Deep Brain Stimulation Lowers Blood Pressure in Extreme Case of Drug And Device Resistant Hypertension

Erin O'Callaghan, BBiomedSci (Hons), Ph.D
Senior Research Associate, School of Physiology, Pharmacology and Neuroscience, University of Bristol, UK (pictured left)

Nikunj Patel, BSC, MBBS, MD, FRCS (SN)
Consultant Neurosurgeon, Southmead Hospital North Bristol NHS Trust Honorary Senior Clinical Lecturer, School of Clinical Sciences, University of Bristol, UK (pictured right)

What is the highest blood pressure (BP) you've ever seen in a patient? Was this patient alert and coherent? You may be as shocked as we were to observe blood pressure readings in excess of 300/170 mmHg (clinic aneroid manometer and finger plethysmography), despite taking 8 antihypertensive medications, receiving chronic baroreflex activation therapy (BAT)(RheoTM, CVRx, MN, USA) and having undergone bilateral renal nerve ablation.

This slim, 54 year old female patient was attending our clinic in Bristol from her home in Germany, in May 2012, for medical and physiological screening in preparation for undergoing the first ever elective Deep Brain Stimulation (DBS) procedure for the indication of hypertension.

She had, for the past 10 years, been treated by internationally renowned hypertension specialists at both the Hannover Medical School and Experimental and Clinical Research Center, Charité Berlin-Buch, and who had provided details of her extensive treatment, meticulous exclusion of secondary causes and last recorded her BP as 280/130 mmHg measured by an intra-arterial line (Schroeder C et al., 2013).

This patient had run out of options. Her lucid behaviour at our first meeting belied the severity of her symptoms. A slim, previously active, mother of 4, was now regularly suffering from debilitating malaise and severe migraines 1-3 times each month. She was also cognisant of the increased risk of stroke, cardiac and renal failure that she faced. Desperate for treatment, she first contacted Mr Patel directly after finding his contact details online.

Remarkably, whilst conducting her own internet searches for new treatments of hypertension, she found reference to Mr Patel's 2011 publication of a case where he prescribed DBS for intractable neuropathic pain in a resistant hypertensive patient, which subsequently resolved that patient's hypertension (such that medication was withdrawn) independent of analgesic effects (Patel NK et al., 2011). Excited by the potential of DBS, she emailed Mr Patel directly, asking him to consider treating her with this technique.

DBS is an established neurosurgical treatment for psychiatric disorders including Parkinson's disease and intractable neuropathic pain. It has been used in >100,000 patients to date and occurrence of SAEs at North Bristol NHS Trust Hospital is less than 0.3 %, most of which are asymptomatic hemorrhagic stroke. In Bristol, Mr Patel and his team use a state-of-the-art, robot-assisted (Renishaw pic, UK) MRI-guided stereotactic technique to implant a thin stimulating electrode precisely into a pre-selected, pre-surgically mapped brain region.

We targeted a brain region called the ventrolateral periaqueductal grey (vIPAG). In humans, acute decreases in BP have been observed in patients receiving DBS of the vIPAG for treatment of intractable, neuropathic pain.

We know from animal studies that this region is involved in the coordination of motor outputs to mediate a survival instinct consistent with ‘playing dead’ to a perceived threat. As such, activation of the vIPAG in animals (feline and rodent species) causes potent analgesia, bradycardia and peripheral vasodilation lowering BP. Whilst the direct mechanism is yet to be discovered, significant evidence suggests that the vIPAG could be directly inhibiting sympathetic neurons that innervate the heart and peripheral vasculature.
There is also new evidence suggesting the vIPAG can increase the sensitivity of the baroreceptor reflex, which may also have an anti-hypertensive effect by a long term lowering of the arterial pressure set point (for a review see O’Callaghan EL et al., 2014).

When we first brought our patient into clinic, we measured her muscle sympathetic nerve activity (a measure of sympathetic drive to the vasculature in the skeletal muscle bed) and found it to be abnormally high for her post-menopausal status and age and weight, notwithstanding the fact that sympathetic activity should be completely shut down with a BP of that magnitude. Whilst we are not convinced that this was the sole source of her extraordinarily high BP, we thought it was at least contributing to maintaining a high BP and, consistent with our understanding of vIPAG in lowering blood pressure, she would benefit from undergoing this procedure.

