Endocrine (2012) 42:182–189
DOI 10.1007/s12020-012-9609-z

ORIGINAL ARTICLE

Effect of age on aldosterone/renin ratio (ARR) and comparison of screening accuracy of ARR plus elevated serum aldosterone concentration for primary aldosteronism screening in different age groups

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Received: 2 November 2011 / Accepted: 15 January 2012 / Published online: 3 February 2012

Abstract The serum aldosterone concentration (SAC)/plasma renin activity (PRA) ratio (ARR) is considered a useful screening test in the differential diagnosis of essential hypertension (EH) and primary aldosteronism (PA). The purpose of this study is to investigate the effect of age on ARR and compare the screening accuracy of ARR plus elevated SAC for PA screening in different age groups. Thirty-nine patients with PA, 274 patients with EH, and 153 healthy volunteers were recruited. Blood was sampled for SAC and PRA measuring under keeping upright posture for 1 h. Levels of SAC, PRA, and ARR were compared at different ages range for the respective three groups of subjects. The screening accuracy of ARR plus elevated SAC was compared in different age groups and PA patients served as the same positive subjects. In the EH group, logarithmically transformed ARR (Log-ARR) increased with advancing age and reached its peak in the ≥60 years group; in the normotensives group, Log-ARR reached its peak in the 40–49 years group and slightly declined with advancing age. In the PA group, Log-ARR was not age dependent. Screening accuracy increased when combined index of ARR and SAC was used in the ≥40 years group but not in the <40 years group. Although the number of EH patients with elevated ARR increased with advancing age, but the screening accuracy and cutoff values of ARR were not affected by age. Using the combined index of ARR and SAC increased the screening accuracy for the patients older than 40 years, but not necessary for the patients younger than 40 years.

Keywords Aldosterone · Aldosterone/plasma renin activity ratio · Plasma renin activity · Primary aldosteronism · Age

Introduction

Primary aldosteronism (PA) in its classic form characterized by hypertension, hypokalemia, and metabolic alkalosis was supposed to be a rare cause of arterial hypertension, with a prevalence of less than 1% of the hypertensives. However, recent studies applying the serum aldosterone concentration (SAC)/plasma renin activity (PRA) ratio (ARR) as a screening test among both hypokalemic and normokalemic hypertensives have reported a much higher prevalence of this disease [1–11]. ARR has been recommended as a screening index for PA detection from hypertensive patients [12, 13].

Although ARR is a useful index for PA detection, the cutoff value of ARR, as well as its sensitivity, specificity, and predictive value have been repeatedly evaluated with wide ranging results [1, 5, 8, 9, 14–16]. One reason is the fact that investigators derived the value from different populations, e.g., healthy, normotensive volunteers, retrospective or prospective surveys of patient population. Of course, the influence of physiologic and pharmacologic factors on renin and aldosterone secretion, such as age, posture, time of day, food and sodium intake, and antihypertensive agents is also partly account for the variation of ARR.

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Accumulated data showed that aldosterone and renin secretion was a gradual decrease with increasing age in hypertensive subjects as well as in normotensives, which may be a physiological phenomenon by aging [17, 18]. As the changes of SAC and PRA with age were parallel, the change of ARR acquired by previous studies was controversial.

Because of high prevalence of PA in hypertensives, even in the prehypertensive and stage 1 hypertensive subjects [11], the number of suspect cases is large. It is meaningful to clarify the influential factors of ARR to optimize the status of measurement and improve the screening efficiency. In this study, we attempt to investigate the effect of age on ARR, and compare the screening accuracy of ARR plus elevated SAC for PA screening in different age groups.

