Nassar *et al.*
Egypt J Neurol Psychiatry Neurosurg (2023) 59:156
https://doi.org/10.1186/s41983-023-00754-z

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH

Open Access

Evaluation of the autonomic nervous system in patients with essential tremor

Mahmoud H. Nassar[1], Elsayed A. Tageldin[1] and Osama A. Ragab[1*]

Abstract

Background Essential tremor (ET) is a prevalent movement disorder that may be linked to neurodegenerative changes. It is marked by a mix of motor and non-motor symptoms, which include disturbances in the autonomic nervous system. Aim of the study: We aimed to assess autonomic dysfunction in individuals with essential tremor. Thirty patients with essential tremor (Group 1) and 30 age and sex-matched healthy subjects as the control group (Group 2) were recruited. Comprehensive medical and neurological examinations were conducted on all participants, followed by electrophysiological assessments of autonomic function, including heart rate variability (HRV) tests (E/I ratio, Valsalva ratio, 30:15 ratio), adrenergic tests (blood pressure responses to active standing and sustained hand grip), and sympathetic skin response (SSR) tests. Finally, the results of these tests were classified according to the Ewing classification of autonomic failure. Results: The study revealed significant differences between ET patients and the control group. Heart rate variability tests showed a marked difference between the groups. Adrenergic tests, measuring sympathetic innervation, also displayed a significant difference. The sudomotor function test exhibited noteworthy differences in onset latencies and amplitudes in the palm and sole, with ET patients showing prolonged onset latencies and decreased amplitudes. Moreover, the study found a significant correlation between disease severity and autonomic function test results and the Ewing score. Conclusion: The study highlights the presence of autonomic dysfunction in essential tremor patients, with disease severity being associated with the level of autonomic affection, as evidenced by various autonomic function tests and the Ewing score.

Keywords Essential tremor, Autonomic function tests, Heart rate variability, Sympathetic skin response

Introduction

Essential tremor (ET) is prevalent across individuals from various ethnic backgrounds. It is estimated that 0.32–1.33% of the global population is affected by ET. The prevalence of ET rises by 74% with every decade of age increase, surpassing 20% in the elderly [1]. The underlying pathology of ET remains not completely understood. Some researchers believe that the symptoms of ET primarily arise from a dysfunction in the central abnormal oscillator located within the Guillain–Mollaret triangle. Additionally, a noticeable decline in Purkinje cells in the cerebellum of patients, compared to healthy individuals, emphasizes the significance of the cerebellum in ET's development [2]. Growing evidence suggests that ET exhibits a range of motor and non-motor symptoms. The previous notion that ET is a simple, benign movement disorder has evolved into an understanding that it might be a neurodegenerative condition with a broad array of both motor and non-motor symptoms [3]. Autonomic dysfunction is recognized in neurodegenerative diseases like Parkinson's disease and Alzheimer's disease. Given that ET is also a neurodegenerative condition with non-motor symptoms, it has been hypothesized that it could potentially impact autonomic functions [2]. Based on these hypotheses, we designed this study to assess the presence and extent of autonomic dysfunction in individuals diagnosed with ET.

*Correspondence:
Osama A. Ragab
osama.ragab@med.tanta.edu.eg
[1] Neurology department, Tanta University, Tanta, Egypt

Methods

This cross-sectional study was conducted at the Neuropsychiatry Department, Faculty of Medicine. We enrolled 30 patients ET (group 1) diagnosed according to Consensus Statement on the classification of tremors (ET is a tremor syndrome characterized primarily by bilateral upper limb action tremor that has been present for at least 3 years. The tremor typically involves rhythmic oscillations of both arms, seen during voluntary movements. While the arms are most affected, essential tremor may also manifest as tremor in other locations like the head, voice, or lower limbs. Importantly, essential tremor is not associated with other neurological signs of disease such as dystonia, ataxia, or parkinsonism [4], from 1st of January to the end of March 2023. The severity of ET was evaluated using the Tremor Research Group Essential Tremor Rating Scale (TRETRS) [5]. Another 30 age- and sex-matched healthy individuals were recruited to serve as the control group (group 2).

