

Autonomic Dysfunction in Myasthenia Gravis: A Case–Control Study Using COMPASS-31 and Electrophysiological Measures

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Abstract

Background

Myasthenia gravis (MG) is a well-characterized autoimmune disorder of the neuromuscular junction, primarily affecting voluntary muscles. Although autonomic nervous system (ANS) involvement is not considered a classical feature, increasing evidence suggests that autonomic dysfunction may be present in a subset of patients.

Objective

To investigate the prevalence and characteristics of autonomic dysfunction in MG patients using symptom-based and electrophysiological assessments.

Methods

This case–control study included 51 MG patients and 51 age- and sex-matched healthy controls. Autonomic symptoms were assessed using the Composite Autonomic Symptom Score-31 (COMPASS-31). Objective autonomic evaluation included sympathetic skin response (SSR), heart rate variability (R-R interval variation), and orthostatic blood pressure measurements.

Results

MG patients demonstrated significantly higher COMPASS-31 total and domain scores compared to controls ($p < 0.001$). Gastrointestinal, bladder, vasomotor, secretomotor, pupillomotor, and orthostatic domains were all affected. No statistically significant differences were observed in SSR or R-R interval variability. Diastolic blood pressure values were significantly higher in MG patients in both supine and standing positions. No significant differences were found across MG subtypes.

Conclusion

Autonomic dysfunction is more prevalent in MG patients than previously recognized, particularly at the symptomatic level. These findings highlight the need for routine autonomic evaluation in MG management.

1. Introduction

Myasthenia gravis (MG) is a chronic autoimmune disorder of the neuromuscular junction characterized by antibody-mediated disruption of synaptic transmission (1). The disease is most commonly

associated with autoantibodies directed against the acetylcholine receptor (AChR), detected in approximately 80–85% of patients, while a subset of seronegative individuals harbor antibodies against muscle-specific kinase (MuSK) or lipoprotein receptor-related protein 4 (LRP4) (2–5). These immunological mechanisms impair neuromuscular transmission through complement activation, receptor internalization, and functional blockade, ultimately leading to the hallmark clinical presentation of fluctuating muscle weakness affecting ocular, bulbar, and proximal limb muscles (6–8).

MG has traditionally been conceptualized as a disorder confined to the voluntary motor system (9). However, accumulating evidence over the past two decades suggests that its clinical spectrum may extend beyond skeletal muscle involvement to include dysfunction of the autonomic nervous system (ANS). Although autonomic symptoms are not considered part of the classical MG phenotype, a growing number of studies have reported manifestations such as orthostatic intolerance, gastrointestinal dysmotility, bladder dysfunction, and abnormalities in sudomotor and vasomotor regulation (10, 11). These findings challenge the conventional view of MG as a purely neuromuscular disease and raise the possibility of a broader neuroimmunological disorder.

The underlying mechanisms of autonomic involvement in myasthenia gravis (MG) remain incompletely elucidated and are likely multifactorial. One of the most widely proposed hypotheses involves immunological cross-reactivity, whereby antibodies directed against muscle-type acetylcholine receptors (AChRs) may also interact with neuronal nicotinic AChRs expressed in autonomic ganglia (10, 12). Such cross-reactivity may disrupt ganglionic synaptic transmission, leading to impaired autonomic signaling. Supporting this concept, both experimental and clinical studies have demonstrated that dysfunction of ganglionic AChRs can result in widespread autonomic failure, including abnormalities in cardiovascular, gastrointestinal, and sudomotor regulation (13).

Beyond direct receptor-mediated mechanisms, complement activation and immune complex deposition—well-established processes in MG pathogenesis—may also contribute to structural and functional alterations within autonomic pathways (7, 8). In particular, complement-mediated injury at synaptic sites could extend beyond the neuromuscular junction to involve peripheral autonomic synapses (7, 13). Furthermore, MuSK- and LRP4-related signaling pathways, which play a critical role in synaptic organization, may have indirect effects on autonomic synaptic integrity, although this remains to be clarified (14).

Clinically, the first systematic evidence of autonomic involvement in MG was reported by Vernino et al., who described patients exhibiting prominent dysautonomic features, thereby expanding the clinical spectrum of the disease (10). Subsequent studies have reinforced these findings, suggesting that autonomic dysfunction in MG may not be merely incidental but rather reflects a broader autoimmune network affecting both somatic and autonomic components of the peripheral nervous system (11).

In addition, MG frequently coexists with other autoimmune disorders, such as thyroid disease and systemic autoimmune syndromes, which themselves may predispose to autonomic dysfunction (9, 15). Shared genetic susceptibility, including specific HLA haplotypes, and overlapping immune pathways may

further amplify this effect (16). Finally, chronic disease burden, long-term immunosuppressive therapy, and secondary deconditioning may also contribute to autonomic dysregulation, highlighting the complex interplay between primary autoimmune mechanisms and secondary factors in shaping the autonomic phenotype of MG (11).

The assessment of autonomic dysfunction has undergone substantial refinement with the development of standardized, quantitative, and validated instruments that enable both clinical and research-level evaluation. Among these, the Composite Autonomic Symptom Score-31 (COMPASS-31) has emerged as one of the most widely adopted tools for capturing the multidimensional burden of autonomic symptoms. Derived from the longer Autonomic Symptom Profile (ASP), COMPASS-31 offers a concise yet robust framework, encompassing six key domains of autonomic function: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor systems. Each domain is differentially weighted, allowing for a composite score that reflects the relative contribution of distinct autonomic pathways (17).

