

Dr. Bland – Veita J. Bland (00:07):

Welcome to the American Heart Association's Hypertension Treatment Options podcast. This podcast series is part of a larger program addressing the unmet needs in hypertension treatment options. In addition to the podcast, this program includes webinars, Spotlight Series (where speakers are presenting grand rounds) and an update to the comprehensive guide on hypertension, which will be released in January of 2023. The overall goals of this program are to improve systems of care and understanding the unmet blood pressure needs along the hypertension patient journey. The overall learning objectives are to recognize treatment and management options for resistant hypertensive patients, to apply shared decision making strategies that improve health equity by better engaging patients in healthcare decisions, patient provider communications and patient centered care. And lastly, identify health disparities in hypertension treatment and management. The views and opinions of this podcast are those of the speakers and reflect the synthesis of science.

(01:19):

Content should not be considered as the official policy of the AHA. Our topic today is renal denervation. Our learning objective is to recognize treatment and management options resistant hypertension patient using renal denervation. Resistant hypertension affects 20% of all hypertensive patients. It is the source of much cardiovascular risk and its ultimate sequelae. To this end, innovative mechanisms of addressing this problem have and are being developed. One of this is renal denervation of the sympathetic system. My name is Dr. Veita(VEE-tah) J. Bland, and I am the CEO of the Bland Clinic in Greensboro, North Carolina. I am a clinical hypertension specialist, a family medicine doctor, a syndicated radio host and syndicated columnist, and I will be your moderator today. We are pleased to be joined in this conversation by Dr. Raymond Townsend and Dr. Ajay Kirtane, both leaders in this space. Doctors, could I get you both to give us a small introduction? Dr. Kirtane, could you go first?

Dr. Kirtane – Ajay Kirtane (02:41):

Thank you so much. Yes, this is Ajay (AH-jay) Kirtane (Keer-TAH-nee). It's a real pleasure to be on the show. I'm a professor of medicine at Columbia University Medical Center. I'm an interventional cardiologist, that's been interested in the hypertension space and involved with renal denervation for about a decade. It's just a real pleasure to be here.

Dr. Bland (02:57):

Here, Dr. Townson, please.

Dr. Townsend – Raymond Townsend (02:59):

And I'm Dr. Ray Townson from the University of Pennsylvania. Also a professor of medicine, but unlike my esteemed colleague, I'm a nephrologist rather than an interventional cardio. I've been, in the space of renal denervation since 2011 when I joined Medtronic's Executive Committee and have been, uh, on that committee even through the turbulent times of 2014 up to the current time. So I'm glad to have an opportunity to discuss the field. Thank you for inviting me.

Dr. Bland (03:32):

We are very pleased to have both of you. Could we first define renal sympathetic denervation? How does the sympathetic denervation work in lowering blood pressure? Why is it that we should be doing this?

Dr. Townsend ([03:47](#)):

So I'll take that first since the location here is closer to me than it is to Dr. Curtin. So the kidney arteries, and there are two of them in most people. Some unfortunately have more or sometimes less depending upon, uh, uh, issues of genetics, et cetera. But on the surface of those kidney arteries are a variety of nerves, not just sympathetic, but non cholinergic, non-allergic nerves, et cetera. What we have learned from animal models as well as the human experience is that there is a two-way communication between the kidneys through the nervous system that travels on the surface of the kidney artery to the brainstem vasomotor centers. And in a reciprocal fashion, there's also output from the brainstem down to the kidney. So those nerves transmit information that influences things like sodium handling, renal release, and even the tone of the vessels within the kidney itself.

([04:50](#)):

And what we have learned from animal experiments is that if you, if you sever or destroy with chemicals, that nervous system on the surface of the kidney arteries, you can either abrogate the development of hypertension in an animal model or blunt the magnitude of blood pressure rise. And to move that into the human field, about, hmm, at this point, about 15 years ago, the first human was denervated, uh, with a use of radiofrequency energy. And since that time there's been an improvement in the science as well as hopefully some of the mechanisms that we think are at play here. When we use energy applied from within the kidney artery, which extends to a, a distance of a couple of millimeters outside the kidney artery, we're able to heat up and destroy those nerves and interrupt that traffic. And the net result in most people, but certainly not all, is a reduction in blood pressure.

