Increased Prevalence of Tricuspid Regurgitation in Patients with Prolactinomas Chronically Treated with Cabergoline

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Background: Cabergoline, a dopamine receptor-2 agonist used to treat prolactinomas, was associated with increased risk of cardiac valve disease in Parkinson's disease.

Objective: Our objective was to evaluate prevalence of cardiac valve regurgitation in cabergoline-treated patients with prolactinomas.

Design and Setting: An observational, case-control study was conducted at a university hospital.

Patients: Fifty treated patients (44 women and six men) and 50 sex- and age-matched control subjects participated; 20 *de novo* patients were also studied.

Intervention: In the treated patients, the last cabergoline dose was 1.3 $\pm$ 1.3 mg/wk ($<$1 mg/wk in 44%, 1–3 mg/wk in 46%, and $>$3 mg/wk in 10%). Treatment duration was 12–60 months in 32% and more than 60 months in 68%. The cumulative (milligrams $\times$ months of treatment) dose of cabergoline ranged from 32–1938 mg (median 280 mg).

Measurements: Valve regurgitation was assessed according to the recommendations of the American Society of Echocardiography.

Results: In *de novo* patients, treated patients, and controls, the prevalence of mild regurgitation of mitral (35, 22, and 12%, $P = 0.085$), aortic (0, 4, and 2%, $P = 0.59$), tricuspid (55, 30, and 42%, $P = 0.13$) or pulmonic (20, 12, and 6%, $P = 0.22$) valves was similar. Conversely, the prevalence of moderate tricuspid regurgitation was higher in the treated patients (54%) than in *de novo* patients (0%) and controls (18%, $P < 0.0001$). Moderate tricuspid regurgitation was more frequent in patients receiving a cumulative dose above the median (72%) than in those receiving a lower dose (36%, $P = 0.023$). A higher systolic ($P = 0.03$) and diastolic blood pressure ($P < 0.0001$) was found in patients with than in those without moderate tricuspid regurgitation.

Conclusion: Moderate tricuspid regurgitation is more frequent in patients taking cabergoline (at higher cumulative doses) than in *de novo* patients and control subjects, but the clinical significance of this finding has not been established. A complete echocardiographic assessment is indicated in patients treated long term with cabergoline, particularly in those requiring elevated doses. **(*J Clin Endocrinol Metab* 93: 3777–3784, 2008)**

Dopamine agonists are first-line agents for the treatment of prolactinomas (1) and Parkinson's disease (2). They are also prescribed in patients with the restless legs syndrome (3) and in selected cases of non-prolactin (PRL)-secreting pituitary tumors, especially GH-secreting and clinically nonfunctioning tumors, alone or in combination with somatostatin analogs (4).

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Abbreviations: BMI, Body mass index; CI, confidence interval; 5-HT, 5-hydroxytryptamine; 5-HT2B, 5-HT receptor subtype 2B; LV, left ventricular; LVM, LV mass; PRL, prolactin.

There is evidence supporting a causal relationship between the occurrence of drug-induced restrictive valve heart disease and treatment with the ergot-derived dopamine agonist pergolide (5–7); in several cases, the valvulopathy improved when pergolide was discontinued (6). Valve heart damage has also been reported with the ergot-derived dopamine agonists bromocriptine and cabergoline (8).

Two recent studies (9, 10) have further demonstrated that both pergolide and cabergoline are associated with an increased risk of a new cardiac valve regurgitation in patients treated for Parkinson's disease. The former study (9) reported data from the United Kingdom General Practice Research Database in a population-based cohort comprising 11,417 subjects 40–80 yr of age treated with anti-parkinsonian drugs between 1988 and 2005. It showed that the rate of cardiac-valve regurgitation was increased with use of pergolide [incidence rate ratio 7.1; 95% confidence interval (CI), 2.3–22.3] and cabergoline (incidence rate ratio 4.9; 95% CI, 1.5–15.6) but not with current use of other dopamine agonists (9). The latter study (10) reported on echocardiographic prevalence of cardiac valve disease in 155 patients taking dopamine agonists for Parkinson's disease and in 90 control subjects. The relative risk for moderate or severe valve regurgitation was significantly higher for the pergolide and cabergoline groups for both mitral and aortic regurgitation but not for tricuspid regurgitation (10). The valve abnormalities observed with ergot-derived dopamine agonists are similar to those observed in patients receiving ergot alkaloid agents (such as ergotamine and methysergide) in the treatment of migraine or fenfluramine and dexfenfluramine in the treatment of obesity.

