Functional Neurosurgery Resident Award: Controlling the Cardiovascular System with Deep Brain Stimulation

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INTRODUCTION

The *defense* reaction in the rat is an integrated response that is associated with survival in the wild. For example, if escape from danger is *possible*, the response involves a "fight or flight" reaction that includes raised blood pressure (BP) and heart rate, non-opioid-mediated analgesia, and emotional effects, such as fear.[6,30] Conversely, if escape is *not possible* and it is safer to remain undetected, the reaction consists of lowered BP, opioid-mediated analgesia, and "freezing" behavior, as well as fear.[13,22] Other components of the defense reaction include vocalization, pupillary changes, micturition, and changes in skeletal blood flow.[38] It has long been known that an important area involved in the *defense* reaction is the periaqueductal gray matter (PAG). This area is organized into longitudinal columns that are functionally distinct and opposite.[7] Activation of the dorsomedial and dorsolateral columns evokes the "fight or flight" response, and activation of the lateral and ventrolateral columns produces the passive coping responses.[3]

On the basis of this knowledge, is it possible to use electrical stimulation of the periventricular gray (PVG)/PAG to control essential hypertension? The anatomic pathways exist. For example, serotonergic and adrenergic sympathetic pathways project to the rostroventromedial medulla,[5,12] the rostroventrolateral medulla (RVLM), locus coeruleus,[11] pontobulbar reticular formation,[32] among others. PAG neurons also project to cardiac vagal preganglionic neurons in the nucleus ambiguus, dorsal motor vagal nucleus, and the nucleus of the tractus solitarius.[11] Evidence in animals shows that stimulating these pathways in non-pain conditions reduces BP in the short term.[26] Although this has not yet been shown with chronic stimulation, mathematical evidence suggests that it is possible.[16]

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INTRAOPERATIVE PVG STIMULATION

The PVG is the most medial part of the hypothalamus and is rostral and continuous with the PAG. These nuclei have long been known to have an important role in the modulation of pain.[31] Indeed, we routinely implant electrodes into the rostral PAG/PVG to treat chronic neuropathic pain. Thus, we have an opportunity to study the effects of deep brain stimulation of this area on the cardiovascular system. Young[42] first noticed that intraoperative stimulation of the PVG produces cardiovascular effects including "lability" of BP. In fact, he used this effect to help with intraoperative electrode localization. We have noticed similar intraoperative effects, as the following case example demonstrates: a 61-year-old man with hypertension presented with intractable neuropathic pain involving the right side of his soft palate and oral cavity, of unknown origin. Despite a range of treatments, including motor cortex stimulation, he had not experienced any pain relief. We implanted an electrical stimulator into his PVG/PAG while he was awake, and continuously recorded arterial BP and heart rate. During a typical procedure, we stimulate at several target sites (along the same track) to find the location with the best pain relief. At the upper (most rostral) target, electrical stimulation produced hypotension (*Fig. 37.1A*). This was reproduced three times. When the electrode was advanced by 3 mm, the same stimulation produced hypertension (*Fig. 37.1B*). On the basis of our knowledge of the defense reaction in the rat, it is likely that the first, more rostral target stimulated was *ventral* PVG/PAG, whereas the deeper target was *dorsal* PAG. This is because the angle of approach of the electrode is through the frontal lobe at approximately 45 degrees. Interestingly, postoperatively, the best pain relief was achieved using the part of the electrode that reduced BP. A second electrode, implanted in the sensory thalamus, had no effect on BP, but did provide good analgesia. These results suggest that pain relief provided by PAG/PVG stimulation is part of the passive coping defense reaction, and would suggest that it is probably opioid mediated. Clinical evidence that supports this hypothesis is