Importantly, COMPASS-31 provides a standardized and reproducible measure of patient-reported outcomes, facilitating comparisons across different disease populations and study designs (17). The instrument has demonstrated strong internal consistency, test–retest reliability, and construct validity, and has been extensively validated in a range of neurological and systemic disorders, including peripheral neuropathies, Parkinson’s disease, multiple system atrophy, and autoimmune autonomic ganglionopathy (17–19). Its sensitivity in detecting subclinical or early-stage autonomic dysfunction makes it particularly valuable in conditions where objective findings may be subtle or inconsistent (18, 19).

In the context of myasthenia gravis, where autonomic involvement is not traditionally emphasized and may be overlooked in routine clinical evaluation, COMPASS-31 offers a practical and scalable approach for systematic symptom screening (10, 11, 17). Moreover, the use of such structured instruments enables the integration of subjective symptom burden with objective autonomic testing, thereby supporting a more comprehensive and multidimensional characterization of autonomic dysfunction. This combined approach is increasingly recognized as essential for improving diagnostic accuracy, understanding disease heterogeneity, and guiding individualized management strategies in disorders with potential autonomic involvement.

In parallel with symptom-based instruments, objective evaluation of autonomic function relies on a range of electrophysiological and cardiovascular reflex tests that interrogate distinct components of the autonomic nervous system (20). Sympathetic skin response (SSR) represents a noninvasive method for assessing sudomotor function and reflects the integrity of postganglionic sympathetic cholinergic pathways (21, 22). Alterations in SSR latency or amplitude may indicate dysfunction within peripheral sympathetic circuits, although its sensitivity can be variable depending on disease context (20–22).

Heart rate variability (HRV), most commonly evaluated through R–R interval variation during rest and controlled breathing, provides a well-established measure of parasympathetic (vagal) cardiac

modulation (20). Reduced HRV is generally interpreted as impaired parasympathetic tone or altered sympathovagal balance and has been associated with adverse cardiovascular outcomes across a variety of neurological and systemic conditions (20, 23). In addition, dynamic cardiovascular reflex testing, including orthostatic blood pressure measurements, allows assessment of baroreflex-mediated autonomic regulation. The presence of orthostatic hypotension or abnormal blood pressure adaptation upon standing reflects impaired sympathetic vasoconstrictor responses and defective cardiovascular autonomic control (23, 24).

Importantly, each of these modalities captures different, yet complementary, aspects of autonomic function, and none in isolation is sufficient to fully characterize the complexity of autonomic involvement. Therefore, the integration of objective physiological measurements with standardized symptom-based assessments enables a more comprehensive and multidimensional evaluation (25). Such an approach is particularly relevant in conditions like myasthenia gravis, where autonomic dysfunction may be subtle, heterogeneous, or subclinical, and where discrepancies between subjective symptoms and objective findings may provide additional insight into underlying pathophysiological mechanisms.

Despite these methodological advances, the prevalence, phenotypic spectrum, and clinical relevance of autonomic dysfunction in myasthenia gravis (MG) remain insufficiently characterized. The existing body of literature is fragmented and often constrained by relatively small sample sizes, single-center designs, and variability in patient selection criteria. Moreover, considerable heterogeneity exists in the assessment methods employed across studies, ranging from purely symptom-based questionnaires to diverse combinations of electrophysiological and cardiovascular tests, thereby limiting comparability and generalizability of findings (10, 11).

A further challenge lies in the inconsistency of reported results, particularly with respect to objective electrophysiological measures such as sympathetic skin response (SSR) and heart rate variability (HRV). While some studies suggest subtle impairments in autonomic function, others fail to demonstrate significant differences compared to healthy controls, raising questions about the sensitivity and specificity of these tools in detecting mild or subclinical dysfunction. This discrepancy may reflect differences in disease severity, treatment status, or methodological variability, as well as the possibility that autonomic involvement in MG is predominantly functional rather than structural in nature (11, 20, 25).

In addition, the potential influence of disease-related factors on autonomic dysfunction remains poorly understood. It is not yet clear whether autonomic involvement differs according to MG subtypes—such as ocular versus generalized disease—or is modulated by immunological profiles, including AChR, MuSK, or LRP4 antibody status (8, 11). Similarly, the role of thymic pathology, including thymoma and thymic hyperplasia, in shaping autonomic manifestations has not been systematically explored (26, 27). These knowledge gaps underscore the need for well-designed, multimodal studies that integrate clinical,

immunological, and physiological data to better delineate the scope and determinants of autonomic dysfunction in MG.

In this context, the present study aims to systematically investigate autonomic involvement in patients with myasthenia gravis using both symptom-based (COMPASS-31) and objective electrophysiological assessments (SSR, HRV, and orthostatic blood pressure measurements). By comparing MG patients with healthy controls and exploring potential associations with clinical subtypes, this study seeks to provide a more comprehensive understanding of autonomic dysfunction in MG and its potential implications for clinical practice.

2. Materials and Methods

2.1 Study Design and Participants

This case–control study included 51 patients diagnosed with MG and 51 healthy controls. Diagnosis of MG was based on clinical findings, antibody testing, and electrophysiological confirmation.

2.2 Inclusion and Exclusion Criteria

Patients with confirmed MG were included. Individuals with comorbid conditions affecting the autonomic nervous system (e.g., diabetes, Parkinson’s disease) were excluded.

