ORIGINAL ARTICLE

Correlation between the activity of the autonomic nervous system and endothelial function in patients with acute coronary syndrome

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KEY WORDS

acute coronary syndrome, autonomic nervous system, endothelial function, sympathetic nervous system

ABSTRACT

INTRODUCTION The endothelium and sympathetic nervous system play an important role in the pathogenesis of acute coronary syndrome (ACS).

OBJECTIVES The aim of our study was to evaluate correlations between noninvasive markers of the endothelial function and the sympathetic nervous system in patients with a recent ACS.

PATIENTS AND METHODS The study included 52 patients who experienced an ACS within the previous 3 to 6 months. Endothelial function was expressed as the reactive hyperemia index (RHI), and the activity of the sympathetic nervous system—as latency and amplitude of sympathetic skin response (SSR) potentials from the 4 limbs. Linear and partial correlations between the RHI and SSR were calculated.

RESULTS There were significant correlations between the RHI and the latency of the SSR in the upper limbs ($r = 0.34$, $P = 0.02$ for the right limb; and $r = 0.34$, $P = 0.01$ for the left limb). After eliminating the effects of age, sex, weight, and glomerular filtration rate, the partial correlation between the RHI and the latency of the SSR in the upper limbs remained statistically significant ($r = 0.41$, $P = 0.004$ for the right limb, and $r = 0.42$, $P = 0.004$ for the left limb). There was no correlation between the RHI and latency of the SSR during the stimulation of the lower limbs.

CONCLUSIONS Our study confirmed the correlations between the sympathetic autonomic nervous system and endothelium in patients with ACS. The correlation of the RHI with the latency of the SSR was observed only in the upper limbs.

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INTRODUCTION Both endothelial function and activity of the autonomic nervous system (ANS) have a significant prognostic value in patients with acute coronary syndrome (ACS).[1-3] A number of studies have reported correlations between the endothelium and sympathetic nervous system (SNS) on the molecular level.[4-11] Conditions that cause chronic or acute hyperactivity of the SNS can lead to the impairment of endothelial function and, secondarily, to cardiovascular events.[12-15] Studies of patients with posttraumatic stress disorder and affective disorders have provided the most reliable conclusions.[16-20] If the correlation between the SNS and endothelium in patients with ACS was confirmed, we would have reasonable grounds for further studies on the role of the ANS in the etiology, pathogenesis, and prevention of cardiovascular diseases.

The main objective of our study was to evaluate a relationship between noninvasive markers of

TABLE 1 Location of electrodes in the evaluation of sympathetic skin response

Receiver electrode	Reference electrode
radial surface of the hand (the area supplied by the median nerve)	back of the hand
medial, plantar surface of the foot (the area supplied by the tibial nerve)	dorsum of the foot

TABLE 2 Clinical characteristics of the study group (n = 52)

women		11 (21)
arterial hypertension		52 (100)
smokers		30 (58)
STEMI		30 (58)
NSTEMI		22 (42)
culprit vessel	LM	0 (0)
	LAD	22 (42)
	Cx	11 (21)
	RCA	19 (37)
pharmacotherapy	ASA	52 (100)
	clopidogrel	52 (100)
	β-blocker	52 (100)
	statin	52 (100)
	ACEIs	48 (92)
	calcium blocker	7 (13)
	sartan	4 (8)
	diuretic	9 (17)
age, y		59.6 ±9.1 (60.0 [43.0–78.0])
height, cm		171.6 ±8.1 (173.0 [153.0–185.0])
weight, kg		84.2 ±13.0 (81.0 [57.0–117.0])
BMI, kg/m^2		28.5 ±3.3 (27.7 [23.2–36.3])
PWV, m/s		9.7 ±2.4 (9.55 [6.0–16.8])
LVEF, %		49.9 ±8.1 (50.0 [30.0–60.0])
TC, mg/dl		144.8 ±29.8 (145.5 [82.0–211.0])
LDL-C, mg/dl		74.5 ±23.2 (70.0 [36.0–117.0])
HDL-C, mg/dl		46.9 ±11.6 (46.5 [26.1–73.0])
TG, mg/dl		117.7 ±44.7 (109.5 [52.0–265.0])
creatinine, mg/dl		1.0 ±0.2 (1.0 [0.5–1.9])
GFR, ml/min/1.73 m^2		85.6 ±24.1 (81.8 [28.5–139.5])

Data are presented as number (percentage) or mean ± standard deviation (median [range]).

