In November 2011, a 31-year-old female patient was referred to the Cardiology Division for uncontrolled hypertension. She had been hospitalized for a urinary tract infection. Her systolic blood pressure was >200 mm Hg. She was obese. Her body mass index was 29 kg/m², which is higher than the average body mass index among Korean women. She had a history of ulcerative colitis currently under remission, and she had a history of preeclampsia 3 and 5 years previously. She had 2 children. She had type 2 diabetes mellitus and was taking regular oral medication. She also had recurrent urinary tract infections. She complained of headache, nausea, vomiting, and blurred vision.

Blood and urine tests were performed. Except for abnormal fasting glucose and hemoglobin A1C, most tests were within the normal range. Her thyroid function was normal, and her albumin:creatinine ratio in the urinary analysis was slightly above the reference range at 41.34. Her electrocardiogram (ECG) showed no evidence of left ventricular hypertrophy or any other abnormalities. Her left ventricular systolic function was normal and left ventricular mass index at 61.8 g/m² was within the normal range. We consulted the Ophthalmology Division as she complained of blurred vision. Ophthalmological examination revealed no retinal abnormalities.

We proceeded to follow the algorithm for resistant hypertension (Figure 1). The first step is to exclude white coat hypertension; second, to identify and reverse contributing factors; and third, to discontinue and minimize potential interfering factors and perform screening for secondary causes of hypertension.

Ambulatory blood pressure monitoring (ABPM) revealed a high average blood pressure. Therefore, we excluded white coat hypertension. Central pressure analysis showed a high central pressure. Measurement of blood pressure in all 4 limbs showed similar values.

We evaluated the patient for possible pheochromocytoma. Her plasma metanephrine and normetanephrine levels were within the reference range. We performed 24-hour urine collection for metanephrine repetitively, but the values were within the reference range. We performed a positron emission tomography-computed tomography to explore a possible mass because she had fever of unknown origin. A positron emission tomography-computed tomography, which was performed 5 months previously, showed no abnormal metaiodobenzylguanidine (MIBG) uptake.

Magnetic resonance imaging (MRI) of the renovascular, to exclude renovascular hypertension, showed normal renal arteries. Evaluation of hyperaldosteronism or Cushing syndrome showed normal renin and aldosterone levels with no increase in the aldosterone:renin ratio. An overnight dexamethasone suppression test revealed normal response, and the 24-hour urinary cortisol level was within the reference range. An MRI of the brain was performed when she complained of blurred vision and headache. There was no focal lesion in the pituitary fossa or brain parenchyma; therefore, we excluded pituitary adenoma.

Next, we examined the plasma hormone levels. Plasma hormone levels were also within the reference range, and an insulin-induced hypoglycemia test was normal.

The patient had poor urinary output despite taking diuretics. She drank >2 or 3 L of water daily, but her urinary output was just <1 L. However, her plasma blood urea nitrogen and creatinine levels were normal. We suspected malignant nephropathy, but a diethylenetriaminepentaacetic acid renogram showed normal glomerular filtration rate. We considered a urinary tract problem and, therefore, performed an urodynamic study that showed acontractile detrusor. She was educated on how to use intermittent catheterization, but her blood pressure was not improved.

Because the patient was obese, we evaluated the possibility of obstructive sleep apnea. Her polysomnography result showed an apnea–hypopnea index of 0.5, which is normal.
Figure 1. Algorithm for diagnosis of resistance hypertension. Adapted from Calhoun et al with permission of the publisher. Copyright © 2008, the American Heart Association. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

The patient was taking >4 oral antihypertension drugs including an angiotensin receptor blocker, β-blocker, calcium channel blocker, and diuretics (Table 1). However, her blood pressure remained uncontrolled. IV nicardipine and a calcium channel blocker improved her blood pressure somewhat. We tried to replace the IV-infused calcium channel blocker with oral medication, unsuccessfully.

