# Haemodynamic indices of the early phase of the tilt test: does measurement predict outcome?

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#### Abstract

**Introduction:** Tilt testing (TT) is a well-established tool in the diagnosis of syncope. However, it is time-consuming. Therefore, identification of parameters that could shorten the duration of TT is desirable.

**Aim:** To identify and assess the usefulness of early haemodynamic parameter changes in prediction of the tilt test results in a group of patients with syncope of unknown aetiology.

**Methods:** The study involved a group of 105 patients, including 61 women and 44 men, with a mean age of 34.2±13.7 (from 13 to 82) years, with at least two episodes of syncope in the last 6 months. The head-up tilt test was carried out according to protocol 60/20 min and if necessary was continued after administration of sublingual nitroglycerine in a dose of 250 g. The assessment of haemodynamic indices was performed employing the beat-to-beat method using the Portapres M2 device. Systolic (SBP) and diastolic (DBP) arterial pressure, heart rate (HR), cardiac output (CO) and stroke volume (SV), and total peripheral vascular resistance (TPR) were analysed. The measured values of haemodynamic indices were calculated by means of averaging 10-second intervals within 3-minute studied periods either before or after tilting a patient. Mean baroreceptor sensitivity (BRS) for the same 3-minute-long intervals was evaluated using the xBRS (cross-correlation) method. In the analysis, differences (R<sub>v</sub>) of the haemodynamic values between the beginning of tilting a patient and the rest period were also calculated.

**Results:** Loss of consciousness was noted in 47 (46%) of the studied patients – group I. The remaining subjects (58 patients, 54%) did not develop syncope during TT (group II). The univariate and multivariate logistic analyses of regression revealed that the mean vascular resistance difference (meanR<sub>TPR</sub>) <-10 dyn.s/cm<sup>8</sup> was an independent risk factor of syncope ( $\chi^2$ =3.4; p<0.0008). The presence of this risk factor was associated with a significantly higher risk of a positive response during the tilt test (65% vs 39%; RR: 1.7, 95% CI: 1.2-3.2). In predicting a positive TT result, sensitivity of this parameter was 65%, specificity was 61% and the prognostic value of the positive and negative result was 32% and 86%, respectively.

**Conclusions:** In patients with syncope of unknown origin, an early (within first 3 minutes of TT) asymptomatic fall in total peripheral vascular resistance is a significant predictor of a positive final result of the test.

Key words: vasovagal syncope, systemic vascular resistance, tilt test

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## Introduction

Excessive vasodilatation is one of the mechanisms responsible for syncope in the course of the vasovagal reaction (VVR). Detailed haemodynamic studies indicate that vasodilatation is the most common repetitive phenomenon occurring just prior to the onset of reflex VVR and a sudden lost of consciousness. It has been

shown that it accompanied not only the vasovagal response or complex reaction, but also preceded syncope of the cardiodepressive mechanism with pathologic bradycardia or asystole lasting several seconds [1-4].

The mechanism of the reaction responsible for arterial pressure fall during VVR remains unclear. Earlier studies stressed the importance of baroreceptor activity and the autonomic nervous system, with their

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functional and anatomical interconnections that control, through a number of neurotransmitters, the systemic and local reflex regulatory mechanisms [1-4]. According to Moak et al. [5], hypotension observed during the vasovagal reaction is a net result of the reduction in systemic peripheral vascular resistance as well as the decreased myocardial contractility in response to a sudden fall of sympathetic activity.

The availability of non-invasive diagnostic techniques capable of continuous acquisition and assessment of haemodynamic parameters facilitates the early diagnosis of significant cardiovascular disturbances, explanation of the pathophysiologal mechanisms involved in a number of clinical forms of reduced orthostatic tolerance and eventually the development of specific treatments. A potential benefits of using continuous methods of analysis include also shortening (i.e. optimisation) the duration of examination and, indirectly, reduction of costs.

The purpose of this study was to identify and assess the usefulness of early haemodynamic parameter changes in prediction of the tilt test (TT) results in a group of patients with syncope of unknown aetiology.

# Methods

#### Study group

The study involved a group of 105 patients, including 61 women and 44 men, with a mean age of 34.2±13.7 (from 13 to 82) years, with a history of at least two episodes of syncope in the last 6 months, who were selected to undergo TT according to the European Society of Cardiology guidelines for the management of patients with syncope [6].

