Aortic Valve Calcification and Mild Tricuspid Regurgitation But No Clinical Heart Disease after 8 Years of Dopamine Agonist Therapy for Prolactinoma

Marleen Kars, Victoria Delgado, Eduard R. Holman, Richard A. Feelders, Johannes W. A. Smit, Johannes A. Romijn, Jeroen J. Bax, and Alberto M. Pereira

Departments of Endocrinology and Metabolic Diseases (M.K., J.W.A.S., J.A.R., A.M.P.) and Cardiology (V.D., E.R.H., J.J.B.), Leiden University Medical Center, 2300 RC Leiden, The Netherlands; and Department of Internal Medicine (R.A.F.), Section of Endocrinology, Erasmus Medical Center, 3000 DR Rotterdam, The Netherlands

Objective: Treatment with ergot-derived dopamine agonists, pergolide, and cabergoline has been associated with an increased frequency of valvular heart disease in Parkinson's disease. The aim of the present study was to assess the prevalence of valvular heart disease in patients treated with dopamine agonists for prolactinomas.

Design: This was a cross-sectional study.

Patients: We performed two-dimensional and Doppler echocardiography in 78 consecutive patients with prolactinoma (mean age 47 $\pm$ 1.4 yr, 26% male, 31% macroprolactinoma) treated with dopamine agonists for at least 1 yr (mean 8 $\pm$ 0.6 yr) and 78 control subjects. Patients were classified according to treatment: patients treated with cabergoline (group 1: n = 47) and patients not treated with cabergoline (group 2: n = 31).

Results: Clinically relevant valvular heart disease was present in 12% of patients (nine of 78) *vs.* 17% of controls (13 of 78) ($P = 0.141$) and 17% (eight of 47) of patients treated with cabergoline *vs.* 3% (one of 31) of patients not treated with cabergoline ($P = 0.062$). Mild tricuspid regurgitation was present in 41% of patients *vs.* 26% of controls ($P = 0.042$), and aortic valve calcification was present in 40% of patients, compared with 18% of controls ($P = 0.003$). There was no relation between the cumulative dose of cabergoline and the presence of mild, moderate, or severe valve regurgitation.

Conclusion: Several years of dopamine agonist treatment in patients with prolactinomas is associated with increased prevalence of aortic valve calcification and mild tricuspid regurgitation but not with clinically relevant valvular heart disease. Therefore, additional studies on the adverse cardiac effects of dopaminergic drugs in prolactinoma are warranted, especially in patients with much longer use of these drugs. **(*J Clin Endocrinol Metab* 93: 3348–3356, 2008)**

Long-term therapy with dopamine agonists is the treatment of choice for patients with prolactinomas because of the high efficacy of these drugs in controlling hyperprolactinemia and tumor size. However, dopamine agonist therapy has been associated with valvular heart disease in patients with Parkinson's disease. Since 2002, several studies reported an association between treatment with pergolide, bromocriptine, or cabergoline and valvular heart disease (1–8). Recently large population-based studies demonstrated an increased incidence and relative risk of developing cardiac valve disease in patients treated with pergolide or cabergoline for Parkinson's disease (9, 10).

The cardiac abnormalities in these patients are manifested by fibrotic changes that cause thickening, retraction, and stiffening of valves. This may result in clinically significant regurgitation requiring valve replacement. However, these data from patients with Parkinson's disease cannot be simply extrapolated to pa-

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Abbreviations: FS, Fractional shortening; 5HT, serotonin; IVST, interventricular septum thickness; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVM, left ventricular mass; PWT, posterior wall thickness.

tients treated with dopamine agonists for prolactinomas because gender and age of these patients, as well as duration and dosage of dopamine agonists, differ considerably from those used in patients with prolactinomas. Furthermore, it cannot be excluded that disease-specific aspects are also involved. Hence, it is presently unclear whether the treatment of prolactinomas with dopamine agonists is also associated with valvular heart disease. Therefore, the aim of the present study was to assess the prevalence of valvular abnormalities in consecutive patients treated with dopamine agonists for prolactinomas.

Patients and Methods

Patients and controls

In a cross-sectional study design, we included 78 consecutive patients with prolactinomas treated with dopamine agonists for at least 1 yr. Diagnostic criteria for prolactinoma were serum prolactin levels at least 2 times above the upper limit of normal and evidence of a pituitary tumor on computerized tomography scan or magnetic resonance imaging. A macroprolactinoma was defined by a diameter greater than 10 mm. Patients with macroprolactinemia, prolactin levels above the normal range secondary to primary hypothyroidism, or pituitary stalk compression, as well as subjects using drugs known to increase prolactin levels, were excluded. In addition, patients with concomitant GH excess or deficiency or Parkinson's disease were excluded. None of the patients had myocardial infarction in the preceding 5 yr, thyrotoxicosis, rheumatic fever, endocarditis, connective tissue disease, carcinoid syndrome or used anorectic drugs. One female patient appeared to be pregnant (gestation duration of 14 wk) at the moment of evaluation and, as a consequence, was excluded.

