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Case Introduction

Our case concerns a 62-year-old Caucasian woman who was referred by her general practitioner in 2012 with a long-standing history of difficult to control blood pressure (BP). She had significant past medical history including an excised meningioma and an implantable cardiac defibrillator (ICD) for a single episode of polymorphic ventricular tachycardia during general anesthesia. She also had a possible diagnosis of epilepsy and tablet-controlled type-2 diabetes.

On referral to our clinic she was on five antihypertensive medications including enalapril 40mg daily, bisoprolol 10mg daily, lercanidipine 10mg daily, losartan 50mg daily and indapamide 2.5mg once daily. She was also on metformin and sodium valproate.

In clinic, she appeared well. She complained of occasional headaches but had no other symptom of note. She had no significant family history of high blood pressure. On examination she had a Body Mass Index in the normal range and after repeated measures, her clinic blood pressure was found to be 195/110 mmHg. There was very little else to find on examination, including no murmurs or renal bruits. On fundoscopy she had grade 2 hypertensive retinopathy.

Baseline investigations did not reveal anything untoward. She had a normal blood count, renal function and electrolytes. On urinalysis she had mild proteinuria, with a urine protein-creatinine ratio of 17 (laboratory reference value 0-13mg/mmol). Her ECG showed sinus rhythm with a normal rate, axis and voltage. Her echocardiogram did not show any evidence of left ventricular hypertrophy (LVH), left ventricular ejection fraction was 58%, and she had evidence of mild diastolic dysfunction.

Ambulatory blood pressure monitoring (ABPM) was performed and her mean 24-hour BP was 190/105 mmHg. The range was 118/67 – 227/127 mmHg, with >90% of readings above 140/90 mmHg. So here we have a patient with a diagnosis of resistant hypertension according to the definition in the European guidelines.

Discussion: managing the hypertension

Dr. George: She is on five medications, including the diuretic, and her blood pressure is sustained. Now, what would you do next in terms of investigation and management of this patient?

Dr. Staessen: I think this definition of resistant hypertension is a very loose one, and we should really leave it. I think without having checked adherence of your patient, you cannot talk about resistant hypertension. It's as simple as that.

Dr. George: You're right. That's exactly the way we approach this. We approach this by saying this person *appears* to have resistant hypertension. However, one of the main causes for this is failure to adhere the prescribed treatment regimen. I'm sure it's the experience of many people here that this may be 'pseudo-resistant' hypertension.

Prof. Touyz: Did you show us her nocturnal blood pressure? Did she have dipping?

Dr. George: No. She didn't dip to a normal degree, so she had nocturnal hypertension as well as sustained day-time hypertension.

Dr. Czubek: I think the echo in this lady doesn't describe any hypertrophy. If she really has resistant hypertension, she should have a hypertensive left ventricle. So, for sure, she is failing adherence to her particular regimen.

Dr. George: I think normally I would agree with you. I think this lady is quite unique in that, even to date, with the up-to-date echo that was done a few months ago she still doesn't have any evidence of LVH, which is surprising when I show you the results of her other tests. Similarly, the lack of renal impairment is surprising as well. I don't have a good explanation for that, so there's no 'big reveal' about why she has no real evidence of any organ dysfunction at this stage!

We all tend to think of at least two major causes of resistant hypertension. First of all, is there an underlying secondary cause? Secondly, does she fail to adhere to her regimen? If it's neither of those, then we can diagnose her with primary resistant hypertension.

We performed a secondary screen. A secondary screen in my institution at the very minimum, after history, examination, and first-line blood tests would include measurement of renin, aldosterone and catecholamines as well as a look at the renal arteries and the adrenal glands. Because of her ICD, this was done with CT rather than MRI. It did not reveal any evidence of renal artery stenosis, and this has been subsequently repeated recently and remains negative.

Dr. Bursztyn: I would think that if someone takes 40 mg Enalapril and has severe hypertension, whether you find renal artery stenosis there or not, will in no way be helpful, as a BP response to ACE inhibitors is perhaps the best predictive measure of non-adherence in my humble opinion. Therefore, looking into adherence makes much more sense than looking into renin aldo.

Dr. George: I agree that investigating her adherence is crucially important and I will be discussing her adherence shortly.

Prof. Touyz: While we're waiting, did you say you did a renal ultrasound as well?

Dr. George: No. We don't tend to go to renal ultrasound unless the patient has altered renal function, so first line will be cross-sectional imaging to look at the renal arteries.

Dr. Parsa: You didn't say what was electrolytes, potassium.

Dr. George: Potassium was in the normal range, she consistently has a normal potassium.

In terms of the rest of her workup, as routine in 2012 when she first came to clinic, we would do urinary catecholamines. This was done on two separate occasions and negative both times. I'm sure a lot of us have moved on to plasma metanephrine readings now because of higher sensitivity. However, we haven't repeated that because of the two negative urine collections.

