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Ville Pursiainen

AUTONOMIC DYSFUNCTION
IN EARLY AND ADVANCED
PARKINSON'S DISEASE

FACULTY OF MEDICINE,
DEPARTMENT OF NEUROLOGY,
UNIVERSITY OF OULU

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VILLE PURSIAINEN

**AUTONOMIC DYSFUNCTION
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PARKINSON'S DISEASE**

Academic dissertation to be presented, with the assent of
the Faculty of Medicine of the University of Oulu, for
public defence in Auditorium 8 of Oulu University
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Abstract

Parkinson's disease (PD) is known to affect both the extrapyramidal system and the autonomic nervous system even in the early phases of the disease. This study was designed to evaluate cardiovascular autonomic regulation in early PD by measuring heart rate (HR) variability from 24-hour ECG recordings. The dynamics of blood pressure (BP), HR and sweating in patients with and without wearing-off were assessed during clinical observations after a morning dose of levodopa. In patients with wearing-off the tests were repeated after selegiline withdrawal.

The power spectral components of HR variability and the SD1 value of the Poincaré analysis that quantifies the short-term beat-to-beat variability were suppressed at night in the PD patients. During the daytime only the SD1 of the Poincaré was suppressed. The results indicate impairment of parasympathetic cardiovascular regulation in untreated patients with PD. The dysfunction was more pronounced at night and in patients with more severe PD.

The patients with wearing-off had fluctuation of BP during the observation period, BP increasing when the motor performance worsened and vice versa ($p < 0.001$). The patients without wearing-off did not show fluctuation of BP.

Sweating increased during the observation period, and reached its maximum level at the time of the highest UPDRS motor score phase (off-stage) in patients with wearing-off, but in the patients without wearing-off no changes in sweating were observed. Sweating of the hands was significantly higher in PD patients with motor fluctuations than in those without.

Selegiline withdrawal decreased systolic BP significantly during the on-stage in a supine position as well as during the orthostatic test. The initial drop of BP in the orthostatic test was significantly smaller after selegiline withdrawal. The HR and sweating remained unaffected.

The results show that the autonomic nervous system is affected in the early phases of PD. The dysfunction becomes more pronounced with the disease progression. Wearing-off type motor fluctuations are associated with fluctuation of BP and sweating and these fluctuations may represent autonomic dysfunction caused by PD, the effect of PD medication, or both. Selegiline withdrawal seems to alleviate the orthostatic reaction in patients with advanced PD.

Keywords: autonomic nervous system, blood pressure, heart rate, motor fluctuations, Parkinson's disease, sweating

Preface

This work was carried out in the Department of Neurology, University of Oulu, during the years 2000–2005.

I wish to express my deepest gratitude to Professor Vilho Myllylä, M.D., Head of the Department of Neurology, who has been my teacher and supervisor in the scientific work. I thank him for his sound advice, encouragement and patience throughout the years of the study. I am also indebted to Docent Kyösti Sotaniemi, M.D., for his advice and constructive criticism, which were essential for the completion of this scientific work.

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Helsinki, February 2007

Ville Pursiainen

Abbreviations

ANS	autonomic nervous system
ApEn	approximate entropy
BP	blood pressure
CAN	central autonomic network
CM	centromedian nucleus
CNS	central nervous system
CO	cardiac output
ECG	electrocardiogram
GABA	gamma-aminobutyric acid
GPe	external globus pallidus
GPi	internal globus pallidus
HF	high frequency
HR	heart rate
HRV	heart rate variability
LF	low frequency
MAO-B	monoamine oxidase-B
MPTP	1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine
NMDA	N-methyl-D-aspartic acid
NTS	nucleus tractus solitarius
PD	Parkinson's disease
PET	positron emission tomography
PPN	pedunculopontine nucleus
PUT	putamen
SD	standard deviation
SDNN	standard deviation of R-R intervals
SNc	substantia nigra pars compacta
SNS	sympathetic nervous system
SPECT	single photon emission computed tomography
STN	subthalamic nucleus
SV	stroke volume
UPDRS	unified Parkinson's disease rating scale

VA/VL ventral anterior and ventrolateral thalamic nuclei
VLF very low frequency

List of original publications

This thesis is based on the following publications, which are referred to in text by their Roman numerals:

- I Haapaniemi TH, Pursiainen V, Korpelainen JT, Huikuri HV, Sotaniemi KA & Myllylä VV (2001) Ambulatory ECG and analysis of heart rate variability in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 70: 305-310.
- II Pursiainen V, Haapaniemi TH, Korpelainen JT, Huikuri HV, Sotaniemi KA & Myllylä VV (2002) Circadian heart rate variability in Parkinson's disease. *J Neurol* 249: 1535-1540.
- III Pursiainen V, Korpelainen JT, Haapaniemi TH, Sotaniemi KA & Myllylä VV (2007) Blood pressure and heart rate in parkinsonian patients with and without wearing-off. *Eur J Neurol*. In Press.
- IV Pursiainen V, Haapaniemi TH, Korpelainen JT, Sotaniemi KA & Myllylä VV (2007) Sweating in parkinsonian patients with wearing-off. *Mov Disord*. In Press.
- V Pursiainen V, Korpelainen JT, Haapaniemi TH, Sotaniemi KA & Myllylä VV (2007) Selegiline and blood pressure in patients with Parkinson's disease. *Acta Neurol Scand* 115: 104-108.

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1 Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders. At the end of the year 2004 a total number of 14329 patients were entitled to reimbursable medication for PD in Finland (The Social Insurance Institution 2005).

PD is characterised by bradykinesia, tremor, rigidity and impaired postural reflexes mainly resulting from dopaminergic deficit in the basal ganglia (Daniel & Lees 1993). The disease is not limited, however, to the extrapyramidal system but it also involves the autonomic nervous system (ANS), dysfunction of which is usually associated with more advanced stages of the disease, though it may be present even in the early phases of the disease (Haapaniemi 2001, Oka *et al.* 2006). The symptoms of ANS dysfunction, e.g. orthostatic hypotension, may cause great discomfort to the patient. Although the central nervous system (CNS) structures undergoing neurodegeneration in PD have been well defined, the underlying mechanisms and causes of the disease are still mostly unknown. The discovery of genetic mutations that predispose people to development of Parkinson's disease provides possibilities to study the cellular mechanisms of the disease (Huang *et al.* 2004).

Long-term cardiovascular autonomic regulation can be assessed by measuring heart rate variability (HRV) analysed from 24-hour ECG recordings (Task Force 1996). The traditional time and frequency domain measures mainly reflect parasympathetic functions, as the sympathetic control of HRV has a more delayed and gradual onset and is thus more difficult to measure (Tulppo *et al.* 1996). Diminished variability of standard R-R intervals and of spectral measures of HRV has been reported in PD (Mastrocola *et al.* 1999). Because PD medication is known to affect autonomic responses (van Dijk *et al.* 1993), studies of untreated PD patients give more accurate information about the ANS dysfunction.

Treatment-related motor fluctuations, of which wearing-off is one of the most common, are an important source of disability in advanced PD. The frequency of motor fluctuations increases after a few years of levodopa therapy at a rate of about 10% per year (Denny & Behari 1999, Barone 2003). The clinical features of motor fluctuations have been well outlined, but their possible relationship with the ANS functions has gained little attention. PD patients have been found to have higher blood pressure (BP) during the off-stage than during the on-stage (Baratti & Calzetti 1984). At the same time,

PD patients with an on-off type of motor fluctuation also seem to have a higher resting heart rate (HR), a greater orthostatic BP fall, and decreased responses to Valsalva and cold pressor stimuli during the off-stage than healthy control subjects (Goetz *et al.* 1986).

Sweating is also related to motor fluctuations (Barbeau 1974). PD patients have been reported to have increased sweating during the off-stage, and it is suggested that the increased sweating may correlate with plasma levodopa levels (Goetz *et al.* 1986, Sage & Mark 1995, Swinn *et al.* 2003).

Monoamine oxidase-B (MAO-B) inhibitor selegiline, used both in early and advanced Parkinson's disease (Myllylä *et al.* 1992, Myllylä *et al.* 1996), has been shown to suppress cardiovascular autonomic responses (Haapaniemi *et al.* 2000a) and to cause orthostatic hypotension (Churchyard *et al.* 1999). Withdrawal of selegiline medication may diminish orthostatic hypotension, perhaps inducing motor decline in early PD (Churchyard *et al.* 1999). However, it is not known how withdrawal of selegiline affects ANS functions in advanced PD.

The present study was designed to evaluate the possible cardiovascular ANS dysfunction in untreated PD patients by measuring HRV from 24-hour ECG recordings. Additionally, the purpose of the study was to assess the characteristics of sudomotor and cardiovascular ANS functions in relation to wearing-off types of motor fluctuations, and the effect of selegiline medication on the ANS in patients with advanced PD.

2 Review of literature

2.1 Autonomic nervous system

The anatomy of the ANS was first depicted by Bartolomeo Eustachius in 1552 (Maximino 1783). However, the functions of the ANS remained unknown until the 19th century, when Claude Bernard was one of the first to observe the vasodilator and vasoconstrictor effects of the ANS. “Le milieu intérieur”, the internal environment, was his original concept to describe the delicate balance between the external environment and the internal functions of our bodies that is nowadays called homeostasis (Bernard 1865). The term “autonomic nervous system” was first proposed by Langley in 1898 (Langley 1898). In 1894 Oliver and Schäfer described the cardiovascular stimulatory effects of adrenal extracts (Oliver & Schäfer 1894). In 1895 Napoleon Cybulski isolated and identified the active component. His findings were repeated by Abel, who called the adrenal extracts *he* prepared epinephrine (Abel 1897). Takamine prepared a pure extract of the active principle from the adrenal gland, 4-[1-hydroxy-2-(methylamino) ethyl]-1,2 benzenediol, which he patented (Takamine 1901) and marketed under the name Adrenalin. Noradrenaline was discovered in 1946 (V Euler 1946). Acetylcholine was isolated in 1921 by Otto Loewi (Loewi 1921).

2.1.1 The role of the autonomic nervous system

Adaptation of the body to variable internal and external conditions is controlled by the ANS, which has an important role in regulating numerous essential body functions. The ANS has an important role in regulating HR, BP, body temperature, perspiration, intestinal peristalsis, pupil diameter and salivation. Although many autonomic functions are beyond conscious control, e.g. HR and force of cardiac muscle contraction, others are controlled voluntarily, e.g. sphincters in urination (Appenzeller 1990).

The peripheral part of the ANS is anatomically and functionally divided into two subsystems, the sympathetic and parasympathetic nervous systems (Shields 1993). Preganglionic autonomic nerve cells are situated in the CNS. Those of the sympathetic

nervous system arise in the thoracic and lumbar segments of the spinal cord and project to the paravertebral sympathetic ganglia. The preganglionic parasympathetic cell bodies lie in the brain stem (cranial) and in the sacral spinal cord (sacral). Axons of the parasympathetic nervous system leave the CNS via distinct cranial nerves, sacral ventral roots and pelvic splanchnic nerves (Jänig & McLachlan 1999).

The presynaptic neurons connect with postsynaptic neurons at ganglia. The ganglia of the sympathetic nervous system are located on each side of the spinal column, whereas the parasympathetic ganglia lie beside the target organs (Jänig & McLachlan 1999). The main neurotransmitter at the ganglia is acetylcholine, which is released from the presynaptic neuron and acts on postsynaptic nicotinic receptors in both the sympathetic and parasympathetic portion of the ANS. The postsynaptic sympathetic neurons release noradrenaline at the effector organs to act on adrenoceptors, with the exception of the sweat glands and the adrenal medulla. At sweat glands, the neurotransmitter is acetylcholine, which acts on muscarinic receptors. At the adrenal cortex the presynaptic neuron releases acetylcholine to act on nicotinic receptors. Stimulation of the adrenal medulla releases adrenaline directly into the bloodstream, which acts on adrenoceptors to cause a widespread increase in sympathetic activity. In the parasympathetic system, all postsynaptic cells use acetylcholine as a neurotransmitter, to stimulate muscarinic receptors in the effector organs (Jänig & McLachlan 1999). An overview of functions and receptor subtypes responsible for the effect of transmitters are presented in Table 1.

The hypothalamus has long been recognized as a key brain region involved in the integration of the physiological responses to various external and internal conditions, but other areas are also involved in processing this information. These areas form the central autonomic network (CAN), which is a complex network of neuronal interconnections in the CNS and has tonic, reflex and adaptive control over ANS functions (Dampney 1994, Kenney *et al.* 2003, Kimmerly *et al.* 2005). It also regulates endocrine, behavioural motor and pain-controlling responses (Price 2005). The cortical network involving the right superior posterior insula, the fronto-parietal cortices and the left cerebellum increases HR and muscle sympathetic nerve activity in response to orthostasis in order to maintain BP homeostasis. The bilateral anterior insular cortices, anterior cingulate cortex, amygdala, midbrain and mediodorsal nucleus of the thalamus act to suppress sympathetic activity at rest (Dampney 1994, Kimmerly *et al.* 2005).

Table 1. Overview of actions of the ANS.

Target organ	Sympathetic nervous system	Parasympathetic nervous system
Circulatory system		
Cardiac output	increases	decreases
Heart rate	$\beta_1, (\beta_2)$: increases	M2: decreases
Cardiac contractility	$\beta_1, (\beta_2)$: increases	M2: decreases
Conduction at atrioventricular node	β_1 : increases	M2: decreases
Smooth muscles in arterioles	M3, α : contracts; β_2 : relaxes	relaxes
Smooth muscles in veins	α_1 : contracts; β_2 : relaxes	
Platelets	α_2 : aggregates	
Skin function		
Sweat gland secretion	M: increases; α_1 : increases	
Erector pili	α_1 : increases	
Respiratory system		
Smooth muscle of bronchioles	β_2 : relaxes	M3: contracts, increased gland secretion
Eye		
Pupil of the eye	α : dilates	M3: contracts
Ciliary muscle	β_2 : relaxes	M3: contracts
Lacrimal glands		M3: increases secretion
Digestive system		
Salivary glands	β : stimulates viscous secretions	stimulates watery secretions
Kidney (renin secretion)	Increases	
Parietal cells		M1: secretes
Liver	α_1, β_2 : glycogenolysis, gluconeogenesis	glycogen synthesis
Adipose tissue	β_3 : lipolysis	
Intestinal mobility	β_2 : decreases	M1, M3: increases
Smooth muscle of intestine	α, β_2 : relaxes	M3: contracts
Sphincters gastrointestinal tract	α_1 : contracts	M3: relaxes
Glands of gastrointestinal tract	inhibits	M3: secretes
Endocrine system		
Pancreatic islet secretion	α_2 : decreases	
Adrenal medulla	N: secretes adrenaline	
Urinary system		
Bladder wall	β_2 : relaxes	contracts
Ureter	α_1 : contracts	relaxes
Sphincter	α_1 : contracts; β_2 : relaxes	relaxes
Reproductive system		
Uterus	α_1 : contracts; β_2 : relaxes	
Genitalia	α : contracts	M3: erection

M1-3=muscarinic receptor subtypes; α_1 -2 & β_1 -2=adrenoceptor subtypes; N=nicotinic receptor

2.1.2 Cardiovascular autonomic control

HR and BP are also controlled by the ANS, which attempts to maintain sufficient arterial BP in changing internal and external conditions. The central autonomic centres responsible for cardiovascular control receive input signals from arterial baroreceptors, cardiac baroreceptors and arterial chemoreceptors. The afferent fibres of these receptors are part of the glossopharyngeal and vagal cranial nerves and terminate in the nucleus tractus solitarius (NTS), which is the centre for cardiovascular signal processing. Spinal afferent somatic and visceral receptors, e.g. skin nociceptors and skeletal muscle chemoreceptors, also influence cardiovascular functions. Signals from these receptors cause reflex changes in sympathetic activity at the segmental level, but the signals are also transmitted over several pathways to various brainstem nuclei (Dampney 1994, Lanfranchi & Somers 2002). The NTS also receives afferent inputs from nuclei at all levels of the brain, including the cortex, amygdala, parabrachial nucleus and ventrolateral medulla. It projects to various regions in the spinal cord, lower brain stem, midbrain and forebrain that are important in cardiovascular control including intermediolateral cell column, dorsomedial hypothalamic nucleus, rostral ventrolateral medulla and caudal ventrolateral medulla (Dampney 1994, Fontes *et al.* 2001, Kimmerly *et al.* 2005).

