Centrally Mediated Effects of Bromocriptine on Cardiac Sympathovagal Balance

Franco Franchi, Chiara Lazzeri, Giuseppe Barletta, Lucia Ianni, Massimo Mannelli

Abstract—Bromocriptine, a dopamine agonist, is known to lower cardiovascular mortality in L-dopa–treated patients with Parkinson’s disease, probably by reducing the cardiac sympathetic activity. We aimed at unmasking the central effects of bromocriptine on the heart by power spectrum analysis. Ten healthy subjects (aged 31 ± 2 years) in supine and sitting positions were evaluated after the administration of bromocriptine (2.5 mg) alone and after pharmacological peripheral D₂-like blockade by domperidone (20 mg). We calculated (autoregressive method) the following: the low-frequency (LF) component (an index of cardiac sympathetic tone), the high-frequency (HF) component (an index of cardiac vagal tone), and the LF/HF ratio (an index of cardiac sympathovagal balance). With subjects in the supine position, bromocriptine alone induced a significant increase in the LF component and the LF/HF ratio, together with a reduction in norepinephrine plasma levels and blood pressure values. These conflicting effects can be explained as the combined result of direct and indirect (reflex-mediated) actions of bromocriptine in vivo. No changes in cardiac autonomic drive were observed with subjects in the sitting position. After domperidone pretreatment, bromocriptine induced a reduction in the LF component and in the LF/HF ratio. The sitting position caused an increase in heart rate and in the LF/HF ratio. We demonstrated both peripheral and central effects of bromocriptine. In particular, pretreatment with a peripheral antagonist (domperidone) allowed us to unmask the central effect of bromocriptine on cardiac sympathetic drive. (Hypertension. 2001;38:123-129.)

Key Words: autonomic nervous system • sympathetic nervous system • dopamine • heart rate

Bromocriptine is a D₂-like receptor agonist that is known to inhibit sympathetic output and to lower the cardiovascular mortality in L-dopa–treated patients with Parkinson’s disease.1 The cardioprotective effect of bromocriptine can be related to a withdrawal of the cardiac sympathetic activity, which could diminish the risk of potentially lethal threatening ventricular arrhythmias. As a matter of fact, it has been shown in experimental animals that bromocriptine increases the ventricular fibrillation threshold by 50%2 and decreases plasma levels of catecholamines.3

Whereas peripheral actions of bromocriptine have been well elucidated not only under resting conditions4 but also in response to hemodynamic maneuvers,5–7 a centrally mediated reduction in sympathetic outflow has not been demonstrated so far.

With this in mind, the design of the present study was aimed at evaluating the effects of acute bromocriptine administration on cardiac sympathovagal balance by means of power spectral analysis. Taking into account that domperidone (DM) is a peripheral D₂-like receptor antagonist that is able to counteract the peripheral effects of bromocriptine,8,9 we analyzed the influence of preadministration of DM on the sympathovagal balance with subjects in supine and sitting positions to unmask the central activity of bromocriptine.

Methods

Subjects

Ten healthy nonsmoking volunteers (6 men and 4 women; mean age, 31 ± 2 years; range, 25 to 48 years) gave their informed written consent to participate in the present study, which was approved by the local ethics committee. No subject had any abnormal finding on history, physical examination, ECG, or echocardiogram, nor was any subject receiving any medication. Each subject was randomly given either oral bromocriptine alone (2.5 mg) or oral DM (20 mg) followed 40 minutes later by bromocriptine on 2 different days a week apart.

Protocol of the Present Study

All subjects were instructed to avoid beverages containing alcohol or caffeine after 10:00 PM of the day preceding the study. On the day of the study, at 8:00 AM, after overnight fasting, the subjects were placed supine in a dimly lit and quiet room at a comfortable temperature. A plastic cannula was inserted in an antecubital vein of the nondominant arm for blood sampling. Arterial pressure was measured every 3 minutes by use of an automated apparatus (Dinamp, Critikon). ECG (lead II) and respiratory activity were continuously recorded by using a conventional AC amplifier and a nasal thermistor, respectively. Subjects were allowed to stabilize for 30 minutes. Thereafter, recordings were performed for 15 minutes with subjects in the supine position and for 15 minutes with subjects in the sitting position. The sitting position was chosen as the hemodynamic challenging maneuver rather than standing or passive
tilting to prevent possible side effects of bromocriptine (such as severe hypotension). Blood samples for norepinephrine measurements were obtained at the end of both the supine and the sitting periods. Therefore, subjects were given either bromocriptine or both DM and bromocriptine, and the above protocol was repeated at the time corresponding to peak plasma concentration of the drugs, ie, after 180 minutes (bromocriptine alone) and 220 minutes (40+180 minutes, DM plus bromocriptine), respectively. No subject was allowed to sleep throughout the entire study period.

