Exploring the Laragh method of treating hypertension: show notes

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Introduction

When encountering the patient with shock, we are accustomed to thinking through the possible etiologies and directing treatment accordingly. Is there a deficit of blood volume, such as from hemorrhage? Is the patient excessively vasodilated, as in sepsis or anaphylaxis? Is the shock cardiogenic?

However, when faced with the hypertensive patient, we tend to treat every patient the same, regardless of the underlying etiology. Has the time come for hypertension treatment directed at a patient's individual pathophysiology? In the first part of today's episode, Dr, Armando Lindner and I discuss the Laragh method of treating hypertension, which proposes to do just that. In part II of the episode, we discuss a few major hypertension trials, and their implications for the most important classes of antihypertensive medications.

Part I
The Laragh method of treating hypertension

Dr. John Laragh was a clinician and hypertension researcher whose work was groundbreaking in describing the role of the renin-angiotensin axis in hypertension. He summarized his twenty-five lessons on treating hypertension and twelve clinical pearls in a 2001 review that serves as a complete primer on his method[1]. A new review published in 2011[2] provides a briefer and more recent summary.

The first step in using Laragh's method is understanding that patients with essential hypertension have an excess of blood volume, vasoconstriction, or both. Via the potent vasoconstricting effects of angiotensin II, the renin-angiotensin axis is largely responsible for causing vasoconstriction. The kidneys control blood volume. If a hypertensive patient has an appropriately suppressed renin level (<0.65ng/mL/hr), this suggests a renin-independent etiology of hypertension causing "low-renin," a.k.a. "volume-mediated," or "V-" type hypertension. If renin activity is inappropriately normal (0.65-6.5ng/mL/hr) despite a high blood pressure, or even elevated (>6.5ng/mL/hr), then there is a relative excess of renin causing "medium/high-renin" a.k.a. "vasoconstriction-mediated", "resistance-mediated," or "R" type hypertension.

The next key insight into Dr. Laragh's method is that treatments correctly directed at the patient's etiology of hypertension will be more effective and less toxic to the patient. Patients with volume-mediated hypertension will benefit most from thiazide and other diuretics, calcium-channel blockers, and alpha blockers (as the latter two cause vasoactive changes in the kidney leading to a diuresis)[12]. Patients with medium to high renin levels will benefit from beta blockers, which decrease the production of renin, and ACEi/ARBs, which will block renin's downstream effects. Patients may have both pathways at play and can certainly benefit from a mix of anti-V and anti-R therapies. In fact, hypertensive patients on more than one drug should be on a "VR combo" unless there is a strong reason to choose another combination (such as ischemic heart disease indicating BB + ACEi therapy, or a suppressed renin level even while taking one anti-V drug such as amlodipine, indicating the addition of a thiazide diuretic).

Determining a patient's etiology of hypertension

There are three strategies to determine your patient's renin status in order to direct the optimal therapy.

Strategy 1. Age, race, and comorbidities

First, you can use a patient's age, race, and comorbidities. Current hypertension guidelines implicitly use this strategy[5,7,4,9,8]. Patients older than 60 are generally more likely to have LREH (low renin essential hypertension), and younger patients (30-55) are more likely to have MREH/HREH. Black individuals are more likely to have LREH, hence why multiple guidelines recommend prescribing thiazides for black patients and white patients over 60 years old, while recommending ACE inhibition for younger patients (or β blockade for pregnant younger patients).

Strategy 2. Treatment response

If a patient's blood pressure drops significantly in response to their treatment, you can assume they were correctly treated, confirming the etiology of their hypertension. If there is little response and they are confirmed to be adherant to the regimen, this might suggest that hypertension is due to the other etiology. Laragh calls this approach *diagnosis ex juvantibus* - diagnosis by finding which treatment helps.

Strategy 3. Plasma renin activity level

For initial treatment The plasma renin activity (PRA) assay can help differentiate the etiology of hypertension for individual patients. It costs $30-75 in the United States, and is covered by Medicare. The lab is inaccurate in patients who have not yet ambulated on the day of testing, such as in hospitalized inpatients undergoing a morning blood draw. The test can otherwise be sent at any time of day, and the patient doesn't need to fast, stop current antihypertensive therapy, or restrict salt intake prior to the test, contrary to prior belief[12].

