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Multi-organ autonomic dysfunction in Parkinson disease

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Abstract

Both pathologic and clinical studies of autonomic pathways have expanded the concept of Parkinson disease (PD) from a movement disorder to a multi-level widespread neurodegenerative process with non-motor features spanning several organ systems. This review integrates neuropathologic findings and autonomic physiology in PD as it relates to end organ autonomic function. Symptoms, pathology and physiology of the cardiovascular, skin/sweat gland, urinary, gastrointestinal, pupillary and neuroendocrine systems can be probed by autopsy, biopsy and non-invasive electrophysiological techniques *in vivo* which assess autonomic anatomy and function. There is mounting evidence that PD affects a chain of neurons in autonomic pathways. Consequently, autonomic physiology may serve as a window into non-motor PD progression and allow the development of mechanistically based treatment strategies for several non-motor features of PD. End-organ physiologic markers may be used to inform a model of PD pathophysiology and non-motor progression.

Keywords

Parkinson; dysautonomia; physiology; non-motor features; autonomic testing

Introduction

Parkinson disease (PD) is diagnosed clinically by a characteristic movement disorder responsive to dopaminergic therapy. Both pathological and clinical studies demonstrate that non-motor symptoms are also intrinsic to PD, occur earlier and impact quality of life more than motor symptoms[1] leading to the recent American Academy of Neurology publication of practice parameters for the treatment of non-motor symptoms of PD[2]. Autonomic physiology in PD is of particular interest because it underlies several non-motor symptoms, including orthostatic dizziness, constipation, urinary problems, erectile dysfunction, drooling, sweating and swallowing problems[3]. Autonomic pathways are also of interest because studies suggest PD neuropathology occurs early in the course of disease in

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peripheral structures, and may spread along autonomic pathways to involve the central nervous system[4–6].

Parkinson disease neuropathology in the Autonomic Nervous System

Anatomically, the autonomic nervous system can be divided into central autonomic networks, sympathetic pathways, parasympathetic pathways and the enteric nervous system. Central autonomic networks integrate autonomic function, linking the neocortex, diencephalon and brainstem[7]. At its core is the nucleus tractus solitarius (NTS) which integrates somatic and autonomic nervous systems and maintains homeostasis with projections to the hypothalamus, limbic structures and descending autonomic tracts. PD pathology has been characterized by intraneuronal inclusions which contain α -synuclein known as Lewy neurites or Lewy bodies (Lewy-related pathology). α -synuclein is a presynaptic protein thought to maintain synaptic integrity and be involved with regulation of dopamine synthesis. Although often seen in the absence of neuronal loss[4], evidence suggests that α -synuclein aggregation is a precursor to neurodegeneration[8]. PD pathology has been observed in a chain of neurons forming autonomic pathways including: the hypothalamus[6], preganglionic parasympathetic projection neurons in the dorsal motor nucleus of the vagus[9] and pre-ganglionic and post-ganglionic sympathetic projection neurons (including the intermediomedial and interomediolateral nuclei of the spinal cord) [4]. PD pathology has also been found in several end-organs including the submandibular gland, lower esophagus, duodenum, pancreas, bronchus, larynx, epicardium, adrenal medulla, parathyroid and ovary[5]. Figure 1 illustrates most areas within autonomic pathways where PD pathology has been found.

Pathological evidence that the autonomic nervous system is involved early in the course of PD comes from studies of incidental Lewy body disease (ILDB). ILDB is a pathological diagnosis given to cases which have no clinical history of Parkinsonism and demonstrating the presence of Lewy-related pathology in the substantia nigra and/or locus coeruleus on autopsy. It is thought that ILDB may be a precursor of PD. In ILDB, 70–100% of cases have pathological findings in the sacral and thoracic segments of the spinal cord as well as paravertebral sympathetic ganglia similar to PD. ILDB also demonstrates involvement of autonomic innervation to several organ systems to be discussed below including cardiovascular, urinary and gastrointestinal systems[10,11].

Cardiovascular System

Cardiovascular (CV) autonomic dysfunction is common in PD. Dizziness is the most reported CV symptom, namely orthostatic hypotension (OH) (fall in blood pressure of ≥ 20 mmHg systolic or 10 mmHg diastolic when moving from supine to standing), and has a prevalence of up to 58% in PD[12].