The sympathetic premotor nuclei are those located in the brainstem and hypothalamus that send output directly to sympathetic preganglionic nuclei. These nuclei include the rostral ventrolateral medulla, caudal raphe nuclei, the paraventricular nucleus and the A5 noradrenergic cell group in the pons. Apart from these nuclei there are other cell groups at different levels of the neuraxis capable of altering cardiovascular function, including the caudal ventrolateral medulla, the medullary lateral tegmental field, the area postrema, various cerebellar nuclei, the locus ceruleus, the midbrain periaqueductal grey, forebrain nuclei (different hypothalamic regions, the amygdala, septal nuclei and cortical regions) and the parabrachial complex. The vagal preganglionic neurons innervating the cardiac ganglia are located in the nucleus ambiguus within the ventrolateral medulla, but also within the dorsal motor nucleus of the vagus (Dampney 1994, Fontes *et al.* 2001).

Under normal conditions the baroreceptor input has the main influence on the activity of the cardiac vagal preganglionic neurons, but their firing rate may also be increased by input from peripheral chemoreceptors, cardiac receptors and trigeminal receptors. Respiration also modulates the influence of the baroreflex on cardiac vagal motoneurons: inspiration decreases and expiration increases the cardiac vagal responses. The sympathetic outflow to blood vessels in different vascular beds forms separate channels, each with their own functional properties that are determined by the pattern of inputs that their respective sympathetic preganglionic neurons receive (Dampney 1994, Lanfranchi & Somers 2002). Moreover a rise in systemic BP triggers reflex parasympathetic activation and sympathetic inhibition, and thus the HR, cardiac contractility, vascular resistance and venous return decrease. Conversely, a decrease in BP causes a reflex increase in HR, cardiac contractility, vascular resistance and venous return (Lanfranchi & Somers 2002). The main components regulating HR and BP are presented in Figure 1.

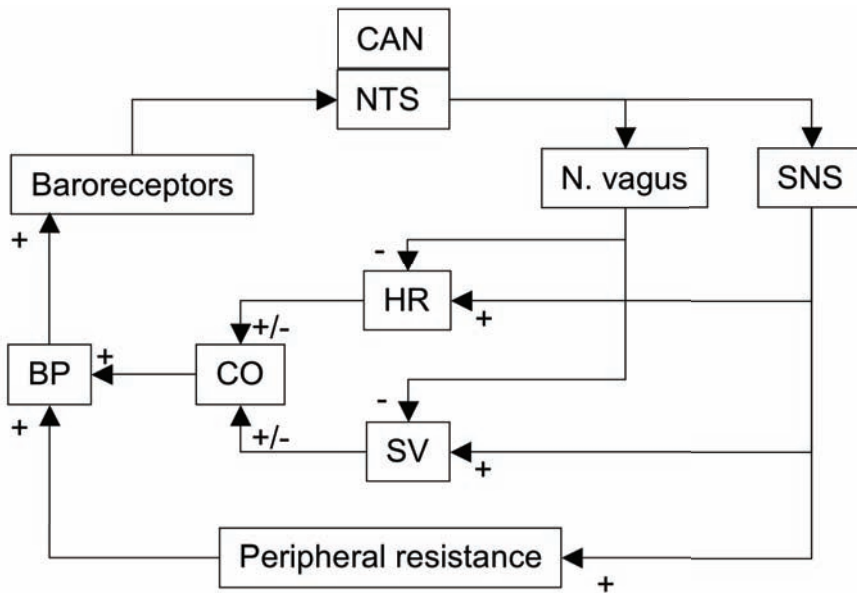


Fig. 1. Schematic representation of components regulating HR and BP. - = inhibition, + = stimulation.

2.1.3 Autonomic control of sweating

Sweating is a fundamental part of the thermoregulatory system. An increase in the body temperature results in skin vasodilatation and increased sweating, whereas a decrease in temperature causes vasoconstriction and piloerection. Body core temperature predominates in the regulation of autonomic and metabolic responses over skin temperature. The sympathetic outflow to the skin is the main regulator of vasomotor and sudomotor functions (Benarroch 1997, Frank *et al.* 1999). In addition to increased temperature, sweating can be initiated by emotional and arousal stimuli (Benarroch 1997).

In the CNS, the thermoregulatory centres are organised at various levels and have been identified in the hypothalamus and the limbic system, including cortical areas, the brainstem, the reticular formation and the spinal cord. They are driven by signals from multiple sensory inputs. Thermal receptors in the periphery terminate in the superficial laminae of the dorsal horn where the signal is processed, e.g. by convergence of warm and cold afferents. The thermal information is then conducted through raphe nuclei to the hypothalamus and thalamus. Trigeminal thermal input is thought to be in the nucleus caudalis and without significant processing (Simon *et al.* 1986, Nakamura *et al.* 2004, Egan *et al.* 2005).

The medial preoptic-anterior hypothalamic region is the main centre of sudomotor integration, containing a large number of warm-sensitive neurons that are excited by increased temperature and initiate responses for heat loss, including skin vasodilatation and sweating (Simon *et al.* 1986, Benarroch 1997, Egan *et al.* 2005). Thermoreceptors are also present in the skin, vagal nerve, viscera and the spinal cord (Figa-Talamanca *et al.* 1985, Simon *et al.* 1986, Adelson *et al.* 1997, Craig *et al.* 2001, Cotter & Taylor 2005). Thermoregulatory outflow from the lateral hypothalamus is predominantly ipsilateral, flowing through the lateral tegmentum of the pons and descending down to the spinal cord (Simon *et al.* 1986, Benarroch 1997). The preganglionic cholinergic neurons form synapses with postganglionic cholinergic neurons in the paravertebral sympathetic ganglia. The postganglionic axons control two types of sweat glands, eccrine and apocrine (Jänig & McLachlan 1999). The control of skin blood flow involves several mechanisms. Reflex control of sweating involves both a vasoconstrictor pathway and an independent active vasodilator system, both of which are of sympathetic origin. The main transmitters of the vasoconstrictor system are noradrenaline, adenosine triphosphate and neuropeptide Y, while the active vasodilatation mechanisms are less well defined but appear to be cholinergic (Kellogg *et al.* 1995, Morris 1999, Minson *et al.* 2001, Johnson *et al.* 2005). The main components of the thermoregulatory system are presented in Figure 2.

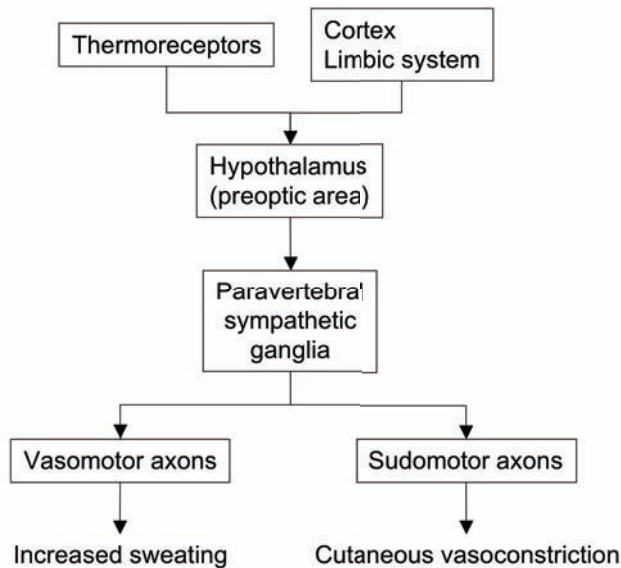


Fig. 2. Simplified representation of components of the thermoregulatory system.

2.1.4 Methods to assess autonomic function

Several methods have been developed to assess ANS function, but most of the clinical methods measure ANS function indirectly as functions of the ANS target organ. Microneurography can be used to directly measure bursts of efferent muscle sympathetic nerve activity. However, because the procedure is invasive and time-consuming, it is used solely for research purposes (Ravits 1997, Hilz & Dütsch 2006).

2.1.4.1 Heart rate variability

A time series of ECG recordings can be used to assess HRV. Each R-wave event of ECGs is initiated by the synchronous depolarization of the sinoatrial node, which is conducted through a specialized conduction system to the two ventricles. Variations in time between sequential R-waves are used in HRV analyses. HRV represents a very complex interaction between various haemodynamic, humoral and electrophysiological variables that are integrated within the ANS and CNS (Task Force 1996, Myllylä *et al.* 1999, Malpas 2002).

HRV reflects long-term cardiovascular autonomic regulation, the parasympathetic function in particular, which can be assessed using a number of methods. Time domain measures of HRV can be obtained by simple calculations on the detected normal-to-normal intervals (i.e. all intervals between adjacent QRS complexes resulting from sinus node depolarisations). The most widely used method is the standard deviation of this normal-to-normal HR (SDNN) (Task Force 1996). The SDNN reflects primarily the low fluctuation in HR behaviour, possibly reflecting the peripheral vascular resistance and thermoregulation (Rosenbaum & Race 1968). Large values of SDNN are thought to represent prevailing parasympathetic activity (Zaza & Lombardi 2001).

Frequency domain methods study the frequency-specific oscillations of HRV by spectral analysis. Differences in the magnitudes of the different frequencies can be attributed to the differences in the neural influences responsible for cardiovascular regulation. The power spectrum is usually divided into three spectrum bands: very low frequency (VLF < 0.04 Hz), low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: >0.15–0.4 Hz) (Task Force 1996). The interpretation of the VLF component in short-term recordings is unclear (Task Force 1996, Zaza & Lombardi 2001, Hilz & Dütsch 2006), but in 24-hour recordings it is thought to reflect the SDNN (Rosenbaum & Race 1968). The HF fluctuation of the R-R interval mainly reflects the cardiovagal modulation and the inspiratory inhibition of the vagal tone (Task Force 1996, Pagani *et al.* 1997, Hilz & Dütsch 2006), whereas the LF band is thought to reflect sympathetic excitation (Berntson *et al.* 1997, Pagani *et al.* 1997, Zaza & Lombardi 2001), sympathovagal balance (Eckberg 1997), and arterial pressure oscillations (Madwed *et al.* 1989). However, in long 24-hour recordings most of the power is contained within the VLF range, rendering the LF and HF components unsuitable for assessment of the autonomic modulation of HRV (Zaza & Lombardi 2001).

Poincaré is a quantitative two-dimensional vector analysis, where each R-R interval is plotted as a function of the previous R-R interval to reveal a scatter gram. The plots can

be interpreted visually and quantitatively, and the SD of the continuous long term R-R interval variability (SD2) and the instantaneous beat-to-beat R-R interval variability (SD1) are analysed (Tulppo *et al.* 1996, Korpelainen *et al.* 1999). SD1 describes the magnitude of the beat-to-beat variability, reflects vagal modulation of the HR and correlates with the HF spectral component, whereas SD2 describes the long term R-R interval fluctuation and reflects the magnitude of both the VLF and LF spectral components. One advantage of the Poincaré method over spectral analysis techniques is that it is not sensitive to stationary irregularities in the R-R intervals, therefore being more suitable for HRV analyses using ambulatory ECG recordings (Tulppo *et al.* 1996).

Non-periodic variability of HR has also been found that can be described by methods based on non-linear dynamics (“chaos theory and fractal analysis”) (Goldberger 1996, Ho *et al.* 1997, Zaza & Lombardi 2001, Barbieri *et al.* 2005). These methods estimate the different correlation properties and complexity of HRV. Approximate entropy (ApEn) quantifies the regularity of time series data, measuring the logarithmic likelihood that runs of patterns that are close to each other will remain close in the following incremental comparisons. A greater likelihood of remaining close provides lower ApEn values, and conversely random data gives higher ApEn values (Pincus & Goldberger 1994, Mäkikallio *et al.* 1996). Analysis of the power-law slope (the slope of a line fit by a least-squares criterion to a log-log plot of power versus frequency) has been found to be a more accurate predictor of survival in patients with heart failure and in elderly subjects than the traditional HRV parameters (Ho *et al.* 1997, Huikuri *et al.* 1998). The detrended fluctuation analysis technique can be used to quantify the presence or absence of long-range (fractal) correlations of HRV (Peng *et al.* 1995). This analysis technique, the short-term fractal-scaling exponent (α_1) in particular, has been proven to be a valuable indicator of survival in patients with heart failure (Ho *et al.* 1997, Huikuri *et al.* 1998). The complexity of HRV has been shown to reduce with aging even in healthy subjects (Kaplan *et al.* 1991, Jokinen *et al.* 2005).

2.1.4.2 Cardiovascular reflex tests

Cardiovascular reflex tests are the most common method used to assess autonomic function. The tests provide information of both the sympathetic and parasympathetic systems, but show great individual variability (Ravits 1997). To assess circulatory responses to standardised stimuli, continuous monitoring of BP, HR and breathing are required. HRV with respiration (sinus arrhythmia) and Valsalva manoeuvre can be used to study the integrity of the cardiovascular function. The sustained handgrip test also reflects the integrity of sympathetic cardiovascular control (Ravits 1997, Hilz & Dütsch 2006).