**Power Spectral Analysis**

Data were analyzed online after appropriate analog-to-digital conversion at a rate of 300 samples per second per channel by using a 12-bit converter (Data Translation), according to Baselli et al. In brief, the ECG signal, a derivative/threshold algorithm provides the continuous series of RR intervals (tachogram). Stationary segments devoid of arrhythmias (200 to 500 RR intervals) were analyzed with an autoregressive algorithm, which automatically furnishes the number, central frequency, and associated power of oscillatory components without the need of any a priori decision. Two major oscillatory components are usually detectable in RR variability: the first one (high frequency [HF]), synchronous with respiration, has a center frequency of ~0.25 Hz; the second one (low frequency [LF]) has a center frequency of ~0.1 Hz. The LF and HF components were expressed as central frequencies (in Hz) and in normalized units (nu), as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Normalization was obtained by dividing each component by the total power, minus the power of the heart rate variability (HRV) below 0.03 Hz, and multiplying this ratio by 100. Total power was expressed in milliseconds.

**Measurements**

Blood samples (3 mL) for norepinephrine determinations were collected in ice-chilled tubes containing a 100-μL solution of glutathione (60 mg/mL) and EGTA (90 mg/mL). Samples were centrifuged at 3000 rpm at 4°C, and plasma was stored at -80°C until further processing. Norepinephrine was measured by using a commercial kit (CAT-A-KIT, Amersham), as previously reported.

<table>
<thead>
<tr>
<th>TABLE 1. Power Spectral Indexes, Blood Pressure Values, and NE Plasma Levels After Administration of Bromocriptine Alone in 10 Normal Subjects in Supine and Sitting Positions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>LF, nu</td>
</tr>
<tr>
<td>Supine</td>
</tr>
<tr>
<td>Sitting</td>
</tr>
<tr>
<td>LF/HF</td>
</tr>
<tr>
<td>RR, ms</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
</tr>
</tbody>
</table>

Values are mean±SE. RR indicates RR interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; and NE, norepinephrine plasma levels.

*Baseline vs bromocriptine.
†Supine vs sitting.
Statistical Analysis

Data are reported as mean ± SE. Comparisons between baseline and bromocriptine data or baseline and DM plus bromocriptine data were performed by paired t test. Comparisons between supine and sitting data were performed by paired t test. The effects of drug administration and of the sitting maneuver and the combined effects of both interventions were analyzed by repeated measures 2-way MANOVA. A level of P < 0.05 was considered significant.

Results

Effects of Bromocriptine Alone

The administration of bromocriptine was associated with nausea in 3 subjects and with malaise and dizziness in 2 subjects. Data for power spectral analysis, blood pressure, and plasma norepinephrine after bromocriptine administration in supine and sitting positions are shown in Table 1.

At baseline, assumption of the sitting position was associated with an increase in the LF component and a reduction in the HF component, so that the LF/HF ratio increased significantly. Postural stimulation also resulted in a reduction in the RR interval and increments in systolic blood pressure, diastolic blood pressure, and plasma norepinephrine.

After administration of bromocriptine, with subjects in the supine position, the LF component showed a significant increase, whereas the HF component significantly decreased in respect to basal values. Hence, the LF/HF ratio remarkably increased. These changes were associated with a decrease in plasma levels of norepinephrine and a significant decrement in both systolic and diastolic blood pressures, whereas no appreciable change was observed in the RR interval. The assumption of the sitting position did not induce any changes in the LF or HF component or the LF/HF ratio or in blood pressure values. Conversely, the RR interval significantly decreased, and plasma levels of norepinephrine significantly increased.

Total variance and central frequencies of LF and HF are shown in Table 2. At baseline, the sitting position was associated with a reduction in the central frequency of the LF component and in total variance. After bromocriptine administration, central frequencies of both LF and HF components remained unchanged, and total variance decreased with subjects in the sitting position.

Effects of Bromocriptine After DM Pretreatment

No side effects of bromocriptine administration were observed after DM pretreatment. Data for power spectral analysis, blood pressure, and norepinephrine plasma levels after DM and bromocriptine administration are shown in Table 3.

At baseline, the assumption of the sitting position induced an increase in the LF component and a reduction in the HF component, resulting in a higher LF/HF ratio. Moreover, a decrease in RR interval and increments in systolic blood pressure, diastolic blood pressure, and plasma norepinephrine were observed.

After bromocriptine following DM pretreatment, with subjects in the supine position, the LF component was significantly lower, but the HF component remained unchanged in respect to basal values, so that the LF/HF ratio was reduced. No significant changes were observed in RR interval, systolic and diastolic blood pressures, and norepinephrine plasma levels. The assumption of the sitting position resulted in an increase in the LF component, with a reduction in the HF component, so that the LF/HF ratio significantly increased. Moreover, the RR interval decreased, whereas systolic and diastolic blood pressure levels increased.