Materials and methods

Subjects

Totally 357 patients with hypertension were recorded in the out-patient and in-patient of the Department of Endocrinology, The Second Affiliated Hospital of Sun Yat-sen University from September 2007 to September 2010. Hypertension was defined as repeated systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least 90 mmHg before initiation of antihypertensive medication. Twenty-one patients were excluded because of incomplete data. Patients with confounding conditions such as congestive heart failure ($n = 1$), renal impairment ($n = 6$) or who had secondary causes of hypertension such as Cushing's syndrome ($n = 7$), pheochromocytoma ($n = 7$), renal artery stenosis ($n = 2$) were excluded. Thirty-nine patients diagnosed as PA and 274 patients diagnosed as essential hypertension (EH) were recruited for analysis in this study.

PA was diagnosed based on the following criteria: (1) repeatedly low renin (<1.0 ng/ml/h) in the presence of high normal or elevated SAC (cutoff value of SAC was 9.0 ng/dl according to the report of Mosso et al.) [4, 19] and lead to elevated ARR (median 460.32 ng/dl per ng/ml/h, range 30.86–1600.00); (2) hypertensives fulfilled the above criteria at least performed one positive confirmatory test, failed suppression of SAC 2 h after 25 mg captopril administration (cutoff 13 ng/dl, $n = 36$) [20] or failed suppression of SAC after 2 l of saline infusion(cutoff 6.75 ng/dl, $n = 3$) [21]; and (3) response to treatment, including improvement of blood pressure and/or normalization of serum potassium after adrenalectomy. A CT scan was performed to differentiate between PA owing to aldosterone-producing adenoma (APA) and PA owing to bilateral adrenal hyperplasia (IHA). The adrenal CT scan was judged compatible with hyperplasia when any adrenal area thicker than 10 mm was detected ($n = 10$). Diagnosis of APA was considered appropriate if the scan showed a unilateral solitary adrenal macroadenoma (>1 cm) ($n = 29$), provided that the contralateral adrenal gland was morphologically normal [9]. For the APA patients, histological examination after surgery showed adrenal cortical adenoma. The serum potassium recovered to the normal range 1 week after surgery for all the APA patients, and the blood pressure recovered to the normal range without antihypertensive treatment for 25 patients in 1 month. Four patients still need antihypertensive agent treatment, but the blood pressure was easier to control because they just need one kind of antihypertensive agent. The levels of the ARR and SAC were obviously decreased after 3 months after surgery (ARR: median 8.28 ng/dl per ng/ml/h, range 2.60–30.00; SAC: median 23.13 ng/dl, range 8.80–16.00).

Furthermore, 153 healthy volunteers were recruited as control. In order to find out if the values might be age dependent, the patients with EH and the healthy volunteers were divided into five groups (20–29, 30–39, 40–49, 50–59, and ≥60 years).

The Ethics Committee of The Second Affiliated Hospital of Sun Yat-sen University approved the study protocol. All the participants gave signed informed consent, including consent to use their data for research purposes.

Procedure

The patients were required to discontinue diuretics and spironolactone for 6 weeks, and to discontinue β-blockers, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARB) at least for 2 weeks. If antihypertensives could not be stopped completely, patients were stabilized with calcium channel blockers or α-blockers. Prior to testing the patients underwent controlled salt intake (160 mmol/day sodium) for 1 week. Serum potassium levels were brought into more than 3.5 mol/l with oral potassium supplementation before the test in patients with hypokalemia. On the day of testing, after at least 15 min rest, all the participants were asked to keep upright posture (standing or walking) for 1 h from 0800 to 0900 h, and then blood was sampled for SAC, PRA, serum potassium, and sodium assaying. All the participants were required to collect urine for 24 h before the testing day. When collecting urine, the samples were required to keep in 4°C fridge. The urine samples were collected totally on the second day, after correctly checking the volume of the urine and then collected 5-ml urine for electrolytes testing.