Patients were divided into two study groups, according to dopamine agonist treatment. Group 1 consisted of patients treated with cabergoline (n = 47). Group 2 consisted of patients treated with bromocriptine, terguride, or quinagolide or patients who received other treatment modalities, such as surgery, without any dopamine agonists (n = 31). All patients underwent a complete clinical and echocardiographic assessment.

We evaluated 78 control subjects matched for age, gender, body surface, and left ventricular systolic function, recruited from an echocardiographic database, as previously described (11). Exclusion criteria for these control subjects were the same as for the patients with prolactinoma. We controlled for left ventricular systolic function to avoid inclusion of patients with mitral regurgitation caused by left ventricular enlargement with subsequent incomplete mitral leaflet closure. Those controls who were referred for echocardiographic evaluation of known valvular heart disease, murmur, congestive heart failure, or cardiac transplantation were also excluded. As a consequence, the control group comprised of subjects, who were referred for atypical chest pain, palpitations, or syncope without murmurs.

The study was performed because of the publications on the association between treatment with dopamine agonists and valvular disease. The Medical Ethics Committee of Leiden University Medical Center judged that this study was therefore part of regular patient care.

Anthropometric parameters

Height, weight, waist circumference, and blood pressure were measured at the outpatient clinic. Waist circumference was measured at the height of the umbilicus, using the same measuring tape for all subjects. Normal values are less than 102 cm for men and less than 88 cm for women. Blood pressure was measured automatically (Dinamap) six times during a 20-min recording session. The lowest systolic and diastolic blood pressures were noted. Hypertension was defined as systolic pressure greater than 140 mm Hg or diastolic pressure greater than 90 mm Hg or the use of antihypertensive medication. All anthropometric parameters were measured by the same investigator.

Prolactin assay and normal values

Prolactin was measured using an electrochemiluminescence immunoassay using Elecsys 1010/2010 and Modular Analytics E170 (Elecsys module; Roche, Basel, Switzerland); the interassay variation coefficient was 2.4–2.6%, and the intraassay variation coefficient was 1.8–1.9%. The detection limit was 0.047 μg/liter (Roche). Normal values for basal prolactin were less than 15 μg/liter in men and less than 23 μg/liter in women.

Echocardiography and data acquisition

Echocardiography was performed with the subjects in the left lateral decubitus position using a commercially available system (Vingmed system Vivid-7; General Electric-Vingmed, Milwaukee, WI). Standard two-dimensional and color Doppler data, triggered to the QRS complex, were obtained using a 3.5-MHz transducer, at a depth of 16 cm in the parasternal (long and short axis) and apical (two and four chamber, long axis) views. The images were stored for off-line analysis (EchoPac 6.0.1; General Electric-Vingmed Ultrasound). Left ventricular (LV) dimensions were measured from M-mode images acquired from the parasternal long-axis view: interventricular septum thickness (IVST), posterior wall thickness (PWT), LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), fractional shortening (FS), and LV ejection fraction (LVEF). Left ventricular mass (LVM) was calculated by the cube formula and using the correction formula proposed by Devereux *et al.* (12): $0.8 \times [1.04([\text{LVEDD} + \text{PWT} + \text{IVST}]^3 - [\text{LVEDD}]^3)] + 0.6$.

The valvular assessment included the evaluation of morphology and function of the mitral, aortic and tricuspid valves. Color Doppler echocardiography was performed in all views after optimizing gain and Nyquist limit. Standard continuous-wave and pulsed-wave Doppler examinations were performed. Two independent expert readers blinded to clinical data performed the evaluation of regurgitated valve disease, using the semiquantitative and quantitative methods recommended by the American Society of Echocardiography (13). The severity of valvular regurgitation was determined on a qualitative scale according to the American College of Cardiology/American Heart Association guidelines for the management of patients with valvular heart disease: mild (grade 1), moderate (grade 2), and severe (grades 3–4) (14, 15). Significant (clinically relevant) valvular heart disease was determined using the U.S. Food and Drug Administration (FDA) case definition: mild, moderate, or severe aortic regurgitation; moderate or severe mitral regurgitation; or moderate or severe tricuspid regurgitation (16). Mild mitral regurgitation accompanied by prolapse is also considered as significant valvular disease. In addition, the presence of leaflet or cusp abnormalities was evaluated. These abnormalities comprised the presence of local or widespread thickening, more than 5 mm, any calcification and motion abnormalities (restrictive or excessive). When tricuspid regurgitation was present, pulmonary artery pressure was estimated using the modified Bernoulli equation.

All echocardiograms were performed with the same equipment by a single experienced independent observer, blinded for study groups. All data were analyzed by the sonographer and another experienced independent observer, also blinded for study groups.

