Ergotamine-derived dopamine agonists and left ventricular function in Parkinson patients: systolic and diastolic function studied by conventional echocardiography, tissue Doppler imaging, and two-dimensional speckle tracking

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Aims Ergot-derived dopamine agonists (EDDA) induce fibrotic heart valve disease. We aimed to investigate whether EDDA treatment also affects left ventricular (LV) function.

Methods and results myocardial function was evaluated in 110 Parkinson patients [mean age ([63.4 ± 9.0 years)] treated for at least 6 months with either EDDA (n = 71) or non-EDDA (n = 39). LV ejection fraction did not differ between EDDA and non-EDDA patients [63 ± 4% vs. 65 ± 4% (ns)]. There was no difference in prevalence of diastolic dysfunction between EDDA and non-EDDA patients [7% vs. 8% (ns)]. Finally, averaged LV systolic myocardial strain and longitudinal displacement analysed by means of two-dimensional speckle tracking showed no difference between EDDA and non-EDDA patients [strain: 19 ± 3% vs. 19 ± 2% (ns) and longitudinal displacement: 12 ± 2 mm vs. 12 ± 2 mm (ns)]. Elevated p-NT-proBNP was found in 38% of EDDA patients and in 59% of non-EDDA patients (ns).

Conclusion In contrast to the well-established association between EDDA treatment and valvular fibrosis, EDDA did not have a detectable adverse impact on myocardial systolic and diastolic function.

KEYWORDS Myocardial function; Fibrosis; Ergolines; Dopamine agonists

Introduction

Several studies indicate that heart valve disease in patients with idiopathic Parkinson disease (IPD) may result from treatment with the ergot-derived dopamine agonists (EDDA).1–4 As in carcinoid syndrome the pathophysiological mechanism is believed to rely on activation of serotonergic receptors. Stimulation of these may induce up-regulation of cytokine transforming growth factor (TGF-β) responsible for differentiation of fibroblasts to myofibroblasts, cell proliferation, and increased production of extracellular matrix.5–7 In animal models serotonin-induced fibrosis was demonstrated not only in the heart valves but also in the myocardium.8,9

Excess formation of interstitial myocardial fibrotic tissue might lead to left ventricular (LV) dysfunction. The conventional measure of LV function is the systolic ejection fraction (EF) but in many conditions LV diastolic dysfunction has been shown to reflect adverse impact on the myocardium even in patients with normal EF.10 It has also been shown that decreased systolic function of the LV myocardial fibres with a predominant longitudinal course from basis to apex (the ‘longitudinal’ fibres) seems to be a more sensitive or earlier sign of systolic dysfunction than decreased EF.11,12 Systolic function of these fibres can be expressed as regional systolic deformation (longitudinal strain) or as longitudinal displacement in systole, either measured by tissue Doppler imaging (TDI) or by another recently introduced echocardiographic technique: speckle tracking.13,14

In order to determine whether or not EDDA induces myocardial fibrosis we used these established and recently...
introduced echocardiographic techniques to compare the various aspects of LV function in IPD patients treated either with EDDA or with a non-EDDA.

**Patients and methods**

The study was part of an investigation of Parkinson medication and heart disease. The study was initiated in February 2005 and patients were enrolled during a period of 18 months. The results regarding the relationship between EDDA and valve disease are recently published.\(^2\) All patients with IPD in the outpatient clinic of our department of neurology were considered eligible for the study if treated with either EDDA or non-EDDA during the past year and if provided a treatment for a period of at least 6 months. Non-EDDA patients were considered as controls but were excluded if earlier treated with EDDA for >6 months. The study included 138 IPD patients,\(^4\) however, patients who earlier underwent open heart surgery (n = 3; one EDDA patient and two non-EDDA-treated patients) or had atrial fibrillation (n = 1 EDDA-treated patient) were excluded from this study on LV function. The heart failure marker p-NT-proBNP was measured if the outpatient visit took place during the opening hour of the laboratory of clinical biochemistry and if the patient accepted the blood test. The threshold for elevated p-NT-proBNP was 125 pg/mL.\(^15\)