Determination

Serum and plasma samples were kept at −70°C until assay. SAC was measured by RIA using a commercial kit from Diagnostic Systems Laboratories (Texas, USA). The

intraassay variation was 4.5% and interassay variation was 9.8%. The reference ranges of SAC for ambulatory and recumbent subjects were 3.81–31.33 ng/dl and 2.94–16.15 ng/dl, respectively. The PRA was measured by RIA of angiotensin I generated after incubation of the plasma sample in standardized conditions (Diasorin, Minnesota, USA). The intraassay variations were 10, 4.6, and 9.4% at PRAs of 1.60, 6.20, and 17.90 ng/ml/h, respectively; interassay variations were 5.6, 7.6, and 6.8% at PRAs of 1.60, 10.70, and 15.20 ng/ml/h, respectively. The reference range of PRA was 2.63 ± 1.32 and 1.24 ± 1.09 ng/ml/h for ambulatory and recumbent subjects, respectively. The lower limit for PRA determination was 0.1 ng/dl. The serum and urine electrolytes were determined by the biochemical analyzer (Japan, Hitachi, 7600-010).

Statistical analyses

The area under the curve (AUC) for the receiver-operating-characteristics (ROC) curves, the cutoff values, and the test performance characteristics were obtained from MedCalc. The optimal ratio value for each clinical condition was defined as the value on the ROC curve that was associated with the minimum Euclidean distance from the curve to the upper left corner of the graph, using the Youder's index according to the formula: $\sqrt{(1-\text{sensitivity})^2+(1-\text{specificty})^2}$. Other statistical analyses were performed with SPSS 13.0. ARR was calculated with SAC as the numerator and PRA as the denominator and expressed in ng/dl per ng/ml/h. In sample with PRA less than 0.1 ng/ml/h, a PRA value of 0.1 ng/ml/h was used for the calculation of ARR. SAC, PRA, and ARR were expressed as mean, median, range, and SD, and other data were expressed as mean ± SD. ARR was logarithmically transformed when compared. ANOVA and DSL-test were performed to estimate differences between groups. Pearson correlation analysis was used to determine the relationship between variables. A value of $P < 0.05$ was considered statistically significant.

Results

Characteristics of the participants

In this study, 39 patients with PA, 274 patients with EH, and 153 healthy volunteers were recruited. The characteristics of the participants are described in Table 1. The mean of age in these three groups were 41.89 years (range 19–73 years), 46.78 years (range 21–65 years), and 44.28 years (range 20–77 years). The percentage of female in the EH patients was less than the PA patients and healthy volunteers. PA patients had lower serum potassium and higher urinary potassium, serum sodium, systolic blood pressure, diastolic blood pressure than the EH subjects and healthy volunteers. The volunteers had lower BMI than the EH and PA patients.

In this study 33 EH patients had ARR more than 25 ng/dl per ng/ml/h (PA patients have been excluded in this group), and was negative to the captopril test, which accounted for 11.5% of the EH patients. Fourteen healthy volunteers had ARR more than 25 ng/dl per ng/ml/h, which accounted for 8.9% of the normotensives.

Levels of SAC, PRA, and ARR in different age groups

In the EH patients, SAC and PRA were negative associated with age ($r = -0.265$, $P < 0.01$ and $r = -0.425$, $P < 0.01$, respectively); whereas logarithmically transformed ARR (Log-ARR) was positive associated with age ($r = 0.236$, $P < 0.01$). In the healthy volunteers, SAC and PRA were negatively associated and Log-ARR was positively associated with age ($r = -0.67$, $P < 0.01$, $r = -0.296$, $P < 0.01$, and $r = 0.185$, $P < 0.01$ respectively).

The EH subjects and healthy volunteers were divided into five groups according to age as followed: 20–29, 30–39, 40–49, 50–59, and ≥60 years. The levels of SAC, PRA, and ARR in different age groups are shown in Table 2. No matter the EH patients or the healthy volunteers, SAC, PRA, and Log-ARR were significantly affected by advancing age ($P < 0.05$ according to ANOVA analysis). In the EH group, SAC level was highest in the 30–39 years group, and declined with advancing age. PRA level was highest in the 20–29 years group, and declined with advancing age even more dramatically. Log-ARR increased with advancing age and reached its peak in the ≥60 years group although there are no statistical differences among the latter three groups. In the normotensives group, the variations of SAC and PRA excepted for Log-ARR with advancing age were accordant to the hypertensive subjects. Log-ARR reached its peak in the 40–49 years group and slightly declined with advancing age. In the PA group, SAC, PRA and Log-ARR were not age dependent.

