Low-Renin and Nonmodulating Essential Hypertension

David G. Warnock

Low-renin hypertension (LREH) accounts for an important subset of the hypertensive human population and is associated with salt-sensitivity and diuretic response and is also common in black patients. An interesting finding in LREH is the presence of normal plasma aldosterone levels. The ratio of plasma aldosterone to renin activity is used to screen for adrenal adenomas and hyperplasia and is usually >100 when plasma renin activity is expressed in ng/mL/hr and the aldosterone concentration is expressed in ng/dL. The plasma aldosterone/plasma renin activity ratios may be somewhat elevated in LREH (>30 but <100), which is especially relevant if the concurrent urinary sodium excretion exceeds 200 mEq/24 hours. It is not known what regulates aldosterone secretion in this setting or whether there is actual mineralocorticoid excess. Undue prior emphasis may have been placed on the continued suppression of plasma renin activity during severe salt restriction or volume depletion in LREH, and the suppression of plasma renin activity and basal aldosterone secretion in the elderly can also confound the analysis of LREH.

Studies by Fisher et al. focus on adrenal and pressor responsiveness to angiotensin II (Ang II) as a function of dietary salt intake in patients with LREH, normal-renin hypertension, and normal controls. Especially striking are the functional similarities between LREH and nonmodulating essential hypertension with normal plasma renin activity (NMEH), including: (1) salt-sensitivity of the blood pressure; (2) blunted plasma aldosterone responses to Ang II infusion and upright posture after 5 days of rigid dietary sodium restriction; and (3) relatively low basal plasma aldosterone levels. These differences compared with normal controls and “modulating” hypertensive subjects disappeared when the dietary salt intake was increased to 200 mEq. The latter results are consistent with suppression of plasma Ang II activity during high-salt intake with desensitization of Ang II receptors and improved Ang II responsiveness. If so, then perhaps the blunted responsiveness to Ang II during sodium restriction could reflect the continuing formation of Ang II, with angiotensin receptor downregulation.

Fisher et al. based the definition of LREH and the Ang II responsiveness on patients who had undergone 5 days of sodium salt restriction (10 mEq/24 hours) rather than “short” protocols with concomitant diuretic administration. It is important to determine if the subjects had actually come into sodium balance because that would affect the interpretation of the basal plasma aldosterone levels. The low basal plasma aldosterone levels in the LREH and NMEH subjects could have reflected relative volume expansion despite the dietary salt restriction. In this regard, at 5 days, the 24-hour urinary sodium excretion rates were slightly (and significantly) higher in these 2 groups compared with the normal controls and normal-modulating hypertensive subjects (See Table 1 in Reference 2).

Our understanding of renal tubule transport defects has expanded in the last several years, providing unique insights into epithelial transport processes and clinical syndromes that result from mutations of these transporters. A major focus of these studies has been the epithelial sodium channel (ENaC), which is the rate-limiting barrier for regulating sodium absorption in the mineralocorticoid-responsive renal collecting tubule. ENaC can be directly affected by mutations or by changes in the response to or production of mineralocorticoids. As a result, we now have defined Mendelian syndromes in which ENaC activity is “dysregulated” with subsequent development of disorders of systemic blood pressure that can be attributed to a primary renal mechanism. The mutations that directly affect the subunits of the ENaC channel can result in gain of function (Liddle’s syndrome) or loss of function (pseudohypoaldosteronism type 1), with the predictable clinical phenotype in the affected individuals. The normal response to dietary salt surfeit is downregulation of ENaC activity so that sodium reabsorption by the collecting tubule is reduced; any impairment in this process would account for dysregulation of ENaC activity, continuing sodium reabsorption, and volume expansion.

The original descriptions of genetically-proven Liddle’s syndrome involved whites. With the re-emphasis of the clinical phenotype, it was quickly appreciated that patients of African ancestry could also be defined with severe low renin hypertension and markedly suppressed aldosterone secretion, often with hypokalemic metabolic alkalosis. Despite the promise of defining a cause of LREH in this important target population, numerous screening efforts of various ethnic populations have not changed the original view that Liddle’s syndrome, with striking suppression of aldosterone secretion, is a rare cause of human LREH. Although there are polymorphisms in the ENaC subunits that can be associated with enhanced ENaC sensitivity to CAMP and/or associated with suppressed
plasma renin activity,

Liddle’s syndrome can be regarded as the phenotypic extreme of LREH, with clear-cut salt-sensitive hypertension.

