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ORIGINAL ARTICLE

The influence of aging on the diagnosis of primary aldosteronism

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Primary aldosteronism (PA) is common in young or middle-aged hypertensive patients, but PA among the elderly has recently become more common. As salt sensitivity increases with age, plasma renin activity (PRA) tends to decrease, whereas the aldosterone-to-renin ratio (ARR) tends to increase in the elderly. The aim of this study was to clarify the influence of aging on the diagnosis of PA. We retrospectively evaluated 155 consecutively admitted patients who were not taking antihypertensive medications or calcium channel blockers and α blockers that underwent PRA and plasma aldosterone concentration (PAC) measurements. The study subjects included 13 PA and 69 essential hypertensive (EHT) patients aged over 65 years, and 32 PA and 41 EHT patients under aged 65 years. Our study clarified the influence of aging through screening and confirmatory tests for the diagnosis of PA. Our results showed the ARR cutoff value for a screening test to be 556 (area under the curve: AUC = 0.906), its sensitivity and specificity to be 84.6% and 89.9%, respectively, and the likelihood ratio to be 8.34 in the elderly, whereas the ARR cutoff value was 272 in the non-elderly. In the saline infusion test, the mean PAC was 86.6 ± 41.8 pg ml^{-1} in the elderly and 158.1 ± 116.5 pg ml^{-1} in the non-elderly (P = 0.04). There was no influence from age in both the captopril challenge test and the furosemide upright test. Aging may influence PA screening and saline infusion tests; thus, we should consider the influence of aging in the diagnosis of elderly subjects with PA.
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Keywords: confirmatory test; diagnosis; elderly; primary aldosteronism; screening test

INTRODUCTION

Primary aldosteronism (PA) is one of the most common forms of secondary hypertension and may account for as much as 5–10% of patients with hypertension.[1–4] The main presentations of PA are aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism. APA is generally curable by surgical treatment, whereas idiopathic hyperaldosteronism is mainly treated through aldosterone blockade.[5,6] Aldosterone is an adrenal hormone that regulates sodium and fluid retention. Because, in addition to these genomic effects, it has been demonstrated that aldosterone might induce inflammation and fibrotic changes in end organs such as the heart, kidney, blood vessels and brain, a high aldosterone state is believed to be one of the causes of high blood pressure, congestive heart failure, coronary artery disease, chronic kidney disease and metabolic syndrome.[7–9] Several studies have reported a high incidence of cardiovascular complications in patients with PA compared with patients with essential hypertension (EHT).[10,11] Therefore, the early diagnosis of PA and treatment planning are necessary to prevent the progression of cardiovascular complications.[12,13] However, the diagnosis of PA is sometimes difficult and consists of three processes: screening, confirmatory tests and imaging tests.[14]

The World Health Organization defines people over the age of 65 years as elderly. The Japanese Health, Labor and Welfare Ministry further defines those between 65 and 74 years as young-old and those over 75 years as old-old. This definition is especially important for the Japanese medical insurance and long-term care insurance sectors, as the increasing costs of medical insurance is a serious issue in Japan. Recently, the number of elderly patients has increased, mainly in developed countries; therefore, elderly PA is becoming more common in patients with refractory hypertension,[15] although PA is generally thought to be common in young or middle-aged hypertensive patients. As salt sensitivity increases with aging, both the plasma renin activity (PRA) and aldosterone concentration (PAC) tend to be low, and, consequently, the aldosterone-to-renin ratio (ARR) increases in the elderly.[16] However, there have been limited studies that have evaluated the influence of aging on the diagnostic procedures for PA.[17] In the present study, we investigated the influence of aging on the screening and confirmatory tests used for PA diagnosis to improve the accuracy of PA diagnosis in patients with

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hypertension. We also clarify the ARR cutoff value for PA diagnosis in elderly patients with hypertension from a medical economic perspective in an effort to reduce the medical insurance costs.

