Is there any role for device therapies in resistant hypertension?

PRO

Raymond R. Townsend MD

Perelman School of Medicine
University of Pennsylvania
3400 Spruce Street
122 Founders Building
Philadelphia PA 19104 USA
townsend@upenn.edu

Disclosures:
Dr. Townsend reports consultant fees from Medtronic during the conduct of the study.

Acknowledgments:
Author Contributions: Raymond Townsend: Conceptualization; Writing - original draft

Companion Articles:
http://kidney360.asnjournals.org/content/early/2020/1/2/KID.0000742019
http://kidney360.asnjournals.org/content/early/2020/1/2/KID.0000682019
In the text to follow, I focus on the role of renal denervation therapies to address the debate topic. This is because so much of the data accumulated on resistant hypertension, at least in the last 10 years, has centered on this approach. I acknowledge that there are studies of other device therapies such as baroreflex amplification [1] and barostimulation [2] in this space, but in the interest of maximally using my word allotment I am deferring discussion of these areas to (hopefully) future debates.

The presence of drug resistant hypertension represents a public health hazard [3]. When blood pressures persist in an elevated state, despite prescription of, and adherence to, a reasonable antihypertensive regimen consisting of diuretic, ACE-inhibitor or angiotensin receptor blocker, and a calcium channel blocker, the likelihood of target organ damage is magnified by the persistent increase in blood pressure [4, 5].

When faced with a patient on a multitude of hypertensive agents, who has persistent elevations of blood pressure, what options are available? A standard recommendation is to reduce sodium intake, which can have impressive reductions in blood pressure, but is challenging to implement outside the confines of a research study where the meals are provided for the patient by a Clinical Research Center Kitchen [6]. Additional medication is typically recommended, and studies like that of the PATHWAY2 Investigators where they observed that when adding either a beta-blocker, or an alpha-blocker or spironolactone to a standardized triple-therapy regimen, spironolactone had the greatest additional BP lowering effect [7].

Sermons are a means intended to persuade an audience (or congregation) to either amend or reinforce a particular behavior. Sermons typically have three points. A good
preacher typically starts their sermon by stating all three points, developing each one, then reviewing all three again in the summary. This is my intent for this topic.

Can I hear an Amen?

The three points I plan to make are as follows:

#1: device-based therapies for hypertension produce a BP reduction similar to drug monotherapies

#2: device based interventions have a reasonable safety record and the BP reduction appears durable

#3: a sizable portion of patients with high blood pressure on three or more drugs have a blood pressure that is not controlled at the level of a prevailing guideline (i.e. resistant hypertensives)

**Point #1: device-based therapies for hypertension produce a BP reduction similar to antihypertensive drugs**

Here we begin by asking “How much blood pressure reduction occurs in a patient with hypertension when started on a single agent, titrated to a reasonable dose?” Every oral agent indicated for use in managing hypertension has been subjected to such scrutiny. In the VA Cooperative Trial of antihypertensive agents, six agents from six different classes of blood pressure medications were randomly assigned as monotherapy to a group of largely men with hypertension. The typical blood pressure reduction associated with each agent, given to about 200 veterans in each group, ranged from as little as 7 mmHg of systolic blood pressure in office-based measurements, to as much
as 17 mmHg [8]. Excluding placebo, an office reduction of 10-12 mmHg systolic was a common magnitude of systolic blood pressure reduction from monotherapies in this large, blinded trial.

When a regimen of two antihypertensive drugs is compared with a regimen of single agent therapy, a recent meta-analysis of 33 randomized trials in 13,095 participants observed that the presence of the second antihypertensive agent’s provides about 5 mmHg more systolic pressure reduction in the dual arm [9]. When a regimen of three antihypertensive drugs is compared with a regimen of dual agent therapy, a recent meta-analysis of 14 randomized trials in 11,457 participants observed that the presence of the third antihypertensive agent’s provides, again, about 5 mmHg more systolic pressure reduction in the triple arm [10].

When used as “monotherapy”, in the absence of antihypertensive drug usage renal denervation is associated with an office systolic BP reduction of 10-11 mmHg [11, 12], similar to single antihypertensive medications. When renal denervation is employed as an adjunct to a regimen of one to three antihypertensive medications, the additional office systolic BP reduction was 9 mmHg [13], which is similar, if not slightly more than, the effects seen in trials that assessed the effect on one additional antihypertensive drug.