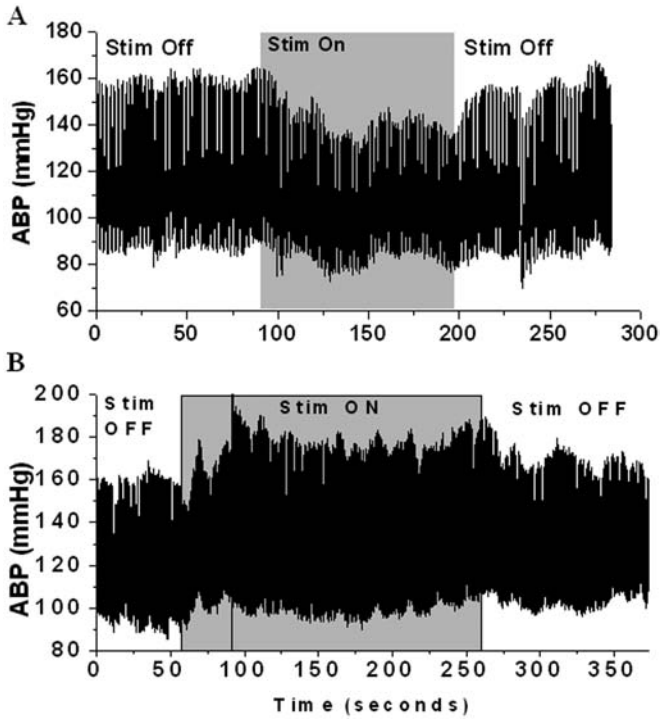

FIGURE 37.1 *A,* reduction of intra-arterial BP with intraoperative stimulation of the rostral PVG. When the electrode was advanced 3 mm, the BP increased with stimulation (*B*). ABP, arterial BP; stim, stimulation.

that the taking of opioid medication affects the response of pain to deep brain stimulation.[19]

LABORATORY-BASED PVG STIMULATION

To assess cardiovascular effects of PVG/PAG stimulation, we performed a study in 15 patients (12 men, 3 women, mean age 51.3 years; *Table 37.1*). Our methods are described in detail elsewhere.[17] In brief, we altered stimulation parameters in the laboratory while simultaneously recording finger arterial BP (Finapres) and three-lead electrocardiogram. We found that, of the 15 patients with PVG/PAG electrodes (2 bilateral electrodes), 5 patients had episodes of significant decreases in BP (5 electrodes), 4 patients had significantly increased BP (4 electrodes), and 2 patients had episodes of both (2 electrodes). Stimulation of the four remaining PVG patients (six electrodes) and six control electrodes caused no significant changes.

REDUCTION OF BP

Figure 37.2 shows the composite data from all seven patients in whom systolic BP (SBP) dropped significantly after the onset of stimulation, without significant changes in pain severity. The average reduction in SBP was 14.2 ± 3.6 mmHg ($P < 0.001$; single-factor analysis of variance [ANOVA]; n = 7; range of reduction, 7–25 mmHg), equivalent to 13.9%, at the end of a 400-second period in which stimulation was started at 100 seconds. The mean *latency*, i.e., the time from initiation of stimulation to the maximum fall in SBP was 160 ± 29 seconds, although there was a considerable range between subjects (34–214 s). It is also worth noting that there was a much shorter time between stimulation onset and the initial change in SBP (mean, 24 ± 8 s). *Figure 37.2* shows that when stimulation was turned off, the latency was much shorter (mean, 48 ± 23 s), and the time between turning off the stimulus and initial change in SBP was even shorter (mean, 6 ± 4 s). In all seven patients, the stimulation parameters required to drop BP were 10 Hz, with a pulse width of 120 μs and a voltage range from 0.6 V to 3.0 V (equivalent to a current of 0.6–3 mA). In three patients, 50 Hz had a similar effect. However, note that not all possible frequencies were tested.

Figure 37.2 shows that the drop in SBP is accompanied by a fall in diastolic BP (DBP) of 4.9 mmHg ± 2.9 ($P = 0.03$; single-factor ANOVA; n = 7; range, 1.5–9.3), equivalent to 6%. This implies a degree of peripheral vasodilatation. However, because the SBP drops more than the DBP (leading to a reduction in pulse pressure), the mechanism is unlikely to be related simply to peripheral vascular changes. We, therefore, measured the change of SBP with time (maximum dP/dt, i.e., the slope of the BP curve). This is known to be a marker of cardiac contractility,[4] because the harder the myocardium contracts, the steeper the slope of this curve. This revealed a mean reduction of 222 ± 126 mmHg/s (19.8%; $P = 0.06$). This suggests, but is not absolute proof, that the contractility of the myocardium was reduced. On the other hand, the R-R interval (a measure of heart rate) did not change significantly throughout the stimulation period (mean change, 0.01 ± 0.04 s; range, 0–0.08). Because heart rate is controlled via the vagal nerve, this implies that there was no change in parasympathetic activity.

