

RESEARCH ARTICLE

Open Access



Patients with pheochromocytoma exhibit low aldosterone renin ratio-preliminary reports

Tomoko Yamada¹, Hidenori Fukuoka^{1*} , Yusei Hosokawa¹, Yukiko Odake², Kenichi Yoshida², Ryusaku Matsumoto², Hironori Bando¹, Yuko Okada¹, Yushi Hirota¹, Genzo Iguchi¹, Wataru Ogawa² and Yutaka Takahashi²

Abstract

Background: Plasma renin activity (PRA) is generally increased in patients with pheochromocytoma (PCC) due to low circulating plasma volume and activation of β -1 adrenergic receptor signaling. However, there has been no study on the aldosterone renin ratio (ARR) in patients with PCC. To elucidate the issue, this study aimed to determine the PRA, plasma aldosterone concentration (PAC), and ARR in patients with PCC and compare them with those in patients with subclinical Cushing's syndrome (SCS) and non-functioning adrenal adenoma (NFA).

Methods: In this retrospective single-center, cross-sectional study, 67 consecutive patients with adrenal tumors (PCC ($n = 18$), SCS ($n = 18$), and NFA ($n = 31$)) diagnosed at Kobe University Hospital between 2008 and 2014 were enrolled.

Results: PRA was significantly higher in patients with PCC than in those with SCS and NFA (2.1 (1.3 ~ 2.8) vs. 0.7 (0.5 ~ 1.8) and 0.9 (0.6 ~ 1.4) ng/mL/h; $p = 0.018$ and $p = 0.025$). Although PACs were comparable among the three groups, ARR was significantly lower in patients with PCC than in those with SCS and NFA (70.5 (45.5 ~ 79.5) vs. 156.0 (92.9 ~ 194.5) and 114.9 (90.1 ~ 153.4); $p = 0.001$ and $p < 0.001$). Receiver operating characteristic curve analysis demonstrated that, in differentiating PCC from NFA, PRA > 1.55 ng/mL/h showed a sensitivity of 70.0% and specificity of 80.6%. Interestingly, ARR < 95.4 showed a sensitivity of 83.3% and specificity of 86.7%, which were higher than those in PRA.

Conclusions: ARR decreased in patients with PCC, which was a more sensitive marker than PRA. Further study is necessary to understand the usefulness of this convenient marker in the detection of PCC.

Trial registration: This study was not registered because of the retrospective analysis.

Keywords: Pheochromocytoma, Adrenal incidentaloma, Renin, Aldosterone, ARR

Background

Pheochromocytoma (PCC) is a tumor arising from adrenergic chromaffin cells that commonly secrete catecholamines (CAs), namely, adrenaline (Ad), noradrenaline (NA), and dopamine (DA). CAs can stimulate all major adrenergic receptors, including α 1, α 2, β 1, and β 2 receptors. Activation of α 1 adrenergic receptors, located in vascular walls, induces

significant vasoconstriction, which chronically causes hypovolemia. Patients with PCC require surgical treatment to prevent fatal changes in hemodynamics [1]. Since life-threatening problems, such as hypovolemic shock, can occur during the perioperative period, α 1 blocker with salt loading should be administered to patients with PCC before surgery. These preoperative treatments can correct vasoconstriction and improve extracellular fluid volume [2]. Therefore, preoperative diagnosis and/or exclusion of PCC is quite important.

Measurement of plasma or urinary metanephrine (uMN) and normetanephrine (uNMN) levels is the gold standard in

* Correspondence: fukuokah@med.kobe-u.ac.jp

¹Division of Diabetes and Endocrinology, Kobe University Hospital, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

Full list of author information is available at the end of the article



© The Author(s). 2020 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

PCC screening. Because of its high sensitivity and specificity, it is quite useful in detecting and excluding pheochromocytoma [3–7]. However, a part of patients with PCC exhibit normal levels or within two-fold of the upper limit of normal levels [8]. Additionally, false-positive results for uMN or uNMN make it difficult to exclude PCC. Furthermore, in general practice, simple screening markers are needed to detect PCC from patients with hypertension.

Plasma renin activity (PRA) is increased in patients with PCC due to low circulating plasma volume and activation of β -1 adrenergic receptor signaling [9, 10]. In the differential diagnosis of adrenal incidentaloma (AI) or secondary hypertension, plasma aldosterone concentration (PAC) and PRA are routinely measured in the screening of primary aldosteronism. However, limited data have been reported regarding PAC, PRA, and aldosterone renin ratio (ARR) in patients with PCC. This study aimed to determine the difference in PAC, PRA, and ARR between patients with PCC and those with subclinical Cushing's syndrome (SCS) or non-functioning adrenal adenoma (NFA).