Discussion: Managing the Hypertension

Professor Park: I am the attending physician for this patient. In summary, the patient was an obese woman in her 30s. She had diabetes mellitus, and she initially had a high blood pressure that was absolutely unresponsive to all oral medications. Initially, because the echocardiogram, the ECG, and the funduscopy results were benign, we initially suspected white coat hypertension. However, when we did an ambulatory blood pressure–monitoring test, we found that her blood pressure was extremely high. I do not think that it was a case of white coat effect. Perhaps the blood pressure elevation happened recently. This is just a cross-sectional slide to show the types of medications that we were using at this period (Table 1). We tried using different combinations. We used different types of β-blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors. Despite our efforts, she was not responsive. I was wondering if any of you experts have any suggestion. What you would do with this particular patient at this moment?

Professor Touyz: Perhaps while the audience is thinking of some questions, I would just like to ask you, in terms of the patient profile, I think there were 2 significant factors: she had preeclampsia and she was obese. Perhaps you could tell us how you took this into account in terms of this complex, severely hypertensive patient?

Professor Park: Preeclampsia itself is a risk factor for future hypertension. However, she had preeclampsia 3 years before she was admitted, and after her second delivery, she did not have hypertension.

Professor Touyz: Did she remain obese?

Professor Park: She was obese. I think she gained close to 20 kg during her pregnancy.

Professor Touyz: Has she remained obese thereafter?

Professor Park: Yes.

Professor Touyz: One more question I would like to ask you in terms of what you have shared with us, I do not recall seeing heart rate variability and characterization of her heart rate. Could you comment on the heart rate?

Professor Park: The heart rate was relatively high. It was between 80 and 100 bpm despite us using full-dose β-blockers.

Professor Dominiczak: I would like to go a step back. To exclude secondary hypertension, you did an extremely detailed set of investigations, and I understand this is an extreme case of high blood pressure (a difficult case). However, I am not sure I would have performed an MIBG scan considering the normal levels of catecholamines and metabolites. The number of tests and the detailed testing is more than I think we would have done in an European patient. Can you explain this difference of approach? My second question is, are you 100% certain that she takes all these complex cocktails of drugs? Have you checked, both by direct observation and measuring the levels, whether the drugs are truly consumed every day (in the appropriate manner)?

Professor Park: That is an excellent point. This positron emission tomography–computed tomography was performed before she was referred to me because she had a fever of unknown origin. In a previous positron emission tomography scan that was performed several months ago, there was no abnormal uptake to suggest pheochromocytoma or extra-adrenal paragangliomas. Because of the patient’s unresponsiveness to the medications, we referred her to Seoul National University Hospital for a second opinion. This particular MIBG scan was performed at Seoul National University Hospital. In our hospital, her urine catecholamines were evaluated, and her MRI renal angiography was performed to rule out renal artery stenosis.

Professor Touyz: Just getting back to the medication. We saw she was on this complex cocktail of many different antihypertensive medications. Yet, she continued to have a relative

Table 1. Antihypertensive Medications Before Procedures

<table>
<thead>
<tr>
<th>Initial Medications</th>
<th>Combination of Medications Used Before the First Renal Denervation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telmisartan 80 mg QD</td>
<td>Captopril 50 mg TID</td>
</tr>
<tr>
<td>Cilnidipine 5 mg QD</td>
<td>Amlodipine 10 mg QD</td>
</tr>
<tr>
<td>Carvedilol 12.5 mg QD</td>
<td>Diltiazem 90 mg QD</td>
</tr>
<tr>
<td>Furosemide 20 mg BID</td>
<td>Bisoprolol 2.5 mg BID</td>
</tr>
<tr>
<td></td>
<td>Doxazosin 4 mg BID</td>
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<tr>
<td></td>
<td>Torasemide 10 mg QD</td>
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<tr>
<td></td>
<td>Chlorthalidone 25 mg BID</td>
</tr>
<tr>
<td></td>
<td>Spironolactone 50 mg BID</td>
</tr>
<tr>
<td></td>
<td>Isosorbide dinitrate 40 mg BID</td>
</tr>
<tr>
<td></td>
<td>Cadralazine 10 mg QD</td>
</tr>
<tr>
<td></td>
<td>Minoxidil 5 mg BID</td>
</tr>
</tbody>
</table>
tachycardia even though she was on all these β-blockers and other blockers. Did you at first suspect whether she was compliant, because that is always a good indication, and second, did you consider an association with sympathetic hyperactivity?