To convert the values to SI units multiply by the following conversion factors: total cholesterol, LDL cholesterol, HDL cholesterol: 0.0259; TG: 0.0113; creatinine: 88.4; for GFR replace 175 with 30,849 in the Modification of Diet in Renal Disease study abbreviated equation

Abbreviations: ACEIs – angiotensin-converting enzyme inhibitors, ASA – acetylsalicylic acid, BMI – body mass index, Cx – circumflex coronary artery, GFR – glomerular filtration rate, HDL-C – high-density lipoprotein cholesterol, LAD – left anterior descending coronary artery, LDL-C – low-density lipoprotein cholesterol, LM – left main coronary artery, LVEF – left ventricular ejection fraction, NSTEMI – non-ST-elevation myocardial infarction, PWV – pulse wave velocity, RCA – right coronary artery, STEMI – ST-elevation myocardial infarction, TC – total cholesterol, TG – triglycerides

the endothelial function and the SNS in patients who had experienced an ACS within the previous 3 to 6 months.

PATIENTS AND METHODS

Patients The study included 52 white patients aged from 35 to 75 years who had experienced myocardial infarction with ST-segment or non-ST-segment elevation within the previous 3 to 6 months and were treated with primary coronary angioplasty at the Department of Cardiology, Medical University of Lodz, Łódź, Poland. The study was conducted from June 2011 to February 2012 as part of the ongoing FOREVER study (Focus On stiffness Reduction, Endothelial function and autonomic nervous system improVement In patient after MI with or without hypErtension after cardiovascular Rehabilitation), which started in 2009. The preliminary data on the correlations of arterial stiffness parameters have already been published.[21]

All participants received a standard pharmacological treatment for ACS.[22,23] The exclusion criteria were as follows: unstable coronary artery disease, indications for coronary artery bypass grafting, peripheral arterial disease, uncontrolled arterial hypertension, use of nitroglycerin, decompensated type 2 diabetes, damage to the peripheral nervous system (sensory, motor, or mixed fibers) or to the ANS, significant ventricular and supraventricular arrhythmias exceeding 10% of the total evolution during the day, allergy to latex, deformations or previous amputation of the fingers, infectious diseases, and significant hepatic failure or chronic kidney disease. All patients gave their written informed consent to participate in the study.

Study protocol All patients underwent examinations conducted independently in 2 centers over 2 days (the Department of Cardiology and the Department for the Diseases of the Extrapyramidal System). First, venous blood samples (5 ml) were taken from each patient for biochemical tests. Then a medical history of each patient was taken and a physical examination and endothelial function test were performed. On the next day, the activity of the SNS was assessed. In addition, all patients underwent a routine neurological evaluation to test for peripheral and central motor (and sensory) neuron dysfunction, which would exclude them from the study.

All test results were compiled for statistical analysis, which was conducted at the Department of Microelectronics and Computer Science, Technical University of Lodz, Łódź, Poland.

Endothelial function Endothelial function was evaluated by peripheral arterial tonometry (PAT), using the EndoPAT 2000 system (Itamar Medical, Caesarea, Israel). This new method, which was approved by the European Society of Cardiology (ESC) Working Group on Peripheral Circulation, is based on the effect of shear stress on the endothelium, which are known to cause vasodilation.[24,25]

The examination was started after 20-minute rest in a supine position in a room with standard conditions. Patients had been asked to stop taking calcium channel blockers 24 hours before the examination. In each patient, pneumatic sensors were placed on the index fingers of both hands,

TABLE 3 Endothelial function and sympathetic skin response parameters (n = 52)

RHI	1.7 ±0.4 (1.6 [1.1–2.9])
RHA, mV	5.2 ±3.4 (4.2 [0.6–16.9])
LHL, s	1.4 ±0.2 (1.4 [1.1–2.3])
LHA, mV	5.2 ±3.5 (4.3 [1.0–14.3])
RLL, s	2.1 ±0.3 (2.0 [1.4–2.9])
RLA, mV	3.6 ±2.7 (2.9 [0.3–11.6])
LLL, s	2.1 ±0.3 (2.0 [1.4–2.8])
LLA, mV	3.4 ±2.4 (2.6 [0.3–11.0])

Data are presented as a mean ± standard deviation (median [range]).