Methods

Subjects and study design

This retrospective cross-sectional single-center study was approved by the ethics committee of Kobe University Hospital, and written informed consent was obtained from all subjects (IRB #1351). We enrolled 83 consecutive patients with PCC, SCS, and NFA who were diagnosed and hospitalized in Kobe University Hospital between 2008 and 2014. We confirmed that all of these subjects had both PRA and PAC evaluated. Among them, patients who had received medication that can affect the renin-angiotensin aldosterone system, including aldosterone receptor blockers, diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and β -adrenergic blockers ($n = 16$), were excluded. The diagnosis of PCC was based on the Endocrine Society Guideline [11], which focused on increased uMN or uNMN levels, tumor demonstration by imaging test, and positive ^{123}I -metaiodobenzylguanidine (MIBG) scintigraphy. In all cases of PCC, the final diagnosis was histologically confirmed after surgery. The diagnosis of SCS and NFA was performed based on each guideline [12, 13].

Hormone assays

The PRA, PAC, and plasma CA levels were measured in the morning after overnight fasting in the supine position. After 24-h urinary excretion of fractionated MNs and CAs, all subjects were instructed to abstain from caffeinated foods and drinks for at least 48 h. PRA, PAC, and plasma CA levels were measured by high-performance liquid chromatography (HPLC) (LSI

Medience Corporation, Tokyo, Japan), enzyme immunoassay (BML, Inc., Tokyo, Japan), and radioimmunoassay (LSI Medience Corporation, Tokyo, Japan), respectively. The intra- and inter assay coefficients of variations for each hormone assay were as follows: PRA, < 10 and $< 15\%$; PAC, < 7.8 and $< 10.6\%$; plasma Ad, < 4.08 and $< 2.23\%$; NA, < 9.34 and $< 2.27\%$; and DA, < 8.96 and $< 2.89\%$. uMN and CA levels were measured by HPLC (LSI Medience Corporation, Tokyo, Japan). The intra- and inter assay coefficients of variations for each hormone assay were as follows: urinary Ad, < 6.21 and $< 6.35\%$; urinary NA, < 4.09 and $< 3.82\%$; urinary DA, < 5.32 and $< 4.46\%$; uMN, < 1.4 and $< 6.2\%$; and uNMN, < 0.7 and $< 5.3\%$.

Statistical analysis

Data were appropriately expressed as mean \pm standard deviation or median (interquartile range). These data were logarithmically transformed to normality before statistical analysis. We defined PCC as a control, and compared to SCS and NFA. Statistical comparisons among patients with PCC, SCS, and NFA were made using the Kruskal-Wallis test with post hoc Bonferroni's test or χ^2 test followed by Tukey's honestly significant difference test, as appropriate. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff value in the diagnosis of PCC. P -values < 0.05 were considered statistically significant. Statistical analyses were performed using with SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL).

Results

Patient characteristics

As a result, we analyzed a total of 67 patients, consisting of 18 patients diagnosed with PCC, 18 patients with SCS, and 31 patients with NFA. The clinical characteristics of 67 patients (PCC; $n = 18$, SCS; $n = 18$, and NFA; $n = 31$) are shown in Table 1. Patients consist of 28 men and 39 women (women, 58.2%), the mean age was 57 ± 15 years, and the mean body mass index (BMI) was 23.1 ± 4.1 kg/m². The mean size of the tumor was 3.3 ± 2.6 cm. Twenty-seven patients (40.3%) had hypertension and treated with calcium channel blocker (CCB) and/or α -blocker. Among the three groups, BMI in the PCC group was significantly lower than that in the SCS group (21.0 ± 3.3 vs. 24.9 ± 4.7 kg/m², $p = 0.019$). One patient with PCC was diagnosed with a familial syndrome, von Hippel-Lindau disease.

Endocrinological findings

Measurements of CA level and its metabolites in plasma and urine, adrenocorticotropin (ACTH), cortisol (F) in the morning, and F after 1-mg dexamethasone suppression test (DST), and dehydroepiandrosterone sulfate (DHEA-S), and imaging findings including tumor size

Table 1 Clinical characteristics of patients with PCC, SCS, and NFA

	Total	PCC	SCS	NFA	p value		
					Kruskal-Wallis	PCC vs SCS	PCC vs NFA
Number	67	18	18	31			
Age (yr)	57 ± 15	53 ± 19	57 ± 14	59 ± 14	0.404	–	–
Sex (males/females)	28 / 39	7 / 11	6 / 12	15 / 16	0.564	–	–
Body Mass Index (kg/m ²)	23.1 ± 4.1	21.0 ± 3.3*	24.9 ± 4.7*	23.3 ± 3.7	0.023	0.019	0.256
Systolic blood pressure (mmHg)	127 ± 19	126 ± 20	132 ± 12	126 ± 22	0.372	–	–
Diastolic blood pressure (mmHg)	74 ± 11	72 ± 9	77 ± 11	73 ± 12	0.370	–	–
Antihypertensive Drugs (%)							
CCB	25 (37%)	5 (28%)	8 (44%)	12 (39%)	0.572	–	–
α blocker	7 (10%)	3 (17%)	2 (11%)	2(6%)	0.527	–	–