**Echocardiography**

The recordings were obtained using a GE-VingMed System FiVe apparatus (General Electric, Horten, Norway). All echocardiographic examinations and post-processing analyses were done without the knowledge of the medical treatment for IPD. Morphological and functional features of aortic, mitral, and tricuspid valve were analysed according to generally accepted guidelines.\(^16\) M-mode and two-dimensional (2D) echocardiography were performed at 1.7 MHz with second harmonic imaging. LV dimensions and wall thicknesses were measured by M-mode echocardiography. LVEF was measured with the use of Simpson’s biplane method or in few cases with reduced endocardial definition estimated visually by an experienced examiner.\(^17\) Transmitral flow velocity profiles were obtained in the apical four-chamber view using pulsed wave Doppler with the beam aligned with the flow direction and sample volume between the tips of the mitral leaflets. The E- and A-wave peak velocities and E-deceleration time (DT) were measured.\(^18\)

Digital TDI loops in the four-chamber view were recorded during quiet respiration and with focus on the mitral annulus. Frame rates of 108–132 frames s\(^{-1}\) were obtained. In a post-processing analysis a 9 × 9 mm\(^2\) sample interrogated the septal part of the mitral annulus.\(^19\) Here the peak systolic annular velocity (S) and early diastolic annular velocity (E) were measured as the average of three consecutive heart cycles. The ratio between the transmitral E velocity and the annular E’ velocity (E/E’)) was used as a surrogate marker of LV filling pressure. E/E’ > 15 was considered to reflect elevated LV filling pressure.\(^19\) The diagnosis of diastolic dysfunction function was based on the transmitral Doppler velocities. The combination of E/A ratio < 1 and DT > 240 was considered to indicate stage I diastolic dysfunction (impaired relaxation). Patients with E/A ratio of 1–1.5 and DT 140–240 were regarded as having diastolic dysfunction stage II (pseudo-normalization) if the E/E’ ratio indicated elevated filling pressure. The combination of E/A ratio > 1.5 and DT < 140 was considered diagnostic of diastolic dysfunction stage III (restrictive filling pattern).

Myocardial systolic strain and systolic displacement were measured using speckle tracking. Both strain and displacement were assessed by using digital stored 2D echocardiographic loops obtained in the apical four-chamber, two-chamber, and long-axis views recorded with a frame rate of ~60 frames s\(^{-1}\). Using the 16-segment model of the American Society of Echocardiography, strain and displacement were analysed in the 12 mid and basal third segments. The calculated average systolic strain and displacement of the segments were used for comparison between the EDDA and the non-EDDA groups. We omitted analysis of strain and displacement in the four apical segments because myocardial motion in these segments is limited resulting in greater inaccuracy of measurements.

All post-processing analyses were done using Echopac software (General Electric, Horten, Norway).

**Statistical analysis**

Descriptive data are presented as number or percentage, mean values with corresponding standard deviation, or median with 25–75th percentile. Fisher’s exact test, χ\(^2\) test, t-test, or non-parametric tests were used as appropriate for comparison of groups. The significance level was set at P < 0.05. The association between EDDA and EF, diastolic dysfunction, myocardial systolic strain, and displacement were tested in multivariate analysis adjusting for possible confounding by the risk variables: age, sex, duration of IPD, IPD medication, diabetes, valvular heart disease, or known ischaemic heart disease. The results were given as odds ratios (OR).

A correlation between increasing doses of EDDA and EF, systolic strain, and longitudinal displacement was checked using & one-way ANOVA whereas the correlation between increasing doses of EDDA and diastolic dysfunction was examined in a R\(^2\) table using Pearson’s χ\(^2\).

All statistical analyses were performed using Stata 9 (College Station, TX, USA).