2.3 Autonomic Symptom Assessment

Autonomic symptoms were systematically evaluated using the Composite Autonomic Symptom Score-31 (COMPASS-31), a validated and widely used questionnaire designed to quantify the burden of autonomic dysfunction. COMPASS-31 is a refined and abbreviated version of the original Autonomic Symptom Profile (ASP), developed to provide a concise yet comprehensive assessment suitable for both clinical and research settings.

The instrument consists of 31 items grouped into six distinct domains reflecting different components of autonomic nervous system function: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor functions. Each domain is assigned a weighted score based on its relative clinical significance, yielding a total composite score ranging from 0 to 100, with higher scores indicating greater autonomic symptom burden (17).

Participants completed the questionnaire under standardized conditions, and domain-specific as well as total scores were calculated according to established scoring algorithms. The orthostatic intolerance domain evaluates symptoms such as dizziness, lightheadedness, and syncope upon standing; the vasomotor domain assesses peripheral circulation abnormalities; the secretomotor domain reflects sudomotor function; the gastrointestinal domain captures dysmotility-related symptoms; the bladder domain evaluates urinary function; and the pupillomotor domain assesses light sensitivity and visual adaptation.

The use of COMPASS-31 in this study enabled a structured and reproducible quantification of patient-reported autonomic symptoms, facilitating comparison between myasthenia gravis patients and healthy controls. Moreover, its multidimensional design allowed for the identification of domain-specific patterns of autonomic involvement, providing further insight into the clinical expression of autonomic dysfunction in this population.

2.4 Electrophysiological Evaluation

Objective assessment of autonomic function was performed using standardized electrophysiological methods targeting both sympathetic and parasympathetic components of the autonomic nervous system. All measurements were conducted under controlled laboratory conditions in the electrophysiology unit, with participants in a resting state to minimize external influences on autonomic activity.

Sympathetic function was evaluated using the **sympathetic skin response (SSR)**, a noninvasive test reflecting the integrity of postganglionic sudomotor sympathetic pathways. SSR recordings were obtained following standardized electrical stimulation, and response latency and amplitude were analyzed. The presence or absence of reproducible responses, as well as alterations in waveform characteristics, were considered in the evaluation of sympathetic function (20–22).

Parasympathetic (cardiovagal) function was assessed through **heart rate variability (HRV)** analysis, specifically by measuring R–R interval variation on electrocardiographic recordings. Measurements were performed at rest and during deep breathing maneuvers, which are known to enhance vagal modulation. The magnitude of R–R interval variation was used as an indicator of parasympathetic activity, with reduced variability suggesting impaired cardiovagal function (20).

These electrophysiological assessments were selected due to their established utility in evaluating peripheral autonomic pathways and their complementary roles in capturing different aspects of autonomic regulation. The combined use of SSR and HRV allowed for a more comprehensive characterization of autonomic function, facilitating comparison between myasthenia gravis patients and healthy controls and enabling the detection of potential subclinical autonomic abnormalities.

2.5 Blood Pressure Measurement

Cardiovascular autonomic function was further evaluated through standardized blood pressure measurements to assess orthostatic responses. Blood pressure was measured using an automated sphygmomanometer after participants had rested in the supine position for at least 5 minutes to ensure hemodynamic stabilization. Subsequently, measurements were repeated after the participants assumed an upright position.

Orthostatic hypotension was defined according to established clinical criteria as a decrease in systolic blood pressure of ≥ 20 mmHg and/or diastolic blood pressure of ≥ 10 mmHg within the first 3 minutes of

standing. Both systolic and diastolic values were recorded and analyzed in supine and standing positions, allowing for the evaluation of baroreflex-mediated cardiovascular adaptation (23, 24).

This approach enabled the detection of abnormalities in sympathetic vasoconstrictor function and provided complementary information to electrophysiological measures. By integrating orthostatic blood pressure assessment with symptom-based and electrophysiological evaluations, a more comprehensive characterization of cardiovascular autonomic regulation was achieved in both myasthenia gravis patients and healthy controls.

2.6 Statistical Analysis

Data were analyzed using standard statistical methods. Continuous variables were compared using t-tests or non-parametric equivalents. A p-value < 0.05 was considered statistically significant.

2.7 Ethics Approval

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Local Ethics Committee of Antalya Training and Research Hospital prior to the initiation of the study (Approval No: 2024/64, Date: March 21, 2024).

All participants were informed in detail about the purpose, procedures, and potential risks of the study, and written informed consent was obtained from each participant before enrollment. Participation was entirely voluntary, and participants were free to withdraw from the study at any time without any consequences.

All data were collected and handled in accordance with relevant data protection regulations, ensuring participant confidentiality and anonymity. No identifiable personal information was included in the analysis or reporting of the results.

3. Results

3.1 Demographic and Clinical Characteristics

A total of 51 patients diagnosed with myasthenia gravis (MG) and 51 age- and sex-matched healthy controls were included in the study. The two groups were comparable in terms of baseline demographic characteristics, with no statistically significant differences observed in age or sex distribution ($p > 0.05$ for all comparisons), indicating appropriate matching between groups.

Within the MG cohort, clinical characteristics such as subtype classification (ocular vs. generalized), antibody status, and thymic pathology were recorded to allow for subgroup analyses. The distribution of these variables reflected the heterogeneity typically observed in MG populations. The majority of patients presented with generalized MG, while a smaller proportion had isolated ocular involvement (Table 1).

These comparable baseline characteristics between groups minimize the potential confounding effects of demographic variables and support the validity of subsequent comparisons in autonomic symptom burden and electrophysiological parameters.