HR and BP responses to standing (the orthostatic test) or tilting can be used to assess both the sympathetic and parasympathetic function. Early cardiovascular response occurs within the first 30 seconds. The early circulatory stabilization occurs after 1–2 min of orthostasis. After standing up 300–900 ml of blood is redistributed to the lower extremity. Contraction of abdominal and leg muscles compresses resistance and capacitance vessels and thus increases venous return and cardiac output (CO). However, this compensation is not sufficient to completely overcome the decline in total peripheral resistance and there

is a transient reduction of BP during active standing. Moreover, muscle contraction activates an exercise reflex that rapidly causes withdrawal of parasympathetic activity and causes HR to increase in the first few seconds after standing up. The initial drop in BP causes inhibition of baroreflexes, which in turn induces the inhibition of cardiac parasympathetic activity resulting in a gradual rise of HR. BP is normalised in less than 10 seconds in a healthy individual. During 5–10 min of active standing the sympathetic outflow is fairly constant and HR and BP remain stable (Ravits 1997, Myllylä *et al.* 1999, Hilz & Dütsch 2006). The Consensus Committee of the American Autonomic Society and the American Academy of Neurology have defined a decrease either in systolic BP of at least 20 mmHg or in diastolic BP of at least 10 mmHg within 3 minutes of the orthostatic test to be criteria of orthostatic hypotension (The Consensus Committee 1996).

2.1.4.3 Sweating measurements

Several methods have been developed to assess sweating. For example, in the thermoregulatory sweat test the humidity of sweat changes the colour of an indicator powder. The quantitative sudomotor axon reflex test assesses the postganglionic sudomotor nerve fibres and the sweat glands by bringing acetylcholine into the skin by iontophoresis. Various types of stimuli, e.g. electrical and acoustic, can evoke sympathetic skin responses, and the activation of sympathetic sudomotor nerve fibres can be seen as changes in skin resistance (Ravits 1997, Hilz & Dütsch 2006).

Sweating can be quantified by means of measuring evaporation from the skin with an evaporimeter, which provides an easy, accurate and non-invasive technique to determine trans-epidermal water loss (Nilsson 1977).

2.2 Parkinson's disease

2.2.1 General aspects of Parkinson's disease

The first clinical description of PD was written by James Parkinson in 1817. The major clinical symptoms of PD are caused by loss of dopaminergic neurons in the substantia nigra pars compacta, first described in 1960 (Ehringer & Hornykiewicz 1960). Arvid Carlsson proved that dopamine functions as a neurotransmitter and, furthermore, demonstrated its role on extrapyramidal symptoms (Carlsson 1964). These findings led to the development of the first effective medication for PD, levodopa, which entered clinical practice in 1967 (Cotzias 1968).

Today the diagnosis of PD is still mostly based on clinical assessment, the clinical features including bradykinesia, muscular rigidity, rest tremor and postural instability (Litvan *et al.* 2003). Symptoms are usually unilateral and of gradual onset at presentation. A therapeutic response to levodopa supports the diagnosis. However, before establishing the diagnosis of idiopathic PD, other potential causes of parkinsonian symptoms should be excluded (Daniel & Lees 1993, Litvan *et al.* 1997, Wenning *et al.* 2000, Hughes *et al.*

2002, Litvan *et al.* 2003). The specificity of the clinical diagnosis of idiopathic PD varies in different clinical and clinico-pathological studies from 73% to 98% (Daniel & Lees 1993, Litvan *et al.* 1998, Jankovic *et al.* 2000, Hughes *et al.* 2002, Schrag *et al.* 2002a). The currently used United Kingdom Parkinson's Disease Society brain bank diagnostic criteria for Parkinson's disease are presented in Table 2.

Table 2. The United Kingdom Parkinson's Disease Society brain bank diagnostic criteria for Parkinson's disease (Daniel & Lees 1993).

Step	Criteria
1	Diagnosis of Parkinsonism Bradykinesia and at least one of the following: muscular rigidity, 4–6 Hz resting tremor, postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction
2	Features tending to exclude Parkinson's disease as the cause of Parkinsonism History of repeated strokes with stepwise progression of parkinsonian features History of repeated head injury History of definite encephalitis Neuroleptic treatment at onset of symptoms >1 affected relatives Sustained remission Strictly unilateral features after 3 years Supranuclear gaze palsy Cerebellar signs Early severe autonomic involvement Early severe dementia with disturbances of memory, language and praxis Babinski's sign Presence of a cerebral tumour or communicating hydrocephalus on computed tomography scan Negative response to large doses of levodopa (if malabsorption excluded) MPTP exposure
3	Features that support a diagnosis of Parkinson's disease (three or more required for diagnosis of definite Parkinson's disease) Unilateral onset Rest tremor present Progressive disorder Persistent asymmetry affecting the side of onset most Excellent (70–100%) response to levodopa Severe levodopa-induced chorea Levodopa response for ≥ 5 years Clinical course of ≥ 10 years

2.2.1.1 Non-motor symptoms

In addition to motor impairment, PD patients experience several non-motor symptoms, e.g. sensory symptoms, anxiety, fatigue, irritability, panic, and autonomic symptoms

including sweating, sensation of being hot or cold, limb oedema, oral dryness and palpitations, that may fluctuate with motor symptoms (Hillen & Sage 1996, Raudino 2001, Witjas *et al.* 2002). The mechanisms of these non-motor fluctuations are poorly understood.

Falls are one of the most serious and common complications of gait disturbances in patients with PD. Falls have been reported to occur in 38% to 68% of PD patients (Wood *et al.* 2002, Bloem *et al.* 2004). Risk factors for falling include previous falls, dementia, duration of PD, gait disturbances and postural instability (Wood *et al.* 2002, Balash *et al.* 2005). Orthostatic hypotension may also contribute to falling (Bloem *et al.* 2004).

Depression and anxiety are common problems among PD patients, affecting up to 50% of PD patients (Rojo *et al.* 2002, Schrag 2004). Dementia is common in advanced PD, affecting up to 78% of patients (Aarsland *et al.* 2003). Hallucinations and psychotic symptoms are also prevalent in PD, affecting approximately 15–20% of patients. They can occur early in the disease course, but increase with the duration of the disease and particularly if dementia develops (Schrag 2004). Sleep disorders are reported to occur in 74% to 98% of PD patients. Especially REM sleep behaviour disorder and excessive daytime sleepiness are typical (Chaudhuri *et al.* 2006). Other sources of sleep disruption in PD patients are nocturia, difficulty in turning over in bed, painful leg cramps, vivid dreams/nightmares, back pain, limb/facial dystonia and leg jerks (Partinen 1997).

Autonomic dysfunction is also common in PD, which is discussed in detail in section 2.3.

2.2.1.2 Incidence and prevalence

Data on PD incidence and prevalence varies significantly between different studies and study populations. Studies in different European countries have presented annual incidence rates ranging from 5 to 346 per 100 000 (von Campenhausen *et al.* 2005), the peak incidence being between 70 and 79 years (Twelves *et al.* 2003). However, the incidence of idiopathic PD in well-designed, comparable studies have been quite similar between different populations, incidences ranging from 16 to 19 per 100 000 per year (Twelves *et al.* 2003). The prevalence rates have ranged from 65 to 12 500 per 100 000 in different studies (von Campenhausen *et al.* 2005). Differences in reported prevalence and incidence rates are probably consequences of differences in study design and diagnostic criteria, and of differences in the age distributions of the study populations. Some studies also have significant methodological problems. However, the differences may also result from genetic or environmental factors (Twelves *et al.* 2003, von Campenhausen *et al.* 2005).

The annual incidence of PD in Finland is estimated to be 14.9 per 100 000 and the age-adjusted prevalence 166 per 100 000 (Kuopio *et al.* 1999b). In the pre-levodopa era the prevalence of PD in Finland was 120 per 100 000, the highest annual incidence being 16.6 per 100 000 (Marttila 1974, Marttila & Rinne 1976).

2.2.1.3 Aetiology

The aetiology of PD remains unknown, and current evidence supports the hypothesis that PD is a multifactorial disorder (Olanow & Tatton 1999). Epidemiologic studies indicate that a number of factors may increase the risk of developing PD, including exposure to well water, pesticides, herbicides, industrial chemicals, wood pulp mills, farming, and living in a rural environment. A number of exogenous toxins have also been associated with the development of parkinsonism, including trace metals, cyanide, lacquer thinner, organic solvents and carbon disulfide (Kuopio *et al.* 1999a, Olanow & Tatton 1999, Engel *et al.* 2001, Zorzon *et al.* 2002). Cigarette smoking, use of coffee or caffeine, and non-steroidal anti-inflammatory drugs all appear to lower the risk of PD (Checkoway *et al.* 2002, Abbot *et al.* 2003, Chen *et al.* 2003). MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine), which is a by-product of an illicit synthetic drug, develops a syndrome that resembles the dopaminergic deficits of PD and has been widely used to produce an experimental animal model of PD. This model has been thought to support the hypothesis of exogenous toxins as the cause of PD. However, the condition caused by MPTP is not progressive and involves only dopaminergic pathways (Zang & Misra 1992, Olanow & Tatton 1999, Wichmann & DeLong 2003). A new proteasome inhibitor animal model causes a progressive neurodegenerative condition that closely resembles idiopathic PD both pathologically and pathophysiologically (McNaught *et al.* 2004, Mytilineou *et al.* 2004), but unfortunately there have been difficulties in reproducing the results (Kordower *et al.* 2006).

2.2.1.4 Pathogenesis

PD is characterized by the progressive death of selected but heterogeneous groups of neurons, with major clinical symptoms of PD caused by loss of dopaminergic neurons in the substantia nigra pars compacta. In the preclinical stage of PD, i.e. prior to motor symptoms, the lesions occur in the dorsal motor nucleus of the glossopharyngeal and vagal nerves and in the anterior olfactory nucleus. Thereafter, the substantia nigra and other nuclear grays of the midbrain and cortical areas gradually become affected, and the disease reaches its symptomatic phase. Cortical involvement follows, beginning at the anteromedial temporal mesocortex. The process spreads to the neocortex, starting with high-order sensory association and the prefrontal areas. First-order sensory association/premotor areas and primary sensory/motor fields then follow (Braak *et al.* 2002, Braak *et al.* 2003). The sympathetic ganglia and parasympathetic neurons in the intestine are also affected (Lang & Lozano 1998a, Harding *et al.* 2002). Lewy bodies and dystrophic neuritis are characteristic pathological findings in PD. Especially Lewy bodies, also found in small numbers in other neurodegenerative disorders (Lang & Lozano 1998a), are thought to be a pathognomic feature of PD, but recent studies suggest that Lewy bodies are not formed in some genetic forms of PD (Dawson & Dawson 2003b).

Oxidative stress has received the most attention in PD pathogenesis because the oxidative metabolism of dopamine can yield excess reactive oxygen species, this

hypothesis being supported by postmortem studies (Olanow & Tatton 1999, Dawson & Dawson 2003a). Epidemiological studies suggest that environmental toxins that inhibit mitochondrial complex I may also be involved in the pathogenesis of PD (Scherer *et al.* 2002, Dawson & Dawson 2003a). Moreover, a decrease in complex I activity and plasma levels of coenzyme Q10 has been found in postmortem studies of PD patients (Schapira *et al.* 1990, Scherer *et al.* 2002, Dawson & Dawson 2003a, Sohmiya *et al.* 2004). This dysfunction leads to increased oxidative stress, free radical formation, and reduced adenosine triphosphate formation (Scherer *et al.* 2002, Dawson & Dawson 2003a, von Bohlen und Halbach *et al.* 2004). As dopaminergic neurons receive an extensive glutaminergic innervation from the cortex and the subthalamic nucleus, glutamate-induced excitotoxicity may also play a part in PD pathogenesis (Lang & Lozano 1998a, Dawson & Dawson 2003a, von Bohlen und Halbach *et al.* 2004).

α -synuclein is a protein thought to have a role in the modulation of synaptic vesicle turnover and synaptic plasticity. Over expression of α -synuclein may increase the level reactive oxygen species. Mutated α -synuclein proteins display a tendency to form fibrils *in vitro*, and the abnormal aggregation of α -synuclein forms the major filamentous component of Lewy bodies (von Bohlen und Halbach *et al.* 2004, Halliday *et al.* 2005, Hasegawa *et al.* 2006). Mitochondrial alterations associated with oxidative stress may trigger α -synuclein accumulation and aggregation (Dawson & Dawson 2003a, Hashimoto *et al.* 2003), which may activate microglia and may promote an inflammatory response (Zhang *et al.* 2005). Synphilin-1 is a presynaptic protein that associates with synaptic vesicles and interacts with α -synuclein. Under pathological conditions it associates with α -synuclein to form cytosolic inclusions (Kawamata *et al.* 2001, von Bohlen und Halbach *et al.* 2004). Increasing amounts of data suggest that protein accumulation due to genetic mutations in individual proteins or a defect in the capacity of the ubiquitin proteasome system to clear damaged proteins is a major factor in the pathogenesis of PD (McNaught & Olanow 2003, Olanow & Jankovic 2005). Parkin protein may also be of importance in PD pathogenesis, its function being to target misfolded proteins for degradation. It has been shown to ubiquitinate Lewy body-like inclusion bodies and thus provide protection against the toxicity associated with α -synuclein (Hyun *et al.* 2002, Kim *et al.* 2003, von Bohlen und Halbach *et al.* 2004) and possibly against mitochondrial failure as well (Darios *et al.* 2003, Kahle & Haass 2004). Although intracellular aggregates may be cytotoxic (Bence *et al.* 2001), some studies show that the presence of inclusion bodies might also be protective (von Bohlen und Halbach *et al.* 2004, Tanaka *et al.* 2004).

The role of genetic factors in PD has received a lot of attention. Several interesting loci and candidate genes have been found, including parkin and α -synuclein (Olanow & Tatton 1999, Huang *et al.* 2004, Sun *et al.* 2006). The relative risk of PD among first-degree relatives of PD patients in Finland is 2.9-fold and the cumulative incidence of PD 3.3-fold higher than those of controls, suggesting a genetic influence or shared environmental factors (Autere *et al.* 2000). PD seems to occur more frequently in men than women, but the reasons for this are not clear, and both environmental causes and genetic factors linked to chromosome X have been suggested (Kuopio *et al.* 1999b, Wooten *et al.* 2004).

It seems that the proteasomal and mitochondrial dysfunctions are linked in the pathogenesis of PD since impairment of one system causes dysfunction in the other

(Sherer *et al.* 2002, McNaught *et al.* 2004). Despite the vast number of studies on PD pathogenesis, there are still numerous unanswered questions about the disease process.