Distribution of ARR with EH patients in different age groups and PA patients

The hypertensive subjects were divided into two groups: <40 years group and ≥40 years group according to the characteristic distribution of ARR in different age groups mentioned above. The distribution of ARR in these two groups of patients with EH and patients with PA are shown in Fig. 1. The range of ARR in the ≥40 years group of patients is much wider than the <40 years group and more overlap of individual values with the PA patients. Percentage of EH patients with ARR more than 25 ng/dl per

Table 1 Clinical and biochemical parameters of subjects

Parameters	Healthy volunteers	EH	PA
No.	153	274	39
Gender (female/male)	98/55	145/129*	24/15
Age (years)	44.28 ± 12.47	46.78 ± 13.17*	41.89 ± 10.26*
BMI (kg/m^2)	22.65 ± 2.95	24.80 ± 3.98*	24.05 ± 4.27*
Systolic blood pressure (mmHg)	113 ± 11	146 ± 20**	152 ± 18**,##
Diastolic blood pressure (mmHg)	74 ± 7	91 ± 13**	98 ± 12**,##
Serum potassium (mmol/l)	4.2 ± 0.4	3.9 ± 0.5**	3.3 ± 0.6**,##
Serum sodium (mmol/l)	139.6 ± 2.1	140.2 ± 2.3**	141.7 ± 2.7**,##
Urine potassium (mmol/24 h)	35.9 ± 15.8	36.2 ± 17.7	74.0 ± 41.4**,##
Urine sodium (mmol/24 h)	154.2 ± 62.5	129.7 ± 66.5**	138.2 ± 59.4

EH essential hypertension, *PA* primary aldosteronism

* $P < 0.05$ versus healthy volunteers

** $P < 0.01$ versus healthy volunteers

$P < 0.01$ versus EH

Table 2 Levels of SAC, PRA, and ARR with different ages in essential hypertensives and healthy volunteers

Age (years)	EH ($n = 274$)					Healthy volunteers ($n = 153$)				
	n	Mean	Median	Range	SD	*n*	Mean	Median	Range	SD
PRA (ng/ml/h)										
20–	29	5.04	5.62	2.33–6.66	1.43	29	3.79	4.07	1.11–6.81	1.38
30–	67	3.98	4.05	0.51–6.88	1.78*	23	3.54	3.33	0.15–5.92	1.77**
40–	55	3.04	3.18	0.18–6.50	1.85**,#	36	3.06	3.39	0.1–5.93	1.84**
50–	71	2.59	2.29	0.12–6.51	1.55**,##	52	2.65	2.56	0.1–5.17	1.47**,#
≥60	52	2.49	2.26	0.10–6.36	1.68**,##	13	2.58	2.46	0.1–5.02	1.71**
SAC (ng/dl)										
20–	29	26.59	26.69	7.50–50.00	12.36	29	20.74	16.72	8.50–65.00	13.23
30–	67	28.65	25.63	6.25–80.00	15.91	23	28.76	25.00	5.00–77.50	18.13
40–	55	23.66	21.88	8.50–71.20	13.13#	36	26.87	23.13	8.28–52.50	12.76
50–	71	20.29	19.80	3.75–47.5	8.71**,##	52	19.38	17.19	7.81–50.00	8.74##
≥60	52	20.54	19.53	5.60–42.50	8.21**,##	13	17.16	14.69	2.34–28.75	7.57##
ARR (ng/dl per ng/ml/h)										
20–	29	5.81	6.25	1.21–11.95	3.04	29	5.98	5.47	1.38–17.10	3.59
30–	67	9.83	5.98	1.03–47.62	9.23	23	11.57	8.44	1.16–58.33	12.44*
40–	55	12.84	7.92	1.39–70.38	12.90**,#	36	18.55	8.45	2.32–100.86	23.35**
50–	71	13.30	8.09	1.24–94.81	14.97**	52	11.19	7.53	2.12–79.70	11.78**
≥60	52	15.76	8.33	1.85–68.420	16.10**,##	13	12.66	7.91	2.74–58.51	14.99*

