The Resistant Hypertension Quandary

A current look at what is known, key questions we should be asking, and some possible paths forward in research and practice.

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What is resistant hypertension? This question is important because for several years, it seemed to define a large group of patients who warranted the development of new therapies and defined a basis for selecting patients for trials of interventions, such as renal denervation. It provided the foundation for the entire scientific dialogue in this field. There have been more than 300 publications on renal denervation in resistant hypertension in the last 5 years.[1] In short, what are we all talking about?

RESISTANT HYPERTENSION: GENETIC MUTATION OR BEHAVIORAL VARIANT?

Although there are formal definitions, clinicians commonly consider resistant hypertension to be a permanent diagnosis of the patient. In routine clinical practice, the diagnosis of resistant hypertension tends to be accepted without formally requiring confirmation that the patient's body is resistant to the blood pressure-lowering effect of therapy that has definitely reached the bloodstream. Our experience in the cath lab is that significant doses of intravenous nitrate never seem to fail to have a blood pressure-lowering effect, even when this is unwanted. Intravenous adenosine, a similarly familiar drug in the cath lab, also seems very reliable in lowering blood pressure.

As endovascular physicians, we are sure that readers share our curiosity that endovascularly administered medication seems to lower blood pressure in essentially all patients, even when inconvenient to the procedure and unhelpful for the patient. We think that this is because prescription of oral medication is different from direct infusion of intravenous medication in that there are many stages at which the agent may not progress to the bloodstream. First, the prescription may not be filled. Second, even if one obtains the medication, everyone's lives are filled with many competing demands for attention, and one could easily forget to take the tablet. Third, although it may be surprising to us as physicians, many people do not think it worthwhile to take medications to substantially increase lifespan, even if they are free of cost, side effects, and loss of autonomy.[2]

AN INTERVENTION TO REDUCE BLOOD PRESSURE BY 35/15: ANYONE WANT TO INVEST?

Our scientific analysis of the field demonstrated that there is a simple procedure that can be undertaken in outpatients to reduce blood pressure by 35/15 mm Hg. This is slightly larger than that claimed for renal denervation even in its headiest early days.[3] It is a molecular approach that has proved effective in controlling an element of the world's second most common cause of death and should

also prove effective if applied systematically for the world's leading cause of death, which is cardiovascular disease.[4]

This technology is noninvasive and reversible. Although it requires skilled professional input, the training necessary is not as extensive as for invasive procedures. This would eliminate any possibility that commentators could suggest there were regional differences in the effectiveness with which therapy was delivered.[5]

Those involved in SYMPLICITY HTN-3[6] rebutted the suggestion of regional differences, explaining that the procedures were done "with a large degree of care" and close involvement of manufacturers to "make sure the procedures were done in the most effective way."[7] We favor this second view. We suspect that the difference between trials arises from the lack of blinding in the non-North American study measurements. The therapeutic approach we describe would sidestep such an unhelpful innuendo about interventionists of any region.

The therapy that delivers a 35/15-mm Hg reduction should be additive to renal denervation, according to the best available scientific information to date, because it engages multiple therapeutic targets.

There are no regulatory hurdles. This may be important for readers in the United States, where the Food and Drug Administration has come under acerbic criticism[8,9] for requiring reliable evidence of nascent[10] therapies. Perhaps an enterprising reader could devise a path to profit? There seems ample corporate funding available to support ventures in this arena.[3] The key intellectual property is described in the Appendix sidebar.

DRUG RESISTANCE OR PRESCRIPTION RESISTANCE?

There may be a chasm between the disease we think we are targeting for clinical study and the patients we are actually recruiting into trials. In recent years, the concept of pseudoresistant hypertension has become established among experts to represent phenomena such as nonadherence. This useful insight may not yet be coming to the forefront of every clinician's mind.

Moreover, clinical trials of resistant hypertension rarely describe any formal strategy to enroll only patients with biological resistance to the molecule in the blood, and exclude those in whom the resistance occurs before the bloodstream (eg, not taking the medication).