INCREASE OF BP

Six patients had episodes of a sustained increase in BP at or shortly after the onset of stimulation (*Fig. 37.3*). One of these patients was hypertensive. Two of these patients also had episodes of decreased BP when the lower contacts were stimulated; see above).

The mean rise in SBP was 16.73 ± 5.9 mmHg ($P < 0.001$; single-factor ANOVA; n = 6; range, 16–31 mmHg), equivalent to 16.4% at the end of a 400-second period in which stimulation was started at 100 seconds (however, the maximum rise of 22.23 mmHg occurred just before this; see *Fig. 37.3*). The mean *latency* was 230 ± 44 seconds (range, 48–289 s). As with reduction in BP, there was also a much shorter time between stimulation and initial rise in BP, of 8 ± 4 seconds.

TABLE 37.1. Demographics[a]

Patient	Age (yr)	Sex	Origin of pain	Deep brain stimulator location	Usual medication (omitted on day of testing)
1	50	M	Thalamic hemorrhage	Left PVG	None
2	39	M	Thalamic hemorrhage	Left PVG	None
3	53	M	Right brachial plexus injury 32 yr ago	Left PVG and VPL	None
4	39	M	Phantom limb (L arm)	Right PVG and VPL	50 mg Amitriptyline
5	71	M	Thalamic infarct	Left PVG	2.5 mg Bendroflumethiazide, od 50 mg Atenolol, od 50 mg Amitriptyline, od
6	34	F	Anesthesia dolorosa of right greater occipital nerve	Left PVG	Co-codamol Zopiclone
7	40	M	Postsurgical supraorbital pain	Right PVG and VPL	None
8	74	M	Thalamic hemorrhage	Right PVG	None
9	34	F	Spinal cord injury	Bilateral PVG	180 mg MST
10	60	M	Thalamic hemorrhage	Left PVG	None (undiagnosed)
11	59	M	Pontine hemorrhage	Right PVG and VPL	Co-codamol
12	56	F	Phantom limb (legs)	Bilateral PVG	Co-codamol
13	34	M	Posttraumatic head pain	Right PVG	Zopiclone
14	67	M	Cortical infarction	Right PVG	40 mg Frusemide, od 30 mg Nicorandil, bd 5 mg Amlodipine, od 0.4 mg Tamulosin HCL, od 30 mg ISMN, od 2 mg Perindopril, od
15	60	M	Thalamic hemorrhage	Right PVG	1.5 mg Indapamide SR, om 300 mg Irbesartan, om 20 mg Citalopram, om 100 mg Tramadol, om 10 mg Diazepam, om
Controls					
3	53	M	As above	VPL	As above
4	39	M	As above	VPL	As above
7	40	M	As above	VPL	As above
11	59	M	As above	VPL	As above
16	32	M	Essential tremor	Bilateral VIM	None
17	49	F	Failed back syndrome	Spinal cord	None

[a]VPL, ventroposterolateral nucleus (of the thalamus); od, once daily; MST, morphine sulphate; bd, twice daily; ISMN, isosorbibe mononitrate; om, everymorning; VIM, ventro intermedius nucleus of the thalamus.

Stimulation parameters required to raise BP were the same as with the episodes of reduced BP (i.e., 10 Hz, 120 μs, and up to 3.0 V), except that 50 Hz did not have the same effect in any patient. As with BP reduction, increases were accompanied by a smaller rise in DBP of 4.9 $\pm$ 2.8 mmHg or 6.4% ($P = 0.04$; single-factor ANOVA; n = 6; range, 2.4 to 12.1 mmHg). There was also an increase in mean pulse pressure and, again, the maximum rise of 17.33 mmHg occurred just before 400 seconds. Maximum dP/dt increased by 212 $\pm$ 97 mmHg/s ($P < 0.03$; single-factor ANOVA). As with reduction in BP, there was no significant change in the R-R interval. Thus, it seems that increasing BP is accompanied by a mirror of the changes that occur during reduction in BP.