In July 2013, our patient underwent surgical implantation of a DBS electrode into the vIPAG. She recovered from surgery without complications. DBS was switched on 4 days after surgery and her BP (intra-arterial line) dropped from 205/130 mmHg to 170/109 mmHg during the day and dipped to 119-77 mmHg overnight. Whilst her daytime BP was still above recommended guidelines (140/90 mmHg) she said she felt lethargic, so her antihypertensive medications were removed with the exception of clonidine and her BP remained low.

During our regular follow up appointments with the patient, we measured her MSNA and found it reduced considerably over the first year of DBS and stabilised 40% lower than pre-DBS levels (Figure 1). After 2 years of DBS, it is maintained at 225/142 mmHg (ABPM), a level substantially lower than that we recorded pre-DBS.

**Figure 1 (below):**

*Blood pressure and MSNA remain decreased with long term DBS therapy. Weekly averages of evening systolic and diastolic BP and heart rate recordings from the patient’s home BP diary over a 4 year period pre- and post- DBS therapy. The timeline of the patient’s regime of anti-hypertensive 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. Patient underwent surgery for prolapsed uterus in October 2013. Data are mean ± SD.*

BAT, bilateral baroreflex activation therapy; DBP, diastolic blood pressure; DBS, deep brain stimulation; HR, heart rate; MSNA, muscle sympathetic nerve activity; RDN, renal nerve ablation; SBP, systolic blood pressure; WDE, whole drug equivalents.

![Graph showing blood pressure and MSNA levels over time with medication and device timelines](image)

Whilst we cannot be precise in the magnitude of the reduction in our patient’s blood pressure, since the year before undergoing DBS her systolic blood pressures exceeded that which could be measured by a standard oscillometric device and ABPM, we are confident that before DBS it regularly exceeded 270 mmHg and likely fluctuated up to 330 mmHg. Thus, the patient, now taking only 1 antihypertensive medication per day with continual and combined BAT and DBS has decreased her BP from between 45-125 mmHg.
She has told us that she feels in much better health (probably also because of the reduction in daily medications), so much so that she even took up horse riding again, a hobby that she had missed during her years suffering from the debilitating side effects of extremely high BP.

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. She was described as both drug- and device-resistant. However, whilst her blood pressure remains pathologically high, DBS has made a quantitative and qualitative improvement to the patient’s health. Given that the patient’s BP remains high despite normal range MSNA, it is clear that other factors are contributing to her hypertension, at which we can only speculate.

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.

This case, ‘Chronic Deep Brain Stimulation Decreases Blood Pressure and Sympathetic Nerve Activity in a Drug and Device Resistant Hypertensive Patient’ is published in the CPC sessions of the January edition of Hypertension. It was led by Mr Nik Patel of North Bristol NHS Trust Hospital with assistance from Erin L. O’Callaghan, Emma C. Hart and Julian F.R. Paton (University of Bristol, UK), Amy E. Burchell, Angus K. Nightingale (University Hospital Bristol, UK), Hugh Sims-Williams, Shazia Javed and Mark Papouchado (North Bristol NHS Trust Hospital, UK) and with the support of her physicians in Germany, Jens Tank, Karsten Heusser, Jens Jordan, Jan Menne and Hermann Haller (Hannover Medical School, Germany). The case was funded by the Severnside Alliance for Translational Research (SARTRE) and British Heart Foundation.

REFERENCES:


- Erin O’Callaghan and Nik Patel

India Certificate Course in Management of Hypertension

An initiative supported by the ISH

CCMH is a ten month course with once- a- month contact sessions, being conducted on a designated weekend at 25 regional training centers across India. The education grant for the program has been provided by Sun Pharma Laboratories Limited.

The program includes a core team of 11 National Experts, 25 Regional Faculty and 28 Observers. The course has received an overwhelming response and over 600 primary care physicians have been enrolled for its first cycle against the initial target of 375. The program was launched on 24th July 2016 across all its centres in India.

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