Her renin was fully suppressed with a reading of <0.17 nmol/l/h (laboratory reference range 2.2-7.7 nmol/l/h) and her aldosterone was 161 pmol/l (laboratory reference range 250-950 pmol/l). This reading was taken on her medication, and I'm sure lots of you are unsurprised, given the result, as she was on a high-dose beta blocker.

Dr. Lappin: I am a nephrologist, but did you deliberately do a CT adrenals in advance of doing the endocrine workup, or were they incidental? Did you incidentally look at the adrenals on the angiogram?

Dr. George: When we request our cross-sectional imaging in all of our patients, we ask for both. We asked if we can have a look at the renal arteries, and also assess her adrenal glands as well.

Dr. Lappin: As you know, scanning the adrenals without the biochemistry is probably putting the cart before the horse. The other thing about the catecholamines, did you check urine metanephrines as well, because you'll miss a small percentage of PPGLs if you just do catecholamines and leave out the metanephrines. However, guidelines now suggest using plasma free or urinary fractionated metanephrines as an initial screening test for PPGL, as they have superior diagnostic value.

Dr. George: Yes, we did and they were negative. I think the cart before the horse argument is interesting. I think the issue we have with a lot of patients, and I'm sure everyone else does, is what do you do with somebody that's already on multiple agents, which tends to interfere with our interpretation of the renin and aldosterone, as opposed to newly referred patients where we can switch them over to alpha blockers quite easily and then get a more interpretable result. I'm obviously interested to hear what your take on that would be.

Dr. Lappin: Yes. There was a recent Dutch study showing that stopping medications in these very resistant people, in order to do the tests, doesn't result in patient harm. Now, occasionally there's the odd patient I think you can't do it, but in the majority of patients you can switch. I think the range of treatment she was on, beta blocker, diuretic, ACE and an ARB, this is not just a dirty screen. I'd call it a very dirty screen. We do try and interpret it, but I just don't think you can interpret that data confidently.

Dr. George: If you were to stop one of her medications in order to get a better interpretation, which one would you stop?

Dr. Lappin: I think the beta blocker.

Dr. George: That was our impression as well, because that's the only one that's really suppressing her renin. In the scenario where you're not sure if an adrenal mass is functional or not we would obviously stop the beta blocker and if the renin remained suppressed, then the index of suspicion for primary hyperaldosteronism is increased.

Dr. Lappin: There's another subtle point on the calcium channel blockade. Dihydropyridine calcium channel blockers can give a false negative ARR, so ideally treated patients should be on a non-dihydropyridine calcium channel blocker, if you really want to be clean about screening on medications.

Dr. George: Agreed. The ideal situation would be to do it on no medications. At this point, we would stop the beta blocker but ideally, she wouldn't be on anything.

Dr. Lappin: The situation with your patient is that you're both extremely worried about this lady and you don't want to stop her medications, but you think Conn's syndrome is the most likely underlying endocrine abnormality. Why not just go to a CT-PET metomidate scan now without further biochemical screening.

Dr. George: We occasionally send our patients up to Cambridge for exactly that. I think if we would've had a higher index of suspicion in her case, we certainly would have done that.

Dr. Bursztyn: The presence of very low renin in the face of high dose of ACE inhibitor certainly indicates volume suppression. This suggests something else that substitutes aldosterone, like licorice. I think at this point it would be, if not done earlier, appropriate to go back to the patient and have some inquiries about her habits.

Dr. George: That's exactly what we were thinking, but the trick here would be to stop the beta blocker first, so you know what the renin's doing in that context. Unfortunately, when we tried to do that, she complained of severe headaches, and essentially started taking her beta blocker again. We tried this on two or three occasions, and were frustrated by the fact that we couldn't measure her renin without the beta blockade.

Prof. Kahan: Before discussing whether you can analyze renin-aldosterone on drugs, it would be interesting to know whether she has any drug concentrations at all. Otherwise, it's a theoretical discussion. On that line, what about heart rate on your ambulatory blood pressure measurement? Because she should be bradycardic if she takes her beta blockers, and if not, that would help. Finally, we stop all anti-hypertensive medications and it hasn't happened anything since 1987. If you are on five drugs and 200 systolic, nothing will happen.

Dr. George: I think on the last point, we could have been braver, certainly. However, there was some resistance from her. I'll show you some data in a second about her heart rate. With regard to metabolites, yes, we would love to have done this but we don't have that facility. We know from a study performed in Leicester in the UK which measured urinary metabolites, that approximately 25% of patients referred to resistant hypertension clinics, do not take their medications as prescribed¹. There's other data that suggests that it could be even higher than that, and I'll discuss some of that shortly.

