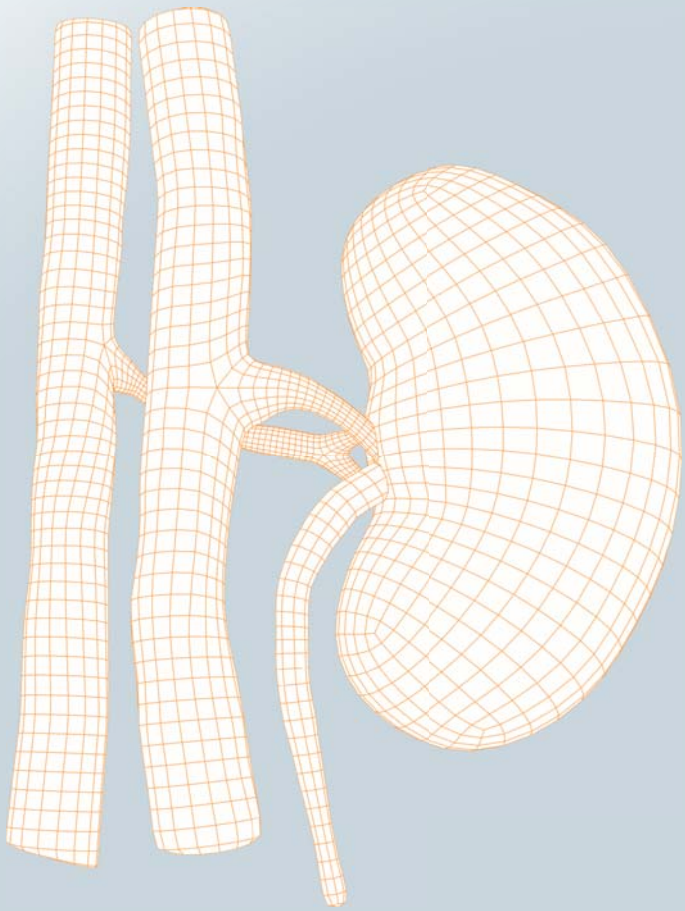
Hypertension

Direct Renin

How, when and why to measure renin



DiaSorin

The Diagnostic Specialist

THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

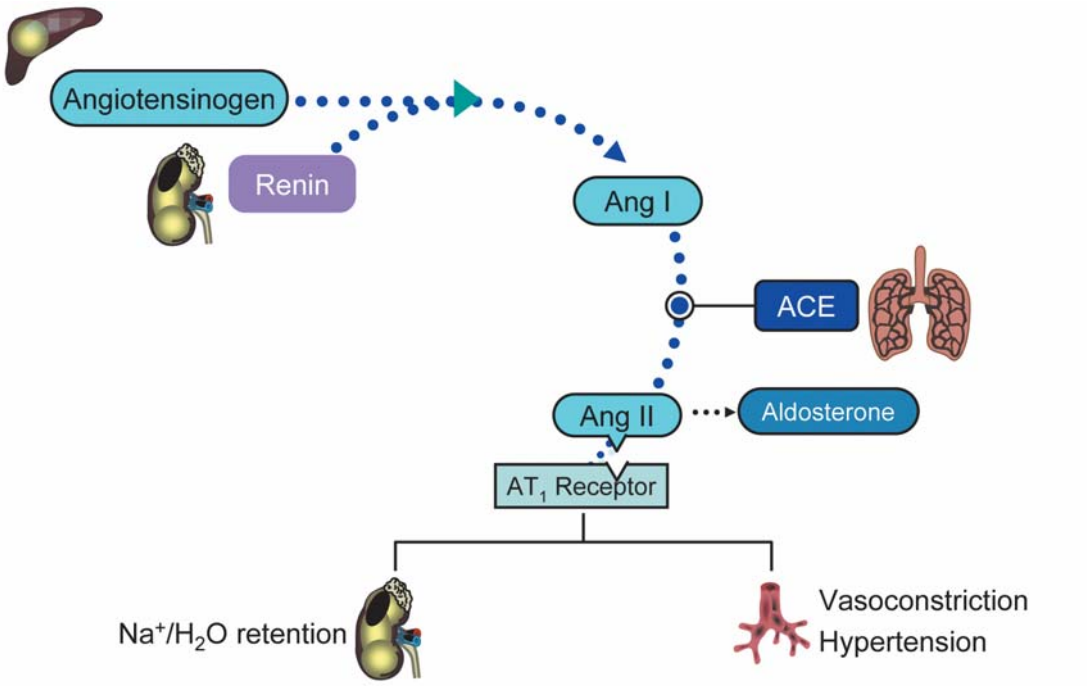
Biochemistry and physiology

The renin-angiotensin-aldosterone system is an enzymatic-hormonal cascade regulating sodium and water homeostasis and blood pressure.

The driving component of renin-angiotensin-aldosterone system is renin, an aspartyl-protease synthesized in the cells of the juxtaglomerular apparatus and released in response to a number of stimuli including sodium depletion, reduction in blood volume, hypotension and adrenergic activation.

Renin action on angiotensinogen, a substrate synthesized in the liver, generates a decapeptide, angiotensin I, which, in turn, is converted by angiotensin-converting enzyme to angiotensin II, the final product of the system.

Classic understanding of the renin-angiotensin-aldosterone system



Adapted from: Laragh JH. 1989

Angiotensin II, via its specific receptors, exerts numerous functions, the most relevant ones being stimulation of aldosterone synthesis and release and arterial vasoconstriction.

Through these two main mechanisms angiotensin II restores blood volume and increases blood pressure, thus offsetting the activation of the system.

In addition angiotensin II potentiates cardiac contraction, enhances noradrenalin release from the nerve endings, stimulates growth factors and favours the production of pro-inflammatory substances which may contribute to the development of atherosclerosis.

Moreover the finding that all the components of the system are present in several organs has led to the recognition of local renin-angiotensin-aldosterone system whose action can reinforce those of circulating angiotensin II.

As a result, renin-angiotensin-aldosterone system has emerged as one of the leading factors in cardiovascular regulation and a therapeutic target in numerous cardiovascular diseases.