([05:53](#)):

We think it's sympathetically mediated cuz there's a small drop in heart rate and a definite drop in blood pressure. And what limited experiments we've done for things like muscle sympathetic nerve activity and belamine turnover and that kind of thing, it suggests that the mechanism is through interruption of the sympathetic nervous system. That's why we hang our hat on that. And the reason why I think we need it, um, I think we'll hold that for just a little bit cuz I have three things to say about that. So I'll just park that thought there and come back to that.

Dr. Bland ([06:24](#)):

Okay, thank you very much. There are several different ways of performing re de before we talk about some of the trials. Could we talk about how this is done with radiofrequency ultrasound, alcohol? How technically are they different? Is there anything else we need to be concerned about?

Dr. Kirtane ([06:47](#)):

A fantastic question and actually it started with surgical denervation back in the 1950s, and this was before we had any medications that were efficacious, uh, without major side effects in terms of treating blood pressure. Um, and so there was a surgeon who published a series in JAMA where actually by doing a sympathectomy surgically was able to reduce blood pressure and adverse events relating to that. But obviously this was a morbid procedure. And so once medications and lifestyle and all the conventional things that we really ought to be doing for our patients anyway, um, came into play. There was obviously less of a need, um, or no need for a morbid surgical procedure like that. And so it wasn't until about 20 years ago that, um, a catheter-based approach was sort of devised to do this. And all the catheter-based approaches, um, act on the same principle that, uh, Dr.

([07:36](#)):

Townsend illustrated, which is to ablate or to reduce signaling through those renal nerves, um, which, which travel very close to the artery. They're actually deeper in, in the, around the tissue, around the artery that they're, that, uh, allow the, the blood pressure to be decreased. And so the unifying theory here is we have to somehow reduce the nerve signaling. And so both radiofrequency and ultrasound, uh, aim to heat up the tissue and by heating up the tissue, those nerves essentially, uh, get denervated, then they lose their signaling function. Uh, that's been shown to be more durable actually probably in humans than even in animal models where there is some late regeneration that's been illustrated. We haven't really observed those effects in humans. And then alcohol aims to denature those nerves, um, those no nerve fibers as well. And essentially what we do is we take a catheter, which is a minimally invasive, um, device that's introduced usually through either the groin or the radial artery. And it's used to basically do an angiogram to identify the nerves themselves. And through that catheter, we're able to advance these specific devices that then ablate the nerves. We remove the devices, we close up the hole that we came in from. Uh, and typically we think when these patients are treated in clinical practice, they would be able to go home the same day or perhaps the next day. But we would think it'd be, would be an ambulatory procedure.

Dr. Bland ([08:56](#)):

Okay. There are several different ways of performing this that you just talked about, but when we look at the landmark studies that have been brought out looking at, uh, renal denervation, they have come back to the forefront for resistant hypertension. Could we talk about them and what they have contributed to this space? You know, how were these trials done in the last few years and how are the new trials different from the original, uh, simplicity trials that were done?

Dr. Kirtane ([09:24](#)):

Well, I think that first it's really important to state that this was a collaborative effort that was done across continents, across specialties, across devices, and in conjunction with the F D A as well as industry. And the reason for that was there was a profound exuberance, uh, for this space. Uh, about 10 years ago. In fact, there was a case report in the Newland Journal of Medicine that showed a reduction in blood pressure and a patient resistant to seven anti-hypertensive medications in commensurate with those reductions in blood pressure. There were reductions in nor epinephrine spillover and everybody thought this was going to be something perhaps to replace medications. Nobody would need to take medicines anymore. That's the degree of exuberance that existed at that time. Um, and when the sham controlled simplicity hypertension three trial was conducted, and I would, I recall at the time there were several people who sort of said, look, we don't need to do a sham control trial.

