CARDIOVASCULAR DYSFUNCTION IN PARKINSONIAN DISORDERS

Christopher J. Mathias

Neurovascular Medicine Unit, Division of Neuroscience & Psychological Medicine, Imperial College School of Medicine at St Mary's and Autonomic Unit, National Hospital for Neurology & Neurosurgery, Queen Square/University Department of Clinical Neurology, Institute of Neurology, University College London, UK.

Reprint requests to: Prof. Christopher J. Mathias, Neurovascular Medicine Unit, St Mary's Hospital, Imperial College Praed Street, London W2 1NY, UK.
E-mail: c.mathias@ic.ac.uk

KEY WORDS: Autonomic failure, Lewy body disease, multiple system atrophy, orthostatic hypotension, Parkinson's disease, progressive supranuclear palsy.

FUNCT NEUROL 2001;16: 257-265

INTRODUCTION

Parkinsonian disorders comprise a variety of diseases, with differing pathology, natural history and prognosis. Although the most common is idiopathic (classical) Parkinson's disease (PD), there is increasing recognition of 'atypical' parkinsonian disorders, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and Lewy body disease (LBD) (1) (Fig. 1, see over). In some parkinsonian patients, and in particular in MSA, autonomic failure characterised by cardiovascular disturbances is a prominent feature. However, the majority of patients with parkinsonism are over the age of 50, when there is an increasing incidence of cardiovascular disease; this may create diagnostic difficulties and also compound problems with management. This review will focus on cardiovascular autonomic dysfunction, especially in MSA, and will deal predominantly with blood pressure and heart rate control together with newer information on cardiac sympathetic innervation in parkinsonian patients.

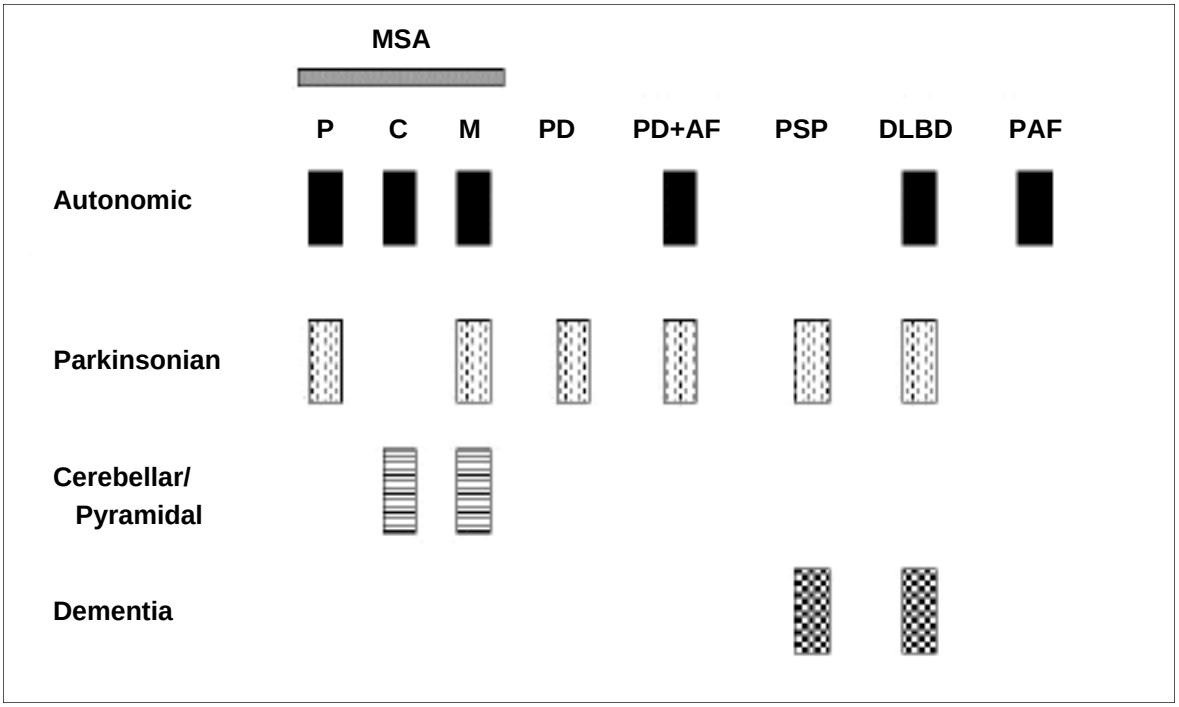

Fig. 1 - Schematic representation indicating the major clinical features in some of the parkinsonian disorders. These include the parkinsonian, cerebellar and mixed forms of multiple system atrophy (MSA-P, C & M respectively), idiopathic Parkinson's disease (PD), PD with autonomic failure (PD+AF), progressive supranuclear palsy (PSP), diffuse Lewy body disease (DLBD) and pure autonomic failure (PAF). (Adapted from ref. 1).

