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Short communication

Switching on the deep brain stimulation: Effects on cardiovascular regulation and respiration ☆

S. Vigneri [a,*], P. Guaraldi [b], G. Calandra-Buonaura [b], R. Terlizzi [b], A. Cecere [b], G. Barletta [b], P. Cortelli [b]

[a] Department of Clinical Neurosciences, University of Palermo, Palermo, Italy
[b] Department of Neurological Sciences, University of Bologna, Bologna, Italy

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ABSTRACT

Background: Objective of this study was to evaluate the acute cardiovascular and respiratory effects of switching on the deep brain stimulation in the follow up of nine Parkinson's disease patients with subthalamic nucleus stimulation and six cluster headache patients with posterior hypothalamic area stimulation.
Methods: Systolic and diastolic blood pressure, heart rate, and respiratory rate were monitored continuously during supine rest in both groups. Each patient was assessed in two conditions: resting supine with stimulator off and with stimulator on.
Results: In supine resting condition switching on the DBS induced no significant changes ($p>0.05$) in systolic and diastolic blood pressure as well as in heart rate and respiratory rate, in both groups of patients, either taking 1 min or 10 heartbeats as a sample for analysis.
Conclusions: Switching on the DBS does not modify heart rate, blood pressure nor respiratory rate in both Parkinson and cluster headache patients under resting conditions.

1. Introduction

The subthalamic nucleus (STN) is a well known target area for DBS in PD, especially in patients with advanced stages poorly responsive to drug therapy (Kumar et al., 1998). The intra-operative stimulation of STN, and the acute effect of switching on the stimulator 6 months after the implantation, have been shown to produce, not only motor-related responses, but also autonomic responses both in animals and humans (mainly a conspicuous increase of heart rate) (Angyan and Angyan, 1999; Sauleau et al., 2005).

The posterior hypothalamic area (PHA) stereotactic DBS was proved to be a successful treatment for chronic drug-resistant cluster headache (CH) patients (Sano et al., 1970). The PHA is involved in the control of sleep–wake cycle (Lin et al., 1989), cardiovascular regulation (Martin et al., 1991) and the expression of defensive–aggressive behavior (Shekhar and DiMicco, 1987). Early experimental animal studies demonstrated that electrical or chemical stimulation of posterior hypothalamus increases respiration frequency, heart rate, arterial pressure and elicits a redistribution of organ blood flow similar to that occurring during voluntary exercise (Hess, 1969). More recent studies pointed at the posterior hypothalamus as an area that integrates information from contracting muscles with central command to generate the necessary responses to exercise (Waldrop and Stremel, 1989; Dampney et al., 2002). Few stimulation studies in humans are available. A previous study reported a rise in blood pressure, tachycardia and pupillary dilation while performing a therapeutic posterior hypothalamus stimulation in pathologically aggressive patients (Sano et al., 1970). The new application of PHA DBS for chronic drug-resistant CH patients has provided a new unique opportunity to study the role of this structure on cardiovascular autonomic regulation in humans (May et al., 1999). Another scientific work described polypnoea, tachycardia and moderate hypertension during the implantation procedure of one cluster headache patient with concomitant panic sensation (Schoenen et al., 2005). Although, no autonomic effects were reported by the Milano's group in patients undergoing intra-operative stimulation of posterior hypothalamic area up to 4 V (Franzini et al., 2003).

Stimulated by these discrepancies, although observed in different settings, having the opportunity to test both patients with PD and CH treated with DBS of STN and PHA respectively during their postoperative follow-up, we evaluated the acute effects on their cardiovascular system by switching on the stimulator.

2. Patients

Nine patients with PD (six males, mean age: 58.7 ± 9) with bilateral DBS of STN and six CH patients (five males, mean age: 36.2 ± 9.9) with

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* Corresponding author at: Department of Clinical Neurosciences, University of Palermo, Via Gaetano La Loggia 1, 90129, Palermo (PA), Italy. Tel.: +39 091 6555101; fax: +39 091 6555102.
E-mail address: simone.vigneri@gmail.com (S. Vigneri).