The exclusion criteria for this study included several conditions. Firstly, patients who exhibit tremors due to other medical conditions, such as liver failure, chronic renal failure, hyperthyroidism, or Wilson's disease (Wilson's disease was clinically excluded due to the absence of Kayser–Fleischer rings, normal liver function test results, and a normal liver size as indicated by ultrasound. The patient with elevated liver function levels, hepatomegaly, or presence of Kayser–Fleischer ring was ruled out), were excluded. Secondly, the authors also exclude those with autonomic neuropathy resulting from other causes like diabetes mellitus or renal disease. Lastly, patients diagnosed with cardiac arrhythmias and ischemic heart disease were also excluded from this study.

All participants underwent the following: comprehensive medical history review, general and neurological examinations. Furthermore, laboratory investigations including fasting and postprandial blood glucose levels, serum electrolytes, renal function tests, liver function tests, abdominal ultrasonography, ophthalmological assessment, and thyroid hormonal profile were performed. Patients' beta-blocker medication was discontinued three days prior to the examination to prevent potential interference with the tests.

All participants underwent electrophysiological assessment of cardiovascular autonomic nervous system function using the TruTrace EMG7®, Deymed Diagnostic, Kudrnáčova, Hronov, Czech Republic which included the following tests:

1- Heart rate variability (HRV) test: This test evaluates cardiovagal innervation, which is the parasympathetic innervation of the heart.

A- HRV with deep breathing by measuring expiratory/inspiratory ratio (E/I): The patients were instructed to lie supine and breathe steadily and deeply at a pace of six breaths per minute. Each inhalation and exhalation lasted five seconds without pausing or gasping. The E/I ratio was measured by calculating the mean maximum R–R interval during expiration (RRmax) divided by the minimum R–R interval during inspiration (RRmin). A normal value is considered to be ≥ 1.21, with a borderline value between 1.11 and 1.20. Values ≤ 1.10 are considered abnormal [6].

B- HRV with Valsalva maneuver by measuring Valsalva ratio (VR): The Valsalva maneuver was performed to assess HRV. The patient was instructed to lie down and blow into a mouthpiece connected to a mercury manometer, maintaining an average pressure of 40 mmHg for 15 s. The onset and termination of the expiration were abrupt. To calculate the VR, the longest R–R interval immediately following the maneuver (RRmax) was divided by the shortest R–R interval during the maneuver (RRmin). A normal value for VR is considered to be ≥ 1.21, with a borderline value between 1.11 and 1.20. Values ≤ 1.10 are considered abnormal [7].

C- HRV with active standing by measuring 30:15 ratio: To assess HRV during active standing, the patient was instructed to stand up after having a continuous electrocardiogram while lying in the supine position. During the first 30 to 45 s of active standing, the R–R interval at approximately the 30th beat (the slowest heart rate at that time) and the R–R interval at approximately the 15th beat (the quickest heart rate at that time) were recorded. The 30:15 ratio was calculated by dividing the R–R interval at the 30th beat by the R–R interval at the 15th beat. A normal value for the 30:15 ratio is considered to be ≥ 1.04, a borderline value falls between 1.01 and 1.03, and values ≤ 1 are considered abnormal [8].

2- Adrenergic (sympathetic innervation) tests: blood pressure (BP) responses to active standing and sustained hand grip:

A- Systolic blood pressure response to active standing: Prior to standing, the patient remained in a supine position for a duration of 5 to 20 min. Blood pressure measurements were taken at this point. Blood pressure was measured again at 1 and up to 3 min After standing. The normal response was characterized by a decrease in systolic blood pressure of less than 10 mmHg, a borderline decline ranging from 11 to 29 mmHg, and an abnormal drop exceeding 30 mmHg [9].