Professor Park: She was admitted to the ward for a long period for follow-up, and because we suspected poor compliance, our attending physicians, our house staff, and our nurses made sure that she took the medications. That is how we ruled out noncompliance.

Dr Jennings: I think we must accept that sometimes we encounter these patients that we cannot explain, with high blood pressure and no evidence of target-organ damage. This patient has been worked up as well as anybody you could ever see. I think most of my questions have been asked. I have a question regarding her fluid balance. I think you showed us records over 9 days when she was theoretically accumulating a liter a day. Are you suggesting that all the urine was in her bladder? Was it collected when she was catheterized or was she somehow doing something with her urine collection?

Professor Park: She seemed to have primary polydipsia, and she would drink 3 or 4 L of water per day. Even when she was admitted, while we told her not to do that, she would drink water continuously. The fluid balance would be incredible. It would be around 4 L of intake and only 500 mL of output. It was very, very bizarre. In 2 or 3 weeks, she would gain 5 kg of weight just by drinking a lot of fluid, and we could not explain why. She did not have an adequate urine output, so we evaluated for neurogenic bladder with vesicoureteral reflux and obstructed uropathy. However, although the results revealed that she had a neurogenic bladder, the renogram showed normal kidney function, and she did not have any vesicoureteral reflux. I cannot explain why she had such a low urine output. However, later, when a cystostomy was performed at Seoul National University Hospital, the urine output was normalized. It may have had to do with the neurogenic bladder.

Professor Cho: I am from Catholic University, South Korea, and my question is also related to her heart rate. Are you sure that you use a blood pressure cuff with appropriate thickness when you measure all patients’ blood pressure? Did you ever try to measure her blood pressure invasively? Because her left ventricle mass is normal. Under 70… I remember, 70 g per blood surface area, so it is too normal for her blood pressure. Also, was there history of or current use of ginseng medication or herbal medication?

Professor Park: Again, she was followed-up for a long period. While she was admitted to the hospital, we made sure she did not take any ginseng or any other herbal medications. The answer to the question whether we evaluated for invasive blood pressure is no. It would have been too invasive for this kind of patient. But to answer your question, while we were doing renal denervation, she received IV anesthesia, and her blood pressure decreased to 130 mmHg. Based on this, I think some components of extreme anxiety and increased sympathetic nervous system activity may have contributed to her extreme high blood pressure.

Professor Cho: How was her urinary secretion of sodium (because she drinks too much water)?

Professor Park: We did not evaluate 24-hour sodium excretion, but I think you make a great point.

**Progress**

During this time, the Renal Denervation SYMPLICITY Korean Registry was started. We were fortunate enough to enroll this patient into the Registry trial and initially, in April of 2012, we performed renal denervation. Eight ablations were made to the right renal artery and 6 to the left. Initially, we thought there was some response, but as you can see, after continued follow-up, there was absolutely no response to the renal denervation during the 3 more months of follow-up (Figure 2). After this, I had no options left. I did not know what to do with this patient. I suggested that maybe she could get evaluated at another leading hospital in Korea, Seoul National University. I sent the patient to Lee, the next presenter. After renal denervation, what other treatment options are there? Are there other treatment options that you are aware of that we could select now? I think some input from the audience would be helpful.

**Treatment Options: Post–Renal Denervation**

Professor Touyz: Could you tell us at this point, when you felt you had no other options, what medications she was taking?

Professor Park: She was still taking all the medications that I previously mentioned.

Professor Touyz: Regarding the ABPM and the heart rate, did you see any nocturnal or 24-hour or circadian rhythm changes in this patient on repeated testing?

Professor Park: This is the ambulatory blood pressure data (Figure 3). You can see the nocturnal blood pressure.

Professor Touyz: The figure shows evidence of reverse dipping. Of course, as we all know, this is not a good marker of cardiovascular risk and worse cardiovascular outcomes. Interestingly, even though there was no evidence of target-organ damage at the age of 31, as determined clinically and by specialized investigations, there is a significant finding in terms of her ABPM with reverse dipping phenomenon.