CCB Calcium channel blocker, PCC pheochromocytoma, SCS subclinical cushing syndrome, NFA Non-functioning adrenal tumor
Data are expressed as mean ± S.D. *p <0.05 compared between group of PCC and SCS

and CT value are shown in Table 2. As expected, levels of CA and its metabolites in urine in patients with PCC were significantly higher than those in patients with SCS and NFA. Plasma ACTH level was lower in patients with SCS than those with PCC (9.7 (8.9 ~ 14.1) vs. 29.8 (22.8 ~ 40.3) pg/mL, *p* < 0.001), and serum F level after 1-mg DST was higher in patients with SCS than that in patients with PCC (6.1 (4.0 ~ 10.6) vs. 1.5 (1.2 ~ 1.7) µg/dL, *p* < 0.001).

PRA, PAC, and ARR in PCC

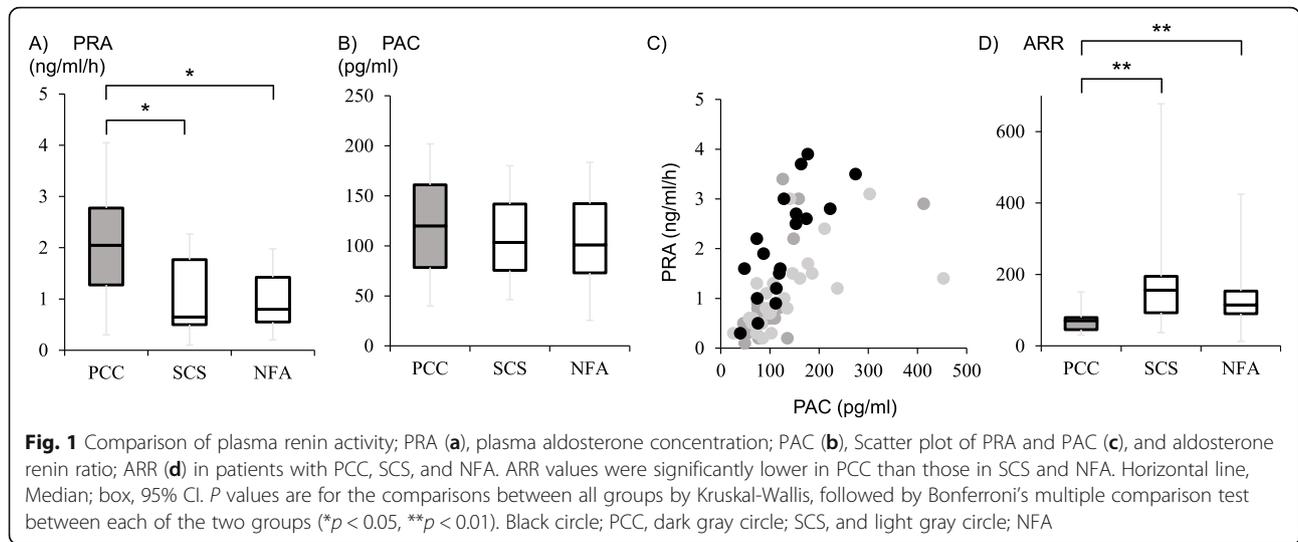
Next, PRA, PAC, and ARR in each group were compared (Fig. 1). PRA was significantly higher in patients with PCC than those with SCS and NFA (2.1 (1.3 ~ 2.8) vs. 0.7 (0.5 ~ 1.8) and 0.9 (0.6 ~ 1.4) ng/mL/h, *p* = 0.018

and *p* = 0.025; Fig. 1a). No difference in PAC was noted among the three groups (Fig. 1b). When PAC and PRA were plotted on the graph, the dots of PCC tended to present on the upper left part, suggesting that PRA was relatively higher than PAC (Fig. 1c). Intriguingly, ARR were significantly lower in patients with PCC than those in patients with SCS and NFA (70.5 (45.5 ~ 79.5) vs. 156.0 (92.9 ~ 194.5) and 114.9 (90.1 ~ 153.4), *p* < 0.001 and *p* < 0.001; Fig. 1d). Clinically, the diagnosis of PCC in patients showing either MN or NMN levels within two-fold of upper limit is challenge. Therefore, we investigated these subjects in our patients (MN; *n* = 7, NMN; *n* = 4, Both; *n* = 1, total; *n* = 10). In these subjects, lower ARR was shown compared to SCS and NFA (PCC vs. SCS and NFA, 72.6 (57.9 ~ 79.5) vs. 156.0 (92.9 ~ 194.5)

Table 2 Biochemical values and tumor characteristics in patients with PCC, SCS and NFA