Confirming Adherence

To investigate patients' adherence, we bring them in to our day unit and observe them take their tablets i.e. directly-observe therapy (DOT). We did this with her in 2013 (**Figure 1**). Her presenting

BP on the day of DOT was 220/100 mmHg with a heart rate of 85 bpm. I observed her taking three of her prescribed medications at 9am: enalapril 20mg, bisoprolol 10mg and indapamide 2.5mg. Three hours later, at 12pm her BP was 213/112 mmHg; however, her heart rate had dropped to 70 bpm. At 12pm she was observed to take her remaining two medications: losartan 50mg and lercanidipine 10mg. At 3pm her BP remained very high: 205/105 mmHg and her heart rate remained 70 bpm. Therefore, we were pretty convinced she had true resistant hypertension!

Modification of Therapy

Dr. George: The next question I wanted to throw to the floor, what do you routinely do when faced with this? I personally don't think that it is that common to find a patient like this who really does appear to religiously take her tablets. We saw that her blood pressure doesn't drop during DOT. We haven't found a secondary cause. She's already on five medications. Remember this is 2013. What would you have done with her?

Dr. Wang: We discussed about the use of beta blockers. Why don't you use, for instance, non-dihydropyridine calcium channel blockers? Because when we consider some biochemical measurements in those patients, we normally replace beta blockers or some other drugs with non-dihydropyridine calcium channel blockers, verapamil, a slow-release verapamil, or the slow-release diltiazem. When you use those drugs and you may see probably even different blood pressure, or in fact in the meantime you can also perform biochemical measurements more accurately. That's our routine work when we have a resistant hypertension for some measurements of secondary hypertension.

Dr. George: Thank you. That's a good idea. I'll take that back.

Dr. Lewis: You didn't mention the calcium. I'm presuming it's normal. Our guideline would say Spironolactone. She had an aldo-renin ratio of over 800:1. She's not responding to a huge dose of an enalapril anyway. The other thing is either up the diuretics and/or up the calcium channel blockers. You're only on 10 of lercanidipine. You could've used 20. You could've used nifedipine 45 BD. You could've added torsemide. The guideline would say add spironolactone first, up the diuretic and then up the CCB, and way down on the enalapril, which above 20 probably didn't achieve anything.

Dr. George: Yes. You can't be 100% sure she doesn't have primary aldosteronism, given the biochemistry, and we actually thought along the same sort of lines. We initially added 25mg of spironolactone, and also as we saw that slight response to the vasodilator during DOT we also added additional vasodilatory therapy with 4mg doxazosin.

Dr. Micali: Other things I would consider optimizing medical treatment, the patient is taking enalapril once a day. We know that enalapril doesn't last 24 hours. The same for losartan. So, first off, I would optimize the medical treatment. Even like this, I think this won't be enough and you will need more drugs like spironolactone, doxazosin anything else. But the first step is optimizing the medical treatment.

Dr. George: Agreed.

Resistant Hypertension: Trials and Tribulations

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Dr. Delmotte: I'd like to go back for just one second on the workup of this patient. First, do you have an idea of her urinary sodium levels?

Dr. George: I don't, no.

Dr. Delmotte: Because it's a known fact that low sodium diet is more effective in resistant hypertensive patient than in general hypertensive population, so that could be one point. My second question is, do you at any point in the care of this patient consider doing polysomnography to look for sleep apnea syndromes, since you mentioned that she was a non-dipper, so I think that might have been interesting.

Dr. George: She doesn't have the body habitus or symptoms to suggest sleep apnea. If we had a high index of suspicion, we would usually start with a more focused history around sleep and use the Epworth sleepiness questionnaire. You'll see from our cohort data that we do diagnose sleep apnea in our patients reasonably frequently. However, I think in retrospect, given that she's a non-dipper we should consider this.

Dr. Delmotte: Because you have this large Brazilian series from a few years ago that showed in that case, in that series at least, that something like 60% of patient with resistant hypertension had (moderate/severe) sleep apnea syndrome².

Dr. George: I think we tend to find this in patients that have got the metabolic syndrome and are overweight. I think we're increasingly recognizing that if you make the diagnosis and can get them on a CPAP machine at home, then actually their blood pressure comes down. You see that with their nocturnal blood pressure improving.

Dr. Barigou: About the treatment of this patient, she had a double blockade of the renin/aldosterone system. Based on ONTARGET results that showed an increase in adverse events in patients with double blockade, why did you not stop this double blockade? (Note: ONTARGET³ showed no difference in the primary endpoint between ramipril alone and in combination with telmisartan but the combination was associated with more adverse events such as hypotensive symptoms and renal dysfunction.)

Dr. George: I failed to mention what the spironolactone replaced. I can't remember if it was the ACE or ARB, but we took her off one. As you quite rightly mentioned, there was no trial data supporting being on dual ACE and ARB blockade in hypertension.

Dr. Barigou: Just for indapamide, you used I think the rapid releasing form. Can you not switch to a long-acting form, or chlorthalidone that is a longer-acting diuretic?

Dr. George: I think those are some brilliant suggestions, particularly the idea of looking at the half-life of these drugs and making sure that she's getting 24-hour anti-hypertensive cover. I will definitely take that back as an idea.