([10:17](#)):

Let's just get this out there. The FDA insisted on doing it. And that trial actually showed a reduction in blood pressure in both groups, both the treatment group as well as the sham group, but it was not appreciably different at six months for that comparison and everything kind of ground to a halt. But that collaboration between all of these parties, everybody came together and said, well, we think there's a signal here. How can we isolate the signal? And subsequent to that, there have been numerous sham control trials that were, uh, designed with newer devices, newer iterations of the devices to get a more consistent denervation effect, first of all. Second of all, typically, um, employing a wash-in or a run-in period as is similarly done with, uh, drug trials to establish a stable baseline third, um, ascertainment of blood pressure endpoints using something like ambulatory blood pressure monitoring or home blood pressure monitoring to reduce the inpatient variability of the measurement, um, and maintaining the high clinical trial standards of blinding, um, et cetera of patients and investigators. And with those new

trials irrespective of device, we now see that clearly in these subsequent trials, renal denervation can lower blood pressure, can comparison to a sham control. Um, that's the reason I think why there's now this renewed interest in talking about it. That's the reason why, you know, when many people say to me, listen, we've been talking about this for a while, I thought that went away. Uh, what's going on different now, the reason that this is different is because now we have several trials across devices showing, uh, efficacy in terms of benefit.

Dr. Bland ([11:48](#)):

As we look at the data for let's say the SPYRAL, the radius, are we seeing durability in the procedure? Is there a way to measure the effect of the denervation and track how well it is working? Do we have data over three years? What have we seen? Are we seeing stenosis? How have we refined the procedure?

Dr. Townsend ([12:10](#)):

We have been enrolling patients who've had renal denervation with radiofrequency energy in what's called the global simplicity with the Y simplicity registry and following them for out to three years to make sure that, or at least to observe whether or not the reduction in blood pressure came back. And in addition to following the blood pressure office, blood pressure, and in some cases ambulatory as well, we've been monitoring the amount of medication used because if the blood pressure comes down but you pile on progressive amounts of med, was it the blood pressure reducing defects of denervation or was it the medication? And what we find is that at least out to three years, the reduction in daytime and nighttime blood pressures seem to be robust and held across time with, if anything, slightly less medication given over time. And the most recently reported, um, long-term outcome from the original htn.

([13:16](#)):

Three that Ajay just mentioned a minute ago showed that not only did blood pressures come down in the original study, as Ajay said, but the degree of reduction at three years was progressively larger than it was at six months or one year. And that was favoring the group that got the innervation compared to those that chose not to when they had the option to cross over. So as far as we're able to tell, yes, it's robust out to three years, and the way we know that is continued blood pressure reduction in the absence of requiring more medication, bearing in mind that over three or four years worth of time in a population, usually the systolic creeps upward, not downward the way we've seen in these, in these trials where we've done registries and followed them in the long haul. So, um, the moral of the story is that savas, were able to tell the results are durable. If

Dr. Bland ([14:12](#)):

We see renovation, you know, we expect sometimes the nerves to grow back. What do we see when that happens?

Dr. Townsend ([14:18](#)):

A lot of interest in this because some animal models show some regrowth of the damage to nerves. We can't really look for that in humans because we can't go in there and, you know, operate and put a, you know, some kind of scope on the, uh, kidney artery in vitro or in vivo and check for this sort of thing. All we can do is to look for functional effects of reinnervation and that would be things like a rise in blood pressure back to the baseline value or above before the, the denervation. Cause they're, they're, they're a little older three years or more older. And so you would expect it to go back up and and climb. We

have not seen that occur. And if anything, there's a guy in England, Andrew Sharp I think is his name, who is a champion of this idea that once the nerves die from the heat exposure in the kidney artery, there's some kind of either fibrosis or some other marker that accumulates in the tissue that actually suppresses the renovation or the functional renovation of the kidney tissue itself. And so far the clinical experience would support that the lack of blood pressure rise and this finding that the whatever it is that gets left behind if the nerves are damaged, reduces functional renovation. So, so far we're saying that the results appear to be robust without evidence of Reva uh, return to baseline over at least three year time period.