B- Diastolic blood pressure (DBP) response to sustained hand grip: Blood pressure measurements were taken

at 3-min intervals in the non-tested arm while the patient applied force on a hand dynamometer, equivalent to or exceeding 30% of their maximal voluntary contraction force during fist closure. "The DBP measurement just prior to releasing the hand grip was subtracted from the DBP measurement before initiating the hand grip. A normal response was defined as an increase in diastolic blood pressure of more than 16 mmHg, a borderline increase ranging from 11 to 15 mmHg, and an abnormal response if the increase in DBP was less than 10 mmHg [9]".

3- Sudomotor function test: Sympathetic skin response (SSR) is utilized to assess the sweating pathway. This test involves stimulating the median nerve for hand-to-hand measurements and the tibial nerve for foot-to-foot measurements. The recording electrode is placed on the palms of either hand or the soles of either foot, while the reference electrodes are positioned on the dorsal surface. The presence and onset latency of the SSR response are evaluated. During the test, stimulation is applied at randomized intervals with variable intensity (ranging from 10 to 40 millivolts) and a duration of up to 0.5 ms. This variability in stimulation parameters aims to prevent habituation effects. In terms of interpretation, a normal amplitude is more than 1 mV for the hand and more than 0.2 mV for the foot. The mean palmar onset latency is 1.4 ± 0.1 s, while the plantar onset latency is 1.9 ± 0.1 s. [10]
4- Ewing classification of autonomic failure:

The Ewing classification of autonomic failure involves categorizing the results of each autonomic test as normal (0), borderline (0.5), or abnormal (1). Based on this classification, patients are then classified into different groups according to their test results. Normal: patients are classified as normal if all test results are normal or if they have only one borderline result. Early: patients fall into the early category if they have one abnormal result in any of the three heart rate tests or if they have two borderline results. Definite: patients are classified as definite if they have two or more abnormal results in the heart rate tests. Severe: patients fall into the severe category if they have two or more abnormal results in the heart rate tests, as well as one or both abnormal blood pressure tests, and if they have both blood pressure tests with borderline results. Atypical: patients with any other combination of test results that do not fit into the above categories are classified as atypical [11].

The severity of autonomic dysfunction is further divided into two categories: Severe: this category includes patients classified as definite, severe, or atypical. Minor: patients are considered to have minor autonomic dysfunction if their test results fall into the normal or early categories. The Ewing classification system provides a framework to assess the severity and type of autonomic dysfunction based on the results of various autonomic tests [11].

A signed informed consent was obtained from all participants as well as their first-degree relatives (three of our patients were illiterate so their relatives signed the consent for them). The study protocol, under the code number 36264PR4/1/23, was approved by the ethical committee.

The statistical analyses were performed using IBM SPSS Statistics version 20, released in 2013 (IBM Corporation, Armonk, NY, USA). To assess the statistical differences between the groups being studied, an independent sample t-test was conducted for numerical variables. A significance level of $P < 0.05$ was considered to indicate statistical significance. Pearson's correlation test was utilized for conducting correlation analysis. All data will be available on request.

Results

The current study included 30 ET patients, of whom 13 were female and 17 were male patients. The control group comprised 13 female and 17 male subjects, with no significant difference between both groups regarding sex and age distribution as illustrated in Table 1.

The heart rate variability (HRV) test results, including E/I ratio, Valsalva ratio, and 30:15 ratio, showed a statistically significant difference between ET patients and the control group, as demonstrated in Table 2.

The results revealed a statistically signifcant difference between ET patients and the control group regarding systolic blood pressure (SBP) response to active standing and diastolic blood pressure (DBP) response to sustained hand grip, as presented in Table 3.

The current study's results showed a statistically significant difference between ET patients and the control group regarding the onset latencies and amplitudes of sympathetic skin response (SSR) in the palm and sole. The patient group exhibited a prolongation of onset latencies and decreased amplitudes of SSR in both palm and sole, as shown in Table 4.