METHODS

Figure 1 presents the process of subject recruitment. Seven hundred and seventy-six consecutive patients were admitted to the Department of Geriatric Medicine and Hypertension at Osaka University Hospital from April 1, 2009 to May 31, 2012. Three hundred and twenty-four patients underwent PRA and PAC measurements, and 174 out of the 324 patients were not taking any antihypertensive medications or were only on calcium channel blockers or α blockers for at least 2 weeks. We excluded 2 patients without high blood pressure, 11 patients with renovascular hypertension, 4 patients post-adrenalectomy and 2 patients with other forms of endocrine hypertension, leaving us with 155 patients who were evaluated for this study. PRA and PAC were determined by radioimmunoassay. All patients had mild-to-severe hypertension, and blood samples were obtained after the patient was in the supine position for over 30 min. The mean salt intake calculated by food was 9.5 ± 1.2 g, which was similar to the average Japanese salt intake.

For subjects with an ARR over 200, we performed three confirmatory tests (captopril challenge test, saline infusion test and furosemide upright test) according to Japanese guidelines.[18,19] In the captopril challenge test, patients received 50 mg of captopril orally after being in a recumbent position for 30 min. Blood samples for the measurements of PRA, PAC and ARR were drawn at 0, 60 and 90 min after drug administration, respectively, and subjects with an ARR ⩾200 at 60 or 90 min after drug administration were considered to be positive for PA. In the saline infusion test, patients remained in the supine position for 30 min before and during the infusion of 2 l of saline over 4 h. Blood samples for the measurement of PRA, PAC and ARR were drawn at time 0 and after 4 h, and subjects with a high PAC ($>60\,pg\,ml^{-1}$) at 4 h after saline infusion were considered to be positive for PA. In the furosemide upright test, patients were intravenously administered 40 mg furosemide after remaining in a recumbent position for 30 min and then maintained at an upright posture for 2 h. Blood samples for the measurements of PRA, PAC and ARR were drawn at time 0 and after 2 h, and subjects with a low PRA ($<2.0\,ng\,ml^{-1}\,h^{-1}$) at 2 h after furosemide injection were considered to be PA-positive. All tests started at 0800–0900 hours local time. If subjects tested positive for more than two-thirds of the confirmatory tests, we diagnosed them with PA according to the guidelines for the detection of PA from the Japan Endocrine Society.[18]

We categorized patients over 65 years to be in the elderly group and placed those under 65 years in the non-elderly group. Sixty-three patients (20 elderly, 43 non-elderly) with an ARR >200 underwent confirmatory tests, and of those, 45 patients (13 elderly, 32 non-elderly) received a diagnosis of PA. Then, patients were divided into 13 PA and 69 EHT patients in the elderly and 32 PA and 41 EHT patients in the non-elderly. In the elderly PA group, six patients received adrenal vein sampling (AVS), and four out of the six patients were diagnosed with APA. Three patients received adrenalectomies, and all of them were diagnosed with APA through pathology. In the non-elderly PA group, 24 patients had AVS, and 14 of them were diagnosed with APA. Seven patients had adrenalectomies and were diagnosed with APA through pathology (Table 1). We compared each clinical background factor and identified a cutoff value of ARR in the elderly and non-elderly subjects from an receiver operating characteristic (ROC) curve. We also compared the elderly with non-elderly PA patients in the confirmatory tests. We excluded 2 PA patients who received confirmatory tests and were diagnosed after the study period, and finally analyzed 13 elderly and 30 non-elderly PA patients.

All data are expressed as the mean ± s.d. Differences between the groups were assessed using the chi-square analysis and *t* test, as appropriate. ROC analyses were used to determine the cutoff value of PRA, PAC and ARR. $P<0.05$ was considered to be statistically significant. All statistical analyses were performed with the JMP Software, Version 9 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The demographics of the study subjects are shown in Table 1. Among the elderly patient group, the average age was 71.5 ± 4.4 years for PA