These abnormalities closely resemble carcinoid-related valvulopathies (11). The valve damage induced by all these agents is hypothesized to be mediated by the serotoninergic system because all the implicated drugs have high affinity for the serotonin [5-hydroxytryptamine (5-HT)] receptor subtype 2B (5-HT2B), which is expressed in heart valves and is known to mediate mitogenesis (12). Proliferation of fibroblasts may therefore occur within valve tissue when the 5-HT2B receptor is stimulated. Pergolide and cabergoline are potent agonists of the 5-HT2B receptor, whereas other agents in this class, such as bromocriptine and lisuride, have antagonistic properties (13).

Cardiac valve disease has never been reported in patients with prolactinomas who require treatment with dopamine agonists even lifelong (1). At variance with patients with Parkinson's disease, patients with prolactinomas are younger and are treated with an average dose of dopamine agonists that is significantly lower. Because of the young age of treatment beginning (most patients with prolactinomas start dopamine agonist treatment in early adulthood), treatment might be continued for over three decades: the cumulative risk of low doses of dopamine agonists for such a long period of treatment is currently unknown.

To assess the prevalence of cardiac valve disease and other possible cardiac structural and functional abnormalities in patients treated with cabergoline, we performed an echocardiography screening in a large representative sample of patients with prolactinoma treated with cabergoline for at least 12 months and in age- and sex-matched control subjects. Changes in cardiac valves, structure and function, were compared with cabergoline treatment dose and duration.

Subjects and Methods

Exclusion criteria

A history of cardiac valve abnormalities, calcification or regurgitation associated with annular dilatation or excessive leaflet motion, mitral regurgitation associated with left ventricular (LV) wall-motion abnormalities or LV dilatation, previous use of anorectic drugs, autoimmune diseases associated with hyperprolactinemia, and treatment with cabergoline within less than 12 months were exclusion criteria for this study. Patients withdrawn from treatment for longer than 1 month, according to our treatment protocol (14), were also excluded from this study.

Subjects

From January 1 to March 31, 2007, of 124 patients attending the outpatient service of the Neuroendocrine Unit in our Department in Naples, 50 patients (named treated patients) who were seen consecutively for an office visit and who met eligibility criteria were asked to participate (Table 1). Of the 74 remaining patients, three patients had microprolactinomas associated with anorexia nervosa (n = 1), lupus erythematosus (n = 1), or rheumatoid arthritis (n = 1); 22 did not complete 1 yr of treatment; 20 were newly diagnosed patients; 13 did previously use anorectic drugs; and 16 were withdrawn from treatment with cabergoline for 12–96 months (14, 15). Every patient and control subject gave specific written informed consent for the study. The first seven patients signed the informed consent on January 18, whereas the last 10 patients signed on March 30, 2007. The 20 newly diagnosed patients (named *de novo* patients) were also included in the study to provide an untreated patients group to use as further control for the prevalence of cardiac valve disease due to hyperprolactinemia (if any).

Control subjects were prospectively recruited from among relatives of the patients or acquaintances of the medical staff. None of the control subjects had hyperprolactinemia or had ever been treated with dopamine agonists or anorectic drugs. Exclusion criteria were the same as for patients with prolactinoma. Control subjects and patients were matched according to sex and age (±1 yr).

Study protocol

Within 1 wk from clinical visit, all patients were admitted to the hospital for a complete endocrine screening, a cardiological visit, electrocardiography, and echocardiography. The clinical profile included blood pressure measurement at the right arm, with the subjects in relaxed sitting position. The average of six measurements (three taken by each of two examiners, in the same day of echocardiography, 0800–0900 h) with a mercury sphygmomanometer was used in all analyses.

Systemic arterial hypertension, if present, was classified as mild (stage 1) when the systolic or diastolic blood pressure was between 140 and 159 mm Hg and between 90 and 99 mm Hg, respectively; severe (stage 2) when the systolic or diastolic blood pressure was more than 160 and more than 100 mm Hg, respectively; pre-hypertension was defined as systolic blood pressure more than 120 and less than 140 and diastolic blood pressure more than 80 and less than 90 mmg (16). Heart rate was also measured.

Treatment protocol

According to our previous studies (17–19), in the patients with microprolactinoma and in those with nontumor hyperprolactinemia, cabergoline treatment was administered orally at a starting dose of 0.25 mg twice weekly for the first 2 wk and then 0.5 mg twice weekly. After 2 months treatment, dose adjustment was carried out every 2 months on the basis of serum PRL suppression. In the patients with macroprolactinoma, the starting cabergoline dose was 0.5 mg once a week for the first