BLOOD PRESSURE ABNORMALITIES

Orthostatic hypotension

Orthostatic (postural) hypotension is a cardinal feature of autonomic failure [defined as a fall in systolic blood pressure of at least 20 mmHg or in diastolic of at least 10 mmHg on either standing or head-up tilt to at least 60° (2)]; in a patient with parkinsonism its presence often leads to consideration of MSA (Fig. 2) (3). The symptoms arising from orthostatic hypotension result from hypoperfusion of vital organs. Prominent are those from cerebral hypoperfusion, such as dizziness, visual disturbances and sometimes impaired cognition, which often precede loss of consciousness (Table I); there is a variety of non-cerebral symptoms (4,5). Symptoms vary substantially between subjects and even in the same subject in different situations and times of the day (Fig. 3, see p. 260). This is because many factors, some relating to essential activities in daily life, such as food ingestion and exercise, influence the degree of orthostatic hypotension (Table II, see p. 260). Non-neurogenic factors, which include the effect of drugs and conditions resulting in fluid and volume depletion, also exacerbate orthostatic hypotension (Fig. 4, see p. 261) (6). Sometimes non-specific symptoms, such as weakness, lethargy, fatigue or falls, may be the only features resulting from orthostatic hypotension (Table I).

Evaluation of orthostatic hypotension is necessary, both in the clinic and ideally in an autonomic laboratory. Details have been described elsewhere, together with methods to evaluate neurogenic and non-neurogenic factors (3); this

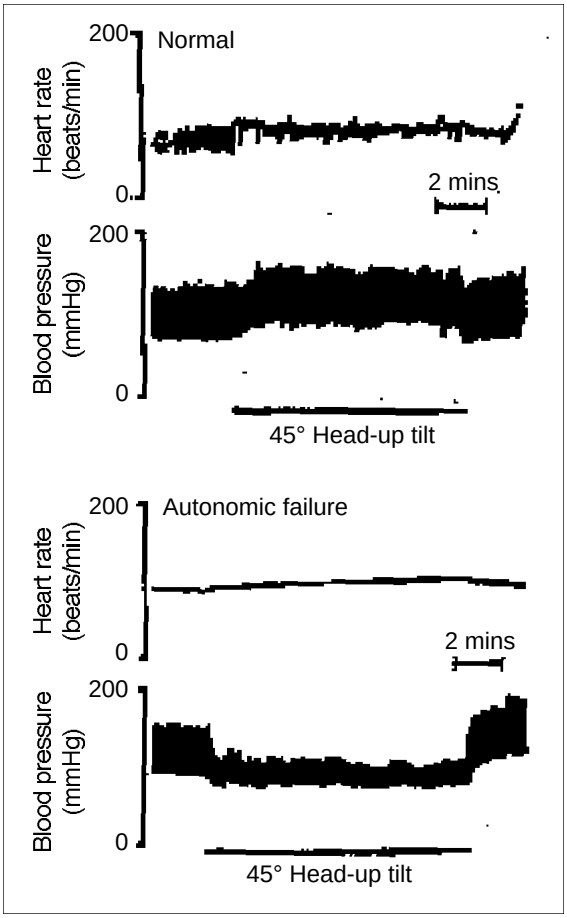

Fig. 2 - Blood pressure and heart rate before, during and after head-up tilt in a normal subject (top panel), and a patient with pure autonomic failure (lower panel). In the normal subject there is no fall in blood pressure during head-up tilt, unlike the patient in whom blood pressure falls promptly and remains low with a blood pressure overshoot on return to the horizontal. In the patient with autonomic failure there is only a minimal change in heart rate despite the marked blood pressure fall. In each case continuous blood pressure and heart rate were recorded with the Portapres II. (From ref. 3).

Table I - Some of the symptoms resulting from orthostatic (postural) hypotension.

