Clinical–Pathological Conference

Chronic Deep Brain Stimulation Decreases Blood Pressure and Sympathetic Nerve Activity in a Drug- and Device-Resistant Hypertensive Patient


We were approached by a 54-year-old female patient wishing to receive deep brain stimulation (DBS), a procedure that we previously discovered to normalize blood pressure (BP) in a drug-resistant hypertensive patient,1 to treat her severe, refractory hypertension. On her first visit to the specialist Hypertension Clinic (Bristol Heart Institute, University Hospitals Bristol NHS Foundation Trust) in May 2012, her BP was in excess of 300/170 mmHg (clinic aneroid manometer and finger plethysmography), despite taking 8 antihypertensive medications, receiving chronic baroreflex activation therapy (Rheos, CVRx, MN) and having undergone bilateral renal nerve ablation (RDN). At this time, the patient reported severe, debilitating headaches occurring 1 to 3 times per month and general malaise. The patient is postmenopausal, a nonsmoker, and of slim build (body mass index, 16 kg/m²).

Despite the sustained, very high BP, the patient had remarkably little end-organ damage. She had mild hypertensive retinopathy but no microalbuminuria or reduction in estimated glomerular filtration rate. She had mild left ventricular hypertrophy, but no evidence of stroke, ischemic heart disease, myocardial infarction, coronary artery disease, or systemic inflammation.

A secondary cause of her hypertension has yet to be found, despite having been thoroughly investigated by hypertension specialists in Germany at the Hannover Medical School and Experimental and Clinical Research Center, Charité Berlin-Buch.2 Evidence for the following causes of hypertension was absent: pheochromocytoma, renin–angiotensin–aldosterone disorders, obstructive sleep apnea, cerebral vessel abnormalities, and Mendelian syndromes. Her arterial stiffness was high (11.5 m/s), as measured by pulse wave velocity; however, this is within the expected range for the European population in her age group and BP category (50–59 years; BP ≥160/100 mmHg; pulse wave velocity mean ±SD, 8.8 [4.8–12.8]).3 She has had 4 children without pregnancy complications or preeclampsia and her hypertension developed before the onset of menopause. She was treated for epilepsy, polygenic hypercholesterolemia, and osteoarthritis and also had symptoms of hyperacusis and tinnitus; however, these were not thought to contribute to her hypertension.

The patient was taking 8 medications licensed as anti-hypertensives (or known to have an antihypertensive effect) daily at doses that equate to a whole drug equivalent (WDE; proportion of maximum dose for any given drug) score of 13 from 7 drug classes4 including a central-acting sympatholytic (clonidine), 2 diuretics (spironolactone and torasemide), an angiotensin receptor blocker (candesartan), a calcium channel blocker (amlodipine), a β-adrenergic receptor blocker (metoprolol), a coronary vasodilator (molsidomine), and an α₁-adrenergic receptor blocker (urapidil). The patient was also taking, daily, 12 other medications related to the treatment of angina (ivabradine), chronic nerve pain (600-mg pregabalin, 400-mg flupirtine, and 60-mg morphine), epilepsy (400-mg lamotrigine and 200-mg zonisamide), allergies, cholesterol (10-mg ezetimibe and 40-mg simvastatin), and vitamin supplements. Adherence to medication had previously been confirmed by urine analysis,5 and deviation from this compliance was highly unlikely given the patient’s proactive attitude to her own health and dedication to maintaining her home BP records.

In 2009, the patient was equipped with a first-generation baroreflex activation therapy device (Rheos, CVRx, MN, USA), which engages baroreceptors more efficiently than the current device,6 and which has reduced BP in a controlled clinical trial.7 Initially, baroreflex activation therapy dropped her BP by 60 to 80 mmHg; however, after 3 months, her BP returned to >240/120 mmHg (clinic). She underwent RDN (Symplicity Catheter System, Ardian, CA) in February 2011, and this procedure had no effect on her BP. At the time, the patient’s home BP diary records (morning, midday, and evening measurements; automated BP cuff; Omron) showed that her average BP from successful readings over a 3-week period

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in May 2011, after RDN, was 280/166 mm Hg (heart rate, 110 bpm). Only 50% of attempted readings over this period were successful (patient’s own records), and the failed attempts were logged as pressure exceeding the limit of the cuff device (>290 mm Hg). Subsequently, and in the 12-month period preceding her visit, she was unable to continue measuring her BP at home because her BP monitor generated an error consistent with a patient’s systolic BP exceeding the detection limit of the cuff (290 mm Hg; Model, Omron Healthcare Co., Japan). Her general practitioner corroborated this, stating that clinic BP could not be recorded and attempts to monitor her using an ambulatory BP monitor (ABPM) were also unsuccessful.