**Ethical considerations**

The study was performed according to the ethical principles in the Declaration of Helsinki. The Local Scientific Ethical Committee approved the study protocol and the study was reported to www.clinicaltrials.gov (no. NCT00234364). Patients were included only after written informed consent.

**Results**

Satisfactory echocardiographic recordings for assessment of all LV function parameters (LVEF, longitudinal systolic function, and diastolic function) were obtained in 110 of the 134 IPD patients. EDDA treatment was administered in 71 patients (65%) while 39 were treated with non-EDDA (35%). Among the 71 EDDA-treated patients 22 were treated with pergolide and 49 with cabergoline. Nine non-EDDA patients received ropinirole and to the remaining 30 non-EDDA patients pramipexole was administered. Baseline characteristics of the 110 included patients are summarized in Table 1. The EDDA and non-EDDA groups were comparable except for the distribution of male and female patients. Moderate or severe valvular regurgitation was found in 25% of the EDDA patients and in 5% of the non-EDDA patients (P < 0.05).\(^2\)

The 24 patients with insufficient echocardiograms were 12 EDDA and 12 non-EDDA-treated patients (ns). These 24 patients did not differ significantly from the study population of 110 patients with regard to distribution of age, gender, duration of IPD, valvular regurgitation, ischaemic heart disease, hypertension, diabetes, or cumulated doses of EDDA medication (Table 2). The visually estimated EF in the 12 EDDA patients was 63.8 ± 4% as compared with 64.7 ± 5% in the non-EDDA patients (ns).
Global left ventricular systolic function and diastolic filling

LV dimensions, wall thicknesses, and EF did not differ significantly between EDDA and non-EDDA patients (Table 3). There was a trend towards lower EF among patients with moderate or severe valvular insufficiency in the univariate analysis, and when adjusting for gender, valvular insufficiency was associated with significantly lower EF [OR = 0.24 (0.04–1.4)]. However, in the multivariate analysis there was no association between EDDA treatment and EF [OR = 0.47 (0.08–2.79), Table 4] regardless of inclusion of valvular insufficiency in the regression model or not. Leaving moderate and severe valvular regurgitation out of the regression model resulted in an OR of 0.24 (0.04–1.4).

Left ventricular longitudinal systolic function

Average systolic longitudinal strain and displacement were similar in the EDDA and non-EDDA groups (Table 3).
Figure 1 shows that strain was the same in the EDDA and non-EDDA groups for any LV region. The average systolic longitudinal displacement was also the same for EDDA (12 ± 2 mm) and non-EDDA patients [12 ± 2 mm (ns)]. In multivariate analysis EDDA was not found to be associated neither with decreased longitudinal strain nor displacement (Table 4).

Brain natriuretic peptide
The N-terminal fragment of brain natriuretic peptide (NT-proBNP) was measured in 56 patients [55% of EDDA patients and 44% of non-EDDA-treated patients (ns)]. Elevated NT-proBNP was found in 38% of EDDA and 59% of non-EDDA-treated patients (ns). Seven out of eight patients with diastolic dysfunction stage II–III had their NT-proBNP measured and three (43%) had elevated NT-proBNP compared with 45% of patients without diastolic dysfunction stage II–III. Patients with elevated NT-proBNP had LVEF of 62 ± 5%, systolic strain of 18 ± 3%, and systolic longitudinal displacement of 12 ± 2 mm as opposed to patients with no elevation of NT-proBNP who had LVEF of 64 ± 4%, systolic strain of 19 ± 2%, and systolic longitudinal displacement of 12 ± 2 mm (ns for all).

Other factors with influence on the left ventricular functional parameters
In the multivariate analysis gender was the only feature associated with EF. Female patients had slightly but significantly higher EF (65 ± 4%) than male patients (63 ± 4%, P < 0.05). In contrast, female gender was the only risk factor associated with lower systolic longitudinal displacement [OR = 0.39 (0.18–0.83)].