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monolateral DBS of PHA were enrolled in the study. The difference between the mean ages of the two groups was significant ($p<0.05$).

The patients' inclusion/exclusion criteria and the surgical technique were previously described (Broggi et al., 2003; Franzini et al., 2003; Leone et al., 2004; Machado et al., 2006). The accuracy of electrode placement was checked by means of a post stereotactic procedure MRI, while the voltage pulse width and the frequency of the stimulator were optimized for the best clinical results by the scientists from Gemelli Hospital (Rome, Italy) and Besta Institute (Milan, Italy) [Table 1].

3. Protocol

PD and CH patients were assessed in our Autonomic Unit 22 ± 22 months (range 1–35) and 2 ± 1 months (range 0.8–3.9) after implantation respectively.

All patients were evaluated in a temperature-controlled (23 ± 1 °C) clinical investigation room between 8 and 12 o'clock in the morning in two different conditions: 1) resting supine with stimulator off and 2) resting supine with stimulator on.

Before the assessment patients were allowed to drink water but otherwise fasted overnight. All had to abstain from smoking or drinking alcohol on the day before the study. For ethical reason patients were free to assume their usual medications with the exception of the morning they performed the autonomic tests. Patients were asked not to sleep or talk during the study.

Systolic and diastolic blood pressure (SBP, DBP; Portapres model 2, TNO-TPD Biomedical Instrumentation, Delft, the Netherlands), heart rate (HR; Grass 7P511 [Astro-Med West Warwick, RI, USA] and Light Work Station for digital R–R quantification), oronasal and abdominal breathing (Grass DC preamplifier 7P1) were monitored continuously. Data were initially acquired for 2 hours in off condition, then the stimulator was turned on and new acquisitions were obtained. All the participants were aware about the time when the stimulator was switched or whether it was switched on or off.

All patients gave their informed consent prior to their inclusion in the study and the research protocol was approved by the Institutional Review Board committees from the University of Bologna.

Data from the last minute in stimulator off were compared to the first minute with stimulator on and data from the last 10 heartbeats with stimulation off were compared to the 10 heartbeats with stimulator on by repeated-measures *t*-tests. The acute effects of switching on the DBS in PD versus CH patients were compared using the Bonferroni/Dunn test. A p value <0.05 was considered significant.

4. Results

In supine resting condition switching on the DBS induced no changes in systolic (SBP), diastolic (DBP), heart rate (HR: calculated as mean R–R intervals), and respiratory rate (RR).

After switching on the stimulator, no significant changes in SBP were observed in the PD and CH patients, neither considering the first minute or the first 10 heartbeats to the previous minute or 10 heartbeats respectively ($p>0.05$) [Table 2].

No significant differences were observed in DBP after switching on the DBS in the two groups, neither considering the first minute or the first 10 heartbeats as a sample for analysis ($p>0.05$) [Table 2].

Mean R–R intervals (RRI) during the first 10 beats or the first minute with stimulator on were not significantly different if compared to the previous 10 heartbeats or minute during stimulator off respectively, neither in the PD nor CH patients ($p>0.05$) [Table 2].

Finally within the first minute of stimulation there were no significative changes in RR in PD and CH patients ($p>0.05$) [Table 2].

5. Discussion

This study shows that in supine resting condition acute switching on the DBS in the follow up of Parkinson's and cluster headache patients does not affect significantly systolic and diastolic blood pressure, heart and respiratory rate in both groups either considering the first minute or the 10 heartbeats following the stimulation.

A previous study demonstrated a significant HR increase during the first 10 heartbeats after switching on the DBS in three PD patients, whereas BP and RR did not show any significant variation (Kaufmann et al., 2002). Nevertheless in this study patients were unaware of either the time when the stimulator was switched or whether it was switched on or off, and this discrepancy could represent the effect of an unspecific arousal, and not being due to the acute effect of DBS stimulation “per se.” In our experience, even if the patients are blind to the DBS status they can “feel” the exact moment in which the stimulator is switched on. Furthermore the small sample of patients and the lack of an adequate baseline monitoring represent important limitations of the above-mentioned study.

