Management of resistant hypertension

J. David Spence

Stroke Prevention & Atherosclerosis Research Centre, Robarts Research Institute, Western University, Canada
email: dspence@robarts.ca

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?"

Table 1. Causes of resistant hypertension

1.Non-compliance

Half of patients will admit it (13)

Better with drugs that have less adverse effects (14)

2. Consumption of substances that aggravate hypertension

Salt, licorice, NSAID's*, EtOH, BCP, decongestants

3. Consensus guidelines that assume all patients are the same

4. Therapeutic inertia

5. Diagnostic inertia

* Except for sulindac (15)

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)

Continued on next page...

Table 2. Physiologically individualized therapy* based on renin/aldosterone profile

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

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

Reproduced by permission of Oxford UniversityPress from: Akintunde A, Nondi J, Gogo K, Jones ESW, Rayner BL, Hackam DG and Spence JD. Physiological Phenotyping for Personalized Therapy of Uncontrolled Hypertension in Africa. Am J Hypertens. 2017;30:923-930.

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),(10) 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 inTable 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). (3)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:

1. Spence JD. Blood pressure control in Canada: the view from a stroke prevention clinic.*Can J Cardiol.* 2015;31:593-595.

2. Achieng' L, Joshi MD, Ogola EN and Karari E. Adequacy of blood pressure control and level of adherence with antihypertensive therapy.*East African Medical Journal.* 2009;86:499-506.

3. Akintunde A, Nondi J, Gogo K, Jones ESW, Rayner BL, Hackam DG and Spence JD. Physiological Phenotyping for Personalized Therapy of Uncontrolled Hypertension in Africa.*Am J Hypertens.* 2017;30:923-930.

Continued on next page..

4. Li C, Engström G, Hedblad B, Berglund G and Janzon L. Blood pressure control and risk of stroke: a population-based prospective cohort study.*Stroke.* 2005;36:725-730.

5.Barnett HJM, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE and Spence JD. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe carotid stenosis.*N Engl J Med.* 1998;339:1415-1425.

6. Spence JD and Rayner BL. J Curve and Cuff Artefact, and Diagnostic Inertia in Resistant Hypertension.*Hypertension.* 2016;67:32-3.

7. Laragh JH, Baer L, Brunner HR, Buhler FR, Sealey JE and Vaughan ED, Jr. Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease.*Am J Med.* 1972;52:633-52.

8. Egan BM, Basile JN, Rehman SU, Davis PB, Grob CH, III, Riehle JF, Walters CA, Lackland DT, Merali C, Sealey JE and Laragh JH. Plasma Renin test-guided drug treatment algorithm for correcting patients with treated but uncontrolled hypertension: a randomized controlled trial.*Am J Hypertens.* 2009;22:792-801.

9. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B and Carey RM. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research.*Hypertension.* 2008;51:1403-1419.

10. Baker EH, Duggal A, Dong Y, Ireson NJ, Wood M, Markandu ND and MacGregor GA. Amiloride, a specific drug for hypertension in black people with T594M variant?*Hypertension.* 2002;40:13-17.

11. Jones ES, Owen EP and Rayner BL. The Association of the R563Q Genotype of the ENaC With Phenotypic Variation in Southern Africa.*Am J Hypertens.* 2012.

12. Jones ES, Spence JD, McIntyre AD, Nondi J, Gogo K, Akintunde A, Hackam DG and Rayner BL. High Frequency of Variants of Candidate Genes in Black Africans with Low Renin-Resistant Hypertension.*Am J Hypertens.* 2017;30:478-483.

13. Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD and Mukherjee J. Can simple clinical measurements detect patient noncompliance?*Hypertension.* 1980;2:757-764.

14. Marentette MA, Gerth WC, Billings DK and Zarnke KB. Antihypertensive persistence and drug class.*Can J Cardiol.* 2002;18:649-656.

15. Wong DG, Spence JD, Lamki L and McDonald JWD. Effect of non-steroidal anti-inflammatory drugs on control of hypertension by beta-blockers and diuretics.*Lancet.* 1986;1(8488):997-1001.

Microbiota and Cardiovascular Risk: The Missing and Found Link

Daniel Monleón

Metabolomics Unit, Health Research Institute INCLIVA, Valencia, Spain
email: daniel.monleon@uv.es

Microbiota and us

Our body is inhabited by trillions of bacteria. The term microbiota refers to the myriad of microorganisms that coexists 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)