**Point #2**: device based interventions have a reasonable safety record and the BP reduction appears durable

The requirements for a femoral artery puncture, selective renal angiograms, and the need for conscious sedation during the denervation procedure, expose the patient to
significant procedure-related risks. Moreover, although the blood pressure lowering effects of renal denervation appears to last for at least three years [14], intercurrent illnesses (such as vomiting, diarrhea, or both) and the use of medications which could have effects on renal blood flow or renal function (such as NSAIDs) might have greater toxicity in the absence of an intact renal nervous supply. Fortunately, the safety record of renal denervation interventions to date, no matter which method of denervation is employed, has been favorable, and at a level less than the incidence of complications in other invasive studies (such as those using renal angioplasty) [14, 15]. To date, the peri-procedural significant adverse event rates surrounding renal denervations is < 2% [16].

In a non-randomized renal denervation intervention in patients with existing chronic kidney disease, kidney function appeared stable when followed for the next 2 years [17]. In the Global Symplicity Registry, with enrollment currently at about 2600 people who have undergone a radiofrequency ablation in the renal artery, no significant safety signal in terms of renovascular anatomy (i.e. unanticipated renal artery stenosis) or greater than expected kidney function decline has been noted.

**Point #3:** a sizable portion of patients with high blood pressure on three or more drugs have a blood pressure that is not controlled at the level of a prevailing guideline (i.e. resistant hypertensives)

Whether using a highly monitored health care system like Kaiser Permanente [18], or stalking the wilds of a National Health and Nutrition Examination Survey [19], the prevalence of treatment resistant hypertension ranges from 2-16% of hypertensive patients. Perhaps most worrisome finding in antihypertensive treatment resistance is
the well documented occurrence of medication non-adherence among these patients. Studies have shown that up to almost half of treatment resistant hypertensive patients either have no antihypertensive medication, or less than the expected number of antihypertensive medications, present in their blood or urine [20]. One of the defining features of renal denervation therapy is that non-adherence is not an issue, since it is not characterized by the need for daily medication taking by the recipient once the procedure has been undertaken.

So where does one turn, in a debate, to find additional support beyond single published studies for one’s side of the discussion? Especially with word count, or time, limits we often turn to reviews of the topic favorable to our point of view. If we are really scrupulous (and lucky), we might find systematic reviews which have thoroughly covered the published literature in a particular area. Fortunately, just such a review appeared this year [21]. It covered, in rigorous fashion, over 3000 articles that touch on the topic of renal denervation, and found 12 randomized clinical trials with 1539 people studied. To be fair, the investigation centered on Uncontrolled Hypertension, of which Resistant Hypertension is a subset. Their bottom line, using the best efficacy measure we have (ambulatory blood pressure monitoring over 24 hours), showed that compared with non-denervation therapy, renal denervation was associated with 7-8 mmHg greater systolic blood pressure reduction over 24 hours.

Two other items regarding denervation approaches are worthy of consideration in this last point. The first is that a recent review comparing current costs of renal denervation therapy to standard of care for treatment resistant hypertension found that renal denervation “would be cost-effective among patients with TRH” (treatment resistant
hypertension) [22]. The second is that specifically intervening on resistant hypertension through sympathetic nerve ablation holds promise for reducing the complications of heart failure and arrhythmia, which are important problems for treatment resistant patients [23].

Summing up, let’s revisit the debate question. Is there any role for device therapies in the treatment of resistant hypertension? The key is the use of the word “any”. I submit that the following simple points are reasonable arguments for considering the use of device therapies in resistant hypertension:

- They lower blood pressure, similar to medications
- They appear reasonably safe, for at least up to 3 years of follow-up
- Unlike medications, these interventions don’t need to be repeated in a daily fashion

Let’s also revisit the period of time following the publication of Symplicity HTN-3. Some thought the device-based intervention approach was dead-on-publication. However, a perhaps optimistic look at the Symplicity HTN-3 data showed that renal denervation effectively lowered SBP in the office and by ABPM. The problem was, so did the sham procedure, though not quite to the same degree. During the time following the publication of HTN-3 we revisited not only the putative effectiveness of the therapy, but also how well we managed the sham control group. The result was a series of more stringent protocols that are active in the current era. The most important modifications included an improved catheter design and protocol-driven antihypertensive drug testing to identify off-protocol medication usage. Fortunately with respect to the current results, as the lawyers say, “res ipsa loquitur”.

