Hypertension Research
https://doi.org/10.1038/s41440-024-01666-y

COMMENT

Where and how are we going? Simplifying the definitive diagnosis of primary aldosteronism

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Received: 15 February 2024 / Revised: 8 March 2024 / Accepted: 13 March 2024

Keywords Chemiluminescent enzyme immunoassay · Liquid chromatography-mass spectrometry/mass spectrometry · Plasma aldosterone concentration · Primary aldosteronism · Radioimmunoassay

Primary aldosteronism (PA) is the most common cause of secondary hypertension in adults [1, 2]. In Japan, plasma aldosterone concentration (PAC) measurements have typically relied on radioimmunoassay (RIA) methods such as the Spac-S® kit (Fujirebio Inc., Tokyo, Japan), which was discontinued in March of 2021. In a recent study, we compared and commutated blood aldosterone measurements using clinical specimens to clarify the commutability among RIA-equivalent values, liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) values, and chemiluminescent enzyme immunoassay (CLEIA) kits [3]. LC-MS/MS is emerging as a promising method for clinical examination, offering more accurate and reproducible aldosterone estimations than traditional methods [4–6]. However, regression analysis indicated significant discrepancies between RIA values estimated using Spac-S® compared to other methods, likely owing to the low specificity of RIA antibodies and variation in measurements [3]. We found that the median LC-MS/MS value corresponding to 120 pg/mL of RIA was 48.5 pg/mL [3]. Tezuka et al. have reported that novel CLEIA methods may serve as alternative standards for PACs, suggesting other applications for CLEIAs in clinical practices [7]. Furthermore, the Japan Endocrine Society has proposed new criteria for PA screening and confirmatory testing, although these diagnostic cutoffs currently lack sufficient validation [8]. The captopril challenge test (CCT) is a well-established method for distinguishing PA from essential hypertension [9]. According to a recent meta-analysis, CCT has been reported to exhibit high and comparable accuracy for diagnosing PA, as it is safe and much easier to perform [10]. Thus, CCT appears to be one of the main and most appropriate confirmatory tests for the definitive diagnosis of PA. The first version of The Japan Endocrine Society guidelines for the diagnosis and treatment of PA (2009) described the CCT procedure as follows: (1) administration of 50 mg captopril (four crushed 12.5 mg captopril [Captoril®] tablets); (2) sampling of blood after 60-min bed rest (or 90 min of rest in the sitting position); and (3) evaluation of the test results, wherein a PAC/plasma renin activity (PRA) ratio (ARR) of >200 pg/mL per ng/mL/h (or a PAC of >120 pg/mL) indicates a positive result [11]. However, Tezuka et al. reported that no studies have yet compared PACs measured using CLEIA and conventional RIA methods in the same blood samples obtained from confirmatory tests [7]. Moreover, there are often questions surrounding PAC values obtained from clinical laboratory centers—such as whether the values are abnormally high (thus suggesting PA) simply because the CLEIA values must be converted to conventional RIA values in order to evaluate PA according to the criteria outlined in the guidelines. Tezuka et al. compared CLEIA-based PACs with RIA using 297 plasma samples [7]. They reported that the distributions of CLEIA- and RIA-PACs (medians with interquartile ranges) were 9.30 [4.00, 17.70] and 19.30 [12.35, 30.50] ng/dL, respectively. They concluded that the use of the conventional cutoff value could result in missing approximately half of patients with PA tested using CLEIA. They also proposed an ARR of 8.2 ng/dL per ng/mL/h as an alternative cutoff value for CLEIA-based CCT to diagnose PA, which is consistent with the former criteria. The Japan Endocrine Society has recently published a new guideline for PA, which sets a new

