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R-R interval variation in Parkinson's disease and multiple system atrophy

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Objective – To investigate whether the cardiac R-R interval variation (RRIV) is of value in differentiating patients with Parkinson's disease (PD) from multiple system atrophy (MSA). *Background* – RRIV assessment is a simple procedure, reflecting mainly vagal efferent activity. Reduced RRIV was reported in MSA. *Methods* – RRIV at rest and after 120 s of deep breathing was assessed blindly to clinical diagnosis in 22 PD and 20 MSA patients. The results were compared with data from 23 age-matched healthy subjects. *Results* – RRIV at rest was 7.1 ± 2.7% in PD and 9.7 ± 7.2% in MSA, increasing after deep breathing to 11.2 ± 6.3 and 12.3 ± 6.6% correspondingly. The frequency of the RRIV abnormalities in the PD group (4/22, 18.2%) and MSA (6/20, 30%) were higher than among controls ($P < 0.004$). *Conclusions* – RRIV, either at rest or after deep breathing, may be abnormal both in PD and MSA, but does not distinguish between these disorders.

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The differentiation of Parkinson's disease (PD) from multiple system atrophy (MSA) may be difficult, especially in the initial stages of the diseases. Several tests have been proposed to assist in this differentiation including positron emission tomography (1), I-123-MIBG-SPECT (2), magnetic resonance spectroscopy (3), anal sphincter electromyogram (EMG) (4) and clonidine-induced growth hormone release (5). None of these tests have been validated and most require expensive equipment. Alternative, less complex techniques are needed to distinguish PD and MSA.

Heart rate provides a non-invasive window into autonomic nervous system function. Measuring the R-R interval variations (RRIV) of the electrocardiogram (ECG) is a relatively simple method that has been used in several studies of the autonomic nervous system function in patients with PD or MSA (6–8). In the present study, we investigated whether the RRIV distinguishes PD from MSA.

Subjects and methods

Forty-two patients were studied (20 with MSA and 22 with PD, see Table 1). The clinical diagnosis was made by at least two movement disorders specialists based on a detailed history and neurological examination. In addition, all patients underwent brain MRI or CT examination to exclude possible focal lesions. Patients with urinary disturbances were also studied with urodynamics. Anal sphincter EMG was performed in the majority, although denervation was not required for the diagnosis of MSA. The diagnosis of PD was based on the United Kingdom Brain Bank clinical criteria, as modified by Douglas et al. (9). MSA was diagnosed according to the criteria of Gilman et al. (10). Among our patients, 14 fulfilled criteria for probable and six for possible MSA. Fifteen of them had parkinsonian type MSA (MSA-P) while five had predominantly cerebellar features (MSA-C). All patients had constipation and some also had other autonomic symptoms (e.g. impotence, sialorrhea, seborrhea, and postural dizziness) that were generally not severe. However, there were five patients with marked autonomic disturbances (urinary incontinence in three and orthostatic hypotension in two) who still fulfilled accepted criteria for PD and not for MSA. These five PD patients were also assigned to a subgroup of 'PD patients with autonomic dysfunction'. Clinical data of the patients is provided in Table 1.