Furthermore a more recent work has shown that PD patients both in basal conditions and during DBS present different autonomic pattern of response according to the site of stimulation: patients who underwent stimulation of the dorsalmost region, produced changes in R–R intervals that were constant over time regardless of the patients' awareness. By contrast, the stimulation of the ventral region produced autonomic and emotional responses that were inconstant

Table 1
Details of PD and CH patients and their corresponding stimulator models, localization and set parameters.

Patients	Age	Sex	Stimulation	Model	Left side					Right side				
	Years				Amp (V)	Wide (Ms)	Freq (Hz)	Polarity	Mode	Amp (V)	Wide (Ms)	Freq (Hz)	Polarity	Mode
PD 1	52	M	Bilateral	Kinetra	2.40	60	185	el −0	Cont.	2.20	60	185	el −7	Cont.
PD 2	56	M	Bilateral	Kinetra	2.20	60	185	el −3	Cont.	2.20	60	185	el −6	Cont.
PD 3	44	F	Bilateral	Kinetra	2.85	60	195	el −1	Cont.	2.65	60	195	el −5	Cont.
PD 4	67	M	Bilateral	Kinetra	UNK	UNK	UNK	UNK	UNK	UNK	UNK	UNK	UNK	UNK
PD 5	53	F	Bilateral	Kinetra	UNK	UNK	UNK	UNK	UNK	UNK	UNK	UNK	UNK	UNK
PD 6	54	M	Bilateral	Kinetra	2.30	60	185	el −0	Cont.	2.60	60	185	el −4 −5	Cont.
PD 7	70	M	Bilateral	Kinetra	3.20	90	180	el −2	Cont.	3.00	90	180	el −6	Cont.
PD 8	66	F	Bilateral	Kinetra	2.70	60	160	el −0 −1	Cont.	2.70	60	160	el −4 −5	Cont.
PD 9	67	M	Bilateral	Kinetra	2.90	60	140	el −1	Cont.	2.95	60	140	el −5	Cont.
CH 1	30	M	Unilateral	Soletra 7426	1.3	60	185	UNK	Cont.	NA	NA	NA	NA	NA
CH 2	45	M	Unilateral	Soletra 7427	2.8	90	130	UNK	Cont.	NA	NA	NA	NA	NA
CH 3	27	F	Unilateral	Soletra 7428	1.6	90	180	C(+)−3(−)	Cont.	NA	NA	NA	NA	NA
CH 4	25	M	Unilateral	Soletra NFW625261	NA	NA	NA	NA	NA	2.1	60	185	C(+)−1(−)	Cont.
CH 5	43	M	Unilateral	Kinetra NFD624515	2.6	60	180	UNK	Cont.	NA	NA	NA	NA	NA
CH 6	47	M	Unilateral	Kinetra NFD624570	NA	NA	NA	NA	NA	1.8	60	180	C(+)−1(−)	Cont.

Amp: amplitude. CH: cluster headache. Cont.: continuous. el: electrode. Freq: frequency. NA: not applicable. PD: Parkinson disease. UNK: unknown data.

Table 2
Switching the stimulator on does not affect cardiovascular nor respiratory parameters in patients with Parkinson's disease and cluster headache.

			PD patients	CH patients
RRI	1 min	OFF (s)	0.868 ± 0.15	0.877 ± 0.07
		ON (s)	0.863 ± 0.15	0.846 ± 0.05
		OFF *vs.* ON *p*-value	NS	NS
	10 beats	OFF (s)	0.868 ± 0.15	0.883 ± 0.07
		ON (s)	0.870 ± 0.15	0.889 ± 0.08
		OFF *vs.* ON *p*-value	NS	NS
SBP	1 min	OFF (mmHg)	135 ± 14	119 ± 12
		ON (mmHg)	135 ± 17	119 ± 11
		OFF *vs.* ON *p*-value	NS	NS
	10 beats	OFF (mmHg)	135 ± 14	119 ± 12
		ON (mmHg)	135 ± 14	121 ± 11
		OFF *vs.* ON *p*-value	NS	NS
DBP	1 min	OFF (mmHg)	73 ± 8	65 ± 10
		ON (mmHg)	73 ± 9	65 ± 10
		OFF *vs.* ON *p*-value	NS	NS
	10 beats	OFF (mmHg)	73 ± 8	65 ± 10
		ON (mmHg)	73 ± 8	65 ± 9
		OFF *vs.* ON *p*-value	NS	NS
RR	1 min	OFF (breaths/m)	24 ± 6	18 ± 4
		ON (breaths/m)	23 ± 6	17 ± 4
		OFF *vs.* ON *p*-value	NS	NS
	10 beats	OFF (breaths/m)	NA	NA
		ON (breaths/m)	NA	NA
		OFF *vs.* ON *p*-value	NA	NA