* $P < 0.05$ versus 20–29 years group

** $P < 0.01$ versus 20–29 years group

# $P < 0.05$ versus 30–39 years group

$P < 0.01$ versus 30–39 years group

ng/ml/h in different age groups is shown in Fig. 2. None of the patients got elevated ARR in the youngest group, and the percentage increased with advancing age. The number reached 21.2% in the oldest group.

Screening accuracy of ARR in different age groups

ROC analysis was conducted in <40 years group and ≥40 years group of EH patients and 39 PA patients served as the same positive subjects. ROC curves are shown in Fig. 3. AUCs were 0.999 (95% CI 0.970–1.000, $P < 0.001$) and 0.994 (95% CI 0.971–0.999, $P < 0.001$), respectively. Optimal cutoff values of ARR that corresponded to the Youden's index are shown in Table 3. In the <40 years group, optimal cutoff was 30.0 ng/dl per ng/ml/h, and the sensitivity and specificity were 100.0 and 96.9%, respectively; whereas in the ≥40 years group, optimal cutoff was 30.77 ng/dl per ng/ml/h, and the sensitivity and specificity were 100 and 92.1%, respectively. The optimal cutoff values of the two groups were almost the same.

In order to improve the screening accuracy, we applied ARR plus elevated SAC as jointly screening index. The

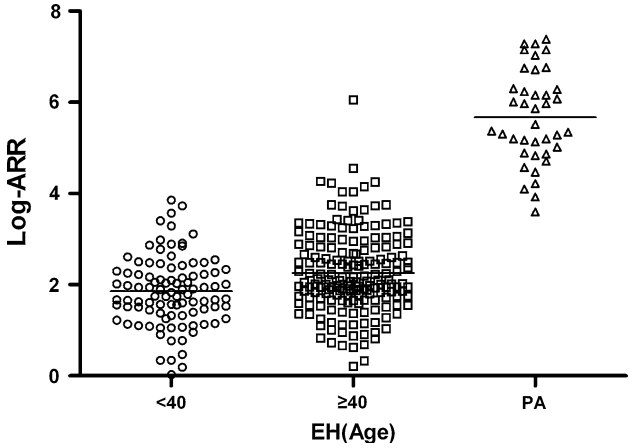

Fig. 1 ARR distribution of patients with EH in different age groups and PA. The range of ARR in the ≥40 years group of patients is much wider than the <40 years group and larger overlap of individual values with the PA patients

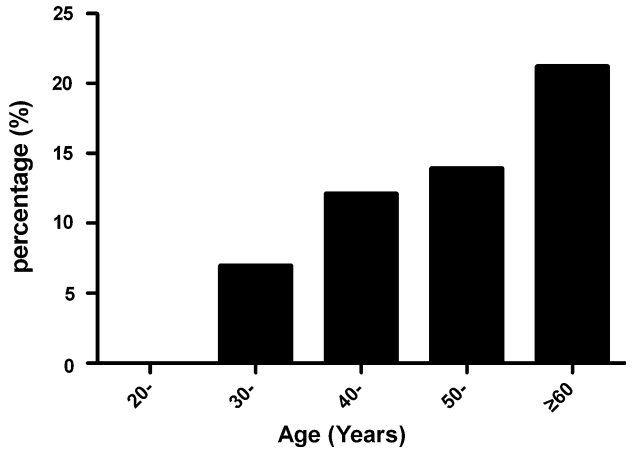

Fig. 2 Percentage of EH patients with elevated ARR in different age groups. None of the patients got elevated ARR in the youngest group, and the percentage increased with advancing age. The number reached 21.2% in the oldest group

