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**Can heart rate variability be utilised to predict compensatory sweating
after endoscopic thoracic sympathectomy in patients with primary focal
hyperhidrosis?**

Да ли се варијабилност срчане фреквенције може користити за предвиђање
компензаторног знојења након ендоскопске торакалне симпатикотомije
код болесника са примарном фокалном хиперхидрозом?

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Can heart rate variability be utilised to predict compensatory sweating after endoscopic thoracic sympathectomy in patients with primary focal hyperhidrosis?

Да ли се варијабилност срчане фреквенције може користити за предвиђање компензаторног знојења након ендоскопске торакалне симпатикотомije код болесника са примарном фокалном хиперхидрозом?

SUMMARY

Introduction/Objective Hyperhidrosis is a condition of pathological excessive sweating that exceeds the body's physiological requirements for thermoregulation. Endoscopic thoracic sympathectomy (ETS) is a commonly used treatment for primary focal hyperhidrosis (PFH); however, it may result in compensatory sweating (CS), which represents its most frequent postoperative complication. This study aimed to investigate whether heart rate variability (HRV) parameters could predict CS.

Methods A prospective single-center study was conducted in 100 patients with primary focal hyperhidrosis (PFH) who underwent ETS. Preoperatively, all patients underwent 24-hour Holter ECG monitoring to assess standard HRV parameters. ETS was performed by transection of the sympathetic chain at the level of the third (R3) and fourth rib (R4), including the accessory Kuntz fibers. One month after surgery, the presence and severity of CS were assessed.

Results CS was absent in 61% of patients ($p=0.028$). Mild CS was the most common form ($p < 0.01$). No statistically significant differences were observed in the analyzed preoperative HRV parameters between patients with and without CS ($p > 0.05$), including the low-frequency (LF)/high-frequency (HF) ratios, which represent balanced autonomic activity ($LF/HF < 2$) and sympathetic predominance ($LF/HF \geq 2$). ROC curve analysis showed that age had significant predictive accuracy for CS (AUC 0.7333; 95% CI 0.634–0.833; $p < 0.01$), with an optimal cutoff of 23.5 years (sensitivity 0.82, specificity 0.47).

Conclusion HRV parameters cannot reliably predict CS following bilateral ETS in patients with PFH. The study confirmed that the optimal age for surgery is below 23.5 years.

Keywords: video-assisted thoracic surgery; sweating; sympathectomy; autonomic nervous system; minimally invasive surgery

САЖЕТАК

Увод/Циљ Хиперхидроза је стање патолошког прекомерног знојења које превазилази физиолошке потребе организма за терморегулацијом. Ендоскопска торакална симпатикотомија (ЕТС) представља уобичајен начин лечења примарне фокалне хиперхидрозе (ПФХ), али може довести до појаве компензаторног знојења (КЗ), које представља њену најчешћу постоперативну компликацију. Циљ ове студије био је да испита да ли параметри варијабилности срчане фреквенције могу предвидети појаву КЗ.

Методе Спроведена је проспективна моноцентрична студија на 100 болесника са хиперхидрозом ПФХ који су подвргнути ЕТС. Преоперативно је код свих болесника урађен 24-часовни Холтер ЕКГ ради процене стандардних параметара варијабилности срчане фреквенције. ЕТС је изведена пресецањем симпатичког ланца на нивоу трећег (Р3) и четвртог ребра (Р4), укључујући и помоћна Кунцова влакна. Након месец дана процењивани су присуство и степен КЗ.

Резултати КЗ није било присутно код 61% болесника ($p = 0,028$). Благо КЗ било је најчешћи облик ($p < 0,01$). Није утврђена статистички значајна разлика у анализираним преоперативним параметрима варијабилности срчане фреквенције између болесника са и без КЗ ($p > 0,05$), укључујући категорије ЛФ/ХФ односа које представљају уравнотежену аутономну активност ($ЛФ/ХФ < 2$) и симпатичку доминацију ($ЛФ/ХФ \geq 2$). Анализа ROC криве показала је да старост има статистички значајну предиктивну тачност за појаву КЗ (AUC 0,7333; 95% CI 0,634–0,833; $p < 0,01$), са оптималном граничном вредношћу од 23,5 година (сензитивност 0,82; специфичност 0,47).