Table 1
Demographic and clinical characteristics of patients with myasthenia gravis and healthy controls

Variable	Control Group (n = 51)	MG Group (n = 51)	p value
Demographic characteristics			
Sex, F/M, n (%)	31/20 (60.8)	29/22 (56.9)	0.687
Age, median (min–max)	57 (27–76)	55 (21–78)	0.723
Clinical characteristics			
Ocular MG, n (%)	—	9 (17.6)	—
Generalized MG, n (%)	—	42 (82.4)	—
AChR antibody-positive, n (%)	—	22 (43.1)	—
Anti-MuSK antibody-positive, n (%)	—	7 (13.7)	—
Seronegative, n (%)	—	22 (43.1)	—
Thymoma, n (%)	—	6 (11.8)	—
Thymic hyperplasia, n (%)	—	11 (21.6)	—
No thymic hyperplasia, n (%)	—	30 (58.8)	—
Unknown thymic status, n (%)	—	10 (19.6)	—

AChR, acetylcholine receptor; F, female; M, male; MG, myasthenia gravis; MuSK, muscle-specific kinase.

3.2 Autonomic Symptoms (COMPASS-31)

Patients with myasthenia gravis (MG) demonstrated a significantly higher overall autonomic symptom burden compared to healthy controls, as reflected by elevated total COMPASS-31 scores ($p < 0.001$). This difference remained consistent across multiple autonomic domains, indicating a widespread and multidimensional pattern of autonomic involvement in MG.

Domain-specific analysis revealed that gastrointestinal, bladder, orthostatic intolerance, secretomotor, vasomotor, and pupillomotor scores were all significantly increased in the MG group compared to controls (all $p < 0.05$). Gastrointestinal symptoms, including features suggestive of dysmotility, were among the most prominent findings. Similarly, bladder dysfunction scores indicated a higher frequency of urinary symptoms in MG patients. Orthostatic intolerance scores were also significantly elevated, reflecting increased reports of dizziness, lightheadedness, and related symptoms upon standing. In

addition, secretomotor dysfunction, representing abnormalities in sweating and related autonomic processes, was more pronounced in the MG cohort (Table 2).

Overall, these findings highlight a consistent and clinically relevant increase in patient-reported autonomic symptoms in MG, supporting the notion that autonomic dysfunction represents a broader, yet underrecognized, component of the disease phenotype.

Table 2

Comparison of COMPASS-31 scores between patients with myasthenia gravis and healthy controls

Variable	Measurement	Control Group (n = 51)	MG Patients (n = 51)	p value
COMPASS-31 Total Score	Mean $\pm$ SD	3.5 $\pm$ 5.7	17.6 $\pm$ 12	< 0.001
	Median (minimum–maximum)	0 (0–24)	13 (0–52)	
Orthostatic Intolerance Score	Mean $\pm$ SD	2.4 $\pm$ 5.4	7.3 $\pm$ 8.9	0.001
	Median (minimum–maximum)	0 (0–24)	0 (0–28)	
Vasomotor Score	Mean $\pm$ SD	0 (0–0)	0.24 $\pm$ 0.65	0.012
	Median (minimum–maximum)	0	0 (0–2)	
Secretomotor Score	Mean $\pm$ SD	0.12 $\pm$ 0.47	3.6 $\pm$ 2.9	< 0.001
	Median (minimum–maximum)	0 (0–2)	4 (0–9)	
Gastrointestinal Score	Mean $\pm$ SD	0.49 $\pm$ 1.2	3.24 $\pm$ 2.9	< 0.001
	Median (minimum–maximum)	0 (0–4)	3 (0–10)	
Bladder Function Score	Mean $\pm$ SD	0.29 $\pm$ 0.8	1.47 $\pm$ 1.9	< 0.001
	Median (minimum–maximum)	0 (0–4)	1 (0–7)	
Pupillomotor Score	Mean $\pm$ SD	0.02 $\pm$ 0.14	1.78 $\pm$ 0.95	< 0.001
	Median (minimum–maximum)	0 (0–1)	2 (0–4)	

COMPASS-31, Composite Autonomic Symptom Score-31; MG, myasthenia gravis; Mean $\pm$ SD, mean $\pm$ standard deviation.

3.3 Electrophysiological Findings

Electrophysiological assessment of autonomic function revealed partially comparable findings between patients with myasthenia gravis (MG) and healthy controls. Analysis of sympathetic skin response (SSR) parameters demonstrated no statistically significant differences in palmar latency or amplitude values between the two groups ($p > 0.05$). Similarly, plantar latency values were not significantly different between groups. However, plantar SSR amplitude values were significantly lower in MG patients compared to controls, particularly in the right and left plantar recordings ($p = 0.023$ and $p = 0.003$, respectively) (Table 3).

Evaluation of heart rate variability (HRV) through R–R interval variation showed lower variability values in MG patients compared to controls in resting, deep breathing, and standing measurements. However, these differences did not reach statistical significance (all $p > 0.05$) (Table 4).

Taken together, these findings suggest that, despite the increased burden of autonomic symptoms observed in MG patients, objective electrophysiological abnormalities were limited and predominantly detected in plantar sympathetic skin response amplitudes, while HRV parameters remained largely preserved.