2.2.1.5 Pathophysiology

The main motor symptoms of PD reflect degeneration of the nigrostriatal system. Deficiency in dopamine is associated with increased activity of GABAergic output nuclei in the basal ganglia, the internal segment of the globus pallidus and the pars reticulata of the substantia nigra. This increased output causes excessive excitation through an indirect pathway from the striatum through the external segment of the globus pallidus, and to the subthalamic nucleus, which in turn stimulates the internal segment of the globus pallidus and the substantia nigra pars reticulata. Because these structures use the inhibitory neurotransmitter GABA, the increased output leads to excessive inhibition and to a shutdown of the thalamic and brainstem nuclei that receive their outflow (Lang & Lozano 1998b, Moore 2003). The excessive thalamic inhibition leads to suppression of the cortical motor system and possibly leads to akinesia, rigidity and tremor. The inhibitory descending projections to the brainstem locomotor areas are thought to contribute to abnormalities in gait and posture (Lang & Lozano 1998b, Ouchi *et al.* 2001). A simplified model of the basal ganglia is presented in Figure 3.

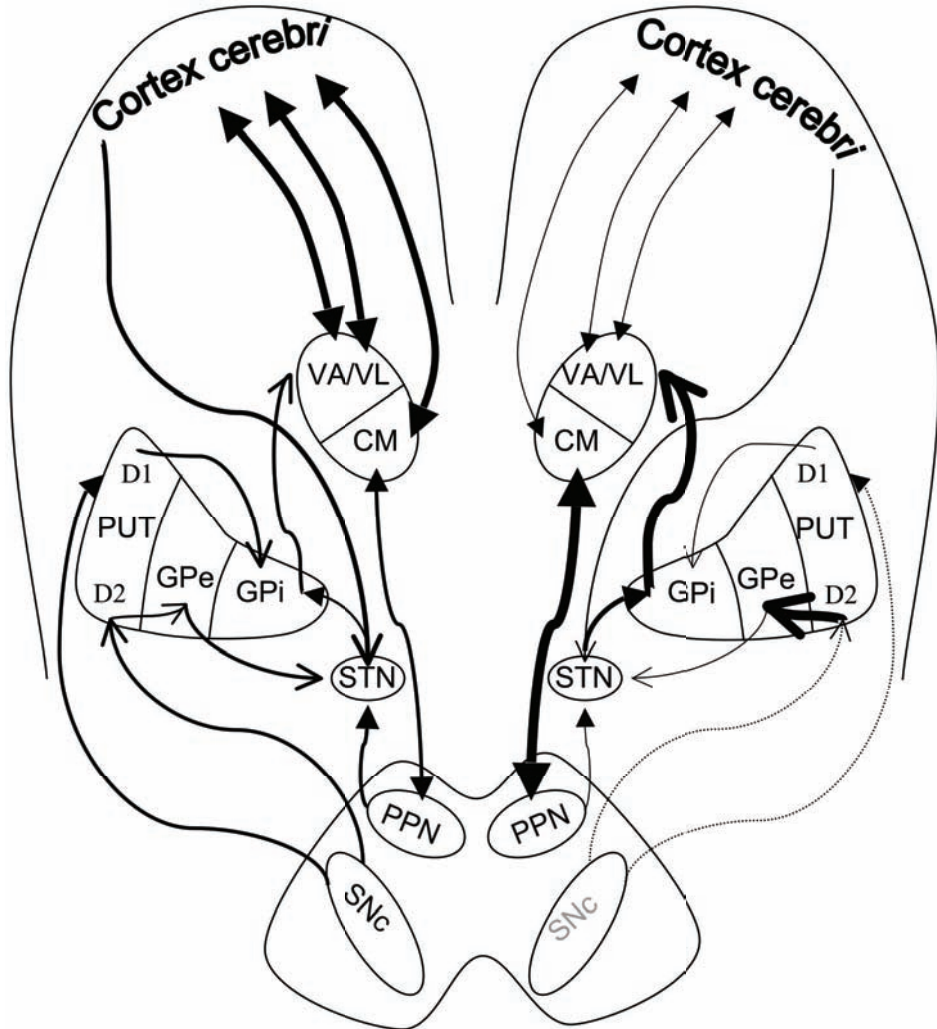


Fig. 3. Simplified functional model of the basal ganglia in persons with normal motor control (left) and with Parkinson's disease (right). \rightarrow = stimulatory pathway, \rightarrow = inhibitory pathway, CM = centromedian nucleus, D1-2 = dopamine receptor subtypes, GPe = external globus pallidus, GPi = internal globus pallidus, PPN = pedunculopontine nucleus, PUT = putamen, SNC = substantia nigra pars compacta, STN = subthalamic nucleus, VA/VL = ventral anterior and ventrolateral thalamic nuclei. Line thickness represents strength of stimulation/inhibition.

2.2.2 Clinical course

The clinical signs of PD progress gradually with time. This progression in disability can be clinically assessed using various rating scales of which the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn & Yahr staging are the most commonly used (Hoehn & Yahr 1967, Ramaker *et al.* 2002, Alves *et al.* 2005). In addition, dopamine transporter imaging using [¹²³I] β-CIT SPECT or [¹⁸F] fluorodopa PET can be used to estimate nigrostriatal neuronal loss in PD, and the results also correlate with disability (Benamer *et al.* 2000, Brucke *et al.* 2000, Pirker 2003).

The natural course of PD can be evaluated based on patients seen before the 1960's and the introduction of levodopa therapy, and also on patients in placebo treatment arms of clinical trials. Untreated patients in the DATATOP study had a 0.38-point worsening in the Hoehn & Yahr staging per year and an 8 to 9 percent per year decline in the UPDRS motor score. (The Parkinson Study Group 1989, The Parkinson Study Group 1993). In patients treated with PD medication the progression in the UPDRS motor score has been reported to be between 1.5 points and 3.6 points per year (Louis *et al.* 1999, Alves *et al.* 2005). The annual decline of striatal dopamine transporter binding has varied in different studies from 3.0 to 6.6 percent (The Parkinson Study Group 2002, Pirker *et al.* 2003).

Several risk factors for the rapid progression of PD have been identified. The progression of disability in PD patients with tremor as the initial symptom seems to be slower than in patients with other presenting symptoms (Hoehn & Yahr 1967, Marttila & Rinne 1991, Gasparoli *et al.* 2002). An older age of onset, poorer response to levodopa, gait disturbances, dementia and cognitive impairment are risk factors for the rapid progression of symptoms (Marttila & Rinne 1991, Poewe & Wenning 1996, Gasparoli *et al.* 2002, Gasparoli *et al.* 2002, Alves *et al.* 2005, Alvin *et al.* 2005). The progression of disability is fastest during the first four years of the disease (Hoehn & Yahr 1967, Poewe & Wenning 1996, Louis *et al.* 1999), and postmortem studies of PD patients also show early rapid neuronal loss in the substantia nigra (Fearnley & Lees 1991). Imaging studies also suggest that the neuronal loss runs a negatively exponential course in contrast to the traditional linear hypothesis (Brucke *et al.* 2000, Pirker *et al.* 2003, Hilker *et al.* 2005).

2.2.3 Medical treatment of Parkinson's disease

2.2.3.1 Medical treatment of motor symptoms

When introduced in the early 1960's levodopa revolutionized the treatment of PD, for it was the first therapeutic agent to provide marked symptomatic benefits to virtually all PD patients (Birkmayer & Hornykiewicz 1961, Cotzias 1968, Markham *et al.* 1974b, Olanow *et al.* 2004). The side effects of levodopa given alone were mostly overcome in the 1970's after the introduction of peripheral dopadecarboxylases that are now given in combination with levodopa (Markham *et al.* 1974a, Markham *et al.* 1974b). Levodopa is still the most effective medication for PD, but it has rather inconvenient long-term complications such as motor fluctuations, which develop in up to 50% of patients after

five years of levodopa therapy (Denny & Behari 1999, Barone 2003). Another concern of levodopa therapy has been its possible neurotoxicity, because the metabolism of levodopa can create reactive oxygen species, and it has been shown to be toxic to cultured neurons. However, there is also evidence to suggest that in certain conditions levodopa can be neurotrophic, especially in low concentrations (Lang & Lozano 1998b, Olanow *et al.* 2004). In clinical trials comparing levodopa to dopamine agonists, slower progression of striatal neuronal loss has been demonstrated in the dopamine agonist group (The Parkinson Study Group 2002, Whone *et al.* 2003). In the ELLDOPA study the UPDRS motor score deterioration was milder in patients treated with levodopa than in patients treated with a placebo, but dopamine transporter imaging showed greater decline in the nigrostriatal function in the levodopa group than in the patients on placebo. Thus levodopa may have a neurotoxic effect, although a confounding pharmacological effect may explain the results of dopamine transporter imaging (Olanow *et al.* 2004, Fahn & The Parkinson Study Group 2005).

Catechol-O-methyltransferase (COMT) inhibitors offer a beneficial therapeutic effect by increasing the bioavailability of levodopa and by producing a more stable pharmacokinetic profile of levodopa. For example, entacapone is widely used, and it has been shown to increase the on-time and decrease the off-time in fluctuating PD patients and so allow a reduction of the levodopa dosage (Brooks *et al.* 2003, Gordin *et al.* 2004). Non-fluctuating patients have also been shown to benefit from entacapone (Brooks *et al.* 2003). The use of tolcapone has also been found to extend the actions of levodopa, but reports of severe hepatotoxicity have limited its use (Leegwater-Kim & Waters 2006).

Dopamine agonists such as bromocriptine, cabergoline, pergolide, pramipexole and ropinirole have been shown to be effective in the treatment of PD, both in the treatment of early PD as monotherapy and in combination with levodopa (Watts 1997, Ramaker & van Hilten 2000, Rascol *et al.* 2000, The Parkinson Study Group 2000, Olanow 2002, Schrag *et al.* 2002b, Curran & Perry 2004). Since ergotamine derivatives (bromocriptine, cabergoline and pergolide) have severe fibrotic side effects (Van Kamp *et al.* 2004, Dhawan *et al.* 2005), the clinical use of these compounds is decreasing. Despite their limited efficacy on PD symptoms, dopamine agonists have been found to delay motor complications compared to levodopa (Rascol *et al.* 2000, The Parkinson Study Group 2000). It has recently been proposed that modern dopamine agonists do not offer sufficient benefit over levodopa to justify the cost difference (Ahlskog 2003).

The MAO-B inhibitors selegiline and rasagiline have a mild to moderate effect on PD symptoms, reduce the need for levodopa and seem to reduce the risk of levodopa complications (Myllylä *et al.* 1992, The Parkinson Study Group 1993, Ives *et al.* 2004, Rascol *et al.* 2005). MAO-B inhibitors could also theoretically have neuroprotective properties (Mandel *et al.* 2005), and early studies on selegiline indeed suggested that selegiline slows down the progression of PD symptoms, but it is not clear if this retardation was due to neuroprotection or to a symptom-alleviating effect (The Parkinson Study Group 1993, Olanow *et al.* 1995, Marras *et al.* 2005, Pålhagen *et al.* 2006). Selegiline was associated for a while with increased mortality rates (Lees 1995), but more recent studies have found no differences in mortality (Olanow *et al.* 1998, Ives *et al.* 2004, Marras *et al.* 2005). As for rasagiline there is insufficient data to clarify its possible neuroprotective properties.

Amantadine, an NMDA-receptor antagonist, is thought to reduce levodopa-induced dyskinesias, but any effect usually wears off after a few months (Lang & Lozano 1998b, da Silva-Junior *et al.* 2005). It has also been suggested that amantadine improves survival (Uitti *et al.* 1996) and delays the onset of dementia in PD patients (Inzelberg *et al.* 2006). However, not all studies have found a neuroprotective effect, and the drug is poorly tolerated due to psychiatric side effects (Olanow & Jankovic 2005).

Various anticholinergic drugs are also used to some extent to control tremor in PD patients. However, due to the vast number of their side effects the use of anticholinergics is usually limited to early PD and young patients (Lang & Lozano 1998b).

2.2.3.2 Medical treatment of autonomic symptoms

The medical treatment of the autonomic symptoms of PD has not received much attention and there have not been any large, blinded and placebo controlled trials. Therefore the medical treatment of autonomic symptoms remains empirical. Vasoconstrictors (e.g. etilefrine) and volume expanders (e.g. fludrocortisone) may reduce symptoms of orthostatic hypotension (Pathak & Senard 2004). Bulking agents, osmotic laxatives and medication increasing peristalsis can be considered for treatment of constipation (Coggrave *et al.* 2006, Johnson 2006). Bladder abnormalities, hyperreflexia in particular, can be treated with various anticholinergic medications such as oxybutynin or tolterodine (Schapira 2005). Sweating and excessive drooling can sometimes be reduced by anticholinergics, but the medication often causes undesirable side effects (Haider & Solish 2005, Schapira 2005). Botulinum toxin is effective for local hyperhidrosis (Bhidayasiri & Truong 2005) and may also be considered for excessive drooling (Mancini *et al.* 2003).

2.2.4 Treatment-related motor complications

PD is associated with several types of complications. After a few years of levodopa treatment motor complications may occur, emerging at a rate of approximately 10% per year (Denny & Behari 1999, Barone 2003). These complications include wearing-off fluctuations, on-off fluctuations, dyskinesias and drug failure response (Quinn 1998, Martignoni *et al.* 2003). Drug response failure is usually related to poor gastric emptying and inadequate absorption (Martignoni *et al.* 2003). However, acute akinesia may also occur with therapeutic plasma levodopa concentrations and may be unresponsive to subcutaneous apomorphine infusion, suggesting that central mechanisms may sometimes be involved (Onofrij & Thomas 2005). Wearing-off, a progressive shortening in response to levodopa, is thought to arise from inadequate presynaptic dopamine storage (Sage & Mark 1994, de la Fuente-Fernández *et al.* 2004), but as a similar pattern of deterioration is observed with dopamine agonist medication, postsynaptic mechanisms may also be involved (Bravi *et al.* 1994, Stocchi 2003), e.g. the down regulation of dopaminergic receptors (Hwang *et al.* 2002). The peripheral pharmacokinetics of levodopa also plays a part in the motor fluctuations as the introduction of COMT inhibitor therapy may

improve these phenomena (Colosimo & De Michele 1999). However, the nature of motor fluctuations remains unclear. On-off fluctuations are characterized by sudden, often unpredictable shifts between under- and over-treated states. Over time an increasing proportion of patients notice that the fluctuation of their symptoms becomes more dramatic and abrupt, reflecting changes in the threshold of dopaminergic stimulation, below which the patients are “off” and above which they are “on”, with a narrowing gap between the two (Quinn 1998). Levodopa responses in different stages of PD are presented in Figure 4.

Dyskinesias are both drug and disease related. They may occur during the peak dose (time of maximal levodopa benefit) or as biphasic (at the beginning and at the end of the levodopa response cycle) (Quinn 1998, Martignoni *et al.* 2003). Dystonia may also occur early in the morning (Martignoni *et al.* 2003). Sudden transient freezing usually occurs later in the course of PD, is frequently provoked by certain specific stimuli (e.g. start hesitation, turns, confined spaces, doorways) and is worsened by stress. The phenomenon may occur at any time, during either “on” or “off” states. “On”-freezing is poorly understood, and although “off”-freezing is common in PD, it does not respond readily to levodopa (Quinn 1998, Martignoni *et al.* 2003).