TABLE 1. Profile of patients and controls at study entry

	De novo patients	Treated patients	Controls	P^1	P^2
No.	20	50	50	1.0	1.0
Women/men	17/3	44/6	44/6	1.0	1.0
Age (yr)	28.2 ± 8.7	36.5 ± 10.5	36.7 ± 10.4	0.74	0.74
Serum PRL levels at diagnosis (μg/liter)	209 ± 234	629 ± 1357			
In women	188 ± 246	418 ± 981			
In men	325 ± 107[a]	2177 ± 2551[a]			
Microprolactinomas	12 (60)	33 (66)			
Macroprolactinomas	6 (30)	16 (32)			
Nontumor hyperprolactinemia	2 (10)	1 (2)			
Serum PRL levels at study entry (μg/liter)	209 ± 234[b]	19.8 ± 27.9	9.2 ± 3.1	<0.0001	0.18
In women	188 ± 246	17.3 ± 23.9	9.6 ± 3.0	0.037	0.037
In men	325 ± 107	37.9 ± 47.8	6.4 ± 2.1	0.14	0.14
Duration of cabergoline treatment (months)		80.7 ± 37.2			
12–60		16 (32)			
>60		34 (68)			
Last cabergoline dose (mg/week)		1.3 ± 1.3			
<1 mg		22 (44)			
1–3 mg		23 (46)			
<3 mg		5 (10)			
Cumulative cabergoline dose (mg)		413.9 ± 390.4			
BMI (kg/m^2)	22.8 ± 5.0	25.4 ± 5.6[c]	22.1 ± 2.6	0.001	0.002
BMI < 25	12 (60)	34 (70)	43 (84)	0.034	0.057
BMI = 25–30	6 (30)	10 (20)	6 (12)	0.20	0.41
BMI > 30	2 (10)	6 (10)	1 (4)	0.15	0.12

Data are shown as mean ± SD or prevalence as number of subjects and percentage in parentheses. The method used to calculate the cumulative cabergoline dose is detailed in *Subjects and Methods*. P^1, Two-tailed *P* values refer to the Kruskal-Wallis test followed by the Dunn's test among *de novo* patients, treated patients, and controls; P^2, two-tailed *P* values refer to the Wilcoxon matched paired test for continuous variables and to the χ^2 test for categorical variables comparing the 50 patients with the 50 controls.

[a] $P < 0.05$ by Mann-Whitney *U* test *vs.* women.

[b] $P < 0.01$ *vs.* treated patients and controls.

[c] $P < 0.05$ *vs.* de novo patients and controls.

week and then twice weekly. Dose adjustment was performed as for patients bearing microprolactinoma or nontumor hyperprolactinemia. In the patients who did not normalize PRL levels, the cabergoline dose was progressively increased to 5–7 mg/wk. In patients achieving serum PRL levels less than 5 μg/liter (the low-normal range), the dose of cabergoline was reduced to maintain serum PRL levels into the normal range; thus, the final cabergoline dose ranged 0.2–7 mg/wk. In this series of patients, follow-up ranged from 16–250 months (median 74 months). To evaluate the role of cabergoline dose and duration on echocardiographic findings, we calculated the cumulative dose for individual patients; because doses changed throughout the follow-up, the cumulative dose was the sum of each dose used multiplied for the months of treatment in which that dose was employed. The cumulative dose ranged from 32–1938 mg (median 280 mg).

Echocardiography

All patients and controls underwent a complete trans-thoracic echocardiographic examination. Echocardiography was performed by a Vivid Seven System machine (GE Healthcare, Piscataway, NJ). Echocardiograms were digitally recorded and measurements performed off-line (20). The echocardiographic quantitative assessment was performed according to standard methods (21). The following measurements were determined on M-mode tracing: interventricular septum thickness (IVST), LV internal end-diastolic diameter (LVID) and posterior wall thickness (PWT), LV mass (LVM) calculation by the Devereux's formula (22): $LVM = 0.8 \times [1.04 (LVID + PWT + IVST)^3 - LVID^3] + 0.6$ g. LVM indexed for body surface area at least 126 g/m^2 in men and at least 95 g/m^2 in women were considered as cutoff points for LV hypertrophy (23). Relative wall thickness was calculated according to the following formula: 2 × posterior wall thickness/LV end-diastolic diameter. LV systolic function was evaluated as systolic minor axis shrinking at endocardial level and reported as endocardial fractional shortening considered normal when more than 25% in males and 27% in females (23). Recording and measurements of Doppler-derived diastolic function were performed according to the recommendations of the American Society of Echocardiography (24). Pulmonary systolic arterial pressure was estimated by continuous wave Doppler as peak regurgitation velocity plus an assumed right atrial pressure in relation to the size and respiratory excursion of inferior cava vein visualized in subcostal view (25). A cutoff point value of pulmonary arterial systolic pressure of more than 25 mm Hg was considered as representative of arterial pulmonary hypertension Measurement of left atrium and aortic root diameters and of LV end-diastolic diameter were normalized for BSA. Based on these criteria, normal values are, respectively, left atrium diameter 2.3 cm/m^2 or less in both genders, aortic root diameter 2.1 cm/m^2 or less in both gender, LV end-diastolic diameter 3.1 cm/m^2 or less in males and 3.2 cm/m^2 or less in females (23). All measurements for quantification of regurgitant valve disease were made by using the vena contracta method, according to recommendations of the American Society of Echocardiography (26). Valve regurgitation was defined and quantified as 0 = absent or trace, 1 = mild, 2 = moderate, and 3 = severe. Because no patient had a jet width of more than 0.7 cm (severe), the mild/moderate distinctions were made on the basis of the extent to which retrograde flow filled the atrium or ventricle (26). Thickening or fusion of the tendinous chords and/or of the leaflets was researched at any valve in all patients. After the study was completed, additionally, the area of tricuspid valve tethering was measured by tracing between the right atrial surface of the leaflets and the tricuspid annular plane at the time of maximal systolic closure (27). Data were available in 40 controls, 43 treated patients, and 15 *de novo* patients. Due to the retrospective measurement, in the other patients, the record did not allow a precise estimation of the valve tethering area.