Hypertension was the only risk factor associated with diastolic dysfunction [OR = 11.8 (1.27–110)] and with lower systolic strain [OR = 0.24 (0.09–0.68)]. A sub-group analysis of patients with hypertension still revealed no difference between EDDA and non-EDDA patients with regard to EF [63 ± 5% vs. 64 ± 5% (ns)], prevalence of diastolic dysfunction [12% vs. 16% (ns)], systolic strain [18 ± 2% vs. 18 ± 2% (ns)], and longitudinal displacement [12 ± 2 mm vs. 12 ± 2 mm (ns)].

Cumulated doses of pergolide and cabergoline were pooled and categorized into four groups. Increasing cumulated doses of EDDA were not associated with decreased LV systolic function (Figure 2). Also no correlation was found between increasing cumulated doses of EDDA and the risk of diastolic dysfunction (Pearson’s χ² 0.14).

Discussion
Both EDDA and non-EDDA are widely used in the treatment of IPD. In addition dopamine agonists are used in the treatment of restless legs and disorders with hyperprolactinemia. The numerous observational studies indicating an association between EDDA treatment and development of valvular heart disease1,2,4 have prompted caution and even resulted in withdrawal of pergolide from the US market (www.fda.gov/cder/drug/advisory/pergolide.htm).

All dopamine agonists stimulate serotonin receptors, but the affinity for subgroups of these receptors differ between the drugs. Only pergolide and cabergoline are known to display agonistic properties to the 5 HT-2B receptor, which is found in heart valves and in the myocardium.20 In rats Gustafsson et al.8 demonstrated that serotonin injections not only affected the heart valves, but also caused development of subendocardial plaques of myofibroblasts and enhanced extracellular matrix formation in the atria and ventricles. Moreover, in mice lacking the membrane-bound transporter, responsible for the clearance of serotonin, fibrotic lesions developed not only in the valves but also focally in the myocardium.9 Thus, theoretically EDDA treatment might be associated with increased myocardial
fibrosis and resulting reduction in the myocardial function. In our study we used conventional and recently introduced echocardiographic techniques for analysis of LV systolic and diastolic function in IPD patients but were unable to demonstrate any adverse impact of EDDA treatment on LV function. LVEF, systolic strain, longitudinal displacement and diastolic function did not seem to be impaired by treatment with EDDA. In addition, we found no difference in p-NT-proBNP between patients who were treated with EDDA or non-EDDA. In theory, p-NT-proBNP might have revealed a difference between the groups as an elevated p-NT-proBNP can be supposed to reflect not only the impact of valve disease on the myocardium but also more subtle primary myocardial abnormalities, e.g. caused by fibrosis. Admittedly p-NT-proBNP was only measured in 51% of the patients but there was equal participation of EDDA and non-EDDA patients.

There was a small but significant difference in EF between genders. Our female patients had slightly higher EF than the male patients although mean EF of both genders were within the normal range. This relationship between gender and EF is also found in healthy volunteers. Although we have no definite explanation of this feature it is possible that the slightly higher EF in our female patients matches the slightly lower systolic longitudinal displacement as compared with the male patients. At least systolic longitudinal velocities are reported to be lower in female than in male normal volunteers.

Female gender was more frequent than male gender in the non-EDDA group and female patients had significantly lower longitudinal displacement in systole than male patients. Hypothetically this could have masked a true difference between longitudinal systolic displacement of EDDA and non-EDDA patients with lower longitudinal systolic function in patients on EDDA medication. However, our multivariate analysis indicated that this was not the case.

It is well established that hypertension is associated with myocardial fibrosis, diastolic dysfunction, impaired longitudinal systolic contractility, and in later stages decreased EF. In our IPD patients we confirmed the relationship between hypertension and diastolic dysfunction and between hypertension and decreased strain. In hypertension angiotensin II up regulates TGF-β, which stimulates the production of extracellular matrix proteins. TGF-β may also be a possible pathway for serotonin receptor mediated fibrosis. Thus, co-existence of hypertension and EDDA treatment might be expected to magnify the risk of myocardial fibrosis and impaired LV diastolic and systolic function. However, such an intensifying effect was not demonstrated in our study.