screening accuracy is shown in Table 3. In the <40 years group, ARR with cutoff value of 30.0 ng/dl per ng/ml/h plus SAC with cutoff value of 10 or 15 ng/dl did not improve or decrease the screening accuracy of ARR. Raise the SAC cutoff value to 20 or 25 ng/dl improved the specificity to 96.6%, the sensitivity drop to 92.3%. In the ≥40 years group, ARR with cutoff value of 30.82 ng/dl per ng/ml/h plus SAC with cutoff value of 10 or 15 ng/dl improved the specificity to 92.7 and 94.9%, respectively, and the sensitivity unchanged. But raise the SAC cutoff value to 20 or 25 ng/dl improved the specificity to 95.2 and 96.1%, respectively, the sensitivity drop to 92.3 and 89.7%, respectively.

Discussion

The use of ARR to screen for PA was first proposed by Hiramatsu et al. [22], who successfully screened 9 patients with APA from 384 hypertensive subjects in 1981. It has recommended as a screening index for PA with hypertensives by the PA diagnosis and treatment guideline [12]. But the levels of renin and aldosterone are affected by plenty of factors such as posture [16, 23], circadian [24], dietary sodium [25], medication [3, 15, 26, 27], measuring methods [28], and age [29]. ARR, as the ratio of SAC and PRA, is more or less affected by the factors mentioned above. It is meaningful to clarify the influential factors of ARR to optimize the status of measurement and improve the screening efficiency.

Accumulated data showed that aldosterone and renin secretion gradually decreased with increasing age in hypertensive subjects as well as in normotensives, which may be a physiological phenomenon by aging [17, 18], but few of these study paid attention to the relation between age and ARR because ARR had not been used before 1981. As the change of SAC and PRA with age was parallel, the

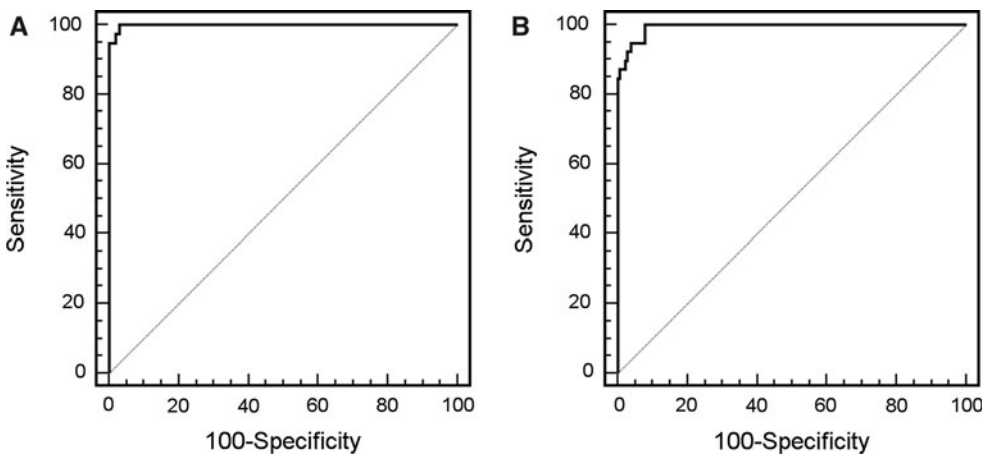

Fig. 3 ROC curves for ARR determined from different age groups of EH patients and 39 patients with PA served as the same positive patients. **a** 96 patients younger than 40 years with EH and 39 patients with PA and **b** 178 patients older than 40 years with EH and 39 patients with PA. AUCs derived from these two groups of patients were 0.999 (95% CI 0.970–1.000, $P < 0.001$) and 0.994 (95% CI 0.971–0.999, $P < 0.001$)

