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Assessment of valvulopathy in Parkinson's disease patients on pergolide and/or cabergoline

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Abstract

Objective: To assess the effect of ergot derivatives on cardiac valves in patients with Parkinson's disease (PD).
Materials and methods: Echocardiography was performed on 46 PD patients who used either pergolide or cabergoline (MonoPD) or both (MixPD) for a minimum of 1 year and 49 age-matched healthy controls. Valvular regurgitation was graded as mild, moderate and severe. MonoPD and MixPD groups were compared with regard to demographic features, drug profile and valvulopathy.
Results: The PD group had a mean age of 63 years, agonist duration of 3.8 years and agonist equivalent dose of 3.5 mg/day. Moderate regurgitation in all three valves was significantly more common in the PD group than the controls. Severe valvular regurgitation was not observed in either group, with the exception of one PD patient. The frequency of valvulopathy and doses of agonists did not differ between MixPD and MonoPD groups.
Conclusion: PD patients on dopamine ergot agonists are prone to moderate valvular regurgitation more than age-matched controls. However, the frequency of valvulopathy was similar in patients who used either one or more agonists.

Keywords: Parkinson's disease; Pergolide; Cabergoline; Valvulopathy

1. Introduction

Dopamine agonists are widely used as monotherapy for patients with mild symptoms of Parkinson's disease (PD) and as adjunctive therapy to levodopa in patients with motor complications [1,2]. In recent years, there has been growing concern with regard to the relationship between the occurrence of drug-induced valvular heart disease and the use of ergot-derived dopamine agonists, in particular pergolide and cabergoline. Valvular side effects due to fibrotic reactions ranged from asymptomatic cardiac involvement to more serious cardiac failure that might be detected by routine echocardiograpic studies [2–12]. Interestingly, fibrotic symptoms related to ergot agonists may develop after a few months or even years [7,8,13,14]. Horvath et al. proposed that agonist-induced valvulopathy is likely to be a chronic process that takes years until it becomes clinically apparent [7].

Here, we used transthoracic echocardiography to compare the frequency of valvulopathy in PD patients on pergolide and/or cabergoline with that in healthy subjects.

2. Materials and methods

The records of PD patients who were referred to the Movement Disorders Unit of the Department of Neurology, Cerrahpasa Faculty of Medicine, Istanbul University between April and September 2005 were reviewed. The diagnosis of idiopathic PD was consistent with the UK Parkinson's Disease Society Brain Bank criteria [15]. Among

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the computer-based files in our data bank, the PD patients who were taking ergot agonists (pergolide and/or cabergoline) for a minimum of 1 year with or without levodopa were invited to the outpatient clinic. PD patients who were treated with dopamine agonists other than the ones mentioned above were excluded. Patients having preexisting coronary or valvular heart disease (rheumatic or other) and those with previous complaints of heart disease such as chest pain, unexplained shortness of breath and refractory cough before treatment with any ergot agonists and having such problems at the time of the study were also excluded. Forty-six PD patients taking either pergolide or cabergoline (MonoPD) or who were exposed to both agonists (MixPD) were enrolled in the study. None of the patients in the MixPD group had ever used two agonists concurrently. In this blind study, both patients and age-matched subjects were assessed by transthoracic echocardiography in the Department of Cardiology by the two cardiologists (L.K. and T.S.). Control subjects were selected from people who had been referred to the outpatient Clinic of Cardiology for routine diagnostic workup of arterial hypertension between April and September 2005. None of the control subjects had rheumatic valvular heart disease, left ventricular systolic dysfunction, left ventricular wall motion abnormalities or congenital cardiac disease and they had never used ergot drugs. Written informed consent was obtained from all individuals.

The echocardiographic equipment we used was a Vingmed System Five and a 2.5 MHz transducer. Patients were examined in a left lateral recumbent position. Measurements were acquired during silent respiration or end-expiratory apnea. The echocardiographic examination was performed in four standard views: parasternal long, short axis, apical four and two-chamber views. Left ventricular volumes were calculated using the biplane Simpson's method. This included a long-axis measurement from the level of mitral cusp insertions to the apex. Aortic, mitral and tricuspid valve regurgitation were graded as mild, moderate and severe. Aortic and mitral calcifications were defined upon the increased thickness and bright echoes of the valve leaflets. Ejection fraction, left ventricular systolic and diastolic pressure, mitral and aortic degeneration, mitral and aortic calcification, mitral, aortic and tricuspid regurgitation were evaluated. Furthermore, MonoPD and MixPD groups were compared with regard to demographic features, duration and doses of ergot drugs as well as for the presence of valvulopathy.

