Evaluation of the effect of non-ergot dopamine agonists on left ventricular systolic function with speckle tracking echocardiography

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Abstract

Objective: Parkinson's disease (PD) is a neurological disorder, and ergot dopamine agonists (DAs) are no longer usually preferred in the treatment due to the increased risk of valvular heart disease. Some recent studies have shown that commonly used non-ergot DA also increases the risk of heart failure. On the other hand, there are studies showing conflicting data about this relationship. The aim of the present study was to investigate the cardiac effects of non-ergot DAs in patients with PD using echocardiography.

Methods: Conventional echocardiography and two-dimensional (2D) speckle tracking strain echocardiography were performed to determine the possible systolic dysfunction prior to the development of apparent systolic heart failure. Ninety-one (55 male, 64±10 years) patients with PD were included in the study. Furthermore, 25 subjects with newly diagnosed PD and using no drug were enrolled as the control group. All patients were divided into groups according to their medication. Patients using levodopa were classified as Group 1 (36), levodopa+pramipexole as Group 2 (27), and levodopa+ropinirole as Group 3 (28).

Results: Left ventricle dysfunction with non-ergot DA use in patients with PD was not established with conventional echocardiographic evaluation. For 2D strain analysis, global longitudinal strain values were obtained as –18.5%, –18.5%, and –18.9% in the groups, respectively. Strain and strain rate values of the left ventricle were not different between the groups (p=0.816 and p=0.881, respectively).

Conclusion: There was no significant relationship between left ventricular dysfunction and use of non-ergot DA in patients with PD. Similar results were obtained in strain analysis showing left ventricular subclinical dysfunction. Our study appears to confirm the safety of non-ergot DA in the point of heart failure risk. To our knowledge, this is the first study to evaluate the effect of this group of drugs on subclinical left ventricular systolic function. *(Anatol J Cardiol 2018; 20: 213-9)*

Keywords: Parkinson's disease, non-ergot dopamine agonist, speckle tracking echocardiography, strain echocardiography

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting approximately 10 million people worldwide (1). The prevalence of PD is observed to increase with age, and the estimated prevalence in the 85 years and above age group is approximately 5% (2, 3). Although physicians use dopamine agonists (DAs) frequently for the treatment of PD, there are concerns due to accumulating data about their adverse cardiac effects. First-generation DAs, the ergot DAs, are no longer commonly prescribed due to the possible risk of valvular heart disease development (4, 5). Thus, second-generation DAs, the non-ergot DAs, are often used in conventional treatment (6). Recently, some studies have suggested that the use of the non-ergot DA pramipexole increases the risk of heart failure (5, 7, 8). In view of the results presented by these studies, in 2012, the Food and Drug Administration (FDA) warned healthcare professionals regarding the possible risk of heart failure on pramipexole use (9). Contrary to these data, there are also new studies showing no significant relationship between heart failure and non-ergot Das (10, 11). It is a fact that heart failure is more prevalent and also more severe in patients with PD, especially in older age (12). The mechanism underlying this risk of heart failure is unknown, and it is difficult to decide whether it is due to medication or as a

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Accepted Date: 02.07.2018 **Available Online Date:** 10.09.2018

DOI:10.14744/AnatolJCardiol.2018.65983

Anatol J Cardiol 2018; 20: 213-9
DOI:10.14744/AnatolJCardiol.2018.65983

result of neurohormonal and autonomic factors related with PD (13, 14). Neither study revealed the etiology of heart failure, and heart failure with reduced ejection fraction (EF) or preserved EF may have been the pathophysiology of the disease.

The aim of the present study was to investigate the effects of using non-ergot DAs on left ventricle (LV) systolic and diastolic functions and to reveal the possible mechanisms of heart failure with non-ergot DAs in patients with PD. For this purpose, we analyzed the diastolic and the systolic functions of the LV by conventional echocardiography. In addition to conventional echocardiography techniques, we used two-dimensional (2D) speckle tracking echocardiography to determine the possible systolic dysfunction in the initial phase before the decline of the left ventricular ejection fraction (LVEF) and the occurrence of apparent heart failure. We also grouped the patients according to their prescribed drug, aiming to reveal the possible relationship between the drug and any LV systolic or diastolic dysfunction.

Methods

Study population

This single-center, cross-sectional study was conducted by the Department of Cardiology in collaboration with the Department of Neurology at the Ankara University Faculty of Medicine. Patients with PD were selected from the Neurology Outpatient Clinic. The diagnosis of PD was verified through specific diagnostic codes. The Hoehn and Yahr (H&Y) stage was used to determine the level of motor function and the severity of PD.