Table 1 Demographic data and heart rate variability (HRV) tests in the study groups

		Control	ET patients	*P*-value
Sex	Male	17	17	1.00
	Female	13	13	
Age (mean ± SD)		61.5 ± 1.8	62.2 ± 2.3	0.728

Table 2 Heart rate variability (HRV) tests in the study groups

	Group	Mean	Std. Devi	t	sig
Heart rate variability (HRV) tests					
E/I ratio	Control	1.26	0.060	3.553	0.001
	ET patients	1.15	0.131		
Valsalva ratio	Control	1.28	0.038	3.760	0.000
	ET patients	1.14	0.155		
30:15 ratio	Control	1.07	0.023	3.561	0.00
	ET patients	1.02	0.071		

Independent sample t-test. E/I: expiratory/inspiratory ratio. HRV: heart rate variability

Table 3 Adrenergic function tests results in the study groups

Adrenergic function tests	Group	Mean	Std. Devi	*t*	Sig
Systolic blood pressure (SBP) response to active standing	Control	9.65	0.98	− 3.954	0.001
	ET patients	20.25	11.91		
Diastolic blood pressure (DBP) response to sustained hand grip	Control	20.95	2.06	7.240	0.001
	ET patients	13.30	4.47		

Independent sample *t*-test

SBP systolic blood pressure. *DBP* diastolic blood pressure

Table 4 Sympathetic skin response (SSR) results between both groups

	Group	Mean	Std. Devi	t	Sig
SSR (palm) onset latency (s)	Control	1.2	0.085	− 3.023	0.004
	ET patients	1.45	0.33		
SSR (palm) amplitude (mv)	Control	1.21	0.093	4.156	0.001
	ET patients	1.01	0.21		
SSR (sole) onset latency (s)	Control	1.5500	0.14327	− 4.654	0.001
	ET patients	2.0000	0.41879		
SSR (sole) amplitude (mv)	Control	0.37	0.065	9.535	0.001
	ET patients	0.20	0.061		

Independent sample t-test. SSR: sympathetic skin response

Our study revealed that autonomic dysfunction (sympathetic and parasympathetic) occurred in approximately 40% of ET patients (12 out of 30). According to the Ewing classification of autonomic failure, 60% of the ET patients were diagnosed as normal (18 out of 30), including 10 borderline and 8 classified as normal. The remaining ET patients in our study, accounting for 40% (12 out of 30), were diagnosed as abnormal, including 4 with early autonomic dysfunction, 6 with definite dysfunction, and 2 with severe dysfunction. Among the ET patients diagnosed as abnormal (12 out of 30), they were further subdivided into two groups: those with severe autonomic dysfunction (definite or severe), representing approximately 66.7% of the abnormal group, and those with minor autonomic dysfunction (normal or early), representing about 33.3% of the abnormal group.

Our results showed a statistically significant correlation between TRETRS and autonomic function tests as well as the Ewing score. We observed that as disease severity increased, there was a greater impact on autonomic function tests. Additionally, we found a negative correlation between TRETRS and heart rate variability (HRV) tests (including E/I ratio, Valsalva ratio, and 30:15 ratio), diastolic blood pressure response to sustained hand grip, and amplitudes of sympathetic skin response (SRR) of the palm and sole. On the other hand, there was a positive correlation between TRETRS and onset latency of sympathetic skin response (SSR) of the palm and sole, as well as systolic blood pressure response to standing. Furthermore, we observed that the severity of autonomic system affection, as evaluated by the Ewing score, increased with the severity and progression of the disease. These results are shown in Table 5.

Discussion

There is growing appreciation for the prominence of non-motor symptoms in patients with movement disorders, including ET. Prospective studies have delineated a diverse range of non-motor features associated with ET, leading to the hypothesis that these symptoms likely antedate the emergence of tremor and thus represent early manifestations of underlying neural pathology rather than secondary responses. Dysfunction within central autonomic pathways may constitute an intrinsic non-motor component of ET with the potential to significantly impair patient quality of life [3].