Statistical analysis

SPSS for Windows version 14.0 (SPSS, Inc., Chicago, IL) was used to perform data analysis. Data were expressed as the mean $\pm$ SE unless otherwise mentioned. The groups were compared with independent samples t test or χ^2 tests, when appropriate. Differences were considered statistically significant at $P < 0.05$. Before the study, we performed a sample size calculation, based on the only available data on valvular regurgitation in patients using cabergoline (10). Given the mean prevalence of any valvular regurgitation of 72% in patients with Parkinson's disease using cabergoline *vs.* 41% in controls, the required sample size for each study group was calculated to be 52, using a 1-degree of freedom χ^2 test with a power of 90% and α at 0.05. However, patients treated with dopamine agonists for prolactinomas differ in many respects from patients treated for Parkinson's disease, *e.g.* in the dosage of dopamine agonist, age, and gender. As a consequence, we considered a prevalence

TABLE 1. Clinical characteristics of patients with prolactinomas and controls

Characteristic	Prolactinoma (n = 78)	Control group (n = 78)	*P* value
Age, yr	47 ± 1.4	48 ± 0.9	0.318
Male sex, n (%)	20 (26)	20 (26)	1.000
Body surface, m^2	1.9 ± 0.02	1.9 ± 0.02	0.314
Left ventricular measurements			
LVEDD, mm	50 ± 0.6	49 ± 0.7	0.366
LVESD, mm	28 ± 0.6	30 ± 1.0	0.195
IVST, mm	11 ± 0.3	10 ± 0.3	0.077
PWT, mm	10 ± 0.2	10 ± 0.2	0.506
LVM, g	192 ± 8	174 ± 7	0.091
FS, %	43 ± 0.8	41 ± 0.8	0.054
LVEF, %	74 ± 1.1	71 ± 0.9	0.128

Data are expressed as mean ± SE unless otherwise mentioned. The groups were compared with independent samples *t* test or χ^2 tests when appropriate.

rate approximately half of that reported for patients with Parkinson's disease as reasonable. Based on this assumption, a prevalence rate of 35% was estimated in the patient group and an estimated prevalence rate of 15% in the control group (according to age and gender data reported from large population based studies) (17). Therefore, in addition, we performed a second power calculation based on all available patients with prolactinoma in our center who fulfilled prior inclusion and exclusion criteria (n = 78). Using this sample size of 78 per group, a 1-degree of freedom χ^2 test with α at 0.05, the power to detect significant differences would be 83%, which was considered sufficient. Accordingly, all 78 consecutive patients with prolactinomas were included who fulfilled the prior inclusion and exclusion criteria.

Results

Clinical characteristics (Tables 1 and 2)

The clinical characteristics of the patients and controls are summarized in Table 1. The patients and controls did not differ with respect to age, gender, and body surface area. In addition, left ventricular systolic function was normal in all patients and controls.

At the moment of assessment, disease duration for all patients was 13 ± 0.7 yr. A macroprolactinoma was present in 31% of the patients. Mean duration of dopamine agonist treatment was 8 ± 0.6 yr (range 0–24.3 yr).

In the cabergoline treatment group (group 1), disease duration was 12 ± 0.8 yr. Duration of therapy with cabergoline was 5.2 ± 0.4 yr (range 1–10.3 yr). The cumulative dose of cabergoline was 363 ± 55 mg (range 24–1768 mg) (Table 2).

In the other or no dopamine agonist treatment group (group 2), disease duration was 14 ± 1.1 yr. None of the patients had ever been treated with cabergoline.

Valvular regurgitation (Tables 3 and 4)

Significant valve regurgitation of any valve was present in 12% of patients (nine of 78) *vs.* 17% of controls (13 of 78) ($P = 0.141$).

Mitral valve regurgitation was present in 28% of patients (22 of 78) *vs.* 23% of controls ((18 of 78) $P = 0.463$). Significant regurgitation of the mitral valve (moderate or severe according to FDA criteria) was present in 3% of patients (two of 78) *vs.* 1% of controls (one of 78) ($P = 0.560$).

Aortic valve regurgitation was present in 6% of patients (five of 78) *vs.* 13% of controls (10 of 78) ($P = 0.174$). Mild aortic valve regurgitation was present in 4% of patients (three of 78) *vs.* 13% of controls (10 of 78) ($P = 0.043$). In patients treated with cabergoline, moderate aortic valve regurgitation was present in one patient, and severe aortic valve regurgitation was present in another patient but was absent in controls. One of these two patients appeared to have an asymptomatic, previously undiagnosed, congenital valvular abnormality (bicuspid aortic valve). Moderate or severe aortic regurgitation was absent in patients treated with other or no dopamine agonist.

Mild, moderate, or severe regurgitation of the tricuspid valve was present in 46% of patients (36 of 78) *vs.* 28% of controls (22 of 78) ($P = 0.020$). Significant regurgitation of the tricuspid valve (moderate or severe according to FDA criteria) was present in 5% of patients (four of 78) *vs.* 3% of controls (two of 78) ($P = 0.405$). Mild, moderate, or severe regurgitation of the tricuspid valve was present in 51% of patients treated with cabergoline (24 of 47) *vs.* 28% of controls (22 of 78) ($P = 0.010$).