CONTROLS AND ELECTRODES THAT HAD NO EFFECT

Six control patients were investigated (six thalamic electrodes, one spinal cord stimulator). Despite extensive investigation using a variety of frequencies and voltages, as

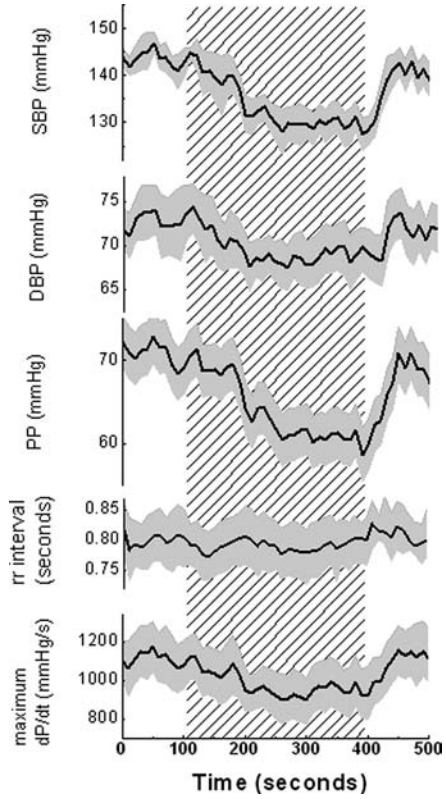

FIGURE 37.2 Changes in cardiovascular parameters associated with reduced BP. Patterned area, period of stimulation; Gray area, ± one standard error of the mean; PP, pulse pressure; R-R interval, time period between R waves on electrocardiogram; dP/dt, change of SBP with time (see text for details).

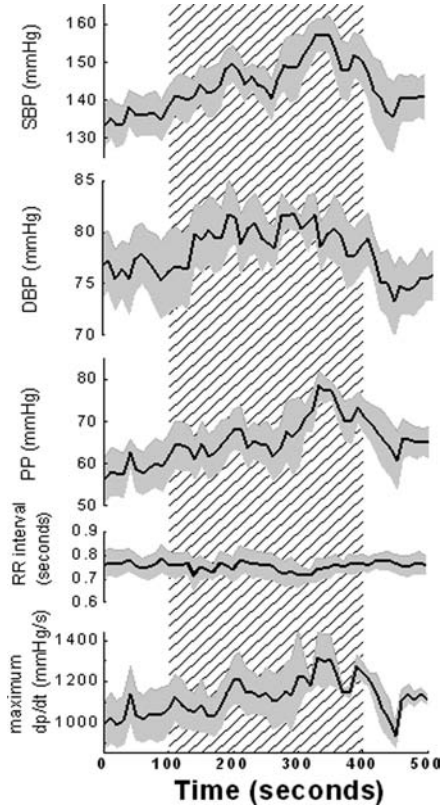

FIGURE 37.3 Changes in cardiovascular parameters associated with increased BP. Patterned area, period of stimulation; Gray area, ± one standard error of the mean; PP, pulse pressure; R-R interval, time period between R waves on electrocardiogram; dP/dt, change of SBP with time (see text for details).

well as a variety of electrode contact configurations, we were unable to modulate the BP in any of these patients.

In addition to the control electrodes that had no effect on BP, four patients with PVG electrodes (six electrodes in total) also had no effect.

POWER SPECTRAL ANALYSIS OF SBP

It is possible to elucidate underlying mechanisms of BP changes by looking at the dominant frequencies in the BP waveform.[33] For example, if the respiratory frequency is constant, there is often a peak at 0.25 Hz (corresponding to a respiratory rate of one breath every 4 s). Similarly, activity in the range just under 0.1 Hz is associated with activity of the sympathetic nervous system—a wave known as Meyer's wave.[14,35] We, therefore, performed *autoregressive power spectral analysis* of the BP waveform in all patients. Frequencies below 0.02 Hz were filtered out to remove the trend in the signal (see[40] for methodology). *Figure 37.4A* shows a typical example in a patient whose BP could be increased or decreased depending on which contacts were used. It can be seen that with an increase in BP, there was a large increase in the low-frequency wave in the 0.1 Hz region. With a reduction in BP, there was a corresponding decrease. This implies that increase in BP is associated with an increase in sympathetic activity, and vice versa.

