

Plasma Renin Activity: An Assay with Ongoing Clinical Relevance

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Featured Article: Fyhrquist F, Soveri P, Puutula L, Stenman U-H. Radioimmunoassay of plasma renin activity. *Clin Chem* 1976;22:250–6.²

In the early 1970s there was a growing need for reliable and clinically useful methods for the determination of the activity of the renin-angiotensin system. Bioassay methods for renin activity, although valuable in early research, were too cumbersome and unreliable for clinical use. RIAs for plasma angiotensin II were of limited clinical value because of their lack of specificity, the need for extraction procedures, and insufficient sensitivity. We therefore developed a sensitive and specific assay of plasma renin activity (PRA)³. Plasma was acidified with a mixture of hydrochloric acid and the enzyme inhibitor hydroxyquinoline, to ensure optimal incubation pH (6.0) (1) and sufficient inhibition of proteolytic breakdown of generated angiotensin I (Ang I). Samples were then incubated for 1 h at 37 °C (blanks at 0 °C), and the amount of Ang I generated was measured by RIA. We used minimal dilution of plasma to avoid dilution bias. A strength of the assay protocol was its simplicity. When stored frozen, the incubation mixture could be assayed repeatedly, a characteristic that is often important, for example in the evaluation of renal venous PRA. In the routine setting, 6.25 pg of Ang I could be detected, corresponding to a rate of 0.16 µg L per hour. Therefore, our assay method covered the whole range of clinically important PRA values.

We showed, using isoelectric focusing, that monoiodinated ¹²⁵I-labeled Ang I used for RIA of generated Ang I remained stable. Recovery of Ang I added before incubation ranged from 92% to 97%. Sensitivity, accuracy, and reproducibility of the PRA assay methods were judged excellent or good. Our assay of PRA was one of the most sensitive of those reported at that time, including 7 commercially available methods. Several other methods required prolonged incubation (>2–3 h) to achieve sufficient sensitivity, usually at the cost of nonlinearity of Ang

I production and hence distortion of PRA results. The PRA measurement dataset we reported, for plasma from 928 healthy or diseased individuals, was probably the largest available published series at that time.

At the time when our report was published, there was a lively debate concerning optimal measurement of PRA (2), and complete consensus still has not yet been reached. The first reports of inactive renin or prorenin in plasma were published at that time (3). These reports reinforced the importance of proper handling of plasma samples to avoid cryoactivation or proteolytic activation of prorenin. The later development of immunoradiometric assays of plasma renin concentration and direct assays of prorenin provided complementary information to PRA determinations, but these assays have not replaced adequate PRA assays, which are still needed for both clinical and research purposes. To mention one example, PRA determinations are needed to evaluate the degree of renin inhibition in patients treated with renin inhibitors (4).

Our PRA assay was extensively used in both clinical research and practice for the next 30 years. Based on our method, a commercially available kit for PRA determination was developed and produced between 1975 and 1998 by Medix Biochemica, Kauniainen, Finland, and was distributed worldwide. The widespread use of this commercial assay obviously led to frequent citations of our article. Our PRA assay was later modified to include an RIA incubation for 1 h at 37 °C for rapid determination of PRA within 2.5–3.0 h (5), probably the first reported RIA method applying a 37 °C incubation temperature. This latter modification most likely stimulated additional interest in our original PRA assay.

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² This paper has been cited more than 235 times since publication.

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³ Nonstandard abbreviations: PRA, plasma renin activity; Ang I, angiotensin I.