Prof. Touyz: Could I also ask you about some of the more potent classical vasodilators, like hydralazine. Did this ever come into consideration in terms of your management?

Dr. George: The discussion was around increasing her vasodilators. We thought that we'd start with an alpha blocker as we use it more frequently.

Dr. Pedrinelli: I don't understand something in this case, in the overall context. Because this patient had no hypertrophy, right? She had no albuminuria, right? Presumably, she had no hemorrhages nor exudates, right?

Dr. George: Just Grade 2 retinopathy.

Dr. Pedrinelli: Probably. So how do you fit in the overall picture of this?

Dr. George: I think it's quite remarkable. Like I said, five years later, having just read her most recent clinic letters and seeing her repeated echo and urea and electrolytes, she still has very little target organ damage, despite persistently elevated blood pressure. Her most recent blood pressure is more controlled, so we're looking at more 160/90 mmHg than we were 200/110 mmHg with the changes that have been made. But you're right, I don't have any bright ideas about why. Therefore, she is quite an interesting patient. She has clearly sustained hypertension without significant end organ damage.

Dr. Pedrinelli: We had a case like that, and we used urapidil, infusion of urapidil, and we found a very brisk hypotension response. Probably what you did, to exclude the pseudo-hypertension, was to give the drug by mouth, correct?

Dr. George: She had all five of the prescribed medications that she was referred to us on at that time point, and her blood pressure didn't change. We haven't repeated that. Her 24-ABPM has improved. We did discuss whether we should bring her in for intravenous therapy to demonstrate that we can lower her blood pressure, but we didn't see a reason for that. She's not at any point presented in an accelerated fashion.

Dr. Faconti: I have a question regarding the treatment, or mainly a comment. The fact that the patient has low renin can also be a sign that the patient probably was volume overloaded, so a different strategy would be to use as many diuretics as possible to assure a right volume. Another comment is the fact that there was no target organ damage, it can be related with the fact that aldosterone itself was low and aldosterone is one of the major mediators of fibrosis, so that can be probably part of the story. What I would have done with this patient is to add chlorthalidone, amiloride, spironolactone, and see what happens.

Dr. Rossi: The question is, did you up titrate your spironolactone adequately, and the reason for that is approximately 1/3 of the patients do respond to a dose between 25 and 100. Then another 1/3 to 100 and 200 mg. Then 1/3 of the patients require a higher dose. If you do so, you probably can withdraw your beta blocker, and that would be very critical because if you would then find very low plasma renin activity, or active renin. With an ARB and spironolactone, then you will have very strong evidence for doing an adrenal vein sampling during the treatment, which would probably show you a lateralized secretion of aldosterone.

Dr. George: I think, again, that's a very good idea. Let's go back and consider doing a PET metomidate scan or get her off the beta blocker by optimizing her other medications and then repeat the renin.

Decision for Renal Denervation

This was 2013 and we thought about something else at that time point. That is, should renal sympathetic denervation (RDN) be considered?

At that time, RDN was very much en vogue. Recall RDN is based on evidence that both afferent and efferent sympathetic renal nerves play a significant role in the pathogenesis of hypertension. Since these nerves are closely juxtaposed within the renal artery adventitia they can be ablated endovascularly. The very first catheter that was brought onto market was the Symplicity catheter, and the idea was to ablate in a corkscrew manner both renal arteries.

There were two studies that had been published at this time that were available to help make the decision whether to offer this new emerging therapy to our patient.

SYMPPLICITY-HTN 1 and 2

The first study was a proof of principle, first into human study published in the Lancet in 2009⁴. This was a non-blinded, single-arm study in which 50 patients with resistant hypertension were enrolled. Resistant hypertension was defined as an office systolic BP >160mmHg on at least 3 antihypertensives (including one diuretic). In the 41 patients that underwent the procedure the change in BP at 1 month was -14/10 mmHg and at 12 months (n=9) was -27/17 mmHg. In addition, norepinephrine spillover was performed in 10 subjects and showed a mean reduction of 47% (95% CI 28-65%) demonstrating that the procedure reduced renal sympathetic tone. The procedure was well tolerated with only two complications: one renal artery dissection (successfully treated with a stent) and one pseudoaneurysm at the puncture site.

The second trial that came out a year later was called 'SYMPPLICITY HTN-2'⁵. This was the first randomized control trial of RDN; however, as with the first trial it was not blinded. The entry criteria were largely the same. The primary endpoint was office systolic BP at 6 months and secondary end-points included measurements of safety as well as change in 24-hour ABPM. 106 patients were enrolled (of 190 screened).

Our patient would have fit the entry criteria but unfortunately, she would have been excluded due to her ICD. As with the first study, SYMPPLICITY HTN-2 had very startling results. Office BP was 33/12 mmHg lower in the treatment group than the controls at 6 months with an ABPM reduction of 11/7 mmHg. It was also well tolerated with one pseudoaneurysm at the puncture site.