Despite comprehensive drug- and device-based antihypertensive treatment, her BP on presentation at our clinic was extremely high and could not be accurately measured using a standard automated oscillometric cuff (Omron). BP was, therefore, measured noninvasively using an aneroid manometer with an analogue display (cuff size small), and beat-to-beat values fluctuated between 300 and 350/140 to 150 mm Hg while in the supine position. Finger plethysmography (Finometer PRO; Finapres Medical Systems BV, The Netherlands) reflected these values. We also attempted to measure her BP using a 24-hour ABPM (Spacelabs); however, only 1 reading was successful at 7:00 AM (235/142 mm Hg) and the remaining attempts exceeded the ABPM limit of 240 mm Hg as recorded in the ABPM error log.

Assessment of Suitability for DBS Treatment

Our plan to use DBS as a novel treatment for resistant hypertension transpired after its use to treat a hypertensive patient for chronic neuropathic pain. DBS serendipitously produced a normalization of the patients BP such that all antihypertensive medication was withdrawn.1 The patient remains normotensive beyond 5 years maintained on chronic DBS and a single antihypertensive medication (perindopril) for protection. In this case, DBS targeted the ventral periaqueductal gray (vPAG), which is a region that mediates analgesia, bradycardia, hypotension, and hypoventilation in animals.7,8 In humans, there is also evidence supporting a hypertensive response when DBS is used in this region.1,9,10 The cardiovascular response to vPAG stimulation is mediated by inhibition of the sympathetic nervous system.11,12 Therefore, we proposed that vPAG DBS could be an effective treatment for patients with severe hypertension driven by pathologically high sympathetic drive.

Our patient certainly has severe, resistant, essential hypertension, a disease commonly associated with, and caused by, high sympathetic nerve activity.13 Indeed, the baroreceptor stimulation was effective, at least transiently, at lowering her BP via reduction of the sympathetic activity.2 A muscle sympathetic nerve activity (MSNA) recording made during bilateral baroreceptor stimulation but before RDN in 2011, was described as normal, albeit not for her level of BP. Additionally, it was not clear whether this MSNA data were normal for her low body mass.5 Her MSNA increased and decreased in response to a vasodilator and vasoconstrictor substances, respectively, indicating an intact baroreflex.10 Schroeder et al also observed respiratory–sympathetic coupling,2 a centrally driven phenomenon that has been described in an animal model of essential hypertension, in which it may be critical for the development and maintenance of hypertension.14

In our hypertension research clinic, we measured the patient’s MSNA 1 week before surgery and found the burst frequency and incidence were 64 bursts/min and 56 bursts/100 heart beats, respectively. This was normal for the patient’s age and menopausal status but not her level of BP. Figure 1A shows the patient’s MSNA compared with normotensive women of a similar age, measured in our group’s autonomic physiology laboratory. However, when we scaled the MSNA for body mass, we found that the patient’s MSNA was much higher than her normotensive counterparts (Figure 1B), suggesting that high SNA may be contributing to the patient’s hypertension. At this point, the patient was still receiving continuous baroreflex stimulation (albeit unilateral, the left-hand side had malfunctioned) and continuing her daily regime of 12 WDE from 7 antihypertensive medications. Therefore, despite receiving treatment to reduce sympathetic nerve activity from multiple medications and 2 different device-based interventions, our patient still had high sympathetic nerve activity and we cannot exclude this as a driving factor of her hypertension. Given this, we justified the use of DBS with the aim of inhibiting sympathetic drive and thereby decreasing her BP.