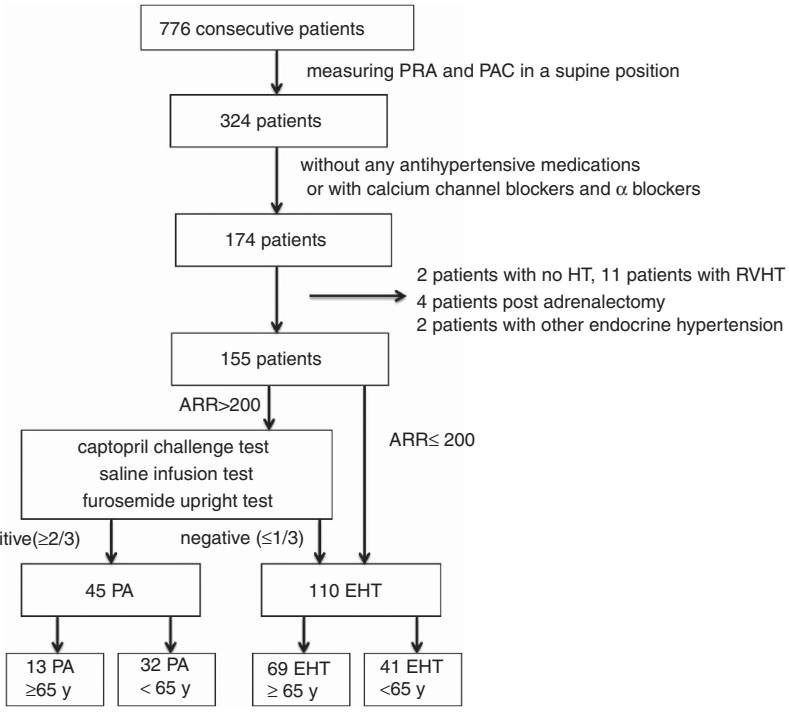

Figure 1 Selection of study subjects. Among the 776 consecutively admitted patients, 324 patients underwent PRA and PAC measurements. A total of 174 out of the 324 patients were not taking any antihypertensive medications or only calcium channel blockers and α blockers. We excluded secondary hypertension except PA, and ultimately evaluated 155 patients for inclusion in our study. PRA, plasma renin activity; PAC, plasma aldosterone concentration; RVHT, renovascular hypertension.

Table 1 Patients' characteristics

	PA ⩾65 years (n = *13*)	*PA <65 years* (n = *32*)	*EHT ⩾65 years* (n = *69*)	*EHT <65 years* (n = *41*)
Age (year)	71.5 ± 4.4††	46.8 ± 10.7††	73.4 ± 6.0††	50.0 ± 11.5††
men, *n* (%)	4 (30.8%)	18 (56.3%)	25 (36.2%)	17 (41.5%)
BMI (kg m^{-2})	22.8 ± 2.5	24.9 ± 5.2	23.5 ± 4.0	24.5 ± 5.4
SBP/DBP(mm Hg)	145.9 ± 17.1/79.5 ± 10.6†	144.2 ± 18.4/88.8 ± 12.3*†	144.6 ± 23.8/79.0 ± 10.9††	152.3 ± 26.1/95.1 ± 13.3*††
PR (b.p.m.)	74.3 ± 11.4	70.6 ± 9.8**	73.4 ± 14.7	78.5 ± 13.2**
PRA (ng ml^{-1} h^{-1})	0.24 ± 0.17*	0.31 ± 0.18**	1.39 ± 1.68*	2.12 ± 2.33**
PAC (pg ml^{-1})	197.8 ± 110.8**	225.7 ± 104.6	120.4 ± 53.0**††	190.3 ± 124.7††
ARR	1244 ± 1145**	1183 ± 1137**	275 ± 380**	191 ± 262**
Serum K (mEq l^{-1})	3.82 ± 0.55*	3.73 ± 0.53	4.15 ± 0.54*†	3.92 ± 0.36†
eGFR (ml min^{-1} 1.73 m^{-2})	62.8 ± 8.6††	83.9 ± 21.2††	64.8 ± 21.5††	83.6 ± 27.3††
FBS (mg dl^{-1})	92.9 ± 13.4	97.5 ± 14.4	103.2 ± 25.7	97.5 ± 20.3
HbA1c (%)	5.65 ± 0.35	5.60 ± 0.34	6.10 ± 0.75	5.89 ± 1.06
Salt intake (g per day)	9.8 ± 0.6	9.8 ± 0.8	9.3 ± 1.4	9.4 ± 1.4
AVS performed, *n* (%)	6 (46.2)	24 (75.0)		
APA, *n* (%)	4 (30.8)	14 (43.8)		