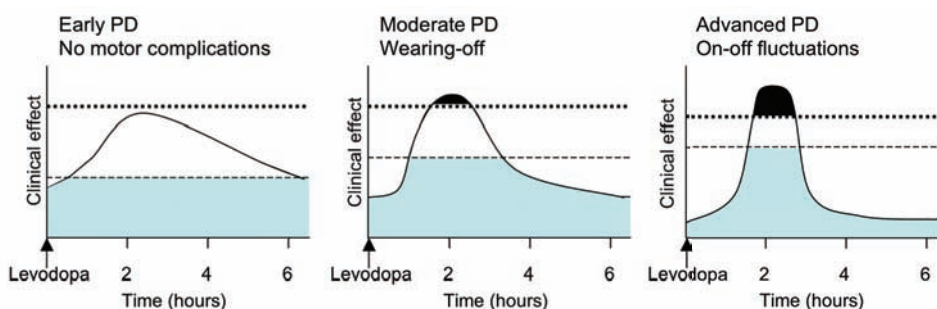


Fig. 4. Schematic representation of levodopa responses in different stages of PD. The area between dotted lines is the therapeutic window. The gray area represents inadequate symptom control; the white area good symptom control; the black area possible treatment-related motor side-effects (e.g. dyskinesias). (Modified from Obeso *et al.* 2000. Printed with permission of Lippincott Williams & Wilkins, Inc.)

2.3 Autonomic dysfunction in Parkinson’s disease

Autonomic dysfunction affects PD patients early in the disease course, even newly diagnosed patients (Haapaniemi 2001, Oka *et al.* 2006). Some autonomic symptoms, in particular constipation, may even precede the motor symptoms (Abbott *et al.* 2001). Lewy bodies have been found throughout the ANS in patients with PD, including in the hypothalamus and parasympathetic and sympathetic ganglia (Wakabayashi *et al.* 1993, Wakabayashi & Takahashi 1997). More than 50% of PD patients have been reported to have disabling symptoms of ANS dysfunction in everyday life (Jost 2003, Korchounov *et*

al. 2005, Magenkurth *et al.* 2005). The most common symptoms of ANS dysfunction are postural dizziness, seborrhoea, bladder and bowel dysfunction as well as hyper- and hypohidrosis (Korchounov *et al.* 2005, Magenkurth *et al.* 2005).

2.3.1 Sweating dysfunction

Sweating dysfunction is a common symptom in PD patients, subjective problems in thermoregulation and sweating being reported in up to 64% of PD patients (Swinn *et al.* 2003). Evaporimetric methods have shown that thermoregulatory sweating is reduced in the trunk and limbs with compensatory hyperhidrosis on the face (Appenzeller & Goss 1971). Increased sweating at rest and in response to heat stimuli has also been reported in PD patients (Turkka & Myllylä 1987). Studies on sympathetic skin response in PD patients have been reported to have either increased latencies (Mano *et al.* 1994, Braune *et al.* 1997, Zakrewska-Pniewska & Jamrozik 2003), or reduced amplitudes (Hirashima *et al.* 1996, Fusina *et al.* 1999, Haapaniemi *et al.* 2000b), or absent responses (Taly & Muthane 1992, Wang *et al.* 1993), indicating dysfunction of central sudomotor regulation and dysfunction of the postganglionic sympathetic neurons (Mano *et al.* 1994, Haapaniemi *et al.* 2000b). Sympathetic skin response is asymmetric in early PD, the abnormalities being more profound on the affected side (Braune *et al.* 1997, Fusina *et al.* 1999), and the presence of abnormalities in sympathetic skin response may increase with disease duration and severity (Braune *et al.* 1997, Haapaniemi *et al.* 2000b). A decrease in the number of functional sweat glands, decreased sweat gland activation, and decreased peripheral autonomic innervation of cutaneous blood vessels and sweat glands in PD patients have also been reported (Mano *et al.* 1994, Dabby *et al.* 2006, Schestatsky *et al.* 2006), suggesting involvement of the postganglionic nerves.

The effect of PD medication on sudomotor control is controversial. Anticholinergics are known to inhibit the activity of sweat glands (Togel *et al.* 2002). In a prospective study, selegiline has been reported to diminish sympathetic skin response amplitudes, whereas bromocriptine and levodopa did not change the responses (Haapaniemi *et al.* 2000b).

Motor fluctuations are also known to affect sweating (Barbeau 1974). Some PD patients report increased sweating during their off-stage and dyskinesias (Swinn *et al.* 2003). The excessive sweating during poor motor performance, i.e. the off-stage, that is reported by some patients seems to correlate with plasma levodopa levels (Sage & Mark 1995). PD patients with motor fluctuations have been found to have increased sweating responses to heat stimuli during the off-stage, but this increase resolves itself during the on-stage (Goetz *et al.* 1986). Thus it seems likely that sweating is also related to motor fluctuations.

2.3.2 Cardiovascular dysfunction

Cardiovascular dysfunction is also a common feature of ANS involvement in PD. One of the most common symptoms of ANS dysfunction in PD patients is orthostatic hypotension, which affects 20% to 50% of PD patients, depending on the definition used (Senard *et al.* 1997, Wood *et al.* 2002, Goldstein 2003). PD patients with orthostatic hypotension show a higher degree of sympathetic dysfunction in cardiovascular reflex tests, a higher extent of cardiovascular sympathetic denervation and decreased supine plasma noradrenaline concentrations compared to patients without orthostatic hypotension, reflecting generalized sympathetic denervation (Goldstein *et al.* 2002, Goldstein *et al.* 2005). Depressed baroreflex sensitivity involving cardiovagal and sympathoneural circuits has been reported in PD (Szili-Török *et al.* 2001, Goldstein 2003) and this together with sympathetic denervation seems to produce orthostatic hypotension (Goldstein *et al.* 2002, Goldstein 2003). The use of [¹²³I]meta-iodobenzylguanide myocardial scintigraphy has demonstrated loss of sympathetic innervation of the heart, even in early untreated PD patients (Goldstein *et al.* 2000, Oka *et al.* 2006). These findings suggest that PD involves a postganglionic lesion of the ANS.

PD patients appear to have abnormal cardiovascular responses, including suppressed HR responses to breathing, the Valsalva manoeuvre and tilting, reflecting parasympathetic dysfunction of cardiovascular control (Linden *et al.* 1997, Mesec *et al.* 1999, Myllylä *et al.* 1999, Haapaniemi *et al.* 2000a, Goldstein *et al.* 2002). Pronounced BP fall in response to tilting has also been reported in PD patients, indicating sympathetic dysfunction (van Dijk *et al.* 1993, Turkka *et al.* 1997). It has been suggested that age could explain most of the variance in HRV (van Dijk *et al.* 1993), and that HRV diminishes with the disease course (Devos *et al.* 2003).

Circadian autonomic control is also disturbed in PD. Diminished variability of standard R-R intervals and of spectral measures of HRV in 24-hour ECG recordings, indicating combined parasympathetic and sympathetic dysfunction and defective autonomic cardiac control in sleep in PD patients, has been reported (Ferini-Strambi *et al.* 1992, Mastrocola *et al.* 1999). However, the increased HRV during non-REM sleep suggests that in the early phase of the disease the cardiovascular system is still able to react to changes in body movements (Kallio *et al.* 2004). Circadian BP variability also seems to be diminished in PD patients (Senard *et al.* 1992).

PD medication is known to affect cardiovascular responses. Levodopa frequently causes both supine and orthostatic hypotension (Yahr *et al.* 1969). The combination of levodopa and peripheral dopadecarboxylase inhibitor prevents supine hypotension caused by levodopa given alone, but orthostatic hypotension may persist (Goetz *et al.* 1986, Iwasaki *et al.* 1990, Bouhaddi *et al.* 2004). However, a recent study suggests that levodopa does not affect cardiovascular ANS control in PD patients (Goldstein *et al.* 2005).

Entacapone seems to have no effect on cardiovascular autonomic control in PD patients treated with levodopa (Lyytinen *et al.* 2000, Lyytinen *et al.* 2001). Similarly tolcapone does not seem to alter HRV or BP, but it may increase plasma catecholamine levels (Meco *et al.* 2000, Rojo *et al.* 2001).

Dopamine agonists have haemodynamic effects that are mediated through central and peripheral interactions with the dopaminergic system (Velasco & Luchinger 1998). They are known to lower supine BP, increase the orthostatic BP fall, and they may also cause acute orthostatic hypotension during therapy initiation (Quinn *et al.* 1981, Cavallini *et al.* 1991, Kujawa *et al.* 2000, Haapaniemi *et al.* 2000a). It has also been claimed that neither lisuride nor bromocriptine significantly alter BP in PD patients when given in combination with levodopa (Micieli *et al.* 1996). However, HRV analysis has shown that bromocriptine has central and peripheral effects on cardiac sympathetic regulation in healthy individuals (Franchi *et al.* 2001).

The effect of selegiline on the regulation of BP and the frequency of orthostatic hypotension is controversial. One study has reported no differences between PD patients treated with either levodopa or selegiline in the orthostatic BP measurements (Battacharya *et al.* 2003), while other studies have reported an increased frequency of orthostatic hypotension and a more pronounced orthostatic drop of BP in patients receiving selegiline (Turkka *et al.* 1997, Haapaniemi *et al.* 2000a, Korchounov *et al.* 2004). Some studies have shown an increased frequency of orthostatic hypotension in PD patients treated with selegiline in combination with levodopa when compared to patients receiving only levodopa (Turkka *et al.* 1997), while other studies have reported identical orthostatic BP responses (Lyytinen *et al.* 2000, Battacharya *et al.* 2003). Rasagiline may be less likely to be hypotensive than selegiline when given in equivalent doses (Abassi *et al.* 2004).

Not much is known about the possible interrelationship of BP and motor fluctuations. It has been suggested that PD patients have higher BP during the off-stage than during the on-stage (Baratti & Calzetti 1984) and that patients with the on-off type of motor fluctuation have a higher resting HR, a greater orthostatic BP fall, and lower responses to the Valsalva manoeuvre and to cold pressor stimuli during the off-stage than healthy control subjects (Goetz *et al.* 1986).

3 Aims of the study

The purpose of this study was to evaluate the cardiovascular and sudomotor ANS regulation in patients with PD. The more specific aims of the individual studies were:

1. To evaluate dynamic measures of HR behaviour in untreated PD patients, using 24-hour ambulatory ECG recordings.
2. To assess the circadian characteristics of HR behaviour in untreated PD patients, using 24-hour ambulatory ECG recordings.
3. To investigate the characteristics of BP and HR responses in PD patients with and without wearing-off, using clinical observation, sequential BP measurements and the orthostatic test.
4. To evaluate the sweating function in patients with and without wearing-off, using clinical observation and repetitive evaporimetric sweating measurements.
5. To determine the cardiovascular effects of selegiline in advanced PD by using clinical observation, sequential BP measurements and the orthostatic test before and after a 4-week washout period.

4 Material and methods

4.1 Subjects

The studies were carried out in the Department of Neurology at Oulu University Hospital and they were approved by the Ethics Committee of the Faculty of Medicine, University of Oulu. The studies were carried out according to the principles of the Declaration of Helsinki. All patients and control subjects gave their informed consent before their inclusion in the study.

In Study I, 60 consecutive untreated patients with idiopathic PD fulfilling the Parkinson's Disease Society Brain Bank clinical criteria (Daniel & Lees 1993), referred to the Department of Neurology, Oulu University Hospital because of extrapyramidal symptoms, were included in the study. The diagnosis of idiopathic PD was confirmed by a follow-up extending for up to 4 years. Patients with medication or other diseases known to affect the ANS were excluded. The control group consisted of 47 age- and sex-matched healthy volunteers.

In Study II, 47 consecutive untreated patients with idiopathic PD fulfilling the Parkinson's Disease Society Brain Bank clinical criteria (Daniel & Lees 1993), referred to the Department of Neurology, Oulu University Hospital because of extrapyramidal symptoms, were included in the study. The diagnosis of idiopathic PD was confirmed by a follow-up extending for up to 4 years. Patients with medication or other diseases known to affect the ANS were excluded. The control group consisted of 43 age- and sex-matched healthy volunteers.

In Studies III and IV, 37 patients selected from 502 patients with advanced idiopathic PD undergoing follow-ups at the Department of Neurology, Oulu University Hospital, with no medication or other diseases known to affect the ANS, were included in the study. Four patients refused to participate. Two patients were excluded because of too severe motor fluctuations or dyskinesias. A total of 31 patients finished the study, 16 with wearing-off and 15 without wearing-off. 16 age- and sex-matched healthy controls with no medication or diseases affecting the ANS were included in Study IV.

In Study V, 24 patients with advanced PD and wearing-off on selegiline medication, selected from 502 patients undergoing follow-ups at the Department of Neurology, Oulu

University Hospital, with no medication or other diseases known to affect the ANS, were included in the study. Three patients refused to participate. Two patients were excluded because of too severe motor fluctuations. Five patients discontinued the study. A total of 14 patients completed the study.

The clinical characteristics of the patients and healthy controls in the various studies are presented in Table 3. The mean ages of the different patient groups in the studies did not differ significantly. The PD medication of the PD patients in Studies III, IV and V are presented in Tables 4 and 5.

Table 3. Characteristics of the subjects in the various studies.

Study	No. of subjects		Age, mean years (SD, range)	Duration of the disease, mean years (SD)	Hoehn and Yahr stage median (range)	UPDRS total score, median (interquartile range)
	women	men				
Study I						
PD patients	22	32	61.4 (10.9, 38–75)	1.7 (1.6)	1.5 (1.0–3.0)	32 (21–40)
Control subjects	15	32	59.6 (9.4, 42–81)			
Study II						
PD patients	18	26	62.6 (10.2, 38–75)	1.7 (1.7)	1.5 (1.0–3.0)	32 (21–40)
Control subjects	14	29	60.4 (9.2, 42–81)			
Study III						
PD patients						
With wearing-off	6	10	64.2 (9.0, 48–80)	11.3 (5.9)	2.5 (1.5–4.0)	45 (31–66)
Without wearing-off	4	11	65.5 (8.7, 52–78)	4.9 (2.5)	1.5 (1.0–2.5)	27 (19–36)
Study IV						
PD patients						
With wearing-off	6	10	64.2 (9.0, 48–80)	11.3 (5.9)	2.5 (1.5–4.0)	45 (31–66)
Without wearing-off	4	11	65.5 (8.7, 52–78)	4.9 (2.5)	1.5 (1.0–2.5)	27 (19–36)
Control subjects	6	10	62.4 (6.9, 53–79)			
Study V						
PD patients	5	9	66.1 (7.8, 53–80)	11.8 (6.0)	2.5 (1.5–4.0)	44 (35–59)

Table 4. PD medication of the patients with and without wearing-off in Studies III & IV.

