Table 4. **Adverse Events during Leuprorelin Administration (48-Week Randomized Controlled Trial and 96-Week Follow-up)**

AEs	Group A (n = 19)[a]	Group B (n = 15)	Group D (n = 10)
At least one AE	18 (95%)	15 (100%)	7 (70%)
At least one AE other than ED	15 (79%)	11 (73%)	5 (50%)
ED[b]	13 (68%)	9 (60%)	2 (20%)
Numbness	7 (37%)	3 (20%)	2 (20%)
Arthralgia	5 (26%)	5 (33%)	1 (10%)
Hot flush	5 (26%)	4 (27%)	0
Injection-site lump	5 (26%)	4 (27%)	0
Lumbago	5 (26%)	1 (7%)	1 (10%)
Myalgia	2 (11%)	2 (13%)	0
Edema	3 (16%)	0	0
Headache	3 (16%)	0	1 (10%)
Fatigue	2 (11%)	1 (7%)	0
Hyperglycemia	2 (11%)	1 (7%)	1 (10%)
Hypertension	1 (5%)	1 (7%)	0
Death	1 (5%)	0	0
Neuralgia	1 (5%)	0	0
Pollakiuria	1 (5%)	0	0
Depression	0	1 (7%)	0
Fracture	0	1 (7%)	1 (10%)
Hyperlipidemia	0	1 (7%)	1 (10%)

[a]All patients were analyzed including Patient 16. [b]Number was calculated by questionnaire on every visit. AE = adverse event; ED = erectile dysfunction.

SBMA.[51] The high tolerability of leuprorelin acetate was also supported by the low dropout rate in this trial.

An important limitation in this study is the trial duration. SBMA is a slowly progressive disease, with a disease duration of approximately 20 years.[7] Given that leuprorelin acetate did not suppress the decline in ALSFRS-R scores in our 48-week RCT, a long-term, placebo-controlled trial may be necessary to evaluate the efficacy of leuprorelin acetate on general motor function in SBMA. Based on this study, cricopharyngeal opening duration in VF appears to be a practical biomarker to evaluate therapy efficacy for SBMA in short-term trials.

In conclusion, the results of this study suggest that leuprorelin acetate administration suppresses nuclear accumulation, stabilization, or both of mutant AR, the causative protein of SBMA, and appears to inhibit functional deterioration of the patients. The results of this phase 2 trial support the start of large-scale clinical trials of androgen deprivation for SBMA.

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B-type natriuretic peptide and cardiovalvulopathy in Parkinson disease with dopamine agonist

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ABSTRACT

Objective: To elucidate the usefulness of plasma B-type natriuretic peptide (BNP) values for evaluating adverse effects of pergolide or cabergoline on cardiovalvulopathy in patients with Parkinson disease.

Methods: Twenty-five patients treated with pergolide or cabergoline (ergot group) and 25 patients never treated with ergot derivatives (non-ergot group) were enrolled. Plasma BNP values and detailed echocardiography were evaluated. Thirty age- and gender-matched controls were similarly evaluated.

Results: Patients with regurgitation more than grade 3 were more frequent in the ergot group than in the non-ergot group as well as control groups (24%, 0%, 3%, $p = 0.001$). Both composite regurgitation scores and plasma BNP values were significantly higher in the ergot group than in controls. In the ergot group, the cumulative dose correlated to both tenting area ($r = 0.57$, $p = 0.004$) and tenting distance ($r = 0.62$, $p = 0.001$). Furthermore, plasma BNP values were higher in patients with severe or multiple regurgitation groups ($p < 0.001$), and were correlated with composite regurgitation score ($r = 0.70$, $p < 0.001$). Multiple regression analyses revealed that BNP values were independently correlated with both composite regurgitation and left ventricular ejection fraction.

