CLINICAL STUDY

Increased prevalence of subclinical cardiac valve fibrosis in patients with prolactinomas on long-term bromocriptine and cabergoline treatment

Atanaska Elenkova¹, Rabhat Shabani², Krassimir Kalinov³ and Sabina Zacharieva¹

¹Clinical Centre of Endocrinology, USHATE Acad.Ivan Pentchev' and ²Department of Internal Medicine, UMHAT 'Alexandrovka', Medical University, Sofia, Bulgaria and ³Department of Informatics, New Bulgarian University, Sofia, Bulgaria

(Correspondence should be addressed to A Elenkova; Email: atanaska@yahoo.com)

Abstract

Background: In contrast to cabergoline, evidence-based information about a possible profibrotic effect of bromocriptine in prolactinoma patients is extremely limited.

Objective: To assess the prevalence of valvular lesions among patients on long-term bromocriptine or cabergoline therapy.

Design: Case–control study.

Methods: A transthoracic echocardiographic evaluation was performed in 334 subjects divided into four groups: 103 cabergoline treated, 55 bromocriptine treated, 74 naïve patients, and 102 controls. **Results:** Clinically relevant valve regurgitations were equally prevalent in all investigated groups whereas subclinical valve fibrosis was significantly more frequent in both bromocriptine- and cabergoline-treated patients (40 vs 43.6 vs 21.6 vs 23.5%; $P=0.004$). The odds ratio (OR) for developing valvular fibrosis was 2.27 (95% CI 1.17–4.41; $P=0.016$) for cabergoline and 2.66 (95% CI 1.22–5.78; $P=0.014$) for bromocriptine groups compared with subjects not exposed to dopamine agonists (DAs). A significantly higher pulmonary arterial pressure corresponding to the longer treatment duration was observed among patients taking bromocriptine compared with cabergoline-treated subjects.

Conclusions: Long-term treatment with cabergoline and bromocriptine seems not to be associated with an increased risk of clinically significant valve disease but possible subclinical lesions should be expected. An echocardiographic examination is recommended at the beginning and periodically during therapy with DAs acting as full or partial agonists of 5-hydroxytryptamine 2B receptors (cabergoline and bromocriptine). Bromocriptine seems not to be a safe alternative for patients receiving cabergoline treatment who have preexisting or diagnosed abnormalities suggesting valvular, interstitial myocardial, or pulmonary fibrosis. Further studies are needed to investigate the possible impact of DA treatment on pulmonary arterial pressure.

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Introduction

Several cross-sectional studies have demonstrated a significantly increased risk of valvular fibrosis in Parkinson's patients treated with the ergot-derived dopamine agonists (DAs) pergolide and cabergoline (1, 2, 3, 4, 5, 6). Extensive research over the last decade has highlighted the crucial role of 5-hydroxytryptamine 2B receptors (HTR2B) in the pathogenesis of this fibrotic valvular heart disease (FVHD) (7). Agonism of HTR2B is not a class effect of the ergolines: pergolide and cabergoline have been shown to exert full agonistic activity whereas lisuride and terguride are potent HTR2B antagonists (8, 9). As ergot-derived DAs represent the first-line agents for the management of

prolactinomas, the risk of FVHD in patients on long-term cabergoline treatment has been one of the current 'hot topics' in endocrine research. In contrast, evidence-based information about a possible profibrotic effect of bromocriptine is extremely limited. Although numerous cases of bromocriptine-associated fibrosis have been reported in the literature, only two studies have provided data on the prevalence of valve regurgitations in bromocriptine-treated patients with Parkinson's disease (10, 11, 12, 13, 14). Even less is known about the long-term bromocriptine cardiovascular safety in patients with prolactinomas. To date, results of only one very small case–control study comprising a separate group of 19 bromocriptine-treated patients have been published (15).