Valvular regurgitation initially causes volume overload of the LV leading to hyperkinetic function and increased EF. With later progression LV systolic function decreases. It has been suggested that early signs of LV dysfunction may be detected by measuring the longitudinal systolic function. It would be reasonable to assume that patients with EDDA-induced valvular regurgitation represented those particularly susceptible to medically induced fibrosis, not only in the heart valves but also in the myocardium. However, such an association could not be demonstrated from our multivariate analyses. The number of patients with moderate or severe valvular regurgitation was, however, limited in the study (Table 1).

The mortality rate among IPD patients is slightly elevated as compared with the background population. However, the risk of cardiovascular disease is not supposed to be higher than in non-IPD controls, although one study showed a significantly higher prevalence of heart failure among 151 PD patients (19.4%) than in 11 752 non-IPD patients (8.7%, OR = 2.27). Yet, the diagnosis of heart failure was based on history of dyspnoea, fatigue, and peripheral oedema, whereas EF or other LV indices were not systematically reported. Generally, epidemiologic studies of mortality and morbidity in IPD patients do not include a history of treatment with EDDA. Based on the results of our study an excess proportion of patients with overt primary myocardial failure cannot be expected in patients treated with EDDA.

**Limitations**

Assessment of LV longitudinal systolic and diastolic function has been widely used to diagnose subclinical LV dysfunction in various diseases associated with myocardial fibrosis. It should be emphasized that a definite diagnosis of myocardial fibrosis only can be made by histopathological examination of the myocardium. In our study population of patients with normal echocardiographic measurements, myocardial biopsy would hardly seem ethical. To our knowledge myocardial fibrosis in IPD patients has not been the subject of necropsy studies.

We did not include a non-IPD control group, but the echocardiographic data in both our EDDA and non-EDDA groups were similar to those reported in asymptomatic and otherwise healthy individuals of comparable age.

We used colour coded digital TDI loops to achieve mitral annular velocities. These values are generally 15–20% lower than those obtained by pulsed tissue Doppler. The calculation of E/E' will therefore tend to give values higher than those achieved by pulsed tissue Doppler. Cut-off values for normal (<8) and increased filling pressures (>15), respectively, are primarily derived from pulsed tissue Doppler. Accordingly, we might have overestimated the number of patients with increased E/E' ratio. However, this overestimation should be equal in the two treatment groups and further, the blinding for anti-parkinson medication be assured against bias. Indeed, the number of patients with elevated E/E' ratio was high (21%), but this is consistent with the high fraction of patients with hypertension.

The number of patients included in the study was limited and unevenly distributed between EDDA and non-EDDA treatment. Still, our EDDA group is relatively large compared with other studies. To ensure proper technical quality and reliability of 2D speckle tracking interpretation we also had to exclude 12 EDDA (and 12 non-EDDA) patients with insufficient echocardiograms. These patients apparently had a normal EF similar to those in the study. There is no reason to believe that diastolic dysfunction or decreased longitudinal systolic function was particularly likely in the 12 EDDA patients with echocardiograms insufficient for reliable measurement of systolic longitudinal function and/or transmitral flow.

The cumulated doses of EDDA in this study might have been too small to result in decreased LV function. However, the cumulated doses were comparable with...
those reported in other studies and even in patients treated with the highest doses of EDDA no impairment of LV function was detectable. Furthermore, the doses were large enough to induce valvular abnormalities in a significant number of the EDDA patients.

Conclusions
In contrast to the well-established association between EDDA treatment and valvular abnormalities we were unable to demonstrate any association between EDDA treatment and myocardial dysfunction (Table 4). Fibrotic lesions have been demonstrated focally in the myocardium in animal models, and may also be present in IPD patients treated with EDDA. However, EDDA-induced myocardial fibrosis does not appear to be a clinical problem of the same magnitude as EDDA-induced valvular disease.

Conflict of interest: none declared.

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References