Recommendations for when to use the plasma renin activity assay vary considerably. Laragh checked the renin activity on the first visit when a patient's blood pressure is elevated, so that the information was available to help him decide the first antihypertensive drug to prescribe[1]. A recent study proposed measuring PRA in those populations with prior probabilities of LREH most approaching 50% (younger black patients and older white patients, using 60 as the age cutoff), but empirically treating other populations based on predicted renin status without using PRA when starting therapy[14]. Official guidelines do not make recommendations for ever using plasma renin activity in the routine management of hypertension.

For patients already being treated There is a small randomized trial suggesting that PRA testing can be helpful in the patient whose hypertension is challenging to control. A small study randomized 39 treated-but-uncontrolled patients to clinical hypertension specialists' care (CHSC) without the use of PRA, versus 38 patients receiving renin-test guided therapy (RTGT) by those same specialists. Although the RTGT care was provided by specialists, they followed a specific algorithm reproduced in Table 1 of the article, which could easily be used by primary care providers. The study found that blood pressure was controlled in 74% of the RTGT arm vs. 59% in the CHSC arm, although this difference was not statistically significant in this small study. Final numbers of antihypertensive medicatiosn were similar, but the RTGT arm allowed more discontinuation of medications since the RTGT started with more therapies at the time of randomization.

The authors conclude that "the number of [hypertension] specialists is quite insufficient to manage the estimated 17 million treated but uncontrolled hypertensive patients in the US. Accordingly, the RTGT algorithm emerges as a practical and objective biochemical alternative to CHSC that can be used in most clinical settings by a wide range of health-care providers for addressing the public health burden of treated but uncontrolled hypertension."

Part II
Antihypertensive medications and trials

Dr. Lindner shared his perspective on a handful of major trials in the treatment of hypertension.

ALLHAT

ALLHAT was the major trial in the early 2000s that established diuretics as the primary first-line antihypertensive. However, ALLHAT has been criticized for a design that favored diuretics fro mthe start. Monotherapy failed to treat most patient's hypertension in the trial, and all patients prescribed a second drug were prescribed beta blockers. A thiazide and beta blocker create a "V/R combo" treatment that is likely more effective for most patients than an "R/R combo" of an ACE inhibitor and beta blocker. Additionally, Dr. Lindner shares concerns in this episode about the excess of metabolic side effects of diuretics that were shown in the trial.

ACCOMPLISH

The ACCOMPLISH trial found that amlodipine performed better than hydrochlorothiazide at reducing cardiovascular events when each was combined with an ACE inhibitor.

ASCOT-BPLA

ASCOT-BPLA studied English and Scandinavian hypertensive patients with or without diabetes, comparing a calcium channel blocker and ACE inhibitor regimen against a diuretic and beta blocker regimen. It was stopped early due to a decrease in many of cardiovascular complications used as secondary endpoints in the calcium channel blocker and ACE inhibitor group.

ACCORD

ACCORD studied strict versus liberalized blood pressure control in diabetic patients, but the drugs that were used (such as alpha and beta blockers) are no longer considered firstline therapies. It found no benefit to strict control, but it is unclear whether these results would be repeated if current first-line therapies were used. Perhaps outcomes are not just driven by the blood pressure achieved, but by the specific drugs used to achieve that blood pressure.

JNC 7 vs. JNC 8

Pertinent to our discussion in this episode, JNC 8 differed from JNC 7 by recommending less stringent blood pressure targets for certain groups. Language about discontinuing ineffective medications is omitted in JNC 8, so one antihypertensive is added after another until the blood pressure is controlled. JNC 8 was not the official statement of any major society, as support was withdrawn from the individuals publishing the guideline, and a dissenting opinion was also published by other members of the committee.

Summary

The Laragh method proposes that hypertension is caused by excess blood volume, excess vasocontriction, or both. By directing treatments at the underlying pathophysiology, it is hypothesized that appropriate blood pressure control may be achieved with fewer drugs, and fewer treatment-related toxicities.

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