#### Tilt test protocol

All patients underwent TT in the morning hours (9 to 11 a.m.) after an overnight rest. The Portapres M2 device equipped with computer software Beatscope v. 1.1 (TNO BMI, the Netherlands) was used for the continuous and non-invasive assessment of the haemodynamic indices. The measurements were taken from the carefully fitted pressure cuff with an integrated photoplethysmographic sensor, placed on the middle phalanx of the III or IV finger of the left hand. After a 15-minute rest period in the supine position, each subject was suddenly brought to an upright position employing a tilt table with footboard support to a tilt angle of 60 degrees. The patient was kept in this position until syncope occurred, which was considered a positive test result, but no longer than for 20 minutes. If the passive test (TT<sub>n</sub>) did not induce syncope, sublingual nitroglycerine (crushed tablet) in the dose of 250 g (TT<sub>NTG</sub>) was administered and TT was continued until a positive response occurred, but again no longer than for an additional 20 minutes.

The syncope reaction type was defined according to the VASIS (the Vasovagal Syncope International Study) classification [7].

During examinations the following parameters were monitored: systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, in mmHg), heart rate (HR, beats per min), stroke volume (SV, mL), cardiac output (CO, L/min) and total peripheral vascular resistance (TPR, dyns/cm<sup>8</sup>). The measured values of the haemodynamic parameters were retrospectively analysed by means of averaging 10-second intervals within 3-minute study periods either before or after tilting a patient.

Sensitivity of baroreceptors (baroreflex sensitivity, BRS, ms/mmHg) was examined employing the technique of cross correlation and regression between SBP and pulse period (PP), taking into account consecutive 10-second sequences of pulse wave evolution in which an increase (or decrease) in arterial pressure was accompanied by gradual prolongation (or shortening) of the length of the pulse period. The final value of BRS was evaluated as the arithmetic mean of all partial calculations derived from 3-minute study periods.

In the further analysis, for each haemodynamic variable the minimum averaged 10-second value from the 3-minute period of acquisition in the supine position was selected. This was used as the reference value (minE1 $_{\rm X}$ ). Then, for each haemodynamic parameter the difference (R $_{\rm X}$ ) between each 10-second mean value acquired within the first 3 minutes of tilt and the reference value minE1 $_{\rm X}$ , was calculated. The following parameters derived from the aforementioned differences were selected for further analysis: maxR $_{\rm X}$  (the largest difference), minR $_{\rm X}$  (the smallest value), and meanR $_{\rm X}$  (the mean value). Additionally, nR $_{\rm X}$  (i.e. the number of variables with lower values during the tilt period than the corresponding reference value in the supine position) was also included in the analysis.

According to Pitzalis et al. [8], only values lower than zero, derived from the calculation of  $\min E1_x$ -R $_x$  (118), were considered in the prognostic assessment of TT results.

## Statistical analysis

The statistical analysis was performed using the Statistica 6.0 PL (StatSoft Poland) software package. The significance of the difference between selected means for parametric and nonparametric variables was assessed by Student's t-test and the Wilcoxon signed rank test, respectively. The frequencies of discrete parameters in the groups were compared using the chisquare test. The power of associations between

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**Table I.** Characteristics of the studied patients

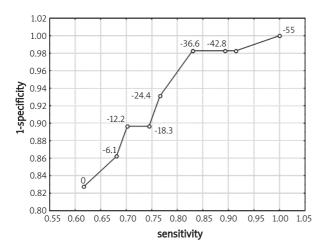
Clinical data Tilt test		est	р
	Positive	Negative	
Number of patients	47	58	NS
Age (years)	33.9±15.3	34.3±12.4	NS
Gender F/M	27/20	34/24	NS
Number of syncope episodes in the last 6 months	2.8±3.7	2.1±2.9	NS
History of syncopal episodes (months)	75.1±97.4	69.4±82.4	NS

variables was estimated based on contingence C — Pearson index. The correlations between TT results and values of haemodynamic parameters were calculated by the logistic regression method and odds ratios (OR) were assessed. Maximum values of the low tercil range were used as a threshold of dichotomous classification of variables. Sensitivity, specificity and the diagnostic value of positive or negative test results were evaluated according to widely accepted principles. Graphic correlations between method sensitivity and specificity were presented using receiver operating characteristic (ROC) curves. The probability of a positive TT result was calculated employing the relative risk (RR) index. A value of P less than 0.05 was considered significant.