Cerebral hypoperfusion
Dizziness
Visual disturbances
blurred-tunnel
scotoma
greying out - blacking out
colour defects
Loss of consciousness
Impaired cognition
Muscle hypoperfusion
Paracervical and suboccipital (‘coathanger’) ache
Lower back/buttock ache
Cardiac hypoperfusion
Angina pectoris
Spinal cord hypoperfusion
Renal hypoperfusion
Oliguria
Non-specific
Weakness, lethargy, fatigue
Falls

(Reproduced from Ref. 3)

evaluation is important in parkinsonian disorders where there may be many reasons for orthostatic hypotension (Table III, see p. 261) (7,8).

In the majority of PD cases, symptomatic orthostatic hypotension is not a major feature, although its prevalence varies (9-12). In a relatively rarer sub-group, with drug-responsive PD, symptomatic orthostatic hypotension results from autonomic failure (PD+AF). In such patients the autonomic lesion is thought to be peripheral, as based on a combination of features that include a low basal level of plasma noradrenaline, and the inability of drugs such as yohimbine (that act on pre-synaptic receptors to activate sympathetic terminals) to raise blood pressure (13,14). These observations are in contrast to MSA where the lesions are predominantly central and pre-ganglionic (15,16); in MSA basal levels of plasma noradrenaline are often within the normal range and there is a pressor response to drugs such as ephedrine, whose activation is dependent on post-ganglionic sympathetic innervation (17). In PD, there is a varying incidence of symptomatic and asymptomatic orthostatic hypotension that may reflect additional factors, ranging from the influence of increasing age, to duration of the

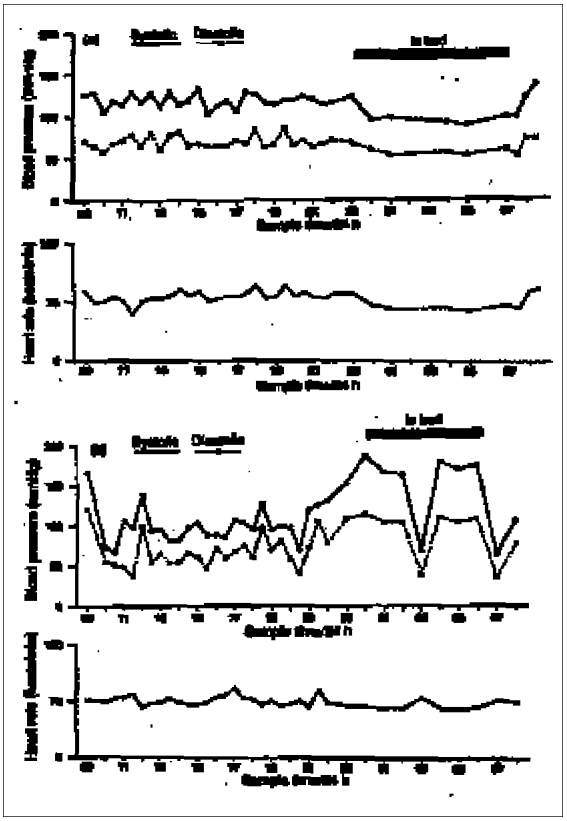

Fig. 3 - Twenty-four hour non-invasive ambulatory blood pressure profile showing systolic (□----□) and diastolic (■ ---- ■) blood pressure and heart rate at intervals through the day and night. (a) Changes in a normal subject with no postural fall in blood pressure; there was a fall in blood pressure at night whilst asleep, with a rise in blood pressure on wakening. (b) Marked fluctuations in a patient with autonomic failure; the falls are usually the result of postural changes, either sitting or standing. Supine blood pressure, particularly at night, is elevated. Getting up to micturate causes a marked fall in blood pressure (03.00 hours). There is a reversal of the diurnal changes in blood pressure. There are relatively small changes in heart rate, considering the marked changes in blood pressure. (From ref. 3).

Table II - Factors influencing orthostatic (postural) hypotension

Speed of positional change
Time of day (worse in the morning)
Warm environment (hot weather, central heating, hot bath)
Raising intrathoracic pressure - micturition, defaecation or coughing
Food and alcohol ingestion
Physical exertion
Manoeuvres and positions (bending forward, abdominal compression, leg crossing, squatting, activating calf muscle pump)*
Drugs with vasoactive properties (including dopaminergic agents)

* These manoeuvres usually reduce the postural fall in blood pressure, unlike the others (Reproduced from ref. 3)

disorder and drug therapy. Furthermore, in PD, there may be dissociation between symptoms and signs of orthostatic hypotension that may occur, albeit occasionally, also in MSA (5).