Conclusion: The combination of comprehensive echocardiography and plasma B-type natriuretic peptide levels elucidates the presence of cardiac damage in patients with Parkinson disease using ergot derivative dopamine agonists. *Neurology*® 2009;72:621-626

GLOSSARY

AR = aortic regurgitation; **BNP** = B-type natriuretic peptide; **MR** = mitral regurgitation; **PD** = Parkinson disease; **TR** = tricuspid regurgitation; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Ergot derivative dopamine agonists including pergolide and cabergoline are some of the most effective drugs to treat parkinsonian symptoms and have the potential to reduce the motor complications observed in patients with Parkinson disease (PD) treated with L-dopa.[1] However, several reports have shown an association of ergot derivative dopamine agonists and cardiac multivalvular regurgitation.[2-18] In particular, high cumulative doses and long-term treatment with pergolide and cabergoline have been considered to be risk factors for increased valvulopathy in patients with PD. The US Food and Drug Administration public health advisory of March 29, 2007, cautions against abruptly stopping pergolide and is looking for ways to provide the drug to those people who cannot successfully switch to alternative treatments. On the contrary, over 60% of patients did not show valvulopathy, despite several years' exposure.[2] In Japan, similar to some European countries, pergolide and cabergoline are still used, and moderate doses of pergolide are associated with a low incidence of restrictive valvulopathy.[4,9]

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Although echocardiography is an essential tool to evaluate valvulopathy, a simple screening test that does not require specialized techniques would be beneficial for management of patients under various conditions in particular institutes without a department of cardiovascular medicine. B-type natriuretic peptide (BNP), which is secreted mainly from the heart and belongs to the natriuretic peptide family, is indicative of cardiac dysfunction in patients with not only heart failure and coronary artery disease but also valvular disorders.[19-21] Since plasma BNP values can be measured in serum by fully automated and commercially available assays with excellent test precision, it would be beneficial for monitoring the cardiac findings in patients with PD.

In this study, we investigated the usefulness of plasma BNP values for identifying and monitoring cardiac involvement in patients with PD treated with ergot derivative dopamine agonists.

METHODS The records of 121 patients with PD who attended the Department of Neurology, Nagoya University Hospital, and were nominated to our clinical cohort study at Nagoya area[22] during January to December 2006 were investigated. Of these, 34 patients with PD who fulfilled probable PD criteria according to the established diagnostic criteria[23] and were continuously taking ergot agonists (pergolide or cabergoline) but not non-ergot ones for a minimum of 1 year with or without levodopa were enrolled. Switching dopamine agonists between pergolide and cabergoline or combined use of pergolide and cabergoline often occurs in clinical practice. Although there are no controlled data for the comparison of two or more dopamine agonists to define equivalent dosages, several reports have been published on the clinical experience of experts.[24] In addition, the stimulus strength on 5-hydroxytryptamine 2B (5-HT_{2B}) receptors is similar between cabergoline and pergolide, in parallel with their molecular weights.[25,26] Thus, according to a previous report,[24] we calculated that 2 mg of pergolide is equal to 3 mg of cabergoline. Age- and sex-matched patients with PD who were never treated with ergot derivative dopamine agonists were also included. Six patients taking nonpermitted medication (anorectic or ergot alkaloid agents, Chinese herbs, anticancer or immune-suppressive drugs before enrollment), having a history of significant coronary heart disease, impaired function/dilatation of left/right ventricle, history of peripheral artery occlusive disease, and any clinically significant illnesses that may interfere with their capability to participate in the study were excluded. We also excluded three patients who were not treated in our institute because their history of taking dopamine agonists was found to be inaccurate. As a result, 25 patients treated with pergolide or cabergoline were enrolled in the ergot group. Thirteen patients were treated with pergolide or cabergoline. Five patients were only treated with pergolide and seven patients only with cabergoline. In addition, 25 patients never treated with ergot derivatives were also enrolled in the non-ergot group. Disease severity was assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn & Yahr stages. All patients showed normal renal function. Two of the ergot group and three of the non-ergot group patients had mild hypertension. Patients were interviewed with a structured questionnaire about the frequency of dyspnea, fatigue, leg edema, and palpitation, and were scored from 0 (no disability) to 4 (maximum). As for the controls, 30 age- and sex-matched normal volunteers who have no history of cardiac disorders and related conditions requiring medication were examined (age at examination: 67 ± 11 years; 16 women, 14 men). This study was approved by the ethics committee of Nagoya University Graduate School of Medicine. We obtained written informed consent from each participant before data collection.