WHEN AND WHY TO MEASURE RENIN

Clinical conditions in which the evaluation of the RAAS is indicated

- **Secondary forms of hypertension**
  - Renovascular-renin-secreting tumours
  - Primary hyperaldosteronism
  - Licorice ingestion / Corticosteroid treatment
  - Contraceptive (pill) hypertension
- **Selection of anti-hypertensive treatment**
- **Cardiac failure**
- **Malignant / Resistant hypertension**
- **Dialysis hypertension**
- **Cirrhosis**

- The evaluation of renin is crucial for the diagnosis of the two most common forms of secondary hypertension, i.e. renovascular hypertension and Conn's syndrome or primary hyperaldosteronism due either to an aldosterone-producing adenoma or to adrenal hyperplasia (idiopathic hyperaldosteronism, IHA).
- Recent epidemiological studies indicate that renovascular hypertension and primary aldosteronism, far from being rare conditions, are responsible for 15-20% of all cases of arterial hypertension.

Identifying primary aldosteronism

- When primary aldosteronism is suspected, measurement of renin and aldosterone are customary to calculate the aldosterone-renin ratio, the most reliable screening test for separating these patients from those with low-renin essential hypertension.
- The combination of elevated plasma aldosterone with suppressed renin generating high aldosterone-renin ratio values is strongly suggestive of primary aldosteronism and is a prerequisite for performing more invasive tests such as saline infusion to examine adosterone suppressibility and adrenal vein sampling.
- A recent comparative study has shown that the LIAISON® Direct Renin assay has the capacity of discriminating patients with very low renin levels (i.e. below 5 µIU/mL), thus allowing accurate determination of aldosterone-renin ratio.

Prevalence of primary aldosteronism in the PAPY study

Patients recruited	**1121**
Primary hyperaldosteronism	**118 (10.5%)**
Aldosteronoma	**49 (41%)**
Adrenal hyperplasia (mono / bilateral)	**69 (59%)**

Rossi GP, et al. J Am Coll Cardiol 2006; 48:2293-2300.

