ORIGINAL ARTICLE

Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease

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ABSTRACT

BACKGROUND

Ergot-derived dopamine receptor agonists, often used in the treatment of Parkinson's disease, have been associated with an increased risk of valvular heart disease.

METHODS

We performed an echocardiographic prevalence study in 155 patients taking dopamine agonists for Parkinson's disease (pergolide, 64 patients; cabergoline, 49; and non–ergot-derived dopamine agonists, 42) and 90 control subjects. Valve regurgitation was assessed according to American Society of Echocardiography recommendations. The mitral-valve tenting area was also measured and used as a quantitative index for leaflet stiffening and apical displacement of leaflet coaptation.

RESULTS

Clinically important regurgitation (moderate to severe, grade 3 to 4) in any valve was found with significantly greater frequency in patients taking pergolide (23.4%) or cabergoline (28.6%) but not in patients taking non–ergot-derived dopamine agonists (0%), as compared with control subjects (5.6%). The relative risk for moderate or severe valve regurgitation in the pergolide group was 6.3 for mitral regurgitation (P=0.008), 4.2 for aortic regurgitation (P=0.01), and 5.6 for tricuspid regurgitation (P=0.16); corresponding relative risks in the cabergoline group were 4.6 (P=0.09), 7.3 (P<0.001), and 5.5 (P=0.12). The mean mitral tenting area was significantly greater in ergot-treated patients and showed a linear relationship with the severity of mitral regurgitation. Patients treated with ergot derivatives who had grade 3 to 4 regurgitation of any valve had received a significantly higher mean cumulative dose of pergolide or cabergoline than had patients with lower grades.

CONCLUSIONS

The frequency of clinically important valve regurgitation was significantly increased in patients taking pergolide or cabergoline, but not in patients taking non–ergot-derived dopamine agonists, as compared with control subjects. These findings should be considered in evaluating the risk–benefit ratio of treatment with ergot derivatives.

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Several studies and case reports strongly support a causal relationship between the occurrence of drug-induced "restrictive" valvular heart disease and treatment with pergolide, an ergot-derived dopamine receptor agonist mainly used to treat Parkinson's disease.[1-6] More specifically, pergolide may induce fibrotic changes in valve leaflets and in the mitral subvalvular apparatus, causing thickening, retraction, and stiffening of valves and resulting in incomplete leaflet coaptation and valve regurgitation.

Valvular heart damage has also been reported with the ergot-derived dopamine agonists bromocriptine and cabergoline.[5-7] This is important, since cabergoline is widely prescribed in many countries for Parkinson's disease and, at low doses, for the treatment of hyperprolactinemia. Furthermore, although non–ergot-derived dopamine agonists may represent a valid alternative for the treatment of Parkinson's disease, their safety with regard to fibrotic reactions has been questioned.[8,9]

The valvular abnormalities seen with ergot-derived dopamine agonists are similar to those observed in patients receiving antimigraine ergot alkaloid agents (such as ergotamine and methysergide) or the anorectic drugs fenfluramine and dexfenfluramine. These abnormalities also closely resemble carcinoid-related valvulopathies.[10-13]

It has been proposed that the valvular damage induced by these agents may be mediated by the serotoninergic system. All the implicated drugs have been shown to have high affinity for, and to be full or partial agonists of, the serotonin (5-hydroxytryptamine [5-HT]) receptor subtype 5-HT_{2B}, which is expressed in heart valves and is known to mediate mitogenesis.[14,15] Proliferation of fibroblasts may therefore occur within valve tissue when the 5-HT_{2B} receptor is stimulated.

To assess the prevalence of valvular disease in patients treated with ergot-derived dopamine agonists, we performed echocardiography in a large representative sample of patients with Parkinson's disease who were treated with pergolide, cabergoline, or non–ergot-derived dopamine agonists and in a group of control subjects without Parkinson's disease. We evaluated the severity of regurgitation for the mitral, aortic, and tricuspid valves, as well as the degree of deformity of the mitral-valve apparatus.

METHODS

SUBJECTS

We recruited a convenience sample of patients from a large cohort of subjects attending the outpatient service of the Parkinson Institute in our hospital in Milan. All patients who were seen consecutively for an office visit between January and June 2005 and who met eligibility criteria were asked to participate. The study was approved by our hospital ethics committee; every patient and control subject gave specific written informed consent.