Blood pressure was measured by a cuff sphygmomanometer at the end of the echocardiographic examination.

Statistical analysis

Statistical analysis was carried out using SPSS software. Values are given as means ± SD, unless otherwise specified. Differences among the two patient groups and controls were analyzed by the Kruskal-Wallis followed by the Dunn's test; those between the treated patients and the controls and those between the patients treated with a lower (≤280 mg) or a higher (>280 mg) cumulative cabergoline dose were analyzed with the Wilcoxon signed rank test for continuous variables. Differences for categorical variables were analyzed with the χ^2 test. For all analyses, a two-sided value of $P < 0.05$ was considered to indicate statistical significance. Relative risks for mild or moderate mitral, aortic, tricuspid, and pulmonic regurgitation were calculated with confidence intervals as compared with the control group. Approximate power (for $P < 0.05$) was also reported. The Kaplan-Meier method was used to analyze the relationship with moderate tricuspid regurgitation in the patients and the controls. The logrank test was used to compare patient and control curves. The criterion for statistical significance was set as mentioned above.

Results

Clinical features (Table 1)

Among *de novo* and treated patients and controls, women were predominant (87.1%), according with the known increased prevalence of hyperprolactinemia in women (28). Microprolactinomas were prevalent over macroprolactinomas and nontumor hyperprolactinemia (64.3 *vs.* 31.4 *vs.* 4.3%, respectively). In the treated patients, hyperprolactinemia was controlled in 41 (82%). Serum PRL levels at study entry were higher in *de novo* patients than in the other two groups (as expected), whereas they were similar in the treated patients and in controls. In nine treated patients (18%), seven women and two men, PRL levels remained higher than normal (33–115.4 μg/liter). Last cabergoline dose was highly variable in the 50 treated patients: it ranged from 0.2–7 mg/wk and was less than 1 mg/wk in 44%, 1–3 mg/wk in 46%, and more than 3 mg/wk in 10% of the patients; median dose at study entry was 1 mg/wk. Higher cabergoline doses were correlated with higher PRL levels at study entry ($r = 0.44$; $P < 0.001$) but not at diagnosis ($r = 0.01$; $P = 0.47$). The cumulative dose of cabergoline during the follow-up (median 74 months) was 413.9 ± 390.4 mg (median 280 mg). Treatment duration ranged 13–128 months (median 74 months).

The mean body mass index (BMI) was significantly higher in treated patients than in *de novo* patients and controls; the prevalence of overweight or obesity was similar in the three groups, although that of normal weight was higher in controls.

Echocardiographic findings (Table 2)

The treated patients had significantly higher systolic and diastolic blood pressure levels and LVM than *de novo* patients and controls, but the prevalence of normal blood pressure, pre-hypertension, or stage 1 arterial hypertension was similar in the three groups. If only normotensive subjects were considered, compared with controls (n = 39), the treated patients (n = 35) still had slightly delayed isovolumic relaxation time (81.7 ± 12.7 *vs.* 73.7 ± 15.6 msec, $P = 0.024$) but also had significantly increased BMI (24.1 ± 3.7 *vs.* 21.8 ± 2.1 kg/m^2, $P = 0.0006$). Even when normalized for BSA, normotensive treated patients had significantly increased left atrial diameter (2.14 ± 0.22 *vs.*