Evaluating renovascular hypertension

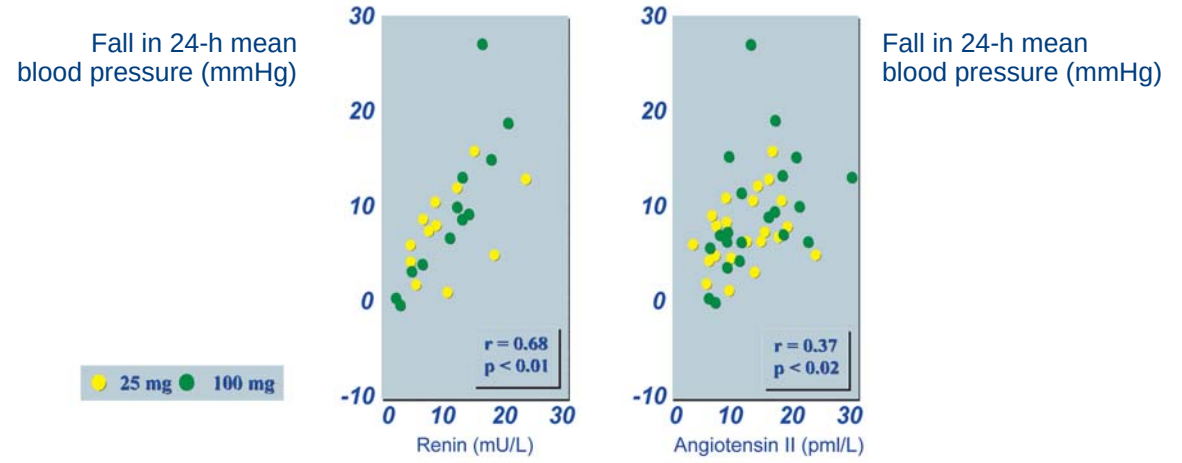
- In renovascular hypertension the reduction in renal blood flow due to renal artery stenosis stimulates renin release with increase in circulating angiotensin II leading to systemic vasoconstriction, augmented aldosterone secretion, volume expansion and, eventually, hypertension.
- Under these circumstances the measurement of renin in peripheral blood or in samples collected from the renal veins is critical for assessing the relevance of renal artery stenosis and/or anticipating whether patients may benefit from dilatation of stenotic arteries.

WHEN AND WHY TO MEASURE RENIN

Driving the anti-hypertensive therapy

- Also in patients with essential hypertension renin profiling is useful for selecting the most effective antihypertensive treatment.
- Early and more recent studies have shown that hypertensive patients with high native renin levels respond better to angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists whereas those with low-normal renin respond better to diuretic or calcium antagonists.

Relationship between basal level of renin and angiotensin II and fall in blood pressure after Irbesartan treatment

