Individualized therapy for hypertension
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The recent publication of the Blood Pressure Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes trial (ASCOT-BPLA) has again occasioned a flurry of media pronouncements and editorials contending that now the truth is known, and that “newer” therapies – calcium channel antagonists and ACE inhibitors – are more effective than “old” therapies for hypertension – beta-blockers and diuretics. In the words of the great wordsmith Yogi Berra, this represents “déjà vu all over again”. A similar flurry of media pronouncements, but in the opposite direction, was trumpeted after the publication of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial, which showed that diuretics were “the best” therapy for hypertension. Largely un-noticed amidst all this fuss was the second Australian National Blood Pressure study (ANBP2), which followed closely on the heels of the ALLHAT trial, and, like ASCOT-BPLA, also showed that ACE inhibitors were better than diuretics. So what are these trials trying to tell us?

The fundamental fallacy underlying all this nonsense is the assumption that all patients are the same, and therefore that there exists a single “best therapy” for all hypertensive patients. We should know better.

It has been clear for many years that patients with African ancestors, on average, had lower levels of plasma renin than did patients without African ancestors, and that patients with African ancestors responded better to diuretics. African-Americans bear a disproportionate share of the stroke burden in the Stroke Belt of the United States; although much of this difference may be due to smoking, diabetes and education, it seems likely that genetic differences in hypertension must account for a substantial proportion of the difference. Investigation of this phenomenon reveals that several genetic variants are involved in this difference. It has also been clear for many years that measuring plasma renin is very helpful in the management of resistant hypertension. As pointed out by the authors of ANBP2, “In ALLHAT, 32 percent of the patients were non-Hispanic blacks, 16 percent were Hispanics, and 47 percent were non-Hispanic whites, whereas in ANBP2, almost the entire study population was white (95 percent)” (and less than 2% had African ancestors; personal communication, Dr. Lindon Wing, 2003). In ASCOT-BPLA, only 5% of the subjects were “ethnic minorities: mainly South Asian or Afro-Caribbean”, only 2.4% had African ancestors (personal communication, Dr. Neil Poulter, 2005). Thus, it seems that there is no mystery.

In a paradoxical way, precisely because there were so few patients in our region with ancestors from Africa, and they therefore stood out, we had the opportunity to learn about this in London, Canada. For 20 years I was the physician of last resort for resistant hypertension for Southwestern Ontario, then a catchment area of ~ 1.8 million people. During that time I saw over 10,000 patients referred for resistant hypertension. Included in the referrals were patients from a nearby community, North Buxton, Ontario, which had been a terminus of the Underground Railroad - an escape route for slaves from the Southern United States. Whereas patients with African ancestors made up only 1% of our clinic population, they accounted for 40% of our patients who needed adrenalectomy for primary hyperaldosteronism. This >10-fold disproportion may in part be related to selective pressures conferring an advantage on people who could retain salt and water in the heat of the African continent, where Arab traders carried salt, like gold, in their saddle bags. Further selective advantage may have arisen in survival of the Atlantic crossing in the heat and privation of slave ships, and while working through the mid-day heat on cotton plantations in the Southern United States. A recent study of hypertension in Sub-Saharan Africa found that urban Africans had more hypertension than did...
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rural Africans\textsuperscript{13}; could air conditioning explain much of the difference?

When our Hypertension Clinic was instituted in 1977, the algorithm used (upon the recommendation of Dr. Adam Linton) for outpatient investigation of our patients was based on the observation by Wallach et al\textsuperscript{14} that stimulated plasma renin levels were more useful than random levels of plasma renin. By 1980 we had identified over 100 patients with stimulated plasma renin activity less than 1 ng/ml/hr. Thinking that we were finding patients with Conn’s syndrome, we began, in 1980, with the help of Dr. Al Dreidger, a Nuclear Medicine colleague, to try to identify those with unilateral adenomas, using iodocholesterol scans before and after dexamethasone suppression. To our astonishment, by 1983 we had studied 100 such patients, and not a single one had a hot unilateral adrenal gland: all but a few (presumably patients with unrecognized Liddle’s syndrome or variants) had hot adrenal glands bilaterally, and about 30% suppressed with dexamethasone. When Biglieri described his first four cases of idiopathic primary hyperaldosteronism due to bilateral adrenocortical hyperplasia in 1985\textsuperscript{15}, we had already subjected 10 such patients to adrenalectomy because they could not be controlled medically; all had bilateral adrenocortical hyperplasia. Of these 4 had African ancestors; one was a visiting clergyman from Africa; the others were from North Buxton. At least one had a 1.5 cm nodule that could easily have been mistaken for a Conn’s tumor. Our subsequent experience has been that, knowing the diagnosis, most such patients can be controlled medically; only 5% require adrenalectomy.

Our experience is not unique. Low-renin hypertension accounts for an important proportion of resistant hypertension, in hypertension clinics around the world. Eide et al\textsuperscript{16}, in Norway, found that two thirds of patients with Conn’s syndrome had low-renin status. Gallay et al., in California, reported that among patients with resistant hypertension, 17% had an elevated ratio of aldosterone to renin\textsuperscript{17}. Ouzan et al\textsuperscript{18}, in France, found that the addition of spironolactone controlled blood pressure in 92% of patients with resistant hypertension. Baker et al\textsuperscript{19} reported in 2002 that in London, UK, 5% of hypertension in black patients (mainly of Afro-Caribbean origin) was due to a polymorphism of renal epithelial sodium channels, i.e. a variant of Liddle’s syndrome, with a specific treatment: amiloride\textsuperscript{20}. Among monogenic disorders causing hypertension, low-renin hypertension is particularly prominent\textsuperscript{21}. A recent study confirmed that aldosterone, and the ratio of aldosterone to renin, were more important among black than among white hypertensives\textsuperscript{22}.