In atypical parkinsonian disorders differences in autonomic function have been described. In PSP, detailed physiological and neuropharmacological studies indicate that orthostatic hypotension and cardiovascular autonomic failure do not constitute a feature (18). This differs from LBD where orthostatic hypotension may be a presenting feature (19,20); orthostatic hypotension has been reported in up to 50% of such patients (21).

The management of orthostatic hypotension due to neurogenic failure should incorporate non-pharmacological approaches and when needed the use of drugs (Table IV, see p. 262). The benefit of therapeutic strategies is enhanced by knowledge of the putative site of lesion and known mechanism of action of drugs; thus with central lesions as in MSA, ephedrine (an indirectly-acting sympathomimetic) is likely to be effective, unlike peripheral lesions (such as PD+AF) where midodrine (an α-adrenoceptor agonist) is often needed. Treatment should combine information from clinical evaluation and appropriate autonomic investigations (such as determining the effect of food and exercise on orthostatic hypotension) to ensure that management is tailored specifically to individual needs (22). There may be differences in responses in the

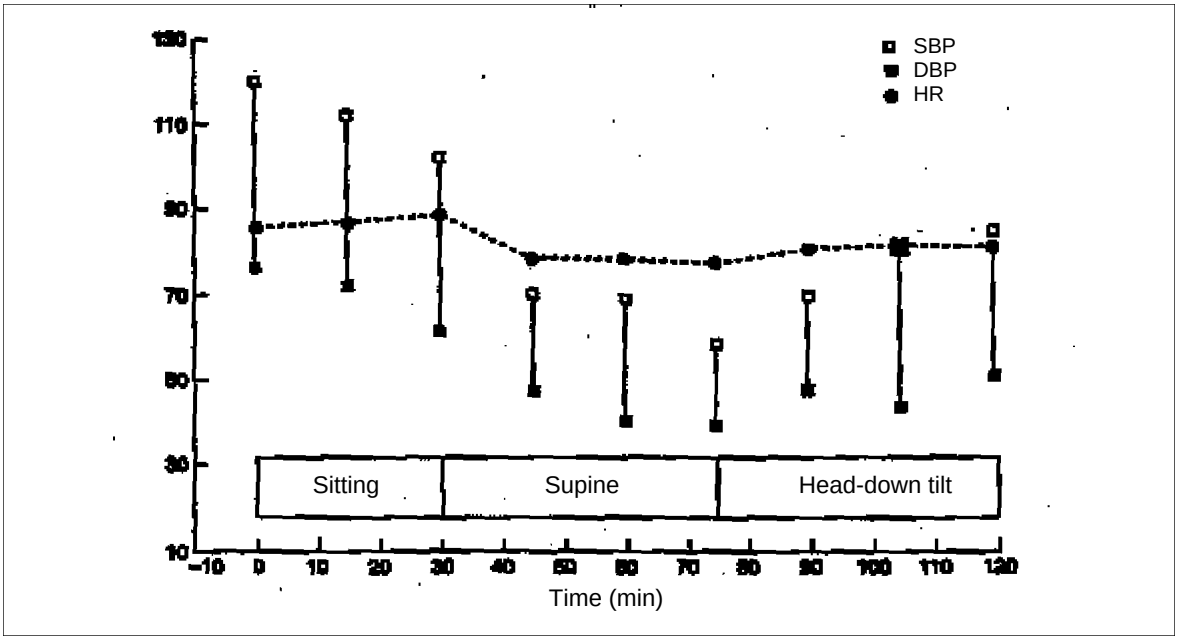

Fig. 4 - The effect of a single standard oral dose of L-dopa (250 mg) and a dopadecarboxylase inhibitor, carbidopa (25 mg) given at time zero on the blood pressure of a patient with parkinsonian features. There was a marked fall in blood pressure after 30 min., resulting in the patient being first placed supine and then head-down. On investigation the patient had autonomic failure with orthostatic hypotension unmasked by L-dopa; the final diagnosis was the parkinsonian form of multiple system atrophy. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate. (From ref. 6).

various disorders; thus even the recent observation of the pressor response to oral water in MSA and pure autonomic failure (PAF) (23,24) does not appear to apply to PD +AF (25). Education of the patient and, where relevant, of family and care-givers is important, as is delineation of treatment limitations and discussion of realistic expectations, especially where the motor deficits impair mobility and enhance susceptibility to the fainting sequela.