#### Results

# Head-up tilt test

The complete protocol of TT resulted in a loss of consciousness in 47 (46%) of the studied patients – group I – while in the remaining subjects (58 patients, 54%) syncope did not occur – group II. In group I, 31



**Figure 1.** Comparison of total diagnostic accuracy for various mean  $R_{TPR}$  values

(66%) patients had mixed, 4 (9%) vasodepressive and 12 (25%) cardiodepressive type of VVR. Eight (17%) patients developed syncope during  $TT_b$ , and 39 (83%) during  $TT_{NTG}$ . There were no significant differences regarding the age of patients when those who developed VVR during  $TT_b$  and those who had syncope after nitroglycerine infusion (38.8±18.1 vs 32.9±14.7; p>0.3) were compared. The clinical characteristics of the studied group of patients are outlined in Table I.

## Haemodynamic parameters

Values of the studied variables calculated for all examined patients with either positive or negative TT results are shown in Table II.

The adopted method of assessment of the haemodynamic indices derived from both stages of the study showed a statistically significant difference between the study groups in regard to the following parameters:  $\max R_{SBP}$ ,  $\min R_{SBP}$ ,  $\min R_{TPR}$  and  $\max R_{TPR}$ .

# Predictive value of haemodynamic indices

The univariate logistic regression analysis for a correlation between the studied indices and an episode of syncope during TT showed that the most predictive in the diagnosis of patients at risk of syncope were the following values: minR<sub>SBP</sub>  $\leq$ 6 mmHg, mean R<sub>SBP</sub>  $\leq$ 3.2 mmHg, minR<sub>TPR</sub>  $\leq$ 18 dyn.s/cm³ and meanR<sub>TPR</sub>  $\leq$ 10 dyn.s/cm³ (Table III). The multivariate regression analysis with the code variable describing the result of TT (positive or negative) identified out of 4 examined indices meanR<sub>TPR</sub>  $\leq$ 10 dyn.s/cm³ as an independent risk factor of syncope ( $\chi$ ²=3.4; p <0.0008). The presence of this risk factor was associated with a significantly higher risk of a positive response during TT (65% vs 39%; RR: 1.7, 95% CI: 1.2-3.2).

In predicting a positive TT result, sensitivity of mean  $R_{TPR}$  value lower than -10 dyn.s/cm was 65%, specificity was 61% and the prognostic values of the positive and negative results were 32% and 86%, respectively. The statistical analysis of ROC revealed the highest predictive value of mean  $R_{TPR}$  values in the range of -10 to -12 dyn.s/cm (Figure 1).

The developed model matching accuracy with the empirical data was confirmed by the value of adjustment merit statistics (reliability logarithm=47;  $\chi^2$ =27.5) and probability level (p<0.0001), which indicated that the analysed model added a new value into a risk stratification according to the proposed method. The results of the assessed correlations between estimated values of mean  $R_{TPR}$  and selected TT variables, and patient characteristics are presented in Table IV.