Abbreviations: APA, aldosterone-producing adenoma; ARR, aldosterone-to-renin ratio; AVS, adrenal vein sampling; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; PAC, plasma aldosterone concentration; PR, pulse rate; PRA, plasma renin activity; SBP, systolic blood pressure.
Data are shown as the mean ± s.d. and were analyzed using chi-square analysis and the *t*-test. *$P<0.05$, **$P<0.01$, PA *vs.* EHT, $^{\dagger}P<0.05$, $^{\dagger\dagger}P<0.01$, elderly *vs.* non-elderly

patients and 73.4 ± 6.0 years for EHT patients (N.S.). In the non-elderly patient group, the average age was 46.8 ± 10.7 years for PA patients and 50.0 ± 11.5 years for EHT patients (N.S.). Sex, body mass index, systolic blood pressure, HbA1c and salt intake were not significantly different among each subject group. Diastolic blood pressure in the elderly was significantly lower than in the non-elderly, and diastolic blood pressure in the non-elderly EHT group was also significantly higher than in the non-elderly PA group. The mean PRA was significantly lower and the mean PAC was significantly higher in the elderly PA patients than in the elderly EHT patients ($P<0.05$, $P<0.001$, respectively), and in the non-elderly subjects the mean PRA was significantly lower in PA patients than in EHT patients ($P<0.001$); however, there were no significant differences in the mean PAC. ARR was significantly higher in PA compared with EHT in both the elderly and non-elderly ($P<0.0001$). Among the elderly, the average serum K level was significantly lower in PA patients than in EHT patients ($P=0.044$), but there were no significant differences in serum K level in the non-elderly subjects. Among EHT patients, the PAC was significantly lower and the serum K value was significantly higher in the elderly than in the non-elderly patients ($P<0.01$, $P<0.05$, respectively).

The distribution of ARR in patients with PA and EHT in the elderly and non-elderly subjects is shown in Figure 2a. The range of ARR among elderly EHT patients is much wider than that among non-elderly EHT patients. The ARR, PAC and PRA were further compared to distinguish between PA and EHT using ROC curves. When the ARR cutoff value was 556 (area under the curve: AUC = 0.906) in the elderly subjects, its sensitivity, specificity and the likelihood ratio of a positive test were 84.6, 89.9 and 8.34, respectively (Figure 2b). In the elderly, its sensitivity and specificity were 84.6 and 50.7% when the PAC cutoff value was 110 pg ml^{-1} (AUC = 0.706), and its sensitivity and specificity were 100 and 59.4% when the PRA cutoff value was 0.6 ng ml^{-1} h^{-1} (AUC = 0.836) (Figures 2d and f). The AUC of ARR was significantly higher than that of PAC and PRA in the elderly ($P=0.018$, $P=0.021$, respectively). When the ARR cutoff value was 272 (AUC = 0.958) in the non-elderly subjects, its sensitivity, specificity and the likelihood ratio of a positive test were 96.9%, 85.4% and 6.62, respectively (Figure 2c). In the non-elderly, its sensitivity and specificity were 96.9 and 31.7% when the PAC cutoff value was 116 pg ml^{-1} (AUC = 0.613), and its sensitivity and specificity were 81.3 and 82.9% when the PRA cutoff value was 0.4 ng ml^{-1} h^{-1} (AUC = 0.908) (Figures 2e and g). The AUC of ARR was significantly higher than that of PAC and PRA in the non-elderly ($P<0.001$, $P=0.029$, respectively).

In the present study, we compared elderly with non-elderly PA patients in three confirmatory tests: the captopril challenge test, the saline infusion test and the furosemide upright test. The captopril challenge test was performed in 58 subjects (42 PA, 16 EHT). Forty-six patients (39 PA and 7 EHT) showed a positive test result, and sensitivity and specificity were 92.9% and 56.3%, respectively. We divided subjects who received the captopril challenge test into 13 elderly PA, 29 non-elderly PA, 10 elderly EHT and 6 non-elderly EHT patients. There were no significant differences in the mean ARR 60 and 90 min after taking captopril (Table 2). On ROC curves of ARR 60 and 90 min after taking captopril, the cutoff value of ARR was 260 after 60 min (AUC = 0.735, sensitivity = 84.6%, specificity = 66.7%) and 306 after 90 min (AUC = 0.685, sensitivity = 75.0%, specificity = 66.7%) in the elderly patients. The cutoff value of ARR was 198 after 60 min (AUC = 0.874, sensitivity = 93.1%, specificity = 66.7%) and 213 after 90 min (AUC = 0.867, sensitivity = 88.0%, specificity = 83.3%) in the non-elderly patients.