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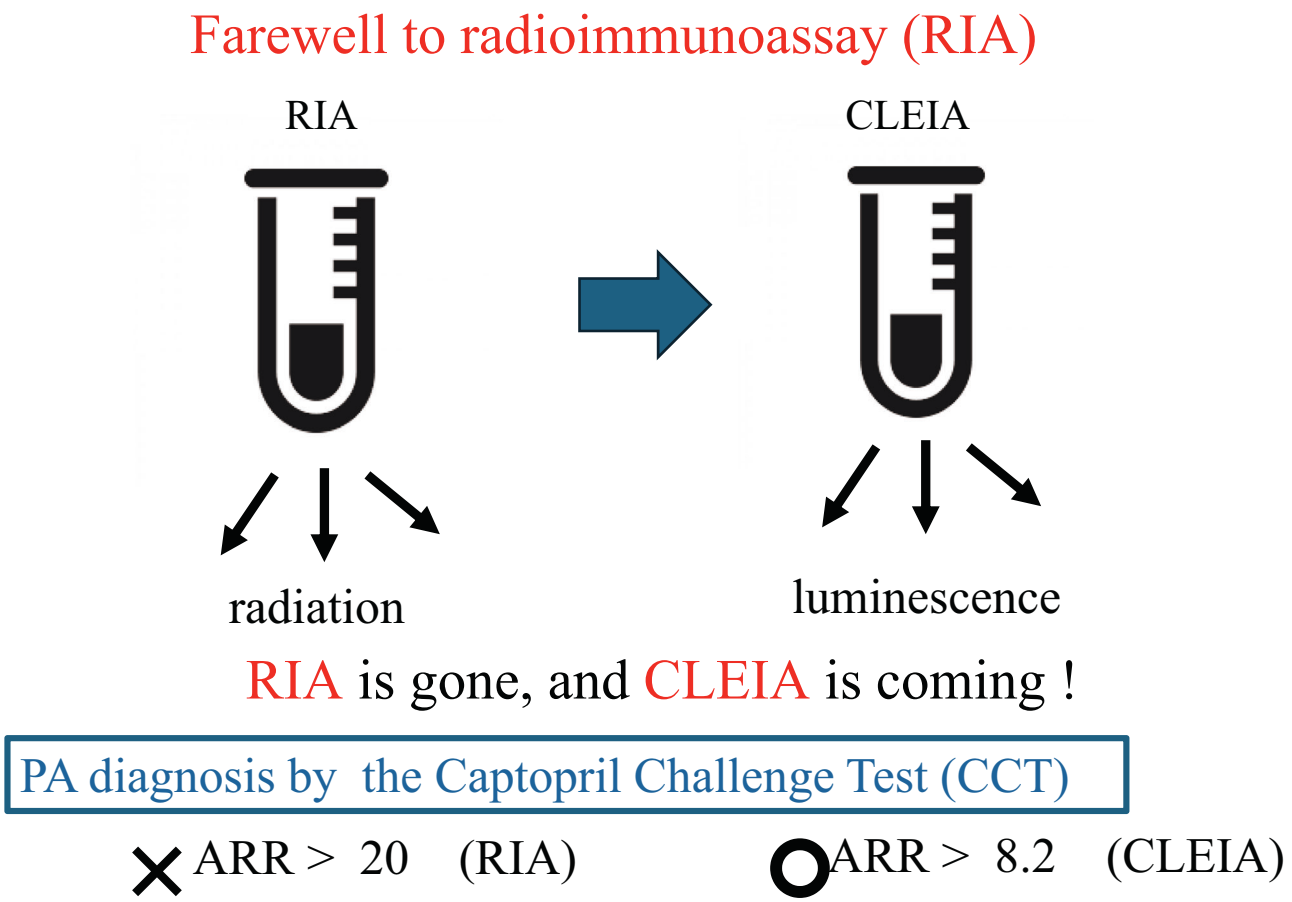
Published online: 08 April 2024