Table II. Haemodynamic indices in the consecutive stages of TT

Parameter	Stage of TT		All patients (n=105)		Group		P
					I (n=47)	II (n=58)	
			Mean ±SD	Low tercil	Mean ±SD	Mean ±SD	
HR [beats/min]	I (minE1 <sub>HR</sub> )		62.4±11.8	55	62±13.5	62.7±9.4	>0.7
	II (R <sub>HR</sub> )	nR	1.4±4.2	0	1.4±4.2	1.3±4.3	>0.8
		minR	12.8±13.7	4	12.5±12.9	13.1±14.5	>0.8
		maxR	29.9±17.7	17.9	32.1±19.9	27.3±14.3	>0.1
		meanR	-0.7±2.2	0	-0.6±2.7	-0.8±2.7	>0.4
SBP [mmHg]	I (minE1 <sub>SBP</sub> )		122±12.6	115	121.3±10.3	122.9±10.6	>0.4
	II (R <sub>SBP</sub> )	nR	3.9±5.6	0	2.9±4.8	5.1±6.3	>0.05
		minR	-3.6±5.5	-5.8	-2.6±4.7	-4.9±6.2	<0.03
		maxR	14.8±11.5	11.5	17.8±12.7	11±8.5	<0.002
		meanR	-1.9±2.6	-3.2	-1.3±1.9	-2.7±3	<0.005
DBP [mmHg]	I (minE1 <sub>DBP</sub> )		7.,5±6.6	66.2	70.5±6.7	70.4±6.4	>0.9
	II (R <sub>DBP</sub> )	nR	2.5±5.4	0	2.2±4.9	2.9±6	>0.4
		minR	5.1±9.7	-0.4	5.6±9.7	4.3±9.8	>0.4
		maxR	14.5±9.7	8.1	15.4±9.5	13.5±10.1	>0.3
		meanR	-1±2.6	-0.3	-0.9±2.5	-1.2±2.8	>0.5
CO [L/min]	I (minE1 <sub>CO</sub> )		5.1±1	4.4	5.1±0.9	5.1±1.1	>0.9
	II (R <sub>CO</sub> )	nR	10.3±10.2	4	9.2±6.4	11.6±13.4	>0.2
		minR	-0.4±0.5	-0.7	-0.4±0.5	-0.5±0.5	>0.7
		maxR	0.8±0.8	0.2	0.9±0.9	0.7±0.6	>0.2
		meanR	-0.3±0.2	-0.4	-0.3±0.2	-0.3±0.1	>0.9
SV [mL]	I (minE1 <sub>SV</sub> )		71.1±15	60	71.4±15.7	70.1±14.3	>0.8
	II (R <sub>SV</sub> )	nR	15.9±8.8	15	14.8±4.7	17.2±12	>0.1
		minR	-14.4±8.2	-19	-14.4±8.9	-14.2±7.2	>0.8
		maxR	-0.1±8.2	-5	0.1±8.8	-0.4±7.2	>0.7
		meanR	-9.5±6.4	-13	-9.3±7.1	-9.6±5.5	>0.7
TPR [dyn.s/cm <sup>8</sup> ]	I (minE1 <sub>TPR</sub> )		933±207	770	918±178	951±239	>0.4
	II (R <sub>TPR</sub> )	nR	1.2±8.9	0	0.2±0.4	2.3±13.2	>0.2
		minR	-18.7±29.8	-18	-7.6±20.8	-29.4±36.5	<0.007
		maxR	322±199	200	354±221	281±160	>0.05
		meanR	-9.1±14.8	-10	-3.6±10	-14.5±18	<0.007
BRS [ms/mmHg]	Stage I		14.5±8.6	8.1	14.4±8.4	14.7±8.9	>0.8
	Stage II		7.1±3.2	4.7	7.1±3.1	7.1±3.3	>0.9

Abbreviations: see "Methods" section

# Discussion

The autonomic nervous system through its sympathetic and parasympathetic components plays a role in the regulatory system that is responsible for adaptation of the arterial pressure, heart rate as well as stroke volume to changing physiological conditions, including stress or exercise. Chemo- and

mechanoreceptors located in the carotid sinuses and aortic arch (high-pressure baroreceptors) and in the large vessel arterial wall or atrial myocardium (low-pressure baroreceptors) as well as in the ventricular myocardium (low- and high-pressure baroreceptors) are responsible for the onset of a number of reflexes controlling the autonomic tone and sympathetic-parasympathetic balance [9-11].

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**Table III.** Univariate analysis of the relationship between the occurrence of syncope episodes during the head-up tilt test and values of assessed parameters lower than the assigned threshold (low tercil)

Parameter	Frequency	OR (95% CI)	χ²	Р
maxR <sub>SBP</sub> [mmHg]	27 (26%)	1.9 (0.9-3.4)	3.1	>0.08
minR <sub>SBP</sub> [mmHg]	24 (23%)	2.6 (1.4-6.9)	4.5	<0.02
meanR <sub>SBP</sub> [mmHg]	26 (25%)	3.2 (1.2-6.3)	4.8	<0.01
minR <sub>TPR</sub> [dyn.s/cm <sup>8</sup> ]	24 (23%)	2.8 (1.3-5.2)	4.7	<0.02
meanR <sub>TPR</sub> [dyn.s/cm <sup>8</sup> ]	23 (22%)	2.9 (1.5-5.8)	4.9	<0.01

It has been shown, employing complex study techniques of the autonomic response, that the impaired baroreceptor control function responsible for vasovagal syncope can have a double nature: a) deviation of the sympathetic control of neuronal activity (SNA, sympathetic nerve activity) and the heart rate towards higher or lower values of arterial pressure (i.e. baroreceptor response reset), b) reduction in the sensitivity of baroreceptors causing restriction of their regulatory function over the cardiovascular system. A possible reason for these disturbances is the impaired – in relation to actual orthostatic load – afferent sympathetic stimulation controlled by activity of the baroreceptors or dysfunction of the efferent path of the reflex [1, 4, 9, 12-14].