Cardiovascular autonomic pathways which control blood pressure are comprised of descending sympathetic fibers from central autonomic networks which synapse in the intermediolateral and intermediomedial columns of the spinal cord onto preganglionic fibers projecting to thoracic paravertebral ganglia. Postganglionic efferents go on to innervate the heart and blood vessels. Parasympathetic fibers from the dorsal motor nucleus of the vagus and nucleus ambiguus descend via the vagus nerve to innervate the heart. In PD, α -synuclein has been found in the dorsal motor nucleus of the vagus, vagus nerve, spinal sympathetic preganglionic neurons and sympathetic postganglionic nerves of the epicardium[4,8,9,13]. The intermediolateral nucleus at the levels of the upper and lower thoracic segments (T2 and T9) have been found to have 30–40% fewer neurons in PD specimens compared to age-matched controls. Lewy bodies have been found in remaining intermediolateral neurons in almost all PD cases[14]. Peripheral, post-ganglionic loss of

sympathetic innervation of the heart is also common in PD and has been confirmed *in vivo* by low myocardial concentrations of sympathetic radiographic ligands 123 I-metaiodobenzylguanidine (MIBG) and 6- 18 F]fluorodopamine[15,16]. In pathological studies of ILDB α -synuclein has been found in sympathetic ganglia in 50–80% of cases[5,8,11]. Looking at both ILDB and PD, Orimo and colleagues have described a series of observations that underlie cardiac sympathetic neurodegeneration. In ILDB they found a subset with no neuronal cell loss of cardiac sympathetic ganglia and a subset in which axonal loss was present. In ILDB with no neuronal cell loss, α -synuclein was found mostly in distal axons in cardiac sympathetic nerves with minimal accumulation within the cell bodies in paravertebral sympathetic ganglia. In ILDB with axonal loss, there was less α -synuclein in distal axons and more in the ganglia. In PD, minimal to no α -synuclein was seen in distal axons (presumably because of axonal loss) and α -synuclein was more abundant in the ganglia. This suggests a chronological and dynamic relationship between α -synuclein aggregation and axonal degeneration in the cardiac sympathetic nervous system in which α -synuclein first aggregates in the axon early in the course of PD and then later is found in the cell body as axonal loss occurs[8].

Blood pressure responses predominantly reflect sympathetically mediated vasoconstriction and heart rate responses predominantly reflect parasympathetic responses via vagal output to the sinus node. The baroreflex is thought to be impaired in PD. In normal circumstances, a drop in blood pressure results in reflexive vasoconstriction to maintain blood pressure. This is seen in when performing the Valsalva maneuver. In the Valsalva, a person is asked to strain which increases intrathoracic pressure and impairs venous return to the heart resulting in a transient fall in systolic blood pressure. The baroreflex causes a compensatory vasoconstriction which then increases systolic blood pressure. This is absent or attenuated in PD[17].

Heart rate variability (HRV) with the use of cardiovascular reflexes has also been used to study autonomic cardiac physiology in PD. Respiratory sinus arrhythmia (RSA) is an approximation of vagal efferent activity to the sino-atrial node[18]. RSA is lower at both rest and with deep breathing in treated and untreated (early) PD patients compared to age and sex-matched controls[19,20]. Furthermore, HRV is lower in a minority of PD patients with reduced cardiac MIBG uptake, which tends to decrease with PD progression[21]. This suggests that pathological changes in cardiac autonomic innervation exist without the development of detectable sympathetic and parasympathetic insufficiency at a physiological level in the cardiovascular system in PD.

Skin and Sweat glands

Both excessive sweating (hyperhidrosis) and decreased sweating are commonly reported in PD. These involve thermoregulatory eccrine sweat glands which are distributed over most of the body surface. Sweating is controlled by sympathetic signals originating in the hypothalamic preoptic sweat center, synapsing with neurons in the intermediolateral cell columns which project to unmyelinated post-ganglionic class C fibers in the paravertebral ganglia that form peripheral nerves to reach the sweat glands. In addition to PD pathology in sympathetic intermediolateral nuclei of the spinal cord[4], skin biopsies have also demonstrated lower cutaneous autonomic innervation in blood vessels, sweat glands and erector pili muscles in PD[22]. Autopsy studies have demonstrated α -synuclein to be present in unmyelinated fibers of the dermis in 20/85 cases with CNS Lewy body pathology[23]. Another autopsy study found no α -synuclein skin staining in 0/11 cases of PD, ILDB and dementia with Lewy bodies[5]. *In vivo* skin biopsies in PD patients found 2/20 (10%) to stain for α -synuclein. There were several methodological differences among these studies

that could account for the differing percentages of positive biopsied cases[24], though heterogeneity within PD may also play a role.