Закључак Параметри варијабилности срчане фреквенције не могу поуздано предвидети појаву КЗ након билатералне ЕТС код болесника са ПФХ. Студија је потврдила да је оптимална старост за извођење операције испод 23,5 године.

Кључне речи: видео-асистирана торакална хирургија; знојење; симпатектомија; аутономни нервни систем; минимално инвазивна хирургија

INTRODUCTION

Hyperhidrosis is defined as a condition of pathological excessive sweating that exceeds the body's physiological needs for thermoregulation. Hyperhidrosis can be secondary, most often

generalized, as a consequence of various diseases and conditions and primary, focal or cryptogenic, with involvement of the palms, soles or axillae. The pathophysiology of primary focal hyperhidrosis (PFH) remains unclear. Excessive sweating in PFH is a direct consequence of increased excretion of sweat glands. Eccrine glands in individuals with PFH are completely normal in anatomy, number, and distribution [1]. It has been suggested that PFH results from complex hyperstimulation of the sympathetic nervous system (SNS) when exposed to emotional stress. Any emotional state or exposure to stress can be an activator of an episode of PFH, but symptoms can also occur without any emotional or thermal stimuli. After the action of activating stimulus, sweating occurs instantly and is continuous. If conservative treatment fails, endoscopic thoracic sympathectomy (ETS) is the method of choice [2, 3]. The most common complication of ETS is compensatory sweating (CS) [4]. CS affects regions of the body that have not been previously surgically altered. The mechanism of action is still unknown [5]. Some research also shows a high prevalence of depression and anxiety disorders in this group, along with specific dietary habits, including increased caffeine consumption and the recognition of spicy and fatty foods as sweating triggers [6, 7]. Consensus of experts stated that the preferred age for surgery, in order to prevent CS, is under 25 years and with a body mass index under 28 [3, 8]. Neuron bodies responsible for the intervention of the sweat glands of the trunk and upper extremities are located at the level of the second to eighth thoracic segments of the spinal cord [9]. With the current evidence level, it is generally accepted that most cardiac sympathetic fibers also originate from the spinal cord at the level of first to fifth thoracic segments [10, 11].

Heart rate variability (HRV) is a non-invasive, easily reproducible method of measuring the influence of the autonomic nervous system on cardiac function. The data were obtained through 24-hour Holter monitoring and subsequent computer processing. HRV indices provide numerical values of cardiac Autonomic Nervous System tone. The basic principle of HRV is

the measurement of the change in the interval between two consecutive heartbeats -rhythm fluctuations [12]. Research worldwide indicates that patients with hyperhidrosis experience a significant decrease in quality of life. This reduction is reflected in lower scores on the mental component of the SF 36 questionnaire and decreased values on the Dermatology Life Quality Index [13, 14]. However, after treatment of primary hyperhidrosis, the quality of life of patients improves significantly, and this improvement is maintained for many years after the intervention[15, 16]. This is shown by global meta-analyses and observations by domestic authors [17].

The aim of this study is to confirm the potential existence of HRV parameters that would serve as a prediction of CS.

METHODS

A prospective, monocentric, non-interventional study was conducted at the Institute of Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia, in the period from March 2022 to July 2024. After voluntarily signing the informed consent form, 100 subjects were included in the study. Patients were divided into two equal groups (50–50) according to the number of affected regions: palmar and plantar (PP) PFH, and Palmar, Plantar and Axillar (PPA) PFH. Inclusion criteria were: first operation for PFH, Hyperhidrosis Disease Severity Scale grades three and four. Exclusion criteria: psychiatric diseases, cardiac diseases and use of drugs, acute infections, use of alcohol, narcotics and tobacco, professional sports. 24-Hour Holter monitoring: "EVO 4 - Spacelabs Healthcare Ltd, United Kingdom" with data processing software "Spacelabs Healthcare 2018 - Sentinel v11.0.0.9904" was undertaken preoperatively. All standard HRV parameters in the time and frequency domains were monitored.