In an early study by Damian et al., it was concluded that, using the SCOPA-Aut questionnaire, patients with PD showed increased autonomic dysfunction in various domains, while those with ET did not exhibit significant autonomic dysfunction, except for sialorrhea [12]. This study has several limitations. Firstly, it relied solely on a subjective questionnaire, which may not provide comprehensive and objective information about autonomic dysfunction. Secondly, the study did not consider the potential influence of educational, cognitive, and psychiatric manifestations within the studied population. These factors could have a significant impact on their results.

In another study, researchers utilized SSR tests to objectively evaluate autonomic functions in patients with essential tremor ET. The results revealed the presence of sympathetic dysfunction, but no abnormalities

Table 5 Correlation between essential tremor severity scale (TRETRS) and autonomic function tests, Ewing score and SSR

		E/I ratio	Valsalva ratio	30:15 ratio	(SBP) response to active standing	(DBP) response to sustained hand grip	SSR (palm) onset latency	SSR (sole) onset latency	SSR (palm) Amp	SSR (sole) Amp	Ewing score
TRETRS	Pearson correlation	− 0.739	− 0.765	− 0.724	0.799	− 0.810	0.455	0.475	− 0.704	− 0.0463	0.871
	Sig. (2-tailed)	0.000	0.000	0.000	0.000	0.000	0.003	0.002	0.000	0.003	0.000

Pearson's correlation test. E/I: expiratory/inspiratory ratio. SBP: systolic blood pressure. SSR: sympathetic skin response. DBP: diastolic blood pressure

were found in the parasympathetic system. However, the exact reason for the lack of parasympathetic dysfunction remains uncertain and could potentially be attributed to technical issues. Overall, the study's findings suggest the presence of sympathetic dysfunction in patients with ET [13].

Building on inconclusive findings from previous studies, we conducted our research to explore the potential presence of autonomic system dysfunction in patients with ET. For our investigation, we compared 30 ET patients with a control group consisting of 30 subjects. Both groups did not show significant differences in terms of gender distribution or age. Nevertheless, our results revealed significant variations between the two groups in various aspects of autonomic function.

Firstly, HRV test, including E/I ratio, Valsalva ratio, and 30:15 ratio, demonstrated a statistically significant difference between ET patients and the control group, suggesting alterations in autonomic regulation in the ET patient group. These results differ from the previous work of Kim et al., [13] who found no significant differences in heart rate between ET patients and the control group. We can explain the difference in results by considering some limitations in the Kim et al., [13] study. Firstly, the ET-patient group had a higher prevalence of hypertension compared to the control group. Furthermore, patients were tested after stopping antihypertensive medications for a week, which raises concerns about the potential influence of drug withdrawal on the results. Another limitation is the discrepancy in sample sizes between the patient and control groups, and this may affect the interpretation of the study's findings.

The current study revealed notable variations in the SBP response during active standing and the DBP response during sustained hand grip in ET patients compared to control subjects, providing further evidence of autonomic dysfunction in ET patients. Interestingly, these results differed from a study conducted by Kim et al. [13], where they did not observe a statistically significant connection between cardiovascular autonomic dysfunctions (e.g., orthostatic hypotension, supine/nocturnal hypertension, non-dipping of blood pressure) and ET patients.

A more recently conducted exercise treadmill tests on two groups: individuals with essential tremor and a control group. Chronotropic index values, indicative of sympathetic nervous system function, were notably lower in the tremor group, suggesting impaired sympathetic activity. Initially (at one- and two-minutes post-test), the resting heart rate index values—indicative of parasympathetic system function—showed no significant difference between the two groups. However, these values were significantly higher in the tremor group at three, four-, and five-minutes post-test, suggesting reduced parasympathetic activity during the recovery phase. Thus, the study concludes that individuals with essential tremor may have abnormalities in cardiac autonomic functions, with evidence of deficits in both the sympathetic and parasympathetic systems [14]. These results confirm our findings.