	PCC	SCS	NFA	p value		
				Kruskal-Wallis	PCC vs SCS	PCC vs NFA
Plasma Ad (pmol/mL)	0.13 [¶] (0.05–0.29)	0.03 (0.02–0.03)	0.03 [¶] (0.02–0.04)	0.018	0.080	0.044
NA (pmol/mL)	0.47 ^{¶¶} (0.28–3.10)	0.25 [*] (0.16–0.35)	0.28 [¶] (0.16–0.40)	0.008	0.027	0.014
Urine Ad (µmol/day)	38.8 ^{¶¶¶} (10.6–98.6)	6.13 ^{¶¶} (4.63–7.48)	7.2 [¶] (4.35–8.88)	< 0.001	< 0.001	< 0.001
NA (µmol/day)	356 ^{¶¶¶¶} (166–1004)	99 ^{¶¶} (85–114)	110 ^{¶¶} (87–149)	< 0.001	< 0.001	< 0.001
MN (µmol/day)	0.74 ^{¶¶¶¶} (0.13–2.23)	0.09 ^{¶¶} (0.08–0.09)	0.10 ^{¶¶} (0.07–0.11)	< 0.001	< 0.001	< 0.001
NMN (µmol/day)	1.89 ^{¶¶¶¶} (1.20–3.87)	0.19 ^{¶¶} (0.16–0.22)	0.19 ^{¶¶} (0.16–0.30)	< 0.001	< 0.001	< 0.001
Plasma ACTH (pg/mL)	29.8 (22.8–40.3)	9.7 (8.9–14.1)	20.8 (13.1–38.8)	< 0.001	< 0.001	0.299
Serum F (µg/dL)	15.1 (12.3–16.9)	13.6 (12.2–16.4)	15.4 (12.7–17.0)	0.741	–	–
DHEA-S (µg/dL)	880 (559–1104)	371 (202–937)	840 (339–1191)	0.562	–	–
F after 1 mg DST (µg/dL)	1.5 (1.2–1.7)	6.1 (4.0–10.6)	1.4 (1.3–2.3)	< 0.001	< 0.001	1.000
Tumor size (cm)	4.0 ^{¶¶} (2.5–7.8)	2.7 (2.2–3.4)	2.4 ^{¶¶} (1.5–3.0)	0.001	0.204	0.001
CT value (HU)	36 ^{¶¶¶¶} (27–42)	15 ^{¶¶} (6–18)	19 ^{¶¶} (4–27)	< 0.001	< 0.001	0.003

Data are expressed as median (25-75th percentiles)
**p* <0.05 compared between group of PCC and SCS
***p* <0.005 compared between group of PCC and SCS
[¶]*p* <0.05 compared between group of PCC and NFA
^{¶¶}*p* <0.005 compared between group of PCC and NFA



and 114.9 (90.1 ~ 153.4), $p = 0.008$, respectively), demonstrating the additive utility of ARR in PCC diagnosis.

ROC curve analysis to determine the optimal cutoff value in the diagnosis of PCC revealed that PRA of 1.45 ng/mL/h was optimal in the differentiation of PCC from SCS and NFA, with a sensitivity of 72.2% and specificity of 73.5% (Table 3a, Fig. 2a). ARR of 80.9 represented the optimal cutoff value with a sensitivity of 77.8% and specificity of 85.4% (Table 3a, Fig. 2c). ARR of 95.4 represented the optimal cutoff value for the differentiation of PCC from NFA, with a sensitivity of 83.3% and specificity of 86.7% (Table 3b, Fig. 2d), while uMN or the sum of uMN and uNMN level showed a sensitivity of 100, 78% and specificity of 75, 93%, respectively. To test whether ARR could be an additional marker to

differentiate PCC from SCS and NFA, AUC (95%CI) for ROC analysis was calculated, revealing that the AUC with uMN, uNMN, and ARR 0.944 (0.889–0.999) was higher than that with uMN and uNMN 0.872 (0.766–0.978), indicating the clinical utility of ARR in PCC diagnosis.

Discussion

In this study, we demonstrated that patients with PCC exhibited low ARR compared with those with SCS or NFA. ARR provided substantial sensitivity and specificity to discriminate PCC from other AIs. Increased ARR has generally been used in the screening of primary aldosteronism in patients with hypertension or AIs. Therefore, both PAC and PRA are commonly measured in the