All patients were assessed by an echocardiography GE VIVID 7 machine (GE Medical Systems, Milwaukee, WI) with two independent observers (A.N. and A.Y.) who were blinded to the clinical information. Mitral, aortic, and tricuspid valves were recorded from all possible views with the zoom function. In addition, a stethoscope examination was performed before echocardiography by A.N. and A.Y. Semiquantitative and quantitative measurements for quantification of regurgitant valvular diseases from the continuous wave, pulsed wave, and color Doppler examinations were assessed. Tenting distance and tenting area of the mitral valve were also evaluated as quantitative data.[7,8,10,15] We quantified regurgitant lesions by integration of all semiquantitative and quantitative measurements, and a final score was given as follows: absent, 0; trace, 1; mild, 2; moderate, 3; severe, 4.[27] A composite regurgitation score was calculated by adding the scores for aortic regurgitation (AR), mitral regurgitation (MR), and tricuspid regurgitation (TR).[7,13] The proportion of patients with any regurgitation grade from 3 to 4 was also assessed.[7] We derived the systolic pulmonary artery pressures from the TR jet, adding 10 mm Hg to the maximum gradient of the TR jet or 5 mm Hg if the vena cava inferior diameter was less than 10 mm with complete respiratory collapse and 15 mm Hg if the vena cava inferior was greater than 20 mm without respiratory variation. Left ventricular end-diastolic and end-systolic dimensions were measured, and the left ventricular ejection fraction was calculated by the Teichholz method. All patients with PD were investigated for both the diameter and flow of the hepatic vein and inferior vena cava using ultrasonography. In addition, a chest X-ray was also performed if necessary.

Blood for BNP quantification was collected in the fasting state in EDTA acid-treated tubes and placed on ice. After centrifugation at 2,500 rpm and 3°C, the plasma was stored at −80°C. BNP levels were measured directly with a specific immunoradiometric assay kit TOSOH AIA-PACK BNP (TOSOH Corp., Tokyo, Japan) including 30 age- and gender-matched controls.

Statistical analyses were performed using SPSS 15.0 for Windows (SPSS Inc.). Comparisons of age and disease duration between groups were performed using one-way analysis of variance followed by post hoc Bonferroni correction. Group comparisons of frequencies of valvular regurgitation were restricted to grades 3 and 4 and were performed using the Fisher exact test. The statistical threshold for post hoc comparisons between each treatment group vs the control group was set at $p < 0.017$ (0.05/3). The relationships between the cumulative dose of ergot derivative dopamine agonists and tenting area, tenting distance, composite regurgitation score, and BNP were analyzed using Pearson correlation test. Statistical significance was considered as $p < 0.05$.

RESULTS Patient characteristics. Patient characteristics were as follows: 22 men and 28 women; age at

examination, 66 ± 9 years; duration, 11.8 ± 9.6 years; mean Hoehn & Yahr stage 2.8. There were no significant differences between the ergot group and the non-ergot group in terms of Hoehn and Yahr staging (3.0 ± 0.9 vs 2.6 ± 0.9), duration of illness (12.9 ± 9.1 vs 10.6 ± 10.2 years), dosages of levodopa (494 ± 216 mg vs 481 ± 257 mg), age at examination (64.9 ± 9.2 vs 66.4 ± 7.7 years), and gender. Mean daily/cumulative dosage of pergolide was 1.1 ± 0.4/1,752 ± 1,512 mg and that of cabergoline was 3.1 ± 1.0/14,230 ± 2,566 mg. There were no patients who required a surgical operation during the course of this study. The frequency of leg edema, dyspnea, palpitation, and fatigue were not significantly different between the ergot group and the non-ergot group. All patients demonstrated more than 50% ejection fraction and did not show heart failure fulfilling the criteria of the Framingham study.[28,29]