Hypertension

The incidence of essential hypertension increases with age. Its presence in parkinsonian patients may reflect other factors. In MSA, supine hypertension occurs despite severe orthostatic hypotension, probably because of movement of intra- and extra-vascular fluid from the peripheral to the central compartment during postural change, in combination with

Table III - Possible causes of orthostatic hypotension in a patient with parkinsonian features

Side effects of anti-parkinsonian therapy, including:
L-dopa, bromocriptine, pergolide, the combination of L-dopa and COMT inhibitors (tolcapone)
The MAO 'b' inhibitor, selegiline
Coincidental disease causing autonomic dysfunction, e.g. diabetes mellitus
Coincidental administration of drugs for an allied condition
Antihypertensives
Alpha-adrenoceptor blockers (for benign prostatic hypertrophy)
Vasodilators (for ischaemic heart disease)
Diuretics (for cardiac failure)
Multiple system atrophy (Shy-Drager syndrome)
Parkinson's disease with autonomic failure
Lewy body disease

(Adapted from ref.s 7 and 8)

Table IV - Outline of non-pharmacological and pharmacological measures used in the management of postural hypotension due to neurogenic failure.

To be avoided
Sudden head-up postural change (especially on waking)
Prolonged recumbency
Straining during micturition and defaecation
High environmental temperature (including hot baths)
'Severe' exertion
Large meals (especially when these contain refined carbohydrate)
Alcohol
Drugs with vasodepressor properties
To be introduced
Head-up tilt during sleep
Small, frequent meals
High salt intake
Increased water intake
Sensible/moderate exercise (including swimming)
Body positions and maneouvres
To be considered
Elastic stockings
Abdominal binders
Pharmacological measures
Starter drug: fludrocortisone
Sympathomimetics: ephedrine, midodrine
Specific targeting: octreotide, desmopressin, erythropoietin

It should be emphasised that non-neurogenic factors such as fluid loss due to vomiting or diarrhoea may substantially worsen neurogenic postural hypotension and will need to be rectified. (Modified from ref.s 17, 22)

impaired baroreflexes and pressor supersensitivity to small amounts of circulating catecholamines or pressor agents used for therapy. Transient hypertension may occur even in normotensive PD patients on L-dopa (26) and during end-of-dose akinesia, being higher in the 'off' than the 'on' phase (27). In PSP, presymptomatic hypertension, mainly transient, with large fluctuations in blood pressure has been reported in 80% of patients and on neuroimaging, small vessel cerebral disease was observed in 50% (28); whether this is due to involvement of brain stem autonomic nuclei or other factors is unclear.

HEART RATE ABNORMALITIES

Impairment of parasympathetic heart rate control in response to various respiratory stimuli is common in MSA. Abnormalities of heart rate variability have also been reported in PD, although it is unclear whether this is a reflection of disease duration, age, drug therapy or a parasympathetic cardiac deficit. In PSP, the small differences in heart rate responses to various tests (29,30), which were attributed to central autonomic involvement, have not been confirmed in a larger study (18).

Cardiac arrhythmias have been reported in parkinsonian patients and may result from factors that include age, the effect of drugs, or an intrinsic propensity to the development of arrhythmias. A prolonged Q-T interval may identify patients at risk of developing ventricular fibrillation and sudden cardiac death. In MSA the Q-T interval is prolonged but Q-T dispersion, which may provide a better measure of tendency to arrhythmias, is unaffected (31).

Studies on cardiac sympathetic innervation in parkinsonian patients have revealed unexpected differences. These studies include use of ^{123}meta-idobenzylguanadine (I-MIBG), which is dependent on active transport into sympathetic nerve terminals by a noradrenaline transporter; gamma scintiscanning of heart and mediastinum provide a measure of cardiac uptake and thus sympathetic innervation. In MSA with a pre-ganglionic lesion, such transport is preserved, with results similar to those seen in normal subjects; this is in contrast to PD, where there is impaired uptake, even in patients without autonomic failure, suggesting cardiac sympathetic denervation or dysfunction

(33-35) (Fig. 5). In PD, dopaminergic drug therapy does not appear to be the cause of the abnormality and such patients differ from other parkinsonian disorders such as vascular parkinsonism and PSP (34). These findings are similar to those described using 18F fluorodopamine and positron emission tomography scanning (36), which indicate minimal uptake in PD with AF, but normal uptake in MSA. Overall, the data suggest that apparently selective cardiac sympathetic denervation occurs at an early stage in PD; the reason for this abnormality and its implications in relation to heart rate control and cardiac arrhythmias remain to be resolved.

