Evaluation of the valvular and biventricular functions in Parkinson patients using ergotamine-derived dopamine agonist: an observational study

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Abstract

Objective: In this study, we aimed to evaluate the impact of cabergoline use in patients with Parkinson's disease on valvular and biventricular functions.

Methods: In this observational cohort study, patients with Parkinson disease were divided into 2 groups as 34 patients (41.2% female, age; 57.4±15.3 years) using cabergoline (Group 1) and 42 patients (61.9% female, age; 53.7±7.1 years) not using cabergoline (Group 2). In addition to conventional echocardiography and diastolic functions, tissue Doppler imaging was used to evaluate both global and regional systolic - diastolic functions. Correlations were assessed using Pearson correlation coefficient for normally distributed variables.

Results: In group 1 patients cabergoline was used for 7.7±5.1 years and mean and cumulative cabergoline dose were 3.3±1.1 mg and 9.8±7.0 g respectively. Left ventricular systolic functions and tissue Doppler measurements of septal and lateral mitral annulus and right ventricular systolic and diastolic velocities were similar between groups. Mitral valve tenting area was significantly higher in patients using cabergoline (p=0.007). The association between cumulative cabergoline dose and diastolic functions was also evaluated which revealed that among diastolic function parameters, Epeak (r=0.253, p=0.042), E/A (r=0.256, p=0.026) and DT (r=-0.382, p=0.001) were correlated with cumulative cabergoline dose. There was a positive correlation between cumulative cabergoline dose and duration of cabergoline therapy with composite regurgitation score (r=0.435, p<0.001; r=0.485, p<0.001, respectively).

Conclusion: Our findings indicated that despite the well known effects of cabergoline on valvular functions, we did not observe any alteration in systolic functions, but diastolic functions which was associated with cumulative cabergoline dose in patients with Parkinson's disease.

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Key words: Parkinson disease, cabergoline, valvular, ventricular function

Introduction

The effects of ergotamine derived dopamine agonists (EDDA) in the development of heart valve diseases were documented in several previous studies (1, 2). Those effects were attributed to the activation of seratonergic receptors which induces molecular pathyways causing myofibroblast differentiation and extracellular matrix production (3-5). The net effect of those changes are fibrotic reactions in heart valves causing valve incompetence or stenosis (6).

Besides the well known effects on heart valves, the effect of EDDA on myocardium was also evaluated in both animal and human studies (7, 8). Myocardial fibrosis may lead to systolic dysfunction in long-term follow-up. However, extracellular matrix changes may be seen in tissue Doppler studies and diastolic dysfunction may develop before the overt clinical sysmptoms. Apart from conventional parameters, myocardial velocity determined by tissue Doppler imaging is an important technique that has been used to analyze global left ventricular functions (9, 10). In a previous study by Rasmussen et al. (11), EDDA had no detectable adverse impact on myocardial systolic and diastolic functions among patients with Parkinson's disease. However, those data were limited regarding clinical or subclinical effects of dopamine agonists on myocardial function in Parkinson's disease. Additionally, right ventricular functions were not evaluated before.

In the light of those data, in this study, we aimed to evaluate both global and regional bi-ventricular systolic and diastolic functions by tissue Doppler imaging and conventional echocar-

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diography as well as valvular effects of cabergoline use in patients with Parkinson's disease.

Methods

Study protocol: an observational cohort study

In this observational cohort study, we enrolled a consecutive subset of 34 patients (41.2% female, mean age; 57.4±15.3 years) with the diagnosis of Parkinson's disease who were scheduled for EDDA treatment -cabergoline- between January 2009 and February 2011 (Group 1). All patients with Parkinson's disease were considered eligible if treated with EDDA for a period of at least one year. Patients with prior cardiovascular disease including valvular disease, coronary artery disease or heart failure, diabetes mellitus or under medications that might affect the echocardiographic indices were excluded from the analysis. Group 2 was consisted of 42 age-matched newly diagnosed Parkinson's disease patients (61.9% female, mean age; 53.7±7.1 years) without a prior diagnosis of cardiovascular disease or any medication usage. Informed consent was taken from each patient and the study was approved by local ethics committee.