One hundred five patients with PD were evaluated, and 91 clinically stable patients who had previously taken the medication were enrolled in the study. The study population was divided into three groups according to their prescribed drugs. Group 1 consisted of levodopa users, Group 2 consisted of levodopa and pramipexole users, and Group 3 consisted of levodopa and ropinirole users. Nine patients were excluded from the study, with four due to previous acute coronary syndrome and five due to previous use of ergot DA (cabergoline). Five patients whose echocardiographic image quality was poor and not appropriate for strain analysis were excluded from the study (Fig. 1).

Patients with diabetes mellitus, atrial fibrillation and other rhythm disturbances, left bundle branch block, pacemaker implantation, known coronary artery disease, moderate to severe valvular heart disease with known etiology (e.g., rheumatic, ischemic, Barlow's, and congenital), or chronic obstructive pulmonary disease were excluded from the study. Patients who had been prescribed drugs belonging to any other group as part of their history were also excluded from the study.

Twenty-five patients who were newly diagnosed and had not yet started medication were included in the study as the control group.

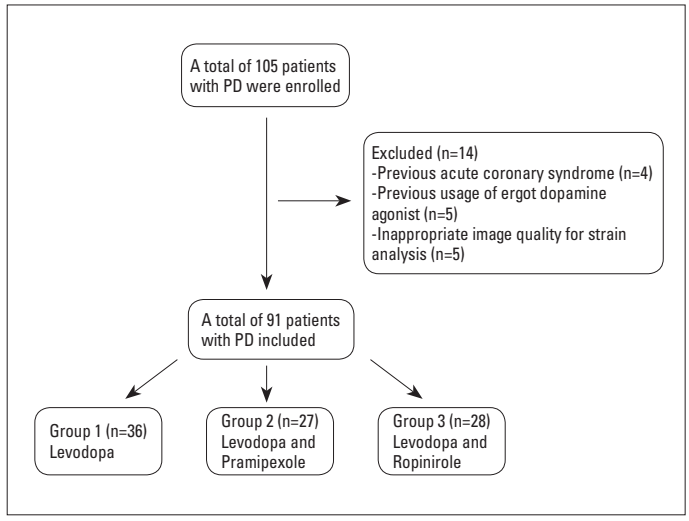

Figure 1. Flow diagram of the patients. The diagram includes detailed information on the excluded patients

Echocardiographic analysis

All patients were evaluated using 2D transthoracic echocardiography. Strain analysis was performed using the speckle tracking echocardiography technique. Written informed consent was obtained from all participants. The Institutional Ethics Committee approved the study.

Transthoracic echocardiographic examination was performed using a GE Vivid 7 and Vivid S5 instrument (GE, Horten, Norway) with a 3.5 MHz transducer. Standard parasternal long- and short-axis views and apical two- and four-chamber views were obtained for all patients. LV diameter and left atrial (LA) diameter were measured from M-mode images in parasternal long-axis view (15).

Peak tricuspid regurgitant velocities were recorded via the continuous wave Doppler technique, and a modified Bernoulli equation was used to estimate pulmonary artery systolic pressure. The modified Simpson's method was used to calculate the LVEF using the apical four- and two-chamber views (15). LA volumes were measured using the biplane disk-summation technique (15).

From the apical window, a 2 mm pulsed Doppler sample volume was placed at the mitral valve tip, and the mitral flow velocities of three cardiac cycles were recorded. Peak velocities of the early diastolic transmitral flow (E), as well as the late diastolic transmitral flow (A) and the early diastolic lateral mitral annulus velocity ($E_{lateral}'$), were thereby obtained. Lateral systolic myocardial velocity (S) was measured by tissue Doppler imaging (TDI) using pulsed wave Doppler. Then, the E/E′ parameter was calculated to obtain the best parameter for estimating LV filling pressure. If E/E′ is <10, pulmonary capillary wedge pressure (PCWP) is normal; if E/E′ is ≥15, PCWP is ≥20 mm Hg (16). Systolic velocity has shown a good correlation with LVEF. S is usually superior to 6 cm/s, and this value has a good correlation with normal EF (17).