Fifty-seven HT patients (40 PA, 17 EHT) underwent a saline infusion test, and 37 patients (34 PA and 3 EHT) were positive, with the sensitivity and specificity reported as 85.0% and 82.4%, respectively. We divided subjects who received the saline infusion test into 13 elderly PA, 27 non-elderly PA, 10 elderly EHT and 7 non-elderly EHT patients. The mean PAC before loading saline showed no significant difference among the elderly and non-elderly PA patient groups. However, PAC after loading was significantly lower in the elderly PA patients than in the non-elderly PA group ($P=0.04$) (Table 3). On ROC curves of PAC after loading, the cutoff value of PAC was 72 pg ml^{-1} (AUC = 0.831, sensitivity = 69.2%, specificity = 100.0%) in the elderly patients, but was 70 pg ml^{-1} (AUC = 0.862, sensitivity = 88.9%, specificity = 85.7%) in the non-elderly patients.

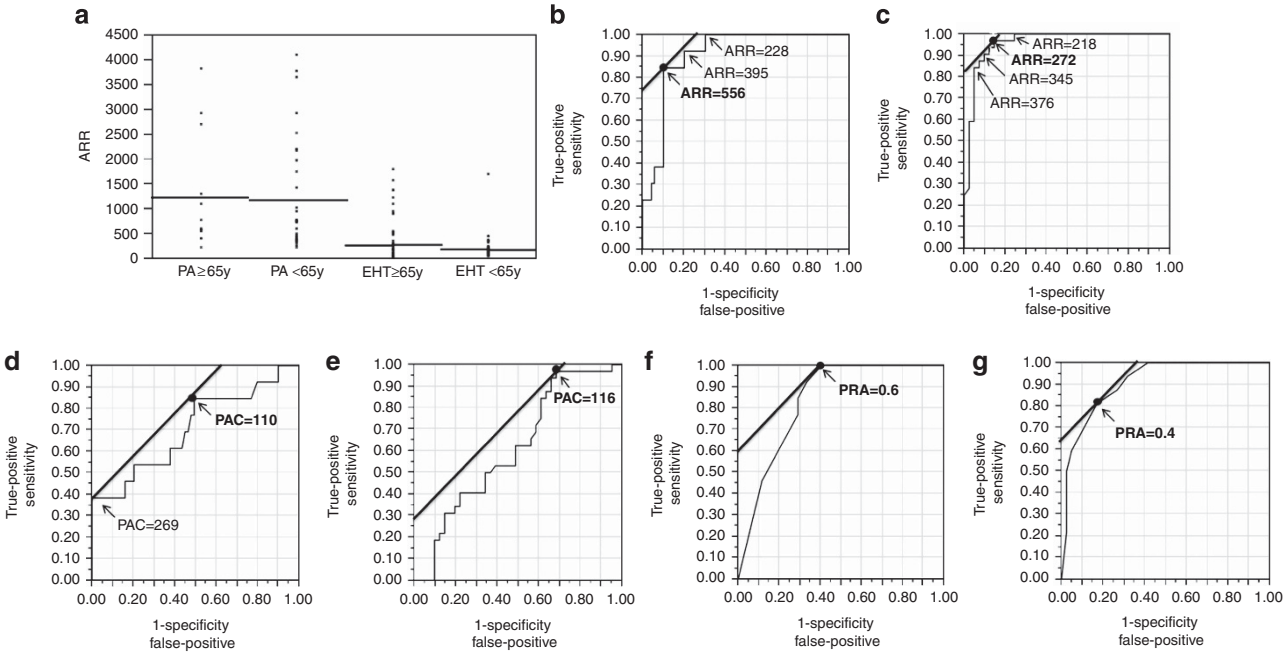

Figure 2 ARR distribution of patients with PA and EHT, and ROC curves of ARR, PAC and PRA on the screening test for PA in the elderly and non-elderly groups. (**a**) ARR distribution of patients with PA and EHT in the elderly and non-elderly. The range of ARR in the elderly EHT is much wider than in the non-elderly EHT. (**b**) ARR in the elderly. The AUC is 0.906. When the cutoff value of ARR is 556, its sensitivity, specificity and the likelihood ratio of a positive test are 84.6%, 89.9% and 8.34, respectively. (**c**) ARR in the non-elderly. The AUC is 0.958. When the cutoff value of ARR is 272, its sensitivity, specificity and the likelihood ratio of a positive test are 96.9%, 85.4% and 6.62, respectively. (**d**) PAC in the elderly. The AUC is 0.706. When the cutoff value of PAC is 110 pg ml^{-1}, its sensitivity, specificity and the likelihood ratio of a positive test are 84.6%, 50.7% and 1.72, respectively. (**e**) PAC in the non-elderly. The AUC is 0.613. When the cutoff value of PAC is 116 pg ml^{-1}, its sensitivity, specificity and the