DBS Surgery

Informed patient consent was acquired, and ethical approval was obtained (NRES Committee South West, Frenchay, United Kingdom; REC reference 11/SW/0050). With use of established protocols1 and a neuromate robot-assisted (Renishaw plc, United Kingdom) magnetic resonance imaging (MRI)–guided stereotactic technique and implantable guide tube (Renishaw plc), an octopolar electrode (Model DB-2201; Boston Scientific Corporation, MN) was implanted into the
vPAG with the electrode tip to the depth of the superior colliculus such that the lower 4 contacts were within the vPAG. The electrode was connected to a Vercise implantable pulse generator (Model DB-1110; Boston Scientific Corporation). Within 24 hours postimplantation (but with stimulation off), her systolic BP reduced to <160 mm Hg, with awake recordings as low as 125/68 mm Hg (intra-arterial measurements), presumably reflecting an effect of the electrode. There was a subsequent rise >72 hours to 205/130 mm Hg.

DBS was activated 4 days post-implantation (2–5 mA, 6 Hz, 100- to 150-μs pulse width) and a week after surgery the patient’s BP was 170/109 mm Hg during the day and dipped to 119/77 mm Hg during the night (ABPM). The patient reported debilitating lethargy; therefore, all antihypertensive medications with the exception of daily clonidine (50 μg twice daily) were withdrawn despite her BP being above the 140/90 mm Hg (cuff) target, and her lethargy improved. Before the patient was discharged, DBS was switched off for 24 hours and her BP increased to 220/160 mm Hg (cuff) overnight. The patient was still receiving chronic baroreflex stimulation throughout the surgical and post-surgical periods. No procedure-related complications occurred, and the patient was discharged with chronic low-frequency DBS of the vPAG (bipolar [contact charges: 1 neutral, 2 and 3 negative, 4 positive], 4.3 mA, 10 Hz, 150-μs pulse width).

Audience Questions About DBS Surgery
Professor Dominiczak: How frequently do you need to do the actual stimulation or is it a continuous stimulation?

Dr Patel: It requires continuous stimulation at low frequency (usually 5–10 Hz). It is also generated with a rechargeable system, and because the frequency is very low, the patient has to recharge the generator usually once every 3 weeks for about an hour.

Dr Stocker: You mention that the periaqueductal gray is about 3-mm³ distance and so, when you start to think about the current intensities and indirect side effects as far as affecting other brain regions, I was curious as the presentation moves forward if you could comment on how those parameters were established.

Dr Patel: I will start by alluding to where I implant the electrode. It is usually implanted within the periaqueductal gray to the depth of the superior colliculus to minimize spreading of the stimulation to the oculomotor nuclei and any other disruption. In relation to the frequency utilized, we know that low frequency has a stimulatory effect and for many years has been consistently and safely used for generating analgesia for the treatment of chronic pain.

Beyond established findings in animal models, the group in Oxford, while implanting electrodes for the treatment of chronic pain, found that stimulating at low frequency in the ventral part of the periaqueductal gray acutely resulted in a hypotensive effect and on the converse stimulating the dorsal part of the periaqueductal gray acutely resulted in increase in BP. The basic science and acute studies in humans guided us in optimizing the location of the electrode and required stimulation parameters.

Professor Jennings: With most forms of chronic physiological nerve stimulation, you get some sort of adaptation. And is there any suggestion in the other applications of this technique if that happens?

BP and MSNA Outcome From Long-Term DBS
Three weeks after initiating DBS, our patient’s BP had decreased to 171/109 mm Hg (daytime ABPM) on DBS and (unilateral) baroreflex stimulation alone. The patient’s own records indicated a weekly, evening average of 198±10/124±7 mm Hg. At our patient’s 2-month follow-up appointment, her office BP was 246/138 mm Hg measured by seated digital BP cuff (Omron). We measured her MSNA and found that burst frequency and incidence reduced considerably (Figure 2) to 18

![Figure 2](https://example.com/figure2.png)
bursts/min (0.37 bursts/min per kilogram) and 33 bursts/100 heart beats (0.67 bursts/100 heart beats/kg), respectively (Figure 3).