Materials and methods

Study design

This observational case-control study was conducted as part of a scientific research project approved by the Central Committee on Research Ethics at the Bulgarian Ministry of Education and Science. The primary objective was to investigate the prevalence of FVHD among patients on long-term bromocriptine therapy compared with cabergoline-treated subjects, medically naïve patients, and healthy controls. In a prospective design from May 2008 to October 2011, a total number of 424 candidates were screened, of whom 338 subjects were recruited. Study participants were enrolled into four groups: group A consisted of 105 patients with prolactinomas taking cabergoline; group B of 57 patients on bromocriptine therapy; group C of 74 newly diagnosed medically naïve patients; and group D of 102 control subjects, recruited among medical staff and their acquaintances. Inclusion criteria for groups A, B, and C: diagnosis of prolactinoma based on current guidelines; for groups A and B: treatment with one DA for at least 12 months before the study; for group D: control group frequency-matched for age, sex, obesity, and arterial hypertension. Exclusion criteria were: i) severe, untreated, or uncontrolled arterial hypertension; ii) ischemic heart disease (all forms); iii) history of previous or concomitant cardiac disease with a substantial risk of heart damage such as myocarditis, pericarditis, rheumatism, connective tissue diseases, and hyperthyroidism; iv) current or previous use of drugs with potential profibrotic effects on heart valves; v) use of more than one DA for treatment of prolactinoma; vi) hyperprolactinemia of nontumoral origin; vii) cosecretion of prolactin and GH (somatoprolactinomas); and viii) Parkinson's disease. The screen failure rate was 39% (86 patients) and was mainly determined by the great number of patients switched from one DA to another. Four participants were excluded from the study: two cabergoline-treated males because of unstable angina, one patient taking bromocriptine with moderate tricuspid regurgitation and a history of rheumatic fever (data were provided by the patient after performing the study procedures), and one young woman on bromocriptine therapy with suspected bicuspid aortic valve who refused the confirmatory transesophageal echocardiography. Data of 334 participants (study completers) were analyzed: 103 cabergoline treated, 55 bromocriptine taking, 74 *de novo* patients, and 102 healthy controls.

Study procedures

Study procedures were performed after signing a specific informed consent by participants and study investigators.

Patient history Data about tumor size, prolactin levels at diagnosis and study entry, treatment duration, initial and therapeutic dose of DA, previous and concomitant diseases, and medication were collected.

Anthropometric parameters Height, weight, and blood pressure (BP) were measured in all the study participants. Arterial hypertension was defined as elevated arterial BP, with systolic pressure over 140 mm Hg and/or diastolic pressure over 90 mm Hg at the time of diagnosis according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (16). Body surface area (BSA) was calculated using the Mosteller formula (17). Office BP was measured in standard fashion with the patient sitting for 5 min. Three measurements were taken and averaged to give the office BP used in this analysis.

Echocardiography A transthoracic M-mode and two-dimensional, with pulsed wave (PW), continuous wave (CW) and Color Doppler echocardiography was performed in all investigated subjects by one experienced cardiologist-echocardiographer who was blind to the study participants' data. All echocardiograms were performed using Toshiba Power Vision 6000 Ultrasound machine. Severity of mitral, aortic, and tricuspid regurgitation was categorized according to the recommendations of the American Society of Echocardiography as follows: none (grade 0), trace (grade 1), mild (grade 2), moderate (grade 3), and severe (grade 4) (18). Pulmonary regurgitation (PR) was graded as mild, moderate, or severe by using two different methods based on color flow imaging according to the current guidelines of the European Association of Echocardiography (19). In order to avoid false-positive results, PR of grade 1 (trace) was not taken into consideration. Valve regurgitation of at least grade 2 for the aortic valve and grade 3 or 4 for mitral, tricuspid, or pulmonary valves was considered clinically significant (18). In case of tricuspid regurgitation, systolic pulmonary arterial pressure (PAPS) was estimated using the modified Bernoulli equation. Mean pulmonary pressure (mPAP) was calculated using the following formula: $mPAP = 0.61 \times PAPS + 2$ mm Hg (20). Pulmonary hypertension was defined by systolic and mean pulmonary artery pressures of more than 40 and 25 mmHg respectively. The following parameters were measured on M-mode tracing: end-systolic and end-diastolic interventricular septum thickness systole (IVSTS and IVSTD), left ventricular internal end-systolic and end-diastolic diameters (LVIDS and LVIDD), and posterior wall thickness in systole and diastole (PWTS and PWTD). Left atrium (LA) diameter, maximum aortic diameter (AO), end-diastolic volume (EDV), end-systolic volume (ESV), and stroke volume (SV) presented as indices ($X_i = X/BSA$) were also compared between investigated study groups. Left ventricular mass indexed for BSA (LVMI) was calculated by Penn cube method according to Devereux's formula: $LVMI (g/m^2) = (1.04 \times (IVST + LVID + PWT)^3 - (LVID)^3 - 13.6) / BSA$ (21). LVMI