Abbreviations: LHA – amplitude of SSR on the left hand, LHL – latency of SSR on the left hand, LLA – amplitude of SSR on the left leg, LLL – latency of SSR on the left leg, RHA – amplitude of SSR on the right hand, RHI – reactive hyperemia index, RHL – latency of SSR on the right hand, RLA – amplitude of SSR on the right leg, RLL – latency of SSR on the right leg, SSR – sympathetic skin response

and an arterial blood pressure cuff was placed on the upper arm. The examination lasted 15 minutes and consisted of 3 phases, during which peripheral arterial pressure was recorded continuously (on a beat-to-beat basis): phase 1, the recording of the initial PAT signal (5 min); phase 2, the recording of the PAT signal while the cuff was inflated 60 mmHg above the systolic blood pressure (5 min); phase 3, the recording of the PAT signal after cuff deflation (5 min).

The reactive hyperemia index (RHI) was calculated as a ratio between the PAT signal recorded on the study arm within 1 to 1.5 minute after cuff deflation and for 3 to 5 minutes before cuff inflation, corrected for systemic changes with the PAT signal from the opposite arm.

Sympathetic nervous system activity The sympathetic skin response (SSR) test is commonly used to diagnose the dysfunction of preganglionic and postganglionic sympathetic fibers, based on the assessment of the sudomotor response to stimuli.

The test was performed using the Keypoint 4 EMG device (Medtronic, Denmark). The physical and chemical parameters of the environment and the parameters of stimulation during the test were compatible with the relevant standards.[26,27] The stimulus was a 0.2-ms electrical impulse of the supramaximal current increasing from 10 to 30 mA. The stimulation sites were the sympathetic postganglionic fibers of both median nerves in the wrist and the sympathetic postganglionic fibers of both tibial nerves in the area of the medial malleolus. A response in the form of skin potential was obtained simultaneously from 4 limbs, by stimulating each of them separately. The location of the receiver and reference electrodes is shown in **TABLE 1**. We analyzed potentials with the shortest latency and highest amplitude.

The following parameters of the response were determined: the configuration and the distribution of the potentials in the recordings, the morphology, latency (s), and amplitude (uV) of point P0, ie, the point of the departure of the potential from the isoelectric line on the graph. Latency is a time interval between the stimulation and response of the sympathetic system to the stimulus, and an expression of the stimulus conduction velocity in the fibers of the sympathetic pathways. Latency is known in neurophysiology to be a more objective parameter for assessing any impulse-conduction system. To compare responses between the sides, we analyzed the differences between the configuration, latency, and amplitude of the P0 potential with an identical stimulus.

Statistical analysis A statistical analysis was conducted using the MATLAB R2013a Statistics Toolbox (MathWorks, Natick, Massachusetts, United States). All variables were expressed as mean ± standard deviation and median. Normal distribution of the parameters was assessed using the Kolmogorov–Smirnov test for 1 sample. For all significant variables, Pearson linear correlation coefficients were calculated. Owing to the size of the population, the analysis did not include correlations in the subgroups. A partial correlation coefficient was used to evaluate the strength of the linear correlation between the SSR parameters (latency for the upper limbs) and the RHI after eliminating the effect of age, sex, weight, and glomerular filtration rate (GFR)—variables that might have affected endothelial function. A P value of less than 0.05 was considered statistically significant.

RESULTS The clinical characteristics of the study population are shown in **TABLE 2**.