In the original studies of the index case, aldosterone secretion was markedly suppressed, accounting for the descriptor “pseudoaldosteronism.”

The index case developed renal failure 25 years after the original description and underwent successful renal transplantation that reversed the clinical phenotype of Liddle’s syndrome.

Two years after transplantation, her plasma renin activity and aldosterone levels were restored to normal, with appropriate responses to postural changes and dietary salt restriction. These findings demonstrated that the suppression of the plasma renin activity in Liddle’s syndrome was the result of the gain of function mutation in the ENaC complex. The continued suppression of aldosterone excretion despite vigorous dietary salt restriction is best explained by chronic suppression of adrenal aldosterone synthase activity as a consequence of chronic volume expansion.

Of note, in the studies by Fisher et al., 5 days of dietary salt restriction restored the normal pressor response to Ang II in LREH and NMEH despite continued blunting of the plasma aldosterone response. It would seem likely that aldosterone synthase activity was still somewhat suppressed in these subjects after 5 days of salt restriction, secondary to their chronic volume expanded state. Studies of urinary aldosterone excretion, as well as other urinary steroid metabolites of the 18-hydroxylase as a function of chronic dietary salt intake, would be of interest in LREH and NMEH and would directly examine the activity of aldosterone synthase in these subjects.

It can be argued that an important pathophysiological mechanism in LREH could be enhanced renal salt absorption mediated by an activated ENaC complex, with subsequent volume expansion and suppression of plasma renin activity. Such activation could be the primary result of a mutation or polymorphism in the ENaC complex or mineralocorticoid receptor response pathways or may reflect the relative excess of endogenous mineralocorticoid. In contrast to Liddle’s syndrome in which there is a striking suppression of plasma renin activity and aldosterone activity, most subjects with LREH have relatively normal plasma aldosterone levels despite suppressed plasma renin activity. Similar findings have been reported for black LREH patients with the T594M polymorphism of the β ENaC subunit; the degree of volume expansion in these patients may be sufficient to suppress plasma renin activity but not sufficient to reduce aldosterone synthase activity.

If correct, then the underlying pathophysiological process would be ENaC dysregulation and volume expansion, with second order effects on plasma renin activity and aldosterone synthase activity. In this context, the plasma renin activity becomes a simple, albeit imperfect, surrogate marker for the effective arterial volume.

Thus, the focus could shift from the absolute value of the plasma renin activity to an assessment of ENaC activity during dietary salt surfeit in which the normal physiologic response would be to downregulate ENaC activity. Along these lines, the article by Fisher et al. demonstrates striking functional similarities between LREH and NMEH, which in the present interpretation become somewhat arbitrarily differentiated on the basis of the plasma renin activity.

Despite apparent mineralocorticoid excess, Liddle’s syndrome is not necessarily associated with overt hypokalemia, which is similar to patients with glucocorticoid-remediable aldosteronism. Nevertheless, enhanced urinary potassium excretion was present in the affected subjects, which became even more evident when the overnight urinary aldosterone excretion was factored by the potassium excretion.

Previous studies have demonstrated suppression of aldosterone excretion in juvenile black subjects, and more recent studies have demonstrated increased overnight urinary aldosterone to potassium ratios in these black subjects, suggesting that there was enhanced activity and/or responsiveness of collect tubule ENaC to endogenous mineralocorticoid hormone.

Although these data are not presented in the paper by Fisher et al., it would be of interest to know if the LREH and NMEH subjects could be further characterized by their overnight urinary aldosterone to potassium excretion ratios. The responses to mineralocorticoid receptor antagonists and angiotensin receptor antagonists are also of interest in LREH and NMEH. Such studies could determine if the adrenal responsiveness to Ang II accounts for the normal plasma aldosterone levels in these conditions and whether there is enhanced ENaC activity that is regulated by mineralocorticoids in these forms of human essential hypertension.

References


---

**Key Words:** blacks ■ renin ■ aldosterone ■ endothelial sodium channel ■ Liddle’s syndrome
Low-Renin and Nonmodulating Essential Hypertension
David G. Warnock

_Hypertension_. 1999;34:395-397
doi: 10.1161/01.HYP.34.3.395

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/34/3/395

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/