Longitudinal 2D strain and strain rate analysis

Global longitudinal strain (GLS) echocardiography images were obtained by a cardiologist (D.M.G.) from standard apical four-chamber, three-chamber, and two-chamber views of the LV. Three stable cardiac cycles were stored for each view. All data collected were transferred to a workstation using a software system (EchoPAC PC; GE Ultrasound, Waukesha, WI, USA) in order to enable off-line analysis. Any rhythm disturbances were excluded. The frame rates used for the GLS analysis were between 40 and 80 frames/s (18). Conventional 2D grayscale echocardiographic images were used by the system, and the activity of the speckles was tracked throughout the myocardial tissue.

The regions of interest (ROIs) were manually outlined by marking the endocardial borders at the mitral annulus level, as well as at the apex of each digital loop; the epicardial surface was automatically generated by the software system. After any manual adjustment required, the ROI was divided into six segments. Each segment was then scored automatically by the software according to image quality. In the present study, the peak systolic strain values in an 18-segment LV model were used (18). The results for all three planes were then combined in a single bull's-eye summary that provided the GLS.

Measurements were repeated at least three times, and their average was determined. Global longitudinal strain rate (GLSR) was measured using the same technique.

Statistical analysis

Statistical analyses were performed using the SPSS version 20.0.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics are expressed as mean ± standard deviation for normally distributed data and as median (interquartile ranges) for non-normally distributed data.

When the number of groups was >2, analysis of variance was performed in order to analyze the significance of the differences in the means; the Kruskal-Wallis test was performed in order to analyze the significance of the differences of medians; and the differences were studied using post hoc tests.

Categorical variables were analyzed, when necessary, using a Pearson chi-square test. A p-value <0.05 was considered statistically significant.

Results

Ninety-one (55 male, 60%) patients with PD were enrolled in the study. There were 36 patients in Group 1, 27 patients in Group 2, and 28 patients in Group 3. The mean age of the patients was 64±10 years. The mean age and gender status of the groups were not statistically significant (Table 1).

The mean H&Y stage was 2.33±0.828 in Group 1, 2.15±0.770 in Group 2, and 2.04±0.429 in Group 3. There was no statistically significant difference between the groups (p=0.242) (Table 1).

The mean time period for which pramipexole had been prescribed was 41.4±42.36 (6-132) months. Similar time periods were calculated for ropinirole and levodopa use at 43.9±36.5 (6–108) and 59.1±54.7 (8–252) months, respectively.

The mean daily dosage of levodopa in the levodopa group was 499.2±22.35 mg, the mean daily dosage of pramipexole in the pramipexole group was 3.5±0.94 mg; and the mean daily dosage of ropinirole in the ropinirole group was 15.0±5.1 mg. These values are recommended dosages in line with established treatment guidelines (2).

The analysis of the M-mode measurements of the left atrium and LV end-diastolic diameters revealed no statistically significant differences between the groups (Table 2).

Table 1. Baseline demographic characteristics of the patients

Parameters	Levodopa (n=36)	Levodopa+pramipexole (n=27)	Levodopa+ropinirole (n=28)	Control (n=25)	*P*-value
Age	67.0±11.8	60.7±8.3	64.4±9.9	61.9±9.5	0.063[a]
Gender					
Male	23 (63.9%)	17 (63.0%)	15 (53.6%)	14 (56%)	
Female	13 (36.1%)	10 (37.0%)	13 (46.4%)	11 (44%)	
Total	36	27	28	25	0.812[b]
BMI (kg/m^2)	23.4±4.5	22.8±4.2	24.1±3.0	24±2.8	0.650[a]
Hypertension	3	2	2	2	0.998[b]
Mean Hoehn and Yahr stage	2.33±0.826	2.15±0.770	2.04±0.429	2.21±0.756	0.242[a]
Mean time period(months)	59.1±54.7 (8-252)	41.4±42.36 (6-132)	43.9±36.5 (6-108)	-	
Mean daily levodopa dosage (mg)	499.2±22.35	500.2±23.40	485±20.5	-	0.655[a]
Mean group drug dosage (mg)		3.5±0.94[x]	15.0±5.1[y]		

[a]One-way analysis of variance, [b]Pearson chi-square, [x]pramipexole dosage, [y]ropinirole dosage.
BMI - body mass index