The sympathetic skin response (SSR) is recorded by electrodes on the palmar and plantar surfaces. SSR is evoked electrodermal activity (EDA) that originates from sweat glands and adjacent skin. A peripheral nerve afferent is electrically stimulated and the EDA is recorded. The EDA is generally biphasic with an initial negativity followed by a positive potential. The initial negativity is from the sweat gland[7]. Positivity varies with circulation, chest pressure, cholinergic activity and arousal. The presence of EDA depends on the integrity of cutaneous innervation, hydration and perspiration, making the EDA difficult to interpret. Many, but not all studies report the SSR in PD to be abnormal (often with a longer latency and diminished amplitude in PD)[21,25–30]. It has been postulated that excessive sweating in PD may occur as a compensatory reaction to lower sympathetic function in the extremities[31].

Sweat function can also be measured by thermoregulatory sweat testing (TST) and the quantitative sudomotor axon-reflex test (QSART). The TST assesses the sweat response mediated by preganglionic and post ganglionic pathways. Subjects are induced to sweat by heat and, causing an indicator powder on the skin to change color. Percent anhidrosis in PD is less than those with multisystem atrophy[32–34]. The QSART assesses the reflex mediated by the postganglionic sympathetic sudomotor axon. An impulse is delivered antidromically from the sweat gland until reaches a branch point where another axon also meets the same peripheral nerve. The impulse then travels orthodromically down that axon to evoke a sweat response which is recorded. In PD patients with confirmed sympathetic cardiac denervation, the QSART was found to be normal suggesting selective loss of post-ganglionic catecholaminergic but not cholinergic nerves[35], while another study found QSART responses to be lower in PD compared to controls[36]. Skin sympathetic peroneal nerve activity has also been found to be lower in PD compared to controls[37], suggesting postganglionic sympathetic sudomotor lesions in PD.

Urinary tract

The prevalence of symptoms attributable to the lower urinary tract (bladder and urethra) is as high as 60% in PD. This includes nocturia, urgency, frequency, incontinence and difficulty in voiding, attributable to bladder overactivity[38]. The bladder is primarily innervated by the parasympathetic pelvic nerve and the urethra by the sympathetic hypogastric nerve and somatic pudendal nerve[38], which receive descending projections from the pontine micturition center. PD neuropathology has been found in pre-ganglionic and post-ganglionic sympathetic neurons as well as sacral parasympathetic nuclei[4,39]. α -synuclein histopathology has been observed in the sacral spinal cord, pelvic plexus and genitourinary tract in PD[5,6]. ILDB cases have also been reported to contain α -synuclein in sacral parasympathetic nuclei[11]. Urodynamic abnormalities in PD include reduced bladder capacity, detrusor overactivity, external sphincter relaxation, detrusor weakness and mild urethral obstruction[38], reflecting parasympathetic and somatic dysfunction.

Gastrointestinal tract

Gastrointestinal (GI) autonomic pathways comprise sympathetic fibers from central autonomic networks which descend in the spinal cord and synapse in the intermediolateral and intermediomedial grey matter onto preganglionic fibers which exit the cord to synapse on thoracic paravertebral ganglia. Postganglionic efferents form splanchnic nerves which project to the celiac ganglion. From here, sympathetic neurons innervate the enteric plexus within the GI tract. Parasympathetic fibers from the dorsal motor nucleus of the vagus descend via the vagus nerve to innervate the GI tract. The dorsal motor nucleus of the vagus,

vagus nerve, sacral parasympathetic nuclei, sympathetic pre-ganglionic and post-ganglionic neurons in the celiac ganglion and the enteric nervous system all have been found to contain PD pathology (α -synuclein)[4,40,41]. Both Auerbach's and Meissner's plexuses have been found to contain Lewy-related pathology in PD as well as ILBD, most frequently in the lower esophagus[5,11,42]. Lewy-related pathology has also been seen in the submandibular glands, stomach, small intestine, colon and rectum in PD and seem to follow a rostrocaudal gradient with the submandibular glands having the most frequency and density of α -synuclein staining and the rectum the least[5]. Inhibitory motor neurons which use vasoactive intestinal peptide and receive vagal preganglionic fibers seem particularly affected in PD[43]. The medullary raphe is also involved, which is thought to affect supraspinal control of defecation.