After 6 months of continuous DBS (bipolar [contact charges: 1 neutral, 2 and 3 negative, and 4 positive], 5 mA, 6 Hz, 150-µs pulse width), the patient’s home BP diary indicated that she was maintaining weekly averages (over a 6-week period) of 209±10/129±6 mm Hg in the morning and 228±11/131±8 mm Hg in the evening (Figure 3). Daily metoprolol had been reinstated to control her HR (resting HR was 80–100 bpm), and the baroreflex stimulator had been repaired to operate bilaterally (continuous mode 8:00 PM to 8:00 AM (485ms, 30 Hz, 4.2 V) and 8:00 AM to 8:00 PM (cycling 300 ms on [30 Hz, 4.2 V] and 450ms off). ABPM data confirmed the maintained reduction in daytime BP (218/149 mm Hg) and revealed nighttime BP dipping to 162/110 mm Hg (Table 1) consistent with a healthy circadian rhythm. Her MSNA had further decreased to 16 bursts/100 heart beats (Figure 3), and this represents a substantial reduction in MSNA which is now comparable to that described in normotensive, postmenopausal women when adjusted for body mass index.15

The patient’s BP and MSNA stabilized, and she maintained a daytime average BP of 230/150 mm Hg (24-hour ABPM) on DBS and bilateral baroreflex stimulation with the addition of only daily metoprolol (1 WDE) for 2 years after initiating DBS (bipolar [contact charges: 1 neutral, 2 and 3 negative, and 4 positive], 4.3 mA, 10 Hz, 150-µs pulse width). This represents a significant improvement in BP when we consider that her BP was often higher than that could be measured by an automated BP cuff (error generated at and above 299 mm Hg systolic BP), she now achieves close to 40% successful readings during 24-hour ABPM (error generated at and above 240/150 mm Hg), and she is down to 1 WDE from 12 WDE of antihypertensive medications (Table 1). Her heart rate is high, despite taking the β-adrenergic blocker metoprolol although it is still linearly related to systolic BP (slope 0.42±0.08 bpm/mm Hg, $R^2=0.44$). The patient reports feeling better in her general health and has less severe headaches after DBS. Her chronic nerve pain has not been improved by DBS, and her pain medications are unchanged with the exception of morphine (20 mg), which is now one third of her daily dose in 2013.

**Discussion**

A critical question to be answered from the outcome of this case is can DBS be used to control BP in severe hypertension where drug and other device therapies have failed? We believe, but cannot be precise in, the magnitude of the reduction in our patient’s BP, since the year before undergoing DBS, her systolic BPs exceeded that could be measured by a standard

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**Figure 3.** Blood pressure (BP) and muscle sympathetic nerve activity (MSNA) remain decreased with long-term deep brain stimulation (DBS) therapy. Weekly averages of evening systolic and diastolic BP (SBP and DBP, respectively) and heart rate (HR) recordings from the patient’s home BP diary over a 4-y period pre- and post-DBS therapy. The timeline of the patient’s regime of antihypertensive medication is indicated below the graph along with the whole drug equivalent (WDE) and number of medications in brackets. The timeline of device therapies is also indicated. DBS was initiated in July 2013, green dashed line. Patient underwent surgery for prolapsed uterus in October 2013. Data are mean±SD. BAT indicates baroreflex activation therapy; and RDN, renal nerve ablation.
Given that the patient’s BP remains high despite a year. Although still lower than pre-DBS, this rise in BP might be explained by increased sensitivity of her vasculature to the removal of 7 antihypertensive medications from her daily treatment, which suggests an improvement in the range of oscillometric device. We can be confident that, before DBS, her BP regularly exceeded 270 mmHg systolic and likely fluctuated between this level and 330 mmHg, as was recorded manually in the Hypertension Clinic. Her average daytime BP stabilized to 225/142 mmHg (ABPM, 2 years of DBS treatment), which suggests an improvement in the range of 45 to 125 mmHg. The patient reported a reduction in the frequency and severity of headaches and feels in better health. This is likely to be a combined effect of decreased BP and of the absence of immediate changes in BP or MSNA during short periods of turning off DBS during clinic visits suggests that DBS may have reset neural networks that drive sympathetic outflow. Indeed, the vPAG has been reported to facilitate the baroreceptor reflex in both humans and experimental animals. The patient’s BP gradually increased 1 month after initiating DBS, reaching its current average after a year. Although still lower than pre-DBS, this rise in BP might be explained by increased sensitivity of her vasculature to MSNA. Given that the patient’s BP remains high despite normal range MSNA, it is clear that other factors are contributing to her hypertension. The patient’s arterial vasculature may have lost compliance in response to the severe hypertension that our patient has experienced over the past 10 years. Her pulse wave velocity, a measure of vascular compliance, was elevated compared with normotensive values, but within the expected range for age-matched European Grade II/III hypertensives. Blood vessel hypertrophy and calcification are commonly reported in patients with long-term hypertension and may contribute to this patient’s hypertension.