$\geq 110 \text{ g/m}^2$ in women and $\geq 134 \text{ g/m}^2$ in men were accepted as cutoff points for left ventricular hypertrophy (21). Assessment of the left ventricular systolic function was mainly based on the ejection fraction (EF) and shortening fraction (EFS) with normal values respectively: EF $> 50\%$ and EFS from 30 to 45%. Diastolic function of the left ventricle was assessed by isovolumic relaxation time (IVRT) and deceleration time (DTE). Values of IVRT over 100 ms and DTE over 240 ms indicated impaired left ventricular relaxation. Restrictive transmitral filling was considered present when DTE was ≤ 140 ms. Structural abnormalities of valvular cusps and annuluses were also evaluated using cross-sectional echocardiogram. Subclinical valvular fibrosis (SCVF) was defined as fibrosis (with or without calcification) not accompanied by regurgitation of any degree. SCVF was considered present in all cases with increased echogenicity (hyperechogenicity) and thickness of valvular cusps (> 3 mm for mitral valve; > 2 mm for aortic, tricuspid, and pulmonic valves). Mitral valve prolapse (MVP) was defined as abnormal systolic valve movement of one or both mitral leaflets toward the LA (≥ 2 mm beyond the annular plane). Based on the thickness (d) of the mitral valve leaflets, MVP was classified as nonclassic ($d \leq 5$ mm) and classic ($d > 5$ mm) subtypes.

Assay methods Serum prolactin concentrations at study entry were measured by RIA (PRL-IRMA Kit, DAsource Immunoassays, Belgium) with an analytical sensitivity $< 0.35 \text{ ng/ml}$ (10.15 mIU/l) and detection range $10.15\text{--}3857 \text{ mIU/l}$. The intra- and interassay coefficients of variation were 5.2 and 4.5% respectively. The reference intervals for males were $52.2\text{--}561.1 \text{ mIU/l}$; for premenopausal women: $78.3\text{--}571.3 \text{ mIU/l}$; and for postmenopausal women: $55.1\text{--}519.1 \text{ mIU/l}$.

Statistical analysis

The following statistical methods were used for data description and statistical inferences.

Descriptive methods Metric variables were described by n (number of observations), arithmetic mean, s.d., and range (minimum and maximum). Nonmetric variables were described by n (number of observations) and relative frequency distribution (in percentage).

Methods for statistical inference One-way ANOVA was applied in the case of more than two groups. Multiple *post hoc* comparisons were made according to the Student–Newman–Keuls approach. Student's t -test was used when there were two groups. The hypotheses about nonmetric variables were tested by χ^2 test. Where possible, the Fisher's exact observed significance level was calculated. Kruskal–Wallis and Mann–Whitney nonparametric tests were used as an addition to parametric ANOVA and t -test. Pearson's correlation coefficient r and η coefficient were used to discover the relationships between variables. The decision was accepted to reject the null hypothesis (of no difference) if the observed significance (P value) was < 0.05 (significance level).

Results

The clinical characteristics of study participants are summarized in Table 1. Investigated groups did not differ by age, BMI, BSA, and systolic blood pressure and diastolic blood pressure. All the three patient groups had comparable percentages of subjects with arterial hypertension, macroadenomas, and hypopituitarism. Patients taking bromocriptine had significantly longer treatment duration compared with cabergoline-treated subjects (58.98 ± 47.03 vs 46.5 ± 27.6 months; $P = 0.037$).

The main parameters obtained by transthoracic echocardiography are depicted in Table 2. Student–Newman–Keuls *post hoc* analysis revealed a significantly higher IVSTD in bromocriptine- and cabergoline-treated patients compared with *de novo* patients and healthy

Table 1 Clinical characteristics of study subjects (data are expressed as mean $\pm$ s.d.).

	Group A, cabergoline	Group B, bromocriptine	Group C, naïve patients	Group D, healthy subjects	P
n	103	55	74	102	
Women/men	82/21	44/11	58/16	81/21	0.997
Age (years)	38.6 ± 9.93	39.1 ± 11.3	35.0 ± 9.85	38.0 ± 9.65	0.072
Macroprolactinomas (n (%))	31 (30.1)	16 (29.1)	22 (29.8)	–	1.000
Arterial hypertension (n (%))	15 (14.6)	9 (16.4)	11 (14.9)	15 (14.7)	0.994
SBP (mm Hg)	119.2 ± 10.5	122.4 ± 11.4	120.8 ± 9.37	122.0 ± 7.90	0.106
DBP (mm Hg)	76.3 ± 6.59	78.2 ± 7.52	77.2 ± 7.09	75.4 ± 5.14	0.419
BMI (kg/m^2)	26.1 ± 6.60	26.6 ± 6.20	26.3 ± 6.37	26.0 ± 6.42	0.944
BSA (m^2)	1.90 ± 0.27	1.91 ± 0.27	1.92 ± 0.29	1.89 ± 0.26	0.991
Hypopituitarism (n (%))	7 (12.7)	14 (13.6)	10 (13.5)	–	1.000
sPRL levels at study entry (mIU/l)	583.9 ± 1040.6	841.9 ± 978.22	$6474.86 \pm 16\,384.8$	353.4 ± 187.04	< 0.001
Treatment duration (range, m)	46.5 ± 27.6 (12–128)	58.98 ± 47.03 (12–240)	–	–	0.037
CD (range, mg)	173.9 (24–1322)	9 427 491 (900–45 000)	–	–	

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; BSA, body surface area; CD, cumulative dose.