There was no relation between the cumulative dose of cabergoline and the presence of mild, moderate, or severe valve regurgitation of the mitral, aortic, and tricuspid valves in patients with prolactinomas (Fig. 1). Clinically relevant regurgitation of any valve was found borderline significant more frequently in the patients treated with cabergoline, compared with the patients treated with other or no dopamine agonist ($P = 0.062$, Table 4). In patients treated with cabergoline, valvular regurgitation of one valve was present in 13% of patients (six of 47), valvular regurgitation of two valves in 4% of patients (two of 47), and none of the patients had valvular regurgitation of three valves.

Valvular morphology (Tables 3 and 4)

The prevalence of thickened leaflets and calcifications of the mitral valve was 24% (19 of 78) and 32% (25 of 78), respectively, in patients and 36% (28 of 78) and 21% (16 of 78), respectively, in controls ($P = 0.116$ and $P = 0.102$, respectively). The number of patients with thickening of the mitral leaflets was borderline significant when compared between patients treated with cabergoline and patients treated with other or no dopamine agonist ($P = 0.056$). Calcifications of the mitral valve was significantly more present in patients treated with cabergoline, compared with controls [38% (18 of 47) *vs.* 21% (16 of 78), $P = 0.030$].

Thickened leaflets of the aortic valve were detectable in 24%

TABLE 2. Clinical characteristics of patients treated for prolactinomas with cabergoline *vs.* without cabergoline

Characteristic	Cabergoline		*P* value
	Yes (n = 47)	No (n = 31)	
Age, yr	46 ± 1.9	49 ± 2.3	0.361
Male sex, n (%)	13 (28)	7 (23)	0.615
Body surface, m^2	1.9 ± 0.03	1.9 ± 0.03	0.388
Left ventricular measurements			
LVEDD, mm	50 ± 0.8	50 ± 1.0	0.828
LVESD, mm	28 ± 0.8	28 ± 1.0	0.924
IVST, mm	10 ± 0.4	11 ± 0.5	0.474
PWT, mm	10 ± 0.3	10 ± 0.4	0.958
LVM, g	189 ± 10	195 ± 13	0.705
FS, %	43 ± 1.1	44 ± 1.3	0.591
LVEF, %	73 ± 1.5	74 ± 1.5	0.502
Years since diagnosis of prolactinoma, yr	12 ± 0.8	14 ± 1.1	0.112
Macroprolactinoma, n (%)	15 (32)	9 (29)	0.797
Prolactin level at visit, μg/liter	24 ± 4	28 ± 5	0.506
No. of patients			
Cabergoline	47		
Bromocriptine	20	7	
Terguride	3	6	
Quinagolide	28	20	
No dopamine agonist		9	
Duration of therapy, yr			
Cabergoline	5.2 ± 0.4		
Bromocriptine	2.9 ± 0.9	3.9 ± 1.6	
Terguride	6.1 ± 3.0	2.0 ± 0.5	
Quinagolide	3.2 ± 0.5	8.9 ± 1.1	
Cumulative dose, mg			
Cabergoline	363 ± 55		
Bromocriptine	4216 ± 899	9779 ± 3679	
Terguride	2038 ± 645	903 ± 259	
Quinagolide	114 ± 18	395 ± 82	

Data are expressed as mean ± SE unless otherwise mentioned. The groups were compared with independent samples *t* test or χ^2 tests when appropriate. Patients not treated with cabergoline were treated with quinagolide, bromocriptine, terguride, or no dopamine agonist at all. Several patients, in both groups had used more than one dopaminergic drug although only one drug at a time.

of patients (19 of 78) and 17% of controls (13 of 78) ($P = 0.234$). The prevalence of calcifications of the aortic valve was significantly higher in patients, compared with controls [40% (31 of 78) *vs.* 18% (14 of 78), $P = 0.003$], and this was due to the higher prevalence of calcifications in the patients treated with cabergoline, compared with controls (45 and 18%, respectively, $P = 0.001$, Table 5).

Thickened leaflets and calcifications of the tricuspid valve were present in 4% (three of 78) and 3% (two of 78), respectively, of patients, compared with the absence of abnormalities of valve morphology in controls ($P = 0.080$ and $P = 0.155$, respectively). All the patients with thickened leaflets of the tricuspid valve were treated with cabergoline (three of 47), and compared with controls (none of 78), this was significantly more prevalent ($P = 0.024$).

Subgroup analysis

Subgroup analysis of the patients treated with a cumulative dose of cabergoline of more than 500 mg (n = 11) showed significant valve regurgitation of two valves in one patient (cumulative dose 578 mg, duration of therapy 9.9 yr) and significant valve regurgitation of one valve in another patient (cumulative dose 1193 mg, duration of therapy 3.3 yr). Significant valvular regurgitation developed in one patient and was treated with quinagolide. The duration of therapy was 11.5 yr, with a cumulative dose of 298 mg. Eight of the nine patients with significant valve regurgitation were treated with cabergoline for mean period of 6.4 yr (range 3.1–9.9 yr), with a mean cumulative dose of 388 mg (range 82–1193 mg).