In all subjects, standardized operative treatment was performed in the form of ETS by cutting the sympathetic chain at the level of R3 and R4 (ultrasound hook, R3, top and bottom - R4, top and bottom) and cutting the accessory Kunz fibers. After the expert consensus from 2011, the term sympathicotomy was established for the cutting of sympathetic fibers, while the term sympathectomy means the removal of part of the sympathetic trunk [8]. Study controls were performed on the seventh day and one month after discharge from the hospital. One month after surgery, the presence and degree of CS was verified. Patients reported the presence of one of four offered degrees of CS: absent, minor, disabling or disabling.

Statistical methods

From the methods of descriptive statistics, the measures of central tendency were used in the study, specifically the arithmetic mean, measures of variability, namely the standard deviation and median, as well as relative numbers. From the methods of analytical statistics, methods for identifying empirical distributions (Kolmogorov-Smirnov test) were used, along with methods for assessing the significance of differences depending on the type of data and distribution, specifically the Independent Samples t-test, Mann–Whitney U test, and χ^2 test. To assess the significance of the relationship between predictor variables and outcome in relation to the time elapsed until the outcome, univariate and multivariate Cox regression analysis were used. The discriminatory capacity, i.e., the predictive accuracy of the examined parameters for the presence of CS, was determined by the area under the ROC curve (c-statistic), and the best cut-off value of variables for predicting CS was also estimated. A C statistic above 0.7 was considered an acceptable discriminative capacity of the model. Statistical data processing was performed in JASP software v 0.96.0, and a $p < 0.05$ was used as the criterion for statistical significance.

RESULTS

The study included 100 patients, aged 18 to 54 years, with an average age of 28.33 ± 8.51 years, a median age of 24 years (10/100), of which 57 (57%) were female. There was no statistically significant difference in the frequency of gender in the observed groups PP and PPA PFH, $p = 0.162$.

CS was absent in 61 (61%) operated patients ($p = 0.028$). The minor CS was most frequent ($p < 0.01$), and the incidence of unpleasant CS was higher than disabling CS ($p = 0.011$) (Figure 1).

There were no statistically significant differences in the mean values of the age of the patients ($p < 0.32$), as well as in the frequency of gender and CS in relation to the type of PFH ($p > 0.05$) (Table 1).

There was no statistically significant difference in the mean values of the examined preoperative HRV parameters in patients with and without CS ($p > 0.05$) (Table 2).

Patients with CS were statistically significantly older ($p < 0.01$). There was no statistically significant difference in the frequency of different sexes in patients with and without CS (Table 3).

In the group of patients with $LF/HF < 2$ patients, there was no statistically significant difference in the mean values of preoperative LF/HF (1.59 vs. 1.44; $p = 0.163$), as well as in the group of patients with $LF/HF \geq 2$ (3.41 vs. 3.50; $p = 0.801$). In the group of PP PFH and $LF/HF < 2$ patients, there was no statistically significant difference in mean LF/HF values 1.66 vs. 1.38; $p = 0.078$), as well as in the group of patients with $LF/HF \geq 2$ (3.24 vs. 3.33; $p = 0.851$). In the group of patients with PPA PFH and $LF/HF < 2$, there was no statistically significant difference

in the mean values of preoperative LF/HF (1.54 vs. 1.51; $p = 0.876$), as well as in the group of patients with $LF/HF \geq 2$ (3.63 vs. 3.61; $p = 0.974$) (Figure 2).

Univariate Cox regression analysis showed that univariate statistically significant predictors of postoperative CS are age ($p < 0.01$), but also HF after statistical control for age ($p < 0.01$) (Table 4).