We can surmise that the patient’s high heart rate may also be contributing to her hypertension. Before DBS treatment, echocardiography revealed her cardiac output, at rest, was 6.4 L/min and this is high relative to sex and body weight. After 2 years of DBS treatment, her pulse pressure and heart rates have not changed appreciably, suggesting her cardiac output is still high and that DBS treatment has not reduced cardiac function. Although MSNA to the vasculature decreased substantially, this does not necessarily inform cardiac sympathetic drive, which may be elevated in this patient. It is possible that there is an organ-specific effect of DBS on sympathetic outflow and that high cardiac sympathetic activity is contributing to her increased heart rate.

With such high BP, it is remarkable that her end-organ damage is limited to mild left ventricular hypertrophy. One possibility for this apparent contradiction would be severe constrictions of the main conduit arteries that could be protecting her organs. Although there is no evidence of vessel narrowing or increased vessel tortuosity as gleaned from cerebral angiography or funduscopic examination, conduit arteries supplying her visceral organs have not been directly examined. Malformations in the renal artery during the RDN procedure were not reported.

We conclude that this case report is the first to suggest that DBS is safe and helpful in reducing BP in a patient with...
severe refractory hypertension in whom aggressive drug therapy, RDN, and chronic baroreceptor stimulation were unsuccessful. Sympathetic vasoconstrictor drive was considerably decreased and is now comparable to sex- and age-matched normotensives. Therefore, we propose that DBS therapy should be systematically tested in patients with grade III, refractory hypertension not responding to existing drug and device therapies. Although the patient is not normotensive by clinical guidelines, this treatment represents a valuable improvement to the patient’s health and significant reduction in antihypertensive medication and cardiovascular risk.

**Audience Responses**

Professor Dominiczak: I am not persuaded by the argument that she needs this pressure to perfuse her organs. In that case, we would have seen many patients of that type and we do not. There is something really unusual.

I think, Professor Luft is going to say this but before he comes, can I ask, you have not shown us any pictures, detailed brain architectures, MRIs etcetera. Was there anything abnormal in this brain to drive this BP?

Dr Patel: She had a preexisting MRI brain scan in Germany before implantation of the carotid sinus stimulating system, which looked unremarkable with very little small-vessel disease change. This preexisting MRI was used for targeting the periaqueductal gray because we could not get another MRI scan, which was contraindicated in view of her implanted Rhes system. A computed tomographic scan was obtained before surgery, which aligned perfectly with the previous MRI, revealing no change in cytoarchitecture or anything to suggest multiple end-organ damage.

Professor Lindholm: I am fascinated, of course, by your story here about this patient. Could you tell us a little more about this lady? Apparently, she is a skinny lady with 4 kids going about life just as any ordinary person. Is there anything else? I mean, you must know a lot about her. How can she cope with this BP?

Dr O’Callaghan: That is exactly what we would like to know as well.

Professor Lindholm: I mean, is not there anything, it is just headaches, of course intermittent headaches, but nothing else?

Dr Patel: She had a history of presumed epilepsy; however, we are wondering whether this was related to a syncopal phenomenon, without obvious transient ischemic attack–related events. She was incapacitated regularly and usually every month, with periods where she could not function, mainly because of these headaches.

She was also on regular medication for angina, but did not suffer any significant bouts of chest pain. When she made contact with me by email, on seeing the complexity of this case, my first instinct was to run in the opposite direction!

Dr Roush: What is the correlation between the level of sympathetic nerve activity and the expected BP? Is it high? Are there data correlating these two variables?