SCIENCE: THE HABIT OF FACING REALITY

How quickly science moves from nowhere to an accurate answer depends not only on the technology available but also on the evaluators' freedom from bias. Two thousand years ago, Eratosthenes estimated the circumference of the Earth by peering down a well and using some mathematics.[11] His answer was correct to within 0.16%. We believe an important driver for Eratosthenes' astoundingly accurate answer was the absence of professional pressure upon him to overestimate or underestimate the value. It is for similar reasons that we know the speed of light: no one stands to gain from overstating its value. Indeed, some have lost from doing so.[12]

Medical research, in contrast, is troubled by our assumption that those who can report large effects from a therapy must have greater clinical skill than those who cannot manage this. In reality, this assumption may fail to reflect other contributors to large reported effects, including unintentional bias in measurements[3,13,14] or even research error.[15]

Clinical therapeutic discoveries have an unenviable track record of early overestimation of effect sizes followed by agonizing years of serial downgrades of expectations. Some leading experts imply that pioneers' exaggeration of therapeutic effects is well-accepted and even apply a name, the *Proteus effect*.[16] Our alternative view is that science should seek to deliver reliable information without regard to any investment cycle.[3]

We should compare the efficiency with which the truth is converged upon, between the example of lonely Eratosthenes measuring the 40,000-km circumference of planet Earth and an entire international scientific community counting the millimeters of mercury of blood pressure decrease resulting from renal denervation.

DENIAL, ANGER, BARGAINING, DEPRESSION, AND ACCEPTANCE: WHICH STAGE ARE WE AT?

Four decades ago, Kübler-Ross[17] laid out the sequence of events when people face a profound emotional loss. We invite readers to examine Table 1. In the left column, we list the reasons enumerated in the most up-to-date analysis[5] by the most eminent authorities of why SYMPLICITY HTN-3[6] did not match the previous studies. In the right column, we have added our observations. We invite readers to write to us via *Endovascular Today* to suggest which stage our field has currently reached (evteditorial@bmctoday.com).

RECOGNIZING AND AVOIDING THE BIG THREE BIASES EXAGGERATING EFFECT SIZES

We have previously written in *Endovascular Today* and described in more detail elsewhere[18] three little-discussed causes for trials of novel therapy to inadvertently overstate efficacy.

First is what we call *big day bias*, which is the tendency of patients, recruited for having unusually high values of a variable, to experience a decrease in that value on the next measurement. Imagine measuring the temperatures of 10,000 people and selecting the hundred with the highest

TABLE 1. PROPOSED EXPLANATIONS FOR SYMPLICITY HTN-3[6] HAVING "FAILED"[5*] WHERE NUMEROUS PREVIOUS UNBLINDED STUDIES SUCCEEDED