Professor Dominiczak: This is a case one encounters once in a lifetime, that is almost unresolvable, and it is puzzling because it is similar to a case that was presented 2 weeks ago, in Orlando, at the meeting of the American Heart Association Council for Hypertension. This was a case presented by a physician and neurosurgeon, because the patient, after having been through all these procedures including renal denervation, etc, has asked to have a neurosurgical procedure, a deep brain stimulation that has helped. This was n=1. Only one such case was done in this Center in Bristol in United Kingdom. I think there is an uncanny similarity between these 2 cases, and I think there must be some neurogenic mechanism that is driving this hypertension. Have you further evaluated sympathetic nerve activity? Have you thought about examining the kidneys again? Maybe, there is still hope in performing another procedure because I think the tablets are not working.

Professor Park: In Korea, vasosympathetic nervous activity measurement is not available.

Dr Hering: It is a difficult case to find the best approach, and I am still wondering whether there may be an association with the anxiety or stress level in this patient. Some patients may not tolerate ABPM, and they may be a little bit stressed. One approach is the automated unobserved blood pressure measurements when we leave the room and leave the patient
alone. We may get similar readings to those of ABPM. With patients who are obese, they often do not tolerate the arm cuffs, which also may trigger the blood pressure.

Considering that the patient has polydipsia, we cannot exclude that she may also get up during the night to drink, which may also have an effect on the night-time blood pressure. It is a complicated case, and in this scenario, we look for the procedure. Maybe 3 months is short term for the effect of renal denervation, and indeed, the sympathetic nervous system activity may help us to identify whether the neurogenic component triggered this scenario. However, this is not available.

There is deep brain stimulation that was reported in one case report, and it is one of the options. However, in another conference presentation, it was reported that there is also a rebound effect after 18 months; even after deep brain stimulation, there is increased blood pressure again after the base (interventional) approaches for the treatment. We still do not know whether it is related to central anastomoses, deep brain stimulation, renal denervation, or even carotid body removal because there is no such data. In some patients, it is really the anxiety level.

Providing the patient with guidance on how to manage stress may help to reduce the blood pressure in some cases.

Professor Park: Yes. I think that is a great point. I have a lot of so-called refractory hypertension patients who respond to antianxiety medications such as alprazolam. However, in this case, I tried all kinds of antianxiety medications. I asked for a psychiatric consultation, and the psychiatric consultation note was that she did not have any psychiatric signs of anxiety disorder. She also did not have any response to alprazolam. The only treatment that was successful was IV antihypertensive drugs. IV nicardipine reduced her blood pressure but not oral medications.

Professor Touyz: That brings me to an important point. As clinicians, we all struggle when see patients such as this who come with 8, 9, or 12 drugs and the blood pressure remains at 180 or 200 mmHg. Did you at any point consider stopping all her medication? Titrating the medication down. I mean, not stopping everything at once, but slowly removing the medication to see if that had an impact at all? Because sometimes, this is an approach to help even from a diagnostic point of view.

Figure 2. Blood pressure during 3 mo after renal denervation.

Figure 3. Ambulatory blood pressure (BP) before renal denervation.
Professor Park: I did not do any down titration. After several weeks or several months, I would switch medications from the same class, different drugs for example. Using bisoprolol, if there was no response, I would switch to nebivolol or carvedilol. However, I did not down-titrate the medications.

Professor Touyz: I think you bring up something extremely interesting, and it is the fact that she responded to IV β-blockers but not to oral β-blockers. Despite all the monitoring, this would make you think, is she taking her oral medication? I think we should still be a little bit cautious in terms of how sincere she is despite the monitoring because as you know, patients can be clever in their maneuvers.

Dr Jennings: Just following up on Hering’s comments on the sympathetic activity, we have learned a lot about renal denervation since SYMPLICITY HTN-3 and particularly about the technique and making sure that the lesions are distal in the renal circulation and that multiple lesions are made. I just wondered when you went back over it, were you satisfied you had used a satisfactory technique? It does emphasize how badly we need simple tests of the effectiveness of these interventions.