likelihood ratio of a positive test are 96.9%, 31.7% and 1.42, respectively. (**f**) PRA in the elderly. The AUC is 0.836. When the cutoff value of PRA is 0.6 ng ml^{-1} h^{-1}, its sensitivity, specificity and the likelihood ratio of a positive test are 100%, 59.4% and 2.46, respectively. (**g**) PRA in the non-elderly. The AUC is 0.908. When the cutoff value of PRA is 0.4 ng ml^{-1} h^{-1}, its sensitivity, specificity and the likelihood ratio of a positive test are 81.3%, 82.9% and 4.76, respectively. PRA, plasma renin activity; PAC, plasma aldosterone concentration; ARR, aldosterone-to-renin ratio; AUC, area under the curve.

Table 2 Captopril challenge test

	PA ⩾65 years (n = *13*)	*PA <65 years* (n = *29*)	P-*value*
Pre-PRA (ng ml^{-1} h^{-1})	0.22 ± 0.16	0.32 ± 0.19	0.132
Pre-PAC (pg ml^{-1})	157.2 ± 79.2	232.8 ± 126.4	0.054
Pre-ARR	956 ± 695	1342 ± 1553	0.398
PRA after 60 min (ng ml^{-1} h^{-1})	0.28 ± 0.23	0.36 ± 0.21	0.339
PAC after 60 min (pg ml^{-1})	141.4 ± 69.6	185.3 ± 110.9	0.197
ARR after 60 min	847 ± 807	875 ± 1002	0.931
PRA after 90 min (ng ml^{-1} h^{-1})	0.33 ± 0.26	0.38 ± 0.28	0.605
PAC after 90 min (pg ml^{-1})	126.7 ± 53.6	181.0 ± 107.2	0.108
ARR after 90 min	714 ± 661	906 ± 1014	0.555

Abbreviations: ARR, aldosterone-to-renin ratio; PA, primary aldosteronism; PRA, plasma renin activity; PAC, plasma aldosterone concentration.
We compared the mean values of PRA, PAC and ARR between 13 elderly and 29 non-elderly PA patients in the captopril challenge test. Data are shown as the mean ± s.d. and were analyzed with the *t* test.

Table 3 Saline infusion test

	PA ⩾65 years (n = *13*)	*PA <65 years* (n = *27*)	P-*value*
Pre-PRA (ng ml^{-1} h^{-1})	0.34 ± 0.34	0.36 ± 0.28	0.809
Pre-PAC (pg ml^{-1})	158.5 ± 75.5	216.0 ± 129.2	0.147
Pre-ARR	680 ± 325	1154 ± 1385	0.234
PRA after 4 h (ng ml^{-1} h^{-1})	0.18 ± 0.15	0.20 ± 0.12	0.727
PAC after 4 h (pg ml^{-1})	86.6 ± 41.8	158.1 ± 116.5	0.039*
ARR after 4 h	704 ± 511	1166 ± 1197	0.192