Because most patients were overweight or obese (body mass index, 23.2–36.3 kg/m^2; mean, 28.5 ±3.3 kg/m^2), the results were corrected for weight, age, and sex. The partial correlation included also the GFR, which was correlated with the RHI (r = 0.4; P = 0.006). The remaining biochemical parameters are shown in **TABLE 2**.

The mean values of the latency and amplitude of sympathetic skin potentials and the RHI were within normal ranges in all patients (**TABLE 3**). We observed correlations between SSR latency values in all limbs. Although we observed some deviations in SSR and RHI values in individual patients, all patients were included in the statistical analysis. A significant correlation was observed between the RHI and SSR latency in the upper limbs in the entire study group (r = 0.34, P = 0.02 for the right limb; r = 0.34, P = 0.01 for the left limb).

No correlation was observed between the RHI and SSR latency in the lower limbs (**FIGURE**). Similarly, there was no correlation between the RHI and SSR amplitude either in the upper or lower limbs.

After excluding the effect of age, sex, weight, and GFR, we observed a significant correlation

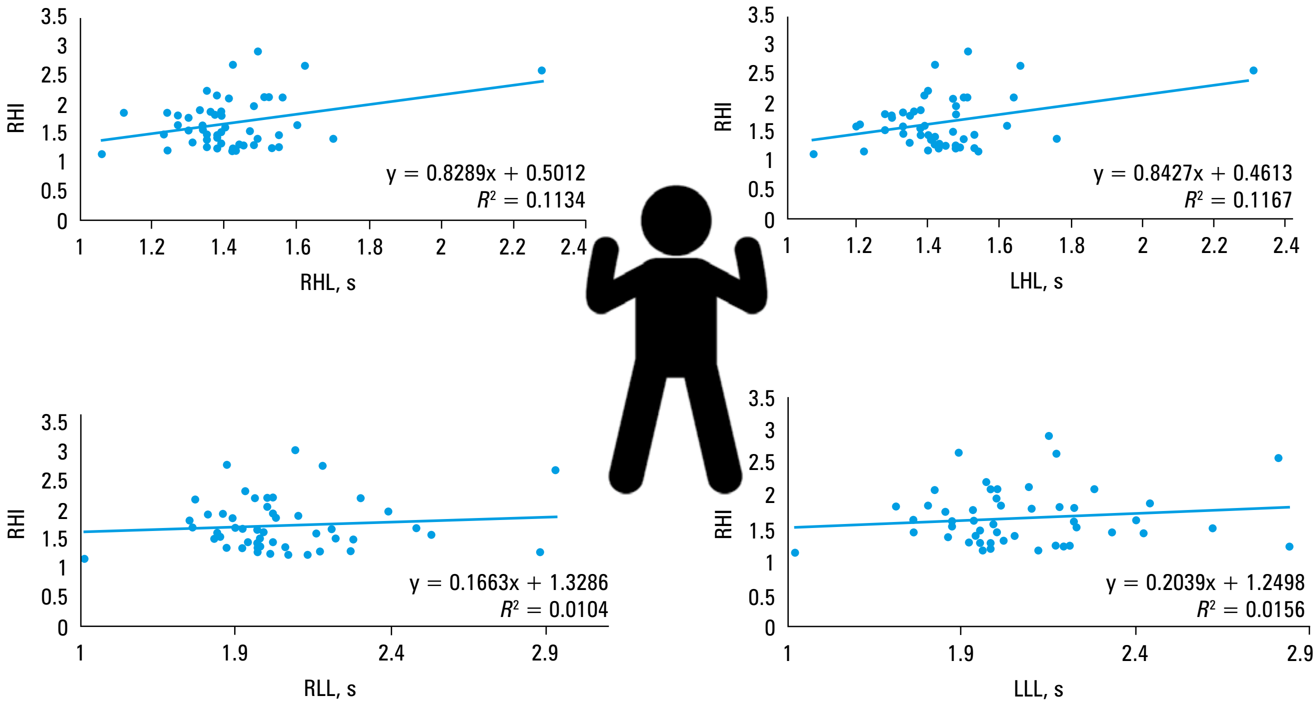

FIGURE Correlations between the reactive hyperemia index and latency of sympathetic skin response in the upper and lower limbs
Abbreviations: see **TABLE 3**

between the RHI and SSR latency in the upper limbs (r = 0.41, P = 0.004 for the right arm, and r = 0.42, P = 0.004 for the left arm).