Lower Gastrointestinal tract

The lower GI tract includes all elements below the stomach, including the small intestine, large intestine and anus. In PD, $\geq 50\%$ report lower GI symptoms such as constipation, diarrhea and fecal incontinence[38]. The enteric nervous system generates the peristaltic reflex of the lower gastrointestinal tract. Contractions are mediated by cholinergic fibers, relaxation by non-adrenergic, non-cholinergic fibers. The small intestine and ascending colon are innervated by the vagus nerve. The descending colon, sigmoid and rectum share innervation with the lower urinary tract as detailed above[38].

In PD, constipation occurs from decreased colonic transport and disturbed defecation. In 80% of PD patients, colonic transport time is increased[44], and most PD patients cannot defecate completely. Normally, as rectal pressure increases, anal pressure decreases to allow passage of stool. Both rectal and anal pressure increase together in 65% of PD patients[38].

Upper Gastrointestinal Tract

The upper GI tract includes the mouth, salivary glands, pharynx, esophagus and stomach. Upper GI autonomic problems in PD include drooling, esophageal dysmotility and delayed gastric emptying. Although salivary production is reduced in PD, drooling occurs partly due to reduced swallowing which may reflect involvement of cranial autonomic ganglia or brainstem salivatory nuclei[41]. The submandibular glands are innervated by the superior cervical ganglia and produce a majority of salivary volume. Both the glands and ganglia as well as other related structures (cervical sympathetic trunk and peripheral vagus nerves) demonstrate Lewy pathology in PD and ILDB[45]. Esophageal dysmotility may be due in part to impairments in vagal motor pathways. Delayed gastric emptying and gastric retention result in nausea, early satiety and abdominal distention. It is likely the result of impaired vagal excitatory pathways.

Electrogastrography has been used to investigate gastric dysmotility. This technique measures gastric myoelectric activity with electrodes on the abdominal surface of the skin, which is identical in frequency to recordings from gastric contractions of the serosal surface of the stomach. Normal gastric slow waves are approximately 3 cycles per min (cpm), with higher frequencies (5.75–10 cpm) being referred to as tachygastrias. Tachygastrias are associated with nausea, vomiting and delayed gastric emptying and vagal withdrawal or sympathetic activation is thought to be the mechanism[46]. Compared to controls the amount of time with normal frequency of gastric slow waves is reduced in PD[47]. These studies represent converging evidence of parasympathetic dysfunction throughout the entire GI tract in PD.

Pupillary system

Pupil diameter reflects integration of autonomic pathways involving several structures. The sympathetic pathway is thought to originate in the hypothalamus, descends to the ciliospinal center at C8-T2 where it synapses on preganglionic neurons which project to the superior cervical ganglion. From here, post-ganglionic fibers travel to the ciliary body and the dilator of the iris. This pathway integrates input from cortical and subcortical influences including frontal, limbic, hippocampal-amygdaloid, and thalamic sources. The parasympathetic pathway integrates information in the Edinger-Westphal nucleus from both ascending reticular fibers and descending fibers from cortical regions. Efferent projections from the Edinger-Westphal nucleus travel via the oculomotor nerve to synapse in the ciliary ganglia and then Short ciliary nerves innervate the iris sphincter and ciliary body. Sympathetic predominance results in dilation, while parasympathetic activity constricts the pupil. Lewy-related pathology has been demonstrated in the Edinger-Westphal nucleus, hypothalamus, amygdala, hippocampus and cerebral cortex[9,48,49].

Reports of the light reflex in PD have observed reduced constriction velocity compared to controls, thought to reflect a parasympathetic deficit[50]. Comparisons of PD patients with and without dementia reveal constriction velocities to be lower in magnitude for the PD group with dementia. This suggests that cortical and subcortical pathology which is thought to underlie PD dementia affects pupillary autonomic function, possibly through cholinergic deficits resulting in less parasympathetic activity.