Professor Park: I think that is a wonderful comment. At the start, she was the second patient from the Registry, so our interventional cardiologist, B.-K. Kim, was relatively conservative in his approach to the intervention. At the time of the procedure, the association between the number of ablations and the degree of blood pressure reduction had not been established, and there was a real concern about the safety of too much ablation of the renal arteries. He did not know whether too much ablation could be harmful to the patient. Later, the number of ablations was not satisfactory to him. With increased cases, he would do more ablations for each artery. I will show you the next procedure that was done in this patient that shows a more aggressive approach by Kim.

Additional Procedures
Before I sent the patient to Seoul National to get a second opinion, I did a lot of searching. What about nitrates or carvedilol. However, I did not down-titrate the medications. We suspected that because the blood pressure is responsive to IV drugs but not to oral medication, she has some sort of an absorption problem of the oral medications. There are some references to show this in patients with history of inflammatory bowel disease, which she had but was in remission. There are cases of high multidrug resistance in patients who fail medical therapy.6-8 There are some cases where some polymorphisms are associated with decreased response to amldopine according to genotype.6 Maybe this is such a case, but we could not confirm this. After that, Seoul National University said, “We give up.” They sent her back to me. However, before that, Lee at Seoul National University and I had a deep discussion about this patient and, “Maybe,” he said, “why don’t you consider a sympathectomy for this patient?” Although sympathectomy has not been performed in the past 60 years, it has shown to be effective for reducing blood pressure. She wanted to get another opinion and came back to me to get further treatment.

After many discussions, we decided to repeat renal denervation in this patient. We contacted Medtronic to get their permission to do another procedure for this patient. Studies have shown that with increasing number of ablations, there is a significantly better reduction in blood pressure. We did a repeat denervation.7 By this time, the interventional cardiologist had more experience doing this procedure so he performed a significantly increased number of ablations of both arteries. After the second denervation, there was a slight decrease in the blood pressure. This got our hopes up, but the blood pressure started to go back up again. After 3 weeks, the blood pressure was at a range of 180/130 to 180/140 mm Hg, and the patient was still taking a high number of medications. What other options are left for this patient at this time? Should we at this point wait for several more months to see a delayed response or other nonpharmacological treatment? Other options such as baroreceptor modulation, arteriovenous fistula, or deep brain stimulation were not available at that time and are still not available in Korea. Any other suggestions at this time?

Discussion: Additional Therapies?
Dr Hering: Some of the patients, in rare cases, have neurovascular compression on the left side that may be seen on an MRI scan. Years ago, a German group published data on many patients.4-10 Some patients with elevated blood pressure have neurovascular compression. When the pressure on the nerve is released, particularly VIII and IX on the left side, there is a related reduction in blood pressure and muscle sympathetic nerve activity. It is not a direct treatment for hypertension but the cause that leads to consistently elevated blood pressure. We sometimes identify the nerve, particularly from VII-X; there could be compression usually on the left side. We tried showing why the risk reduction in blood pressure and mass sympathetic nerve activity in patients with resistant hypertension who have neurovascular compression and a release of the pressure could show a rebound effect ≤8 months later.10 This is a different procedure to the deep brain stimulation, but it was the case in some patients, including children. Even if you give a high dose of angiotensin receptor antagonist like candesartan (Atacand) or telmisartan, some patients may have neurovascular compression. A simple MRI (looking at the nerve, particularly on the left side) may identify that this is the cause of the consistently elevated blood pressure.
History of Sympathectomy

I am going to briefly show you the history of sympathectomy because this was the last option to consider. It was a treatment for severe hypertension during the 1930s and 1950s. However, after the development of powerful antihypertensive drugs, it was discarded into the history books. Although it was effective, it had a significant morbidity and mortality rate (serious complications, <2%; transient back pain, 96%; transient diarrhea, 44%; and lower extremity paralysis with loss of bladder and bowel function, <0.15%).

The celiac plexus is an important plexus of sympathetic nerves. It consists of the greatest splanchnic nerve, the lesser splanchnic nerve, and the least splanchnic nerve. It supplies most of the organs of the upper abdomen. This is an important article published in the JCI in 1996 when they did sampling from 7 subjects undergoing abdominal surgery. They sampled blood from the portal vein, the systemic arteries, and the hepatic veins. What they found was that out of the total norepinephrine spillover, 42% of the norepinephrine spillovers are contributed by the mesenteric and the hepatic spillover. This shows that the celiac plexus is associated with a significant portion of the total neurohormonal stimulation in normal subjects.