Table 2 Echocardiographic parameters of patients and healthy controls (data are expressed as mean $\pm$ S.D.).

	Group A, cabergoline	Group B, bromocriptine	Group C, naïve patients	Group D, healthy subjects	P
n	103	55	74	102	
LVIDS (mm)	27.4 $\pm$ 4.67	28.4 $\pm$ 6.1	27.5 $\pm$ 5.09	27.7 $\pm$ 6.06	0.747
LVIDD (mm)	44.1 $\pm$ 4.62	44.9 $\pm$ 5.19	44.0 $\pm$ 5.79	44.6 $\pm$ 4.53	0.666
IVSTS (mm)	13.5 $\pm$ 1.85	13.8 $\pm$ 2.13	13.5 $\pm$ 2.00	13.6 $\pm$ 1.37	0.833
IVSTD (mm)	9.49 $\pm$ 1.81	10.0 $\pm$ 1.88	9.28 $\pm$ 1.60	9.19 $\pm$ 1.43	0.027
PWTS (mm)	14.7 $\pm$ 2.65	15.1 $\pm$ 4.14	14.4 $\pm$ 2.16	14.5 $\pm$ 1.84	0.426
PWTD (mm)	9.60 $\pm$ 1.73	9.72 $\pm$ 1.85	9.23 $\pm$ 1.43	9.31 $\pm$ 1.25	0.183
LAI (mm/m ²)	18.5 $\pm$ 2.44	18.4 $\pm$ 2.68	17.8 $\pm$ 2.22	17.9 $\pm$ 2.13	0.134
LVM (g/m ²)	97.4 $\pm$ 24.9	104.5 $\pm$ 30.4	93.1 $\pm$ 24.1	95.1 $\pm$ 20.9	0.057
AOi (mm/m ²)	16.5 $\pm$ 2.34	16.9 $\pm$ 2.59	16.2 $\pm$ 2.14	16.2 $\pm$ 2.23	0.257
EF (%)	68.3 $\pm$ 7.87	67.7 $\pm$ 7.14	67.9 $\pm$ 8.61	69.5 $\pm$ 6.84	0.410
FS (%)	38.2 $\pm$ 6.37	38.4 $\pm$ 5.17	37.9 $\pm$ 6.32	39.4 $\pm$ 5.51	0.377
DTE (ms)	165.4 $\pm$ 28.81	172.7 $\pm$ 34.98	167.8 $\pm$ 36.26	163.9 $\pm$ 22.62	0.364
IVRT (ms)	87.3 $\pm$ 13.44	93.36 $\pm$ 19.29	89.32 $\pm$ 19.59	83.95 $\pm$ 8.38	0.003
EDVi (ml/m ²)	52.1 $\pm$ 11.63	53.5 $\pm$ 13.06	49.4 $\pm$ 10.73	51.4 $\pm$ 10.27	0.226
ESVi (ml/m ²)	16.6 $\pm$ 5.14	17.3 $\pm$ 5.78	15.9 $\pm$ 4.63	15.6 $\pm$ 4.37	0.156
SVi (ml/m ²)	35.5 $\pm$ 9.09	36.1 $\pm$ 9.70	33.5 $\pm$ 8.44	35.8 $\pm$ 7.99	0.267
PAPS (mm Hg)	25.56 $\pm$ 4.41 (n=60)	27.93 $\pm$ 4.50 (n=37)	24.93 $\pm$ 4.33 (n=34)	25.55 $\pm$ 4.44 (n=53)	0.039
mPAP (mm Hg)	17.6 $\pm$ 2.69 (n=60)	19.0 $\pm$ 2.74 (n=37)	17.2 $\pm$ 2.64 (n=37)	17.6 $\pm$ 2.71 (n=53)	0.039