Echocardiography

Standard echocardiographic imaging was performed in the left lateral decubitus position in the parasternal and apical views. Two-dimensional, M-mode, pulsed and color flow Doppler echocardiographic examinations of all subjects were performed by the same examiner with a commercially available machine (Vingmed System Five GE ultrasound, Horten, Norway, 2.5-3.5 mHz phased array transducer) who was blinded to the clinical details of the subjects in the study and control group. During echocardiography, a one-lead electrocardiogram was recorded continuously. Left ventricle end-diastolic (LVEDD), left ventricle end-systolic (LVESD), right ventricular end diastolic (RV) and left atrial endsystolic (LA) diameters were measured from M-mode in the parasternal long-axis views according to the standards of the American Society of Echocardiography (12). Left ventricular ejection fraction (LVEF), and fractional shortening (FS) were calculated using M-mode echocardiography. In case of reduced endocardial definition, LVEF was estimated visually by the examiner. Three consecutive cycles were averaged for every parameter.

Morphological and functional features of aortic, mitral, tricuspid valve and pulmonary valves were analysed according to generally accepted guidelines as absent, trace, mild, moderate and severe (13). We also used a composite scoring system derived from the sum of mitral, aortic, and tricuspid scores (value range of the composite score: 0 to 12; higher scores indicate more severe disease) as used in previous studies (14). Abnormal leaflet or cusp thickening was accepted to be present when the thickness was >5 mm. We also measured mitral tenting area was obtained from the parasternal long-axis view as described before to evaluate leaflet stiffening (15).

Mitral inflow indices were obtained by pulsed-wave (PW) Doppler from the apical 4-chamber view to assess LV filling according to the recommendations of the American Society of Echocardiography (16). Those measurements of mitral inflow included the peak early filling (*Epeak*) and late diastolic filling (*Apeak*) velocities, the E/A ratio, deceleration time (DT) of early filling velocity, and the isovolumic relaxation time (IVRT) measured by placing the cursor of CW Doppler in the LV outflow tract to simultaneously illustrate the end of aortic ejection and the onset of mitral inflow.

Doppler tissue imaging echocardiography was performed by transducer frequencies of 3.5-4.0 MHz, adjusting the spectral pulsed Doppler signal filters until a Nyquist limit of 15-20 cm/s was reached, and using the minimal optimal gain. The monitor sweep speed was set at 50-100 mm/s to optimize the spectral display of myocardial velocities. The Pulsed-wave TDI was performed in the apical views by placing a 3 mm sample volume at the level of left ventricular lateral mitral annulus, septal mitral annulus, and right ventricular tricuspid annulus. The sampling window was positioned as paralel as possible with the myocardial segment of interest to ensure the optimal angle of imaging. Peak systolic (S'), early (E') and late diastolic myocardial velocities (A') were recorded. Several cardiac cycles were evaluated and the best three consecutive ones were analyzed and averaged.

Statistical analysis

Continuous variables were expressed as mean±SD and categorical variables were expressed as percentages. Kolmogorov-Smirnov (K-S) test was used for testing normal distribution of continuous variables. Among all variables, septum and posterior wall thickness and RV diameter showed skewed distribution. For numerical variables, an independent sample t-test (for normally distributed data) and Mann-Whitney U test (for skewed distributed data) were used for inter-group comparisons. Chi-square test and Fisher's exact chi-square test were used for comparisons of categorical variables. Correlations were assessed using Pearson correlation coefficient for normally distributed variables. SPSS 15.0 statistical program (SPSS Inc., Chicago, IL, USA) was used for statistical study. A p value <0.05 were considered significant.

Results

Baseline characteristics of the study population

Baseline characteristics were similar between 2 groups (Table 1). In group 1 patients cabergoline was used for 7.7±5.1 years; mean and cumulative cabergoline doses were 3.3±1.1 mg and 9.8±7.0 g respectively.