Multivariate Cox regression analysis showed that age (RR 1.11 95% CI (1.05–1.18); $p < 0.01$) and HF before ETS (RR 1.00 95% CI (1.00–1.001), $p < 0.01$) were independent predictors of CS. The analysis of ROC curves for the patient age variable showed that it has a statistically significant predictive accuracy for the occurrence of HF (area under the ROC curve 0.7333; 95% CI (0.634–0.833); $p < 0.01$), while it was not shown for HF. On that occasion, the best threshold value of the patient's age for predicting CS after ETS was determined, which is 23.5 years, with a combination of sensitivity 0.82 and specificity 0.47.

DISCUSSION

CS as the most frequent side effect of ETS was present in 39% of subjects (39/100), whereby it was characterized as unpleasant by 9% (9/100) and disabling by 1% (1/100). The literature reports a remarkably wide range in the prevalence of CS, varying from 3% to 98%. CS has been identified as the main culprit for patient dissatisfaction after ETS [4]. Such a large incidence range was a consequence of the unclassified nomenclature, as well as the definition of the CS itself. In some studies, CS was reported exclusively when it reached incapacitating levels, while others documented even minimal subjective feeling of increased sweating [5, 18, 19]. Many studies have indicated that the degree of CS is directly proportional to the height of the transection level of the sympathetic trunk, with a note that the degree of CS is the highest with

R2 transection [18, 19]. Our study was designed so that all sympathetic chain transections were performed at the R3-R4 level precisely to avoid an increased incidence of CS.

We believe that our study degree of CS is at a satisfactory level, which is primarily a consequence of the standardized operative technique, suitable selection of patients for ETS and preoperative detailed information of the patient about potential side effects and complications. It is interesting that the only patient with a disabling form of CS was 37 years old male (recommended age for CS prevention is 25 years) and that he suffered from malaria in childhood.

An easily available, non-invasive predictor of CS would greatly improve patient selection and the success of the ETS. Hyper stimulated sympathetic fibers responsible for sweating also partially innervate the heart. It makes sense to examine the potential use of HRV as a diagnostic method for the prediction of CS. There are three types of HRV measurement: ultra short (under five minutes), short (five minutes) and 24h measurement. These measurements cannot be compared with each other due to different influences on the 24-hour measurement, which best reflects the real situation [20, 21]. This is why we have used the 24-hour measurement of HRV.

The LF/HF ratio has been proposed as an indicator of sympathovagal balance, with values between 0.5–2. The values of LF/HF which are considered as indicators of this balance are 0.5–2. Values over two units are considered a consequence of pathological SNS stimulation or parasympathetic nervous system (PNS) inactivity, while values below 0.5 are a consequence of pathological PSN stimulation [12, 20, 22]. We singled out LF/HF as a parameter to determine whether CS is more common in the group with sympathetic predominance ($LF/HF \geq 2$). It was determined that there is no difference in the occurrence of CS in relation to LF/HF values. The difference did not exist even when this group was divided into PP and PPA PFH. The lowest measured value of LF/HF in our study was 0.9. Consequently, not a single patient had

parasympathetic predominance, as expected, but all were either in balance or in the zone of sympathetic predominance.

After the analysis of the HRV parameters to predict the occurrence of CS, the existence of a statistically significant correlation of HF with CS was established. However, after ROC curve testing, significance was not obtained. We identified only two studies that correlated HRV and CS. Hyan et al. do not report any HRV parameter as a possible predictor of CS [23]. Jeong et al. report HF as a positive predictive factor for CS [24]. Unlike our study, HF prediction was not tested on ROC curves. Both studies were performed with 5-minute HRV recordings, which is a major limitation.

Although none of the HRV parameters in our study can be used to predict CS, we confirmed that CS is correlated with age and that age below 23 has a lower probability of CS. In current recommendations, a patient aged below 25 years is the appropriate time for ETS [3,5,8].