Dr O’Callaghan: It is difficult in premenopausal women, where it is not so correlated. But in postmenopausal women, such as our patient and in men, there is a correlation between high sympathetic activity and higher BPs but we do not have a huge understanding yet of the causative role.

Dr Roush: Sure, but I assume that the BP is much higher than one would have expected for that level or nerve activity.

Dr O’Callaghan: Yes. Yes, it is, absolutely.

Professor Jennings: But just on that, we do see people with other disorders who are normotensive such as panic disorder, some people with heart failure who have got this kind of burst frequency so it is not a direct relationship.

Professor Luft: This lady was under our care when she was in the Berlin area for several years and then when Jens Jordan and Christoph Schroder moved to Hannover, they took over her care there. There are several remarkable things: at these kinds of pressures, her sympathetic nerve activity ought to be zero. And that is not zero at all. She had MR angiography as I recall looking at for a putative neurovascular contact syndrome at the rostroventral medulla and that did not seem to be the case.

She reminds me of the genetic hypertension that we are studying that is caused by mutations in phosphodiesterase 3A because these people also have normal sympathetic nerve activity at profound BPs and they also have no target organ damage. They die of stroke, presumably, cerebral hemorrhage although we do not know that for certain because we did not have an opportunity to study that since they respond to medications. It takes three classes but they do respond to medications.

One comment and a question, I think it might be worth asking, and I am sure she would allow this. We never gathered cells from her. If she would undergo a fat biopsy, we could culture mesenchymal stem cells and convert these to vascular smooth muscle cells and look to see whether the pathways are somewhat similar to what we found in this genetic form of hypertension.

My question is, would bilateral stimulation be perhaps more effective because it looks like you are about halfway there?

Dr Patel: It is a good question. We do know that with unilateral stimulation of the periaqueductal gray, you will get bilateral effects and the stimulation will spread across the midline. I think the potential risk of putting two electrodes in the periaqueductal gray bilaterally outweighs trying to capture more changes in BP.

I still feel we have maneuver and room for further programming and stimulation setting change to try and enhance the BP effect that she has sustained to date. Throughout she is being fairly adamant that she does not want any further anti-hypertensive therapy reintroduced, which is also likely to be adjunctive in lowering her BP further, primarily as she felt that the side effects were intolerable.

Professor Zucker: One way you can get increases in sympathetic nerve activity in the face of high BP is by enhanced input from excitatory inputs from the periphery. We have a study that we are showing this afternoon in spontaneously hypertensive rats, showing that ablation of dorsal root ganglia afferents in the thoracic region can reduce BP. You mentioned that she had angina. I wonder whether there were any other pain syndromes that could be driving the increase in BP even if there was not a conscious awareness of pain and the second comment is whether or not the DBS is activating vagal pathways such as would occur for vagal stimulation for depression.
or Parkinsonism? Do you have any further insight, since you did microneurography, you probably did things like cold pressor tests and Valsalva maneuvers to evaluate those 2 arms of the regulatory pathways for sympathoexcitation?

Dr O’Callaghan: We did not do those regulatory tests; we did not feel comfortable with it given her high pressures. But she did undergo a Valsalva maneuver and pharmacological baroreflex testing, conducted previously by the specialist hypertensive team in Berlin. And, impressively, her baroreflex control of BP was still intact although set to a much higher level.

Dr Zucker: Really?

Dr O’Callaghan: Yes, it is surprising. Regarding DBS activation of vagal pathways, we do know from animal studies that there are neural projections from the ventrolateral periaqueductal gray to cardiac preganglionic neurons and activation of the ventrolateral periaqueductal gray can facilitate the arterial baroreflex. So, we assume that there could be cardiac parasympathetic and baroreflex modulation by DBS of this region, but we have not analyzed it specifically in this patient.

Professor Dominiczak: I think this is an incredible case and we are really, really keen to publish it with all your comments because I think that will be something that will stay in the literature and will be referred to for years to come as a case of extreme hypertension. It is more than resistant, it is sort of super resistant hypertension.

Professor Jennings: I have just got one last question for the audience. How many of you are ready for a randomized control trial?

Professor Dominiczak: Nobody wants to do, oh yes, there is one, two. Okay. We are not very brave, clearly, not very brave.

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