The patients were subdivided into three groups. In the pergolide group were patients who had been taking pergolide for at least 12 months and had never been treated with cabergoline or with non–ergot-derived dopamine agonists. The cabergoline group consisted of patients who had been taking cabergoline for at least 12 months and had never been treated with pergolide or with non–ergot-derived dopamine agonists. Patients in the "non-ergot" group had been taking non–ergot-derived dopamine agonists (pramipexole or ropinirole) for at least 12 months and had never been treated with ergot-derived agonists.

Clinical exclusion criteria were a history of cardiac valvular abnormalities and previous use of anorectic drugs or other ergot-derived drugs. Echocardiographic exclusion criteria were valve calcification, valve regurgitation associated with annular dilatation or excessive leaflet motion, and mitral regurgitation associated with left ventricular wall-motion abnormalities or left ventricular dilatation.

Control subjects were recruited from among relatives of the patients or acquaintances of the medical staff or were selected from a group of patients referred to our echocardiography laboratory for arterial hypertension or for fitness evaluation before participation in sports. None of the control subjects had Parkinson's disease or had ever been treated with dopamine agonists or anorectic drugs. Exclusion criteria were the same as for patients with Parkinson's disease. Control subjects and patients were matched according to sex and age (one control subject for every two patients for each sex; the age for all control subjects was within 5 years of the mean age of the patient group). Hypertensive patients were recruited to reproduce in the control group the same frequen-

cy of hypertension found in the entire patient group.

ECHOCARDIOGRAPHY

All enrolled patients and control subjects underwent a complete transthoracic echocardiographic examination. All echocardiograms were performed with the same equipment (Acuson Sequoia, Siemens) by two experienced echocardiographers who were unaware of the treatment status of the patients; patients and physicians were instructed not to discuss the medication history of the patients. Special attention was given to the morphologic study of the mitral, aortic, and tricuspid valves. Echocardiographic and Doppler data for patients and control subjects were stored on optical disks for off-line analysis and were interpreted independently and in blinded fashion by the two sonographers.

All semiquantitative and quantitative measurements for quantification of regurgitant valve disease were made according to recommendations of the American Society of Echocardiography.[16] Valve regurgitation was defined and quantified as follows: absent, 0; trace, 1; mild, 2; moderate, 3; severe, 4. If one of the two readers differed from the other by one grade, the higher rating was assigned; no rating differences greater than one grade were found in our study. To evaluate the global risk of regurgitant valve disease, we also used a composite scoring system derived from the sum of mitral, aortic, and tricuspid scores (value range of the composite score, 0 to 12; higher scores indicate more severe disease). Abnormal leaflet or cusp thickening was judged to be present when the thickness, local or widespread, was more than 5 mm.

To create a quantitative index for leaflet stiffening and apical displacement of mitral leaflet coaptation, we measured the mitral-valve tenting area as previously described in a study on the valvular effects of pergolide[3]; this measurement has been used mainly for the evaluation of mitral regurgitation in ischemic heart disease.[17,18] The mitral tenting area was obtained from the parasternal long-axis view and was measured as the area enclosed between the annular plane and the mitral leaflets at end systole (Fig. 1). Stiffening of the leaflets and their displacement toward the apex cause an increase in this area and result in incomplete leaflet coaptation and valve regurgitation.

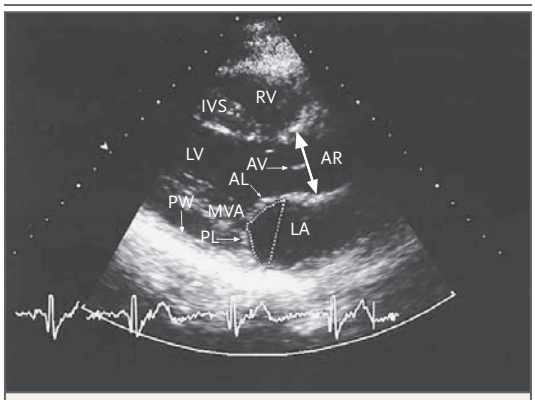

Figure 1. Mitral Tenting Area.

The mitral tenting area (dotted triangle) is shown from the parasternal long-axis view at end systole. The double-headed arrow shows the aortic root (AR). AL denotes anterior mitral leaflet, AV aortic valve, IVS interventricular septum, PW posterior wall, LA left atrium, LV left ventricle, MVA mitral-valve apparatus, PL posterior mitral leaflet, and RV right ventricle.