Additionally, the results showed significant differences in the onset latencies and amplitudes of SSR in the palm and sole between the two groups. ET patients exhibited prolonged onset latencies and decreased amplitudes of SSR in both palm and sole, pointing towards autonomic involvement in ET.

A prospective study was conducted at Razi Hospital [15], including patients with ET. The sympathetic nervous system was assessed using the SSR, evaluated at all four limbs. The parasympathetic system was evaluated according to Ewing's battery. The researchers reported neurophysiologic dysautonomia in 74% of ET patients, with reduced heart rate variability in 60% of the cases. Early parasympathetic dysfunction was observed in 86.7% of patients and definite dysfunction in 13.3%. Sympathetic dysautonomia was identified in 30% of patients. These findings confirm the high prevalence of autonomic dysfunction in ET, affecting both parasympathetic and sympathetic systems as assessed through electrophysiological methods. Our results are in alignment with these conclusions.

Moreover, we found significant correlations between the TRETRS and various autonomic function tests and the Ewing score. As the severity of ET increased, there was a greater impact on autonomic function tests. Notably, TRETRS showed a negative correlation with HRV tests, diastolic blood pressure response to sustained hand grip, and amplitudes of SSR in the palm and sole. Conversely, a positive correlation was observed between TRETRS and the onset latency of SSR in the palm and sole, as well as systolic blood pressure response to standing. These findings indicate that as the disease progressed, autonomic system involvement became more pronounced.

Reduced GABAergic function within the locus coeruleus, and subsequent adrenergic changes due to this GABAergic dysfunction in ET patients, have been proposed as potential explanations for autonomic dysfunctions, such as orthostatic hypotension. However, these hypotheses require validation through autopsy studies of ET patients, both with and without orthostatic hypotension [16].

Becktepe et al. demonstrated differences in the pupillary light response between early-onset and late-onset ET patients of the same chronological age. Their findings are interpreted as reflecting age-related biological differences between these two ET subgroups. This

supports the concept that late-onset ET represents a distinct form of aging, affecting the brain stem, which in turn influences autonomic nervous system functions [17].

Conclusion

The study indicates that individuals with essential tremor (ET) may experience dysfunction in their autonomic nervous system. Both parasympathetic tests and adrenergic sympathetic tests were used to assess this dysfunction. The research highlights a significant correlation between the severity of autonomic dysfunction in ET patients and the overall severity and advancement of the disease.

Study limitations

We sincerely apologize for the poor and short discussion of the current manuscript. We conducted a comprehensive web search on Google Scholar and PubMed, but unfortunately, we did not come across any prior studies that have compared the Total Tremor Rating Scale with various autonomic functions. This lack of existing literature has limited our capacity to enhance and expand upon our discussion.

Abbreviations

BP	Blood pressure.
DBP	Diastolic blood pressure.
E/I	Expiratory/inspiratory ratio.
ET	Essential tremor.
HRV	Heart rate variability.
PD	Parkinson's disease
SBP	Systolic blood pressure.
SSR	Sympathetic skin response.
TRETRS	Tremor Research Group Essential Tremor Rating Scale.
VR	Valsalva ratio

Acknowledgements

We wish to express our great appreciation to our patients and their family for supporting us during this work.

Author contributions

All authors have participated in designing of the study, acquisition of data, data interpretation and revising. MN recruited the patient and carried out clinical, neurological evaluation, participated in interpretation of the study results and editing the manuscript. ET recruited the patient and carried out clinical, neurological evaluation, participated in interpretation of the study results and editing the manuscript. OR recruited patients and carried out clinical, neurological evaluation and participated in interpretation of the study results. All authors have read and approved the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

All raw data will be available on the editor request.

Declarations

Ethical approval and consent for participation

The study protocol was approved by the ethical committee in Tanta University, Egypt, under the code number (36264PR4/1/23). Participation was voluntary and all contributors received detailed information about the aims of this research work and an informed written consent was obtained prior to the commencement of the study.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interest to disclose.