Anatol J Cardiol 2018; 20: 213-9
DOI:10.14744/AnatolJCardiol.2018.65983

Table 2. 2D and Doppler echocardiographic parameters for the subjects

Parameters	Levodopa (n=36)	Levodopa+pramipexole (n=27)	Levodopa+ropinirole (n=28)	Control (n=25)	*P*-value
LA diameter, mm	40.5±4.3	41.1±2.9	39.0±4.3	40.0±2.6	0.528[b]
LAVI (mL/m^2)	26.4±1.5	26.4±1.57	25.7±1.29	25.8±1.6	0.090[b]
LVEDD (mm)	45.1±1.3	45.3±2.0	44.9±1.8	44.6±1.7	0.425[b]
LVESD (mm)	28.0±0.13	27.8±0.10	27.6±0.11	27.5±0.15	0.414[b]
PASP (mm Hg)	30.0 (27-33)	27.5 (26-32)	25.0 (26.5-28)	26.5 (25-35)	0.300[a]
EF (%)	53.7±3.7	53.4±5.3	54.4±2.1	54.5±4.3	0.407[b]
Diastolic filling pattern					
Normal pattern	20 (55.6%)	19 (70.4%)	20 (71.4%)	19 (69.8%)	
Grade 1	14 (38.9%)	7 (25.9%)	7 (25%)	8 (26%)	0.689[c]
Grade 2	2 (5.6%)	1 (3.7%)	1 (3.6%)	2 (5.1%)	
Grade 3	0	0	0	0	
$E/E_{lateral}'$	9.1±3.0	10.5±3.8	8.8±3.0	8.9±2.8	0.504[b]
S lateral (cm/s)	6.0 (5.5-8)	6.0 (5.4-7.5)	7.0 (5.8-8)	7.0 (5-10)	0.448[a]

[a]Kruskal-Wallis test. [b]One-way analysis of variance. [c]Chi-square test.
E - early diastolic transmitral flow; $E_{lateral}'$ - early diastolic lateral mitral annulus velocity; EF - ejection fraction; LA - left atrium; LAVI - left atrium volume index; LVEDD - left ventricular end-diastolic diameter; LVESD - left ventricular end-systolic diameter; PASP - pulmonary arterial systolic pressure; S - lateral systolic flow velocity

Table 3. Global longitudinal strain values of the subjects

Variable	Levodopa	Levodopa+pramipexole	Levodopa+ropinirole	Control	*P*-value[a]
GLS (%)	–18.5±3.0	–18.5±2.3	–18.9±2.7	-18.7±2.3	0.816
GS4 (%)	-18.5±3.4	-18.5±2.9	-18.9±2.9	-18.8±3.6	0.712
GS2 (%)	-17.7±3.6	-18.3±2.6	-18.1±3.4	-18.5±2.8	0.748
GSAPLAX (%)	-19.1±3.4	-18.5±2.6	-19.6±2.8	-19.1±3.1	0.428

[a]One-way analysis of variance.
GLS - global longitudinal strain; GSAPLAX - global strain from apical long-axis view; GS2 - global strain from two-chamber view; GS4 - global strain from four-chamber view

Table 4. Global longitudinal strain rate values of the subjects

Variable	Levodopa	Levodopa+pramipexole	Levodopa+ropinirole	Control	*P*-value[a]
GLOBALSR (s–1)	-1 (-0.7-1.8)	-1 (-0.8-1.5)	-1 (-0.7-1.7)	-1 (-0.7-1.7)	0.881[a]
GSR4 (s–1)	-1 (-0.6-1.7)	-1 (-0.6-1.6)	-1 (-0.7-1.7)	-1 (-0.6-1.6)	0.404[a]
GSR2 (s–1)	-1 (-0.6-1.7)	-1 (-0.5-1.5)	-1 (-0.7-1.6)	-1 (-0.7-1.6)	0.745[a]
GSRAPLAX (s–1)	-1.1 (-0.8-2)	-1.1 (-0.7-1.6)	-1 (-0.8-1.7)	-1 (0.7-1.8)	0.924[a]

[a]Kruskal-Wallis test.
GSRAPLAX - global strain rate from apical long-axis view; GSR2 - global strain rate from two-chamber view; GSR4 - global strain rate from four-chamber view; SR - strain rate

The mean LA volume indices (LAVIs) of the three groups were 26.4±1.5 mL/m^2, 26.4±1.57 mL/m^2, and 25.7±1.29 mL/m^2, respectively (p=0.09).

All patients had preserved EF >50%, and there was no statistically significant difference between the groups with respect to LVEF (Group 1=53.7%, Group 2=53.4%, and Group 3=54.4%; p=0.407) (Table 2).

The median systolic pulmonary artery pressure was 30.0 mm Hg in Group 1, 27.5 mm Hg in Group 2, and 25.0 mm Hg in Group 3 (p=0.300). The diastolic filling patterns of the groups were mostly

normal or Grade 1 dysfunctional (Table 2). According to Grade 1 diastolic dysfunction, there was no statistically significant difference between the groups (p=0.689), and p-value of comparison of all drug groups with control group was 0.095, 0.655, and 0.785, respectively.