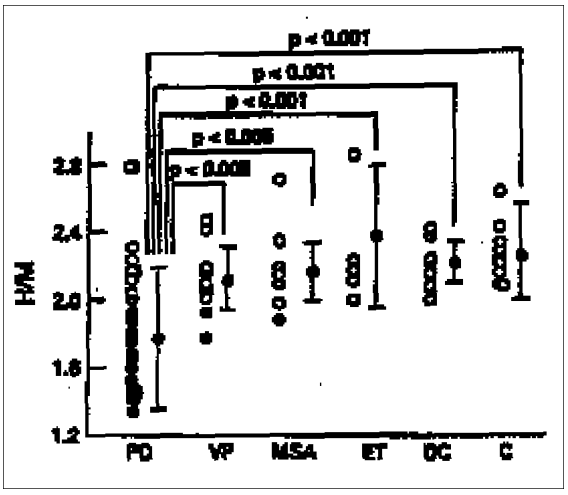

Fig. 5 - Comparison of the early phase, heart/mediastinum ratio (H/M), using ^{131}meta-iodo-benzylguanadine scintigraphic scanning in different neurological disorders and in controls. Open circles show normal and filled circles abnormal H/M ratios. PD = Parkinson's disease, VP = vascular parkinsonism, MSA = multiple system atrophy, ET = essential tremor, DC = disease controls, C = healthy controls. (From ref. 34).

CONCLUDING REMARKS

In parkinsonian disorders, a variety of cardiovascular abnormalities affecting blood pressure control and heart rate variability occur, a prime example being MSA where autonomic failure is an integral component of the disease. The abnormalities reported in PD may have other causes and explanations; thus, evaluation of cardiovascular autonomic dysfunction in these disorders is important. It aids diagnosis, in MSA where such abnormalities are characteristic, and in PSP where cardiovascular autonomic abnormalities are an exclusionary feature. Furthermore, such evaluation is necessary for appropriate overall management in parkinsonian disorders.

REFERENCES

1. Mathias CJ. Autonomic disorders and their recognition. N Eng J Med 1997;10:721-724
2. Schatz IJ, Bannister R, Freeman RL et al. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Clin Auton Res 1996;6:125-126
3. Mathias CJ, Bannister R. Investigation of autonomic disorders. In: Mathias CJ, Bannister R eds Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System. 4th Edition. Oxford; Oxford University Press 1999:169-195
4. Mathias CJ. Orthostatic hypotension - causes, mechanisms and influencing factors. Neurology 1995;45:s6-11
5. Mathias CJ, Mallipeddi R, Bleasdale-Barr K. Symptoms associated with orthostatic hypotension. J Neurol 1999;246:893-898
6. Mathias CJ. Autonomic dysfunction. In: Grimley-Evans J, Franklin Williams T, Lynn Beattie B, Michel J-P, Wilcock GK eds Oxford Textbook of Geriatric Medicine. Second Edition. Oxford; Oxford University Press 2000:833-852
7. Mathias CJ. Disorders affecting autonomic function in Parkinsonian patients. In: Battistin L, Scarlato G, Caraceni T, Ruggieri