To derive systolic pulmonary-artery pressure, we calculated the tricuspid-valve pressure gradient from the tricuspid regurgitant jet velocity. We then increased the gradient by 5 mm Hg if the diameter of the inferior vena cava was less than 10 mm with complete respiratory collapse, by 15 mm Hg if the diameter of the inferior vena cava was more than 20 mm without respiratory variation, and by 10 mm Hg in intermediate cases.[19]

STATISTICAL ANALYSIS

Values are given as means ±SD. We tested differences between the groups of patients and the controls for continuous variables with an unpaired Student's t-test or Mann–Whitney test according to the characteristics of the data distribution. We tested differences for categorical variables with the chi-square test; we used the chi-square test for trend to assess a linear trend for the increasing degree of valve regurgitation. Relative risks for moderate or severe mitral, aortic, and tricuspid regurgitation were calculated for the pergolide and cabergoline groups as compared with the control group.

We analyzed the relationship between regurgitation grade and the mitral tenting area, using analysis of variance; we used linear contrasts to assess for changes in the mean values with increasing degree of mitral regurgitation. We used regression analysis to assess the relationship

between cumulative dose and composite score. Statistical analysis was carried out using SPSS software. For all analyses, a value of P<0.05 was considered to indicate statistical significance.

RESULTS

STUDY POPULATION

During enrollment, we screened 180 patients for whom a review of their records showed that they met the requirement for consistent use of a single drug for Parkinson's disease. Five were excluded for a history of cardiac valvulopathy preceding treatment for Parkinson's disease, and 175 met eligibility criteria. Of these, 4 missed their appointment at the echocardiography laboratory; the remaining 171 patients had an echocardiographic examination. Sixteen were excluded from the analysis on the basis of echocardiographic criteria — five for calcified valves, five for poor image quality of the ultrasonograms, four for left ventricular wall-motion abnormalities, and two for mitral-valve prolapse.

For the control group, 98 subjects were screened: 49 were recruited on a voluntary basis among relatives of the patients or acquaintances of the medical staff, and the remaining subjects were selected from a series of persons referred to our echocardiography laboratory for arterial hypertension (29 persons) or for fitness evaluation before participation in sports (20) on the basis of the aforementioned matching requirements. Two subjects were not included because of a history of cardiac valvular abnormalities; 96 met eligibility criteria and underwent echocardiography. Six control subjects were excluded from the analysis because of poor image quality (three subjects), mitral-valve prolapse (two), or dilatation of the aortic root (one).

CLINICAL FEATURES

The principal demographic and clinical features of the 155 patients and 90 control subjects included in the analysis are summarized in Table 1. Patients in the cabergoline group were slightly younger than those in the pergolide group (P=0.008); none of the groups of patients were significantly different from the control group with respect to age. Among patients and controls, men were predominant, although there were no significant differences between the percentages of men and women. The frequencies of hypertension, diabetes, and coronary heart disease were similar in each group of patients and in the control group. The mean body-mass index and the mean systolic and diastolic blood pressure in each group of patients were not significantly different from those in the control group. The mean duration of Parkinson's disease was significantly higher in the pergolide group than in either the cabergoline group (P<0.001) or the group taking non–ergot-derived dopamine agonists (P=0.02); the difference between the non-ergot group and the cabergoline group was not significant. The mean duration of therapy was significantly higher in the pergolide group than in either the cabergoline group (P<0.001) or the non-ergot group (P<0.001) and was also higher in the non-ergot group than in the cabergoline group (P<0.001). A high degree of variability was found for mean cumulative doses in all groups.

ECHOCARDIOGRAPHIC FINDINGS

The principal valvular abnormalities detected in the groups of patients and in the control group are summarized in Table 2. The prevalence of abnormalities and the regurgitation grade for each group of patients and controls are reported separately for the mitral, aortic, and tricuspid valves. At each site a significantly higher prevalence of grades 2, 3, and 4 regurgitation was found in the pergolide group and in the cabergoline group than in the control group, with a linear trend for greater severity of valve regurgitation in the two treatment groups. No significant differences were found between the non-ergot group and the control group. The frequency of clinically significant valve disease (grade 3 to 4 regurgitation) was significantly higher in both the pergolide and cabergoline groups (23.4% and 28.6%, respectively), but not in the non-ergot group (0%), than in the control group (5.6%) (Table 2). Mean composite regurgitation scores were significantly higher in both the pergolide and cabergoline groups than in the control group, whereas no significant difference was found between the mean composite scores in the non-ergot group and in the control group (Table 2).