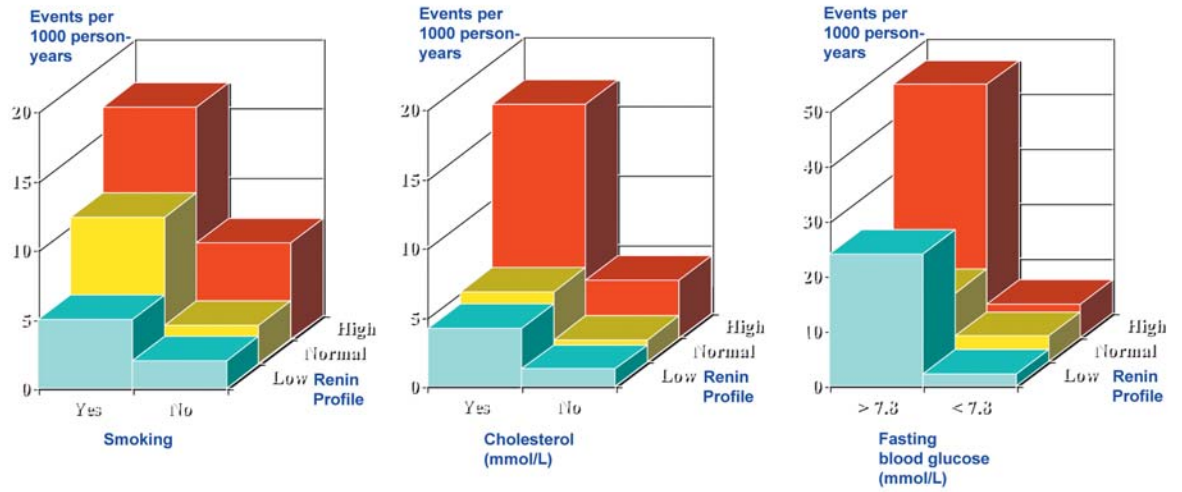


From: Van den Meiracker et al., Hypertension 1995; 25: 22-29

Risk of myocardial infarction

- Finally there is increasing evidence that renin, in itself, is a cardiovascular risk factor.
- Indeed hypertensive patients with high renin values are at greater risk of myocardial infarction than those with low-normal renin, being equal the other known risk factors.
- Moreover in patients with heart failure a high renin profile is associated with shorter survival.
- Thus renin profiling could be useful for risk stratification.

Incidence of myocardial infarction according to renin profile and other cardiovascular risk factors



From Alderman MH et al., N Engl J Med 1991; 324: 1098-1104

HOW TO MEASURE RENIN

Plasma renin activity assays

The activity of renin-angiotensin-aldosterone system is usually evaluated with the measurement of plasma renin activity (PRA) expressed in ng/mL/h.

This enzymatic method is based on the RIA quantification of angiotensin I generated by the reaction between renin and angiotensinogen during 1 – 3 hours of incubation carried out at 37° C and pH 5.7 – 6.0.

PRA has the advantage of taking into account angiotensinogen concentrations, which may be variable among individuals, and of being accurate in measuring very low levels of renin by prolonging the incubation time.

Yet PRA measurement is a complex procedure with poor interlaboratory reproducibility, a limitation which has prevented more extensive use of PRA for diagnostic purposes and for selecting the most appropriate antihypertensive treatment.

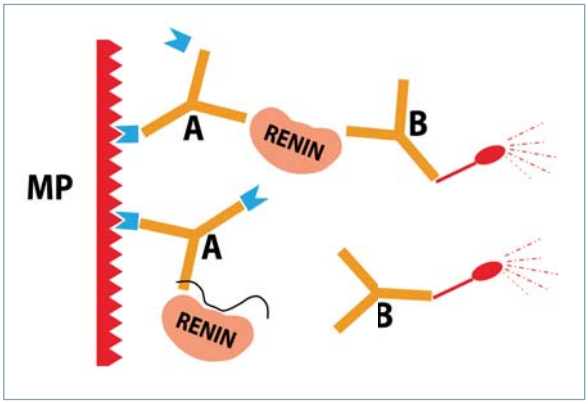
The LIAISON® Direct Renin assay

The recent availability of monoclonal antibodies directed against specific epitopes of the renin molecule has made possible its direct quantification as an alternative to PRA.

In the LIAISON® Direct Renin assay renin is sandwiched between a capture antibody adsorbed on magnetizable beads and a second isoluminol-linked antibody that detects the reaction.

The relative light units developed by the mixture when exposed to a basic environment are proportional to the concentration of renin and allow its quantification expressed in µIU/mL.

LIAISON® Direct Renin specificity of the assay



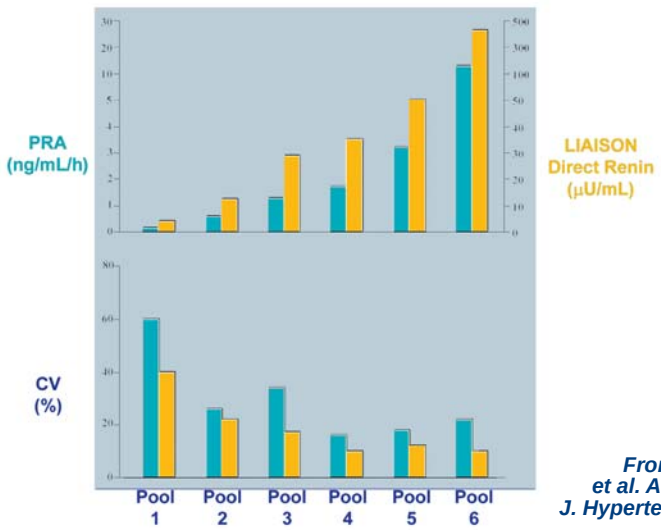
The LIAISON® Direct Renin assay is performed in a fully automated analyzer platform (LIAISON®) allowing the determination of 170 samples within 40 minutes.