DISCUSSION Our study confirmed a correlation between the markers of endothelial function and the activity of the SNS in patients after ACS. We analyzed the results using a novel approach, ie, PAT and the RHI, a noninvasive and easy-to-obtain parameter of endothelial function. The RHI significantly correlated with the SSR latency in the upper limbs. A longer latency period, implying reduced excitability of the SNS, is associated with a higher RHI, which means better endothelial function, assuming that there is no damage to pre- and postganglionic sympathetic fibers, although this must be verified by neurological examination. Considering that all patients received the same pharmacological treatment that affected the neurohumoral system and endothelium, it was excluded from the analysis.[28,29] The correlation remained significant, even after including the combined effect of age, weight, sex, and GFR.

The available studies on the correlation between the markers of endothelial function and the activity of the ANS differed in methodology and study populations but they provided similar results. Sverrisdóttir et al.[30] studied 10 healthy individuals and reported a correlation between the RHI and muscle sympathetic nerve activity (MSNA), ie, sympathetic potentials in muscle nerves, obtained by microneurography (r = –0.8; P = 0.005). A similar correlation was reported by Lambert et al.[31] who studied 18 patients with Fontan circulation. Earlier, the same group of investigators reported a correlation between the RHI and MSNA in 25 generally healthy obese students.[32] Padilla et al.[33] showed an association between increased MSNA and increased shear stress within the brachial artery in 14 healthy volunteers. Considering the available literature on neurophysiology, the microneurographical parameters closely correlated with the SSR potentials used in our study to assess the sympathetic system.[34]

Truccolo et al.[35] used the frequency analysis of heart rate variability to assess the function of the ANS. They reported a significant correlation between high frequency (HF), low frequency (LF), and the LF-to-HF ratio and flow-mediated dilation (FMD) in 13 patients with Chagas disease. This parasitic disease, which is the third most common disease in the world, develops into a chronic cardiovascular disease in one-third of the patients. Truccolo et al.[35] suggested that the progression of this disease results from the interaction between the ANS and endothelium. Using a similar method, Wehrens et al.[12] found that this mechanism may also apply to shift workers. As shown in our previous study, heart rate variability parameters correlated significantly with the SSR.[36] On the other hand, Kuvin et al.[37] demonstrated a significant correlation between FMD and the RHI during the same episode of reactive hyperemia.[37] A correlation between FMD and the RHI was also observed by Wilk et al.[38] in patients with moderate-to-low cardiovascular risk.[38]

Pharmacological studies have also significantly contributed to the discussion on the correlations between the SNS and endothelium. Patients with a history of cardiovascular incidents might benefit from possible drug interventions that target any of the reactions leading to endothelial dysfunction. Numerous studies have suggested that β-blockers have a beneficial effect on the endothelium. Matsuda et al.[39] studied a population of 29 patients with coronary artery disease, including 17 patients with a history of myocardial infarction, and reported improved FMD after 4 months of carvedilol treatment, which they linked to the antioxidant effect of the β-blocker.[39] Recent studies have provided evidence that endothelial function is improved not only by the pleiotropic effect but also by the antiadrenergic effect itself. Nerla et al.[40] reported improved FMD in patients with type 2 diabetes after a 4-week course of atenolol, but not in those receiving ivabradine. A significant decrease in the concentration of endothelin 1 associated with β-blocker use has been noted, while some researchers have also reported changes in von Willebrand factor in hypertensive and hyperthyroid patients when combined with α-blockers.[41,42] The preliminary data from studies on the use of statins are also promising.[43,44] Lambert et al.[45] reported that dyslipidemia impairs endothelial function and increases sympathetic drive.[45]

Of note, our study showed correlations of the SSR latency and RHI only in the upper limbs. This may indicate that the interaction between the ANS and endothelium is only local. However, this finding is not supported by any of the available studies so further research is needed to provide more evidence.