Table 1 Demographic and clinical features and RRIV of patients and controls

	Controls	All patients	All PD	Pure PD	PD with autonomic disturbances	MSA
Total no.	23	42	22	17	5	20
Female/male	10/13	16/26	7/15	5/12	2/3	9/11
Mean age ± SD (years)	68.4 ± 9.4	64.7 ± 13.7	66.5 ± 8.6	65.3 ± 9.0	69.8 ± 7.3	65.0 ± 10.6
Mean disease duration ± SD (years)		8.6 ± 5.3	9.3 ± 6.0	8.7 ± 6.0	8.8 ± 7.6	6.9 ± 4.1
Mean H & Y stage during `off ' state		3.5 ± 0.9	3.3 ± 0.7	3.3 ± 0.8	3.3 ± 0.7	3.8 ± 0.9
With arterial hypertension, treated by beta-blockers	0	4	1	0	1	3
With NIDDM	0	5	2	2	0	3
Taking L-dopa medications	0	29	18	13	5	11
Taking dopamine-agonists	0	17	11	9	2	6
Taking amantadine	0	15	11	8	3	4
Taking anticholinergics	0	12	8	7	1	4
Taking selegiline	0	6	3	3	0	3
Mean RRIV at rest	12.3 ± 4.5	8.0 ± 4.9	7.2 ± 2.6	6.9 ± 3.0	8.1 ± 1.9	9.7 ± 6.6
RRIV after deep breathing	20.2 ± 7.9	11.6 ± 6.5	11.2 ± 6.3	10.8 ± 6.7	12.1 ± 5.8	12.3 ± 6.7

H & Y, Hoehn & Yahr; MSA, multiple system atrophy; NIDDM, non-insulin dependent diabetes mellitus; PD, Parkinson's disease; PDA, PD with marked autonomic disturbances; RRIV, R-R interval variation; SD, standard deviation.

For assessment of the RRIV, we used the simple and well-standardized method first described by Shahani et al. (11). RRIV was measured in the supine position after at least 10 min of rest and again following 120 s of deep breathing (while the patient was still hyperventilating) by automatic analysis of the ECG using a Nicolet Viking IV EMG system (Nicolet Biomedical Inc., Madison, WI, USA). Recordings were made using silver/silver chloride surface electrodes placed on the dorsum of each hand with registration of the R-R intervals for 1 min. The potentials were recorded using a trigger line placed on the R peak while the first potential is constant and the second is variable. The time difference between the earliest and the latest R peaks in the variable group of potentials was determined as R-R variability. The mean R-R difference was also calculated. RRIV was expressed then as a percentage of the R-R variability with respect to the mean R-R interval. The RRIV results were unknown to the movement disorders specialists at the time of the evaluation of the patients.

Patients with cardiac pacemakers and/or cardiac arrhythmias were excluded from the study. Anti-parkinsonian treatment of the patients was not interrupted before RRIV investigation and we did not exclude patients having somatic disorders or taking medications, even those that might affect autonomic function (e.g. diabetes mellitus). Data about concurrent diseases and medications of the patients at the time of RRIV investigation are presented in Table 1. The results were compared with data from 23 healthy subjects of similar age (Fig. 1). Fisher's exact test and Wilcoxon's signed rank tests were used to compare the groups.

Results

The patient groups were similar with respect to age, disease duration and Hoehn and Yahr stage (Table 1). Control subjects were also of similar age.

In the PD group, the mean RRIV at rest was 7.1 ± 2.7%, i.e. normal for this age. After deep breathing, the RRIV increased to 11.2 ± 6.3%, also normal for this age (Table 1). In one PD patient, RRIV was abnormal at rest, and he also had abnormal RRIV with deep breathing. Three other PD patients developed abnormal RRIV after deep breathing. Among the five PD patients with autonomic dysfunction, none had abnormal RRIV, either at rest or after deep breathing. Thus, although the mean RRIV parameters were normal in the group as a whole, abnormally low RRIV in this group occurred in four of 22, i.e. 18.2%, significantly higher than among 23 healthy controls ($P = 0.004$) (Fig. 2).