S. eds Parkinson's Disease. New York; Raven Press 1996; ch. 69:383-391
8. Mathias CJ. Cardiovascular autonomic dysfunction in parkinsonian patients. Clin Neurosci 1998;5:153-166
9. Sandroni P, Ahlskog JE, Fealey RD, Low PA. Autonomic involvement in extrapyramidal and cerebellar disorders. Clin Auton Res 1991;1:147-155
10. Senard J-M, Rai S, Lapeyre-Mestre M et al. Prevalence of orthostatic hypotension in Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;63:578-589
11. Wenning GK, Scherfler C, Granata R et al. Time course of symptomatic orthostatic hypotension and urinary incontinence in patients with postmortem confirmed parkinsonian syndromes: a clinicopathological study. J Neurol Neurosurg Psychiatry 1999; 67:620-623
12. Mathias CJ. Can the early presence of autonomic dysfunction aid diagnosis in parkinsonism? J Neurol Neurosurg Psychiatry 1999;67:566 (editorial)
13. Senard JM, Valet P, Durrieu G et al. Adrenergic supersensitivity in parkinsonians with orthostatic hypotension. Eur J Clin Invest 1990;20:613-619
14. Senard J-M, Rascol O, Durrieu G et al. Effects of Yohimbine on plasma catecholamine levels in orthostatic hypotension related to Parkinson's disease or multiple system atrophy. Clin Neuropharmacol 1993;16:70-76
15. Daniel S. The neuropathology and neurochemistry of multiple system atrophy. In: Mathias CJ, Bannister R eds Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System. 4th Edition. Oxford University Press, Oxford 1999;321-328
16. Matthews MR. Autonomic ganglia and preganglionic neurones in autonomic failure In: Mathias CJ, Bannister R eds Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System. 4th Edition. Oxford; Oxford University Press 1999:329-339
17. Mathias CJ, Kimber JR. Treatment of postural hypotension. J Neurol Neurosurg Psychiatry 1998;65:285-289
18. Kimber JR, Watson L, Mathias CJ. Physiological, pharmacological and neurohormonal assessment of autonomic function in progressive supranuclear palsy. Brain 2000;123:1422-1430
19. Hishikawa N, Hashizume Y, Hirayama M et al. Brainstem-type Lewy body disease presenting with progressive autonomic failure and lethargy. Clin Auton Res 2000; 10:139-143
20. Larner AJ, Mathias CJ, Rossor MN. Autonomic failure preceding dementia with Lewy bodies. J Neurol 2000;247:229-231
21. Kosaka K. Diffuse Lewy body disease in Japan. J Neurol 1990;237:197-204
22. Mathias CJ, Kimber JR. Postural hypotension - causes, clinical features, investigation and management. Annu Rev Med 1999;50:317-336
23. Jordan J, Shannon JR, Grogan E, Biaggioni I, Robertson D. A potent pressor response elicited by drinking water. Lancet 1999;353:723 (letter)
24. Cariga P, Mathias CJ. Continuous hemodynamic responses to distilled water ingestion in pure autonomic failure. Clin Auton Res 2000;10:89-90
25. Senard J-M, Brefel C, Carel C, Tran M-A, Montastruc J-L. Water drinking and the heart. Lancet 1999;353:1971-1978
26. Cotzias GC, Papvasilou PS, Gellene R. Modification of parkinsonism – chronic treatment with l-dopa. N Engl J Med 1969;280:337-334
27. Baratti M, Calzetti S. Fluctuation of arterial blood pressure during end-of-dose akinesia in Parkinson's disease. J Neurol Neurosurg Psychiatry 1984;47:1241-1243
28. Ghika J, Bogousslavsky J. Presympto-

matic hypertension is a major feature in the diagnosis of progressive supranuclear palsy. Arch Neurol 1997;54:1104-1108
29. Gutrecht JA. Autonomic cardiovascular reflexes in progressive supranuclear palsy. J Auton Nerv Syst 1992;39:29-35
30. van Dijk J, Haan J, Koenderink M, Raymund A, Roos C. Autonomic nervous function in progressive supranuclear palsy. Arch Neurol 1991;48:1083-1084
31. Lo SS, Mathias CJ, St John Sutton M. QT interval and dispersion in primary autonomic failure. Heart 1996;75:498-501
32. Hakusui S, Yasuda T, Yanagi T et al. A radiological analysis of heart sympathetic functions with meta-(^{123}I) iodobenzylguanadine in neurological patients with autonomic failure. J Auton Nerv Syst 1994;49: 81-84
33. Yoshita M. Differentiation of idiopathic Parkinson's disease from striatonigral degeneration and progressive supranuclear palsy using iodine-123 and metaiodobenzylguanadine myocardial scintigraphy. J Neurol Sci 1998;155:60-67
34. Orimo S, Ozawa E, Nakade S, Sugimoto T, Mizusawa H. 123I-metaiodobenzylguanidine myocardial scintigraphy in Parkinson's disease. J Neurol Neurosurg Psychiatry 1999;67:189-194
35. Braune S, Reinhardt M, Schnitzer R, Riedel A, Lucking CH. Cardiac uptake of (^{123}I) MIBG separates Parkinson's disease from multiple system atrophy. Neurology 1999;53:1020-1025
36. Goldstein DS, Holmes C, Cannon RO III, Eisenhofer G, Kopin IJ. Sympathetic cardioneuropathy in dysautonomias. N Engl J Med 1997;336:696-702