CONCLUSION

Heart rate variability parameters cannot be used as predictors for the occurrence of CS after bilateral thoroscopic sympathectomy in persons suffering from primary focal hyperhidrosis. Although the HF parameter was singled out in our study as a potential predictive factor, after ROC curve testing, significance was not obtained. -Our study confirmed that the optimal time to perform bilateral thoroscopic sympathectomy is below 25 years, more precisely below 23.5 years.

Ethics: The study was approved by the Ethics Commission of the Institute for Pulmonary Diseases of Vojvodina under the number "6-VI/1" on December 9, 2021, and in accordance with the principles of the Declaration of Helsinki.

Conflict of interest: None declared.

Paper accepted

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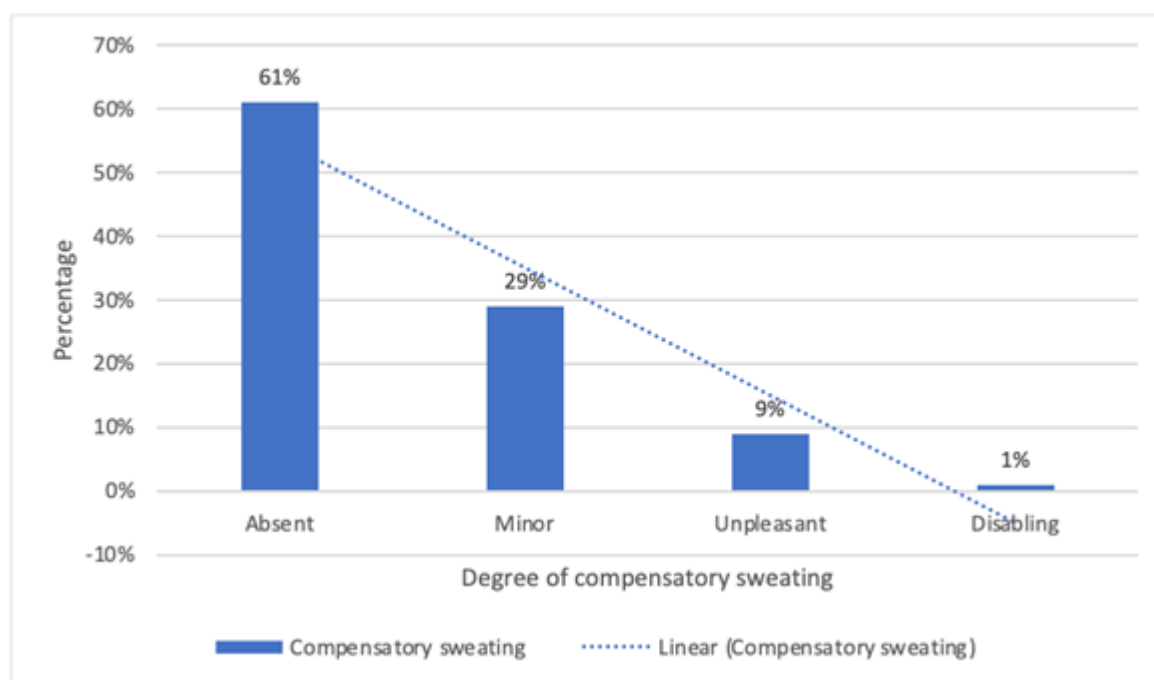


Figure 1. Frequency of different degrees of postoperative compensatory sweating

Table 1. Mean patient age and gender and incidence of postoperative compensatory sweating in relation to type of primary focal hyperhidrosis

Parameters		Type of hyperhidrosis								p
		Palmar-plantar				Palmar-plantar-axillary				
		Mean	SD	N	%	Mean	SD	N	%	
Age (years)		29.18	8.73			27.48	8.27			0.320 ^a
Gender	Male			30	52.6			27	47.4	0.545 ^b
	Female			20	46.5			23	53.5	
Compensatory sweating	Absent			32	52.5			29	47.5	0.666 ^b
	Minor			13	44.8			16	55.2	
	Unpleasant			5	55.6			4	44.4	
	Disabling			0	0.0			1	100.0	
Compensatory sweating	No			32	52.5			29	47.5	0.539 ^b
	Yes			18	46.2			21	53.8	