In the MSA group, the mean RRIV at rest was 9.7 ± 7.2%, increasing with deep breathing to 12.3 ± 6.6%. Thus, in this group, like in the PD group, the mean RRIV was within normal age limits. Abnormal RRIV both at rest and after deep breathing was found in one patient. Four other MSA patients had abnormal RRIV only during deep breathing (30%). Thus, in the MSA group as well, the frequency of the RRIV abnormalities (6/20, 30%) was significantly higher than among healthy subjects ($P = 0.0002$), and slightly but non-significantly more common than in PD ($P > 0.05$). Interestingly, when pooling all subjects, disease severity, as measured by the Hoehn and Yahr stage, tended to be lower in subjects with

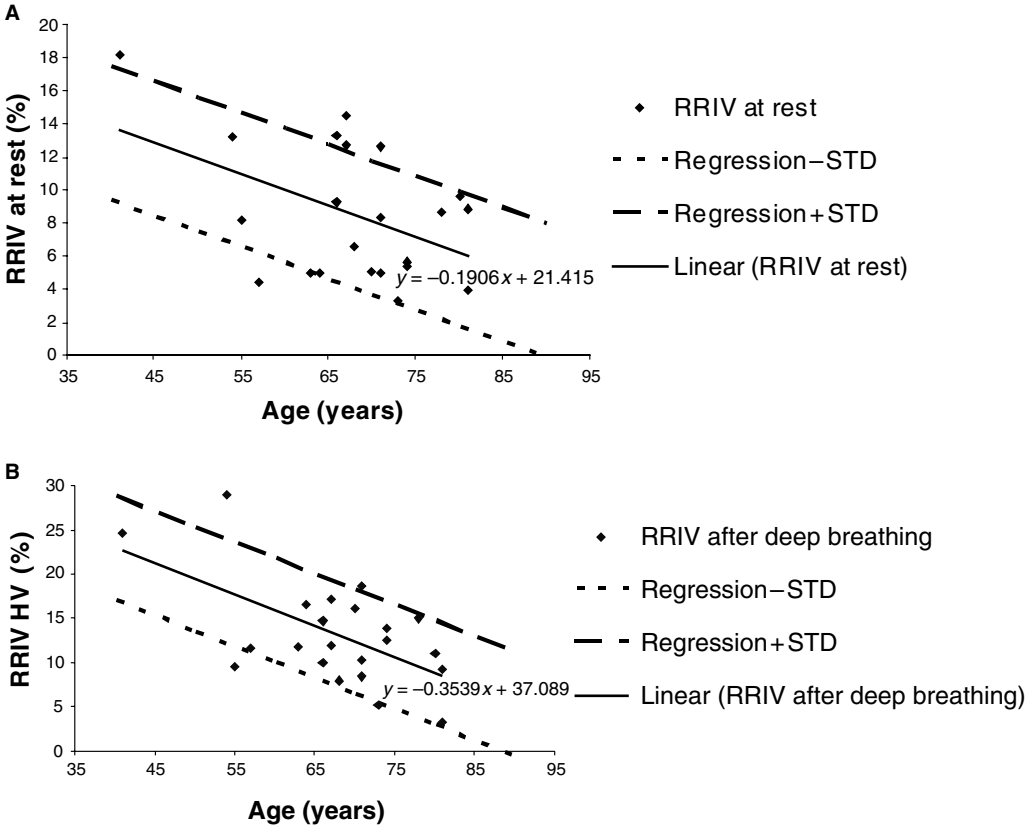

Figure 1. (A) RRIV at rest in healthy controls. (B) RRIV after deep breathing in healthy controls.

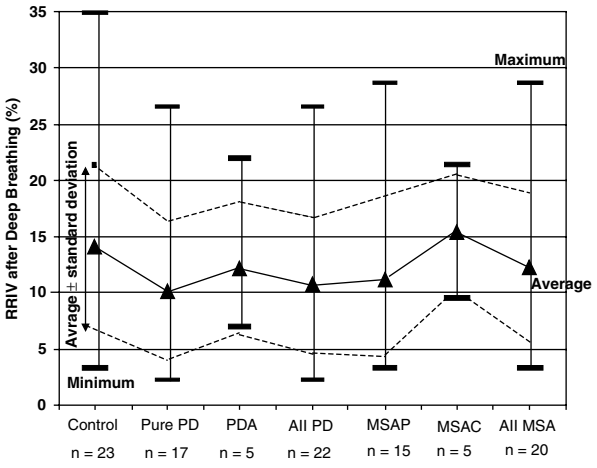

Figure 2. RRIV after deep breathing in different groups of patients and controls.

an abnormal RRIV compared with those with a normal RRIV during deep breathing, while age and other measures were similar in these two groups. Frequency of the somatic disorders that could affect the autonomic system was not higher in the group with abnormal RRIV after deep breathing (Table 2).