To look at the group results, we calculated the power of the low- and high-frequency components as the integral of the power spectra between 0.05 and 0.15 Hz and between 0.15 and 0.4 Hz. The logarithm of the low- and high-frequency power for the two groups of patients (BP increase or decrease) on and off stimulation were analyzed using a paired *t* test (*Fig. 37.4C, D*). This revealed that, for the group as a whole, there was a change in low-frequency power spectra that corresponded to BP changes. There were also changes in high-frequency power, but these were not significant (this may be because of low numbers).

ELECTRODE POSITION

Episodes of decreases or increases in BP were consistent for any particular pair of electrode contacts that were stimulated. For this reason, and because BP changes in animals depend on

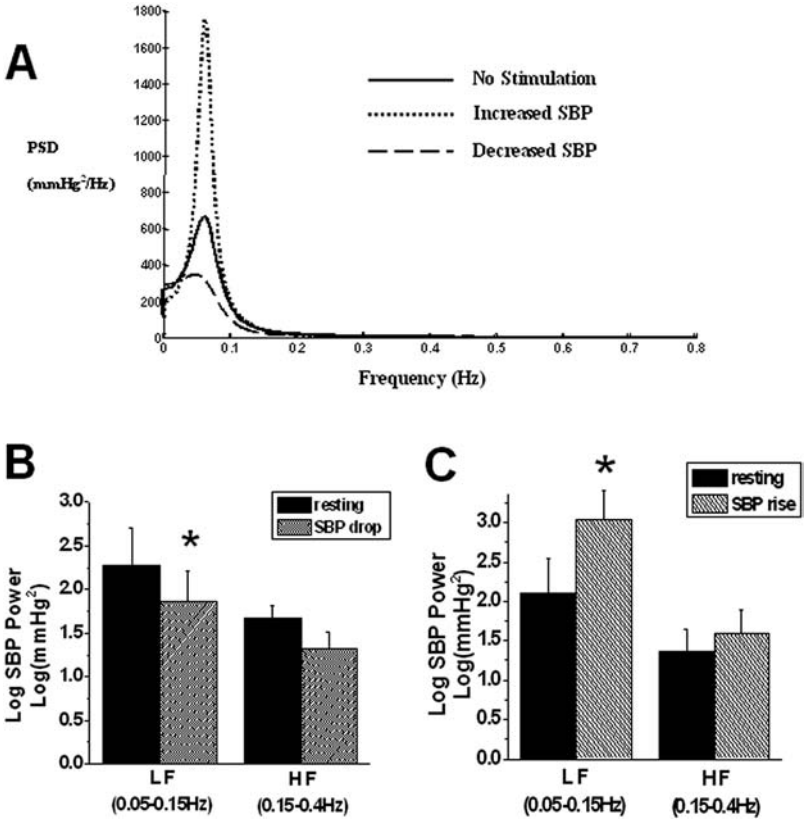

FIGURE 37.4 Changes in low- and high-frequency power spectra of SBP. *A*, example in one patient, in whom BP could be increased or decreased, depending on which contacts were used. A change in the low frequency component was associated with change in BP, implying changes in sympathetic nervous system activity. *B* and *C*, changes for the groups in whom BP decreased (n = 7) or increased (n = 6), respectively. Error bars denote ± one standard error of the means (SEM). *$P < 0.05$, two-tailed, *t* test. PSD, power spectral density; LF, low frequency; HF, high frequency.

whether the electrode is in ventral or dorsal PAG, we looked at electrode position in our patients. The electrode positions were plotted on a brain atlas[28] using the postoperative magnetic resonance imaging (MRI) scan and a manipulation program (MRIcro version 1.38 build 1; Chris Rorden). First, the scan was rotated such that the anterior commissure (AC) and posterior commissure (PC) were on the same slice. The mid-commissural point was then calculated, followed by the position, relative to the AC and PC, of the electrode contacts. The contacts are visible, circular thickenings in the low signal on the axial scan (*Fig. 37.5*). The center of each contact was taken as the position of the electrode, and this corresponds to the center of the contacts in *Fig. 37.6*. Using the coronal and sagittal scans, the angles of the electrode to the midline and AC-PC line, respectively, were calculated. Once plotted on the brain atlas, the relative position of the lowest contact to the posterior wall of the superior colliculus was verified, as was the relative position of the upper electrode to the mid-commissural point. As a further verification, the relative positions of the electrodes from all patients were compared, to exclude inconsistencies among the groups.

