The spectrum of low-renin hypertension

THE SPECTRUM OF LOW-RENIN HYPERTENSION

Fabrizio Buffolo MD[a], Silvia Monticone MD PhD[a], Alessio Pecori MD[a], Jacopo Pieroni MD[a], Isabel Losano MD, Giovanni Cavaglià MD, Martina Tetti MD, Franco Veglio MD, Professor[a], Paolo Mulatero MD, Professor [a]

[a] Division of Internal Medicine and Hypertension Unit, Department of Medical Sciences, University of Torino, Via Genova 3, 10126, Torino, Italy

Corresponding author:

Paolo Mulatero, MD, Division of Internal Medicine and Hypertension, Department of Medical Sciences, University of Torino, Via Genova 3, 10126, Torino, Italy.

e-mail: paolo.mulatero@unito.it

Phone: +390116336959 Fax: +390116336931

Abstract

Low-renin hypertension (LRH) is a frequent condition in patients with arterial hypertension, accounting for 30% of patients. Monogenic forms can cause LRH in a minority of cases. However, in the large majority of patients, LRH is caused by the combined effects of congenital and acquired factors, comprising dietary habits. Several genetic variants have been proposed as co-factors in the pathogenesis of LRH with normal-low serum aldosterone. Emerging evidences support the hypothesis that a large proportion of LRH with normal-high serum aldosterone is associated with subclinical primary aldosteronism (PA). The recent identification of aldosterone-producing cell clusters (APCCs) as the possible cause of subclinical PA, further supported the concept of a continuous spectrum of autonomous aldosterone secretion, from subclinical forms towards overt PA. In this review we describe the main aspects of LRH, focusing on molecular basis, clinical risk profile and patients' management.

Key words: primary aldosteronism, low renin hypertension, aldosterone producing adenoma, aldosterone producing cells cluster

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(A) Introduction

High blood pressure level is the most important risk factor for cardiovascular disease (1) and the leading risk factor of the global burden of disease in 2017, accounting for 10.4 million of deaths worldwide (2). Its prevalence is increasing in both low-income and high-income countries, along with an increase in lifetime expectancy (3).

Patients with arterial hypertension can be classified in three groups according to direct renin or plasma renin activity (PRA): low, normal and high renin hypertension (4). Cut-offs used to define low renin hypertension (LRH) are not strictly defined, however PRA is generally considered suppressed below 0.65-1 ng/ml/h and direct renin below 15μU/mL (5). LRH accounts for about one third of the patients with arterial hypertension (6*), with higher prevalence among elderly and patients of black African origin (7,8). New insights from clinical and preclinical studies recently expanded the spectrum of low renin phenotype towards patients without hypertension, providing clues on the progressive increase of cardiovascular risk in this particular subgroup of patients (9*).

(A) Historical background

The role of renin-angiotensin-aldosterone system (RAAS) in the pathophysiology of arterial hypertension has been investigated since 1960s, particularly by the group of John H. Laragh from Columbia University (10–12). Brunner et al., in 1972, classified arterial hypertension according to RAAS profile in a group of 219 patients (13). Comparing PRA to the nomogram drawn from normotensive individuals, they identified three subgroups of patients: 30% with

subnormal PRA, 60% with normal PRA and 10% with elevated PRA. Patients with low-renin activity displayed a lower risk of cardiovascular events, comprising stroke and myocardial infarction, despite similar blood pressure levels and cardiac organ damage. The authors concluded that low PRA could be considered a protective factor in patients with arterial hypertension (13).

One year later, Buhler FR et al. (14) further divided the low renin hypertensive group according with the response to oral sodium loading. One group displayed normal sodium-induced decrease of aldosterone levels; a second group displayed persistently unsuppressed serum aldosterone despite sodium administration. The features of the second group of patients were similar to those of patients with autonomous aldosterone secretion due to adrenal adenoma, suggesting a continuum of autonomous aldosterone secretion between low-renin essential hypertension (LREH) and PA.

In contrast with these findings, several subsequent studies reported an inverse relationship between PRA levels and blood pressure (15,16). PRA was significantly lower in patients with previous myocardial infarction than in patients without cardiac disease, suggesting increased cardiovascular risk in patients with a low-renin phenotype (15).

The pathogenesis of LRH has been debated for many years and volume expansion was the most accepted hypothesis. Many causes of volume overload have been proposed, including renal sodium retention, genetical predisposition and high sodium intake. Additionally, some authors hypothesized the presence of an unidentified mineralocorticoid hormone as the responsible of the hypervolemic state in these patients (17).