Discussion

The results of RRIV at rest and after deep breathing in normal controls were similar to those reported by Shahani et al. (11). Our results also show that the RRIV, either at rest or after deep breathing, may be abnormal in both PD and MSA, but apparently cannot be used to differentiate between the two disorders. Furthermore, even in patients with abnormal RRIV, the abnormality is not more pronounced in the MSA group. This occurred despite the fact that the number of patients suffering from somatic disorders, potentially influencing the autonomic nervous system, was slightly higher in the MSA group.

We found more frequent RRIV abnormalities among PD patients as well as among MSA patients compared after the control group. RRIV abnormalities with deep breathing in our MSA patients were less frequent then in other studies (7, 8), although these groups reported findings similar to ours in PD patients. However, RRIV at rest in the present study was abnormal in only a small number of patients. This is somewhat surprising especially considering the fact that our patients did not interrupt taking L-dopa, anticholinergics or

Table 2 Comparison of the groups according to the RRIV results after deep breathing

	Patients with normal RRIV with deep breathing	Patients with abnormal RRIV with deep breathing	*P* value
Total number of patients	32	10	
PD/MSA patients	18/14	4/6	
Mean age (years)	67.5 ± 10.0	63.9 ± 8.6	NS
Having diabetes mellitus	4	2	
Having arterial hypertension, treated by beta-blockers	3	1	
Mean disease duration (years)	8.9 ± 5.3	7.5 ± 4.9	NS
Mean H & Y stage at `off' state	3.6 ± 0.8	3.0 ± 0.76	0.05
Mean RRIV after deep breathing	12.7 ± 6.4%	7.5 ± 4.0%	

other drugs and patients with somatic disorders that might cause autonomic disturbances were also included in the series.

Looking for simple and available methods of differentiating MSA from PD, one has to take into account that it is sometimes difficult to interrupt medications and frequently patients have comorbid conditions in addition to the movement disorder. Thus, we have to select diagnostic methods that are widely applicable and that do not require special preparations of the patients.

Because of the difficulties in the clinical differentiation between PD and MSA and the possibility that some MSA patients will have a good response to dopaminergic medications, the group of PD with marked autonomic disturbances (persistent urinary incontinence and/or orthostatic hypotension) was also analyzed separately. Even in this subgroup RRIV abnormalities were not found. These results are similar to those of Wang et al. (6), who did not find a correlation between the number of autonomic symptoms in PD patients and RRIV abnormalities. Furthermore, our patients who had normal RRIV after deep breathing had more advanced PD, longer disease duration and were older than those with abnormal values, although these differences were not significant statistically.

Interestingly, among 5 MSA-C patients who took part in the study, two had abnormal RRIV with deep breathing. Unfortunately this small group of patients does not permit to making definite conclusions.

None of our patients had abnormal RRIV only at rest, while two patients (one with PD and one with MSA) who had abnormal RRIV at rest also had abnormal RRIV after deep breathing. These results are similar to those of Shahani et al. (11) concerning RRIV abnormalities in patients with peripheral neuropathy. Thus, measuring RRIV after deep breathing seems to be more sensitive in detecting parasympathetic dysfunction of the heart. In the present study, we did not find differences between MSA and PD using a relatively simple measure of heart rate variability. In the future, it might be helpful to perform a larger study that also evaluates other aspects of heart rate variability that sometimes may be more sensitive to subtle changes in the underlying disease state.

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