Total variance and central frequencies of the LF and HF components are shown in Table 4. At baseline, the sitting position induced a reduction in the central frequency of the LF component and in total variance. After DM pretreatment and bromocriptine administration, the sitting posture was associated to a reduction in central frequency of LF component and in total variance.

### Table 2. CLF, CHF, and TV After Administration of Bromocriptine Alone in 10 Normal Subjects in Supine and Sitting Positions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Bromocriptine</th>
<th>P *</th>
<th>Sitting</th>
<th>Drug Sitting</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLF, Hz</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>7.160 ± 0.025</td>
<td>0.089 ± 0.007</td>
<td>NS</td>
<td>0.091</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>7.075 ± 0.005</td>
<td>0.078 ± 0.008</td>
<td>NS</td>
<td>0.089</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>CHF, Hz</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>0.029 ± 0.015</td>
<td>0.289 ± 0.022</td>
<td>NS</td>
<td>0.289</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>0.025 ± 0.016</td>
<td>0.293 ± 0.018</td>
<td>NS</td>
<td>0.293</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>TV, ms²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>4446 ± 889</td>
<td>2477 ± 682</td>
<td>0.01</td>
<td>2477 ± 682</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>2552 ± 697</td>
<td>1648 ± 651</td>
<td>0.006</td>
<td>1648 ± 651</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SE. CLF indicates central frequency of LF band; CHF, central frequency of HF band; and TV, total variance.

*Baseline vs bromocriptine.
†Supine vs sitting.
The Figure shows an example of HRV spectra at baseline, after bromocriptine, and after domperidone plus bromocriptine.

**Discussion**

HRV is a generally accepted noninvasive tool to assess cardiac autonomic function.\footnote{11–14} In particular, the cardiac sympathovagal balance, viewed as a reciprocal relationship, can be explored by power spectral analysis.\footnote{13,14,16,17} In the resting normal subject, this methodological approach reveals 2 main rhythmic oscillations in the cardiac period: the LF component, which has a central frequency usually at \(0.1\) Hz, and the HF component, which has a central frequency at \(0.25\) Hz. It is accepted that the efferent vagal activity to the heart is expressed by the HF component of HRV, inasmuch as it shows appropriate changes in response to autonomic maneuvers, such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy.\footnote{18–20} Despite some previous controversial interpretations mainly involving methodological issues,\footnote{12,19,21} the LF component, when expressed in normalized units, can be considered as an index of cardiac sympathetic activity because it is increased by various sympathetic stimuli.\footnote{13,14,16,17} Recently, Cooley et al.\footnote{22} observed that during total circulatory support with a left ventricular assist device (which is independent of any influence of blood pressure on cardiac autonomic drive via the baroreflex), the LF oscillation in the RR interval of the native heart, absent in chronic heart failure, was restored, suggesting that this component is also a fundamental property of central autonomic nervous outflow.

Several studies\footnote{2–7} have evaluated the effects of bromocriptine on the sympathetic nervous system mainly with the aim of clarifying whether this drug exerts only peripheral effects or whether it also has central effects. So far, it is still unclear. In fact, available data are somewhat conflicting. Starke et al.\footnote{23} using the norepinephrine spillover technique, substantiated a
Peripheral mode of action of bromocriptine, and more recently, Schobel et al24 documented a peripheral inhibition of neurotransmitter release in the absence of any changes in resting central sympathetic outflow. On the other hand, bromocriptine lowered plasma and cerebrospinal fluid levels of norepinephrine in normotensive individuals,25 supporting the suggestion of Mohanty et al6 and Mannelli et al7 that bromocriptine may exert both central and peripheral actions.

In this context, we evaluated the effects of short-term bromocriptine administration on the cardiac sympathovagal balance after a peripheral dopamine receptor blockade by DM, a D2-like receptor antagonist, which does not cross the blood barrier.9

The administration of bromocriptine alone was associated with a reduction in blood pressure and an increase in cardiac sympathetic drive (as inferred by higher values of LF), which is probably related to the sympathetic efferent loop of the baroreflex. Nevertheless, norepinephrine plasma levels were reduced. In this respect, it is worth noting that the RR interval remained unaffected by drug administration despite an increase in the LF component and a decrease in blood pressure. These findings seem controversial, but they are likely explained by the combined effect of opposite actions exerted by bromocriptine in vivo. In fact, bromocriptine is able to lower norepinephrine levels,4–7 thus causing hypotension; on the other hand, reduced blood pressure values induce a reflex activation of the sympathetic output (as indicated by the increased LF component in the supine position).