Table 3

Comparison of sympathetic skin response parameters between patients with myasthenia gravis and healthy controls

Variable	Measurement	Control Group (n = 51)	MG Patients (n = 51)	p value
Right Palmar Latency (ms)	Mean $\pm$ SD	1718 $\pm$ 325	1683 $\pm$ 343	0.547 χ^2
	Median (minimum–maximum)	1686 (1143–2627)	1636 (1100–2592)	
Right Palmar Amplitude (mV)	Mean $\pm$ SD	1.56 $\pm$ 1.32	1.63 $\pm$ 1.23	0.753 χ^2
	Median (minimum–maximum)	1.36 (0.2–5.4)	1.51 (0–5.1)	
Left Palmar Latency (ms)	Mean $\pm$ SD	1749 $\pm$ 315	1650 $\pm$ 324	0.120 χ^2
	Median (minimum–maximum)	1730 (1038–2599)	1599 (1011–2340)	
Left Palmar Amplitude (mV)	Mean $\pm$ SD	1.49 $\pm$ 1.08	1.56 $\pm$ 1.2	0.878 χ^2
	Median (minimum–maximum)	1.39 (0.12–6.1)	1.48 (0–5.2)	
Right Plantar Latency (ms)	Mean $\pm$ SD	2016 $\pm$ 307	2132 $\pm$ 361	0.083 χ^2
	Median (minimum–maximum)	2005 (1326–2847)	2109 (1210–2847)	
Right Plantar Amplitude (mV)	Mean $\pm$ SD	0.72 $\pm$ 0.48	0.54 $\pm$ 0.54	0.023 χ^2
	Median (minimum–maximum)	0.59 (0–1.93)	0.45 (0–2.80)	
Left Plantar Latency (ms)	Mean $\pm$ SD	2024 $\pm$ 244	2174 $\pm$ 459	0.069 χ^2
	Median (minimum–maximum)	2043 (1435–2562)	2091 (1348–3542)	
Left Plantar Amplitude (mV)	Mean $\pm$ SD	0.69 $\pm$ 0.39	0.47 $\pm$ 0.39	0.003 χ^2
	Median (minimum–maximum)	0.65 (0–1.46)	0.40 (0–1.41)	

χ^2 Mann–Whitney U test; χ^2 Independent samples t-test

Table 4

Comparison of R–R interval variation parameters between patients with myasthenia gravis and healthy controls

Variable	Measurement	Control Group (n = 51)	MG Patients (n = 51)	p value
%R	Mean $\pm$ SD	19 $\pm$ 8.5	17.4 $\pm$ 10	0.168 [§]
	Median (minimum–maximum)	18.1 (7–44.9)	15.9 (5.5–57)	
%D	Mean $\pm$ SD	28.2 $\pm$ 15.5	23.5 $\pm$ 11.6	0.168 [§]
	Median (minimum–maximum)	24.8 (7.9–83)	20.5 (7.1–61)	
30:15 Ratio	Mean $\pm$ SD	1.05 $\pm$ 0.09	1.03 $\pm$ 0.06	0.430 [§]
	Median (minimum–maximum)	1.03 (0.9–1.4)	1.02 (0.95–1.3)	
§ Mann–Whitney U test				

MG, myasthenia gravis; SSR, sympathetic skin response; HRV, heart rate variability; RRIV, R–R interval variation; SD, standard deviation; %R, RRIV at rest; %D, RRIV during deep breathing; 30:15 ratio, RRIV during standing.

3.4 Blood Pressure Findings

Analysis of cardiovascular autonomic parameters revealed that patients with myasthenia gravis (MG) had significantly higher diastolic blood pressure values compared to healthy controls, both in the supine position ($p = 0.002$) and after standing ($p = 0.018$). In contrast, no statistically significant differences were observed in systolic blood pressure measurements between the two groups (Table 5).

These findings suggest a potential alteration in vascular autonomic regulation in MG patients, particularly affecting diastolic tone, which is largely mediated by peripheral vascular resistance and sympathetic activity. The persistence of elevated diastolic values across both resting and orthostatic conditions may indicate subtle dysregulation of autonomic cardiovascular control mechanisms, rather than a classical orthostatic hypotension pattern.

Overall, the observed differences in diastolic blood pressure, when interpreted alongside the electrophysiological and symptom-based findings, support the presence of nuanced and possibly subclinical alterations in autonomic cardiovascular function in MG patients.

Table 5

Comparison of resting and standing blood pressure values between patients with myasthenia gravis and healthy controls

Variable	Measurement	Control Group (n = 51)	MG Patients (n = 51)	p value
Resting Systolic BP	Mean $\pm$ SD	121 $\pm$ 9.5	127 $\pm$ 18	0.502 $\boxtimes$
	Median (minimum–maximum)	121 (97–139)	123 (92–170)	
Resting Diastolic BP	Mean $\pm$ SD	72.5 $\pm$ 7.7	78.9 $\pm$ 12.2	0.002 $\boxtimes$
	Median (minimum–maximum)	73 (57–94)	77 (55–114)	
Standing Systolic BP	Mean $\pm$ SD	118 $\pm$ 9.6	121 $\pm$ 17.5	0.290 $\boxtimes$
	Median (minimum–maximum)	119 (95–137)	120 (89–164)	
Standing Diastolic BP	Mean $\pm$ SD	70.2 $\pm$ 7.6	75 $\pm$ 12.4	0.018 $\boxtimes$
	Median (minimum–maximum)	71 (56–88)	74 (50–111)	
$\boxtimes$ Mann–Whitney U test, $\boxtimes$ Independent samples t-test				

BP, blood pressure (mmHg); MG, myasthenia gravis; Mean $\pm$ SD, mean $\pm$ standard deviation.