Echocardiographic findings and plasma BNP levels. With respect to regurgitation, frequencies of equal to or greater than grade 3 regurgitation were only observed in the ergot group (12%, aortic valve; 12%, mitral valve; and 8%, tricuspid valve), except for one subject in the control group. The frequency of any grade 3 to 4 regurgitation was significant between the ergot group and non-ergot group as well as the ergot group and control group (ergot group vs non-ergot group; $p < 0.001$, ergot group vs control group; $p < 0.001$). Composite regurgitation scores in the ergot group were higher than in the control group ($p < 0.001$), but there were no differences between the ergot group and non-ergot group as well as between the non-ergot group and control group. Differences of tenting area and tenting distance between the ergot group and non-ergot group were slight (tenting area; ergot group, 1.26 ± 0.42, non-ergot group, 1.05 ± 0.21, $p = 0.04$, tenting distance; ergot group, 7.53 ± 2.57, non-ergot group, 6.10 ± 1.65, $p = 0.09$).

The plasma BNP levels as well as the composite regurgitation score were elevated in the ergot group vs the control group ($p = 0.004$, $p < 0.001$) (table). The BNP levels and composite regurgitation score in the ergot group showed a tendency to be increased as compared to those in the non-ergot group but did not show a significant difference. The BNP levels and composite regurgitation score in the non-ergot group were slightly elevated compared to control, although there was no significant difference.

Relationship between cumulative dose of ergot derivative dopamine agonists and echocardiographic findings. The cumulative dose of ergot derivative dopamine agonists was related to tenting distance ($r = 0.62$, $p = 0.001$) as well as to tenting area ($r = 0.57$, $p = 0.004$) but did not show any relationship with the composite regurgitation score ($r = 0.36$, $p = 0.08$). Within the high dose group (more than 4,000 mg), 33.3% of patients showed grade 3 to 4 regurgitation, while 15.4% of the low dose group (less than 4,000 mg) exhibited similar grades.

Plasma BNP levels in patients with severe valvulopathy. Plasma BNP values were higher in the ergot patient group with grade 3 to 4 regurgitation, which were seen only in the ergot group, than in those without such a high grade of regurgitation in the ergot group as well those in the non-ergot group (65.3 ± 47.8 pg/mL vs 24.7 ± 17.1 pg/mL vs 21.1 ± 15.4 pg/mL, $p < 0.001$). Patients with multiple regurgitation equal to or greater than grade 2 also had higher BNP values than those without (57.8 ± 46.1 vs 22.5 ± 11.9 vs 21.1 ± 15.4 pg/mL, $p < 0.001$).

According to receiver operating characteristic curve analyses to determine the adequate values for discriminating patients with severe regurgitation from those without, the most appropriate cutoff level of plasma BNP was 39.6 pg/mL, which showed 67.4% sensitivity and 84.4% specificity. In the ergot group, the positive predictive value was 66.7% and the negative predictive value was 89.4% if the plasma BNP level of 39.6 pg/mL was determined as the cutoff value.

Relationship between BNP and echocardiographic findings. The BNP levels showed a correlation to the composite regurgitation scores ($r = 0.70$, $p < 0.001$, figure) and a correlation to the left ventricular ejection fraction ($r = -0.42$, $p < 0.04$) but not age at examination, motor examination section (part III) of the UPDRS, and disease duration. Multiple regression analyses demonstrated that BNP values were independently correlated with composite regurgitation scores ($t = 4.08$, $p = 0.001$) and the left ventricular ejection fraction ($t = -2.07$, $p = 0.045$, $R^2 = 0.60$).