(A) Renin-angiotensin-aldosterone system and arterial hypertension

In the PATO study, among 1672 patients with hypertension, 34% displayed low-renin, 57% normal-renin and 9% high-renin hypertension (6*), confirming the data reported by Brunner et al. 35 years before (13). After exclusion of patients with PA, 75% of LREH patients had a negative screening test for PA and 25% a positive screening test and negative confirmatory test (6*).

The most frequent cause of high renin hypertension is drug interference, including diuretics and RAAS inhibitors. Even patients with PA can have high or very high renin-level during medical treatment with mineralocorticoid receptor (MR) antagonist (18). High renin levels are present in some secondary forms of hypertension: renovascular hypertension, pheochromocytoma, oral contraceptive assumption and the extremely rare juxtaglomerular renin-secreting tumors (19).

LRH is a heterogenic group of disorders, including common acquired secondary forms and rare monogenic forms. Drug treatments are commonly associated with low renin values, including nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitor and beta-blockers. High-salt diet can cause LRH by inhibiting renin activity and aldosterone secretion (18). High doses of licorice intake can cause LRH by glycyrrhetinic acid inhibition of 11BHSD2 and consequent cortisol activation of MR. Grapefruit, containing endogenous glycyrrhetinic acid like factors, may cause LRH by similar mechanism (20*). Since renin is secreted in the nephrons by juxtaglomerular cells, several renal diseases (e.g. diabetic nephropathy) may cause LRH by direct reduction of renin secretion (21).

Excluding familial forms of PA, monogenic forms of LRH display a low-renin/low-aldosterone pattern: Liddle syndrome (22), apparent mineralocorticoid excess syndrome (AME) (23), congenital adrenal hyperplasia (24) and other extremely rare disorders, including activating mutation of MR (25) and glucocorticoid resistance syndrome (26). Finally, Gordon

96 syndrome, also known as pseudohypoaldosteronism type 2, is a monogenic form LRH with
97 low or normal aldosterone levels and hyperkalaemia (27).

98 Low renin essential hypertension (LREH) is considered the most common cause of LRH.
99 However, LREH is a diagnosis of exclusion and the exact pathophysiology of LREH has yet
100 to be determined. In most cases, multiple acquired and congenital factors may play a complex
101 and synergic role (28).

102 LREH is more common in the elderly and in black African individuals (7,8). Several studies
103 have demonstrated that mild or "non-classical" monogenic form of LRH may be associated
104 with low-renin in patients with hypertension (4). Recent clinical and preclinical studies
105 demonstrated that subclinical form of PA may be comprised in this group of patients and
106 therefore, the borderline between LREH and PA became of difficult definition (29).

107 **(A) Sodium-intake and renin levels**

108 Definitions of low, normal or high sodium intake varies according to different studies and
109 institutions. World Health Organization recommend to reduce sodium-intake to less than 2
110 g/day of sodium (<5 g/day of salt) and consider an intake of more >3 g/day of sodium as
111 "high" (30). The mean dietary sodium intake worldwide is 3.7 g/day (31); according to
112 quintile distribution, sodium intake <2.6 g/day is considered low and >4.8 g/day is considered
113 high.

114 A large metanalysis recently reported that a reduction of sodium-intake from 4.6 g/day to 1.5
115 g/day, increase PRA of 1.60 ng/mL/h (55%) and aldosterone of 9.78 ng/dl (127%) (32). The
116 effect is more evident in patients with normotension than hypertension.

117 The increase of PRA with low-sodium diet is greater in the first month, followed by a
118 progressive trend towards baseline levels (33). The long-term effect of low-salt diet on renin-
119 angiotensin system has been described in Yanomami, in the tropical equatorial rain forest of

northern Brazil and southern Venezuela. Major staple of Yanomami diet are banana, plantains and vegetables, rarely supplemented by game, fish and insects. At the time of the study (1975) there was no substantial influence of the industrialized culture in the Yanomami dietary habits and the daily intake of sodium of this population was extremely low with average urinary sodium excretion of 1 mmol/day (34), compared with an average of 180 mmol/day in the North American population (35*). The low sodium-intake resulted in high mean PRA (13 ng/mL/h) and high aldosterone urinary excretion.

(A) Molecular basis of low-renin essential hypertension

(B) *Low-renin and normal/low-aldosterone*

In the presence of low renin and normal/low aldosterone profile, some rare monogenic syndrome should be excluded, especially in young patients (see above). However, "non classical" phenotypes of monogenic disorders can play a role in association with acquired and dietary factors (28).