Dr. Bland ([15:52](#)):

But what do we know about the safety of, uh, renal denervation? You know, do we see any anatomical problems? Do we see stenosis? Do we see anything of that nature that we should be concerned about?

Dr. Kirtane ([16:08](#)):

Well, for procedural safety, um, there have been numerous sham controlled studies looking at this. And at least acutely there does not appear to be any deleterious effects. We don't appear to see drops in blood pressure immediately after the procedure. We don't see anything other than the vascular complications that can be incurred. That having been said, I'm a procedural clinician and what I know from doing a lot of procedures is that there will be complications that occur with these procedures when they're done outside of the, uh, confines of a very carefully controlled clinical trial. So like anything, we have to be super cautious. We have to employ our best vascular to access techniques. We have to have people trained to do these types of procedures and to do the bailout procedures that are necessary if that were to occur. But thus far, in a large number of patients that are treated in the, both the randomized trials as well as the registry studies, we don't appear to be seeing deleterious safety events that can occur. I know that Professor Townsend's published in this area and so, he'll be able to give you his perspective about things like, you know, do people get hypotensive afterwards? How do they respond to this and beyond?

Dr. Bland ([17:12](#)):

Dr. Townsend?

Dr. Townsend ([17:16](#)):

So we have followed people out as there's three year data at both in the SYMPLICITY Registry, and by the way, recor is also starting a paradise registry. So there will be an ultrasound three year registry as well as a radio frequency energy three year registry. And one of the things that FDA in particular has been concerned about is either emergent or worsening of existing atherosclerosis in the kidney artery itself. So we, we diligently looked at every published study and published case report of treatment requiring renal artery stenosis in the first six months post procedure, you will find a couple of cases of that happening per thousand people. And beyond that, it's probably as infrequent, if not less frequent than the typical difficult to control hypertension population in the first place. As far as we're able to tell with more than 5,000 patient years accumulated in the follow up of these studies, renal artery stenosis arising de novo is unlikely as a result of the denervation procedure. And as far as we're able to tell so far, it does not worsen or remarkably accelerate inherent atherosclerosis is already present in the kidney artery. We do allow in these studies based on protocol design, a certain degree of athero is narrowing of the kidney artery up to usually 40% because that's considered non-obstructive. And honestly, it's not uncommon, and especially in older patients with a cigarette history and other things behind them

who've got difficult to control hypertension, that's often been difficult to control for years. So as a pragmatic issue on the, at the time the, uh, arteriogram is done and they're randomized usually to an intervention versus a control arm, you're gonna find some atherosclerosis and a fair number of them. And so far we're able to tell it's safe to go on with the procedure, because of a lack of evidence that we greatly enhance the rate of atherosclerosis progression as a result of applying energy, whether it's ultrasound or radio frequency.

Dr. Bland ([19:41](#)):

So let me just ask one question here though, but the actual data that we have that looks at this is no more than six months out. Is that true?

Dr. Townsend ([19:50](#)):

Actually, that's not quite true because the FDA requires us to monitor and the monitoring is a little different in the RECOR trials versus the Medtronic trials. We follow people with ultrasound, doppler ultrasound in the original studies out to two years, and the RECOR folks, and we've done some with magnetic resonance angiography as well as, computed tomographic angiography. The RECOR people don't rely as much on renal ultrasounds, Doppler ultrasounds, they go right for r a or CT angio. And those, monitoring procedures have been done out to a year or two after the actual procedure of record. We found some issues trying to get the MR done because most places do not do MR'S uh, magnetic resonance/angio. They don't really do them for a lot of this kind of research trials. So the, the technical quality we need is a little higher grade than the typical do they have RAS or not kind of question that's often answered. And so we've seen some issues with respect to timing in the gadolinium administration and some other things. It's just been a little bit more difficult to get consistently good quality MR/angio. But the Doppler ultrasounds, we've had our techs trained at Medtronic that, uh, through the folks on the West coast that have been doing this like forever. And so our doppler ultrasounds we think are pretty good. And so that's what we've been relying on from the Medtronic side.