Discussion

This study demonstrates that several years of treatment with dopamine agonists is not associated with increased prevalence of clinically relevant valvular heart disease in patients with prolactinomas, even after the use of high cumulative doses of cabergoline up to 1768 mg. However, additional findings of uncertain clinical relevance, like a higher prevalence of mild regurgitation of the tricuspid valve and calcifications of the aortic valve, did occur.

Dopamine agonists are used for several indications, such as Parkinson's disease, restless legs syndrome, and prolactinoma. In prolactinoma, dopamine agonist therapy is the treatment of choice. Dopamine agonists decrease prolactin levels, restore gonadal function, improve visual field defects and reduce tumor size. In contrast to patients with Parkinson's disease, patients

TABLE 3. Valvular abnormalities in patients with prolactinomas and controls

Variable	Prolactinoma (n = 78)	Control group (n = 78)	*P* value
Mitral valve			
Mitral regurgitation, n (%)			
No MR	56 (72)	60 (77)	0.463
MR grade mild	20 (26)	17 (22)	0.572
MR grade moderate	2 (3)	1 (1)	0.560
MR grade severe			
Mitral annulus, mm	32 ± 0.4	31 ± 0.5	0.557
Mean gradient, mm Hg	1.2 ± 0.06	1.3 ± 0.06	0.188
Mitral area, cm^2	2.9 ± 0.06	3.1 ± 0.03	0.005
Mitral valve morphology, n (%)			
Thickened leaflets	19 (24)	28 (36)	0.116
Calcifications	25 (32)	16 (21)	0.102
Leaflet motion abnormality	2 (3)	4 (5)	0.405
Aortic valve			
Aortic regurgitation, n (%)			
No AoR	73 (94)	68 (87)	0.174
AoR grade mild	3 (4)	10 (13)	0.043
AoR grade moderate	1 (1)		0.316
AoR grade severe	1 (1)		0.316
Aortic annulus, mm	20 ± 0.3	20 ± 0.2	0.237
Aortic sinus, mm	31 ± 0.5	31 ± 0.4	0.701
Sinotubular junction, mm	23 ± 0.4	24 ± 0.4	0.095
Ascending aorta, mm	30 ± 0.6	29 ± 0.6	0.281
Aortic area, cm^2	2.4 ± 0.07	2.5 ± 0.07	0.174
Mean gradient, mm Hg	4.0 ± 0.14	3.6 ± 0.15	0.057
Aortic valve morphology, n (%)			
Bicuspid	2 (3)	1 (1)	0.560
Thickened leaflets	19 (24)	13 (17)	0.234
Calcifications	31 (40)	14 (18)	0.003
Leaflet motion abnormality	4 (5)	1 (1)	0.173
Tricuspid valve			
Tricuspid regurgitation, n (%)			
No TR	42 (54)	56 (72)	0.020
TR grade mild	32 (41)	20 (26)	0.042
TR grade moderate	4 (5)	2 (3)	0.405
TR grade severe			
Pulmonary artery pressure, mm Hg	29 ± 0.8	30 ± 1.3	0.474
Tricuspid valve morphology, n (%)			
Thickened leaflets	3 (4)		0.080
Calcifications	2 (3)		0.155
Leaflet motion abnormality	1 (1)	1 (1)	1.000
Any significant valve regurgitation, n (%)	9 (12)	13 (17)	0.141
Any thickened leaflets, n (%)	30 (38)	31 (40)	0.870
Any calcifications, n (%)	39 (50)	26 (33)	0.035

Data are expressed as mean ± SE unless otherwise mentioned. The groups were compared with independent-samples *t* test or χ^2 tests when appropriate. MR, Mitral regurgitation; AoR, aortic regurgitation; TR, tricuspid regurgitation.

treated for prolactinoma are predominantly young females, who are treated for at least 3–5 yr with dopamine agonists. Cabergoline is the most potent dopamine agonist and, due to its favorable pharmacokinetic profile and good tolerance, is the most commonly used dopamine agonist in the treatment of prolactinoma. Recently, however, reports indicated an increased risk of developing valve regurgitation in patients with Parkinson's disease treated with the ergot-derived dopamine agonists pergolide or cabergoline, with a mean cumulative dose cabergoline of 2820 g for a mean duration of 2 yr (9, 10). As a consequence, questions regarding safety of medical treatment of prolactinoma patients with cabergoline emerged. Prospective trials evaluating the effect of dopamine agonists on cardiac valves in patients with prolactinoma have not been published.