Missense SNPs of *SCNN1B* gene, whose mutations are responsible for Liddle's syndrome, are described in patients with LRH. The prevalence of SNP rs1799979, resulting in the substitution T594M, was reported in 5-8% of patients with hypertension of African origin, associated with a low-renin profile (36,37). Similar findings were reported for the substitution R563Q (38).

Beyond the classical presentation of AME, some mutations or SNPs of *HSD11B2* can results in mild or "non classical" phenotype, according with the severity of HSD11B2 deficiency (39). Two SNPs of *HSD11B2* gene were reported to be more prevalent in patients with hypertension compared to normotensive control (40). The activity of HSD11B2 enzyme tend

to decrease with aging (41), supporting the hypothesis that a progressive HSD11B2 deficiency could partially justify the LRH phenotype in elderly hypertensives (4).

Recently, a genome-wide association study (42) of 757,601 individuals revealed 901 loci for blood pressure traits, explaining 27% of estimated heritability. Functional analysis demonstrated association with several loci involved in aldosterone secretion. Among these, *CTNNB1* locus was found to be associated with systolic blood pressure levels. *CTNNB1* encodes β-catenin, a protein mutated in 3% of aldosterone producing adenoma (APAs) and involved in adrenocortical development and zonation (43). Whether some of these SNPs have a role in LREH development has yet to be determined.

(B) ***Low-renin and normal/high-aldosterone***

Subclinical forms of PA are probably responsible for a large proportion of patients with hypertension and low-renin and normal/high, but still suppressible with sodium loading, aldosterone levels.

Aldosterone producing cell clusters (APCC) are non-neoplastic nodules of CYP11B2-expressing cells that have been identified in normal adrenal gland of patient without PA and in adrenal tissue near APAs (44). The number and total area of APCC increase with age in patients without PA together with a reduction of the physiological zona glomerulosa CYP11B2-expressing area (45*). Therefore, APCCs may be associated with autonomous aldosterone secretion in elderly.

Absent biochemical response is encountered after 2% of total adrenalectomy (46*) and after 7% of adrenal-sparing nodulectomy (47). For this reason, some authors hypothesized that lacking of biochemical response could be due to APCC persistence after surgical treatment. However, Meyer et al. reported no significant differences in the numbers of APCC surrounding the nodule of patients with complete and partial/absent biochemical outcome

(48). Instead, cortical hyperplasia was more frequent in patients with persistent PA, suggesting nodular hyperplasia as the main risk factor of absent biochemical response (48).

Mutations in genes previously identified as drivers of aldosterone secretion in APA, were observed also in APCC. The increased aldosterone production is mediated by increase of intracellular calcium and *CYP11B2* transcription. Mutation in *CACNA1D*, encoding for a subunit of L-type calcium channel, are the most frequent in APCC (26% to 58% of the cases) (49*,50). *ATP1A1* mutations (encoding the α1-subunit of Na^+/K^+ transporters ATPase) in up to 9% of APCCs (49*,50).

KCNJ5 gene encode for the G protein-activated inward rectifier potassium channel 4 (GIRK4). Mutations of *KCNJ5* alter the selectivity filter of the potassium channel, resulting in inward Na^+ current, depolarization, Ca^{2+} entry in the cell and increased *CYP11B2* transcription (51). Germline mutations of *KCNJ5* have been identified in patients with familial hyperaldosteronism type III (52) and sporadic mutations in 40% of APA (53). Only one APCC carrying a mutation of *KCNJ5* was identified (50).

It is possible to speculate that the transition from APCC to APAs is a potential mechanism associated with the formation of *CACNA1D* and *ATP1A1* mutated APAs, but not with APAs harboring *KCNJ5* mutations (Figure 1).

KCNJ5 mutations are most common in female and young patients and they are associated with higher chance of a complete clinical outcome after unilateral adrenalectomy (54–56). Histologically *KCNJ5* mutated APA have zona fasciculata-like cells, whereas *ATP1A1* and *CACNA1D* mutated APA cells are composed prevalently by zona glomerulosa-like cells (57,58*).

ATP2B3 is a gene encoding for a calcium-transporting ATPase mutated in about 1-2% of APAs (59,60). Histological features of *ATP2B3* mutated APAs are similar compared to

ATP1A1 and *CACNA1D* mutated APAs (57). However, no *ATP2B3* mutations has been identified in APCCs.