UK Guidelines

In January 2012, in response to these studies, guidelines were produced by the National Institute of Clinical Excellence (NICE) in the UK⁶. The limited evidence-base was recognized, but it was suggested that RDN could be performed in routine clinical practice if there was adequate clinical governance in place, the patient understood the uncertainty, and there were mechanisms in place for audit and review. Performing RDN in clinical practice also had to be overseen by a multidisciplinary team (MDT) including hypertension specialists and interventionalists.

These guidelines were supported by a statement from the relevant specialist societies in the UK, including the British Hypertension Society⁷. The entry criteria suggested was similar to that used in the trials (BP >160mmHg on 3 or more anti-hypertensives), but the criteria were fleshed out in a way that may be considered robust. It mandated using ABPM to rule out white coat hypertension, a measure of concordance (e.g. DOT), and the exclusion of secondary causes with suggestions of first-line investigations. None of these important measures were included in the protocols of the trials.

It was decided that RDN might be a useful option for patients such as the one I've described. Therefore, funding was secured to set-up a service in our hospital and several radiologists and cardiologists went to Europe to be trained in how to perform RDN. A regular MDT to discuss potential candidates was also established.

Searching for potential candidates in our clinic

It was time to determine whether there were patients in our clinic that fit the criteria for RDN. We looked prospectively at our cohort. There were 298 patients with a diagnosis of hypertension booked into the clinic in 2013. The mean age was 62 (range 19-102) with a mean clinic BP of 143/80mmHg on 2.5 antihypertensives (range 1-6).

The selection pathway derived from the guidelines was applied (**Figure 2**). A patient must have a clinic blood pressure more than 160 mmHg, a 24-hour ambulatory blood pressure systolic daytime average of more than 150 mmHg, a secondary screen and DOT to ensure concordance.

Of the 298, 31 (10.4%) had a clinic BP more than 160 mmHg. Of these 24 (77%) had white coat hypertension and/or a secondary cause identified and 3 were excluded for co-morbidities or incomplete investigations (**Figure 3**). 4 were admitted for DOT and 2 of these had a significant drop in BP leaving just 2 potential candidates (including the patient I have presented) (**Figure 1**).

Interestingly, we found a high prevalence of the white-coat effect which was present in 14/26 (53.8%) patients who underwent ABPM.

SYMPPLICITY HTN-3

Therefore, there were two potential candidates in October 2013. In January 2014, Medtronic, who make the Symplicity catheter announced that their next trial; SYMPPLICITY HTN-3, which was the first blinded sham-controlled trial, failed to meet its primary end-point⁸. There was an immediate response from the UK joint societies working group who produced a statement recommending a temporary moratorium on RDN⁹, so we had to stop our nascent service for RDN! After review of the evidence, that temporary moratorium become permanent. Indeed, clinicians in the UK are still not allowed to perform RDN outside the context of a clinical trial.

A brief review of the trial that has caused so much controversy is appropriate. SYMPPLICITY HTN-3 was published in the NEJM in March 2014¹⁰. 535 patients were enrolled (of 1441 screened (37%)) across 88 sites in the USA. The entry criteria were similar to the previous two trials, however for this study ABPM was included to rule out white coat hypertension and it was mandated that there be no change in medications for 2 weeks before the start of the trial. Randomization was performed in a 2:1 manner and crucially, for the first time, a sham-procedure was included to blind the control patients. The primary end-point was office systolic BP at 6

months. Unlike in the first trial, there was no measurement of the procedure's technical success using norepinephrine spillover.

The unexpected result was not that there wasn't a reduction in BP in the patients who underwent RDN – indeed the office systolic BP at 6 months was -14.13 mmHg. The unexpected result was that the reduction in blood pressure in the treatment arm was matched in the control arm (-11.74 mmHg, difference between groups -2.39 mmHg P=0.26). There was also no difference in the change in BP measured by ABPM. Complication rate was not statistically different.

Discussion: Failure of SYMPLICITY HYPERTENSION-3

Dr. George: A question that has taxed the hypertension community is: why did this trial fail? Does anyone have any other thoughts about why that trial specifically failed to demonstrate any benefit of renal sympathetic denervation?

Dr. Lappin: The early trials were very poor, patients were their own controls, for example, and it wasn't until SYMPLICITY HTN-3 that we had proper trial data for RDN. Even with that poor data, a lot of people went ahead and did renal denervation.

You still hadn't ruled out a Conn syndrome in your patient. My own experience with this is when we have taken the renal denervation patients into our clinic, we've diagnosed Conn syndrome in a lot of those patients. It has never been clear to me from the studies that the patients were properly worked up from an endocrine perspective in advance.

Another couple of points. I think the average number of patients treated per interventionist in SYMPLICITY HTN-3 was two, so probably the wrong people were doing the procedure in the study.

Also, there is incomplete science around RDN still. That hasn't all been tidied up. Another potential concern is that when they were denervating, they weren't deep enough into the artery. They're now saying you must go deeper into the artery and possibly treat branch arteries to get an effect. In addition, a number of patients may not have had their arteries complete circumference treated.

