Laragh's Lessons in Pathophysiology and Clinical Pearls for Treating Hypertension

Introduction

Treatment of Hypertension is a Worldwide Failure

As indicated in Fig. 1, the worldwide results for the treatment of hypertension reveal a dismally poor success rate in the various countries shown.\(^1\)\(^2\) These results prevail even when the relatively conservative treatment goals used such as 160/95 mm Hg are taken into account. Surprisingly, too, this generally poor success in treating hypertension bears no significant relationship to the medical resources and skills available in various nations. In fact, those countries with the most sophisticated intellectual, technical, and fiscal resources perform no better than the rest. It is also amusing to note that the published guidelines of the various countries are extremely similar to each other, indicating that these various national committees do little innovating in the face of an unsolved public health problem.

Other parameters confirm this generalized failure of treatment. Thus, heart attack rates in the US have been actually increasing slightly in recent years\(^3\) despite massive efforts by industry and government aimed at both dietary modifications and the promotion of antihypertensive as well as antilipid drug treatments. It is also interesting to learn that most practicing physicians in the US ignore their government's guidelines (JNC VI) for treatment.\(^4\)

Why is there such ineffectiveness in the promotion of government-sponsored treatment systems around the world? Of course there is no shortage of opinions about this. But whatever people may say, the system is broken, so there are a number of factors worth discussing that might be relevant to fixing it.

First, is the explosion in hypertension research of the past 40 years involving a whole new hypertension research track launched in 1960 by the discovery of the renin-angiotensin-aldosterone control system by our group in research.\(^5\)\(^6\)\(^7\)\(^8\) that concurrently revealed a key role for massive overactivity of the new renin-angiotensin-aldosterone system for causing malignant hypertension and its generalized vasculitis.\(^5\)\(^6\)\(^7\)\(^8\) Our subsequent definition of \(\beta\)-blockade as the first potent and selective antihypertensive anti-renin system drug\(^9\)\(^10\) and our characterizations of the first angiotensin receptor blocker, saralasin, from 1973–1976,\(^11\)\(^12\)\(^13\)\(^14\) and of the original converting enzyme inhibitor from snake venom, teprotide, from 1974–1977,\(^14\)\(^16\) demonstrated the powerful specific and congruent antihypertensive effects of these three different anti-renin system drugs, each of which blocks the hormonal cascade at one of three different biochemical sites. We showed that each of these three probes produce dramatic prompt corrections of malignant hypertension, its attendant vasculitis, and they also corrected the hypertension of most essential hypertension, in whom induced decrements in pressure were closely related to the prior height of their plasma renin levels, thereby implicating a direct causal role of the plasma renin levels in medium and high renin essential hypertension. Our results using saralasin and teprotide in this work preceded industry development of the many orally active converting enzyme inhibitors (CEI) analogs of teprotide. First, captopril was synthesized in 1977,\(^17\) and enalapril and lisinopril in 1980\(^18\) and clinical trials begun thereafter. This was followed by the invention of losartan, the first saralasin-like orally active angiotensin receptor blocker (ARB) by Timmermans and Wang in 1990.\(^19\) Captopril, lisinopril, and losartan were each followed in turn by the introduction of many more analogs, so that today there are probably more than 20 CEI on the market and perhaps six ARB with more to come.

This, plus the companion development of other potent antihypertensive drugs notably the many dihydropyridine calcium channel blockers (CCB) has created a marketing crunch directed at doctors who treat hypertension as each company tries valiantly to claim some uniqueness for their version of the many drugs existing in the same class, as well as for each class of drug. This has led to such claims as better penetration of cells, greater potency, or the ability to reach a possibly remote tissue renin site. Such claims have undoubtedly confused busy physicians but they have also swayed them, leaving physicians to choose among scores of drugs for the patient in his or her office. Moreover, drug companies would like their antihypertensive product to be for all hypertensive patients. They want no exclusions and no required blood tests before selecting a drug; they want their drug to be a one-size fits-all antihypertension drug. Notwithstanding this ecumenical profiling, another marketing ploy uses the opposite strategy, to stake out demographic targets (ie, the claim that a particular drug is better for blacks, or elderly, or obese, or female hypertensives). Such differences, if they do exist, are generally so small statistically that, in choosing a drug type for the individual patient sitting in your office, you will probably have less than a 50% chance of guessing correctly on this basis from among all the treatment options available. In this setting, logic, science, and reality evaporate as does the real truth, that is, that a particular patient in any demographic category may respond to different antihypertensive drugs differently than does the next person of similar demography.

It is possible to develop order out of this chaos. In fact,
today there are six major classes of antihypertensive drugs: (1) diuretics and aldosterone antagonists; (2) \( \alpha \)-blockers; (3) calcium channel blockers, two types; (4) \( \beta \)-blockers; (5) CEI and (6) ARB; and within each class there are from 1 to 20 different candidates on the market. But, actually, from the practitioner’s standpoint as will be discussed, there are basically only two differently acting types of antihypertensive drugs. Nonetheless, the newest drugs (ie, those still on patent) receive the heaviest marketing and this works. Their usage often leads the pack, sometimes irrespective of their mode of action or range of effectiveness.

This leads to another conceptual belief that impairs the drug selection process. Hypertension is considered by many to be a single, genetically guided process for which any drug that lowers blood pressure, regardless of how it works, is suitable.