Table 3 Test characteristics of ARR plus elevated SAC to screen for PA

Age	Optimal cutoff of ARR	Cutoff of SAC	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
<40	30.00	–	100.0 (90.9–100.0)	96.9 (91.1–99.3)	92.9 (80.5–98.4)	100.0 (96.1–100.0)	32.0 (30.9–33.2)	0
		10	100.0 (90.9–100.0)	96.9 (91.1–99.3)	92.9 (80.5–98.4)	100.0 (96.1–100.0)	32.0 (30.9–33.2)	0
		15	100.0 (90.9–100.0)	96.9 (91.1–99.3)	92.9 (80.5–98.4)	100.0 (96.1–100.0)	32.0 (30.9–33.2)	0
		20	92.3 (83.9–100.0)	96.6 (93.4–100.0)	92.3 (83.9–100.0)	96.9 (93.4–100.0)	29.50 (9.7–90.3)	0.08 (0.03–0.24)
		25	92.3 (83.9–100.0)	96.6 (93.4–100.0)	92.3 (83.9–100.0)	96.9 (93.4–100.0)	29.50 (9.7–90.3)	0.08 (0.03–0.24)
≥40	30.77	–	100.0 (90.9–100.0)	92.1 (87.2–95.6)	73.6 (59.7–84.7)	100.0 (97.8–100.0)	12.7 (12.2–13.3)	0
		10	100.0 (90.9–100.0)	92.7 (88.9–96.5)	75.0 (63.2–86.8)	100.0 (97.8–100.0)	13.7 (8.1–23.1)	0
		15	100.0 (90.9–100.0)	94.9 (91.7–98.2)	81.3 (70.2–92.3)	100.0 (97.8–100.0)	19.8 (10.5–37.4)	0
		20	92.3 (83.9–100.0)	95.2 (92.5–98.5)	81.8 (70.4–93.2)	98.3 (96.3–100.0)	20.5 (10.4–40.7)	0.08 (0.03–0.24)
		25	89.7 (80.2–99.3)	96.1 (93.2–98.9)	83.3 (72.1–94.6)	97.7 (95.5–99.9)	22.8 (10.9–47.5)	0.11 (0.04–0.27)

Unit: ARR ng/dl per ng/ml/h, SAC ng/dl

results acquired by previous studies were controversial. Baas et al. [23] demonstrated that ARR measured under keeping upright posture for 2 h was not affected by age in the 50 healthy volunteers aged 20–70 years. However, Olivieri et al. [6] testified that ARR increased with age, and remained constant beyond 55 years in hypertensives. In this study, our results supported the conclusion that ARR increased with advancing age in hypertensives. The contradiction of the conclusion from different investigations maybe related to the lower limit of detection of different PRA assays. ARR may highly amplified by very low PRA levels if a more accuracy PRA assay was used (e.g., the lower limit detection was 0.1 ng/dl per ng/ml/h) or the PRA values which were less than the lower limit of the PRA assay have not been adjusted, although previous study reported that adjustment of PRA did not change the screening accuracy of ARR [30].

Since age was an important influential factor on ARR, we paid attention to the screening accuracy and optimal cutoff value of ARR in different age groups. Although the AUC of ROC analyzed on younger patients were slightly larger than it analyzed on the older patients, the optimal cutoff values of the two groups of patients were almost the same. There are three main explanations for the phenomenon: (1) the prevalence of PA is not age dependent; (2) ARR values of PA patients were not age dependent. Log-ARR was positive associated with age in the EH patients and healthy volunteers but not in the PA patients; (3) There was a marked overlap of individual values across groups. Reference intervals for ARR in different age groups (25–54 and 55–74 years) proposed by Hannemann et al. [31] showed overlapping values in these two groups (1.4–14.2 and 0.9–22.4 ng/dl per ng/dl for male and 0.9–20.3 and 0.7–25.5 ng/dl per ng/dl for female). Our results showed that 6.9% of EH patients younger than 40 years of age with elevated ARR. Olivieri et al. [6] demonstrated that 15% patients of age 35–44 years had ARR > 32 ng/dl per ng/ml/h. The patients with EH were divided into two groups according to age and the Log-ARR in these two groups represented for two independent gauss distribution of data. But after all, age is a continuous course, an overlapping values of Log-ARR is unavoidable. The data above showed that it is not necessary to use different cutoff values for PA screening in different age groups of hypertensive patients.