Proposed Explanation	Observation
Only works in animals and not humans.	Not an explanation for why it works in humans in ***unblinded*** studies.
SYMPLICITY HTN-3 was underpowered. Antihypertensive drug trials to prevent events are usually much larger.	Not accompanied by a power calculation to clarify. SYMPLICITY HTN-3 was the world's largest randomized, controlled denervation trial and the only one to publish explicit power calculations in advance in a peer-reviewed journal. The previous positive studies were not larger but smaller, and they were all ***unblinded***. It may not help resolve the question to adversely compare the sample size of SYMPLICITY HTN-3 with trials that focus on counting events, which have to be very large.
SYMPLICITY HTN-3's American operators may not have performed denervation as well as the previous studies' non-American operators.	This would necessitate either American operators being inherently less skillful at procedures, which does not seem possible to us, or the effect size growing by 10-fold with experience, which does not seem to have been reported in the previous ***unblinded*** positive reports.
Patients in the control arm may have increased their medications.	No mention of why this should happen specifically in the control arm of SYMPLICITY HTN-3 and not in the control arm of the ***unblinded*** SYMPLICITY HTN-2.
The final measurements may have been too early and should be repeated during long-term follow-up.	Not clear how this explains the difference or exactly what information would be gained. The ***unblinded*** studies reported large effects at this time point or earlier. Moreover, SYMPLICITY HTN-3 is now unblinded. If an effect appears only after unblinding, wouldn't this be evidence not for, but against, a renal nerve-mediated effect?
Because prescribing more drugs to patients already on more than five antihypertensive drugs does not seem to reduce blood pressure, denervation might also be less effective in them.	The publications suggest it was, in fact, easy to demonstrate such a reduction. Denervation achieved this consistently in patients on multiple drugs as long as the study was ***unblinded***. Indeed, SYMPLICITY HTN-3 also showed substantial office pressure reduction, the only disappointment being that it was much the same in both arms. Some patients with persistent high blood pressure despite prescription of numerous drugs may not be taking the medication. If this is the origin of their resistance, denervation should have more (rather than less) opportunity for efficacy than additional prescription.
SYMPLICITY HTN-3 included a substantial proportion of African Americans. The corresponding ethnicities were a very low proportion of the previous reports.	This would explain a small part of the mismatch. The 30-mm Hg effect in ***unblinded*** studies largely of Caucasians still conflicts with the 6-mm Hg effect in Caucasians in SYMPLICITY HTN-3. The remaining 24 mm Hg of mismatch seems unexplained.
SYMPLICITY HTN-3 may be "accidental" like VALIANT or COURAGE; these studied therapies are still heavily used.	We calculate that the probability of a true 30-mm Hg effect accidentally emerging as small as 2.39 mm Hg, when the standard error is 2.30 mm Hg, is ϕ [(2.39–30)/2.30] which is 2×10^{-33}. We should not assume that the VALIANT and COURAGE results were accidental. VALIANT shows that in myocardial infarction, there is no routine need to add angiotensin receptor blockade therapy on top of the angiotensin-converting enzyme inhibition. The heavy use of stents after COURAGE is not evidence that COURAGE was an accident.

Eight explanations are currently proposed for the conflict between SYMPLICITY HTN-3 and previous studies. Sadly, the entire list neglects the possibility that the difference between the results of the blinded SYMPLICITY HTN-3 trial and the previous unblinded studies might lie in the omission of blinding.

**The article was chosen for its eloquence and thoroughness, and because its authors are our friends who share our preference for outspokenness and clarity over fudging and obscurity.*

values for enrollment in a single-arm trial of an emerging therapy.[10] Six months later, those 100 patients will certainly show a statistically significant decline in temperature, even if the therapy was a placebo. Statisticians call this *regression to the mean*, but we offer the simpler term *big day bias* to make the mechanism more instantly recognizable. Having a randomized control arm eliminates this bias.

Second is what we call *check once more* bias, which is our universal habit as clinicians of remeasuring a value, be it blood pressure or ejection fraction, if the first measured value is clinically doubted. The problem is that in routine clinical practice (unblinded to treatment allocation), we generally cannot resist doing this in a way that (clinically) seems sensible but (scientifically) amounts to bias. We have established this publicly by polling numerous audiences totaling thousands of specialists.[19] A measure that cannot be easily discarded and remeasured (eg, ambulatory blood pressure monitoring) can eliminate this bias.

Third is what we call *I'd better take them now* bias, which is the potential for patients to be inspired to greater concordance with their medication regimen once faced with the seriousness of their condition through undergoing an invasive procedure, perhaps sharing a ward with patients suffering the sequelae of unsuccessfully controlled cardiovascular risk factors. Blinding the patients and their clinical team to the randomization arm eliminates this bias.

WHERE NOW FOR RESISTANT HYPERTENSION?