In previous studies,26,27 we have demonstrated that D2-like receptors are present on human chromaffin cells and that they

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>DM + Bromocriptine</th>
<th>Sitting</th>
<th>Drug Sitting</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLF, Hz</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>0.069±0.003</td>
<td>0.084±0.007</td>
<td>NS</td>
<td>18.241</td>
<td>0.002</td>
</tr>
<tr>
<td>Sitting</td>
<td>0.054±0.004</td>
<td>0.076±0.007</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P†</td>
<td>0.009</td>
<td>0.037</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF, Hz</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>0.272±0.013</td>
<td>0.276±0.014</td>
<td>NS</td>
<td>3.358</td>
<td>NS</td>
</tr>
<tr>
<td>Sitting</td>
<td>0.262±0.013</td>
<td>0.262±0.015</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P†</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TV, ms²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>3745±286</td>
<td>3876±655</td>
<td>NS</td>
<td>71.709</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sitting</td>
<td>2590±264</td>
<td>3106±774</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P†</td>
<td>0.004</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SE.
*Baseline vs DM+bromocriptine.
†Supine vs sitting.

An example of power spectra at baseline (top), after bromocriptine administration (middle), and after DM+bromocriptine treatment (bottom), with subjects in the supine position (left) and the sitting position (right). PSD indicates power spectrum density.
inhibit the catecholamine release. Nevertheless, when bromocriptine was administered to healthy subjects, plasma levels of epinephrine remained unchanged when subjects were in the supine position, whereas they increased slightly when subjects were in the standing position. These data can be viewed as the result of 2 opposite stimuli on the adrenal medulla exerted by bromocriptine administration in vivo: a direct inhibition through D2-like receptors and an indirect reflex-mediated stimulation induced by hypotension. The final outcome (ie, plasma levels of epinephrine) depends on the degree of hypotension: in other words, in the standing position, blood pressure values are low enough to induce epinephrine release in spite of a direct inhibition of the chromaffin cells.

Similarly, in the present investigation, the unchanged RR interval can be considered as the outcome of these 2 opposite stimuli. In addition, after bromocriptine administration, the sitting position was associated with the expected reduction in the RR interval but in a lack of significant changes in the LF/HF values. The different behavior of these 2 parameters can be explained by the fact that the LF/HF ratio, different from RR interval, is considered a more sensitive marker of neural modulation to the heart, reflecting the cardiac sympathetic drive. However, after bromocriptine administration, the interval can be considered as the outcome of these 2 opposite stimuli. In the present study, the administration of bromocriptine and DM does not seem to have affected the respiratory pattern, inasmuch as the central frequency of HF, which is known to be synchronous with respiration, remained unchanged throughout the study.

In conclusion, we have demonstrated both the peripheral and central effects of bromocriptine, a dopamine agonist. In fact, the pretreatment with a D2 peripheral antagonist (DM) allows us to mask the central inhibitory effect of bromocriptine on the cardiac sympathetic drive.

As possible limitation of the present study, spectral analysis of blood pressure and muscle sympathetic nerve activity measurements were not performed; nevertheless, the aim of the present study was to assess the effects of drug administration on the cardiac sympathetic drive and not on the systemic sympathetic tone.

The increase in the cardiac sympathetic tone (as indicated by higher values of the LF component), observed after acute oral bromocriptine, seems to be in disagreement with the finding of a reduction in cardiac sympathetic activity in L-dopa–treated patients with Parkinson’s disease given bromocriptine, as reported by Przuntek et al. This discrepancy can probably be related to the fact that (unlike Przuntek et al) we evaluated the drug effects after an acute and not a chronic administration and with healthy subjects rather than those in disease conditions. However, further investigations are needed to assess the dopaminergic modulation of the cardiac sympathetic drive after chronically administered bromocriptine. Besides, dopamine has been reported to exert an inhibitory influence on ventilation acting through the stimulation of dopaminergic receptors present in the carotid bodies. Central dopaminergic transmission within the brain seems to lead to increased ventilation. Moreover, studies in humans have suggested that peripheral dopaminergic stimulation may decrease minute ventilation during hypoxia. In the present study, the administration of bromocriptine and DM does not seem to have affected the respiratory pattern, inasmuch as the central frequency of HF, which is known to be synchronous with respiration, remained unchanged throughout the study.

In conclusion, we have demonstrated both the peripheral and central effects of bromocriptine, a dopamine agonist. In fact, the pretreatment with a D2 peripheral antagonist (DM) allows us to mask the central inhibitory effect of bromocriptine on the cardiac sympathetic drive.

References

Franchi et al. 2018. Bromocriptine and Cardiac Autonomic Tone.

Bromocriptine and Cardiac Autonomic Tone

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