SD – standard deviation;

^aMann–Whitney U-test

Table 2. Mean values of the examined heart rate variability parameters in patients with and without compensatory sweating

Heart rate variability parameters	Compensatory sweating								p
	No				Yes				
	Mean	SD	Min	Max	Mean	SD	Min	Max	
HR maximum	127.7	19	85	173	121.3	16.8	92	162	0.088 ^c
HR minimum	53.9	8.5	40	77	52.7	6.6	38	70	0.466 ^c
HR	74.3	9.4	55	98	72.7	9.3	49	92	0.390 ^c
SDNN (ms)	144.1	31.9	86.5	229.7	146.2	28.8	99.9	232.2	0.849 ^c
NN (RR)	822.6	104	598	1072.	842.9	114.9	649.4	1222.5	0.363 ^c
SDANN	153.1	71.3	60.1	402.9	142.8	65.8	75.9	428.6	0.377 ^c
RMSSD (ms)	53.2	51.2	21	412.7	55.2	30.6	23.5	151	0.283 ^c
pNN50%	20.8	30.3	2.4	236.1	19.9	12.8	1.9	57.1	0.322 ^c
LF (ms2)	1290.6	721.8	298.4	4213.5	1519.4	1037.1	359.9	3951	0.621 ^c
LF normalized	68.6	9.6	47	91.7	65.3	13.8	16.1	86.2	0.300 ^c
HF	532.1	359.1	98.2	1466.1	945.8	1513.9	10.7	8585.5	0.276 ^c
HF normalized	27.9	9.2	12.1	51.2	31.7	19.81	4	127.9	0.527 ^c
LF/HF	2.9	1.4	1	6.7	2.7	1.42	0.8	7.1	0.334 ^c

HR – heart rate; RR – relative risk; SDNN – standard deviation of normal RR intervals; NN – normal RR interval; SDANN – standard deviation of all average five-minute RR intervals; RMSSD – square root of the mean value of the square of the difference of successive RR intervals; pNN50% – The proportion of adjacent normal RR intervals that differ by more than 50 ms; LF – low-frequency range of heart rate variability; HF – high-frequency range of heart rate variability;

^cindependent samples t-test

Table 2. Mean age and frequency by gender in patients with and without compensatory sweating

Parameters		Compensatory sweating								p
		No				Yes				
		Mean	SD	N	%	Mean	SD	N	%	
Age (years)		25.61	6.60			32.59	9.45			< 0.01 ^a
Sex	Male			35	61.4			22	38.6	0.924 ^b
	Female			26	60.5			17	39.5	