Dr. Staessen: I agree, no experience. But where I don't agree is I don't think you need a sham procedure because you can measure the blood pressure by device. You can do 24-hour ambulatory monitoring. You can have a central reading station. The person or the device who reads the blood pressure doesn't know whether it's an intervention or whether it's a sham. Therefore, I really don't think that a sham procedure is needed.

Dr. George: You're not alone. There is a recent meta-analysis that looked to that question and suggested that a sham design isn't necessary¹¹. I think from the FDA point of view, they mandated a sham control trial and the major ongoing studies all include a sham procedure in the control arm given the results of SYMPLICITY HTN-3.

Reason for the null-result of SYMPLICITY HTN-3

There has been a lot of discussion in the literature exploring the potential reasons for the null result of the SYMPLICITY HTN-3 trial – including those that have already been mentioned.

One of the reasons may be that RDN does not actually lower BP and that this trial should be lauded because it showed the flaws in the design of the previous two trials, particularly the lack of a sham that contributed to the positive result. This has been attributed to the Hawthorne effect, i.e. unblinded patients in a trial who know they've had a novel therapy start taking their medications more regularly. In addition, there is also a reverse effect where those that didn't have the new intervention stop taking their medications. Therefore, the addition of a sham in SYMPLICITY HTN-3 was crucial to remove this source of bias.

However, another position is that RDN may indeed work but that serious flaws in the design of SYMPLICITY HTN-3 contributed to the null result. There has been particular criticism that the inclusion criteria and trial design were not rigorous enough and that the patients enrolled likely had high-levels of non-concordance¹². In addition, the technical success of the procedure has been called into question¹³.

Entry criteria and study design

None of the SYMPLICITY trials included an objective measure of concordance at any point. This is important as non-concordance is extremely prevalent in the 'resistant hypertension' cohort. For example, in the Sympathy trial¹², which measured people's urinary and plasma drug levels without their knowledge, approximately 70% of patients were either completely non-concordant or poorly concordant with their regimen. By not accounting for this, there was significant scope for patients to succumb to the Hawthorne effect and reduce their BP during the trials, simply by increasing their adherence.

In a similar vein, there was very poor medication stability throughout the trial. The study design only mandated a 2-week period of medication stability before being enrolled and during the study 40% of patients had their medications changed¹⁰. This clearly confounds the results. In addition, there was also no per-protocol secondary hypertension screen.

When we applied the more rigorous UK guideline entry criteria to our cohort (**Figure 2**), which included directly observed therapy, ABPM, and a secondary hypertension screen, only 6% of patients were potentially eligible. Other studies using a similar approach have found eligibility rates of around 15%¹. In the trial nearly 40% of screened patients were enrolled¹⁰. Taken together, this suggests that the SYMPLICITY HTN-3 patients were not worked up sufficiently to control for important sources of bias and confounding.

Technical success of the procedure

A major criticism of SYMPLICITY HTN-3 is that the technical quality of the procedure was poor. The study protocol mandated 4-6 ablations in a corkscrew manner in both renal arteries. However, only 5% actually had a per protocol ablation performed¹³. This was because of inexperience. The 535 patients were treated across 88 sites and 34% of interventionists performed just one procedure¹³. How can they possibly be expected to get it right the first time?

Furthermore, there has been an increasing realization that the approach employed during these studies may not adequately achieve renal denervation, even when performed appropriately. Looking at technical success, in SYMPLICITY HTN-1, a mean 47% reduction in norepinephrine spillover⁴ was achieved. However, in animal models, approximately 85%¹³ reduction in norepinephrine spillover is achieved. In another small (unpublished) study in patients that had renal sympathetic denervation by an experienced group the spread of effect was very large¹³. It has become apparent from porcine models that ablating the main renal artery alone may not be sufficient, and that ablation of branch arteries is also required to reliably achieve denervation¹⁴.

Dr. Bursztyn: All the points that you made are important and extremely relevant, but the major fallacy is that resistant hypertension is not a physiologic entity. It is a mixture. Some patients are resistant to my treatment. That does not necessarily mean they will be resistant to your treatment, and vice versa. So, I think the major fallacy is the idea that you can take a bag of all sort of things and treat them with a specific treatment.

Moreover, I would like to cite a study from Streeten, a quarter of a century ago or more, who worked up over 4,000 people for secondary hypertension, and ended up finding all sort of findings. The majority of those with treated secondary hypertension, were not free from anti-hypertensive treatment regardless of the etiology or therapy¹⁵. So longstanding secondary hypertension is quite an elusive challenge.

Dr. Barigou: Thank you for all these clinical trials data. However, there is one trial that was not mentioned: “The DENERHTN HTN” trial in France¹⁶, in which there was a standardized treatment of four weeks before confirmation of resistant hypertension, and then patients were randomized to an intervention or to a stepped escalation in treatment. The results showed a significant difference between the two groups, and this difference was more important in those who had renal denervation. So even if there was no sham procedure, we can talk about this positive study. This is really important.