The TDI results revealed that E/E′ lateral and S flow velocity values were similar in all three groups (Table 2). Recorded E/E′ lateral values for the three groups were 9.1±3.0, 10.5±3.8, and 8.8±3.0, respectively (p=0.504). S values for the three groups were 6 cm/s, 6 cm/s, and 7 cm/s, respectively (p=0.448).

The results of the strain analysis demonstrated that there were no statistically significant differences between the groups with respect to GLS values. The GLS values for the groups were determined as −18.5 (±3.0), −18.5 (±2.3), and −18.9 (±2.7), respectively (p=0.816) (Table 3). The median GLSR values of the groups were estimated to be −1, −1, and −1, respectively (p=0.881) (Table 4).

Discussion

Data generated as a result of our study did not demonstrate LV systolic or diastolic dysfunction with non-ergot DA use in patients with PD. Chamber sizes, pulmonary artery pressure, LVEF, and diastolic functions were within the normal ranges according to the ASE/EACVI Cardiac Chamber Quantification Guidelines (15). The mean GLS and strain rates determined for the different groups were also within the normal ranges (18-20), and there were no significant differences between the groups.

Owing to the claims of previous studies that non-ergot DAs may increase heart failure risk in patients with PD, the aim of the present study was to reveal the possible mechanisms of heart failure development in this population (5, 7, 8). Similarly, since previous studies did not reveal the etiology of heart failure in patients with PD, and reduced EF or preserved EF heart failure may have been the pathophysiology of the disease, we analyzed the diastolic functions of the LV in addition to the systolic functions. The LV systolic and diastolic functions were analyzed using conventional echocardiography techniques (2D, Doppler, and tissue Doppler), and systolic functions were also studied using 2D speckle tracking, which is an advanced echocardiography technique and can determine the possible systolic dysfunction in the initial phase before the decline of the LVEF and the occurrence of apparent heart failure.

Several echocardiographic studies have clearly demonstrated an association between ergot DA treatment, valvular heart disease, and pulmonary hypertension (21-28). Although the mechanism of ergot DA-induced valvular disease is not clearly elucidated, the stimulation of various subtypes of serotonin receptors may be related to the excessive production of extracellular matrix and fibroblast proliferation (such as fenfluramine-induced cardiac damage) (29-31). Second-generation DAs, the non-ergot DAs, are currently the drug of choice for PD (6).

In 2012, two studies linked the use of the non-ergot DA pramipexole with the risk of heart failure in patients with PD (7, 8). The first report was a case–control study from the United Kingdom General Practice Research Database (7). The study results showed that the rate of heart failure increases with the current use of any DA. The authors noted that this increase is more evident when the drug in question is pramipexole. Mokhles et al. (8) conducted another case–control study in the same year. Their results revealed that pramipexole is associated with an increased risk of heart failure in patients with PD, especially during the first month of therapy and in patients with very advanced age. Based on the results of the above-mentioned studies, the FDA warned healthcare professionals in 2012 about the possibility of an increased risk of heart failure connected to pramipexole use (9).

There is recent contradictory evidence suggesting no relationship between increase of heart failure and non-ergot DA use. In the observational study by Hsieh and Hsiao (32), ergot DAs, but not non-ergot DAs, were found to cause an increased risk of heart failure. A case/non-case analysis conducted by Montastruc et al. (10) displayed a significant association between exposure to ergot DA and appearance of heart failure, whereas this association was not significant for non-ergot DA. In addition, a meta-analysis reported no increase in the occurrence of heart failure in patients with PD using non-ergot DA, even if compared with placebo (11).

Even if there is a heart failure risk associated with pramipexole, the mechanism is unclear and remains to be elucidated. However, there are some speculations. Heart failure can appear as a result of valvular cardiomyopathy due to increased ventricular volume, causing myocardial strain deterioration (33). However, there are no supporting data reporting the causal relationship of non-ergot DA with an increased risk of valvular disorders (5). Moreover, sympathetic denervation of the heart, which can be encountered in patients with PD, may lead to heart failure (34, 35). In addition to being a DA, pramipexole has an affinity to alpha-2 adrenergic receptors, and via this pathway, it can lead to a decrease in myocardial contraction and sympathetic tone (36, 37). The mechanism of the development of heart failure in patients with PD may be a result of primary myocardial systolic or diastolic dysfunction, and that mechanism has not been demonstrated in previous studies. Thus, if non-ergot DAs elevate the risk of systolic heart failure, then subclinical deterioration of the myocardial functions could be discernible prior to a decrease of LVEF and the development of overt disease. For this reason, assessment of subclinical myocardial dysfunction was one of the areas covered by the deformation imaging.