Medication	Patients with wearing-off		Patients without wearing-off	
	N	Mean dose mg (range)	N	Mean dose mg (range)
Levodopa	16		15	
morning dose		122 (50–200)		107 (100–150)
total daily dose		606 (250–1000)		353 (200–450)
Pramipexole	5		4	
morning dose		0.25 (0.18–0.36)		0.20 (0.18–0.27)
total daily dose		0.76 (0.54–1.08)		0.61 (0.54–0.81)
Pergolide	2		0	
morning dose		0.38 (0.25–0.50)		-
total daily dose		1.00 (1.00–1.00)		-
Bromocriptine	4		1	
morning dose		3.8 (2.5–5.0)		5.00 (5.00–5.00)
total daily dose		11.9 (7.5–15.0)		15.00 (15.00–15.00)
Entacapone	11		0	
morning dose		200 (200–200)		-
total daily dose		945 (600–1200)		-

Table 5. PD medication of the patients in Study V.

Medication	N	Mean dose mg (range)
Levodopa	14	
Morning dose		125 (50–200)
Total daily dose		636 (250–1000)
Pramipexole	4	
Morning dose		0.27 (0.18–0.36)
Total daily dose		0.81 (0.54–1.08)
Pergolide	2	
Morning dose		0.38 (0.25–0.50)
Total daily dose		1.00 (1.00–1.00)
Bromocriptine	3	
Morning dose		3.3 (2.50–5.00)
Total daily dose		10.8 (7.50–15.00)
Entacapone	11	
Morning dose		200 (200–200)
Total daily dose		1000 (800–1200)

4.2 Methods

4.2.1 Clinical examinations (Studies I & II)

An experienced neurologist examined all the patients in Studies I and II with special attention paid to PD symptoms. The clinical examination was performed before the tests. The patients were graded using the Hoehn and Yahr stages (Hoehn & Yahr 1967) and the UPDRS total score (Fahn *et al.* 1987).

The clinical severity of ANS symptoms was obtained using a 3-point rating scale of 11 different modalities of ANS measures (postural dizziness, disturbances of sweating, urinary function, bowel function, sexual function, HR regulation, salivation, breathing, signs of peripheral circulation disturbances, pupillary reactions and seborrhoea), the dysfunction being graded from 0 to 2 (0 = absent, 1 = mild, 2 = moderate to severe) (Turkka 1987).

4.2.2 Clinical monitoring (Studies III, IV & V)

The tests were started at 8 a.m., and the PD patients with and without wearing-off were observed for up to 4 hours thereafter. After the baseline measurements the morning dose of each patient's individual PD medication was given. The patients were graded using the UPDRS part III (the motor sub score) (Fahn *et al.* 1987) at one hour intervals. The timeline of the tests is presented in Figure 5.

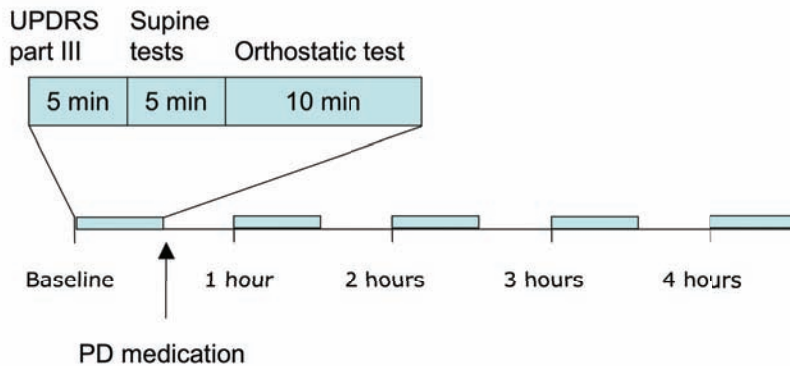


Fig. 5. Timeline of the tests.

4.2.3 Analysis of heart rate variability (Studies I, II & III)

In Studies I and II, all the subjects and controls were monitored for 24 hours with an ambulatory two-channel ECG recorder (Electrocardiocorder[®], Del Mar Avionics, California). All the subjects were encouraged to continue their daily activities during the recordings.

The ECG data were sampled digitally and transferred from an Oxford Medilog scanner to a microcomputer for analysis of the HRV. All the R-R interval time series were first edited automatically. Thereafter the data was manually edited by visual inspection of the R-R intervals. Each R-R interval was passed through a filter that eliminates premature beats and artefacts and deletes the filling gaps (Korpelainen *et al.* 1999). In the final analysis the 24-hour measurements were divided into segments of 8000 R-R intervals (Study I) or of 3600 seconds (Study II), and only segments with >85% sinus beats were included.

An autoregressive model was used to estimate the power spectrum densities of HRV (Kay & Marple 1981). The power spectra were quantified by measuring the area in three frequency bands: <0.04 Hz (very low frequency, VLF), 0.04–0.15 Hz (low frequency, LF) and >0.15–0.4 Hz (high frequency, HF).

For quantitative two-dimensional vector analysis (Poincaré), the SD of the continuous long term R-R interval variability (SD2) and the instantaneous beat-to-beat R-R interval variability (SD1) were analysed (Tulppo *et al.* 1996, Korpelainen *et al.* 1999). In the analysis, the Poincaré plot was first turned 45° clockwise, and the standard deviation of the plot data was then computed around the horizontal axis passing through the centre (SD1). The standard deviation of the continuous long-term R-R-intervals was quantified by turning the plot counter clockwise (SD2) and by computing the data points around the horizontal axis passing through the centre of the data.

The power-law relationship of the R-R interval variability was calculated from the frequency ranges of 10^{-4} to 10^{-2} by a previously described method (Bigger *et al.* 1992). The power spectrum was logarithmically smoothed in the frequency domain, and the power was integrated into bins spaced $0.0167 \log(\text{Hz})$ apart. A robust line-fitting algorithm of $\log(\text{power})$ on $\log(\text{frequency})$ was then applied to the power spectrum between 10^{-4} to 10^{-2} , and the slope of this line was calculated. The frequency band was chosen on the basis of previous observations regarding the linear relationship between $\log(\text{power})$ and $\log(\text{frequency})$ in the frequency band (Bigger *et al.* 1996).

The fractal correlation properties of the HR were quantified by using the detrended fluctuation analysis technique, which is a modified root-mean-square analysis of random walk. The fractal properties were defined separately for short-term (≤ 11 beats, α_1) and long-term (> 11 beats, α_2) correlation of the R-R interval data (short- and long-term scaling exponents) (Iyengar *et al.* 1996).

In Study III, computerized ECG was sampled on a microcomputer using a Nellcor Pulseoximeter (Nellcor, Hayward, CA, USA) for 5 minutes with patients in a supine position and for 10 minutes during the orthostatic test, first at baseline and thereafter hourly during the observation period. The data was carefully manually edited by visual inspection of R-R intervals. Power spectrum and Poincaré analyses were performed as described above.

4.2.4 Blood pressure measurements (Studies III & IV)

In Study III, the BP and HR were measured with an automated sphygmomanometer (BP-103N Mark III, Nippon Colin Co. Ltd., Komaki, Japan) at rest, after standing up, and after 2, 5, 7 and 10 minutes of standing. The measurements were performed at baseline and repeated at one-hour intervals during the observation period.

In Study IV, the tests were repeated after a 4-week selegiline washout period.

4.2.5 Evaporation measurements (Studies IV & V)

During the clinical monitoring an evaporimeter (Evaporimeter EP-3, Servo Med AB, Kinna, Sweden) was used to assess evaporation from the skin surface, and a digital thermometer (TFN-1293, Ebro Electronics GmbH, Ingolstadt, Germany) was used to measure skin temperatures. Sweating and skin temperatures were measured at baseline and at one-hour intervals thereafter on the chest at the angulus sterni and on both hands at the second metacarpo-phalangeal joint. The investigations were performed in a standardized environment in an air-conditioned room with an air temperature of 23–24°C and no airflow. The patients wore standard hospital clothes during the tests.

4.3 Data analysis

The Mann-Whitney U test was used in all studies to compare the demographic data of the PD patients with and without motor fluctuations, and the *de novo* PD patients and the healthy controls. The test was also used to compare the sweating of patients with and without motor fluctuations (Study IV). The results of the clinical evaluation of disease severity (the Hoehn and Yahr staging, the UPDRS scores) and the various measurements of BP, HR and sweating were correlated with the Spearman's correlation coefficients.

The Student's paired-samples t test was used to compare BP and HR values between different study phases within groups (Studies III and V). Student's independent-samples t test was used to compare the BP and HR values of different patient subgroups (Studies III and V). One-way ANOVA and the Bonferroni post hoc test were used to estimate the differences between all the values during the observation period in Study III.

The Friedman test for repeated measurements was used to estimate the significance of the differences between all the measured sweating and temperature values during the observation period (Study IV). The Wilcoxon test was used to compare the values measured at different phases during the observation period (Study IV). A general linear model for repeated measurements was used to compare the sweating values of the whole observation period between the groups (Study IV).

5 Results

5.1 Clinical findings

Most of the *de novo* PD patients (87%) had some subjective symptoms of ANS dysfunction. The most common complaints were peripheral circulatory disturbances (50%), sweating disturbances (42%), urinary disturbances (41%), postural dizziness (37%), constipation (36%), and seborrhoea (28%).

All of the patients with advanced PD in Studies III–V had some subjective symptoms of ANS dysfunction. The most common symptoms were sweating disturbances (81%), peripheral circulatory disturbances (75%), excessive salivation (70%), constipation (59%), urinary disturbances (52%), seborrhoea (48%) and postural dizziness (41%).

5.2 Heart rate variability (Studies I, II & III)

HRV measurements showed that *de novo* PD patients have clear dysfunction of cardiovascular autonomic control. In Study I, all the spectral components ($p<0.01$) and the slope of the power-law relation ($p<0.01$) were lower in the PD patients than in the healthy controls. The UPDRS total score and the motor scores had a negative correlation with the VLF and LF power spectrum values and with the power law relation slopes. Patients with mild hypokinesia had higher HF values than patients with more severe hypokinesia. In Study II, the PD patients had significantly lower LF ($p=0.017$) and HF ($p=0.029$) power spectral components than the controls, and the SD1 value ($p=0.018$) of the Poincaré analysis was suppressed at night. Only the SD1 of the Poincaré analysis was suppressed during the daytime ($p=0.013$). The 24-hour fluctuation of the HF component of the HRV is presented in Figure 6.

In Study III, PD patients with wearing-off had slightly shorter R-R-interval in the supine position during the highest UPDRS motor score phase compared to PD patients without wearing-off. The HRV data is presented in Table 6.

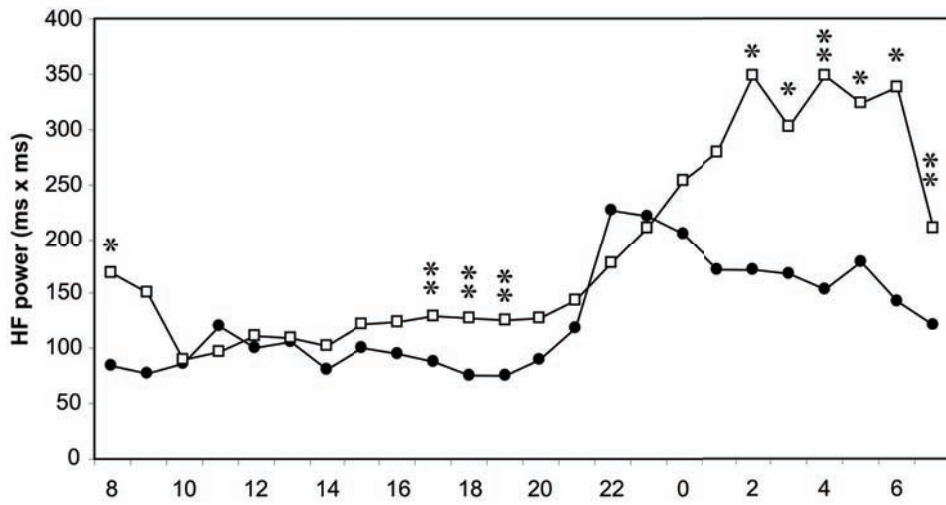


Fig. 6. The 24-hour circadian fluctuation of the high-frequency component of HRV (medians) in patients with PD (●) and in healthy control subjects (□). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for comparison between patients and controls, the Mann-Whitney two-sample test.

Table 6. HRV parameters in PD patients with and without motor fluctuations (Study III).

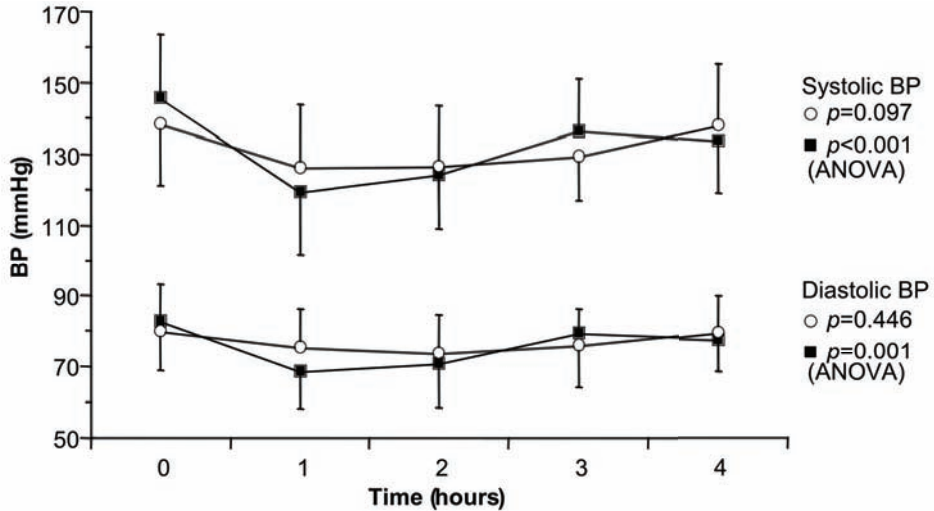
HRV variable	With wearing-off (n=16)	Without wearing-off (n=15)	p-value (Mann-Whitney U)
Supine			
Lowest UPDRS motor score phase			
Mean RR-intervals	825 (778–1000)	946 (818–1063)	0.155
LF-power	0.24 (0.09–0.36)	0.26 (0.09–0.34)	0.793
HF-power	0.17 (0.13–0.25)	0.15 (0.11–0.25)	0.616
SD1	14.9 (11.0–27.4)	16.9 (11.3–22.0)	0.943
SD2	42.7 (27.3–64.5)	62.7 (28.3–71.2)	0.402
Highest UPDRS motor score phase			
Mean RR-intervals	874 (697–1055)	1063 (917–1139)	0.033
LF-power	0.19 (0.09–0.36)	0.25 (0.14–0.32)	0.430
HF-power	0.21 (0.13–0.24)	0.18 (0.13–0.27)	0.720
SD1	17.3 (12.5–24.8)	22.5 (12.1–29.0)	0.325
SD2	39.2 (30.9–58.8)	71.5 (50.0–79.8)	0.022
During orthostatic test			
Lowest UPDRS motor score phase			
Mean RR-intervals	723 (657–848)	791 (719–886)	0.169
LF-power	0.15 (0.06–0.26)	0.12 (0.10–0.19)	0.724
HF-power	0.12 (0.07–0.17)	0.11 (0.08–0.14)	0.762
SD1	10.1 (7.3–18.5)	10.1 (7.6–15.9)	0.880
SD2	35.2 (27.3–55.3)	52.1 (29.7–73.6)	0.336
Highest UPDRS motor score phase			
Mean RR-intervals	740 (662–960)	891 (790–991)	0.183
LF-power	0.17 (0.07–0.35)	0.15 (0.08–0.20)	0.467
HF-power	0.12 (0.08–0.21)	0.11 (0.07–0.17)	0.536
SD1	10.3 (7.1–15.0)	13.1 (8.4–20.5)	0.154
SD2	43.5 (29.0–50.0)	45.8 (33.6–67.4)	0.285

Values are presented as medians (interquartile range).