The relative risk for moderate or greater valve regurgitation in the pergolide group as compared with the control group was 6.3 for mitral regurgitation (95% confidence interval [CI], 1.4 to 28.3; P=0.008), 4.2 for aortic regurgitation (95% CI, 1.2 to 15.0; P=0.01), and 5.6 for tricuspid regur-

gitation (95% CI, 0.7 to 49.7; P=0.16). In the cabergoline group the relative risk was 4.6 for mitral regurgitation (95% CI, 0.9 to 22.8; P=0.09), 7.3 for aortic regurgitation (95% CI, 2.2 to 24.8; P<0.001), and 5.5 for tricuspid regurgitation (95% CI, 0.6 to 51.6; P=0.12).

Among patients treated with ergot-derived dopamine agonists, 17 cases of localized or diffuse leaflet thickening were found in the pergolide group and 8 in the cabergoline group. No cases of leaflet thickening were found in the non-ergot group or in the control group (Table 2).

The mitral tenting area in each of the three treatment groups was significantly higher than in the control group (Table 2). In the ergot group (the combination of the pergolide and cabergoline groups), the mean mitral tenting area changed significantly with an increasing grade of mitral regurgitation (grade 0 to 1, 2.68±0.72 cm^2; grade 2, 3.07±0.75 cm^2; grade 3 to 4, 3.56±0.89 cm^2; P=0.003, calculated by analysis of variance); using linear contrasts, we found a significant linear relationship between mitral tenting area and severity of mitral regurgitation (P=0.001). Within the ergot group, patients with leaflet thickening of any valve had a significantly higher mean composite regurgitation score than did patients without this abnormality (6.6±1.9 vs. 4.4±1.5, P<0.001); the mean composite score for patients in the ergot group who had no leaflet thickening was significantly higher than the score in the control group (4.4±1.5 vs. 3.27±2.02, P<0.001) (Fig. 2).

In both the pergolide and cabergoline groups, patients with grade 3 to 4 regurgitation of any valve had received, on average, a significantly higher mean cumulative dose of the drug than those with lower grades (Table 3). A significant linear relationship was recorded between cumulative doses and composite scores in the pergolide group (r=0.34, P=0.005), and a trend toward such a relationship was observed in the cabergoline group (r=0.26, P=0.06).

The mean systolic pulmonary-artery pressure was significantly higher in the pergolide group than in the controls (31±5.1 vs. 28.8±5.5 mm Hg, P=0.02); no significant differences were found between the other groups of patients (cabergoline, 28.6±5.1; non–ergot-derived dopamine agonists, 27.9±4.1 mm Hg) and the control group. Patients receiving pergolide who had grade 3 to 4 aortic regurgitation, mitral regurgitation, or both had a mean systolic pulmonary-artery pres-

Table 1. Main Clinical Features of the Subjects.*

Characteristic	Pergolide Group (N=64)	Cabergoline Group (N=49)	Group Receiving Non–Ergot-Derived Dopamine Agonists (N=42)		All Patients (N=155)	Control Group (N=90)
			Pramipexole (N=36)	Ropinirole (N=6)		
Age — yr	65.3±8.5	61.5±9.8	62.7±9.8		63.4±9.2	63.5±10.1
Male sex — no. (%)	41 (64)	27 (55)	29 (69)		97 (63)	52 (58)
Body-mass index	24.7±3.4	25±3.3	25.4±3.5		25.1±3.4	26.1±3.4
Hypertension — no. (%)	18 (28)	13 (27)	10 (24)		42 (27)	26 (29)
Systolic blood pressure — mm Hg	138.8±13.3	136±12.6	133.1±11		136.2±12.9	136.5±10
Diastolic blood pressure — mm Hg	78.9±8.1	79.4±6.2	77.5±8.2		78.7±7.9	77.2±7.8
Diabetes — no. (%)	4 (6)	4 (8)	2 (5)		10 (6)	4 (4)
Coronary heart disease — no. (%)	3 (5)	2 (4)	3 (7)		8 (5)	3 (3)
Years since diagnosis of Parkinson's disease	11.2±5	7±5.8	8.8±4.5		NA	NA
Daily dose — mg	2.8±1.2	3.6±2.1	3±1.1	10±3.3	NA	NA
Months of therapy	62.7±28.3	24.44±15.4	40.1±23.6	45±27	NA	NA
Cumulative dose — g	5019±2787	2820±2513	2948±1822	19,180±10,334	NA	NA

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. NA denotes not applicable.