Received: 26 July 2023 Accepted: 31 October 2023
Published online: 20 November 2023

References

1. Pan MK, Kuo SH. Essential tremor: clinical perspectives and pathophysiology. J Neurol Sci. 2022;435: 120198.
2. Habipoglu Y, Alpua M, Bilkay C, Turkel Y, Dag E. Autonomic dysfunction in patients with essential tremor. Neurol Sci. 2017;38:265–9.
3. Lee SM, Kim M, Lee HM, Kwon KY, Koh SB. Nonmotor symptoms in essential tremor: Comparison with Parkinson's disease and normal control. J Neurol Sci. 2015;349(1–2):168–73.
4. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, Raethjen J, Stamelou M, Testa CM, Deuschl G, Tremor Task Force of the International Parkinson and Movement Disorder Society. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018. 33 (1): 75–87.
5. Ondo WG, Pascual B. Tremor Research Group Essential Tremor Rating Scale (TETRAS): Assessing Impact of Different Item Instructions and Procedures. Remor Other Hyperkinet Mov. 2020;10:36.
6. Salsone M, Vescio B, Novellino F, Morelli M, Lupo A, Arabia G, Quattrone A. Heart rate variability in patients with essential tremor: A cross sectional study. Parkinsonism Relat Disord. 2016;33:134–7.
7. Pop-Busui R, Backlund JY, Bebu I, Braffett BH, Lorenzi G, White NH, Lachin JM, Soliman EZ, DCCT/EDIC Research Group. Utility of using electrocardiogram measures of heart rate variability as a measure of cardiovascular autonomic neuropathy in type 1 diabetes patients. J Diabetes Investig. 2022;13(1):125–33.
8. Schneider C, Wiewelhove T, Raeder C, Flatt AA, Hoos O, Hottenrott L, Schumbera O, Kellmann M, Meyer T, Pfeiffer M, Ferrauti A. Heart rate variability monitoring during strength and high-intensity interval training overload microcycles. Front Physiol. 2019;10:582.
9. Hamed SA, Elhadad AF, Abdel-aal RF, Hamed EA. Cardiac autonomic function with iron deficiency anemia. J Neurol Exp Neurosci. 2020;6(2):51–7.
10. Idiaquez J, Casar JC, Fadic R, Iturriaga R. Sympathetic and electrochemical skin responses in the assessment of sudomotor function: a comparative study. Neurophysiol Clin. 2023;53(2): 102840.
11. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care. 1985;8(5):491–8.
12. Damian A, Adler CH, Hentz JG, Shill HA, Caviness JN, Sabbagh MN, Evidente VG, Beach TG, Driver-Dunckley E. Autonomic function, as self-reported on the SCOPA-autonomic questionnaire, is normal in essential tremor but not in Parkinson's disease. Parkinsonism Relat Disord. 2012;18(10):1089–93.
13. Kim JS, Oh YS, Park HE, Lee SH, Park JW, Song IU, An JY, Park HJ, Son BC, Lee KS. Cardiovascular autonomic dysfunctions in elderly patients with essential tremor: comparison with healthy controls. Neurol Sci. 2016;37:711–6.
14. Yaşar H, Büyüklü M. Investigation of the cardiac autonomic functions in patients with essential tremor. Koşuyolu Heart J. 2022;25(2):170–6.
15. Rekik A, Nasri A, Kacem I, Mrabet S, Gargouri A, Djebara MB, Gouider R. Autonomic dysfunction in patients with essential tremor. J Neurol Sci. 2019;405:275.

16. Kaya D, Aydin AE, Isik AT. Orthostatic Hypotension in elderly patients with essential tremor. Clin Interv Aging. 2021;22:155–60.
17. Becktepe JS, Govert F, Kasiske L, Yalaz M, Witt K, Deuschl G. Pupillary response to light and tasks in early and late onset essential tremor patients. Parkinsonism Relat Disord. 2019;66:62–7.

Publisher's Note