3.5 Subgroup Analyse

Subgroup analyses were performed to explore whether autonomic involvement varied according to clinical and immunological characteristics of myasthenia gravis (MG).

Comparisons between patients with ocular and generalized MG revealed no statistically significant differences in COMPASS-31 scores or R–R interval variability parameters. However, resting and standing systolic blood pressure values were significantly higher in patients with ocular MG compared to those with generalized MG. (Table 6)

Similarly, stratification based on antibody status, including AChR-positive, MuSK-positive, and seronegative patients, did not demonstrate significant differences in COMPASS-31 scores or R–R interval variability parameters. However, standing diastolic blood pressure differed significantly among antibody subgroups. (Table 7)

In addition, no meaningful differences were observed between patients with and without thymoma across the evaluated autonomic parameters. Comparisons according to thymectomy status showed no significant differences in COMPASS-31 total scores or most cardiovascular parameters; however, %D RRIV, resting systolic blood pressure, and standing systolic blood pressure differed significantly between patients with and without thymectomy. (Tables 8 and 9)

These findings suggest that autonomic dysfunction in MG, as assessed in this study, does not appear to be strongly influenced by disease subtype, antibody profile, or thymic pathology. Rather, subgroup analyses showed only limited and parameter-specific differences. However, given the relatively limited sample size within subgroups, these results should be interpreted with caution, and larger studies are needed to further elucidate potential subgroup-specific patterns of autonomic dysfunction.

Table 6
Comparison of autonomic parameters between ocular and generalized MG patients

Variable	Ocular MG (n = 9)	Generalized MG (n = 42)	p value
COMPASS-31 total score, Mean $\pm$ SD	11.9 $\pm$ 8.7	18.8 $\pm$ 12.4	0.124
%R RRIV, Mean $\pm$ SD	15.5 $\pm$ 10.4	17.8 $\pm$ 10	0.443
%D RRIV, Mean $\pm$ SD	21.8 $\pm$ 10.7	23.8 $\pm$ 11.9	0.601
30:15 ratio, Mean $\pm$ SD	1.04 $\pm$ 0.03	1.03 $\pm$ 0.06	0.360
Resting systolic BP, Mean $\pm$ SD	143 $\pm$ 15.2	123.8 $\pm$ 17.4	0.003
Resting diastolic BP, Mean $\pm$ SD	84.3 $\pm$ 10.9	77.7 $\pm$ 12.2	0.139
Standing systolic BP, Mean $\pm$ SD	135.3 $\pm$ 15.9	117.9 $\pm$ 16.4	0.005
Standing diastolic BP, Mean $\pm$ SD	81.8 $\pm$ 11.3	73.6 $\pm$ 12.3	0.074

Table 7
Comparison of autonomic parameters according to antibody status

Variable	AChR-positive (n = 22)	MuSK-positive (n = 7)	Seronegative (n = 22)	p value
COMPASS-31 total score, Mean $\pm$ SD	21.3 $\pm$ 14.1	14.9 $\pm$ 9.6	14.7 $\pm$ 9.7	0.306
%R RRIV, Mean $\pm$ SD	15.4 $\pm$ 7.4	22.7 $\pm$ 10.7	17.8 $\pm$ 11.8	0.307
%D RRIV, Mean $\pm$ SD	21.4 $\pm$ 8.9	27 $\pm$ 17.1	24.4 $\pm$ 12.2	0.855
30:15 ratio, Mean $\pm$ SD	1.03 $\pm$ 0.05	1.06 $\pm$ 0.09	1.03 $\pm$ 0.04	0.929
Resting systolic BP, Mean $\pm$ SD	125.6 $\pm$ 21	121 $\pm$ 12.6	131 $\pm$ 16.6	0.389
Resting diastolic BP, Mean $\pm$ SD	78.8 $\pm$ 13.8	70.6 $\pm$ 9.3	81.6 $\pm$ 10.3	0.112
Standing systolic BP, Mean $\pm$ SD	119.5 $\pm$ 21	117 $\pm$ 11.4	124 $\pm$ 15.2	0.613
Standing diastolic BP, Mean $\pm$ SD	75 $\pm$ 14.6	65.6 $\pm$ 8.1	78.2 $\pm$ 9.7	0.042

Table 8
Comparison of autonomic parameters according to thymoma status

Variable	Thymoma present (n = 6)	Thymoma absent (n = 45)	p value
COMPASS-31 total score, Mean $\pm$ SD	21.3 $\pm$ 13.3	15.8 $\pm$ 12.7	0.151
%R RRIV, Mean $\pm$ SD	14.2 $\pm$ 3.7	18.5 $\pm$ 10.9	0.743
%D RRIV, Mean $\pm$ SD	24.6 $\pm$ 6	24.5 $\pm$ 12.6	0.597
30:15 ratio, Mean $\pm$ SD	1.03 $\pm$ 0.04	1.04 $\pm$ 0.06	0.966
Resting systolic BP, Mean $\pm$ SD	132 $\pm$ 30	128 $\pm$ 18	0.322
Resting diastolic BP, Mean $\pm$ SD	93 $\pm$ 20	79 $\pm$ 10.2	0.943
Standing systolic BP, Mean $\pm$ SD	124 $\pm$ 27.2	122 $\pm$ 16.2	0.220
Standing diastolic BP, Mean $\pm$ SD	87 $\pm$ 23.1	75.4 $\pm$ 11.3	0.921