Table 2. Valvular Abnormalities in the Groups of Patients and in the Control Group.*

Variable	Pergolide Group (N=64)	Cabergoline Group (N=49)	Group Receiving Non–Ergot-Derived Dopamine Agonists (N=42)	Control Group (N=90)
Grade of mitral regurgitation — no. of patients (%)				
0 to 1	19 (30)	11 (22)	26 (62)	48 (53)
2	36 (56)	33 (67)	16 (38)	40 (44)
3	6 (9)	4 (8)	0	2 (2)
4	3 (5)	1 (2)	0	0
P value	<0.001	<0.001	0.27	
Grade of aortic regurgitation — no. of patients (%)				
0 to 1	34 (53)	22 (45)	31 (74)	66 (73)
2	21 (33)	15 (31)	11 (26)	21 (23)
3	8 (12)	12 (24)	0	3 (3)
4	1 (2)	0	0	0
P value	0.02	<0.001	0.68	
Grade of tricuspid regurgitation — no. of patients (%)				
0 to 1	17 (27)	8 (16)	23 (55)	47 (52)
2	43 (67)	38 (78)	19 (45)	42 (47)
3	4 (6)	2 (4)	0	1 (1)
4	0	1 (2)	0	0
P value	0.002	<0.001	0.70	
Any grade 3 to 4 regurgitation — no. of patients (%)	15 (23)	14 (29)	0	5 (6)
P value	0.001	<0.001	0.17	
Composite regurgitation score	4.8±2.01	5.14±1.84	3.4±1.29	3.27±2.02
P value	<0.001	<0.001	0.44	
Leaflet thickening of any valve — no. of patients (%)	17 (27)	8 (16)	0	0
P value	<0.001	<0.001		
Mitral-valve tenting area — cm^2	2.95±0.81	3.1±0.80	2.8±0.62	2.37±0.49
P value	0.001	<0.001	0.002	

* Plus–minus values are means ±SD. Regurgitation grades are as follows: 0, absent; 1, trace; 2, mild; 3, moderate; and 4, severe. P values were obtained by Student's t-test and chi-square test for the comparison between each patient group and the control group, and by the chi-square test for trend where applicable.

sure that was not significantly different from those who had grade 0 to 2 aortic and mitral regurgitation (32.8±4.4 vs. 30.5±5.2 mm Hg, P=0.16).

CLINICAL EVENTS

After echocardiographic examination during the study, one 69-year-old man who was taking pergolide underwent mitral-valve and aortic-valve replacement for severe mitral regurgitation and moderate aortic regurgitation. The surgeon described the leaflets of the mitral and aortic valves in this patient as diffusely thickened and retracted, but no pathologic specimen was available for our examination because the operation was performed at another institution. A 72-year-old man in the cabergoline group with moderate mitral

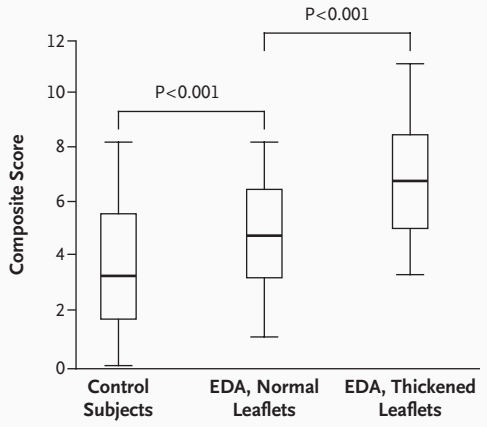

Figure 2. Composite Regurgitation Score in Control Subjects and in Patients Receiving Ergot-Derived Dopamine Agonists (EDA) Who Had Either Normal or Thickened Leaflets.

In this box-plot diagram, the horizontal line within each box represents the median, the limits of each box the interquartile range, and the whiskers the maximum and minimum values.