Echocardiographic data of the study groups

Conventional and tissue Doppler echocardiography parameters were shown in Table 2. The LVEDD (p=0.564), LVESD

(p=0.611), LVFS (p=0.744), LVEF (p=0.274), LA (p=0.098) and RV diameter (p=0.440) were similar between Group 1 and 2. However, systolic pulmonary artery pressure was higher in patients using cabergoline (p=0.001).

The tissue Doppler measurements of septal and lateral mitral annulus and right ventricular velocities including E´, A´ and S´ were similar between 2 groups. In addition we also analyzed the diastolic functions between 2 groups (Table 2). The transmitral flow features of E_{peak} (p<0.001), E/A (p=0.039), E/E´ (p=0.043) and DT (p=0.002) were higher in patients using cabergoline (Group 1) compared to control subjects (Group 2). The association between cumulative cabergoline dose and diastolic functions was also evaluated which revealed that among diastolic function parameters, E_{peak} (r=0.253, p=0.042), E/A (r=0.256, p=0.026) and DT (r=-0.382, p=0.001) were correlated with cumulative cabergoline dose (Fig. 1).

Comparison of valvular functions and morphology of study groups

We also evaluated the differences regarding both valvular functions and morphology between 2 groups (Table 3). In aortic and mitral valve, leaflet thickening, and regurgitation were increased in patients using cabergoline compared to control subjects. In addition, mitral valve tenting area and subvalvular apparatus thickening were significantly higher in patients using cabergoline (p=0.007 and p=0.003). Also tricuspid regurgitation was higher in cabergoline group compared to control group (p=0.01). When composite regurgitation score involving the three valves was evaluated, there was a positive correlation between cumulative cabergoline dose and duration of cabergoline therapy with composite regurgitation score (r=0.435, p<0.001; r=0.485, p<0.001, respectively) as shown in Figure 2 and 3. Additionally, there was a positive correlation between systolic pulmonary artery pressure and composite regurgitation score (r=0.530, p<0.001) (Fig. 4).

Table 1. Baseline characteristics of the study population

Parameters	Group 1 (n=34)	Group 2 (n=42)	*P*
Age, years, mean±SD	57.4±15.3	53.7±7.1	0.196
Female, n (%)	14 (41.2%)	26 (61.9%)	0.117
Smoking, n (%)	11 (32.4%)	18 (42.9%)	0.484
BMI, kg/m^2	25.3±2.4	26.1±2.6	0.224
Heart rate, bpm	68±12	66±14	0.442
Blood pressure, mm Hg			
Systolic	132±28	116±18	0.245
Diastolic	75±12	72±10	0.176
Years since initation of cabergoline	7.7±5.1	NA	NA
Daily dose of cabergoline, n (%)			
2 mg	12 (15.8%)	NA	NA
3 mg	3 (3.9%)	NA	NA
4 mg	17 (22.4%)	NA	NA
6 mg	2 (2.6%)	NA	NA
Mean daily dose, mg	3.3±1.1	NA	NA
Cumulative cabergoline dose, g	9.8±7.0	NA	NA

Data are means±SD for normally distributed variables and median for skewed variables or n (%) For numerical variables, an independent sample t test (for normally distributed data) and Mann-Whitney U test (for skewed distributed data) were used for inter-group comparisons. Chi-square test and Fisher's exact chi-square test were used for comparisons of categorical variables.
BMI - body mass index; bpm-beats per minute; SD - standard deviation

Discussion

In this observational study, we evaluated the effects of ergot derived dopamine agonists in patients with Parkinson disease on both valvular and biventricular functions. Our findings indicated that i) valvular regurgitation was more significant in patients using cabergoline use, ii) although a clinically significant restrictive valvular disease was not observed, mitral tenting area was higher in patients using cabergoline, iii) tissue Doppler parameters of right and left ventricle were similar between study and control groups, iv) diastolic dysfunction was more prevalent in patients using EDDA.