In this study, we compared echocardiographic data in patients with prolactinoma to control subjects derived from a database. Furthermore, patients treated with cabergoline were compared with patients treated with bromocriptine, terguride, or quinagolide or no dopamine agonist therapy at all and with control subjects. Matched database analysis is necessary for several reasons. First, gender and age of patients with prolactinoma differ significantly from population based prevalence studies. Therefore, we individually matched each patient with prolactinoma for age, gender, body surface, and left ventricular systolic

TABLE 4. Valvular abnormalities in patients treated for prolactinomas with cabergoline *vs.* without cabergoline

Variable	Cabergoline		*P* value
	Yes (n = 47)	No (n = 31)	
Mitral valve			
Mitral regurgitation, n (%)			
No MR	33 (70)	23 (74)	0.702
MR grade mild	12 (26)	8 (26)	0.978
MR grade moderate	2 (4)		0.245
MR grade severe			
Mitral annulus, mm	31 ± 0.6	32 ± 0.7	0.432
Mean gradient, mm Hg	1.3 ± 0.08	1.1 ± 0.05	0.016
Mitral area, cm^2	2.9 ± 0.07	2.9 ± 0.11	0.790
Mitral valve morphology, n (%)			
Thickened leaflets	15 (32)	4 (13)	0.056
Calcifications	18 (38)	7 (23)	0.146
Leaflet motion abnormality	2 (4)		0.245
Aortic valve			
Aortic regurgitation, n (%)			
No AoR	43 (92)	30 (97)	0.351
AoR grade mild	2 (4)	1 (3)	0.817
AoR grade moderate	1 (2)		0.414
AoR grade severe	1 (2)		0.414
Aortic annulus, mm	19 ± 0.4	20 ± 0.4	0.305
Aortic sinus, mm	31 ± 0.7	31 ± 0.7	0.525
Sinotubular junction, mm	23 ± 0.6	23 ± 0.6	0.901
Ascending aorta, mm	30 ± 0.8	31 ± 0.7	0.361
Aortic area, cm^2	2.3 ± 0.10	2.5 ± 0.09	0.441
Mean gradient, mm Hg	4.0 ± 0.17	4.1 ± 0.25	0.735
Aortic valve morphology, n (%)			
Bicuspid	2 (4)		0.245
Thickened leaflets	12 (26)	7 (23)	0.766
Calcifications	21 (45)	10 (32)	0.273
Leaflet motion abnormality	3 (6)	1 (3)	0.536
Tricuspid valve			
Tricuspid regurgitation, n (%)			
No TR	23 (49)	19 (61)	0.284
TR grade mild	20 (43)	12 (39)	0.736
TR grade moderate	4 (9)		0.095
TR grade severe			
Pulmonary artery pressure, mm Hg	29 ± 1.0	29 ± 1.3	0.636
Tricuspid valve morphology, n (%)			
Thickened leaflets	3 (6)		0.151
Calcifications	1 (2)	1 (3)	0.764
Leaflet motion abnormality	1 (2)		0.414
Any significant valve regurgitation, n (%)	8 (17)	1 (3)	0.062
Any thickened leaflets, n (%)	22 (47)	8 (26)	0.062
Any calcifications, n (%)	26 (55)	13 (42)	0.247

Data are expressed as mean ± SE unless otherwise mentioned. The groups were compared with independent-samples *t* test or χ^2 tests when appropriate. MR, Mitral regurgitation; AoR, aortic regurgitation; TR, tricuspid regurgitation.

function to a control subject. Second, the influence of prolactin or prolactinoma on cardiac valves is unknown. Endocrine diseases, such as acromegaly and hypothyroidism, are associated with valvular regurgitation, cardiomyopathy, and congestive heart failure, but so far the influence of prolactin or prolactinoma on cardiac function and morphology has not been investigated (11, 18–20). Therefore, in our study we compared the patients treated with cabergoline with patients treated with other or no dopamine agonist, and compared them with control subjects. However, confounding of the results can occur by using different equipment or nonblinded interpreters of the echocardiographic data. Furthermore, interobserver variation is an important, generally known confounding factor. Therefore, all echocardiograms were performed with the same equipment by a single experienced, independent observer, blinded for study groups. Furthermore, all echocardiographic data, including those of the control subjects, were analyzed by both the sonographer and another experienced, independent reader, also blinded for study.

A randomly selected control group without clinical indication for echocardiography would have been an optimal control group. However, controls from a database can also be used as representative controls (10, 11). We recruited controls from a database and excluded the control subjects referred for echocar-

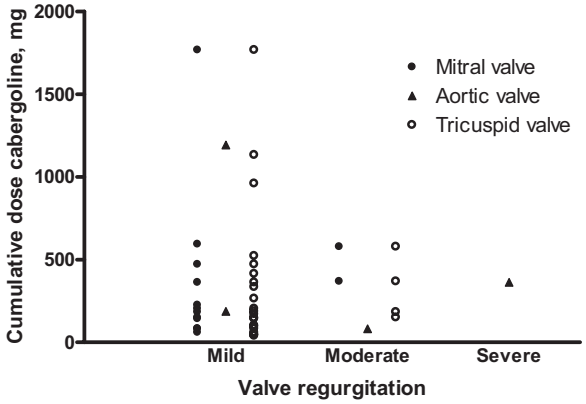

FIG. 1. There was no significant correlation between the cumulative dose of cabergoline and the presence of mild, moderate, or severe valve regurgitation of the mitral, aortic, and tricuspid valves in patients with prolactinomas.

diographic evaluation of known valvular heart disease, murmur, congestive heart failure, or cardiac transplantation. Other exclusion criteria were myocardial infarction in the preceding 5 yr, thyrotoxicosis, rheumatic fever, endocarditis, connective tissue disease, carcinoid syndrome, or use of anorectic drugs. Moreover, the prevalence of valvular regurgitation in our controls was within the range reported in large population-based studies (17). If selection bias of control subjects would nonetheless have occurred, this would have strengthened our conclusion because this would have overestimated the prevalence of valvular disease in the controls and consequently underestimated the effects of dopaminergic drugs in patients with prolactinomas.