According to Béchir et al. [15], a direct consequence of the reduced rest sensitivity of baroreceptors is inadequate detection of changes in the arterial pressure, and then impaired unload of the receptor afferent activity, which may overestimate the SNA value essential to sustain the vascular resistance. Schroeder et al. [4] postulated that stress-induced postural hypotension is the result of insufficient vascular adrenergic support. As

a sequel of these changes the authors indicated a negative feedback compensating activation of alternative mechanisms aimed at sustaining the arterial pressure by an increase in the peripheral vascular resistance. The most important mechanism of the excessive release of the neurohormone epinephrine from an adrenal medulla that apart from expected direct haemodynamic benefits causes also prolonged adaptation of the baroreceptor activity causing an inhibition of sympathetic tone [4, 15-18].

Our observations confirmed earlier reports that stressed the role of peripheral vascular resistance disorders in VVR pathophysiology. The choice of length and location of the analysed study segments was made after an analysis of our results, where the correlation between the impaired vasoconstricting response in the early phase of the upright tilt and final examination result was proved [1-2, 8]. We employed an original averaging technique of consecutive 10-second-long recorded haemodynamic threads aimed at diminishing the influence of the respiratory function on the results of the measurements.

The findings of the presented study may have important clinical implications. First, they support the concept of cardiovascular balance conversion preceding vasovagal syncope caused by sympathetic activation. Second, they add significantly to TT optimisation. The results of the peripheral vascular resistance assessment justify the thesis that the average value of drop in TPR – less than 10 dyn.s/cm<sup>8</sup> – identifies patients at low risk of syncope during TT and gives a reason to terminate the test earlier without the necessity to continue the passive phase and active pharmacological provocation.

The haemodynamic algorithm of *Modelflow* used to estimate the stroke volume from the pulse wave

Table IV. Characteristics of the patients based on the dychotomous classification of the mean RTPR index

Clinical data	meanR <sub>TPR</sub> value		Р
	≥-10 (n=82)	<-10 (n=23)	
Age, years	33.9±13.7	34.9±13.6	>0.7
Gender (women/men)	44/38	17/6	>0.07
Number of syncope episodes in the last 6 months, N (range)	2.5±3.5 (2-20)	2.4±2.5 (2-16)	>0.9
Syncope duration time, months (range)	77.4±94 (6-240)	52.8±66.6 (6-240)	>0.2
Concomitant injuries, N (%)	31 (38)	8 (35)	>0.8
Positive result of TT, N (%)	32 (39)	15 (65)	<0.03
Response type during TT			
– mixed, N (%)	20 (24)	11 (44)	>0.2
– vasodepressive, N (%)	3 (4)	1 (4)	>0.3
– cardiodepressive, N (%)	9 (11)	3 (13)	>0.9

contour analysis enables one to judge that every acquired drop in the TPR value below the minimum noted earlier in the supine position predicts a positive response during TT (Figure 2). It must be stressed that falls in vascular resistance exceeding the reference value negatively influence the specificity of the proposed risk stratification algorithm.

An explanation of the lack of a correlation between changes of TPR and sensitivity of the baroreceptors is also needed. In our opinion, it may be due to the analytical model employed. In our study, the BRS value used for the analysis represented averaging of 3-minute-long intervals. In contrast, the TPR derivatives used in the analysis represented exclusively the differences between 10-second averaged mean values at rest and at the beginning of TT, being most likely just an effect of temporary variations.

In our opinion, the attempts to develop a reliable TT result prognostic tool should be focused on the study periods preceding syncope, i.e. early enough to ensure that a decision to terminate the test would not be limited by subjective factors, e.g. overlooking by supervising personnel of sudden shifts of the arterial pressure and heart rate just prior to the fainting. The presyncope symptoms accompanied by a haemodynamic reaction indicating a possibility of activation of the vasovagal reflex do not always meet strict criteria of the primary end-point of the study, i.e. syncope. In the future, it will be crucial to bridge the gap between the extensive knowledge resulting from clinical studies on neurocardiogenic syncope pathophysiology and the treatments, still far removed from the ideal, used in patients suffering from the disease.