Just as electorates get the government they deserve, we as clinicians get the science we deserve.[20] If we are an inattentive audience, we will be responsible for incorrect information filling lectures and literature. Undoing this will take many years, loss of face, and millions of dollars of unnecessary effort. Fortunately for us, the present liability situation is that when the most carefully bias-resistant research is eventually completed,[21] we are safe from ever being handed the bill for the cost of reaching that point, which is the true price of our earlier uncritical applause.[22]

If we want to help our own field, we should help it recognize good research design and bad research design by pointing out the differences at every opportunity. Hesitancy in pointing out design errors in research should be considered as inexcusable as failure to point out to a colleague that they are about to saw off the wrong leg of a patient. It may not be one's job, but it is one's professional responsibility.

PROCEDURAL INTERVENTION'S UNIQUE POTENTIAL FOR PATIENTS WHO DO NOT WANT TO TAKE MORE MEDICATION

We believe that our community could be more explicit about the patients who could benefit from procedural intervention. Instead of defining them by the number of tablets prescribed, their doses, or their nationality,[23] we could openly offer to enroll patients who would rather take the potential risk of an invasive procedure than take additional tablets.

There is zero reason for there to be a scientifically solid cutoff in the number of medications to reliably identify for which patients renal denervation is more appropriate than taking additional tablets. Those who think otherwise should ask themselves, "What is the cutoff on the level of near-sightedness that makes a laser eye surgery superior to wearing glasses?" Having done that, they should see if colleagues answering the same question without conferring come to the same answer.

Instead, we suggest considering procedures genuinely complementary to medical therapy.[24] We must recognize that individual patients will vary in their preferences: some will ask for procedural approaches as the first choice while, at the other extreme, others will view it as a last resort. To predetermine that the threshold should be the same for all, without rational quantitative reasoning, is not wise.

APPENDIX

Sadly, for those reaching for their checkbooks, the therapy that reduces blood pressure by 35/15 mm Hg already exists. The innovation is in moving forward from providing a paper prescription to providing observed therapy (ie, watching the patient take his or her medication[25]). This ensures that the drug molecule reaches the body. Direct supervision of medication ingestion has improved the efficacy of antibiotic therapy for infectious diseases, such as tuberculosis. When applied in resistant hypertension, a cohort beginning at a level of 179/98 is brought down to 144/83.[25] What this shows is that once the molecule reaches the circulation, apparent "resistance" may, for many, melt away.

Formal definitions of *resistant hypertension* do emphasize the need to exclude "pseudoresistant hypertension," which covers nonadherence to prescribed regimens. Whether this wise advice is commonly followed in clinical practice, and if so by exactly what methods, is unknown. Instead, one might look to trials of new technology that are lightning rods of clinical medicine, drawing in and concentrating best practice and displaying it through publication. We invite readers to evaluate the published trials of new treatments for resistant hypertension: exactly how was drug resistance confirmed?

This is not merely a theoretical matter. If many patients in trials of a novel therapy for seemingly resistant hypertension were, in fact, not taking their medication, what would happen if the psychological engagement resulting from undergoing a procedure increased their success with taking their prescribed medication? What would we expect to happen to blood pressure? How can we confirm whether this is the mechanism? For example, what would we expect to see in a sham control arm? Is that what was seen in SYMPLICITY HTN-3? What does this imply for pressure reductions reported in trials without sham control?

ENLIGHTENED APPROACH TO RESISTANCE

For the future, we should think carefully about how to manage what we currently describe as resistant hypertension. Even when it occurs due to unwillingness to take medications consistently, simply repeatedly telling patients to take their tablets may not be the only option. By the time they reach the specialist readers of *Endovascular Today*, they are likely to have had this advice many times; even innocently describing them as *resistant* risks conveying to patients that they possess a biochemical block to tablet efficacy. It might be preferable to accept that they have simply reached the limit of the medication that they can sustain.

Our clinical scientific community should work together to identify reliable effect size estimate data, which, in our opinion, arises from blinded, randomized, controlled trials.[3,6] When we attempt to mix and match effect sizes from different trial designs, there is a risk of introducing confusion at the higher level.

Wrong trial design gives the wrong answer that leads to wrong directions in further research and wrong treatment decisions. It is up to all of us to build the future, and the future begins now. ■

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