Ergot derived dopamine agonists including cabergoline that often used in the treatment of Parkinson's disease were associated with the fibrotic reactions in leaflets and subvalvular apparatus (17). Those fibrotic changes include thickening, retraction, and stiffening of valves causing impaired leaflet coaptation and valvular regurgitation. The effects of EDDA on valvular functions including cabergoline was extensively studied in previous studies. Zannettini et al. (15) reported that the frequency of clinically important valve regurgitation was significantly increased in patients taking cabergoline compared to control group. In our study, valvular regurgitation was increased in all ranges including mild-moderate and severe regurgitation. In our study, despite the similarity of mean daily doses of cabergoline, duration of therapy and therefore cumulative dose was higher compared to other studies (15). Moreover composite regurgitation score was higher in patients using cabergoline which was associated both with duration and cumulative dose of cabergoline therapy as in line with previous studies (15, 18). In addition to valvular regurgitation, morphologic features including leaflet and subvalvular apparatus thickening were more prevalent in patient using cabergoline similar to previous studies (19).

In addition to valvular fibrotic reactions, several previous studies reported that use of EDDA was associated with an increased risk of pericardial, pleural, pulmonary and retroperitoneal fibrotic reactions (4, 20). Among dopamine agonists, cabergoline displays agonistic properties to 5 HT-2B receptor, which is found in the myocardium as well as valves (21). Recently, the effects of EDDA on myocardial fibrosis was also assessed in animal studies which revealed serotonin-induced fibrosis in the myocardium due to the stimulation of serotonin receptors by dopamine agonists (8). In an animal study, injection of seratonin

Table 2. Echocardiographic parameters of the study population

2D & Doppler parameters	Group 1 (n=34)	Group 2 (n=42)	*P*
LVEDD, mm	51.9±5.2	48.8±5.3	0.564
LVESD, mm	33.1±4.	031.5±3.5	0.611
LVEF, %	66.5±4.0	65.4±4.2	0.274
FS, %	36.1±3.2	35.8±3.3	0.744
Septum thickness, mm	10	9.7	0.925
Posterior wall thickness, mm	9.2	9.0	0.342
RV diameter, mm	25	23	0.551
LA diameter, mm	35±5	34±5	0.098
sPAP, mm Hg	29.2±7.3	23.5±3.4	0.001
E_{peak}	0.80±0.20	0.66±0.13	<0.001
A_{peak}	0.80±0.17	0.85±0.22	0.293
E/A	0.99±0.29	0.85±0.26	0.039
E/ E´	0.108±0.040	0.091±0.028	0.043
IVRT, msec	78.8±16.2	81.8±26.0	0.542
DT, msec	194.1±46.2	162.8±37.3	0.002
Tissue Doppler parameters			
Septal E´, cm/s	8.12±2.3	7.64±1.9	0.326
Septal A´, cm/s	9.7±2.3	10.4±2.3	0.175
Septal S', cm/s	7.5±1.4	7.2±1.6	0.350
Lateral E´, cm/s	10.5±3.1	9.8±3.1	0.377
Lateral A´, cm/s	10.4±2.3	11.4±2.3	0.178
Lateral S´, cm/s	8.3±1.9	7.6±2.0	0.100
Right ventricular E´, cm/s	11.8±3.1	10.9±2.8	0.193
Right ventricular A´, cm/s	16.0±4.1	17.2±4.2	0.228
Right ventricular S´, cm/s	13.1±3.1	13.0±3.2	0.891

Data are means±SD for normally distributed variables and median for skewed variables or n (%)
For numerical variables, an independent sample t test (for normally distributed data) and Mann-Whitney U test (for skewed distributed data) were used for inter-group comparisons. Chi-square test and Fisher's exact chi-square test were used for comparisons of categorical variables.
DT - deceleration time; FS - fractional shortening; IVRT - isovolumic relaxation time; LA - left atrium; LVEDD - left ventricular end-diastolic diameter; LVEF - left ventricular ejection fraction; LVESD - left ventricular end-systolic diameter; RV - right ventricle; sPAP - systolic pulmonary artery pressure