Neuroendocrine structures

Sympathetic nerves innervate endocrine organs, several of which have demonstrated α -synuclein staining in PD. These include the adrenal glands, pancreas, parathyroid gland and ovary[5]. Of these, the adrenal gland has been studied most extensively as a clinical manifestation of adrenal insufficiency is orthostatic hypotension. Furthermore, the adrenal gland is part of several routine autopsy protocols and represents a substitute for peripheral sympathetic ganglia. α -synuclein has been found in sympathetic ganglion cells in the adrenal medulla, sympathetic nerves in the adrenal cortex, sympathetic ganglia surrounding the adrenal capsule and in nerves within the periadrenal fatty tissue[23,51]. In one study, five of six autopsied cases with orthostatic hypotension demonstrated adrenal Lewy pathology. Although no Lewy pathology has been reported specifically in the renal cortex and thyroid gland, these areas demonstrate reduced sympathetic innervation in PD[16].

Distinguishing Parkinson disease from other Parkinsonian and Lewy body syndromes

Pathologically, PD is categorized as a synucleinopathy along with dementia with Lewy Bodies, pure autonomic failure and multiple system atrophy (MSA). The first three of these disorders are all Lewy body disorders given their Lewy-related pathology[43,52]. MSA is not a Lewy body disorder as it is characterized by glial cytoplasmic inclusions[8]. Given the pathological overlap of Lewy body disorders, some have suggested that PD, dementia with Lewy bodies and pure autonomic failure may be considered Lewy body synucleinopathies with distinct but overlapping motor, cognitive and autonomic features. Clinical manifestations depend on the predominant sites of Lewy body formation and neuronal loss[43,52]. Such a proposition is far from certain, however, given that the biological significance of Lewy-related pathology and its impact on neurodegeneration remains unclear. It is possible Lewy-related pathology interferes with normal cell function or that they are the result of a protective response to cytotoxic proteins[53].

The clinical and pathological overlap of Lewy body disorders is still being resolved and whether PD falls within the spectrum of Lewy body disorders or is truly distinct from pure autonomic failure or dementia with Lewy bodies remains to be seen.

Autonomic pathophysiology distinguishes PD and other Lewy body disorders from MSA because the sympathetic cardioneuropathy differs in MSA. In MSA, α -synuclein in cardiac sympathetic ganglia or post-ganglionic nerves is seldom found and quite limited. Furthermore, axonal loss of cardiac sympathetic nerves is mild if present at all. This markedly differs from PD where post-ganglionic pathology and axonal loss is seen. This can also be shown *in vivo* with cardiac MIBG uptake, which is normal or slightly lower in MSA, or cardiac 6-[^{18}F]fluorodopamine radioactivity which is normal or higher in MSA. Both cardiac MIBG uptake and cardiac 6-[^{18}F]fluorodopamine radioactivity are markedly lower in PD[8,54]. These studies demonstrate that the post-ganglionic cardiac sympathetic lesion seen in PD is either absent or mild in MSA. Although initially it was reported that cardiac MIBG uptake could be a means by which to clinically separate PD and MSA[55], there have since been reports of overlap in MIBG uptake between the two groups[56]. Other autonomic testing has not been found to discriminate PD from other Parkinsonian syndromes[57,58].

The effect of dopaminergic medications on autonomic measures in Parkinson disease

Human autopsies reveal dopamine receptors to be in the nucleus tractus solitarius and the dorsal motor nucleus of the vagus[59], suggesting that dopaminergic signals regulate visceral autonomic function. Epidemiologic studies observe higher doses of dopaminergic medications and higher disease severity to be related to more autonomic problems, independent of one another[60]. Levodopa can be further metabolized to small amounts of epinephrine and norepinephrine which may lead to sympathomimetic effects. Some studies have found a positive correlation of levodopa and norepinephrine concentrations, while others have not[16,61]. Constipation in PD may improve with dopaminergic treatment[38]. Although treatment with levodopa has been thought to cause OH, this has not been consistently supported in physiological studies[16].