Abbreviations: ARR, aldosterone-to-renin ratio; PA, primary aldosteronism; PRA, plasma renin activity; PAC, plasma aldosterone concentration.
We compared the mean values of PRA, PAC and ARR between 13 elderly and 27 non-elderly PA patients in the saline infusion test. Data are shown as the mean ± s.d. and were analyzed with the *t* test. $^{*}P<0.05$, $^{**}P<0.01$

Forty-one HT patients (34 PA, 7 EHT) underwent the furosemide upright test and 37 patients (33 PA and 4 EHT) had a positive test result, with a sensitivity and specificity of 97.1% and 42.9%, respectively. We divided subjects who received the furosemide upright test into 10 elderly PA, 24 non-elderly PA, 2 elderly EHT and 5 non-elderly EHT patients. There were no significant differences in the mean PRA after injecting furosemide and standing (Table 4). On ROC curves of PRA, the cutoff value of PRA was 0.4 ng ml^{-1} h^{-1} (AUC = 0.750, sensitivity = 50.0%, specificity = 100.0%) in the elderly patients, but was 1.4 ng ml^{-1} h^{-1} (AUC = 0.796, sensitivity = 95.8%, specificity = 60.0%) in the non-elderly patients.

DISCUSSION

In the present study, we assessed the influence of age on the screening and confirmatory tests for the diagnosis of PA. We drew an ROC curve of ARR on the screening test considering the influence of age. Consequently, the cutoff value of ARR was 556 in elderly subjects over

Table 4 Furosemide upright test

	PA ⩾65 years (n = *10*)	*PA <65 years* (n = *24*)	P-*value*
Pre-PRA (ng ml^{-1} h^{-1})	0.23 ± 0.18	0.25 ± 0.14	0.729
Pre-PAC (pg ml^{-1})	150.9 ± 88.0	192.9 ± 101.5	0.263
Pre-ARR	835 ± 377	1181 ± 1173	0.372
PRA after 2 h (ng ml^{-1} h^{-1})	0.63 ± 0.57	0.75 ± 0.59	0.576
PAC after 2 h (pg ml^{-1})	383.1 ± 181.9	456.6 ± 268.0	0.435
ARR after 2 h	1256 ± 1213	1123 ± 1367	0.791

Abbreviations: ARR, aldosterone-to-renin ratio; PA, primary aldosteronism; PRA, plasma renin activity; PAC, plasma aldosterone concentration.
We compared the mean values of PRA, PAC and ARR between 10 elderly and 24 non-elderly PA patients in the furosemide upright test. Data are shown as the mean ± s.d. and were analyzed with the *t* test.

65 years and its sensitivity and specificity were 84.6% and 89.9%, respectively, whereas the cutoff value of ARR was 272 in non-elderly subjects under 65 years and its sensitivity and specificity were 96.9% and 85.4%, respectively. In addition, the AUC of ARR was the highest among the three indexes (ARR, PAC and PRA) and the cutoff value of ARR indicated the best sensitivity and specificity (Figure 2).

The usefulness of ARR is emphasized, and has been recommended as the screening test for PA in all age groups of patients with hypertension.[20] The cutoff value of ARR has been reported to be 200–500,[21–23] and a value >200–300 is recommended in guidelines.[14,18,19] In the present study, ARR was the best index for the screening test for PA diagnosis, and the cutoff value of ARR in non-elderly patients was 272, supporting previous reports.[21–23] However, there are few reports on the best value for PA screening in the elderly. Salt sensitivity increases with age and PRA tends to be low while ARR increases in the elderly.[16] Our study suggested that ARR is superior to only PRA or PAC as a screening test for PA diagnosis even in elderly patients, and ARR criteria in the elderly may need to be much higher than in the non-elderly.

In confirmatory tests, it is also expected that salt sensitivity will influence these results in elderly subjects. The PAC of the elderly after saline loading was significantly lower than that of the non-elderly. This outcome suggested that PAC could easily be used to determine a negative test result among elderly PA patients for the saline infusion test. However, there were no significant differences between the elderly and non-elderly subjects both in the captopril challenge test and furosemide upright test. This outcome may be because of the fact that the saline infusion test only utilizes the PAC value to determine the test result.