Dr. Kirtane ([21:28](#)):

I would just add also that the, um, the GFR has been looked at in, in these registry studies as well. And um, if anything, there's less of a reduction in GFR than one might predict based upon just that degree of hypertension if left untreated.

Dr. Townsend ([21:43](#)):

I've just gotta say I am very grateful to the cardiologist for reminding the nephrologist about the role of kidney function as a long-term safety outcome. So thank you Ajay. That's quite true. Moreover, when it's done in people with preexisting impaired kidney function, it also does not worsen. If anything, it might blunt a little bit the rate of loss of kidney function over time. So thank you for pointing that out.

Dr. Bland ([22:11](#)):

When we look at SYMPLICITY, it showed huge decreases in blood pressure readings at three years, the recent higher quality trials show a smaller effect of four to seven millimeters loss. Is this a significant enough decrease to see changes in cardiovascular risk? Are there any data support? Uh, the ethics of this outcome? What do we think of this?

Dr. Townsend ([22:39](#)):

Well, I'll take the first crack at this question. The four to seven millimeters you're quoting is the ambulatory systolic blood pressure reduction over 24 hours. Now you can look at daytime, which is usually a little larger. We're daytime and nighttime together, which is typically how it's done. And the four to seven I would accept, is a reasonable estimate of what you seek three to six months after the procedure is done. But what, and by the way, if you have a six here, it's sort of in the middle there between four and seven, a six millimeter, 24 hour systolic blood pressure reduction is a win in terms of cardiovascular outcome protection. You will have less stroke, less heart failure, and a little bit less heart attack as a result of a 24 hour six millimeter systolic blood pressure reduction that's in the books. And FDA would agree with that and is in print saying that, and it is a valid surrogate for an actual outcome trial and FDA is on record for that as well.

But the key issue I think that we often forget when we look at the three and six month data is that there's a progressive production beyond just the six month follow up. When Deepak Bot presented the three year simplicity hypertension three outcome data, the ambulatory reduction in blood pressure at three years compared to baseline was almost 19 millimeters of systolic blood pressure over 24 hours. And that's without a lot of extra medication piled on. That's just the long-term effects. So part of what we see, and this has been one of the most difficult to understand, at least for me, is the nephrologist. This is one of the most difficult things to understand about renal denervation is it continues to have some effects on blood pressure long after the original procedure is done. There's something going on here that our simplistic barrow receptor related, you know, drop the blood pressure, heart rate goes up immediately kind of thinking this is a long-term consequence and I think that when we look at the reduction in blood pressure, we really need to look long term as well as short term.

Dr. Kirtane ([24:49](#)):

Yeah, I mean, so for me, I mean this is where we get, may get a little bit of disagreement between Professor Townson and me, and maybe it's because I'm a more strict interpreter of the data. Um, I think that, I believe the truly blinded data that occurs when the primary endpoints of studies are ascertained, I think it's a little bit of a stretch to speculate, with regards to the longer term comparisons versus SHAM. And the reason I say that is because it's actually not a true comparison of an apple to an apple, in these trials. And, and it's not, it's irrespective of device. If you sort of compare when patients cross over to a fixed time point before they cross over, you don't know what would've happened to that control group in the additional six months between those two time points. And the reason I'm worried about that a little bit is because from zero to six months in the SYMPLICITY sham arm, there was a drop of 12 millimeters of mercury. So to assume that from six to 12 months there's zero change whatsoever is a stretch for, it's a little bit too far for me. Um, especially because we know medications can change and especially because we know patients drop out of the analysis because follow up is incomplete. So what I would say is that to me, I think that if a patient came to see me and asked, you know, what do I think, what do you think the reduction in blood pressure's gonna be-first, it's not the comparison to Sham that's so relevant. It's a comparison from baseline. And for most studies that's a drop of about 8 to 10 millimeters of mercury. Um, certainly by ambulatory, and it could be even more than that by office and home blood pressure measurements.

