determined PRC in a subgroup of randomly selected controls and hypertensive patients.

PRC and PRA results have a significant correlation in subjects with PRC values ranging between 5 and 20 pg/mL ($p < 0.001$). A significant correlation was also found between ARR and ARC both in controls and hypertensive patients ($p < 0.0001$).

PRA and PRC are not comparable in absolute values because PRC measures renin concentration, while PRA measures enzyme activity and their results are expressed in different units. When comparing ARR *vs.* ARC, the diagnostic concordance of values above or below 36 or 2.39 for ARR and ARC respectively, was 79.1%. Our comparative analysis of ARR and ARC data shows that DC% is acceptable only for PRA values ≥ 0.3 ng/mL/h (86%) and PRC ≥ 5.0 pg/mL (88%).

In conclusion, this first multicenter prospective study performed in Argentina establishes a cut-off value for ARR in our population. In hypertensive patients, we consider ARR ≥ 36 along with ALD ≥ 15 ng/dL, as suspicious for PA. Applying an ARR ≥ 36 in the hypertensive group, and even taking into consideration that confirmatory tests could not be performed in all hypertensives with ARR ≥ 36 , we found that PA was confirmed in a higher percentage of patients than the previously reported one in our population. As for ARC, further studies are needed for its clinical application, since the diagnostic concordance between ARR and ARC is acceptable only for medium range renin values.

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