IVSTD, interventricular septum thickness diastole; IVSTS, interventricular septum thickness systole; PWTD, posterior wall thickness diastole; PWTS, posterior wall thickness systole; LVMi, left ventricular mass index; EF, ejection fraction; EFS, ejection fractional shortening; IVRT, isovolumic relaxation time; DTE, deceleration time; LAi, left atrium; AO, maximum aortic diameter; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; PAPS, systolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure.

controls ($P < 0.05$). This parameter was comparable between subjects not exposed to DAs (naïve patients vs healthy controls: $P = 0.491$). No differences were found in the other left ventricular and LA dimensions as well as the parameters related to left ventricular function between all investigated groups. LVMi was nonsignificantly higher in bromocriptine group in comparison with the other study groups (104.5 ± 30.4 vs 97.4 ± 24.9 vs 93.1 ± 24.1 vs 95.1 ± 20.9 ; $P = 0.057$). On the basis of additional analyses, we excluded the testosterone-induced cardiac hypertrophy in male subjects as a possible factor influencing LVM. None of the study participants were diagnosed with pulmonary hypertension even though significantly higher systolic (PAPS) and mean arterial pulmonary pressures (mPAP) as well as significantly prolonged IVRT were registered in bromocriptine-treated patients compared with the other study groups.

Data on the prevalence of cardiac valve lesions are presented in Table 3. Mitral regurgitation (MR) was equally prevalent in all investigated groups (27.2 vs 27.3 vs 24.3 vs 29.4%; $P = 0.912$). None of the study participants were classified as having clinically relevant (moderate or severe) MR. MVP was detected in 5.1% of patients ($n = 12$) and in 3.9% ($n = 4$) of healthy subjects. In all registered cases, MVP was classified as nonclassic prolapse of one mitral leaflet and was not associated with clinically relevant regurgitation. No significant differences were found in the prevalence of aortic regurgitation (AR) between four study groups (5.8 vs 10.9 vs 4.1 vs 2%; $P = 0.113$). PR of more than trace degree (mild, grade 2) was detected in one woman on bromocriptine treatment. We did not find significant

differences in the prevalence of either pathological or clinically significant regurgitations of the mitral, aortic, or pulmonary valves between investigated groups. Prevalence of tricuspid regurgitation (all grades) was comparable in all investigated groups (58.3 vs 67.3 vs 45.9 vs 52.0%; $P = 0.086$), but controversial results were obtained when the frequencies of only pathological regurgitations were analyzed: 3.9 vs 7.3 vs 5.4 vs 0%; $P = 0.079$ (Pearson's χ^2); $P = 0.029$ (Fisher's exact test). Paired comparisons revealed a significant difference between bromocriptine-treated and healthy subjects ($P = 0.014$) as well as a borderline significance between cabergoline-treated patients and healthy controls ($P = 0.062$).

Hemodynamically relevant regurgitations were observed in four study participants: three patients with mild AR (two cabergoline and one bromocriptine treated) and one newly diagnosed patient with moderate tricuspid regurgitation. Their main characteristics are shown in Table 4. Partial hypopituitarism (hypogonadism and hypothyroidism) was present in one patient and mild-to-moderate well-controlled arterial hypertension in three of them. All the four subjects were asymptomatic.

Statistically higher frequency of SCVF (with or without calcinosis) not accompanied by regurgitation was found in medically treated patients (cabergoline and bromocriptine) compared with *de novo* patients and healthy controls (40 vs 43.6 vs 21.6 vs 23.5%; $P = 0.004$). Monovalvular involvement was observed in relatively small comparable proportions of subjects in all investigated groups (Table 3). In the majority of cases, there was bi- or trivalvular involvement,

Table 3 Prevalence of valvular lesions in patients and healthy subjects.