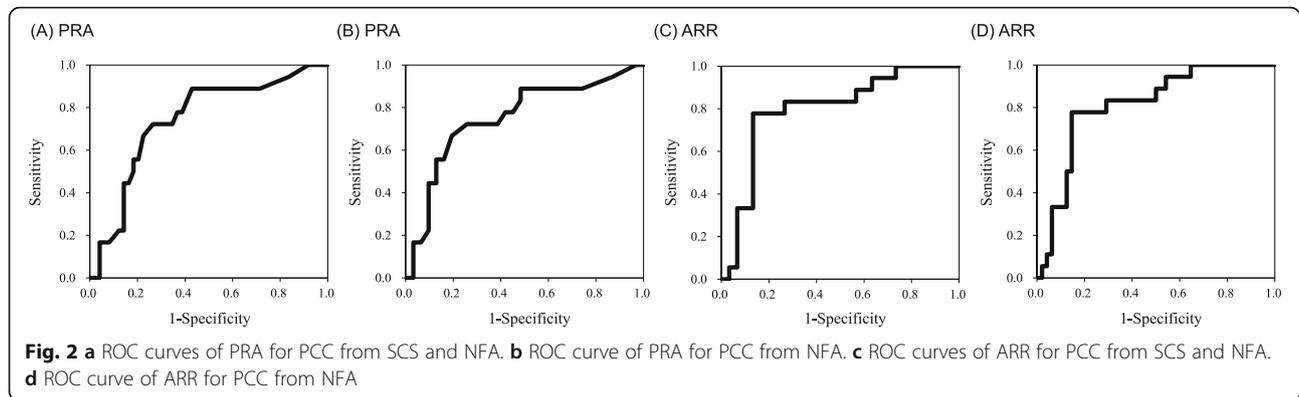
Table 3 Receiver Operating Characteristic (ROC) curves

	cutoff value	AUC	Sensitivity	Specificity	p value	confidence interval
(A) ROC curves for PCC from SCS and NFA.						
PRA	1.45	0.741	72.2	73.5	0.003	0.609–0.874
ARR	80.9	0.811	77.8	85.4	< 0.001	0.700–0.923
uMN + uNMN	0.146	0.872	77.8	92.6	< 0.001	0.766–0.978
PRA + uMN + uNMN	0.132	0.935	88.9	82.6	< 0.001	0.876–0.993
ARR + uMN + uNMN	0.213	0.944	94.4	86.7	< 0.001	0.889–0.999
(B) ROC curves for PCC from NFA.						
PRA	1.55	0.751	70.0	80.6	0.004	0.603–0.899
ARR	95.4	0.858	83.3	86.7	< 0.001	0.764–0.983
uMN + uNMN	0.218	0.859	61.1	100	< 0.001	0.743–0.975
PRA + uMN + uNMN	0.819	0.946	94.4	83.3	< 0.001	0.890–1.003
ARR + uMN + uNMN	0.718	0.939	94.4	86.2	< 0.001	0.872–1.006

PRA plasma renin activity, ARR aldosterone renin ratio

(A) uMN + uNMN; $-2.738 + 8.019 \times uMN - 0.002 \times uNMN$, PRA + uMN + uNMN; $-3.314 + 0.319 \times PRA + 8.111 \times uMN - 0.002 \times uNMN$, ARR + uMN + uNMN; $-0.054 - 0.028 \times ARR + 10.076 \times uMN - 0.004 \times uNMN$

(B) uMN + uNMN; $2.203 - 6.983 \times uMN + 0.003 \times uNMN$, PRA + uMN + uNMN; $2.798 - 0.338 \times PRA - 7.032 \times uMN - 0.003 \times uNMN$, ARR + uMN + uNMN; $-0.584 + 0.031 \times ARR - 9.848 \times uMN + 0.005 \times uNMN$



routine diagnostic process in AIs and suspicion of secondary hypertension. The present data suggest that the application of ARR in the screening of PCC as in primary aldosteronism may be useful.

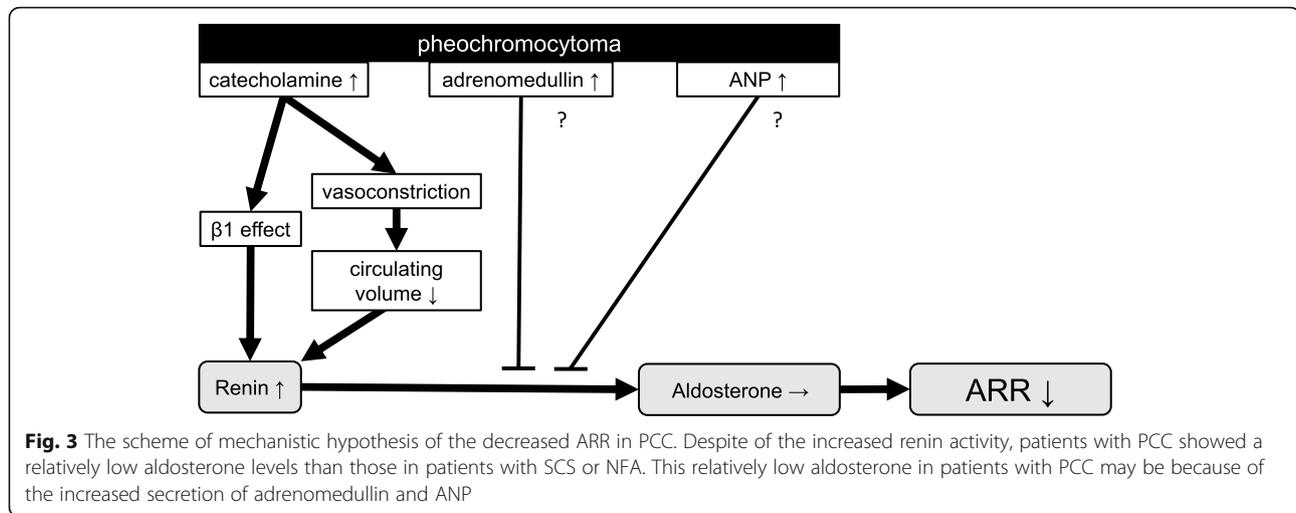
Measurement of plasma MN and uMN levels in the diagnosis of PCC shows excellent sensitivity (70.8–100.0% and 80.0–97.0%) and specificity (79.4–97.6% and 69.0–95.1%) [3–7]; therefore, it has been used as a gold standard. Indeed, in the present study, increased levels of uMN and uNMN provided the highest sensitivity (80 and 100%, respectively) and specificity (100 and 75%, respectively) in the diagnosis of PCCs with an area under the ROC curve of 0.875 and 0.950, respectively. Thus, our data supports that measurements of MN level are recommended to screen PCC as demonstrated in the guidelines [11].