TABLE 2. Echocardiographic findings in patients and controls

	De novo patients	Treated patients	Controls	P^1	P^2
No.	20	50	50	1.0	1.0
Women/men	17/3	44/6	44/6	1.0	1.0
Systolic blood pressure (mm Hg)	115.2 ± 15.4	124.0 ± 13.8[a]	115.2 ± 14.5	0.005	0.0071
Diastolic blood pressure (mm Hg)	74.0 ± 8.3	77.4 ± 9.4[a]	72.3 ± 8.6	0.018	0.01
No hypertension	14 (70)	35 (70)	39 (78)	0.62	0.37
Pre-hypertension	5 (25)	8 (16)	8 (16)	0.63	1.0
Stage 1 hypertension	1 (5)	7 (14)	3 (6)	0.30	0.32
Heart rate (bpm)	70.6 ± 9.3	74.1 ± 9.3	72.1 ± 9.2	0.31	0.16
LVM index (g/m^2)	59.5 ± 11.6	70.1 ± 17.4[b]	66.4 ± 16.6	0.049	0.46
LV fractional shortening (%)	33.4 ± 5.4	33.6 ± 7.0	33.9 ± 6.1	0.95	0.58
Peak velocity E/A ratio	1.42 ± 0.31	1.37 ± 0.38	1.42 ± 0.27	0.64	0.10
Aortic root diameter (mm/m^2)	2.34 ± 0.36	1.57 ± 0.21	2,66 ± 0.35	0.53	0.53
Left atrial diameter (mm/m^2)	2.34 ± 0.36	2.12 ± 0.24	3,22 ± 0.40	0.0003	0.0003
Isovolumic relaxation time (msec)	69.3 ± 12.4	81.1 ± 12.3	73.6 ± 15.3	0.011	0.011
Total peripheral resistance (mm Hg/liter·min·m^2)	2620 ± 832	2929 ± 805	2773 ± 866	0.75	0.75
Pulmonary pressure (mm Hg)		27.9 ± 6.4	30.1 ± 5.0	0.32	0.32
Mild mitral regurgitation	7 (35)	11 (22)	6 (12)	0.085	0.29
Mild aortic regurgitation	10 (0)	2 (4)	1 (2)	0.59	1.0
Mild tricuspid regurgitation	11 (55)	15 (30)	21 (42)	0.13	0.29
Moderate tricuspid regurgitation	0 (0)	27 (54)	9 (18)	<0.0001	<0.0001
Mild pulmonic regurgitation	4 (20)	6 (12)	3 (6)	0.22	0.48

Data are shown as mean ± SD or prevalence as number of subjects and percentage in parentheses. P^1 values are two tailed by the Kruskal-Wallis test followed by the Dunn's test for continuous variables and the χ^2 test for categorical variables comparing *de novo* patients *vs.* treated patients *vs.* controls; P^2 values are two tailed by the Wilcoxon matched paired test for continuous variables and the χ^2 test for categorical variables comparing treated patients *vs.* controls. Pulmonary pressure was measured only in the patients with moderate tricuspid regurgitation. *P* values refer to the Mann-Whitney *U* test. bpm, Beats per minute; E/A, early/atrial.

[a] $P < 0.05$ compared with *de novo* patients and controls.

[b] $P < 0.05$ compared with *de novo* patients.

1.94 ± 0.22 mm/m^2, $P = 0.001$) than normotensive controls. *De novo* patients had cardiac parameters similar to controls (Table 2).

The prevalence of valve abnormalities and the regurgitation grade for patients, treated and *de novo*, and controls are reported separately for the mitral, aortic, tricuspid, and pulmonic valves. None of the patients had morphological valve alterations. Both in the two patient groups and in controls, regurgitation for the mitral, aortic, and pulmonic valve was minimal and not clinically significant and was equally prevalent, similar to that observed for mild tricuspid valve regurgitation. In contrast, moderate tricuspid regurgitation was significantly more prevalent in the treated patients (54%) than *de novo* patients (0%, $P < 0.001$) and controls (18%, $P < 0.0001$). Pulmonary arterial hypertension was diagnosed in 17 of 27 treated patients, in none of *de novo* patients, and in seven of nine controls with tricuspid valve insufficiency ($P = 0.68$). Tricuspid tethering area was significantly wider in the patients than in the controls (0.60 ± 0.11 *vs.* 0.51 ± 0.11 cm^2, $P < 0.0001$) even when only those with mild/moderate tricuspid regurgitation were considered for comparison (0.60 ± 0.11 *vs.* 0.54 ± 0.06 cm^2, $P = 0.003$). In *de novo* patients, the tricuspid tethering area was similar to controls (0.52 ± 0.11 cm^2, $P = 0.52$).

Table 3 shows the relative risk for valve regurgitation in the treated patients as compared with controls. The risk to develop mitral, aortic, or pulmonic regurgitation was nonsignificantly different from controls, whereas the risk to develop moderate tricuspid regurgitation was three times higher (95% CI, 1.63–5.77). Additionally, the onset of tricuspid regurgitation in the treated patients group occurred significantly earlier by approximately 10 yr than controls (Fig. 1). When among the treated patients, those with moderate tricuspid regurgitation (n = 27) were compared with the patients without (n = 23), age, last PRL levels, duration, and cumulative dose of cabergoline treatment and BMI were similar (data not shown), whereas systolic blood pressure (126.4 ± 7.1 *vs.* 121.5 ± 8.3 mm Hg, $P = 0.03$), diastolic blood pressure (79.5 ± 6.6 *vs.* 73.9 ± 5.8 mm Hg, $P < 0.0001$), and LVM indexed for body surface area (74.1 ± 11.7 *vs.* 63.5 ± 10.1 g/m2, $P = 0.002$) were higher in the former.