Strain echocardiography is a type of deformation imaging technique based on the evaluation of myocardial mechanics into two ways: Doppler-based velocity measurements and tracking-based displacement measurements (38). Tracking-based function measurements provide true regional and global information (38). Previous studies have shown that normal strain values can

Anatol J Cardiol 2018; 20: 213-9
DOI:10.14744/AnatolJCardiol.2018.65983

vary from 16% to 19% (19, 20). Normal LV strain values, as determined from meta-analysis and recent studies using EchoPAC and also by the system that we used in the present study, have shown that the lower limit of normal longitudinal strain is 17% (15).

In our study group, the GLS values for nearly all subjects were above the normal limit, but, for a few patients, GLS was below the normal limit as defined by standard deviation. The slightly lower values did not reduce the mean GLS values of the groups. A small proportion of the study population may have had an unknown etiology, such as subclinical coronary artery disease, and those patients would have to be investigated individually.

The EF, an important parameter of the systolic function of the ventricle, can be obtained in a reproducible manner using echocardiography. In the present study, the LVEF of the groups was between normal values as defined by the ASE/EACVI Cardiac Chamber Quantification Guidelines (15). In normal clinical routine, under conditions of mild systolic dysfunction, uncertainties are likely to occur. Global strain offers information of a quality comparable with that of EF but at lower inter- and intraobserver variability. In daily practice, owing to the lack of time and technical facilities, it is very difficult–but very important–to apply deformation imaging techniques.

In the present study, we evaluated diastolic functions and diastolic parameters. The diastole filling pattern, E/E′, and LAVI were within the normal ranges; therefore, we did not find a relationship between heart failure with preserved EF and these drugs. None of the study population had moderate or severe valvular pathology or right ventricle dysfunction; therefore, we did not specify that data in our study.

In summary, we analyzed conventional echocardiographic parameters and GLS and strain rates of non-ergot dopamine user patients with PD and compared those values according to the patients' prescribed drugs in the current study. We did not find an association between systolic and diastolic dysfunctions and non-ergot DAs. We did not demonstrate a reduction in the strain or strain rate of the LV. In the present study, we used 2D strain echocardiography in order to assess left ventricular systolic function of non-ergot DA user patients with PD. The findings of other previous studies were mostly based on clinical data, except for a previous study on strain echocardiography that demonstrated that levodopa has no unfavorable effect on systolic function (39). However, our findings are also based on both conventional and advanced echocardiographic data of non-ergot DA user patients with PD. Our preliminary study may provide a foundation for further studies in the future.

Study limitations

This was a single-center, cross-sectional study with a limited number of patients. However, prospective studies using advanced echocardiography techniques should be conducted on larger sample sizes in order to accurately assess the probable cardiac effects associated with the prescribed drugs in patients with PD. In the present study, we were limited by our ability to assess only longitudinal strain. If newer studies define radial as well as circumferential strain in the myocardium of patients with PD, data are likely to be of higher value. Another limitation is that we were unable to perform a prospective study. The ability to measure parameters before and after drug use would have significantly improved the value and importance of our results.

Conclusion

Our study appears to confirm the safety of non-ergot DA in the point of heart failure risk. We assessed left ventricular systolic and diastolic functions in patients with PD and analyzed systolic function with speckle tracking echocardiography and did not find a reduction. Although we did not find any causal association between non-ergot DA, pramipexole and ropinirole, and myocardial dysfunction, close cardiac monitoring should be made for patients taking DAs. Further prospective study with larger cohorts is needed to evaluate the safety of chronic treatment with non-ergot DA in patients with PD.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – H.E.P., S.T.; Design – H.E.P., S.T.; Supervision – H.E.P., D.M.G.U., B.T.T., T.H.E.; Fundings – B.T.T., M.H.S., C.A.; Materials – H.E.P., D.M.G.U., M.H.S., C.A.; Data collection &/or processing – D.M.G.U., M.H.S., C.A., S.T.; Analysis &/or interpretation – B.T.T., T.H.E., A.A.; Literature search – H.E.P., D.M.G.U., A.A.; Writing – H.E.P., D.M.G.U., A.A.; Critical review – H.E.P., D.M.G.U.

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