The results are shown in *Fig. 37.6*. This shows that those electrodes that reduced BP were placed ventrally, as compared with the dorsal electrodes that increased BP. Patients with no BP changes are not shown, for clarity. However, we plotted electrode positions for five of these six electrodes (one had not had a postoperative scan). Four of the five electrodes were dorsal to the group that raised BP and were, therefore, probably outside the PAG/PVG. The remaining electrode was in mid-PVG.

STATISTICAL COMPARISON OF VENTRAL VERSUS DORSAL ELECTRODES

Changes in BP were compared between the two groups of ventral and dorsal electrodes (n = 8 and n = 9 respectively; unlike the changes described above, this included all patients, even those without significant changes in BP). The mean peak change in SBP was -10.3 ± 2.8 mmHg for the ventral group and +10.8 ± 3.1 mmHg for the dorsal group. Comparison using one-way ANOVA showed significance ($P = 0.003$). Similarly, the mean peak change in DBP was −4.6 ± 1.2 mmHg and 3.5 ± 0.8 mmHg, respectively ($P = 0.007$). Mean peak change in pulse pressure ranged from −8.6 ± 3.5 mmHg for the ventral and 7.4 ± 2.1 mmHg for the dorsal group ($P = 0.01$). dP/dt ranged from −181.6 ± 28 mmHg/s for ventral and 82 ± 26 mmHg/s for dorsal electrodes ($P = 0.007$). Comparison of R-R interval between the two groups did not reveal any significant difference ($P = 0.13$).

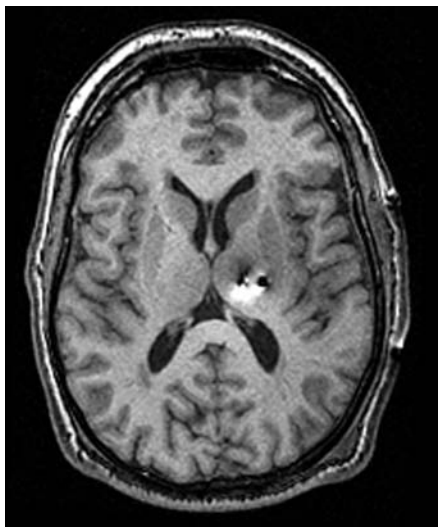

FIGURE 37.5 Postoperative MRI. This T2-weighted MRI scan shows the contact visible as a circular low density in the sensory thalamus (laterally). The wire leading to the lower PVG electrode can be seen medially.

DISCUSSION

We have shown for the first time in awake humans that electrical stimulation of the PVG/PAG can influence arterial BP and that there is a functional localization whereby ventral stimulation has a depressor effect and dorsal stimulation has a pressor effect. Furthermore, the electrically induced BP modulation is frequency dependent, working most often at 10 Hz and sometimes at 50 Hz.

As early as 1935, Kabat showed that PAG stimulation influenced BP in the cat.[23] It later emerged that the PAG is organized into four longitudinal columns.[2,6–8] Stimulation of the dorsomedial and dorsolateral columns produces an increase in BP, whereas stimulation of the lateral and ventrolateral columns produces hypotension and freezing behavior.[1,6,10,25–27]

In the human, there is some evidence that stimulation of deep brain nuclei, such as the subthalamic nucleus, can influence the cardiovascular system.[36,37,41] However, to date, there have been no such reports related to the PVG/PAG. This is the first study to directly investigate the role of this region in the human. We have found that ventral stimulation at 10 Hz can have a consistent depressor response, whereas dorsal stimulation can have a pressor response. The decrease or increase of BP was consistently found when repetitive stimulation was applied. The response was repeatable on different days, and similar patterns of changes were found under different recording conditions (i.e., laboratory based and intraoperative). We also found that similar electrode locations have a similar response to stimulation. As well as changes in SBP, we have found analogous changes in DBP, pulse pressure, and maximum dP/dt, but no change in the R-R interval. This suggests that the changes are elicited by a mixture of altered myocardial contractility (change in dP/dt) and a change in total peripheral resistance (changes in pulse pressure). In turn, this implies that the changes are caused by an altered sympathetic activity, with little or no change in parasympathetic activity. This is further corroborated by the power spectra of SBP, which show a change in the low-frequency component, implying a change in sympathetic activity, i.e., the spectral estimate of Mayer's wave.[14,34,35]