Some investigators require elevated SAC levels in addition to elevated ARR for a positive screening test for PA [19, 32, 33]. An alternative approach is to avoid a formal cutoff level for SAC, but to recognize that the likelihood of a false positive ARR becomes greater when renin levels are very low. Our results demonstrated that percentage of elevated ARR increased with advancing age while SAC decreased and suggested that elevated SAC

levels in addition to elevated ARR for a positive screening test in older EH patients would be more effective. Our results further showed in the <40 years group, ARR plus SAC ≥ 15 ng/dl did not improve or decrease the screening accuracy of ARR, while raise SAC to 20 ng/dl, sensitivity began to drop. But in the ≥40 years group, ARR plus SAC ≥ 15 ng/dl improved the specificity to 94.5%, while sensitivity kept the same. The data above suggested that ARR plus SAC ≥ 15 ng/dl improved screening accuracy for the EH patients older than 40 years of age. The EH patients younger than 40 years is not necessary to use the combined screening index.

However, some investigations showed that using elevated SAC in addition to ARR would lead to missed diagnosis of PA. For example, Mosso et al. [4] reported SAC levels of 9–16 ng/dl in 16 of 37 patients diagnosed with PA by FST; Schwartz and Turner [34] showed that using a threshold value of SAC > 15 ng/dl increased the specificity from 74 to 97% but markedly decreased the sensitivity from 73 to 33%. Umpierrez et al. [10] showed that only 43% of PA subjects had a SAC > 15 ng/dl during the initial screening. In fact, previous studies reported a large range of SAC with the PA patients. PAPY study, a prospective study of prevalence of PA in newly diagnosis of hypertension showed that SAC values of all the PA patients were more than 17 ng/dl [8]; our results showed that SAC of the PA patients more than 16.1 ng/dl. There are maybe two important reasons represent the phenomenon. First, the status of SAC and PRA measuring, include posture, time of day, food and sodium intake, and antihypertensive usage were quite different from each other. Second, some investigators believed that IHA and low renin EH may be spectrum stages from the same disease, and have no obvious borderline [33]. Different stages of patients were recruited, for biochemical and clinical characteristics are not obvious at the early phase, and even some suspect patients need follow-up for a few years before diagnosis.

One limitation of our study was the patients with PA did not perform adrenal venous sampling (AVS) which was considered as the gold standard for differentiation of the subtypes of PA. The sensitivity and specificity of AVS (95 and 100%, respectively) for detecting unilateral aldosterone excess are superior to that of adrenal CT [35, 36]. Rossi et al. [8] showed that the proportion of PA patients with APA and IHA with or without AVS was converse. The different proportion of PA patients with APA and IHA may lead to the variation of cutoff values of ARR. Furthermore, when we analyzed screening accuracy of ARR plus elevated SAC, 39 PA patients were served as positive subjects in the both age groups because ARR was not age dependent in the PA patients. The construction of subtypes of PA would be changed if the PA patients were divided into two groups according to age.

In conclusion, this study demonstrates that the number of EH patients with elevated ARR was increased with advancing age, but the screening accuracy and cutoff values of ARR were not affected by age. Using the combined index of ARR and SAC increased the screening accuracy for the patients older than 40 years and saved the cost of the unnecessary confirmatory test. The patients younger than 40 years of age were not necessary to use the combined index.

Acknowledgment This work was supported by the 10th Five Years Programs for Science and Technology Development of China (2004BA720A29).

Conflict of interest The authors have no conflict of interest.

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