Although a disproportionate number of the patients I have seen with primary hyperaldosteronism had African ancestors, I have also seen patients with African ancestors who had renovascular hypertension. Thus, treating patients solely on the basis of the color of their skin is inappropriate. What is appropriate, in patients with resistant hypertension, is to do two blood tests, to sort out the underlying cause of the hypertension. Here I speak not of a diagnostic rubric, but of the physiological drivers of the hypertension. From the over 10,000 adult patients I have seen with resistant hypertension, only 9 were due to licorice, only 3 were due to coarctation of the aorta, and only 51 were due to pheochromocytoma. The vast majority were due to disorders of the powerful feedback loop that regulates salt and water retention: the renin/angiotensin/aldosterone system.

Table 1. Some causes of low-renin hypertension

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparent mineralocorticoid excess\textsuperscript{30}</td>
<td>- Licorice</td>
</tr>
<tr>
<td>Conn’s syndrome*</td>
<td></td>
</tr>
<tr>
<td>Primary adrenocortical hyperplasia\textsuperscript{15}</td>
<td></td>
</tr>
<tr>
<td>Adrenal enzyme deficiencies</td>
<td>- 11beta-Hydroxylase, 17 alpha-hydroxylase deficiency\textsuperscript{31}</td>
</tr>
<tr>
<td>Dexamethasone-suppressible hypertension</td>
<td>- chimaeric aldosterone synthase gene\textsuperscript{32, 33}</td>
</tr>
<tr>
<td>Gordon’s syndrome\textsuperscript{34}</td>
<td></td>
</tr>
<tr>
<td>Liddle’s syndrome and variants\textsuperscript{19, 20, 35, 36}</td>
<td>- renal tubular Na channel abnormality;</td>
</tr>
<tr>
<td>GIP dependent cortisol excess with nodular hyperplasia\textsuperscript{37}</td>
<td>* it seems likely that many, if not all cases of “Conn’s syndrome”, represent nodules in patients with bilateral hyperplasia</td>
</tr>
</tbody>
</table>

By measuring plasma renin and aldosterone, patients can be divided into three categories, each requiring different medical therapies. Table 1 lists some of the causes of low-renin hypertension. Table 2 outlines an algorithm for individualizing therapy of hypertension, based on levels of plasma renin and aldosterone.
Table 2. Individualized therapy for hypertension

<table>
<thead>
<tr>
<th>Renin</th>
<th>Aldosterone</th>
<th>Primary hyperaldosteronism</th>
<th>Liddle’s syndrome and variants, or minerallocorticoid excess</th>
<th>Renal or renovascular hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>High</td>
<td>Aldosterone antagonists: spironolactone or eplerenone* (Rarely surgical)</td>
<td>Amiloride</td>
<td>Angiotensin receptor blockers (Rarely decompression or revascularization)</td>
</tr>
</tbody>
</table>

* amiloride for men, where eplerenone is not available

Patients with low renin and high aldosterone have primary hyperaldosteronism, which is almost always due to bilateral hyperplasia, and the primary treatment is with aldosterone antagonists. Where eplerenone is not available for men (because of gynecomastia from spironolactone), amiloride in high doses (80mg/day or more) may be used. Such doses would never be used in the absence of a diagnosis, but may be necessary for medical control in such patients. If the renin is low and the aldosterone is low, the problem is a variant of Liddle’s syndrome, or minerallocorticoid excess, and the primary treatment is amiloride. (Triamterene is problematic because of casts and interstitial nephritis.) If the renin and aldosterone levels are both high, the problem is secondary hyperaldosteronism, due to a renal or renovascular problem. (Not uncommonly this may be due to renal microvascular disease secondary to hypertension itself; I call this “tertiary hypertension”). In this setting the primary treatment is angiotensin receptor blockers; in some cases patients with obstruction may require decompression of the urinary tract, and patients with true renovascular hypertension may require revascularization. The most difficult patients are those who have more than one cause of hypertension: I have seen a dozen who began with primary hyperaldosteronism, and went on to develop renovascular hypertension; such patients may need both aldosterone antagonists and angiotensin-receptor blockers, a combination that would be contraindicated in the absence of a physiological diagnosis.

What ASCOT-BPLA, ALLHAT and ANBP2 have been trying to tell us is that there is no single “best therapy” for all patients with hypertension: what physicians need to do is to define the underlying cause of the hypertension in each patient, and individualize the therapy for that patient. Doing so has tremendous potential for reducing the burden of cardiovascular disease, particularly of stroke, and particularly among African-Americans in the US Stroke Belt, and perhaps among Africans. Effective blood pressure control has the potential to reduce stroke by half; the types of stroke that are prevented are lacunar infarctions, and intracerebral hemorrhages, both due to hypertensive small vessel disease. In the North American Symptomatic Carotid Endarterectomy Trial, we reduced intracranial hemorrhage to 0.4% of stroke, and this included subarachnoid hemorrhages, which are not caused by hypertension. It is long past time that clinical trials of this strategy, which has the potential to improve the cost-utility of therapy for hypertension by about two thirds, be carried out. A straightforward approach would be to randomize Hypertension Clinics in the Stroke Belt, and/or in Africa, to usual care vs. individualized therapy for hypertension based on aldosterone:renin ratios, using a cluster randomization design. Data needed to calculate cost-utility should be collected.

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