Dr. George: Agreed, it wasn’t a blinded trial. However, the key message of that study design, which has been incorporated into the latest trials, is that medication stability and a standardized regimen is vital to see a signal.

Renal Denervation Moving Forward

More recent RDN trials have integrated the lessons learned from the SYMPLICITY studies and introduced some novel trial designs.

Firstly, most studies are now routinely including a sham procedure in the control arm.

Secondly, the technical aspects of the procedure are being addressed with novel technologies. Medtronic’s SPYRAL catheter, for example, applies radiofrequency ablation to 4 quadrants of the renal artery simultaneously and the new protocol includes ablation of both the main and branch arteries¹⁷. In addition, the number of interventionists is being restricted to ensure adequate proficiency.

Thirdly, to reduce heterogeneity in drug therapy, study designs have incorporated standardized medications regimens as per the approach taken in the aforementioned DENERHTN HTN trial.

For example in the SPYRAL ON-MED and the RADIANCE-HTN studies, patients will be treated with a consistent triple therapy regimen^{18,19}.

Fourthly, in order to ensure compliance, measures such as directly observed therapy and direct measurement of drug levels are being included in the study protocols¹⁸.

Finally, in a very novel step, several studies are performing RDN in patients who are not taking any antihypertensives at all^{17,19}, thereby completely removing the confounders and biases associated with medications.

With all these steps now being taken to address the design flaws in the original trials, the data necessary to make an informed judgment about the place of RDN in clinical practice may soon be available.

Addendum: Shortly after this meeting the SPYRAL HTN-OFF MED trial was published¹⁷. In this trial, patients with an office BP of 150-179mmHg (24-h ambulatory SBP of 140-169 mmHg) who were either drug-naïve or had discontinued their medication were randomly assigned to RDN or a sham procedure. 80 patients were enrolled and followed-up for 3 months. The mean difference in clinic and 24-h BP between the groups favored RDN (24-h SBP -5mmHg p=0.0414).

Case Resolution

From our patient's point of view, her BP has improved on the additional medications but is still around 160/90 mmHg. Some of the excellent recommendations from everyone on the floor about how we might manage this patient's therapy and confidently rule-out primary aldosteronism will be taken back to London. She isn't eligible for enrollment in the RDN studies because of her ICD. As a center, we feel that we (and indeed the community as a whole) should have waited for a definitive, blinded randomized control trial before setting up a clinical service. Indeed, I think that is the most important lesson here; we must only offer our patients novel interventional therapies once their efficacy has been demonstrated in appropriately designed and conducted clinical trials.

Summary

In summary, I have presented a case of a patient with true resistant hypertension. We have discussed how to optimize her medical management as well as investigations of secondary causes, particularly primary aldosteronism. We have also discussed the evidence base for renal sympathetic denervation and the deficiencies of the original SYMPLICTY trials. Several lessons have been learned about the design and conduct of clinical trials in this field that are now being implemented to definitively assess the efficacy of this approach.

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Figure Legends

Figure 1: Patients admitted for DOT

Patient A (The Case) had received her 5 antihypertensives (3 at 9am and 2 at 12pm) and had truly resistant hypertension.

Patient B had 2 antihypertensives at 10am and 2 at 12pm. BP after all 4 was higher than before given treatment and was therefore considered to have resistant hypertension.

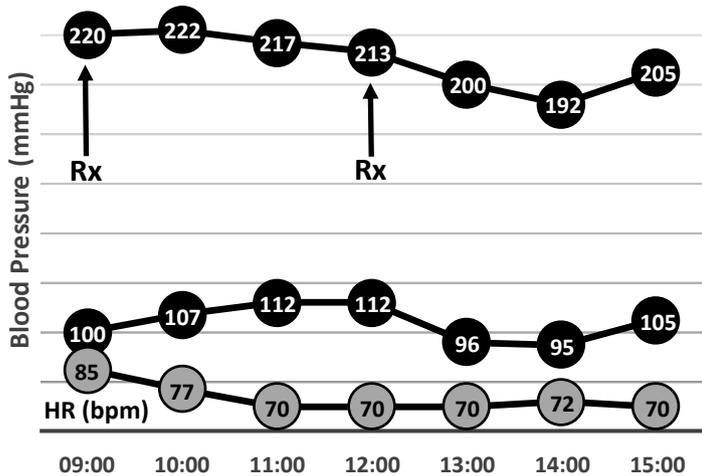
Patients C & D responded to antihypertensives. Patient D required fluid resuscitation after systolic BP dropped from 160/90 mmHg to 82/55 mmHg after receiving all prescribed antihypertensives. After this the protocol was modified so that doses were split (half in morning, half a lunch time).

Figure 2: RDN selection criteria (based on UK Joint Societies' Consensus Statement (8)).