There are, however, some important differences between our findings and those in animals. For example, the latency between stimulus and peak response in animals has been consistently reported at approximately 5 to 20 seconds.[1,18,23,24] We found much longer latencies to peak effect, in the order of minutes, rather than seconds. A second difference is that we

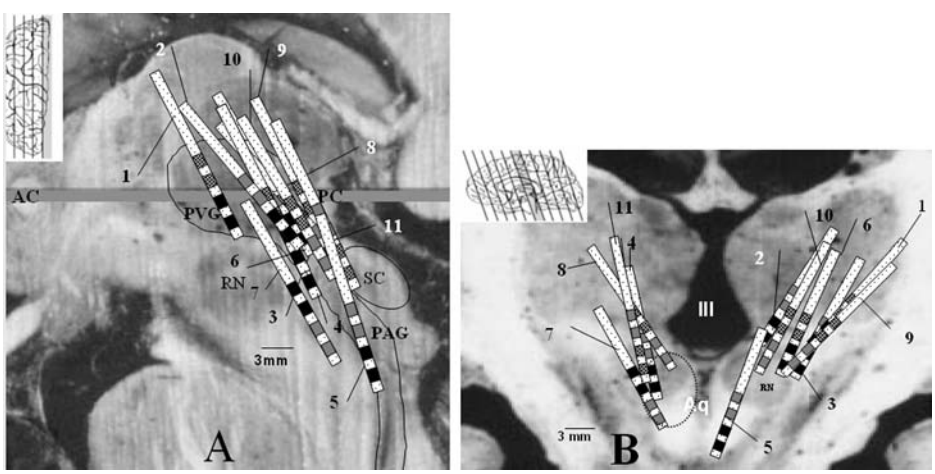

FIGURE 37.6 *A*, sagittal positions of the electrodes in patients in whom there were changes in BP. *B*, coronal positions. For clarity, patients with no changes are not shown. Note that Patients 1 to 7 all had reduction in BP (black contacts) and are the most ventral electrodes. Conversely, Patients 8 to 11 and the upper two contacts of patients 1 and 6 had a rise in BP (patterned contacts). Gray contacts are those that, when stimulated, had no effect on BP. SC, superior colliculus (the level of which is depicted by the dotted circle in *B*); RN, red nucleus; III, third ventricle; Aq, aqueduct. Inset of *A* shows the AC-PC plane, inset of *B* shows the slice position.

found no significant change in R-R interval with stimulation. This may, in fact, be the reason why our latencies are so much longer. It would seem that we are altering BP by a nonvagal, i.e., a sympathetic, pathway that takes longer to exert its effect. Anatomic substrates for this sympathetic pathway have been demonstrated. For example, the ventrolateral PAG projects to the nucleus raphe magnus (NRM),[15] and PAG neurons are excited antidromically by NRM stimulation.[39] PAG also sends collaterals to the RVLM,[20] and serotonin receptor agonists applied to the RVLM produce hypotension.[29]

Other ways in which this study differs from animal experiments, which might explain the latency of response, include the fact that our subjects were awake, as opposed to the anesthetized, decerebrate animals that would not have had the influence of higher brain centers, such as prefrontal cortex that has been shown to inhibit cardiovascular responses in animals.[43] In addition, our methodology differs in that we stimulated continuously for several minutes, rather than giving a "pulse" of stimulation for 5 to 10 seconds.

Limitations of this study include the use of a finger plethysmograph that has been shown to have a bias of approximately 2 to 4 mmHg.[9] However, the Finapres has been shown to be reliable when looking at BP variability.[21] We have attempted to verify the Finapres recordings by comparing them with an intra-arterial measurement in one patient. Note that the direction of the change in BP with stimulation was the same and the pattern of a gradual increase during stimulation and immediate recovery after stimulation was similar in these two conditions.

In summary, we have shown that electrical stimulation of different regions of the human PVG/PAG can selectively modulate BP, almost certainly via a sympathetic effect. These findings are important because demonstrating these changes in humans provides the "gold standard" by which future therapies can be targeted. In the future, perhaps hypertension or indeed postural hypotension may be controlled by manipulation of this area.

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