We noted the age of onset of the first symptom, duration of the disease, mean duration of treatment and doses of the mentioned ergot dopamine agonists. PD severity was scored using the scale of Unified Parkinson's Disease Rating Scale (UPDRS) [16]. We calculated the equivalent dose of the agonists using a conversion table published previously as follows: 1 mg pergolide = 1.33 mg cabergoline [17]. Data were entered and analyzed using SPSS for windows 11.0. Comparisons for clinical variables between PD patients and controls as well as two subgroups of patients were performed using an independent sample *t*-test, chi-square test, and Mann–Whitney *U*-test, as appropriate. The threshold level for statistical significance was established at $p < 0.05$.

3. Results

Demographic features of the PD patients and echocardiographic results of both patients and controls are summarized in Table 1. The mean age of 46 PD patients (20 men and 26 women) was 63.9 ± 10.8 years and that of controls (23 men and 26 women) was 60.3 ± 9.8 years. The mean age of PD onset was 55 ± 9.7 years and mean duration of the disease was 8.9 ± 6.4 years. The mean agonist duration was 3.8 ± 2.9 years and the agonist equivalent dose was 3.5 mg/day. Patients had a mean UPDRS (parts I–III) score of 27.8 ± 17.5. In the PD group, mitral and aortic degeneration as well as mitral and aortic calcification were significantly more common than in controls. Mild aortic regurgitation was also significantly more common in the PD group than in controls ($p = 0.013$). Similarly, moderate regurgitation in all three valves of PD patients was found to be significantly higher than in the control group. None of the patients in either group had severe valvular regurgitation with the exception of one PD patient in the MonoPD group who was having severe aortic regurgitation.

Demographic and echocardiographic features of the MonoPD and MixPD groups are shown in Table 2. The MixPD patients had a significantly longer disease and agonist administration duration than the MonoPD group ($p = 0.033$

Table 1
Demographic features of the PD patients and echocardiographic results of the study group

	Patients $n = 46$	Controls $n = 49$	p
Age (yrs)	63.9 ± 10.86	60.3 ± 9.8	0.093
Onset of PD (yrs)	55.04 ± 9.7		
Duration of PD (yrs)	8.93 ± 6.45		
UPDRS (I–III)	27.89 ± 17.59		
Agonist duration (yrs)	3.84 ± 2.96		
Mean eq. DA (mg/day)	3.58 ± 1.76		
EF	61.8 ± 9.57	59.16 ± 5.61	0.094
LVSP	31.82 ± 5.02	31.02 ± 6.32	0.495
LVDP	49.32 ± 4.69	48.4 ± 4.63	0.340
MD	22 (47.8%)	8 (16.3%)	**0.001**
MC	11 (23.9%)	3 (6.1%)	**0.014**
AD	28 (60.9%)	12 (24.5%)	**0.0001**
AC	17 (37%)	7 (14.3%)	**0.011**
Mild MR	25 (54.3%)	22 (44.9%)	0.357
Moderate MR	9 (19.6%)	1 (2%)	**0.005**
Mild AR	18 (39.1%)	8 (16.3%)	**0.013**
Moderate AR	7 (15.2%)	1 (2%)	**0.021**
Mild TR	11 (23.9%)	8 (16.3%)	0.356
Moderate TR	7 (15.2%)	1 (2%)	**0.021**

PD: Parkinson's disease; UPDRS: unified Parkinson's disease rating scale; DA: dopamine agonist; eq.: equivalent dose; EF: ejection fraction; LVSP: left ventricular systolic pressure; LVDP: left ventricular diastolic pressure; MD: mitral degeneration; MC: mitral calcification; AD: aortic degeneration; AC: aortic calcification; MR: mitral regurgitation; AR: aortic regurgitation; TR: tricuspid regurgitation.
Values are mean ± S.D. or *n* (%).