Cumulative cabergoline dose and valve regurgitation (Table 4)

The treated patients were divided according to the median cumulative dose observed in this population, *i.e.* 280 mg. The two groups were comparable for age, BMI, systolic and diastolic blood pressure, and heart rate and for LV mass and performance. As expected, the patients requiring higher cabergoline dose had higher serum PRL levels than the patients requiring a lower dose. Patients treated with a higher cumulative dose had higher prevalence of moderate tricuspid regurgitation than those treated with a lower dose (relative risk = 2.0; 95% CI, 1.17–3.69; 63%). Five patients treated with lower doses and 12 patients treated with higher doses had pulmonary hypertension ($P = 0.9$). The patients treated with a cumulative cabergoline dose lower than 280 mg had moderate tricuspid regurgitation similar to controls (36 *vs.* 18%, $P = 0.15$).

TABLE 3. Calculation of the relative risk to develop valve regurgitation in patients treated with cabergoline compared with controls

	Relative risk		
	Risk ratio	95% CI	Power 5% significance (%)
Mild mitral regurgitation	1.83	0.76–4.49	18.3
Mild aortic regurgitation	2.0	0.27–15.0	9.0
Mild tricuspid regurgitation	0.71	0.42–1.2	17.7
Moderate tricuspid regurgitation	3.0	1.63–5.77	95.6
Mild pulmonic regurgitation	2.0	0.58–7.02	10.2

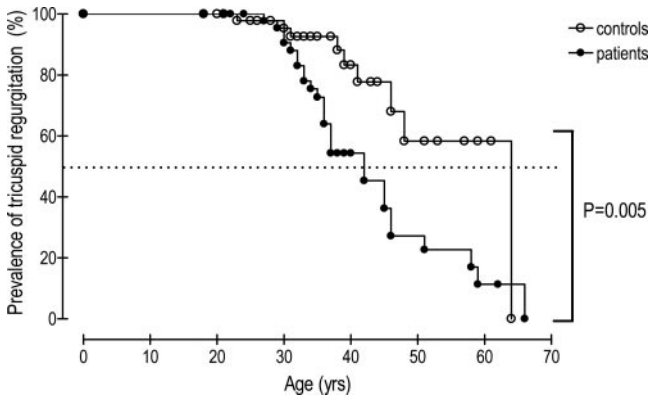

FIG. 1. Kaplan-Meier estimate of age of onset of moderate tricuspid regurgitation in the 50 controls and the 50 patients. The *interrupted line* indicates 50% of the population.

Clinical events

None of the treated patients referred symptoms related to cardiac valve disease, and the cardiological visit was negative. Pregnancy was a common event in the follow-up of the patients but was not related to the presence or absence of tricuspid regurgitation (22.2 *vs.*30.4%, $P = 0.74$). The presence of tricuspid regurgitation was not associated with overweight or obesity both in the controls (57 *vs.* 43%, $P = 1.0$) and in the patients (62.5 *vs.* 37.5%, $P = 0.29$) or with the presence of a micro- or a macroprolactinoma in the patients (51.5 *vs.* 50%). Of the 16 patients with macroprolactinoma, five patients had some degree of hypopituitarism (persistent hypogonadism and hypothyroidism under standard replacement therapy); all had moderate tricuspid regurgitation ($P = 0.011$), but all but one were treated with higher doses of cabergoline. Of all subjects with stage 1 arterial hypertension, moderate tricuspid regurgitation occurred in six of seven patients (85.7%) and in one of three controls (33.3%; $P = 0.37$).

Discussion

This study reports an approximately three times higher relative risk to develop moderate tricuspid valve regurgitation in patients with prolactinomas receiving cabergoline therapy than in age- and sex-matched healthy controls. Importantly, no significant valve regurgitation was found in *de novo* patients with prolactinoma at their diagnosis. Increased prevalence of tricuspid regur-

TABLE 4. Comparison between patients treated with lower or higher cumulative cabergoline dose according to the median dose of the current population