^aMann–Whitney U-test;^b χ^2 test

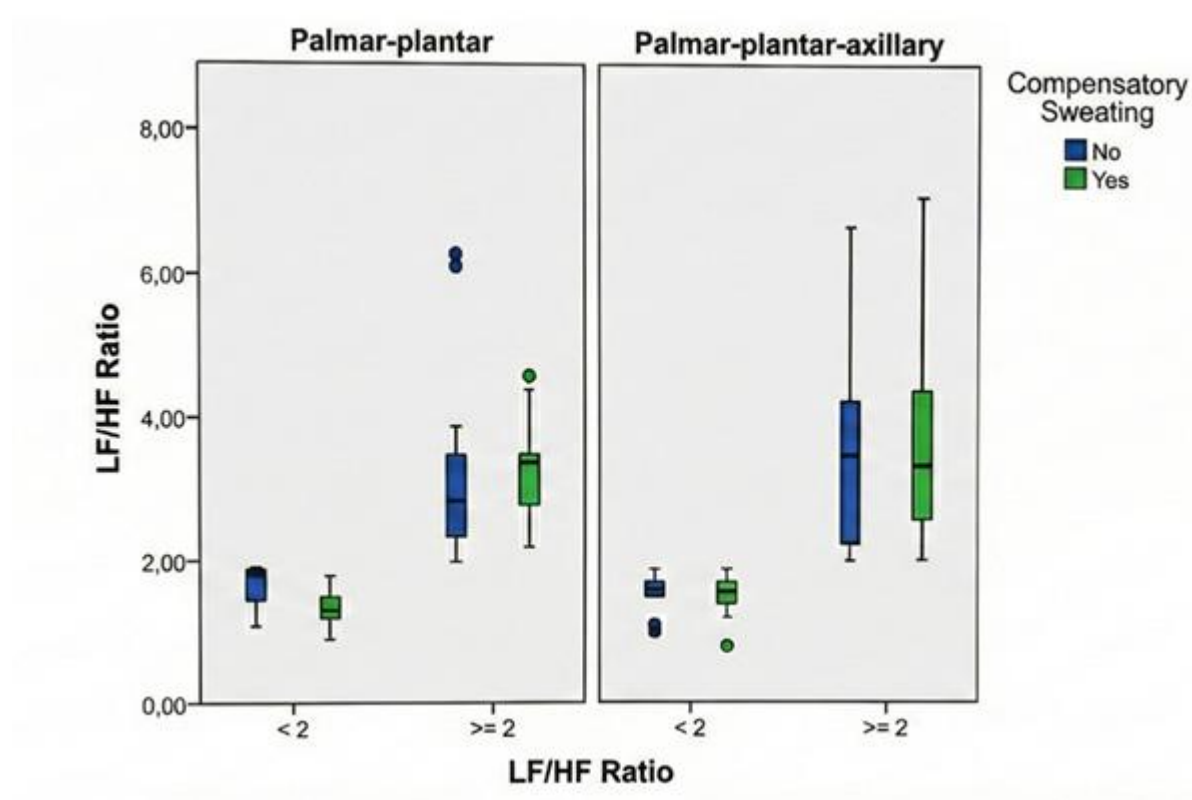


Figure 2. Mean values of LF/HF ratio in groups according to the presence of compensatory sweating, in patients with different types of hyperhidrosis; LF – low-frequency range of heart rate variability; HF – high-frequency range of heart rate variability

Table 3. Univariate Cox regression for the prediction of compensatory sweating, controlled for age

Variable	RR	95% – CI	p
Age (years)	1.11	1.05–1.18	< 0.01 ^d
Gender	1.04	0.46–2.34	0.92 ^d
HR maksimum	0.99	0.97–1.01	0.32 ^d
HR minimum	0.97	0.94–1.01	0.15 ^d
HR	0.99	0.94–1.04	0.67 ^d
SDNN (ms)	1.01	0.99–1.02	0.11 ^d
SDNN (125–149) (ms)	2.307	0.99–5.71	0.07 ^d
SDNN (> 150) pre (ms)	2.069	0.84–5.11	1.15 ^d
NN (RR)	1.00	0.99–1.01	0.14 ^d
SDANN	1.00	0.99–1.01	0.59 ^d
RMSSD (ms)	0.82	0.99–1.01	0.82 ^d
pNN50%	0.99	0.98–1.01	0.91 ^d
LF (ms ²)	1.00	1.00–1.00	0.07 ^d
LF normalized	0.98	0.96–1.01	0.23 ^d
HF	1.00	1.00–1.01	< 0.01 ^d
HF normalized	1.01	0.99–1.03	0.08 ^d
LF/HF	0.97	0.75–1.23	0.77 ^d

HR – heart rate; RR – relative risk; SDNN – standard deviation of normal RR intervals; NN – normal RR interval; SDANN – standard deviation of all average five-minute RR intervals; RMSSD – the square root of the mean value of the square of the difference of successive RR intervals; pNN50% – the proportion of adjacent normal RR intervals that differ by more than 50 ms; LF – low-frequency range of heart rate variability; HF – high-frequency range of heart rate variability; CI – confidence interval;

^dunivariate Cox regression