Our study has several limitations. The study group was relatively small but was larger than the groups in other studies. Moreover, in our centers, we had no access to the reference method, ie, microneurography, for assessing the activity of the SNS, which subjects the patients to additional stress associated with the use of needle electrodes. In addition, our study had no follow-up that could provide further information on the relationship between endothelial function and SNS activity. Finally, the correlation between the RHI and SSR latency in the upper limbs, which we observed in our study, might have resulted from the fact that there is a large autonomic component in the RHI parameter itself, as emphasized by the ESC Working Group on Peripheral Circulation.[24] Unfortunately, it was impossible for us to evaluate endothelial function by any other method than SSR, and, more importantly, by a method that would allow us to evaluate the function both in the upper and lower limbs and thus evaluate local correlations between the endothelium and the SNS.

In Central and Eastern European countries, morbidity and mortality rates from cardiovascular diseases are significantly higher than those in other parts of Europe.[46] In countries that have undergone social, economic, and political transition, such as Poland, people are more exposed to stress stimuli, which affect the SNS, than people in stable countries. It seems that the sympathetic–endothelial axis may play a key role in the pathogenesis of acute cardiovascular events.

In conclusion, our study is the first to confirm the correlation between the noninvasive markers of endothelial function (RHI) and ANS activity (SSR latency) in patients with a recent ACS. Further time-consuming research is needed to elucidate all the direct and indirect correlations between the endothelium and ANS; however, the results may bring substantial benefit to patients after cardiovascular events, those at higher cardiovascular risk, and those undergoing such procedures as denervation of the renal arteries.

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Contribution statement UIC-G and MF conceived the idea of the study. MK, ET, BUL, and TR contributed to the design of the research. MK and RF analyzed data and prepared graphs, tables, and figures. UIC-G performed the EndoPAT test, and MF performed neurophysiological tests. KW-D performed echocardiography. JDK coordinated funding for the project. JW made the final language edition. All authors edited and approved the final version of the manuscript.

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ARTYKUŁ ORYGINALNY

Korelacja aktywności autonomicznego układu nerwowego i funkcji śródbłonka u pacjentów po ostrym zespole wieńcowym

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SŁOWA KLUCZOWE

autonomiczny układ nerwowy, funkcja śródbłonka, ostry zespół wieńcowy, współczulny układ nerwowy

STRESZCZENIE

WPROWADZENIE Śródbłonek i współczulny układ nerwowy odgrywają ważną rolę w patogenezie ostrego zespołu wieńcowego (OZW).

CELE Celem naszego badania była ocena korelacji nieinwazyjnych markerów funkcji śródbłonka i współczulnego układu nerwowego u pacjentów po niedawno przebytym OZW.

PACJENCI I METODY W badaniu uczestniczyło 52 pacjentów po OZW przebytym w ciągu minionych 3–6 miesięcy. Funkcję śródbłonka wyrażono jako wskaźnik reaktywnego przekrwienia (*reactive hyperemic index* – RHI), a aktywność współczulnego układu nerwowego – jako latencję i amplitudę współczulnych potencjałów skórnych (*sympathetic skin response* – SSR) z czterech kończyn. Obliczono korelację liniową i cząstkową między RHI oraz SSR.

WYNIKI Stwierdzono znamienną korelację między RHI oraz latencją SSR w obrębie kończyn górnych (dla kończyny prawej: r = 0,34; p = 0,02; dla kończyny lewej: r = 0,34; p = 0,01). Po uwzględnieniu wpływu wieku, płci, wagi i wskaźnika filtracji kłębuszkowej korelacja cząstkowa między RHI a latencją SSR w obrębie kończyn górnych pozostała istotna statystycznie (dla kończyny prawej: r = 0,41; p = 0,004; dla kończyny lewej r = 0,42, p = 0,004). Nie stwierdzono korelacji między RHI a latencją SSR podczas stymulacji kończyn dolnych.

WNIOSKI Badanie potwierdza interakcje między współczulnym układem autonomicznym a śródbłonkiem u pacjentów po OZW. Korelacja RHI z latencją SSR była ograniczona tylko do kończyn górnych.

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