Table 3. Comparison of valvular abnormalities in cabergoline and control groups

Parameters	Group 1 (n=34)	Group 2 (n=42)	*P*
Aortic valve			
Leaflet thickening, n (%)			<0.001
No thickening	9 (26.5%)	33 (78.6%)	
Localized	13 (38.2%)	6 (14.3%)	
Diffuse	12 (35.3%)	3 (7.1%)	
Aortic regurgitation, n (%)			<0.001
No/Trace	16 (47.1%)	40 (95.2%)	
Mild	6 (17.6%)	1 (2.4%)	
Moderate	12 (35.3%)	1 (2.4%)	
Mitral valve			
Mitral valve tenting area, cm^2	2.80±0.52	2.48±0.46	0.007
Anterior leaflet thickness, n (%)			<0.001
No thickening	12 (35.3%)	33 (78.6)	
Localized	13 (38.2%)	7 (16.7%)	
Diffuse	9 (26.5%)	2 (4.8%)	
Posterior leaflet thickness, n (%)			0.002
No thickening	13 (38.2%)	33 (78.6%)	
Localized	16 (47.1%)	7 (16.7%)	
Diffuse	5 (14.7%)	2 (4.8%)	
Subvalvular apparatus thickening, n (%)			0.003
No	15 (44.1%)	33 (78.6%)	
Localized	12 (35.3%)	8 (19%)	
Diffuse	7 (20.6%)	1 (2.4%)	
Mitral regurgitation, n (%)			<0.001
No/Trace	12 (35.3%)	37 (88.1%)	
Mild	14 (41.2%)	3 (7.1%)	
Moderate	6 (17.6%)	2 (4.8%)	
Severe	2 (5.9%)	0 (0%)	
Tricuspid valve			
Tricuspid regurgitation, n (%)			0.010
No/Trace	16 (47.1%)	31 (73.8%)	
Mild	11 (32.4%)	10 (23.8%)	
Moderate	7 (20.6%)	1 (2.4%)	

Data are presented as n (%)
Chi-square test and Fisher's exact chi-square test were used for comparisons of categorical variables

caused extracellular matrix formation in the myocardium beyond the well known effects on heart valves. Beyond those, the effects of EDDA on myocardium was also assesed in human studies. In a recent study, Rasmussen et al. (11) investigated the effects of EDDA on left ventricular systolic and diastolic functions in Parkinson patients which revealed that EDDA did not have an adverse impact on myocardial systolic and diastolic function. In hypothesis, seratonergic agonists are associated with myocardial fibrosis which may deteriorate systolic functions assessed by conventinal and tissue Doppler parameters. However, similar to previous findings, we have found no difference in patients using cabergoline and control groups despite a higher cumulative cabergoline dose regarding right and left ventricular systolic functions. Those findings implicate that despite the effects of dopaminergic agonists on myocardial functions, cabergoline was not associated with any disturbance on systolic functions; however more sensitive tools like magnetic resonance imaging might show any possible myocardial fibrosis.

In our study, we also evaluated the left ventricular diastolic functions which revealed that several parameters of diastolic