<i>n</i>	Group A, cabergoline	Group B, bromocriptine	Group C, naïve patients	Group D, healthy subjects	<i>P</i>	
					Pearson's χ^2	Fisher's exact test
MiR total % (<i>n</i>)	27.2 (28)	27.3 (15)	24.3 (18)	29.4 (30)	0.909	0.912
Pathological regurgitations	3.9 (4)	5.5 (3)	2.7 (2)	1 (1)	0.427	0.407
Clinically relevant regurgitations	Ø	Ø	Ø	Ø		
AoR total % (<i>n</i>)	5.8 (6)	10.9 (6)	4.1 (3)	2 (2)	0.103	0.113
Pathological regurgitations	2 (2)	3.6 (2)	Ø	Ø	0.106	0.106
Clinically relevant regurgitations ^a	2 (2)	1.8 (1)	Ø	Ø	0.344	0.344
PR total % (<i>n</i>)						
Pathological regurgitations	Ø	1.8 (1)	Ø	Ø	0.383	0.383
Clinically relevant regurgitations	Ø	Ø	Ø	Ø		
TR total % (<i>n</i>)	58.3 (60)	67.3 (37)	45.9 (34)	52.0 (53)	0.086	0.086
Pathological regurgitations	3.9 (4)	7.3 (4)	5.4 (4)	Ø	0.079	0.029
Clinically relevant regurgitations ^b	Ø	Ø	1.4 (1)	Ø	0.384	0.384
All hemodynamically relevant regurgitations (<i>n</i> , %)	2 (2)	1.8 (1)	1.4 (1)	0 (0)	0.645	0.535
Subclinical valvular fibrosis (<i>n</i> , %)	40 (41)	43.6 (24)	21.6 (16)	23.5 (24)	0.004	0.004
Monovalvular involvement (without regurgitation)	3 (3)	3.6 (2)	2.7 (2)	4.9 (5)	0.847	0.894
Bi- or trivalvular involvement (with regurgitation of 0–2 valves)	37 (38)	40 (22)	18.9 (14)	18.6 (19)	0.001	0.001

^aMild aortic regurgitation (grade 2).^bModerate tricuspid regurgitation (grade 3).

i.e. coexistence of SCVF of one or two valves and trace or mild regurgitation of another valve(s). Fibrosis of more than one valve was twice as common in both groups of DA-treated patients than in *de novo* patients and healthy controls (Table 3). Hemodynamically relevant regurgitations were not registered among these subjects.

In addition, asymptomatic pericardial effusions (50 and 150 ml respectively) were detected in two female patients treated with cabergoline and bromocriptine respectively.

Logistic regression analysis was performed to evaluate the predictive value of age, sex, arterial hypertension, and DAs (treatment duration and cumulative dose) as risk factors for valvular fibrosis. It was confirmed that age (odds ratio (OR) 1.07, 95% CI 1.04–1.10; $P < 0.0001$) and arterial hypertension (OR 2.35; 95% CI 1.16–4.41; $P = 0.018$) significantly elevated the risk of valvular fibrosis. In contrast, gender (OR 1.13; 95%

CI 0.55–2.30; $P = 0.739$) and hypopituitarism (OR 1.07; 95% CI 0.39–2.91; $P = 0.899$) were not associated with an increased valve fibrotic risk. We found a significantly increased risk of valvular fibrosis in both groups of DA-treated patients compared with healthy controls: cabergoline- and bromocriptine-treated patients are 2.27 times (OR 2.27 95% CI 1.17–4.41; $P = 0.016$) and 2.66 times (OR 2.66 95% CI 1.22–5.78; $P = 0.014$) respectively more likely to develop valve fibrosis compared with subjects not exposed to DAs. Naïve prolactinoma patients did not differ from the healthy subjects in respect of their valve fibrosis risk (OR 1.08; 95% CI 0.49–2.38; $P = 0.846$; Fig. 1; Table 5).

We found a strong quadratic relationship between valve fibrosis and treatment duration in both cabergoline- and bromocriptine-treated patients (η coefficients of correlation: 0.773 and 0.865 respectively). A similar nonlinear correlation between fibrosis and cumulative

Table 4 Characteristics of the subjects with clinically relevant regurgitations.

Age (years)	Sex	Group	AH ^a	Hypopi- tuitarism	TD (m)	CD (mg)	Affected valves/grade of regurgitation		
							Mitral	Aortic	Tricuspid
50	F	Cabergoline	N	N	48	96	Fibrosis (grade 0)	Fibrocalcinosis (grade 2)	Fibrosis (grade 1)
62	M	Cabergoline	Y	N	96	284	Fibrocalcinosis (grade 1)	Fibrocalcinosis (grade 2)	Fibrosis (grade 1)
50	F	Bromocriptine	N	N	240	36 000	Fibrosis (grade 2)	Fibrosis (grade 2)	Fibrosis (grade 1)
69	M	Naïve patient	Y	Y	–	–	Fibrosis (grade 1)	Fibrosis (grade 0)	Fibrosis (grade 3)

Y, yes; N, no. AH, arterial hypertension; TD, treatment duration; CD, cumulative dose

Figure 1 Relative risk for development of subclinical valvular fibrosis in bromocriptine-treated, cabergoline-treated, and medically naïve prolactinoma patients in comparison with healthy subjects.

dose was also observed ($\eta=0.888$ for cabergoline and $\eta=0.896$ for bromocriptine groups). For comparison, the respective Pearson's coefficients were 0.117, -0.073 and 0.280 , 0.238 .