	Cumulative dose < 280 mg	Cumulative dose > 280 mg	*P*
No.	25	25	
Women/men	24/1	20/5	0.19
Age (yr)	36 ± 12	37 ± 9	0.79
Serum PRL levels at diagnosis (μg/liter)	408 ± 863	850 ± 1706	0.31
Serum PRL levels at study entry (μg/liter)	10.7 ± 14.4	28.9 ± 34.8	0.017
BMI (kg/m^2)	24.7 ± 4.6	26.1 ± 3.4	0.89
Systolic blood pressure (mm Hg)	124.6 ± 14.0	123.4 ± 13.9	0.59
Diastolic blood pressure (mm Hg)	77.3 ± 8.8	77.5 ± 10.2	0.78
LVM index (g/m^2)	68.7 ± 15.8	71.6 ± 19.0	0.51
LV fractional shortening (%)	34.3 ± 8.1	33.0 ± 6.0	0.73
LV internal diastolic diameter (mm/m^2)	2.82 ± 0.24	2.71 ± 0.28	0.13
Peak velocity E/A ratio	1.34 ± 0.40	1.39 ± 0.29	0.35
Deceleration time of E velocity (msec)	179.8 ± 29.9	177.1 ± 22.0	0.77
Aortic root diameter (mm/m^2)	1.57 ± 0.21	1.57 ± 0.21	0.85
Left atrial diameter (mm/m^2)	2.08 ± 0.22	2.16 ± 0.24	0.27
Isovolumic relaxation time (msec)	81.8 ± 9.4	80.5 ± 14.6	0.47
Total peripheral resistance (mm Hg·liter·min·m^2)	2897 ± 792	2962 ± 832	0.58
Pulmonary pressure (mm Hg)	27.9 ± 6.4	27.8 ± 6.5	0.85
Mild mitral regurgitation	6 (24.0)	5 (20.0)	1.0
Mild aortic regurgitation	1 (4.0)	1 (4.0)	1.0
Mild tricuspid regurgitation	11 (40.0)	4 (16.0)	0.064
Moderate tricuspid regurgitation	9 (36.0)	18 (72.0)	0.023
Mild pulmonic regurgitation	3 (12.0)	3 (12.0)	1.0

Data are shown as mean ± SD or prevalence as number of subjects and percentage in parentheses. *P* values refer to the Wilcoxon matched pair test for continuous variables and to the χ^2 test for categorical variables. E, Early; E/A, early/atrial.

gitation was not related to the presence of systemic arterial hypertension and/or obesity, whereas it was slightly associated with a higher cumulative cabergoline dose. However, blood pressure levels were significantly higher in the patients with than in those without moderate tricuspid regurgitation. Conversely, age, last PRL levels, and BMI were similar in the two groups. The tricuspid valve tethering area was greater in treated patients than in controls and in *de novo* patients as well, at least in those patients in which this parameter was measured. In this series, we did not observe any increased risk for mitral, aortic, or pulmonic regurgitation in treated patients compared with controls.

Awareness for valve regurgitation in patients treated with cabergoline, or with other ergot-derivative dopamine agonists, has recently been brought up by Schade *et al.* (9) and Zanettini *et al.* (10) who confirmed previous data (5–8). All of these studies were performed in patients with Parkinson's disease so that older and treated with doses of cabergoline three times of more higher than patients with prolactinomas. Adjusted incidence-rate ratio for valve regurgitation among patients with Parkinson's disease taking cabergoline ranged from 4.6–7.3 with a dose effect on severity of valve dysfunction (10). In patients with Parkinson's disease treated with ergot-derivative drugs, the relationship between severity of functional valve impairment and presence of the typical morphological alterations (9, 10) supports the hypothesis of a fibrotic process involving the valve leaflets and subvalve apparatus. No morphological changes were, however, demonstrated in the patients with prolactinoma enrolled in the current study.

Cabergoline is a well established primary therapy for most patients with micro- or macroprolactinomas and is administered usually at median doses of 1 mg/wk, so three to five times lower than in patients with Parkinson's disease. However, as mentioned by Stephens *et al.* (29), young patients with hyperprolactinemia often receive therapy for life; therefore, safety data on long-term cabergoline treatment on valve heart disease are essential from a clinical and prognostic point of view.

The current observational, cross-sectional, case-control study enrolled patients with prolactinoma treated chronically with cabergoline at variable doses for at least 12 months (minimum follow-up 16 months) up to 260 months (median 74 months). Patients were compared with *ad hoc* recruited healthy subjects and with a group of newly diagnosed patients coming to our observation in the same period of time. The echocardiographic examination demonstrated a similar prevalence of mild regurgitation at any valve in the three groups, whereas moderate tricuspid regurgitation was significantly more prevalent in treated patients with prolactinoma than in *de novo* patients and controls. The absence of any increase in mitral and aortic regurgitation is at variance with the results reported in patients with Parkinson's disease (9, 10) but can be explained both by the younger age of our patients (20 or more years younger than those with Parkinson's disease) and the lower doses of cabergoline employed. However, if patients were divided according to the cumulative cabergoline dose, the prevalence of moderate tricuspid valve regurgitation was higher in patients treated with higher doses. It is worth noting that apart from higher PRL levels in the patients treated with higher cabergoline doses, the two groups were comparable for all the remaining variables. This finding clearly raises a question on the duration of treatment related to the dose of cabergoline employed in patients with prolactinoma