PRA and PAC are generally influenced by various conditions such as blood sampling at outpatient clinics or hospitals, posture, time of day, and water, sodium and potassium intakes. It has been reported that PAC tends to be lower in blood samples from outpatients compared with those collected during hospitalization, whereas no significant change has been reported for ARR.[20,24] For all study subjects, PRA, PAC and ARR were measured in the supine position 30 min after resting on the morning of the screening test for PA diagnosis. We examined the effect of age under the same conditions to the extent possible.

Performing a confirmatory test is an important step after the screening test for PA diagnosis. It is necessary to verify the autonomous secretion of aldosterone for the diagnosis of PA. Japanese guidelines[18,19] recommend performing one or two confirmatory tests out of the captopril challenge test, saline infusion test and furosemide upright test. The captopril challenge test,[25–27] saline infusion test,[22,28–30] furosemide upright test,[31,32] oral salt loading test[23] and fludrocortisone suppression test[30] are generally performed in Japan and other countries; however, the drug doses, posture during testing and criteria for determining a positive test result are not uniform. We performed the captopril challenge, saline infusion and furosemide upright tests according to the protocol and criteria from The Japan Endocrine Society.[18] If a patient had more than two positive confirmatory tests, they were diagnosed with PA. Therefore, we chose to investigate the influence of age on these three confirmatory tests.

As elderly patients often have reduced cardiac function or other organ damage, confirmatory tests and AVS may cause more complications than in non-elderly patients. If the cutoff value of ARR in the elderly is 200–300 as in the non-elderly subjects, or we interpret the results of the saline infusion test using the same criteria as for non-elderly people, many elderly subjects with hypertension may receive unnecessary confirmatory tests or AVS. Furthermore, confirmatory tests and AVS are usually performed upon hospital admission and are costly. Therefore, patients targeted for confirmatory tests and AVS should be selected carefully, especially in elderly subjects.

In our study, the prevalence of PA was much higher than in previous reports[1–4] because our study excluded patients who tested negatively for PA in the screening test and were taking angiotensin converting enzyme inhibitors, AT1 receptor antagonists or β blockers. Additionally, subjects consisted of patients who were suspected of having PA and were referred to our department. The effects of antihypertensive agents on PRA and PAC should be taken into account for the screening and confirmatory tests of PA. Angiotensin converting enzyme inhibitors, AT1 receptor antagonists and calcium channel blockers decrease PAC and increase PRA, and β blockers and α blockers decrease both PRA and PAC. However, calcium channel blockers and α blockers have less of an effect on the renin-angiotensin-aldosterone system.[33,34] Therefore, previous Japanese guidelines have recommended that antihypertensive drugs other than calcium channel blockers and α blockers cease prior to measuring PRA and PAC.[18,19] Thus, the subjects in the present study either took no medication or took only calcium channel blockers and α blockers.

Our study has some limitations. Only13 elderly patients received a diagnosis of PA. As only 66.7% of PA patients received AVS, none of the study subjects had detailed diagnoses, such as the type of PA. We performed three confirmatory tests and made a diagnosis of PA when more than two-thirds of the tests were positive; however, no HT patients whose ARR was over 200 received all three confirmatory tests. Some elderly patients did not receive the furosemide upright test because of hypotension during testing or weakness of the legs.

In conclusion, our study suggests that in the elderly, the ARR criteria for the screening test of PA diagnosis may be set up at a much higher level than in the non-elderly, and ARR is useful as a PA screening test even in elderly patients with hypertension. In confirmatory tests, the saline infusion test but not the captopril challenge test or the furosemide upright test may be significantly influenced by aging because of low PAC level in the elderly. The incidence of cardiovascular complications is higher in PA than in EHT, and recent studies have indicated that aldosterone induces congestive heart failure, coronary artery disease, chronic kidney disease and metabolic syndrome;[7–9] therefore, the diagnosis of PA is becoming more important. Now, opportunities to perform the diagnostic tests for PA are becoming more common for elderly hypertensive patients. As aging influences the screening and saline infusion test, on the basis of our present study, we should be careful with diagnostic tests for PA in the elderly.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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