Recently, some authors raised the hypothesis of the existence of APCC-to-APA transitional lesions (pAATLs), composed of an outer part similar to an APCC and an inner part similar to an APA (61).

(A) The continuum from subclinical to overt PA

Since its first description until the 1990s, PA was considered a very rare disorder with a prevalence of less than 1%, characterized by drug-resistant hypertension and severe hypokalemia (62). The widespread adoption of ARR and the expanded screening of PA in patients with normokalaemia increased PA recognition of 5 to 15 times (63).

It is now accepted that PA is largely more prevalent than initially believed, 6% in unselected hypertensive patients (6) and 11% in patients referred to tertiary centers (64). The prevalence of PA increases with hypertension severity, with a prevalence of 12-13% in grade 3 (65) and up to 20% in resistant hypertension (66). However, the prevalence of PA is not negligible even in the in grade 1 hypertension or pre-hypertension, varying from 2 to 6% according to patient selection and diagnostic criteria (64,67). The relative prevalence of unilateral forms increases with hypertension grades: from 20% in grade 1 up to 30% in patients with grade 3 hypertension (6). Hypokalemia is present in 30% of patients with PA and is more prevalent in unilateral PA than in bilateral forms (≈50% *vs* ≈20%) (6,64).

Recent studies expanded the spectrum of PA towards individuals with normotension and normokalaemia, using a broad definition of autonomous aldosterone secretion. In one study Markou *et al*. (68) performed fludrocortisone-dexamethasone suppression test in 100 normotensive individuals. In the second study, Baudrand *et al*. (8) performed an oral sodium suppression test to 210 individuals with normal blood pressure levels and low-renin values. In

both cases the prevalence of autonomous aldosterone secretion was 13-14% (8,68). However, the strict application of the ES Guidelines (20) (positive screening test followed by confirmatory test), resulted in lower figures, with a prevalence of 3% (6 of 210 patients) (8).

Notably, patients with autonomous aldosterone secretion displayed increased 24-hours urinary aldosterone excretion and reduced urinary sodium-to-potassium excretion (8). The 24 hours urinary potassium excretion was increased, despite normal potassium levels. Patients recruited were relatively young and healthy. In this type of patients, natriuretic compensatory mechanisms can probably overcome the aldosterone-mediated volume overload and mask the hemodynamic effects of PA. On the other side, some extra-renal compensatory mechanisms can tackle potassium tubular wasting, that become overt when the compensatory effect get ineffective. Natriuretic compensatory mechanism is usually the first that become inefficient, resulting in rise of arterial hypertension with normokalaemia. Sometimes, potassium-sparing mechanisms exhaust firstly, more often in young females (69). In this cases hypokalemia may be present with normal blood pressure levels (70). Since subtype diagnosis was not performed in any of these studies, the proportion of normotensive patients with autonomous aldosterone secretion due to unilateral PA is unknown.

The prevalence of subclinical PA progressively increases with aging; *Nanba et al.* (45*) explored RAAS profile and aldosterone regulation in 667 patients without PA, using ARR and sodium-modulated aldosterone suppression-to-stimulation index (SASSI). SASSI is calculated as the ratio of suppressed serum aldosterone/stimulated serum aldosterone, induced by sodium-loading and sodium-restriction respectively (45*). High SASSI suggests renin-independent aldosterone secretion, whereas low SASSI suggests normal aldosterone regulation (71*); SASSI and ARR progressively increase with age independently of other confounding conditions (45*).

(A) Cardiovascular risk profile associated with subclinical primary aldosteronism

Vasan *et al.* (72*) showed the role of aldosterone as a risk factor in the development of hypertension in 1688 normotensive participants of the Framingham Offspring Study. Subjects with aldosterone levels in the highest quartile displayed 1.61-fold increased risk of hypertension. Subsequently, in the Framingham Heart Study cohort of 3326 individuals, it was shown that ARR was significantly associated with blood pressure progression and hypertension incidence (73). The authors concluded that aldosterone is a risk factor for hypertension development only when is inappropriate for renin levels.

Brown *et al.* confirmed this findings, reporting higher incident hypertension (85.4 per 1000 person/years) in patients with low renin phenotype (PRA $\leq$ 0.50 ng/m/h) than in patients with PRA $\geq$ 1.00 ng/ml/h. Serum aldosterone was significantly associated with incident hypertension only when renin activity was suppressed (18% of increased risk per 100 pmol/l of increased serum aldosterone) (35). In another study, 85% of patients with autonomous aldosterone secretion developed hypertension in the following 5 years, versus 23% in patients without autonomous aldosterone secretion (68). It is currently unknown whether the risk of developing overt PA is increased in patients with subclinical PA.