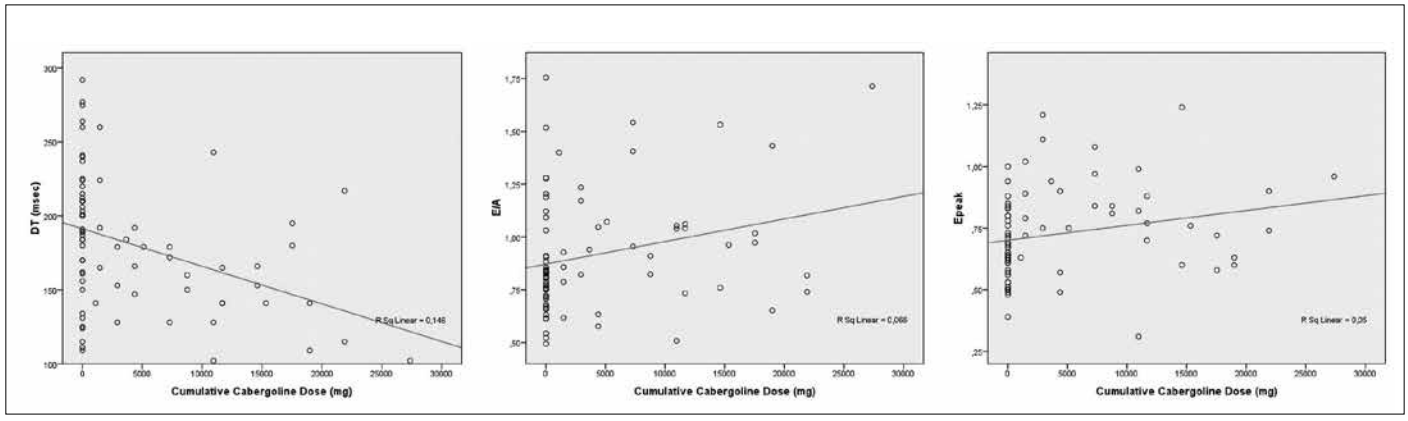

Figure 1. The association between cumulative cabergoline dose and diastolic functions including E_{peak} (r=0.253, p=0.042), E/A (r=0.256, p=0.026) and DT (r=-0.382, p=0.001)

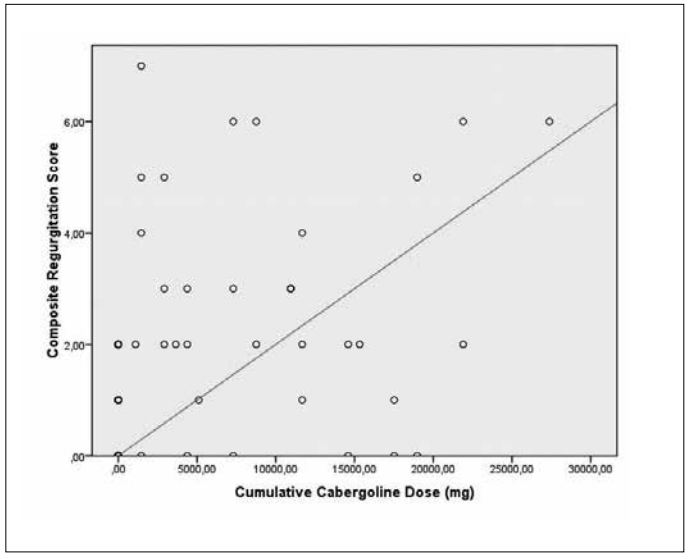

Figure 2. The correlation between cumulative cabergoline dose and composite regurgitation score (p<0.001)

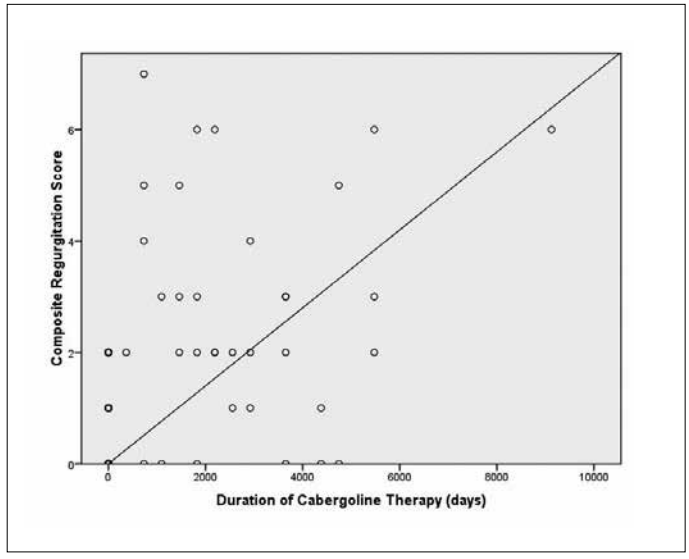

Figure 3. The correlation between duration of cabergoline therapy and composite regurgitation score (p<0.001)

functions including E_{peak}, E/A, E/ E´and DT were different between cabergoline and control groups. Moreover, cumulative cabergoline dose was associated with E_{peak}, E/A and DT. In contrary to those findings, Rasmussen et al. (11) did not found any impact of EDDA on diastolic functions. In our study group, valvular regurgitation might be proposed for the differences in diastolic functions between cabergoline and control groups. Conventional measures of diastolic functions including mitral inflow velocities were commonly affected by filling pressures which might partly explain the presence of diastolic dysfunction in cabergoline group with incresed valvular regurgitation. However, in addition to conventional measures, load independent measurements of LV relaxation such as E/E´ was higher in cabergoline group which were less influenced by the left atrial pressure and preload changes.