In general, the prevalence of clinically relevant mitral, aortic, or tricuspid valve regurgitation was not significantly higher in patients, compared with controls. However, mild regurgitation of the tricuspid valve was significantly more prevalent in patients, compared with controls (41 *vs.* 26%) and especially when only the patients treated with cabergoline were compared with controls (43 *vs.* 26%), whereas pulmonary artery pressures were not significantly different between these groups. The number of patients with thickening of the mitral leaflets was borderline significant when compared between patients treated with cabergoline and patients not treated with cabergoline ($P = 0.056$, Table 4), and thickening of the tricuspid leaflets was significantly higher in patients treated with cabergoline, compared with control subjects. In addition, clinically relevant regurgitation of any valve was found borderline significant more frequent in the patients treated with cabergoline, compared with the patients not treated with cabergoline ($P = 0.062$).

It is interesting to note that by coincidence two patients treated with cabergoline had bicuspid aortic valve. One of these two patients had severe aortic regurgitation, which was an indication for cardiac surgery. We observed that eight of the nine patients with significant valve regurgitation were treated with cabergoline for mean period of 6.4 yr with a mean cumulative dose of 388 mg. Although we found no relationship between the cumulative dose of cabergoline and severity of valvular regurgitation, the data do raise the question of whether a high cumulative dose of cabergoline is associated with valvulopathy.

On pathological examination, the cardiac valve abnormalities, such as regurgitation and mitral valve thickening, seen with ergot-derived dopamine agonists have the appearance of myxoid degeneration, which resemble the appearance of valves obtained from patients treated with anorectic drugs [dexfenfluramine, (nor)fenfluramine], antimigraine ergot alkaloids drugs (ergotamine, methysergide) and patients with serotonin-secreting, carcinoid tumors (21–26). In accordance with those observations, stimulation of the serotoninergic system mediates the effects of dopamine agonists on cardiac valves. The ergot-derived dopamine agonists (cabergoline and pergolide) have binding affinity for D_2-receptors as well as serotonin (5HT) receptors, in particular the 5-HT_{2B} receptor, which are highly expressed on cardiac valves. Stimulation of 5-HT_{2B} receptors activates fibroblast mitogenesis, leading to valvular fibrosis and subsequent valvular dysfunction (23, 27). In contrast to bromocriptine and lisuride, which have a weak agonist activity, cabergoline and pergolide are potent agonists of 5-HT_{2B} receptors, with high affinity for 5-HT_{2B} receptors, compared with bromocriptine (28).

Remarkably, calcifications of the mitral valve and of the aortic valve were significantly more present in patients treated with cabergoline, compared with controls. The clinical relevance of calcifications of cardiac valves is unclear. Furthermore, the pathogenesis of these calcifications remains uncertain. Nonetheless, we cannot exclude that this might be an early sign of the activation of the serotoninergic system on cardiac valves. It cannot be excluded either that hyperprolactinemia influences cardiac valve architecture. Therefore, additional studies are warranted, with a special focus on the pathological examination of the affected valves. Increased prevalence of significant tricuspid regurgitation associates with right-sided-related cardiac valve disease in the carcinoid syndrome, supporting a pathological substrate in the association between ergot-derived dopamine agonists and activation of the serotoninergic system on cardiac valves (25, 29).

The current study does not confirm the associations previously observed in patients with Parkinson's disease between valvular regurgitation and treatment with the ergot-derived dopamine agonists pergolide or cabergoline. This may be related to differences in clinical characteristics between patients with Parkinson's disease and patients with prolactinomas. Patients with Parkinson's disease are much older than patients with prolactinomas. Moreover, there is a female preponderance in patients with prolactinomas. Finally, there are differences in the dosages of the dopamine agonists between the two diseases. In general, the dose of dopamine agonist treatment in Parkinson's disease is much higher than that used for treatment of prolactinomas. For example, the mean daily dose of cabergoline in the study of Zanettini *et al.* was 3.6 mg, whereas patients treated with cabergoline for prolactinoma in the present study received a mean dose of 1.3 mg/wk (10). We speculate that these discrepant factors are, at least in part, responsible for the discrepant associations between valvular heart disease and the use of dopamine agonists in these two conditions.