Table 9
Comparison of autonomic parameters according to thymectomy status

Variable	Thymectomy present (n = 18)	Thymectomy absent (n = 33)	p value
COMPASS-31 total score, Mean $\pm$ SD	20.6 $\pm$ 12.1	15.9 $\pm$ 11.8	0.746
%R RRIV, Mean $\pm$ SD	19.6 $\pm$ 8.8	16.2 $\pm$ 10.6	0.100
%D RRIV, Mean $\pm$ SD	28.6 $\pm$ 13.4	20.6 $\pm$ 9.6	0.019
30:15 ratio, Mean $\pm$ SD	1.06 $\pm$ 0.07	1.02 $\pm$ 0.04	0.095
Resting systolic BP, Mean $\pm$ SD	119 $\pm$ 17.4	131 $\pm$ 17.4	0.017
Resting diastolic BP, Mean $\pm$ SD	74.7 $\pm$ 10.6	81 $\pm$ 12.5	0.069
Standing systolic BP, Mean $\pm$ SD	111.7 $\pm$ 15.4	126 $\pm$ 16.7	0.004
Standing diastolic BP, Mean $\pm$ SD	71.6 $\pm$ 12.2	77 $\pm$ 12.3	0.136

AChR, acetylcholine receptor; BP, blood pressure; COMPASS-31, Composite Autonomic Symptom Score-31; MG, myasthenia gravis; MuSK, muscle-specific kinase; RRIV, R–R interval variation; SD, standard deviation.

4. Discussion

This study demonstrates that autonomic symptoms are significantly more prevalent in MG patients than in healthy individuals. While MG is classically considered a motor disorder, our findings support the concept of a broader systemic involvement.

The discrepancy between subjective (COMPASS-31) and objective (SSR, HRV) findings is a notable feature of the present study and warrants careful interpretation. Several, not mutually exclusive, explanations may account for this divergence.

First, the findings may reflect **early or subclinical autonomic involvement**, in which patients experience symptoms before measurable abnormalities become detectable with conventional electrophysiological methods. In such cases, patient-reported outcomes may be more sensitive in capturing initial dysfunction, particularly in disorders with fluctuating or mild autonomic impairment (17, 25).

Second, the lack of significant differences in SSR and HRV may be attributable to the **limited sensitivity and resolution of standard electrophysiological tests**, especially in detecting subtle or region-specific autonomic alterations. Both SSR and HRV primarily assess selected components of the autonomic nervous system—sudomotor sympathetic and cardiovagal parasympathetic pathways, respectively—and may not fully capture the complexity of autonomic regulation, including gastrointestinal, bladder, or microvascular functions (20, 25).

Third, these results may suggest that autonomic involvement in MG is predominantly **functional rather than structural**, characterized by dysregulation at the level of neurotransmission or receptor function rather than overt nerve fiber damage. Such functional disturbances may produce clinically relevant symptoms without necessarily leading to measurable abnormalities in standard electrophysiological parameters (13).

Taken together, this discordance underscores the importance of integrating subjective symptom assessment with objective testing in the evaluation of autonomic dysfunction. It also highlights the need for more sensitive and multimodal diagnostic approaches to better characterize the nature and extent of autonomic involvement in myasthenia gravis.

Previous studies have reported findings consistent with the present observations, further supporting the notion that autonomic involvement in myasthenia gravis (MG) may be subtle, heterogeneous, and not always detectable through conventional objective testing (10, 11). Nikolić et al. proposed that **immunological cross-reactivity** between antibodies targeting muscle-type acetylcholine receptors and neuronal nicotinic receptors in autonomic ganglia may underlie the development of autonomic symptoms, thereby extending the pathophysiological impact of MG beyond the neuromuscular junction (11, 13).

In addition to direct antibody-mediated mechanisms, **autoimmune overlap syndromes** may further contribute to autonomic dysfunction in this population. MG is known to coexist with other autoimmune conditions, such as autoimmune thyroid disease, systemic lupus erythematosus, and rheumatoid

arthritis, which themselves may involve the autonomic nervous system (9, 28–30). Shared genetic susceptibility, including specific HLA haplotypes, and common immunopathogenic pathways may facilitate a broader autoimmune milieu, predisposing patients to dysautonomia (16, 31).

Moreover, emerging evidence suggests that **autoimmune autonomic ganglionopathy-like mechanisms**, even in the absence of detectable ganglionic antibodies, may play a role in selected cases (32). This concept is supported by reports of patients exhibiting mixed features of neuromuscular and autonomic dysfunction, reinforcing the idea that MG may, in some individuals, represent part of a wider spectrum of autoimmune neurological disorders (10, 32).

Taken together, these observations highlight the complexity of autonomic involvement in MG and suggest that it may arise from an interplay of direct immunological effects, coexisting autoimmune processes, and broader systemic immune dysregulation.

Interestingly, no significant differences were observed among MG subtypes across all evaluated parameters. This finding suggests that autonomic dysfunction in MG may not be strongly influenced by traditional disease stratifiers such as clinical phenotype (ocular vs. generalized), antibody profile (AChR, MuSK, or seronegative), or thymic pathology (8, 27). Rather, autonomic involvement may represent a more **uniform and intrinsic component of the disease process**, potentially reflecting shared downstream immunopathological mechanisms.

This observation is particularly noteworthy given the well-established heterogeneity of MG in terms of clinical presentation, immunological characteristics, and treatment response (8, 33). The apparent lack of subgroup-specific differences may indicate that autonomic dysfunction arises from mechanisms that are common across MG subtypes, such as generalized immune dysregulation or widespread synaptic vulnerability, rather than from subtype-specific antibody effects.