But I also think we need to be good physicians and emphasize all of the other things that are important, lifestyle modification, weight loss, talking to people in language they can actually understand this barbershop study, for instance, was super important to me in terms of understanding that aspect of things. Um, and whether they're gonna get additional drops over time. I'm not at present confident that that's due to the denervation versus them being enrolled in the clinical trial and them having other ascertainment. But I will say that if you contrast this to the recent publication from Sprint, where we

saw that once the trial ended, blood pressures went back up again exactly as Professor Townson pointed out earlier on in the conversation, what is unique about denervation thus far is you don't see that effect. So I think it is durable, whether it increases over time is something that's for me, a stretch a little bit too far.

Dr. Bland ([27:14](#)):

You know, we're talking about ah, renal denervation, but at this point it is not an approved procedure by the FDA. What do you feel has to happen for this to become approved?

Dr. Kirtane ([27:30](#)):

I can start because I know we're short on time. Number one, both devices, ultrasound and radiofrequency, have completed enrollment in their pivotal trials that were designed under the auspices of the FDA for approval. We feel that as trials, if those trials meet their primary endpoints and with, um, the Recor device, it has through the Radiance 2 trial with that it has to be submitted to the FDA that has to be assessed. But my sense is that with that device and hopefully with, um, the SPYRAL device as well, we will hopefully see approvals for these devices in the next one to two years. Um, and of course under those trials, we need to continue with post-market surveillance, we have to make sure safety is ascertained, et cetera, but for clinicians to take home messages that you'll likely be seeing this in the next one to two years.

Dr. Bland ([28:15](#)):

Dr. Townsend?

Dr. Townsend ([28:17](#)):

I'd have nothing to add. My colleague has stated it well.

Dr. Bland ([28:21](#)):

Okay, so my last question for you guys, and you've been most great doing this for me. What are your words of wisdom or pearls that you'd like to leave on this subject?

Dr. Townsend ([28:31](#)):

So we have an issue with treatment adherence, and that is a long discussion in and of itself, but with renal denervation, there's no issue of adherence per se because it's done and you are done. You don't need to take it every day. That's one thing that I think is a, a factor worth considering. Secondly, our ability to control blood pressure has suffered somewhat, particularly in the last three or four years. And so we need more, I think, tools in the toolbox, so to speak, in broadening our portfolio in order to reduce blood pressure. And so for those couple of reasons, I believe, um, then there's some people that just can't or won't take blood pressure medications and this might represent an alternative for them. So for those three reasons, I think that that's part of my "pearls of wisdom" for how to look at this area. And so I will hand it over to you, Ajay, for a final comment.

Dr. Kirtane ([29:35](#)):

Oh, I couldn't agree more. I think that, um, look, everybody knows that medicines can work. Everybody knows that that lifestyle modification can work, and yet we see rates of blood pressure control that languish. And as both nephrologists and cardiologists and as doctors, we recognize that this is a real

problem. And so the addition of new tools, if they're shown to be beneficial and safe, as we have hopefully demonstrated to you this, this data with renal denervation has been shown, is a welcome addition. It doesn't mean this to supplant medications or lifestyle modification, and that's super important. We do need to be good doctors. We have to tell people that they need to lose weight. We need to make sure we rule out secondary causes of hypertension that are treatable without an invasive procedure. But if all those things are still failing, um, we should hopefully embrace tools that would be beneficial to patients to further lower their blood pressure. And so in that regard, I have a lot of hope for this field and, and once again, I do want to mention it was a collaborative effort from a lot of people and I think that we're pretty reserved and circumspect, um, about the way in this, that this is being proposed. I don't think anybody's going out there and saying, we should start denervating a lot of people because this is gonna be the panacea of the blood pressure. Not at all. This is just one tool in the toolbox exactly as Professor Townson said.

Dr. Bland ([30:51](#)):

Well, I thank you guys very much for spending some time with us and giving us your words of wisdom. The next podcast will explore more about renal denervation, specific about which set of patients we should consider for this procedure and patient purposes in this aspect. This will be the last episode in the series and will be moderated by Dr. Hiremath. I'm Dr. Veita Bland, and we thank you so much for spending this time with us.