DISCUSSION We demonstrated that a significant elevation of plasma BNP values was observed in the ergot group vs in control groups. In particular, the BNP values were significantly elevated in the ergot group with more severe or multiple regurgitation than those with no to mild regurgitation and those in the non-ergot group. Furthermore, composite scores of regurgitation were well correlated with BNP values. Serum BNP is elevated in patients with valvular disorders due to ventricular pressure and volume load,[20,21] and this may be one reason why plasma BNP values increased in the ergot group. More recently, animal models have demonstrated that left ventricular cardiomyocytes were hypertrophic in both serotonin and pergolide-treated animals com-

Table Valvular abnormalities and plasma BNP values in the ergot group and non-ergot group

Grade of regurgitation, no. (%) of patients	Ergot group (n = 25)	Non-ergot group (n = 25)	Control (n = 30)
Aortic regurgitation			
0 to 1	13 (60)	22 (88)	27 (90)
2	7 (28)	3 (12)	3 (10)
3	2 (8)	0 (0)	0 (0)
4	1 (4)	0 (0)	0 (0)
Mitral regurgitation			
0 to 1	13 (60)	18 (72)	26 (87)
2	7 (28)	7 (28)	3 (10)
3	3 (12)	0 (0)	1 (3)
4	0 (0)	0 (0)	0 (0)
Tricuspid regurgitation			
0 to 1	19 (76)	21 (84)	25 (83)
2	4 (16)	4 (16)	5 (17)
3	1 (4)	0 (0)	0 (0)
4	1 (4)	0 (0)	0 (0)
Any grade from 3 to 4 regurgitation, mean (SD)	6 (24)*	0 (0)	1 (3)
Composite regurgitation score	3.30 (2.31)†	2.39 (1.29)	1.73 (1.83)
BNP (pg/mL)	33.6 (31.8)‡	21.1 (15.4)	14.2 (8.3)

Composite regurgitation score is the sum of mitral, aortic, and tricuspid regurgitation scores.

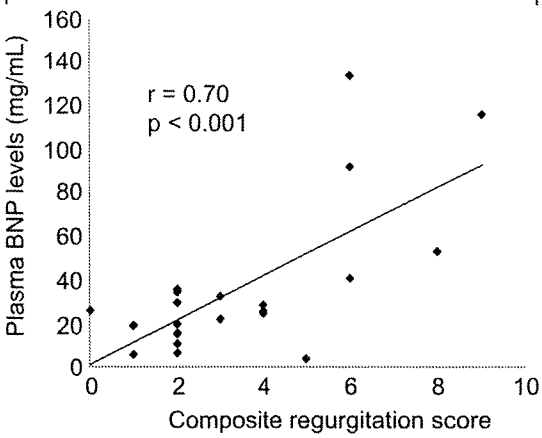
* The frequency of any grade 3 to 4 regurgitation was statistically significant between the ergot group and the non-ergot group ($p < 0.0001$) as well the ergot group and the control group ($p < 0.001$).

† Composite regurgitation score in the ergot group was significantly higher than that in the control group ($p < 0.001$). Composite regurgitation score of the ergot group tended to be increased when compared to the non-ergot group, but was not significantly different. Patients with grade 3 to 4 regurgitation were seen only in the ergot group.

‡ The plasma BNP level was significantly elevated in the ergot group vs in the control group ($p = 0.004$). The plasma BNP level of the ergot group tended to be increased when compared to the non-ergot group, but was not significantly different. The plasma BNP of patients with grade 3 to 4 regurgitation seen only in the ergot group was significantly elevated.

BNP = B-type natriuretic peptide.

Figure Correlation between composite regurgitation scores and serum B-type natriuretic peptide (BNP) values



Composite regurgitation scores were correlated with BNP values ($r = 0.70$, $p < 0.001$). Composite regurgitation score was calculated by adding the score of aortic regurgitation, mitral regurgitation, and tricuspid regurgitation.

pared with placebo-treated animals, and macroscopically, left ventricular cavities were more dilated in both the serotonin and pergolide groups.[30] Thus, the second possible explanation is that direct toxic effects on the cardiomyocytes may have an influence on increased plasma BNP values. Since ventricular involvement in patients with PD using ergot derivative dopamine agonists has not been fully assessed, further prospective and pathologic studies will be needed to clarify this issue.