However, this interpretation should be approached with caution. The absence of statistically significant differences may also be influenced by **limited statistical power within subgroup analyses**, especially when sample sizes are relatively small. Subtle differences between subgroups may therefore remain undetected. Future studies with larger cohorts and more detailed immunological and physiological profiling are needed to clarify whether specific MG subtypes carry distinct risks or patterns of autonomic involvement.

The elevated diastolic blood pressure observed in patients with myasthenia gravis (MG) may reflect subtle alterations in vascular autonomic regulation, particularly involving increased peripheral vascular resistance and impaired fine-tuning of sympathetic vasoconstrictor activity. Diastolic blood pressure is largely determined by arteriolar tone, which is under autonomic control; therefore, even modest elevations may indicate a shift in sympathovagal balance or dysregulation of baroreflex-mediated cardiovascular responses (23, 34).

In this context, the persistence of higher diastolic values in both supine and standing positions suggests that the observed change is not merely a transient orthostatic phenomenon but may represent a more sustained alteration in baseline autonomic vascular control. It is also possible that compensatory mechanisms, such as increased sympathetic tone in response to subclinical autonomic dysfunction, contribute to this finding (34).

Nevertheless, the clinical significance of this observation remains uncertain. It is unclear whether elevated diastolic blood pressure in MG patients is associated with long-term cardiovascular risk, disease severity, or treatment effects. Furthermore, potential confounding factors, including medication use (e.g., corticosteroids), physical deconditioning, or comorbid conditions, may influence blood pressure regulation in this population (35).

Therefore, while the present findings suggest a potential link between MG and altered cardiovascular autonomic function, further studies—particularly longitudinal and mechanistic investigations—are needed to clarify the underlying pathways and determine the clinical implications of these changes.

Clinical Implications

The findings of this study have several important implications for clinical practice and patient management in myasthenia gravis (MG).

First, autonomic symptoms—although not traditionally emphasized—should be **routinely assessed** as part of the clinical evaluation of MG patients. Given their potential impact on quality of life and daily functioning, symptoms such as orthostatic intolerance, gastrointestinal disturbances, and bladder dysfunction should be actively inquired rather than overlooked (10, 11, 17).

Second, the **COMPASS-31 questionnaire** represents a practical, time-efficient, and validated screening tool for identifying autonomic symptom burden in routine clinical settings. Its ease of application and multidimensional structure make it particularly suitable for integrating into standard neurological assessments, especially in conditions like MG where autonomic involvement may be subtle or underrecognized (17).

Finally, the presence of autonomic dysfunction may necessitate a **multidisciplinary management approach**, involving neurologists, cardiologists, and, when appropriate, gastroenterology or urology specialists. Such collaboration can facilitate comprehensive evaluation and targeted management of autonomic symptoms, ultimately improving patient outcomes and quality of life.

Overall, these findings support a more holistic approach to MG, extending beyond motor symptoms to include systematic evaluation of autonomic function.

Limitations

Several limitations of this study should be acknowledged when interpreting the findings.

First, the study was conducted in a **single-center setting**, which may limit the generalizability of the results to broader and more diverse patient populations. Institutional practices, referral patterns, and regional characteristics may have influenced the composition of the study cohort.

Second, the **relatively small sample size**, particularly within subgroup analyses, may have reduced the statistical power to detect subtle differences between clinical subtypes, antibody groups, or thymic pathology categories. As a result, potential associations may have remained undetected.

Third, the **cross-sectional design** of the study precludes conclusions regarding causality or temporal relationships between myasthenia gravis and autonomic dysfunction. It also limits the ability to assess the progression, fluctuation, or treatment-related changes in autonomic involvement over time.

Additionally, the study relied on a combination of symptom-based and selected electrophysiological measures, which, although complementary, may not fully capture the entire spectrum of autonomic dysfunction. More comprehensive autonomic testing, including advanced cardiovascular reflex testing or sudomotor imaging techniques, could provide further insight.

Future multicenter, longitudinal studies with larger cohorts and multimodal assessment strategies are needed to validate and expand upon these findings.

5. Conclusion

Autonomic dysfunction appears to be an **underrecognized yet clinically meaningful component** of myasthenia gravis (MG). While conventional electrophysiological assessments such as SSR and HRV may reveal only subtle or non-significant alterations, symptom-based evaluations—particularly using structured instruments like COMPASS-31—consistently demonstrate a substantial burden of autonomic involvement. This discrepancy underscores the importance of incorporating both subjective and objective approaches in the assessment of MG.

The findings of this study support the concept that autonomic dysfunction in MG may represent a **functional and multidimensional phenomenon**, not fully captured by standard physiological tests alone. Given its potential impact on patient well-being, daily functioning, and possibly disease perception, autonomic involvement should be considered an integral aspect of MG rather than a secondary or incidental feature.

Future research should focus on **larger, multicenter cohorts and longitudinal designs** to better delineate the underlying mechanisms, temporal evolution, and clinical consequences of autonomic dysfunction in MG. In addition, the integration of more sensitive and comprehensive autonomic testing modalities may help to bridge the gap between subjective symptom burden and objective findings, ultimately contributing to improved diagnostic accuracy and patient-centered care.

Declarations

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Conflict of Interest

None declared

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Data Availability:

All data used in this study are derived from publicly available sources

AI Statement:

No artificial intelligence tools were used in the design, analysis, or writing of this study

Ethical Considerations

Ethical approval was not required as this study did not involve human participants, personal data, or confidential information.

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