Yet our work has shown that, mechanistically, in every hypertensive situation, there is either a primary salt factor, or a primary renin-angiotensin factor that sustains the hypertension—two different well-accepted pressor mechanisms that are easily demonstrable. Each of these two pressor factors is correctable, respectively, by one of two different classes of antihypertensive drugs. Thus, the sodium volume or the renin-mediated factor is readily demonstrable or excludable in individual patients by simply doing a plasma renin test in the ambulatory setting. The presence of one of these two mechanisms is confirmable by a positive response to an appropriate antirenin system-type drug, or in the case of sodium-mediated hypertension, instead to an antisodium volume-type drug.

We call this process *diagnosis ex juvantibus*, that is, the response to the drug confirms or excludes the causal mechanism in question. Thus, salt-mediated hypertension is reliably indicated by a suppressed ambulatory renin level (<0.65 ng/mL/h), and this is verifiable by a good depressor response to a diuretic (its diagnosis ex juventibus all over again). Conversely, in those patients whose renin is not suppressed, plasma renin activity (PRA >0.65), the hypertension is primarily renin-angiotensin-mediated and responds brilliantly to an antirenin angiotensin-type drug. Accordingly, getting the blood pressure corrected with a single drug—the right drug—is now not a big deal. But it becomes a big deal if you guessed wrong at the outset, and especially if you then keep testing different drugs in the same class because you think they differ from each other.

But, it is also important to recognize that correcting the blood pressure per se is not enough. Ideally, the drug strategy prescribed should also have the potential to prevent later cardiovascular morbid events, such as heart attack, heart failure, kidney failure, or stroke that shorten the useful life of a hypertensive person. The ideal treatment regimen should be designed primarily to achieve these two goals by blocking the plasma renin-angiotensin system whenever it is involved, because plasma renin-angiotensin levels sustain more than half of essential hypertension, because we have highly specific drugs we can use to reveal it, leaving little room for diagnostic doubt, and because there is much evidence now that such milder excesses in plasma renin-angiotensin over time are also vasculotoxic to heart, brain, and kidney vessels. Whatever is done to achieve this treatment goal, two end points must be satisfied (1) the blood pressure must be reduced and (2) the renin factor must be blocked if there is any possibility that excess renin-angiotensin is contributing to the hypertension. The same rules applies if the salt factor is implicated instead, by renin testing (PRA <0.65) and a diuretic trial given first.

In this course, we will tell you exactly how to do this in your office practice. We guarantee that this method brings order out of the chaos of current drug selection processes and it will result in the use of fewer, better, targeted drugs for long-term therapy.

Accordingly, in this course, we will show you that there are basically two types of essential hypertension, pathophysiologically and mechanistically speaking, the sodium volume-mediated form and the renin-angiotensin-mediated form plus a transitional form involving a little too much of each. And for all patients there are in fact only

![FIG. 1. Percentage of hypertensive patients (expressed by numbers in each panel) with controlled blood pressure values in different countries. (Italy, not shown, reports 10%). (redrawn with permission from Mancia G and Grassi G.)²](https://academic.oup.com/ajh/article-abstract/14/1/84/136058)
two available classes of drugs mechanistically speaking, the antisyroid volume drugs and the antirenin-angiotensin system drugs. All of the six major classes of antihypertensive drug fit into one of these two categories. The plasma renin test identifies which type of patient you have and it guides your starting choice of either a “V” (sodium volume drug) or an “R” (antirenin drug) the response to which verifies your drug choice for correcting both the pathophysiological lesion and the blood pressure. Thus, if you are willing to enjoy and use a little physiology you can dig your way out of this chaos and find a solution that works.

For this review course I will draw heavily on the experiences of my long-time colleagues, and working partners, Michael Alderman, Jon Blumenfeld, Daniel Catanzaro, and of course my wife, and longest colleague, Jean Sealey, all of whom directly or indirectly, have contributed vitally to our research work and to these lessons. Many others as trainees from all parts of the world also have contributed importantly. Altogether, this has been synergism at its best. When I use the word we instead of I in these lessons, this is what I am expressing.

In this course we describe the pathophysiology of hypertension through the eyes of the renin system because the renin system is our blood pressure control system. It constantly reacts to and corrects deviations in blood pressure and flow by responding to central and autonomic nervous signals and by also constantly reacting to postural changes in blood pressure as well as to changes in dietary sodium and potassium intake. Getting a feel for the cybernetics of these interactions and how to recognize them will make the treatment of hypertension a joy and a source of gratification.

Readers of these lessons and our accompanying clinical pearls in following issues of the Journal are invited to communicate with us by e-mail or by fax. We will try to answer all of your questions promptly. As we proceed, we will also provide a number of simple review questions, to reinforce your learning.

References


Clinical Pearl #1: Diuretic-Induced-K+ Depletion May be Hazardous: The Miracle of Low-Dose Spironolactone

Since 1960, sulfonylurea thiazide diuretic therapy has been a cornerstone of long-term antihypertensive therapy and also for the treatment of patients with congestive heart failure (CHF). Since the beginning it was recognized that such natriuretic–diuretic therapy is regularly accompanied by demonstrable body potassium and magnesium deficiencies, often reflected by significant, albeit generally mild, observed decrements in plasma K+ and Mg2+ levels.