Even in wealthy countries, blood pressure control is still not very good. In Canada, despite many years of effort by the Canadian Hypertension Education Program, about half of patients referred to a stroke prevention clinic do not have systolic pressures below 140 mmHg, and about 20% have diastolic pressures above 90 mmHg. (1) In less developed countries, the situation is much worse. In a hypertension clinic in Nairobi, Kenya, only ~ 25% of patients had their blood pressure controlled, (2) and in a recent clinical trial in Africa among patients with uncontrolled hypertension, only 12.5% of the patients had achieved blood pressures below 140/90 mmHg after a year. (3)This is important because uncontrolled hypertension has serious consequences; in a Swedish study, 90% of strokes occurred in patients with uncontrolled hypertension.(4)

Some causes of resistant hypertension are listed in Table 1. Therapeutic inertia can be overcome. In the North American Carotid Endarterectomy Trial, site principal investigators received a stiff letter reminding them to follow the protocol, whenever a patient had a blood pressure above the target and medication was not increased. At a time when ~ 20% of strokes were due to intracerebral hemorrhage, we reduced intracranial hemorrhage to 0.5% of strokes. (5)

What seems more difficult to overcome is Diagnostic Inertia. (1, 6) Physicians seem to persist in assuming that all patients are the same, and are failing to ask, “If this patient’s blood pressure is not being controlled by usual therapy, what is the cause of the hypertension?”

Laragh first proposed that management of hypertension should be guided by measurement of plasma renin activity. (7) A randomized trial of this approach reported lower systolic pressures, a trend to improved blood pressure control, and a greater reduction of medication needed among patients with volume hypertension (with low plasma renin activity). (8)

However, there are two different kinds of low renin hypertension, and to distinguish them it is necessary to measure plasma aldosterone. Patients with primary aldosteronism (~ 20% of resistant hypertension) (9) have a low plasma renin activity and a high plasma aldosterone, and are best treated with aldosterone antagonists (spironolactone or eplerenone). High-dose amiloride can be used for men (who get gynecomastia and mastalgia from spironolactone) when eplerenone is not available or affordable. Patients with Liddle syndrome, a mutation of SCNN1B, the renal tubular epithelial sodium channel (ENaC), or one of several mutations that affect the function of ENaC, have salt and water retention suppressing both renin and aldosterone, so have low plasma renin activity and a low level of aldosterone (Liddle phenotype). The specific treatment for this condition is amiloride. (10)

Table 1. Causes of resistant hypertension

1. Non-compliance
   - Half of patients will admit it (13)
2. Better with drugs that have less adverse effects (14)
3. Consumption of substances that aggravate hypertension
   - Salt, licorice, NSAID’s*, EtOH, BCP, decongestants
4. Consensus guidelines that assume all patients are the same
5. Diagnostic inertia
   - * Except for sulindac (15)

Continued on next page…
Table 2. Physiologically individualized therapy* based on renin/aldosterone profile

<table>
<thead>
<tr>
<th>Primary hyper-aldosteronism</th>
<th>Liddle's syndrome and variants (renal Na+ channel mutations)</th>
<th>Renal/renovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin</td>
<td>Low***</td>
<td>Low</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>High**</td>
<td>Low</td>
</tr>
<tr>
<td>Primary treatment</td>
<td>Aldosterone antagonist (spironolactone or eplerenone) Amiloride for men where eplerenone is not available</td>
<td>Amiloride</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angiotensin receptor blocker*** (rarely revascularization)</td>
</tr>
</tbody>
</table>

*It should be stressed that this approach is suitable for tailoring medical therapy in resistant hypertensives; further investigation would be required to justify adrenalecetomy or renal revascularization.

** Levels of plasma renin and aldosterone must be interpreted in the light of the medication the patient is taking at the time of sampling. In a patient taking an angiotensin receptor blocker (which would elevate renin and lower aldosterone), a plasma renin that is in the low normal range for that laboratory, with a plasma aldosterone in the high normal range, probably represents primary hyperaldosteronism, for the purposes of adjusting medical therapy.

*** Angiotensin converting enzyme inhibitors are less effective because of aldosterone escape via non-ACE pathways such as chymase and cathepsin; renin inhibitors are seldom used.


It seems that most physicians are unaware of, or underestimate the frequency of the Liddle phenotype. One variant of SCNN1B(T594M) was present in 5% of black hypertensives in the UK (mainly of Caribbean origin), another (R563Q) was present in 6% of hypertensives in Cape Town, South Africa. (11) In a hypertension clinic in Louisiana, 6% of patients had a Liddle phenotype.

In a recent clinical trial in Africa, patients with uncontrolled hypertension were randomized to usual care (UC) vs. physiologically individualized therapy (PhysRx) based on plasma renin activity and plasma aldosterone levels. (3) As mentioned above, there was no benefit of this approach in the study site in Kenya, where amiloride was not available and there were other factors influencing poor control. (3) However, at the Nigerian site, where patients were randomized to UC vs. PhysRx and conditions were more similar to developed countries, there was a marked improvement in blood pressure control: systolic control was obtained in 15% of UC vs. 85% of PhysRx (P = 0.0001), diastolic control in 45% vs. 75% (P = 0.11) and control of both systolic and diastolic pressure in 15% vs. 75% (P < 0.0001), even though the renal function was worse at that site. The algorithm used in the study is shown in Table 2. We found a very high prevalence of nonsynonymous SNPs affecting both primary aldosteronism and the Liddle phenotype. (12)

The most important difference in the medication change from baseline to the end of the study was that a much higher proportion of patients allocated to PhysRx received amiloride (19% on PhysRx vs. 2.8% on UC).

The Liddle phenotype is far more common than most physicians suppose.

In patients with resistant hypertension it is important to overcome diagnostic inertia. After excluding rare causes of hypertension, such as pheochromocytoma, licorice or adult coarctation of the aorta, most patients will have their blood pressure controlled using physiologically individualized therapy based on their plasma renin activity and aldosterone.

- J. David Spence

REFERENCES:


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Our body is inhabited by trillions of bacteria. The term microbiota refers to the myriad of microorganisms that coexist with their hosts. In mammals, they colonize mainly the gastrointestinal tract in mostly anaerobic and rich nutrient environment. The gut microbiota codevelops with the host in a complex interplay between host genome, nutrition, and life-style. The role of gut microbiota in the regulation of multiple host metabolic pathways arise from interactive host-microbiota metabolic, signaling, and immune-inflammatory axes which in turn connect the gut, liver, muscle, and brain [1].

Gut microbiota and host immune system interact from birth. The microbiota shapes the development of the host immune system, and this in turn shapes the composition of the microbiota. This crosstalk is transmitted through hundreds of signaling pathways and different classes of molecules. The effects extend beyond the immune system and act upon multiple organs such as the gut, liver, muscle and brain through host-microbe metabolic axes, exemplified by production of bile acids, choline, and short-chain fatty acids (SCFAs).