LIAISON® Direct Renin assay versus plasma renin activity assay

Moreover a recent multicenter comparative study has shown that the interlaboratory reproducibility of the new chemiluminescent assay is greater than that of PRA throughout the range of renin levels usually encountered in clinical practice.

Thus, the new chemiluminescent renin assay (LIAISON® Direct Renin) appears to be simpler, faster and more reproducible than PRA.

Absolute values and coefficient of variations of PRA and LIAISON® Direct Renin in plasma pools



From Morganti et al. Accepted by J. Hypertension 2010

Hypertension

LIAISON® Direct Renin, is FAST and PRACTICAL

Summary

The renin-angiotensin-aldosterone system (RAAS) is one of the main regulators of blood pressure and of sodium/water metabolism and its alterations are relevant in the pathophysiology of numerous cardiovascular diseases.

Increasing published evidence shows that the pharmacological antagonism of RAAS markedly reduces the major cardiovascular events and the progression of renal insufficiency.

The evaluation of RAAS activity is crucial for diagnostic and therapeutic purposes.

This evaluation turned out to be difficult because the commonly used method to assess the effects of RAAS, i.e. the measurement of plasma renin activity (PRA), is a complex procedure with poor interlaboratory reproducibility.

This drawback has led to limited use of PRA determination, depriving the clinician of a powerful tool for diagnosing relatively frequent forms of hypertension and for selecting the most effective therapeutic regimen.

The LIAISON® Direct Renin assay, which exploits the high specificity of monoclonal antibodies to detect the renin molecule, offers the possibility of evaluating RAAS activity which is methodologically simpler, faster and more reproducible than PRA.

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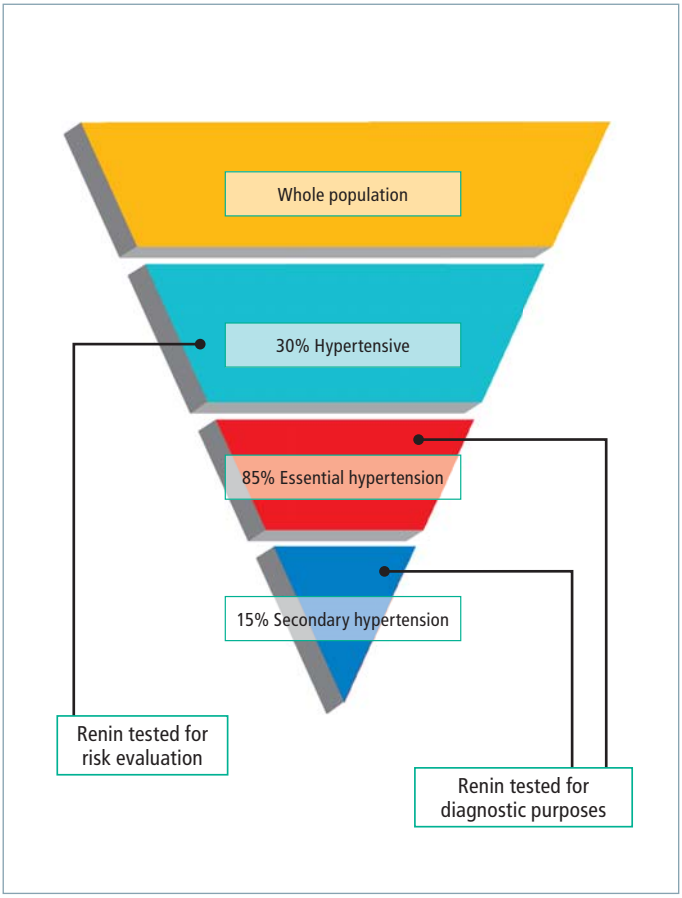

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