BNP is expected to detect preclinical structural and functional myocardial alterations not detectable by current techniques. Thus, BNP testing for structural heart disease screening in community-based populations is useful for cohorts with a high prevalence of heart disease.[31,32] However, age, renal dysfunction, and fluid overload can also contribute to elevated BNP concentrations.[33] Furthermore, elderly hypertensive subjects with orthostatic systolic blood pressure decrease also show significantly higher BNP values than in the control group, suggesting greater cardiac burden although the influence of orthostatic hypotension on BNP is not well known.[34] In this study, no patients exhibited symptomatic orthostatic hypotension but sympathetic dysfunction in PD might result in a slight elevation of plasma BNP levels in the non-ergot group compared with controls. Since ergot derivative dopamine agonists can exacerbate not only cardiac fibrosis but also renal dysfunction and orthostatic hypotension, measurement of plasma BNP values may be beneficial to detect and prevent the worsening of these clinical conditions by means of administration of such dopamine agonists.

This study showed that plasma BNP values were significantly higher in the ergot group than in controls, while the plasma BNP values showed a tendency to be elevated in the ergot group vs the non-ergot group, but did not show a significant difference. In this study, over three-quarters of patients in the ergot group did not develop significant valvular regurgitation. Such a low occurrence of severe valvulopathy may be a consequence of the lower dose of pergolide and cabergoline prescribed to our Japanese patients when compared to Western countries.[2,9] However, six patients of the ergot group with grade 3 to 4 regurgitation clearly showed a significant elevation of plasma BNP values compared to those of the non-ergot group. These results demonstrate that plasma BNP values can be used as a marker for patients who have reached a significant degree of heart valve involvement prior to heart failure.

This study also showed that the composite regurgitation score in the non-ergot group showed a slight elevation when compared to controls. We cannot rule out the possibility that other drugs including L-dopa or sympathetic dysfunction have an influence on the increase of regurgitation in the non-ergot group, but no patients with grade 3 to 4 regurgitation were observed in this group. According to a recent review, a considerably large proportion of patients do not develop valvulopathy, despite several years' exposure to high doses of pergolide, suggesting the presence of patients with a low susceptibility to pergolide.[2] Furthermore, the low dose of pergolide used in Japan can be associated with the low frequency of severe valvulopathy in our patients treated with ergot as mentioned above.[2,9] The striking point here is, as mentioned above, patients with a grade 3 to 4 composite score were present in the ergot group but not in the non-ergot group.

Both pergolide and cabergoline are potent agonists of not only dopamine but also the 5-HT_{2B} receptor. It is supposed that stimulation of 5-HT_{2B}, which is expressed in heart valves, induces prolonged activation of fibroblast mitogenesis resulting in valvular fibroplasia.[35,36] Thus, high dose and long-term ergot derivative administration is thought to be a risk factor for valvulopathy in patients with PD.[2-18] The significant association of the cumulative dose of ergot derivatives and mitral valve tenting area/distance, which have been proposed as restrictive changes due to valvular fibroplasia, was observed.[7,8,10,15] However, these significant adverse events did not occur in all ergot patients, including those administered high cumulative doses as previously reported,[2] suggesting that patients who receive benefit from ergot-derived dopamine agonists without valvulopathy will exist at a constant rate under careful follow-up.

In Germany, if any abnormalities are seen on echocardiography, non-ergot dopamine agonists are recommended.[37] Although there has been no report concerning plasma BNP values in patients with PD, our results support the view that plasma BNP levels will be a beneficial marker for monitoring cardiac fibrosis due to ergot derivative dopamine agonists. Measurement of plasma BNP levels is quicker, more accessible, and cheaper than echocardiography and may contribute to the assessment of not only the development of valvulopathy and myocardium damage but also several other important factors deteriorated by ergot derivative dopamine agonists in patients with PD. In addition, plasma BNP values can predict the prognosis of patients with chronic heart failure[38] and mitral regurgitation.[39] Echocardiography is effective and able to identify valvulopathy as a cause of incipient or present right heart failure, and it is a satisfactory screen for valvulopathy itself, but BNP is a suitable marker for the relevant forms of cardiac dysfunction. The combination of comprehensive echocardiography and plasma BNP levels will complementarily elucidate the presence of cardiac damage in patients with PD using ergot derivative dopamine agonists.

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