However, in clinical practice, there are some atypical AIs, such as PCCs without an increase in MN level and NFAs with a marginal increase in MN level [14]. In our series, we encountered a patient with NFA who showed increased plasma NA and uNMN levels (plasma NA, 0.63 pmol/mL [reference range, 0.15–0.57 pmol/mL], uNMN, 0.186 µg/day [reference range, 0.029–0.120 µg/day]). Additionally, the patient had bilateral adrenal tumors (2.8 cm on the left, 1.9 cm on the right). ¹²³I-MIBG scintigraphy demonstrated that accumulation was detected only in the left tumor. This patient underwent left adrenalectomy, and the final diagnosis was NFA. Preoperative endocrinological examination showed PRA of 0.2 ng/mL/h, PAC of 85 pg/mL, and ARR of 425. To exclude primary aldosteronism, we repeated the examination showed low PRA (0.3 ng/mL/hr), with rather less PAC (31.9 pg/mL), suggesting this high ARR might be due to pseudo-aldosteronism rather than autonomous aldosterone hypersecretion. In fact, both PRA and PAC were not altered after adrenalectomy (0.6 ng/ml/hr. and 57 pg/mL, respectively). These data suggest that the evaluation of ARR provided additional information for accurate diagnosis. Furthermore, PCCs with normal MN levels have also been reported [8, 15]. In such cases,

ARR may be helpful in the diagnosis of PCC as an additional marker. In fact, our data suggested ARR was useful in patients with PCC, who showed MN level within two-fold of upper limit.

It is well known that increased CA secretion in PCC causes chronic vasoconstriction, resulting in low circulating volume, which increases PRA [9]. Moreover, CAs directly stimulate renin secretion via a β1-adrenergic receptor-mediated process [10] (Fig. 3), leading to increased PRA in PCCs (Fig. 1a). In contrast, there were no differences in PAC between the three groups (Fig. 1b). Interestingly, ROC curve analysis revealed that low ARR had higher sensitivity and specificity than increased PRA to discriminate PCC. These data suggest that aldosterone levels were relatively low despite the increased PRA in each case of PCC. Indeed, when PAC and PRA were plotted on the graph, the dots of PCC tended to present on the upper left part, suggesting that PAC was relatively lower than PRA in each case (Fig. 1c). There are several plausible explanations for this phenomenon. First, adrenomedullin (AM) is a peptide hormone that lowers blood pressure via vasodilation, which was originally isolated from PCC, and has been shown to induce renin resistance with ARR suppression [16]. Since plasma AM level is generally high in PCC [17], this could suppress ARR. Another possibility is atrial natriuretic polypeptide (ANP), whose plasma levels are generally increased in PCC [18]. ANP reduces angiotensin II-dependent aldosterone secretion that causes decreased ARR. Moreover, ANP-dependent renal sodium excretion also leads to suppression of aldosterone production [18–20] (Fig. 3).

Regarding preoperative preparation of PCC, it is critical to normalize circulating volume by α-blocker administration to prevent perioperative complications [21]. In this aspect, it is important to have multiple biomarkers in the diagnosis or exclusion of PCC in addition to CAs preoperatively. Computed tomography (CT) value < 10 HU is a useful marker to rule out PCC in AIs [22]. However, CT value is high in various pathological conditions, such as adrenocortical carcinoma and



metastatic adrenal mass. ^{123}I -MIBG scintigraphy is also quite useful in the diagnosis of PCC with sensitivity of 85–88% and specificity of 84–100% [23–26]. However, the availability of this imaging equipment is limited especially in primary physicians. It is considered that the additional use of the convenient biomarker ARR in combination with the general information may help in obtaining a more accurate diagnosis.