Table 3. Regurgitation Grade for Any Valve and Mean Cumulative Dose of Ergot-Derived Dopamine Agonist.

Grade	Pergolide	Cabergoline
	cumulative dose (mg)	
0 to 2	4566±2700	2341±2039
3 to 4	6498±2624	4015±3208
P value*	0.02	0.03

* Regurgitation grades are as follows: 0, absent; 1, trace; 2, mild; 3, moderate; and 4, severe. P values were obtained by Student's t-test for the comparison of different grades of valve regurgitation (0 to 2 vs. 3 to 4) within each group of patients.

and aortic regurgitation was hospitalized for heart failure; after several days of intensive medical therapy, he improved and was discharged.

DISCUSSION

Our findings confirm safety concerns related to the use of pergolide and show that an increased risk of cardiac valvulopathy also exists in patients taking cabergoline. Taking into consideration the differences in scoring systems, the frequency of grade 3 to 4 valve regurgitation in our population (23.4% in the pergolide group and 28.6% in the cabergoline group) closely resembles the results of a study on pergolide,[3] as well as those of studies on appetite-suppressant drugs.[11,12] Moreover, we noted in both the pergolide and cabergoline groups a significant association between cumulative dose and severity of valve regurgitation. We also observed a significant linear relationship between the cumulative dose of pergolide and the composite regurgitation score. A trend toward a linear relationship between dose and composite regurgitation score was seen for cabergoline; however, duration of therapy and sample size might have been insufficient to achieve significance in this cohort. No increase in the risk of valve regurgitation was observed in patients treated with non–ergot-derived dopamine agonists (mostly pramipexole). Leaflet thickening was detected in a minority of patients taking pergolide or cabergoline, but it was not seen in any of the patients taking non–ergot-derived dopamine agonists or in any of the control subjects.

Use of the mitral tenting area as a quantitative index for stiffening of the mitral leaflets produced the following findings: within the ergot group, the mitral tenting area increased significantly with increases in the severity of mitral regurgitation, and more important, in patients in the ergot group who did not have clinically significant valve regurgitation, the mitral tenting area was greater than in the control group. We speculate that this index might be used as a marker of early mitral-valve damage during treatment with ergot-derived dopamine agonists. The fact that many patients in the ergot group who had no leaflet thickening had a significant degree of valve regurgitation suggests that leaflet thickening may be a late marker of valvular disease.

The observed relationship between the severity of valvular functional impairment and the presence of the typical morphologic alterations found in patients in the ergot group supports the hypothesis of a fibrosing process involving the valve leaflets and subvalvular apparatus. Although the observation that this process occurs with both pergolide and cabergoline suggests a class effect, studies of the activity of serotonin-receptor–subtype 5-HT_{2B} agonists suggest that some other agents in this class, such as lisuride and terguride, may not have similar consequences.[15] The finding of a significantly greater mitral tenting area in the non-ergot group than in

the control group could be evidence of a weak agonist effect by this drug class on serotonin receptors that is not sufficient to produce the valvular damage observed in patients taking ergot-derived dopamine agonists. The mean mitral tenting area in the non-ergot group is similar to that observed in patients in the ergot group who have grade 0 to 1 valve regurgitation (2.80±0.62 vs. 2.68±0.72 cm^2).

The finding of a significantly higher mean systolic pulmonary-artery pressure in the pergolide group than in the other groups of patients or in the control group is apparently independent of valvular effects, since patients without clinically significant valve regurgitation had a mean systolic pulmonary-artery pressure that was not significantly different from that of patients with grade 3 to 4 regurgitation. Moreover, the mean systolic pulmonary-artery pressure in the cabergoline group, which had a composite valve-regurgitation score that was similar to the score in the pergolide group, did not differ significantly from that in the control group. The clinical meaning of this finding is probably negligible, if we consider that the mean systolic pulmonary-artery pressure in the pergolide group, after a mean duration of therapy of about 5 years, is only 2.4 mm Hg higher than in the control group.

In conclusion, we found a significant increase in the risk of heart-valve regurgitation in patients taking ergot-derived dopamine-receptor agonists for Parkinson's disease. The finding of a significantly increased mean mitral tenting area, not only in patients receiving ergot-derived dopamine agonists but also in patients treated with non–ergot-derived dopamine agonists, suggests that follow-up echocardiographic monitoring is advisable in all patients with Parkinson's disease who are treated with dopamine agonists.

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