5.3 Blood pressure, heart rate and wearing-off (Study III)

During the observation period BP significantly fluctuated in PD patients with wearing-off (systolic BP, $p < 0.001$; diastolic BP, $p = 0.001$), but not in PD patients without wearing-off. The mean supine BP was at its highest at the baseline measurement (patients with wearing-off, 145 ± 18 mmHg; patients without wearing-off, 138 ± 17 mmHg), fell during the first hour (patients with wearing-off, 119 ± 17 mmHg; patients without wearing-off, 126 ± 18 mmHg), and then rose again towards the end of the observation period (patients with wearing-off, 136 ± 15 mmHg; patients without wearing-off, 138 ± 18 mmHg). HR did not change during the observation period in patients with ($p = 0.154$) or without ($p = 0.649$) wearing-off phenomenon. There were no significant differences in the absolute BP values

between the patients with and without wearing-off. The supine systolic and diastolic BP values during the observation are presented in Figure 7.



Bonferroni Post Hoc test, in comparison with baseline					
Systolic BP	○ p=	0.498	0.536	1.000	1.000
	■ p=	0.001	0.004	1.000	1.000
Diastolic BP	○ p=	1.000	1.000	1.000	1.000
	■ p=	0.002	0.018	1.000	1.000

Fig. 7. Mean (\pm SD) supine systolic and diastolic blood pressure during the 4-hour observation period after the morning dose of PD medication in patients with (■) and without (○) wearing-off. Bonferroni post hoc test was used to compare baseline to other measurements.

The mean BP values during standing of the patients with wearing-off were similar to those of the patients without wearing-off. The HR responses were similar during the lowest and highest UPDRS motor score phases in both groups. HR was significantly higher during active standing in patients with wearing-off than in those without wearing-off. The HR values during the orthostatic test are presented in Figure 8.

The daily levodopa dose of the patients with wearing-off correlated significantly with the magnitude of change in the UPDRS motor score during the observation (Spearman $R=0.598$, $p=0.007$). Such a correlation was not found in the patients without wearing-off (Spearman $R=0.000$, $p=0.500$). The total daily levodopa dose or use of dopamine agonists did not correlate with the systolic or diastolic BP change during the tests in either group.

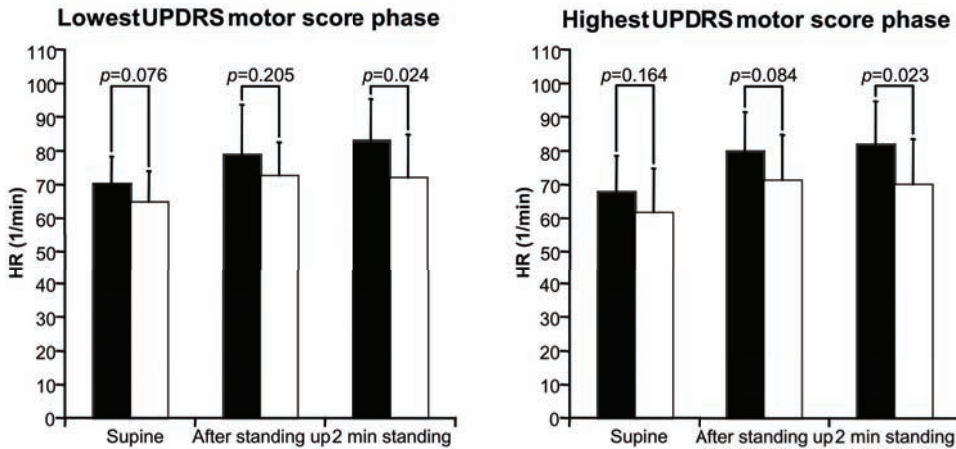


Fig. 8. Mean \pm SD HR in response to the orthostatic test during the lowest and the highest UPDRS motor score phases in patients with (black bars) and without (white bars) wearing-off. *p*-values obtained using the Student's independent-samples *t* test.

5.4 Sweating and wearing-off (Study IV)

In Study IV, sweating was shown to fluctuate in patients with wearing-off, the fluctuation in sweating being significant in patients with wearing-off ($p=0.010$) but not in patients without wearing-off ($p=0.857$).

In the patients with wearing-off, sweating was significantly more abundant during the highest UPDRS motor score phase than during the lowest UPDRS motor score phase on the initially affected hand ($p=0.007$), left hand ($p=0.004$) and right hand ($p=0.034$). The sweating of the chest did not change significantly during the observation period. Skin temperatures did not fluctuate in the measured sites. The patients without wearing-off showed no fluctuation of sweating.

Sweating of the left hand ($p<0.001$), right hand ($p<0.001$) and the initially affected hand ($p=0.008$) during the whole observation period were significantly higher in patients with wearing-off than in those without wearing-off. The measured skin temperatures in the right hand ($p=0.040$) but not in the left hand, the initially affected hand or the chest were slightly cooler in the patients without wearing-off than in those with wearing-off. The UPDRS motor scores and sweating values of PD patients with and without motor fluctuations are presented in Table 7.

The patients with motor fluctuations had significantly more sweating during the highest UPDRS motor score phase than the healthy controls (left hand, $p=0.008$; right hand, $p=0.050$). The sweating of the patients without motor fluctuation did not differ significantly from that of the healthy controls.

*Table 7. UPDRS motor scores and sweating (g/m²/h) in patients with Parkinson's disease with and without wearing-off. Values are presented as medians (interquartile range). * $p < 0.05$, ** $p < 0.01$ comparing values at the highest and lowest UPDRS motor score with each other (Wilcoxon) (Study IV).*

Variable	With wearing-off (n=16)	Without wearing-off (n=15)	Controls (n=16)
UPDRS motor score			
Baseline	31 (22–36)	17 (11–19)	
Lowest UPDRS motor score	14 (11–20)	16 (10–18)	
Highest UPDRS motor score	33 (23–42)	17 (11–20)	
Sweating			
Initially affected hand			
At baseline	7.3 (23–42)	5.5 (4.3–9.1)	
At lowest UPDRS motor score	7.6 (5.3–9.5)	4.9 (4.3–9.3)	
At highest UPDRS motor score	8.9 (5.7–11.3) **	6.0 (4.0–8.8)	
Left hand			
At baseline	7.3 (4.6–10.5)	6.0 (4.6–10.9)	5.5 (4.0–7.0)
At lowest UPDRS motor score	6.4 (4.6–9.2)	5.5 (4.3–10.3)	
At highest UPDRS motor score	8.4 (6.1–11.0) **	6.2 (4.3–9.2)	
Right hand			
At baseline	6.1 (4.2–7.8)	5.9 (3.6–11.9)	5.5 (4.0–7.0)
At lowest UPDRS motor score	6.0 (3.9–9.6)	6.3 (4.6–10.0)	
At highest UPDRS motor score	8.0 (5.0–12.5) *	6.0 (4.5–9.4)	
Chest			
At baseline	3.6 (3.0–6.7)	3.4 (3.0–4.0)	
At lowest UPDRS motor score	3.7 (3.1–6.4)	3.2 (2.3–4.3)	
At highest UPDRS motor score	4.6 (2.7–8.2)	2.3 (3.4–4.3)	

5.5 Selegiline withdrawal in advanced PD patients (Study V)

Selegiline washout affected BP reactions. The systolic BP was significantly higher during the on-stage while on selegiline medication in the supine position (132±21mmHg vs. 117±13mmHg, $p=0.026$) and after 10 minutes of standing (128±21mmHg vs. 119±21mmHg, $p=0.014$) than after selegiline washout. The diastolic BP right after standing up was also significantly higher during the on-stage in patients on selegiline medication than after selegiline washout (68±14mmHg vs. 63±13mmHg, $p=0.036$). The HR and BP responses during the on-stage before and after selegiline washout are presented in Figure 9.

During the off-stage both the systolic and diastolic BP values for patients on selegiline were similar to those after the washout.

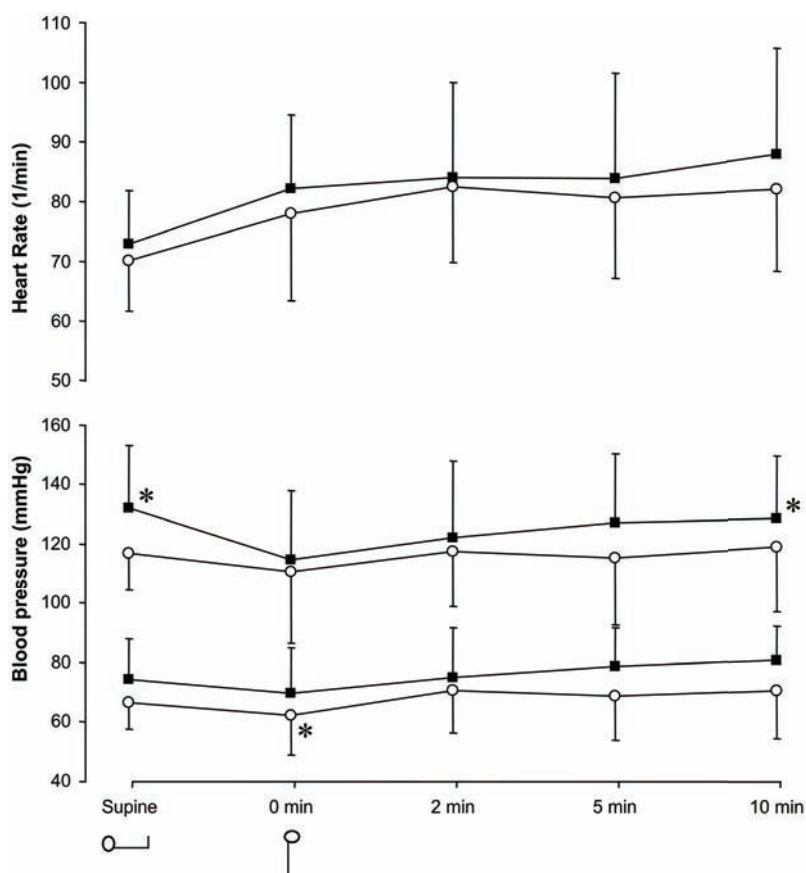


Fig. 9. HR and BP responses to the orthostatic test during the on-stage on selegiline medication (■) and after washout (○). * $p < 0.05$ using the paired-samples t test.

The initial drop in systolic BP in the orthostatic test during the on-stage was significantly higher before the § selegiline washout compared to that after the washout. However, selegiline withdrawal did not significantly change the number of patients with orthostatic hypotension.

The UPDRS motor scores, sweating and skin temperatures of the PD patients while on selegiline medication and after washout are presented in Table 8. There were no significant differences between the measures. However, five patients discontinued the study during the wash-out because of aggravation of PD symptoms.

Table 8. UPDRS scores, sweating and skin temperatures of the PD patients during the on and off phases before and after selegiline washout. Values are presented as medians (interquartile range) (Study V).

Variable	On selegiline (n=14)	After washout (n=14)
UPDRS motor scores		
On phase	14 (9–20)	13 (10–20)
Off phase	29 (21–37)	33 (23–40)
Evaporation (g/m ² /h)		
On phase		
Left hand	6.9 (4.3–9.7)	6.8 (4.7–9.3)
Right hand	6.9 (4.8–8.9)	7.0 (4.6–10.0)
Chest	5.2 (2.9–8.4)	4.6 (3.3–6.9)
Primarily affected hand	6.9 (4.6–10.3)	8.3 (5.6–9.6)
Off phase		
Left hand	10.7 (4.6–27.2)	8.9 (6.2–11.2)
Right hand	8.6 (5.8–10.4)	9.5 (5.2–13.0)
Chest	5.2 (2.8–12.1)	4.7 (2.8–8.7)
Primarily affected hand	10.6 (5.2–27.2)	9.6 (6.0–12.1)
Skin temperature (°C)		
On phase		
Left hand	31.8 (29.7–32.4)	31.0 (30.3–31.5)
Right hand	31.7 (30.1–32.9)	31.4 (30.5–31.8)
Chest	33.7 (33.1–34.3)	33.2 (32.8–33.8)
Primarily affected hand	31.9 (30.0–32.6)	31.0 (30.5–32.0)
Off phase		
Left hand	31.5 (29.7–32.6)	31.7 (29.9–32.7)
Right hand	32.1 (29.9–32.4)	31.7 (29.7–32.7)
Chest	33.6 (32.9–34.5)	33.3 (33.0–33.8)
Primarily affected hand	31.8 (29.5–32.6)	32.0 (29.9–32.9)

6 Discussion

6.1 General aspects

Autonomic dysfunction in patients with PD patients has been recognized since the original description by James Parkinson in 1817. Although prominent ANS dysfunction is mostly associated with advanced PD, it affects patients even in the early phases of the disease. The symptoms of ANS dysfunction, especially orthostatic hypotension and excessive sweating, may greatly compromise the patients' well being. After 15 years of PD diagnosis the most disabling long-term problems seem to be non-levodopa responsive symptoms including those associated with autonomic dysfunction (Hely *et al.* 2005).

Postmortem studies have shown that the pathologic process in PD involves both the sympathetic and the parasympathetic systems, Lewy bodies being found throughout the CAN (Jellinger 1999). The PD process also involves the peripheral ganglia of the sympathetic and parasympathetic nervous systems as well as the hypothalamus (Wakabayashi & Takahashi 1997). Involvement of the peripheral portions of the ANS has also been demonstrated in vivo, as loss of sympathetic innervation of the heart in early PD has been shown by isotope imaging techniques (Goldstein *et al.* 2000, Oka *et al.* 2006).