There are several limitations in this study. This is a retrospective study, and the sample size is small, so it is necessary to validate these results in a large-scale cohort study. In addition, because there were few borderline MN and NMN values patients in this study, we cannot conclude whether ARR was really useful for these borderline cases. Further larger scale investigation is necessary to verify this point. Additionally, because some patients with NFA did not undergo surgery, we cannot completely exclude the possibility that PCC may be present in the NFA group. In this study, the patients taking α -blocker was included. Since α -blocker can restore the circulating plasma volume in patients with PCC, the effect of this drug on lowering PRA levels cannot be excluded. In this study, PCC patients taking α -blocker included 3 subjects. These indicate that ARR can be used as an additional marker even if these drugs have been taken. Finally, because postoperative ARR could not be sufficiently studied, further longitudinal prolong evaluation is required to clarify whether this convenient index could be a useful biomarker at the post-operative state. To simplify the design, we restricted the patients in this study to α -blocker and/or CCB users only. However, in the primary care clinic, it sometimes difficult to adjust the drugs for screening test. We think further investigation will be required whether this convenient ARR will also be useful in patients using other antihypertensive drugs such as β -blocker, diuretics, and ARB/ACEi. β -

blockers are expected to increase ARR and diuretics and ARB/ACEi decrease [27]. However, the antihypertensive drugs might be adjusted for screening of adrenal-dependent hypertension including PA in patients with adrenal incidentalomas. We think this study could be helpful at least in these groups.

Conclusion

We demonstrated that patients with PCC exhibited low PAC/PRA than those with NFA or SCS, indicating that low ARR indicated the possibility of PCC. Further investigation is necessary to clarify whether this convenient index, “ARR,” will help in the diagnosis of PCC.

Abbreviations

PRA: Plasma renin activity; PCC: Pheochromocytoma; ARR: Aldosterone renin ratio; PAC: Plasma aldosterone concentration; SCS: Subclinical Cushing's syndrome; NFA: Non-functioning adenoma; ROC: RECEIVER Operator Characteristic; CA: Catecholamine; Ad: Adrenaline; NA: Noradrenaline; DA: Dopamine; MN: Metanephrine; NMN: Normetanephrine; AI: Adrenal incidentaloma; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; MIBG: Metaiodobenzylguanidine; HPLC: High performance liquid chromatography; EIA: Enzyme immunoassay; RIA: Radioimmunoassay; BMI: Body mass index; CCB: Calcium channel blocker; ACTH: Adrenocorticotropic; F: Cortisol; DST: Dexamethasone suppression test; DHEA-S: Dehydroepiandrosterone sulfate; CT: Computed tomography; AM: Adrenomedullin; ANP: Atrial natriuretic polypeptide

Acknowledgements

We thank our biostatisticians of the clinical & translational research center at Kobe University Hospital for their excellent discussion and suggestions.

Authors' contributions

TY and HF designed the study. TY, HF, YH, OY, KY, RM HB, YO, and YH collected the data. TY, HF, YH, GI, and YT analyzed the data. TY, HF, WO, and YT wrote the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported in part by Grants-in-Aid for Scientific Research from the Japanese Ministry of Education Science, Culture, Sports, Science, and Technology (15 K09432 (HF), and 24790945 (HF)), Grants-in-Aid for Scientific

Research (research on hypothalamic-hypophyseal disorders) from the Ministry of Health, Labor and Welfare of Japan.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and its amendments, and it was approved by the institutional review boards of the participating facilities (Kobe University Hospital ethical committee; IRB #1351). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests in this section.

Author details

¹Division of Diabetes and Endocrinology, Kobe University Hospital, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. ²Division of Diabetes and Endocrinology, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan.