Graphical Opinion



CCT criterion of "provisional positive" for PA (ARR: 10–20 ng/dL per ng/mL/h) in addition to a "positive" category (ARR: >20 ng/dL per ng/mL/h) [8]. Tezuka et al. emphasized that the "provisional positive" cutoff was designed based on the conversion formula from CLEIA-PAC to RIA-PAC, but not on any validation using actual blood samples. They found that 28.2% and 17.2% of patients with positive RIA-based CCTs fell into "provisional positive" and "negative" criteria, respectively, of the CCT-based novel CLEIA evaluation. Furthermore, these groups harbored 17 and 5 unilateral PA (UPA) cases, respectively, in which adrenalectomy procedures would likely lead to PA remission. Furthermore, their study revealed that CLEIA-ARR could identify surgically treatable PA cases more efficiently than RIA-ARR. This was the first study to verify these CCT cutoff values for accurately diagnosing PA in patients with hypertension. They also reported that the lowest CLEIA-based ARR at CCT was 3.32 ng/dL per ng/mL/h (33.2 pg/mL per ng/mL/h) among patients with UPA. Of their 95 UPA cases, 85 had aldosterone-producing adenomas (APAs) and 10 had aldosterone-producing nodules or multiple micronodules. The CLEIA-ARR was higher in APA cases than in others. In addition, the CLEIA-ARRs correlated with the maximum APA diameters, in the cases with APAs. Thus, CLEIA-ARRs may also be useful for diagnosing UPA and predicting the size and pathology of aldosterone-producing lesions, although further investigations of this notion are warranted. We previously reported that CCT revealed higher ARRs in patients with aldosterone-producing macroadenoma than in those with aldosterone-producing microadenoma (APmicroA) or idiopathic hyperaldosteronism (IHA), whereas the ARRs of patients with APmicroA were similar to those of patients with IHA [12]. Therefore, APmicroA may be misdiagnosed as IHA if clinicians attempt to distinguish APA from IHA based on the findings of imaging methods such as adrenal computed tomography and magnetic resonance imaging. We emphasize that it is important to accurately diagnose APmicroA, in which the aldosterone excess is only detectable by ACTH-stimulated adrenal vein sampling, and to treat these patients via unilateral adrenalectomy to avoid long-term medical treatment and prevent hypertensive vascular complications, as has been previously reported [12]. It is generally accepted that

Table 1 Proposed CLEIA-PAC and CLEIA-ARR cutoff values for diagnosing primary aldosteronism

RIA value	CLEIA value
PAC[a] >120 pg/mL	>47.51 ± 2.93 pg/mL (LC-MS/MS equivalent values. The lower and upper limits of the 95% confidence intervals in the kit ranged between 35.8–53.9 pg/mL) [3]
ARR[b] >200 pg/mL per ng/mL/h	>82 pg/mL per ng/mL/h (8.2 ng/dL per ng/mL/h)

CLEIA chemiluminescent enzyme immunoassay, *PAC* plasma aldosterone concentration, *ARR* plasma aldosterone concentration/plasma renin activity ratio, *RIA* radioimmunoassay, *LC-MS/MS* liquid chromatography-mass spectrometry/mass spectrometry, *CCT* captopril challenge test

[a]Basal aldosterone

[b]Plasma renin activity and aldosterone after CCT

an RIA-ARR of >200 pg/mL per ng/mL/h (20 ng/dL per ng/mL/h) can be used to diagnose PA following CCT before using CLEIA kits. Alternatively, the cutoff ARR value of 82 pg/mL per ng/mL/h (8.2 ng/dL per ng/mL/h) for CLEIA-based CCT can now be used to diagnose PA, according to the well-established data reported by Tezuka et al. [7]. The new guidelines [8] recommend judging the screening test to be positive when ARR is ≥200 pg/mL per ng/mL/h and PAC is ≥60 pg/mL, although there is still no strong evidence for the CLEIA-ARR or -PAC cutoff values. We are entering a new era in terms of accurately diagnosing PA, as well as investigating its pathogenesis and related disorders clinically, using CLEIA kits that measure LC-MS/MS equivalent values of aldosterone. We therefore propose new cutoff values for both CLEIA-ARR and CLEIA-PAC in Table 1.

Acknowledgements This study was partly supported by the Grant Research on Intractable Diseases provided by the Japanese Ministry of Health, Labor, and Welfare. We would like to thank Editage (www.editage.jp) for English language editing.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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