DBP: diastolic blood pressure. mmHG: millimeters of mercury. NA: not applicable. NS: not significant. SBP: systolic blood pressure. RR: respiratory rate. RRI: r–r interval. s: seconds.

over time and different responses were elicited with hidden and open stimulations (Benedetti et al., 2004).

Possible confounders compared to prior studies must be taken in account; the intensity of stimulation may surely influence the autonomic responses by spreading the stimulus to nearby structures but even if in our Parkinson's patients the mean intensity (2.6 ± 0.3 V) was slightly higher than in Kauffmann's work (2.3 ± 0.5 V) we did not observe any change in heart rate; therefore it is unlikely that intensity influenced our results.

The finding of cardiovascular and autonomic responses following STN and the surrounding areas stimulation have been described both in animals (Angyan and Angyan, 1999) and humans (Priori et al., 2001); it seems to involve complex relationships between central and peripheral areas. The basal ganglia project to several nuclei that may modify autonomic outflow. High frequency stimulation has been proven to inhibit neuronal activity around the implanted electrodes and this effect on fibers and cell bodies does not allow to ascertain the neurons involved in the pattern (Beurrier et al., 2001) and, consequentially, the exact role of nearby structures on autonomic outflow.

With regard to the timing of post-implantation evaluation, a wider time interval between electrodes positioning and testing could be associated with a more serious neuronal degeneration and, consequentially, a blunted autonomic response. This could play a role in a long-term perspective, although, a previous work (Erola et al., 2006) evaluated Parkinson's patients after a shorter period than we did (i.e. 1 year) showing no autonomic function changes post-DBS; therefore it is unlikely that this factor may have affected our results.

Studies evaluating the effects of acute switching on of the deep brain stimulator in the follow-up of CH patients are missing. Previous intraoperative studies are limited and led to conflicting results, probably because of differences in both the targeting and the stimulation parameters (Franzini et al., 2003; Schoenen et al., 2005).

This study demonstrates for the first time that in supine resting condition, acute switching on of the DBS in the follow up of PD and CH patients does not affect significantly SBP, DBP, HR and RR in PD and CH patients, despite their different pathologies and stimulation site and technique, suggesting that the complex mechanisms that maintain autonomic parameters around the "set point" in basal condition are not affected in our patients.

Some unavoidable limitations of our study should be addressed: first we could not obtain information about ventral or dorsal placement of PD patients stimulator which could give rise to different autonomic responses after switching on the DBS; second, we could not ask the patients to withdraw their usual medication for ethical considerations, and this could have influenced the autonomic response; last, we cannot exclude a main direct primary disease or medication effect, affecting the results. Nevertheless, although theoretically possible, we did not observe any abnormality in autonomic control of cardiovascular reflexes in both groups of patients.

6. Conclusions

No significant change in heart rate, blood pressure nor respiratory rate was appreciated in both Parkinson and cluster headache patients after switching on the stimulator either considering 1 min or 10 heartbeats as a sample for analysis. A possible explanation could be that our patients were aware of either the time when the DBS was switched or whether it was turned on or off. Noteworthy, our patients were tested in supine resting conditions almost 2 years post implantation; this may explain the differences between our results and previous studies.

Conflict of interest statement

The authors have no financial interest to disclose.

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