Received: 14 January 2020 Accepted: 31 August 2020

Published online: 11 September 2020

References

- Pacak K. Preoperative management of the pheochromocytoma patient. *J Clin Endocrinol Metab.* 2007;92(11):4069–79.
- Perry LB, Gould AB Jr. The anesthetic management of pheochromocytoma: effect of preoperative adrenergic blocking drugs. *Anesth Analg.* 1972;51:36–40.
- Perry CG, Sawka AM, Singh R, Thabane L, Bajnarek J, Young WF Jr. The diagnostic efficacy of urinary fractionated metanephrines measured by tandem mass spectrometry in detection of pheochromocytoma. *Clin Endocrinol.* 2007;66(5):703–8.
- Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P, et al. Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA.* 2002;287(11):1427–34.
- Unger N, Pitt C, Schmidt IL, Walz MK, Schmid KW, Philipp T, et al. Diagnostic value of various biochemical parameters for the diagnosis of pheochromocytoma in patients with adrenal mass. *Eur J Endocrinol.* 2006;154(3):409–17.
- Hickman PE, Leong M, Chang J, Wilson SR, McWhinney B. Plasma free metanephrines are superior to urine and plasma catecholamines and urine catecholamine metabolites for the investigation of pheochromocytoma. *Pathology.* 2009;41(2):173–7.
- Grouzmann E, Drouard-Troalen L, Baudin E, Plouin PF, Muller B, Grand D, et al. Diagnostic accuracy of free and total metanephrines in plasma and fractionated metanephrines in urine of patients with pheochromocytoma. *Eur J Endocrinol.* 2010;162(5):951–60.
- Kota SK, Kota SK, Panda S, Modi KD. Pheochromocytoma: an uncommon presentation of an asymptomatic and biochemically silent adrenal incidentaloma. *Malays J Med Sci.* 2012;19(12):86–91.
- Skøtt O, Jensen BL. Cellular and intrarenal control of renin secretion. *Clin Sci.* 1993;84(1):1–10.
- Kopp U, DiBona GF. Interaction of renal beta 1-adrenoceptors and prostaglandins in reflex renin release. *Am J Phys.* 1983;244(4):F418–24.
- Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al; Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2014;99(6):1915–42.
- Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2008;93(5):1526–40.
- Zeiger MA, Thompson GB, Duh QY, Hamrahian AH, Angelos P, Elaraj D, American Association of Clinical Endocrinologists; American Association of Endocrine Surgeons, et al. American Association of Endocrine Surgeons. American Association of Clinical Endocrinologists and American Association of endocrine surgeons medical guidelines for the Management of Adrenal Incidentalomas: executive summary of recommendations. *Endocr Pract.* 2009;15(5):450–3.
- Lee JA, Zarnegar R, Shen WT, Kebebew E, Clark OH, Duh QY. Adrenal incidentaloma, borderline elevations of urine or plasma metanephrine levels, and the "subclinical" pheochromocytoma. *Arch Surg.* 2007;142(9):870–4.
- Heavner MG, Krane LS, Winters SM, Mirzazadeh M. Pheochromocytoma diagnosed pathologically with previous negative serum markers. *J Surg Oncol.* 2015;112(5):492–5.
- Charles CJ, Lainchbury JG, Nicholls MG, Rademaker MT, Richards AM, Troughton RW. Adrenomedullin and the renin-angiotensin-aldosterone system. *Regul Pept.* 2003;112(1–3):41–9.
- Bravo EL. Evolving concepts in the pathophysiology, diagnosis, and treatment of Pheochromocytoma. *Endocr Rev.* 1994;15(3):356–68.
- Hu W, Shi L, Zhou PH, Zhang XB. Plasma concentrations of adrenomedullin and atrial and brain natriuretic peptides in patients with adrenal pheochromocytoma. *Oncol Lett.* 2015;10(5):3163–70.
- Atarashi K, Mulrow PJ, Franco-Saenz R, Snajdar R, Rapp J. Inhibition of aldosterone production by an atrial extract. *Science.* 1984;224(4652):992–4.
- Nicholls MG. Hemodynamic and hormonal actions of adrenomedullin. *Braz J Med Biol Res.* 2004;37(8):1247–53.
- Prys-Roberts C, Farndon JR. Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. *World J Surg.* 2002;26(8):1037–42.
- Buitenwerf E, Berends AMA, van Asselt ADI, Korteweg T, Greuter MJW, Veeger NJM, et al. Diagnostic accuracy of computed tomography to exclude Pheochromocytoma: a systematic review, meta-analysis, and cost analysis. *Mayo Clin Proc.* 2019;94(10):2040–52.
- Bhatia KS, Ismail MM, Sahdev A, Rockall AG, Hogarth K, Canizales A, et al. 123I-metaiodobenzylguanidine (MIBG) scintigraphy for the detection of adrenal and extraadrenal pheochromocytomas: CT and MRI correlation. *Clin Endocrinol.* 2008;69(2):181–8.
- Wiseman GA, Pacak K, O'Dorisio MS, Neumann DR, Waxman AD, Mankoff DA, et al. Usefulness of 123I-MIBG scintigraphy in the evaluation of patients with known or suspected primary or metastatic pheochromocytoma or paraganglioma: results from a prospective multicenter trial. *J Nucl Med.* 2009;50(9):1448–54.
- Fiebrich HB, Brouwers AH, Kerstens MN, Pijl ME, Kema IP, de Jong JR, et al. 6-[F-18]Fluoro-L-dihydroxyphenylalanine positron emission tomography is superior to conventional imaging with (123I)-metaiodobenzylguanidine scintigraphy, computer tomography, and magnetic resonance imaging in localizing tumors causing catecholamine excess. *J Clin Endocrinol Metab.* 2009;94(10):3922–30.
- Milardovic R, Corssmit EP, Stokkel M. Value of 123I-MIBG scintigraphy in paraganglioma. *Neuroendocrinology.* 2010;91(1):94–100.
- Mulatero P, Rabbia F, Milan A, Paglieri C, Morello F, Chiandussi L, et al. Drug effects on aldosterone/plasma renin activity ratio in primary aldosteronism. *Hypertension.* 2002;40(6):897–902.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