Lastly, for our closing hymn, please turn with me to https://clinicaltrials.gov and use the search term **resistant hypertension**, applying the filters of: “recruiting”, “not yet recruiting”, and “active not recruiting”. As of November 13, 2019 you will find, after applying these filters, 53 studies. Of these, 25 are using a device approach, 7 are medication related, and the rest are a variety of lifestyle and other behavioral interventions. Resistant hypertension continues to be a significant public health problem and many of the current investigations into the area are using device-based approaches. Just sayin’.

Brothers and Sisters, the **PRO**secution rests it’s case.
References

1. Spiering, W., et al., Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle clinical study. Lancet, 2017. 390(10113): p. 2655-2661.
2. Rossignol, P., Carotid barostimulation in the treatment of resistant hypertension. Nephrol Ther, 2016. 12 Suppl 1: p. S133-4.
3. Carey, R.M., et al., Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. Hypertension, 2018. 72(5): p. e53-e90.
4. Sim, J.J., et al., Impact of achieved blood pressures on mortality risk and end-stage renal disease among a large, diverse hypertension population. J Am.Coll.Cardiol., 2014. 64(6): p. 588-597.
5. Tsioufis, C., et al., Dynamic resistant hypertension patterns as predictors of cardiovascular morbidity: a 4-year prospective study. J Hypertens, 2014. 32(2): p. 415-22.
6. Pimenta, E., et al., Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. Hypertension, 2009. 54(3): p. 475-481.
7. Williams, B., et al., Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet, 2015. 386(10008): p. 2059-68.
8. Materson, B.J., et al., Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. New England Journal of Medicine, 1993. 328(13): p. 914-921.
9. Salam, A., et al., Efficacy and safety of dual combination therapy of blood pressure-lowering drugs as initial treatment for hypertension: a systematic review and meta-analysis of randomized controlled trials. J Hypertens, 2019. 37(9): p. 1768-1774.
10. Salam, A., et al., Efficacy and safety of triple versus dual combination blood pressure-lowering drug therapy: a systematic review and meta-analysis of randomized controlled trials. J Hypertens, 2019. 37(8): p. 1567-1573.
11. Townsend, R.R., et al., Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet, 2017. 390(10108): p. 2160-2170.
12. Azizi, M., et al., Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet, 2018. 391(10137): p. 2335-2345.
13. Kandzari, D.E., et al., Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet, 2018. 391(10137): p. 2346-2355.
14. Mahfoud, F., et al., Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. Eur Heart J, 2019. 40(42): p. 3474-3482.
15. Kario, K., et al., Sufficient and Persistent Blood Pressure Reduction in the Final Long-Term Results From SYMPLICITY HTN-Japan- Safety and Efficacy of Renal Denervation at 3 Years. Circ J, 2019. 83(3): p. 622-629.
16. Bhatt, D.L., et al., A Controlled Trial of Renal Denervation for Resistant Hypertension. N.Engl.J Med., 2014. 370(15): p. 1393-1401.
17. Prasad, B., et al., Central Blood Pressure and Pulse Wave Velocity Changes Post Renal Denervation in Patients With Stages 3 and 4 Chronic Kidney Disease: The Regina RDN Study. Can J Kidney Health Dis, 2019. 6: p. 2054358119828388.
18. Daugherty, S.L., et al., Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation, 2012. 125(13): p. 1635-1642.
19. Egan, B.M., et al., *Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008*. Circulation, 2011. 124(9): p. 1046-1058.

20. Berra, E., et al., *Evaluation of Adherence Should Become an Integral Part of Assessment of Patients With Apparently Treatment-Resistant Hypertension*. Hypertension, 2016. 68(2): p. 297-306.

21. Cheng, X., et al., *Effect of Catheter-Based Renal Denervation on Uncontrolled Hypertension: A Systematic Review and Meta-analysis*. Mayo Clin Proc, 2019. 94(9): p. 1695-1706.

22. Chowdhury, E.K., et al., *Cost-Effectiveness of Renal Denervation Therapy for Treatment-Resistant Hypertension: A Best Case Scenario*. Am J Hypertens, 2018. 31(10): p. 1156-1163.

23. Hoogerwaard, A.F. and A. Elvan, *Is renal denervation still a treatment option in cardiovascular disease?* Trends Cardiovasc Med, 2019.