Motor fluctuations pose another source of discomfort to PD patients, but fluctuation of non-motor symptoms has also been recognized (Raudino 2001). There have been some studies suggesting that PD patients have raised BP and increased sweating during off-stage (Baratti & Calzetti 1984, Goetz *et al.* 1986), but the available data is fairly limited.

The present study was designed to assess the possible autonomic dysfunction in early PD by measuring HRV from 24-hour ambulatory ECG recordings in newly diagnosed PD patients who had never received PD medication. *De novo* PD patients were followed for up to 4 years to confirm the accuracy of the diagnosis. The study was also designed to quantify the fluctuation of BP, HR and sweating in patients with advanced PD with and without the wearing-off type of motor fluctuation. For the first time, fluctuation of autonomic functions was observed with careful clinical monitoring in standardized conditions.

6.2 Cardiovascular autonomic dysfunction in early PD

Because PD medication is known to affect cardiovascular responses (Haapaniemi *et al.* 2000a, Franchi *et al.* 2001, Cavallini *et al.* 1991, Kujawa *et al.* 2000), studies on untreated *de novo* patients give the most accurate information on ANS involvement in the disease process in PD. Earlier studies have shown cardiovascular autonomic dysfunction in *de novo* PD patients using cardiovascular reflex tests. Abnormalities include suppressed HR responses to breathing, the Valsalva manoeuvre and tilting, reflecting parasympathetic dysfunction of cardiovascular control (Mesec *et al.* 1999, Haapaniemi *et al.* 2000a), and pronounced BP fall in response to tilting, indicating sympathetic dysfunction (Turkka *et al.* 1997). Loss of sympathetic innervation of the heart in early PD has also been reported (Goldstein *et al.* 2000, Oka *et al.* 2006). As the disease process is also known to involve the peripheral ganglia of the sympathetic and parasympathetic nervous systems (Wakabayashi & Takahashi 1997), these findings suggest that PD also involves the postganglionic portion of the ANS.

Circadian fluctuation of HRV is impaired in various cardiovascular and neurological diseases, including coronary heart disease (Huikuri *et al.* 1994) and stroke (Korpelainen *et al.* 1997). HRV dynamics have been shown to predict mortality in the elderly (Huikuri *et al.* 1998) as well as in people who have suffered an acute myocardial infarct (Huikuri *et al.* 2000) or ischemic stroke (Mäkikallio *et al.* 2004). The clinical significance of suppressed HRV in PD, however, may be different from that in cardiovascular diseases, because PD is a degenerative disease of the CNS and is not known to be associated with increased risk of sudden death.

Diminished HRV during night time has been found both in *de novo* PD patients (Kallio *et al.* 2004) and in patients with advanced PD (Mastrocola *et al.* 1999), results reflecting combined sympathetic and parasympathetic dysfunction. Studies on sleep movements have found disturbed HR reactions to sleep movements in PD patients both during non-REM and REM sleep, reflecting combined sympathetic and parasympathetic defects in the cardiovascular regulation (Laihininen *et al.* 1987, Ferini-Strambi *et al.* 1992, Ferini-Strambi & Smirne 1997, Kallio *et al.* 2004). This dysfunction of cardiovascular autonomic control is thought to correlate with the severity of the disease and with the duration of its medication (van Dijk *et al.* 1993, Devos *et al.* 2003).

The results of the current study show that the HRV is clearly suppressed during night time, but it is also suppressed during the daytime, though to a lesser extent. All the HRV power spectrum components, SD1 of the Poincaré analysis and the SDNN values, were lower in the patients with PD than in the controls, and the dysfunction seems to be more severe in patients with more severe Parkinson's disease. The results of the present study give further clinical support for the concept, based on pathological studies, that the pathological disease process in PD already extensively involves the autonomic centres of the CNS by the time the clinical motor symptoms of PD first emerge. However, the methods used here to study HRV cannot separate the possible peripheral nervous system involvement from central autonomic dysfunction. Because of great interindividual variability in HRV parameters, HRV analysis cannot be used to assess cardiovascular autonomic control in individual patients.

In conclusion, our finding that in untreated *de novo* PD patients the spectral components of the HRV are significantly suppressed during night time, and the SD1 Poincaré component all day, suggests that the parasympathetic cardiac control is already affected by the pathological process of the disease in *de novo* patients.

6.3 Cardiovascular autonomic dysfunction in advanced PD

Wearing-off is a frequent complication of long-term levodopa therapy, with prevalence increasing at a rate of 10% per year (Denny & Behari 1999, Barone 2003). It has been suggested that PD patients have higher BP during the off-stage than during the on-stage (Baratti & Calzetti 1984), and higher resting HR, greater orthostatic BP fall, and lower responses to the Valsalva manoeuvre and to cold pressor stimuli during the off-stage than healthy control subjects (Goetz *et al.* 1986).

The action of dopamine on the cardiovascular system is complicated. Low infusion rates of dopamine cause vasodilatation of renal and splanchnic vascular beds and increase tubular sodium excretion. Intermediate infusion rates increase CO by stimulation of cardiac adrenergic β 1-receptors. High doses of dopamine induce stimulation of adrenergic α -receptors and thus cause vasoconstriction and an increase in systemic BP (Emilien *et al.* 1999). Thus dopaminergic PD medication could potentially affect systemic BP by acting on central or peripheral dopamine receptors.

Dopaminergic PD medication is known to affect cardiovascular autonomic responses, an action that could be explained by the role of dopamine in cardiovascular autonomic regulation. Dopamine agonists have been found to lower BP responses to tilting (Haapaniemi *et al.* 2000a, Kujawa *et al.* 2000), although it has been suggested that dopamine agonists do not alter the cardiovascular effects of levodopa when the two are given together (Bouhaddi *et al.* 2004). The effects of levodopa on BP are controversial. It has been found to diminish the BP fall in response to tilting (Haapaniemi *et al.* 2000a), and reduce BP, HR, and plasma catecholamine levels when first administered to newly diagnosed PD patients (Bouhaddi *et al.* 2004). It has been proposed that orthostatic hypotension in PD patients may be related to higher levodopa dosage (Senard *et al.* 1997), although some claim that orthostatic hypotension is a phenomenon independent of levodopa treatment (Goldstein *et al.* 2005). In the present study all patients were on levodopa and some patients also used dopamine agonist medication, but no correlation was found between levodopa doses and BP responses. There were no differences between patients with and without dopamine agonist medication. This finding could be because of the small number of patients, or because of adaptive changes caused by long-term treatment.

HRV decrease seems to correlate with the disease severity (Devos *et al.* 2004), a finding confirmed in Study I. The results of the current study, however, did not find clearly significant differences between PD patients with and without wearing-off. This is likely due to the small sample size and the large interindividual variability of HRV parameters.

The results of our study show that BP fluctuates in conjunction with motor performance in PD patients with wearing-off. However, BP rises when motor

performance declines and falls as the motor performance improves. These changes in BP may arise from increased systemic vascular resistance during poor motor disability, possibly related to diminished dopaminergic stimulation. The fluctuation of BP is clearly seen in patients with wearing-off as well as in both patients with and without dopamine agonist medication. This suggests that motor performance and the cardiovascular autonomic regulation may be interrelated through the disease process itself. However, the direct action of PD medication on the peripheral dopamine receptors responsible for vasodilatation, or a direct effect on central ANS control centres, cannot be excluded. The mean difference between supine systolic BP during the on-stage and off-stage in patients with wearing-off was over 25mmHg and thus could be clinically significant, although no clear difference in rate of symptomatic orthostatic hypotension was seen. Therefore PD patients with wearing-off with symptoms of orthostatic hypotension should be monitored in both the on-stage and the off-stage.

6.4 Sweating dysfunction in advanced PD

One major function of the human skin is to take part in maintaining the water balance and controlling the heat balance of the body by sweating and superficial blood flow regulation. Sweating is a fundamental part of the thermoregulatory system, and is controlled mainly by sympathetic outflow to the skin (Benarroch 1997).

Sweating dysfunctions are a common complaint among PD patients affecting up to 64% of PD patients (Swinn *et al.* 2003). Earlier studies have shown not only reduced sweating in the trunk and limbs and compensatory hyperhidrosis on the face (Appenzeller & Goss 1971), but also increased sweating both at rest and in response to a heat stimulus (Turkka & Myllylä 1987). PD patients have been reported to have various pathological sympathetic skin responses indicating both dysfunction of central sudomotor regulation and dysfunction of the postganglionic sympathetic neurons, and these responses seem to get more pronounced with the progression of the disease (Wang *et al.* 1993, Fusina *et al.* 1999, Haapaniemi *et al.* 2000b, Zakrzewska-Pniewska & Jamrozik 2003).

Motor fluctuations also affect sweating. Several PD patients have reported increased sweating during the off-stage and dyskinesias (Swinn *et al.* 2003). PD patients with motor fluctuations seem to have increased sweating responses to heat stimuli during the off-stage, that resolve during the on-stage, suggesting that sweating fluctuates with motor performance (Goetz *et al.* 1986). The excessive sweating during the off-stage is thought to correlate with plasma levodopa levels (Sage & Mark 1995). The present study, corroborating earlier findings, shows that sweating fluctuates with motor performance in PD patients with wearing-off, sweating increasing as the motor performance becomes progressively impaired.

In the present study patients with wearing-off did not show increased sweating during the baseline measurement despite poor motor performance at that time. This could be an effect of sleep benefit (Merello *et al.* 1997) or the natural circadian rhythms of e.g. cortisol and thermoregulation (Kenney *et al.* 2003). It could also reflect diurnal fluctuation and rebound worsening after the beneficial effect of levodopa has worn off (Quinn 1998).

In the current study the PD patients with wearing-off had significant fluctuation of sweating in contrast to the patients without wearing-off. Sweating was more abundant in the patients with wearing-off during the highest UPDRS motor score phase compared to patients without wearing-off and healthy controls. These findings indicate that the thermoregulatory ANS control is related to the wearing-off type of motor fluctuations and that thermoregulatory dysfunction may worsen with time as the disease progresses. However, the increase in sweating could also be a thermoregulatory response following rigidity during the highest UPDRS motor score phase, although no correlation between various UPDRS subscores (rigidity and tremor) and sweating were found.

6.5 Selegiline and autonomic dysfunction in advanced PD

MAO-B inhibitor selegiline has a mild to moderate effect on PD symptoms and it seems to reduce the risk of levodopa complications (Myllylä *et al.* 1992, The Parkinson Study Group 1993). It is thought to affect the ANS functions, although the effect of selegiline on BP and orthostatic hypotension is not clear. When selegiline or levodopa/carbidopa are given alone, some studies have reported similar effects on orthostatic BP responses (Battacharya *et al.* 2003), while others have reported a higher frequency of orthostatic hypotension in patients receiving selegiline (Turkka *et al.* 1997, Haapaniemi *et al.* 2000a, Korchounov *et al.* 2004). Levodopa is known to frequently cause both supine and orthostatic hypotension (Yahr MD *et al.* 1969), and combining it with a peripheral dopadecarboxylase inhibitor prevents supine but not orthostatic hypotension (Goetz *et al.* 1986, Haapaniemi *et al.* 2000b). It has been found that PD patients treated with levodopa/carbidopa combined with selegiline have a higher frequency of orthostatic hypotension than those patients treated with selegiline alone (Turkka *et al.* 1987), but another study has reported similar orthostatic BP responses for both of the treatment groups (Battacharya *et al.* 2003). The peripheral mechanisms of levodopa's hypotensive effects are mediated through its end product, dopamine, which is an important regulator of systemic BP. Selegiline could possibly potentiate the central hypotensive effect of levodopa by increasing dopamine availability through MAO-B inhibition (Myllylä *et al.* 1992). Changes in catecholamine turnover and decreased CO have also been suggested as being responsible for the hypotensive effect of selegiline in PD patients (Churchyard *et al.* 1997). In animal models of heart failure selegiline exerted a sympatholytic and cardiac neuroprotective effect and may thus be beneficial in heart failure (Shite *et al.* 2000, Qin *et al.* 2003). The deleterious effect of selegiline on the ANS in PD patients may therefore be partly explained by the distinct cardiac sympathetic denervation that occurs even in the early phases of the disease, denervation that is indeed aggravated by selegiline (Oka *et al.* 2006).

The present study shows that cessation of long-standing selegiline medication in PD patients with wearing-off both decreases BP at rest and diminishes orthostatic BP drop during the on-stage. However, despite the diminishing of the orthostatic reaction, the number of patients with orthostatic hypotension did not change in the present study. However, all the patients had advanced PD, all were on levodopa and several patients were also taking dopamine agonists, which are known to increase the risk of orthostatic

hypotension (Senard *et al.* 1997, Kujawa *et al.* 2000). Our findings conform with earlier studies that have also reported a fall in supine systolic and diastolic BP and an increase in plasma noradrenaline and adrenaline levels in response to head-up tilt after the stopping of long-term selegiline treatment (Churchyard *et al.* 1997, Churchyard *et al.* 1999). Most patients seem to tolerate selegiline withdrawal without any aggravation of motor symptoms, although more than a quarter of the patients in our study had to discontinue the study due to aggravation of PD symptoms. None of the patients who went through the washout continued with selegiline later on. The observed supine systolic BP fall and diminished orthostatic reaction may be caused by a supine suppressor effect of selegiline. In clinical practice, withdrawal of selegiline may be helpful in PD patients with frequent symptoms of orthostatic hypotension.

The data available for the effect of selegiline on sweating is limited, though the drug has been reported to diminish sympathetic skin response amplitudes in early PD (Haapaniemi *et al.* 2000b). In the present study, the cessation of long-term selegiline treatment in patients with wearing-off did not affect sweating.

7 Conclusions

PD involves the ANS early in its course and the symptoms of ANS dysfunction seem to increase over the disease course.

1. PD causes dysfunction of the autonomic cardiovascular regulation that can be assessed by HRV analysis. The dysfunction seems to be more pronounced in patients with more severe PD.
2. In untreated *de novo* PD patients several components of HRV are significantly suppressed during the night, but only the measures of sympathetic activity during the day, suggesting that the sympathetic cardiovascular control is affected more severely than the parasympathetic one by the pathological processes of the disease.
3. BP seems to fluctuate with motor impairment in PD patients with wearing-off, which may represent autonomic dysfunction caused by the PD process itself, the effect of the PD medication, or both.
4. Sweating fluctuates in conjunction with motor dysfunction in PD patients with wearing-off, but not in PD patients without wearing-off. Sweating seems to be more abundant in PD patients with wearing-off than in PD patients without wearing-off.
5. Selegiline withdrawal decreases systolic BP during the on-stage in a supine position as well as during the orthostatic test. The drop of BP during the orthostatic test diminishes after selegiline withdrawal.

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- I Haapaniemi TH, Pursiainen V, Korpelainen JT, Huikuri HV, Sotaniemi KA & Myllylä VV (2001) Ambulatory ECG and analysis of heart rate variability in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 70: 305-310.
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