In the review process of the manuscript, there was concern with respect to the presentation of the data without adjustments for multiple comparisons. Simply defined, these adjustments test for no effects in all the primary end points undertaken *vs.* an effect in one or more of those end points (30, 31). This is a

TABLE 5. Valvular abnormalities in patients treated for prolactinomas with cabergoline and controls

Variable	Cabergoline (n = 47)	Control group (n = 78)	*P* value
Mitral valve			
Mitral regurgitation, n (%)			
No MR	33 (70)	60 (77)	0.405
MR grade mild	12 (26)	17 (22)	0.632
MR grade moderate	2 (4)	1 (1)	0.293
MR grade severe			
Mitral annulus, mm	31 ± 0.6	31 ± 0.5	0.901
Mean gradient, mm Hg	1.3 ± 0.08	1.3 ± 0.06	0.892
Mitral area, cm^2	2.9 ± 0.07	3.1 ± 0.03	0.012
Mitral valve morphology, n (%)			
Thickened leaflets	15 (32)	28 (36)	0.650
Calcifications	18 (38)	16 (21)	0.030
Leaflet motion abnormality	2 (4)	4 (5)	0.825
Aortic valve			
Aortic regurgitation, n (%)			
No AoR	43 (92)	68 (87)	0.459
AoR grade mild	2 (4)	10 (13)	0.115
AoR grade moderate	1 (2)		0.196
AoR grade severe	1 (2)		0.196
Aortic annulus, mm	19 ± 0.4	20 ± 0.2	0.120
Aortic sinus, mm	31 ± 0.7	31 ± 0.4	0.505
Sinotubular junction, mm	23 ± 0.6	24 ± 0.4	0.141
Ascending aorta, mm	30 ± 0.8	29 ± 0.6	0.599
Aortic area, cm^2	2.3 ± 0.10	2.5 ± 0.07	0.136
Mean gradient, mm Hg	4.0 ± 0.17	3.6 ± 0.15	0.127
Aortic valve morphology, n (%)			
Bicuspid	2 (4)	1 (1)	0.293
Thickened leaflets	12 (26)	13 (17)	0.230
Calcifications	21 (45)	14 (18)	0.001
Leaflet motion abnormality	3 (6)	1 (1)	0.117
Tricuspid valve			
Tricuspid regurgitation, n (%)			
No TR	23 (49)	56 (72)	0.010
TR grade mild	20 (43)	20 (26)	0.050
TR grade moderate	4 (9)	2 (3)	0.132
TR grade severe			
Pulmonary artery pressure, mm Hg	29 ± 1.0	30 ± 1.3	0.407
Tricuspid valve morphology, n (%)			
Thickened leaflets	3 (6)		0.024
Calcifications	1 (2)		0.196
Leaflet motion abnormality	1 (2)	1 (1)	0.715
Any significant valve regurgitation, n (%)	8 (17)	13 (17)	0.959
Any thickened leaflets, n (%)	22 (47)	31 (40)	0.439
Any calcifications, n (%)	26 (55)	26 (33)	0.016

Data are expressed as mean ± SE unless otherwise mentioned. The groups were compared with independent-samples *t* test or χ^2 tests when appropriate. MR, Mitral regurgitation; AoR, aortic regurgitation; TR, tricuspid regurgitation.

difficult methodological issue because there are divergent views on the need for statistical adjustment for multiplicity. This is also reflected in the Lancet papers by Schulz and Grimes (30, 31), who advocate a restrictive approach toward adjustments for multiple comparisons. If we consider our own data and if we would assume that the differences would mostly reflect false-positive results, it is to be expected that the positive significant results would have been randomly distributed among the different variables. However, this is not the case, as shown in Tables 3–5. Moreover, there are several arguments that dopamine agonists can indeed cause valvular pathology. We designed this study in our patients treated with dopamine agonists for prolactinoma with the primary aim to evaluate valvular morphology and function in detail, in view of the documented abnormalities found in patients with Parkinson's disease. Indeed, the main results of our study point toward the same adverse effect of dopamine agonists in patients with prolactinoma. In the patients with Parkinson's disease, a reasonable pathological mechanism for valvular pathology through activation of the serotonin receptor was proposed. According to Schulz and Grimes, statistical adjustments somewhat rescue the positive results of scattershot analyses. However, we performed a targeted evaluation and analysis focused on valvular pathology related to the use of dopamine agonists rather than a scattershot analysis. Therefore, in our opinion, our data should not be neglected merely because of the absence of adjustments for multiple comparisons. Moreover, this would carry

the serious risk of missing an important association between the use of dopamine agonists and valvular pathology.

In conclusion, this study indicates that several years of treatment with dopamine agonists is associated with an increased prevalence of aortic valve calcification and mild tricuspid regurgitation in patients with prolactinomas. However, this treatment was not associated with an increased prevalence of clinically relevant valvular heart disease. These data indicate that additional studies on the adverse cardiac effects of dopaminergic drugs in prolactinoma are warranted, especially in patients with much longer use of these drugs, than documented in the present study.

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Address all correspondence and requests for reprints to: M. Kars, M.D., Department of Endocrinology and Metabolic Diseases, C4-R, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands. E-mail: m.kars@lumc.nl.

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