

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

To the Editor We read with great interest a recent paper by Cieřlik-Guerra et al.,¹ confirming the correlation between the activity of the autonomic nervous system and endothelial function in patients after acute coronary syndrome. The authors¹ evaluated endothelial function using peripheral arterial tonometry (EndoPAT 2000 system, Itamar Medical, Caesarea, Israel). This relatively simple noninvasive technique indeed correlates with microvascular coronary endothelial function. However, the measured reaction (reactive hyperemia index) is only partly endothelial-dependent, and other factors affecting microcirculation, such as the sympathetic nervous system, may affect the results. Thus, other methods of the assessment of endothelial function such as brachial artery flow-mediated vasodilation² or invasive measurement of coronary vasomotion after the administration of intracoronary vasoactive stimuli, mainly acetylcholine,³ would seem to be more appropriate for assessing such a correlation. Importantly, the correlation between the activity of the autonomic nervous system (measured with the sympathetic skin response test) and endothelial function was confirmed only in the upper limbs. These findings are in line with the previous studies in healthy subjects.⁴ In such individuals, the latency values of sympathetic skin response measured from the hands are significantly shorter than those from the legs, and the amplitude values are significantly higher from the hands in comparison with those from the legs.⁴ It could also be observed in the group of patients after acute coronary syndrome and may explain the lack of correlation within the lower limbs.

Endothelial dysfunction is considered an important early marker of atherosclerotic plaque formation and also an important predictor of serious cardiovascular events in patients with confirmed coronary artery disease.³ Endothelial dysfunction is even more pronounced in patients with acute coronary syndromes, which might be caused by

significantly elevated inflammatory activity in this group of patients.³ However, an improvement of endothelial function occurs in most cases within a few months after acute coronary syndrome. Thus, the assessment of patients soon after the onset of acute coronary syndrome might provide a more definite answer as to the importance of the correlation between the activity of the autonomic nervous system and endothelial function in this group of patients.

As discussed by Cieřlik-Guerra et al.,¹ endothelial function is affected by the use of pharmacological agents. We have confirmed that even short-term anti-inflammatory therapy with high-dose atorvastatin and selective cyclooxygenase-2 inhibitor improves coronary endothelial function within 7 days in patients presenting with non-ST-segment elevation acute coronary syndrome. We agree with the authors that all patients received the same pharmacological treatment that affected the neurohumoral system and endothelium, and the assessment of pharmacotherapy was not crucial for this analysis.

We congratulate Cieřlik-Guerra et al.¹ for identifying such an important correlation between the activity of the autonomic nervous system and endothelial function in patients after acute coronary syndrome. Importantly, this study may have clinical implications but comparative analyses between invasive and noninvasive methods of the assessment of endothelial function and the activity of the autonomic nervous system are needed before implementation in clinical practice. Further research should take into account the complex and multifactorial nature of endothelial dysfunction. We are looking forward to the next reports from such a significant project as the FOREVER study (Focus On stiffness Reduction, Endothelial function and autonomic nervous system improvement In patient after MI with or without hypertension after cardiovascular Rehabilitation).^{1,5}

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Authors' reply We would like to thank Dr. Dziewierz and colleagues for their interest in our article and insightful comments. We appreciate their effort in the analysis of the methodology used in our study and their important conclusions.

In this substudy, our priority was to use methods that were relatively simple, required little time, and allowed to coordinate tests performed in each patient within 24 hours in 2 study centers. It is important to emphasize that only 3 researchers performed the tests (and that they were simultaneously involved in other clinical activities), which limited the selection of possible methods.

Dr. Dziewierz and colleagues suggested that "other methods of the assessment of endothelial function such as brachial artery flow-mediated vasodilation or invasive measurement of coronary vasomotion after the administration of intracoronary vasoactive stimuli, mainly acetylcholine, would seem to be more appropriate for assessing such a correlation". As far as the latter method is concerned, we did not consider invasive testing of endothelial function at all because, in our opinion, it is not the best method after a recent acute coronary syndrome treated by percutaneous coronary intervention. As for the former method, brachial flow-mediated dilation (bFMD) indeed seemed to be the method of choice for noninvasive assessment of endothelial function, but it is not that simple. In a statement from the European Society of Cardiology Working Group on Peripheral Circulation we can read:

"well-trained operators are essential to obtain accurate and reproducible measurements".¹ Moreover, endothelial function tests were performed before noon when an echocardiographic laboratory at our department is maximally exploited. Furthermore, bFMD is much more time-consuming than EndoPAT. There are numerous studies that confirmed a significant correlation between these 2 methods.^{2,3} Considering the above, we decided to use the EndoPAT system in our study.

We agree that the PAT signal could have been affected by neurohormonal and environmental factors, but we tried to minimize their effects by providing appropriate test conditions.

Responding to the objections related to the use of sympathetic skin response (SSR), we would like to explain that we decided to use it because this electrophysiological method is simple, easy to perform, cheap, relatively short, and noninvasive as an evaluation of the sudomotor outflow in the central and peripheral nervous system.⁴ SSR specifically tests skin sudomotor fibers, which do not participate in thermoregulatory sweating.⁴ It has been used in clinical practice more often than microneurography (muscle sympathetic nerve activity, skin sympathetic nerve activity) because this latter method is not easily available, and the equipment is definitely more expensive and difficult to obtain. Also the quantitative sudomotor axon reflex test is less specific and less sensitive than SSR, and it is used more often in the case of diagnosis of autonomic dysfunction in the peripheral rather than the central nervous system lesions and pathology.⁵

Explaining the differences between the parameters obtained from the upper and lower limbs seems to be easy. It is a result of the length of the way that the stimulus has to cover along the sympathetic stimulation path from the stimulation of the nerve endings in the skin to the central sympathetic centers in the encephalon (the hypothalamus, mesencephalon, and cerebral cortex).⁴ It is clear that this excitement has to cover a definitely longer way in the case of stimulating the sympathetic endings within the lower limbs in comparison with the stimulation within the upper limbs. Therefore, in the case of the stimulation of sympathetic ends within the upper limbs, the latencies are shorter, while in the case of the appropriate stimulation within the lower limbs, they are longer. On the other hand, amplitudes are lower in the case of the lower limbs when compared with those of the upper limbs because the path along which the stimulations travel from the lower limbs is definitely longer, so that they may be subject to more adverse influences.

We fully agree with Dr. Dziewierz and colleagues that more comparative analyses between the invasive and noninvasive methods of assessing endothelial function and the activity of the autonomic nervous system are needed, and that "further research should take into account the complex and multifactorial nature of endothelial dysfunction".

In conclusion, our study has proved the correlation between endothelial function and sympathetic activity in patients with acute coronary syndrome. The methods we used are not the gold standard, but they are simple and efficient in terms of the time and staff. We hope that these results will open new perspectives for studies that will explain the pathways connecting the endothelium and autonomic nervous system in physiological and pathological conditions.

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