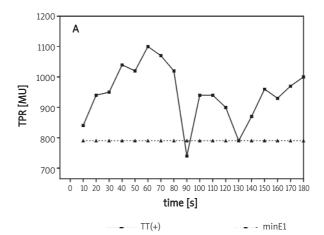
The presented study is a retrospective one. Thus, the long term prognostic value of decreased TPR can only be alleged. The final solution as well as the answer to the question of whether vascular resistance may only be a risk factor or should also be a target for therapeutic interventions requires further prospective studies with real-time analytic models of haemodynamic variables.

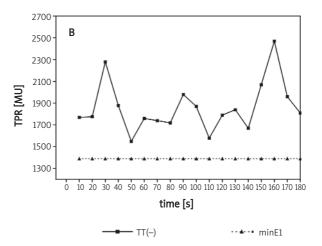
#### **Conclusions**

In patients with syncope of unknown origin, an early (within first 3 minutes), asymptomatic fall in the total peripheral vascular resistance is a significant predictor of a positive final result of the test.

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**Figure 2.** Comparison of TPR values in the consecutive examined period in patients with positive [TT (+)] and negative [TT (-)] tilt test results; minE1 – corresponding TPR values in the first stage of the examination

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# Wskaźniki hemodynamiczne wczesnej fazy testu pochyleniowego: czy pomiar prognozuje wynik?

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#### Streszczenie

**Cel:** Identyfikacja oraz ocena przydatności wczesnych zmian wartości wskaźników hemodynamicznych w prognozowaniu wyniku testu pochyleniowego w grupie chorych z omdleniami niewyjaśnionego pochodzenia.

**Metody:** Badaniom poddano grupę 105 chorych, tj. 61 kobiet i 44 mężczyzn, w średnim wieku 34,2±13,7 (zakres 13–82) lat, z co najmniej dwoma incydentami utrat przytomności w okresie ostatnich 6 miesięcy. Pionizację wykonywano wg protokołu 60°/20 min, uzupełniając ją, w przypadkach tego wymagających, o podjęzykowe podanie 250 μg nitrogliceryny. Oceny wskaźników hemodynamicznych dokonywano metodą *beat-to-beat* za pomocą urządzenia Portapres M2. Analizie poddawano skurczowe (SBP) i rozkurczowe (DBP) ciśnienie tętnicze, częstotliwość rytmu serca (HR), pojemność minutową (CO) i objętość wyrzutową (SV) serca, całkowity obwodowy opór naczyniowy (TPR). Uzyskane wartości wskaźników hemodynamicznych analizowano, uśredniając 10-sekundowe segmenty pomiarowe w czasie 3 ostatnich min wypoczynku w pozycji leżącej oraz w 3 pierwszych minut od rozpoczęcia pionizacji. Dla tych samych 3-minutowych okresów wyznaczano średnią czułość baroreceptorów (BRS) za pomocą metody xBRS (*cross-correlation*). W analizie oceniano różnice (R<sub>x</sub>) wartości hemodynamicznych między początkiem pionizacji a okresem wypoczynku.

**Wyniki:** Utrata przytomności wystąpiła u 47 (46%) badanych pacjentów, którzy stanowili grupę I, podczas gdy pozostałych 58 (54%) było niewrażliwych na zastosowaną prowokację – w dalszej ocenie tworzyli oni grupę II. Metodą jedno- i wieloczynnikowej regresji logistycznej wyodrębniono średnią wartość różnicy oporu naczyniowego – śr $R_{TPR}$  <-10 dyn.s/cm $^8$  jako niezależny wskaźnik zagrożenia utratą przytomności ( $\chi^2$ =3,4; p<0,0008). Jego obecność wiązała się z istotnym zwiększeniem ryzyka pozytywnej odpowiedzi na pionizację (65% vs 39%; RR: 1,7, 95% CI: 1,2–2,5). W prognozowaniu dodatniego wyniku TT czułość tego parametru wynosiła 65%, swoistość 61%, a wartość prognostyczna wyniku dodatniego i ujemnego 32% oraz 86%.

**Wnioski:** Wykrycie wczesnego – w trakcie 3 minut od rozpoczęcia pionizacji – bezobjawowego spadku całkowitego obwodowego oporu naczyniowego ma istotną wartość w prognozowaniu wystąpienia dodatniego wyniku testu pochyleniowego w grupie chorych z utratami przytomności niewyjaśnionego pochodzenia.

Słowa kluczowe: omdlenie wazowagalne, obwodowy opór naczyniowy, test pochyleniowy

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