Autonomic dysfunction: implications for the pathophysiology and treatment of Parkinson disease

Both pathologic and physiologic studies demonstrate widespread involvement of the autonomic nervous system in PD (Figure 1 and Table 1). Several excellent reviews discuss treatment of autonomic symptoms which is currently limited and symptom-based[62–65]. The American Academy of Neurology's practice parameter for non-motor features in PD recommends only two medications for autonomic dysfunction: Sildenafil for erectile dysfunction and polyethylene glycol for constipation. This highlights the lack of evidence for specific treatments and the need for research in this area[2]. Understanding PD pathophysiology of autonomic dysfunction would allow more mechanistically based treatments to be developed.

A fundamental question that remains unanswered is whether or not α -synuclein pathology begins in the brain, within the spinal cord or peripheral autonomic nervous system. Clinical studies of PD have found several non-motor symptoms referable to peripheral autonomic end organs occur early in the course of the disease, perhaps even prior to motor signs[3]. An intriguing hypothesis emerging is that an environmental neurotrophic agent may initiate the pathogenic process in the periphery and centripetally spread ultimately leading to PD, in which case areas which communicate with portals of entry (e.g., GI tract, olfactory bulb)

may be expected to be affected first[43]. But definitive neuropathologic evidence for such a proposition has yet to be reported. Although ILBD, a possible precursor to PD, has demonstrated a high prevalence of α -synuclein staining in the spinal cord, sympathetic ganglia and GI tract, only two cases out of more than a thousand reported have had cord or peripheral pathology without brain involvement[5]. However, it has been shown that autonomic pathology in the cord and periphery is present in conjunction with brainstem and/or olfactory bulb involvement without nigral degeneration[11]. This could potentially represent a “pre-motor” state of PD though a subset of ILDB may be a preclinical stage of dementia with Lewy bodies given the observed distribution of neuropathology[66]. There is currently no biomarker or biopsy specimen that can identify preclinical PD (prior to the appearance of motor signs) in the clinical setting. Further clinicopathologic studies are needed to identify patterns of autonomic dysfunction across multiple organ systems which may serve as physiologic markers of PD neuropathology. This could provide a window to earlier detection and treatment of PD prior to motor signs, something that would greatly facilitate neuroprotective strategies for future PD treatment.

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Figure 1.

Neuropathology of autonomic structures in PD. (Grey structures have been observed to contain PD pathology (either α -synuclein staining, Lewy formations or neuronal loss); s=superior, n=nucleus, g=ganglion; lines indicate autonomic pathways)

Table 1

Observations of autonomic electrophysiology in Parkinson's Disease

Organ system	Condition/Maneuver	Results in PD relative to controls	Interpretation
Cardiovascular system	Valsalva	Lower compensatory increase in SBP[17]	Sympathetic deficiency in baroreflex
	Premature Ventricular Contractions	Lower compensatory increase in SBP[67]	Sympathetic deficiency in baroreflex
	Respiratory Sinus Arrhythmia (measured during Valsalva, deep breathing, standing up or hand grip)	Lower heart rate variability[19,20]	Parasympathetic deficiency in vagal influence
Skin/sweat gland	Sympathetic skin response	Lower amplitude and longer latency[21,25–28,30,68,69]	Sympathetic deficiency in distal extremities
	Thermoregulatory Sweat test	10–40% anhidrosis[32–34]	Cutaneous sympathetic deficiency
	QSART	Normal or lower sweat response[35,36]	Post-ganglionic cutaneous sympathetic deficiency
Urinary Tract	Microneurography	Lower skin sympathetic peroneal nerve activity[37]	Post-ganglionic cutaneous sympathetic deficiency
	Urodynamic testing	Reduced bladder capacity, detrusor overactivity, external sphincter relaxation[38]	Parasympathetic dysfunction in nigrostriatal and ventral-tegmental-mesolimbic systems
	Colonic scintigraphy	Longer colonic transit time[44]	Parasympathetic dysfunction in enteric network and vagus
Gastrointestinal Tract	Esophageal manometry and scintigraphy	Esophageal dysmotility[41]	Parasympathetic dysfunction in vagus motor pathways
	Gastric scintigraphy	Delayed gastric emptying time[70]	Parasympathetic dysfunction in vagus motor pathways
	Electrogastrography	More time with gastric dysrhythmia[47]	Relatively lower gastric parasympathetic tone
Pupillary System	Light reflex pupillography	Lower constriction velocity[50]	Lower parasympathetic function from the Edinger-Westphal nucleus

SBP=systolic blood pressure; QSART=quantitative sudomotor axon reflex test;