The main strength of our study is evaluation of left - right ventricular both systolic and diastolic functions in conjunction with valvular effects. In the cabergoline group, we did not observe any systolic dysfunction assessed by tissue Doppler imaging although early signs of LV dysfunction may be detected by measuring the longitudinal systolic function. Although some differences in diastolic functions were observed between cabergoline and control groups, those effects may not be wholely attributed to the fibrotic effects on myocardium. Additionally, mitral tenting area was increased in patients using cabergoline. In consistent with a recently published study by Cordoba-Soriano et al. (22), mitral valve tenting area could be a useful parameter for predicting the development of valve disease in the follow up. Beyond those, the fibrotic reaction may affect pulmonary system as well as other cardiovascular structures. In a previous study by Van Camp et al. (6), pulmonary artery pressure was significantly increased in patients using EDDA after exclusion of patients with significant valvular regurgitation. However, in our study group, systolic pulmonary artery pressure was higher in the cabergoline group and we thought that the difference was mostly due to moderate to severe valvular regurgitation.

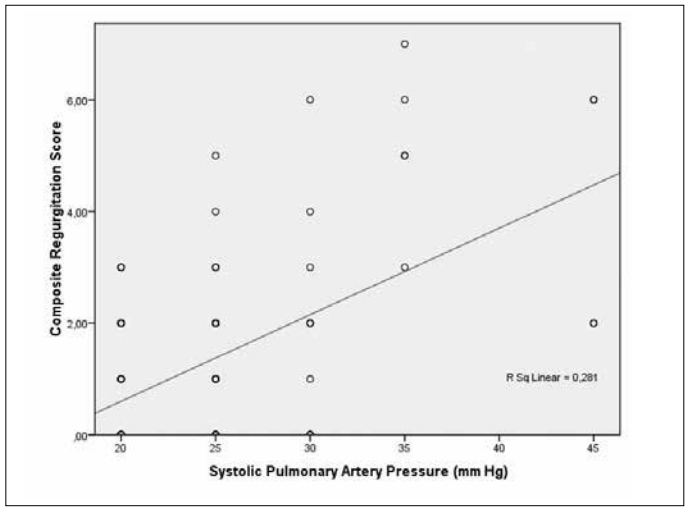

Figure 4. The correlation between systolic pulmonary artery pressure and composite regurgitation score (p<0.001)

Study limitations

Our study was a cross-sectional and observational study which has been consisted of a limited number of patients using cabergoline. Further prospectively designed studies evaluating echocardiographic data both before and after cabergoline therapy may be more valuable for highlightening this issue. Second more comprehensive methods might be needed in order to document systolic alterations in response to cabergoline; however previous studies did not document any systolic dysfunction using myocardial strain and two-dimensional speckle tracking methods (11). Third, valvular regurgitations were evaluated visually instead of using new techniques such as proximal isovelocity surface area (PISA) and effective regurgitant orifice area (EROA). Additionally, histopathologic examination or cardiac magnetic resonance imaging might give more valuable data regarding myocardial alterations in those patients using cabergoline.

Conclusion

Our findings indicated that despite the well known effects of cabergoline on valvular functions as in our patients, we did not observe any alteration in systolic functions but diastolic functions which was associated with cumulative cabergoline dose in patients with Parkinson's disease. Further large scale studies with newer methods are needed to clarify the exact effects of dopamine agonists over myocardium despite the clinically insignificant results obtained up to now.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - N.Ö., B.E.; Design - H.Y., U.C.; Supervision - N.Ö.; Materials - B. E., N.Ö.; Data collection&/or processing - H.Y., U.C.; Analysis &/or interpretation - U.C., H.Y., N.Ö.; Literature search - U.C.; Writing - U.C., H.Y.; Critical review - H.Y., B.E.

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