Discussion

Our results demonstrate that the long-term treatment with the ergo-derived DAs cabergoline and bromocriptine in patients with prolactinomas is not associated with clinically relevant cardiac valve regurgitation. On the other hand, we have found an increased prevalence and a significantly elevated risk for development of subclinical valve fibrosis among cabergoline- and bromocriptine-treated subjects in comparison with medically naïve patients and healthy controls. Furthermore, fibrosis of more than one valve was twice as common in both groups of DA-treated patients than in *de novo* patients and healthy controls in contrast to monovalvular involvement, which was equally prevalent in all study groups. Data analysis, however, showed that the valve fibrosis is nonlinearly related to either cabergoline or bromocriptine treatment duration and to the cumulative dose. Quadratic model seems to fit the data best. A clear linear dose and duration dependency of fibrotic valvular disease was found in Parkinsonian patients who are usually treated with approximately tenfold higher doses than the prolactinoma patients (6, 22). In contrast, results of the previous studies in prolactinoma patients are controversial, but most of them reported no linear relation between the severity of valvular lesions and cumulative dose (23, 24, 25, 26, 27, 28). We could, therefore, suggest that the dose-response relationship may be different in low- and high-dose regimens. Another possible explanation could be that at low doses, valvular fibrosis could develop only in the presence of additional profibrotic factors (genetic predisposition, unknown underlying valvular degenerative disease, hypertension, etc.).

Table 5 Relative risk for the development of subclinical valvular fibrosis in bromocriptine-treated, cabergoline-treated, and medically naïve prolactinoma patients in comparison with healthy subjects.

	<i>P</i>	Odds ratio	95% CI	
			Lower	Upper
Age	0.000	1.070	1.040	1.100
Hypopituitarism	0.899	1.067	0.391	2.912
Hypertension	0.018	2.350	1.160	4.410
Gender	0.739	1.129	0.554	2.301
Naïve patients	0.846	1.081	0.491	2.380
Bromocriptine	0.014	2.658	1.223	5.775
Cabergoline	0.016	2.269	1.168	4.406

Results from ten observational studies investigating the risk of fibrotic valvulopathy in cabergoline-treated patients have been published to date (23, 24, 25, 26, 27, 28, 29, 30, 31, 32). Five of them have shown no relevant findings (24, 25, 27, 29, 30). Four trials have demonstrated an increased prevalence of clinically insignificant valvular changes such as mild tricuspid regurgitation (23, 28, 32), pulmonic regurgitation (32), aortic calcification (28), and an increased mitral tenting area (26). So far, only one study has reported an increased prevalence of moderate tricuspid regurgitation with a positive correlation between cumulative dose and the risk of clinically relevant valvular damage in subjects with prolactinomas taking cabergoline (31). In contrast, evidence-based information about a potential profibrotic effect of bromocriptine is scarce. A possible explanation could be the fact that bromocriptine has been previously incorrectly considered to be an antagonist of HTR2B (33). As opposed to this concept, Tan *et al.* (22) have demonstrated an elevated dose-dependent risk of FVHD in bromocriptine-treated subjects with Parkinson's disease. In addition, there have been reports in the literature of pleuropulmonary, pericardial, retroperitoneal, and cardiac valve fibrosis in patients on long-term bromocriptine therapy (10, 11, 12, 13, 14, 15). These data are consistent with the recent evidence for partial agonistic activity of bromocriptine on HTR2B (34).

Recruitment of patients on bromocriptine is extremely difficult because cabergoline with its superior efficacy and tolerability has almost completely replaced bromocriptine as a first choice of drug for treatment of prolactinomas. Subjects on bromocriptine therapy have been included in only two studies published so far. In the cross-sectional study of Kars *et al.* (28), comparisons were made between a group of patients on cabergoline therapy and a combined group of subjects treated with three other DAs with completely different activity on HTR2B: bromocriptine (partial agonist), quinagolide (non-ergoline derivative), and terguride (potent HTR2B antagonist). The study of Bogushevsky *et al.* (15) has included a separate, but very small from a statistical point of view, sample of bromocriptine-taking subjects ($n=19$). To our knowledge, our study is the first