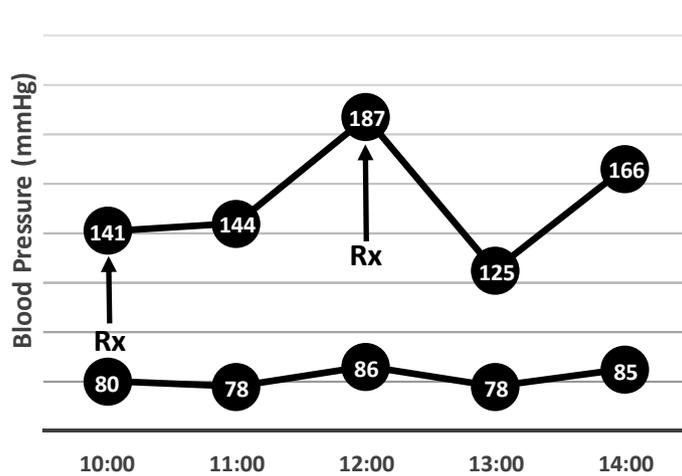
*Minimum 3 agents at maximally tolerated doses. **Where only mean 24-hour BP available a cut-off of 145mmHg used. *** Routine screening for renal disease, renovascular disease, primary hyperaldosteronism and phaeochromocytoma. Additional investigations (e.g. for Cushings) based on clinical presentation. **** Concordance assessed by directly observed therapy as an inpatient or on the day-unit. All potential candidates to be discussed at an MDT.

Figure 3: UCLH Resistant Hypertension Cohort: Of 298 patients on treatment for hypertension screened, 31 (10%) were found to have 'resistant hypertension' as defined by a clinic BP >160 mmHg on at least 3 antihypertensives. Of these 26 (83%) had either a secondary cause, WCH or pseudo-resistant hypertension. Only 2 (6%) were considered to be potential candidates for RDN.

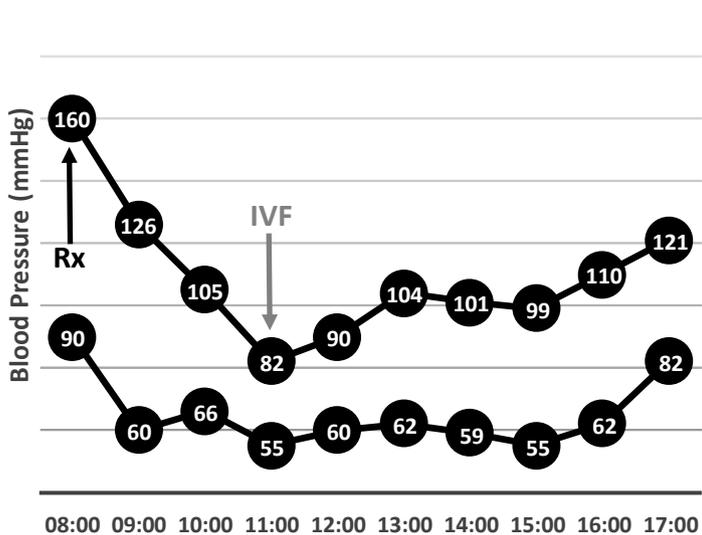
Patient A (The Case)



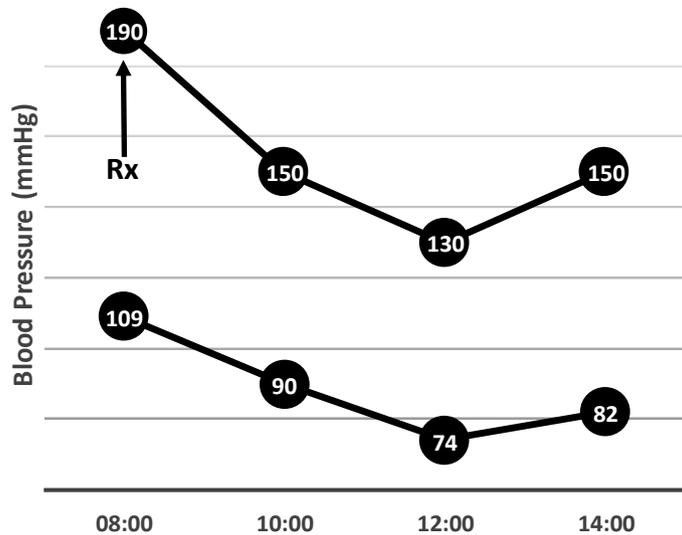
Patient B



Patient C



Patient D



UCLH RDN Selection Criteria

Clinic systolic BP >160mmHg and on optimal antihypertensive therapy

Daytime average systolic BP > 150mmHg

Causes of secondary hypertension investigated
(inc R:A, renal artery imaging, phaeo screen)

Concordance assessed (DOT)

**Patient a potential candidate for RDN
For discussion at MDT**

UCLH Resistant Hypertension Cohort