This was another study that was published in Hypertension where they induced angiotensin II and salt-induced increase in sympathetic nervous system activity and hypertension. This study showed that in rats, celiac ganglionectomy, but not renal denervation, was associated with significant control of blood pressure. When they analyzed the norepinephrine level in each major organ, the renal denervation did not cause changes in the norepinephrine content, but celiac ganglionectomy had a significant reduction in the norepinephrine content of the major organs. You can see that blocking the celiac nervous system is more powerful than renal denervation in reducing sympathetic outflow. Currently, the celiac plexus block indication is intractable abdominal pain. This is a major indication, but historically, this was performed for other indications such as ischemic ulceration, hyperhidrosis, and hypertension.

If it is performed with an expert hand, the rate of serious complication is <1%. The major complication from this procedure is hypotension, which has been reported to be ≤50% and transient diarrhea. It has been performed since 1914 as a procedure by anesthesiologists.

Case Resolution

We contacted the Anesthesiology Department, and they initially performed a test block of the right celiac plexus. She showed a significant drop in her blood pressure. Because the test celiac plexus block seemed to work, a second plexus block at the right celiac plexus with dehydrated alcohol was performed. This was also associated with a significant drop, close to 50 mm Hg, in her blood pressure. After that, we did a third block of the left celiac plexus with lidocaine and ropivacaine with a similar level of blood pressure drop.

After I reported this case in a Korean meeting, there was another case reported by the Catholic University of Korea, which involved an 18-year-old male patient who was absolutely refractory to all kinds of oral medications. The renal denervation failed, and they performed a celiac plexus block with botulunim toxin after which the blood pressure was controlled. The case was reported in the journal Toxins.

In our case, after the second renal denervation and the plexus block, the blood pressure started to fall, approximately around April. The patient had symptoms of hypotension, so all medications were removed. Currently, her progress is very, very good. Her nocturnal blood pressure was elevated, but her awake mean blood pressure with ABPM dropped to 134/83 mm Hg without any medications. Her progress until now is recurrent hospitalization because of complications from the cystostomy, but she is currently normotensive without any antihypertensive medications.

Final Comments and Questions

Professor Touyz: I just want to go back one more time. When you repeated the ABPM, did she still exhibit the reverse dipping phenomenon?

Professor Park: She still did, yes.
Professor Touyz: Even though her blood pressure had come down by 50 mm Hg, did she still have the higher nighttime blood pressure?

Professor Park: Yes, she did.

Professor Dominiczak: I think you succeeded which is great. We do not completely understand why. It must be a neurogenic mechanism. When things went really wrong, and she was on all these drugs, and you were doing first and second renal denervation and things did not work, how did she feel? Was she a sick lady? Or was she somebody who had high blood pressure but otherwise was fine when you went to see her in the morning?

Professor Park: It was the second case. The only thing she had was elevated blood pressure, and when the blood pressure was elevated >180 to 200 mm Hg, she had some headaches, nothing more.

Professor Dominiczak: Great success for you.

Professor Park: Yes.

Professor Touyz: Thank you. Indeed, the patient is lucky. We still do not understand the mechanisms. Maybe essential hypertension after all.

Summary

We present a case of refractory hypertension controlled through renal denervation and celiac plexus block. The mechanism for hypertension remains unclear, but the patient is now normotensive without oral medication after repeat renal denervation and celiac plexus block.

Acknowledgments

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Disclosures

None.

References


Case of Refractory Hypertension Controlled by Repeated Renal Denervation and Celiac Plexus Block: A Case of Refractory Sympathetic Overload
Chan Joo Lee, Byeong-Keuk Kim, Kyung Bong Yoon, Hae-Young Lee, Anna F. Dominiczak, Rhian M. Touyz, Garry L.R. Jennings, Eun Joo Cho, Dagmara Hering and Sungha Park

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