to reduce the risk to develop tricuspid regurgitation. Because our patients had a variable period of cabergoline treatment duration, an analysis of the role of treatment duration was difficult. The suspicion of a direct role of cabergoline in determining tricuspid regurgitation was also reinforced by the small but significantly larger tethering area in treated patients. Ergotamine, methysergide, amphetamine derivatives, ecstasy, pergolide, and cabergoline are 5-HT2B agonists, so they can affect valve structure and function (13). Even if our results did not show any abnormal tethering area, reported to be higher than 1 cm^2 in patients undergoing valve replacement (27), in any other cardiac valve, the increase in tricuspid tethering area suggests a possible direct effect of cabergoline on the tricuspid valve. However, the results of the tethering area deserves further confirmation in a larger series to understand its pathophysiological value because it was measured retrospectively and, therefore, not available in all cases. Data available in the literature refer to the measurement of this parameter in the patients undergoing valve replacement who represent a very different setting from patients with prolactinomas.

Recently, Bogazzi *et al.* (30) and Vallette *et al.* (31) reported data in a subset of 100 and 70 hyperprolactinemic patients, respectively, and did not find any increased risk of regurgitation in any valve. Clearly, some differences between our results and the ones just published might depend on an unwilling inclusion of patients with different baseline cardiac status, because both studies have a cross-sectional design. Moreover, also recently, Kars *et al.* (32) in a series of patients similar to ours and with a similar study design, found similar data with an increase in tricuspid regurgitation with some aortic calcification.

We previously proposed withdrawal from cabergoline treatment in all the patients achieving disappearance of the tumor on magnetic resonance imaging and control of PRL levels during treatment to spare patients from unnecessary lifelong treatment (14). The current data reinforce the suggestion to perform periodical cabergoline treatment withdrawal to possibly prevent the development of moderate tricuspid regurgitation. In our experience, patients achieving suppressed PRL levels during treatment had a high chance to maintain normal PRL levels after treatment withdrawal (14, 15).

No apparent effect of elevated PRL levels has been so far reported on cardiac valve apparatus, and no description of cardiac alterations were reported in patients with prolactinomas at their diagnosis. Indeed, in the small group of *de novo* patients studied in the same period as treated ones, no significant valve regurgitation (at any valve) or changes in the different echocardiographic variables were observed. It should be mentioned that none of the treated patients had any cardiac symptom related to valve disease or to pulmonary arterial hypertension, which should be thus considered subclinical at the stage of the examination. However, the cardiac alterations should be carefully investigated in the subsequent follow-up.

Lastly, the treated patients with prolactinomas had unexpectedly significantly higher systolic and diastolic blood pressure than controls and *de novo* patients. When patients with moderate tricuspid regurgitation during cabergoline treatment were compared with those with no or mild tricuspid regurgitation, the former had higher systolic and diastolic blood pressure than the latter. The presence of increased arterial blood pressure levels was never reported in patients with prolactinomas treated with dopamine agonists, although it is well known as an initial hypotensive effect of these drugs (1). Because data on blood pressure have never been reported in patients with prolactinomas chronically treated with dopamine agonists, their role in contributing to cardiac valve disease should be better investigated. Of interest, both left atrial enlargement and aortic root dilatation are frequently associated with arterial systemic hypertension in the general clinical setting (24, 33, 34). Of note, normotensive treated patients had significantly increased left atrial diameter (even when indexed by body surface to normalize the higher BMI of the patients) and delayed isovolumic relaxation time, a sign of LV diastolic dysfunction, compared with normotensive controls. At present, the role of mild systemic arterial hypertension in the determination of valve heart disease in patients with prolactinomas cannot be discussed because of the small series of patients bearing such a condition. However, as already mentioned, in porcine pulmonary arteries, cabergoline, as well as pergolide, turned out to be a potent agonist of the 5-HT2B receptor-mediated relaxation, whereas bromocriptine was a partial agonist and lisuride and terguride were potent antagonists (29). A direct role of cabergoline in inducing changes in endothelial function at different vascular districts can be thus hypothesized, and prospective studies on this aspect are necessary before any definitive conclusion can be drawn. In the two studies performed in patients with Parkinson's disease (9, 10), hypertension was not considered to represent a relevant factor in explaining the presence and severity of cardiac valve disease.

Conclusion

We found that chronic cabergoline treatment in patients with prolactinoma does not induce any regurgitation of mitral, aortic, or pulmonic valves, but it induces a three times higher prevalence of subclinical moderate tricuspid regurgitation compared with controls and *de novo* patients. Tricuspid tenting area was significantly greater in treated patients than in controls and *de novo* patients. Tricuspid regurgitation was two times more frequent in patients treated with higher cumulative cabergoline doses. These data should prompt more careful echocardiographic follow-up studies in patients with prolactinoma treated with cabergoline or other ergot-derivative drugs.

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