statistically powerful study to investigate the impact of long-term bromocriptine treatment on cardiac valves in patients with prolactinomas. We did not demonstrate significant difference in frequency of clinically relevant regurgitation of any valve between cabergoline-treated, bromocriptine-treated, medically naïve patients and healthy subjects. These results are not unexpected given the fact that the usual doses for treatment of prolactinomas are considerably less than those for Parkinson's disease. The highest cabergoline cumulative dose (1.32 g) in our study is three times lower than the doses associated with an increased relative risk for FVHD in Parkinson's patients. The hemodynamically significant regurgitations in our patients were even less common than in the general population (35, 36). This is not surprising considering the relatively young age of the study participants and exclusion of subjects with severe, uncontrolled, or long-lasting arterial hypertension as well as ischemic heart disease and all other factors with a potential profibrotic action. According to the largest population-based studies, age and hypertension are two of the most important clinical determinants of the valvular regurgitations' prevalence and severity (35, 36, 37). As a consequence of the restrictive exclusion criteria, only eight of our patients were diagnosed with clinically significant regurgitations. Four (50%) of them dropped out after performing the study procedures: three patients who met the exclusion criteria and one patient because of a suspected bicuspid aortic valve. Data of the remaining four patients were analyzed. Although the age, the presence of arterial hypertension, and multivalvular involvement suggest an underlying degenerative valve disease in three of them, there are some contra-arguments. Calcific aortic stenosis and mitral insufficiency are the most typical degenerative valve lesions, whereas we found aortic and tricuspid regurgitations and did not observe any pathological mitral lesions. We could not exclude the drug-induced valvular fibrosis in the last patient, a 50-year-old woman without any potential risk factors for valvulopathy. She has been exposed to a very high cumulative dose (36 g) as a result of 20-year treatment with bromocriptine.

Surprisingly, although none of the investigated subjects were diagnosed with pulmonary hypertension, the systolic and mean arterial pulmonary pressures were significantly higher in the bromocriptine group compared with the other study groups. One recent meta-analysis based on the data from well-designed observational trials has shown an increase in pulmonary artery pressure in pergolide-treated Parkinsonian patients (38). Of note, Colao *et al.* (31) reported pulmonary hypertension in a substantial proportion of cabergoline-treated subjects with prolactinomas.

Hemodynamically, arterial pulmonary pressure may be elevated by an increase in right ventricular output, pulmonary venous pressure, or pulmonary vascular resistance (PVR). As there was no evidence for the

presence of the first two mechanisms in our patients, higher PVR may be presumed. Drug-induced interstitial lung fibrosis and 5-HT-mediated vasoconstriction could be speculatively discussed as probable underlying causes. Such a hypothesis seems possible in the light of recent data supporting the crucial role of HTR1B and HTR2B receptors in the pathogenesis of pulmonary arterial hypertension in humans (39, 40, 41). Significantly prolonged IVRT in our patients on bromocriptine and even the increased LVM index could also be speculatively explained by underlying interstitial myocardial fibrosis due to 5-HT1b-mediated collagen oversecretion by human cardiac myofibroblasts. As both bromocriptine and cabergoline are potent HTR1B agonists, (33) significantly higher values of these parameters in the bromocriptine group could be explained by the statistically longer treatment duration compared with the cabergoline group. All these mechanisms are hypothetical in the absence of data from prospective studies investigating pulmonary function in patients on long-term DA treatment.

This study has several major advantages. This is the first study with sufficient statistical power to investigate the potential effect of long-term bromocriptine treatment on cardiac valves in patients with prolactinomas. Secondly, the control group consisted of randomly selected healthy subjects without clinical indication for echocardiography. Thus, we avoided the selection bias of some previous studies in which the control groups have been recruited from echocardiographic databases (25, 29). In addition, we eliminated the influence of the most important risk factors for development of fibrotic valvulopathy such as advanced age, severe and uncontrolled arterial hypertension, and ischemic heart disease. Finally, special attention was given to the pulmonary hypertension as a potential adverse event in the high-dose DA therapy.

Conclusions

Long-term treatment with cabergoline and bromocriptine at conventional doses and with duration in accordance to the current guidelines for the management of prolactinomas seems not to be associated with an increased risk of clinically significant valvular heart disease but possible subclinical valvular changes could be expected. Large prospective studies are needed to identify the risk in subjects with invasive macroadenomas who are usually under lifelong high-dose DA treatment. We strongly recommend an echocardiographic examination in patients with prolactinomas before and periodically during therapy with DAs acting as full or partial agonists of 5-hydroxytryptamine 2B receptors (cabergoline and bromocriptine). Based on the recent data about the upregulation of HTR1B and HTR2B receptors in the pathogenesis of pulmonary hypertension, further studies are needed to investigate

the possible impact of long-term DA treatment on pulmonary arterial pressure. Bromocriptine seems not to be a safe alternative in subjects receiving cabergoline treatment who have preexisting or diagnosed abnormalities, suggesting valvular or interstitial myocardial or pulmonary fibrosis.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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