It is uncertain if patients with subclinical PA or mild PA have an increased risk of cardio-cerebrovascular events or metabolic disorders before the development of overt PA. A recent study, evaluating patients with both normotension or hypertension but without PA, reported a correlation of ARR with metabolic syndrome, body mass index, blood pressure levels and markers of endothelial dysfunction (74). In the PATO study, Monticone *et al.*, compared a large group of 464 patients with LREH and 1109 patients with normal or high PRA: patients in the LREH group displayed higher blood pressure levels but no significant differences in terms of metabolic disorders, cardiovascular events or target organ damage (6). Similarly, in the study

of Markou *et al.* normotensive patients with autonomous aldosterone secretion display similar metabolic profile compared with patients with normal aldosterone secretion (68).

(A) Future perspectives in PA diagnosis

The existence of an expanding horizon of PA towards mild and subclinical forms raise several questions on the optimal and cost-effective approach for PA diagnosis.

In order to maximize PA recognition, *Vaidya et al.* (9) recently suggested to loosen the criteria to define positive the screening test for PA. They proposed to consider PA diagnosis even in patients with aldosterone in normal range (5-10 ng/dl) and suppressed renin levels, suggesting to repeat the screening test or directly performing a confirmatory test in these patients.

Using wider criteria for PA diagnosis would increase costs for PA diagnosis and subtype differentiation. A part of this cost may be covered by the reduced risk of cardiovascular events in these patients.

At the same time, no study directly investigated the prevalence of APAs in subclinical PA. Therefore, whether patients with subclinical PA should undergo a complete subtype diagnosis is another unmet issue. Adrenal venous sampling (AVS), the current gold standard for subtype characterization (20), is an expensive and invasive technique. Therefore, performing a complete subtype diagnosis for an increasing number of patients could be challenging even for specialized centers. Scoring system or laboratory tests, aimed at identifying patients with a low probability of having unilateral PA may be of help in reducing the number of procedures. Patients with low probability of APAs, could probably avoid further invasive procedures and benefit of specific treatment with MR antagonist (9).

Finally, it should be noted that even with the current criteria for PA, the large majority of patients with PA remain undiagnosed (75*). Therefore, widening the criteria for PA without

an effort for an improvement in PA awareness would probably solve just a part of the problem.

(A) Summary

Low renin hypertension is highly prevalent condition in individuals with arterial hypertension, involving one third of the patients. The causes of LRH comprise rare monogenic forms of hypertension and more common acquired forms, in which congenital predisposing factors play a role together with acquired condition and dietary habits. The expansion of the spectrum of PA supports the hypothesis that a large part of LRH, particularly if associated with normal-high aldosterone levels, is probably caused by subclinical form of PA.

Understanding the molecular basis that underlie the pathogenesis of low renin hypertension opened new unexpected areas of research. At the same time, the best diagnostic and therapeutic approach for this particular subgroup of patients has yet to be determined. Future studies should address these issues guiding the clinicians towards a new tailored approach of the patients with arterial hypertension.

Practice point

- Low-renin hypertension (LRH) is generically defined as arterial hypertension with plasma renin activity below 0.65-1 ng/ml/h or direct renin below 15μU/mL
- LRH account for about 35% of patients with arterial hypertension, with higher prevalence among elderly and patients of African origin
- LRH is caused by some rare monogenic forms and most common acquired forms, caused by a complex admixture of congenital predisposition and dietary and acquired factors

- Subclinical primary aldosteronism (PA) is probably the cause of a large part LRH with normal-high aldosterone levels

Research agenda

- Investigate the genetic variants determining the heritability of low-renin essential hypertension
- Determine the cardiovascular risk of patients with subclinical PA, the risk of development of overt PA and the prevalence of unilateral forms in subclinical PA
- Define the management of patients with subclinical PA in terms of diagnosis, treatment and follow-up

Conflict of interest

Paolo Mulatero received fees for educational speech from DIASORIN.

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None

Figure 1

Histopathological and clinical features of the spectrum of primary aldosteronism (PA) from subclinical to overt PA. APA=aldosterone producing adenoma. IHA=idiopathic hyperaldosteronism. APCC=aldosterone producing cell clusters.

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