

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

**To the Editor** Cieřlik-Guerra et al.<sup>1</sup> wrote in the introduction to their interesting research paper that: “If the correlation between the SNS [sympathetic nervous system] and endothelium in patients with ACS [acute coronary syndrome] was confirmed, we would have reasonable grounds for further studies on the role of the ANS [autonomic nervous system] in the etiology, pathogenesis, and prevention of cardiovascular diseases”.<sup>1</sup>

It is widely recognized that the etiology of atherosclerosis and coronary heart disease (CHD) is multifactorial. Any discussion of this etiology should include lipid and coagulation disturbances as well as inflammatory processes in vascular walls. However, the question arises which of these pathogenic mechanisms are the most important.

According to Williams et al.,<sup>2</sup> atherosclerosis is initiated by inflammatory processes in the endothelial cells of the vascular wall in response to retained low-density lipoprotein molecules.<sup>2</sup> However, it would be interesting to investigate which mechanism is the primary cause of endothelial damage that seems to be the starting point for all pathogenetic processes.

Already in the 1980s, Gutstein<sup>3</sup> reported experiments that consisted in electrical stimulation of the lateral hypothalamus in conscious, unrestrained animals on normal diet. He stated that such a stimulation induced severe endothelial damage in the aorta and coronary arteries. He concluded that the mechanism whereby the stimulation lead to endothelial injury consisted in the induction of vasospasm.

Gutstein's hypothesis has been recently further discussed by Serano et al.,<sup>4</sup> who concentrated on the association of depression and its behavioral components with the development of CHD.

Cieřlik-Guerra et al.<sup>1</sup> are convinced that “Conditions that cause chronic or acute hyperactivity of the SNS can lead to the impairment of endothelial function and, secondarily, to cardiovascular events.”

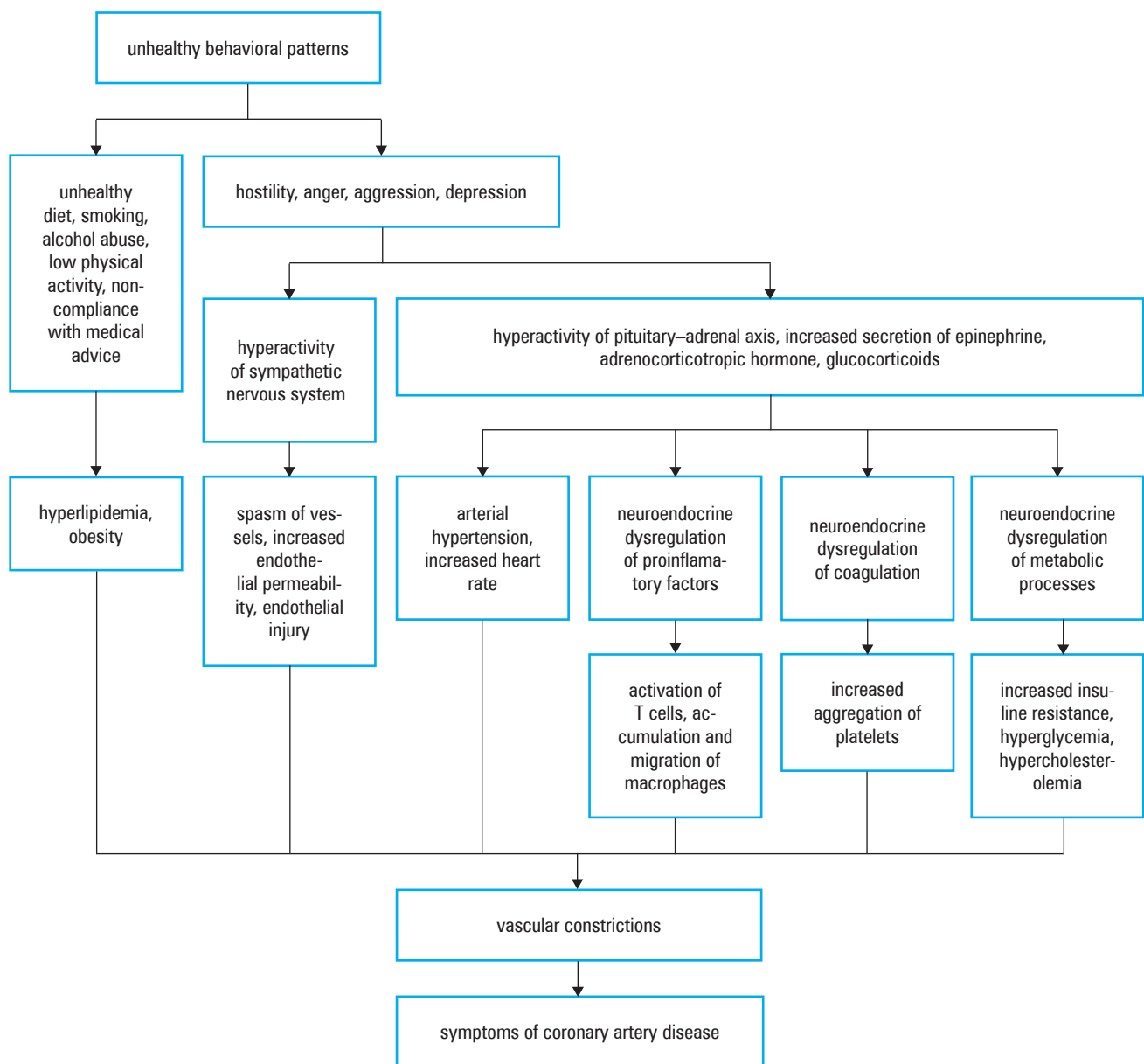
I believe that the above statement should be explained more comprehensively by analyzing the interactions between etiological and pathogenetic factors and determining which emotions are the most dangerous. The main interactions of the pathogenetic factors are shown in the **FIGURE**, which illustrates that there are some behavioral underlying mechanisms, such as common unhealthy lifestyle factors, for example, smoking, heavy alcohol use, and physical inactivity. Moreover, reduced adherence to prescribed regimens and recommended lifestyle changes is frequently observed.

Serrano et al.<sup>4</sup> also indicated other independent mechanisms linking depression and heart disease, including autonomic imbalance, platelet-endothelial interaction, neurohumoral activation, inflammation, and a specific polymorphism in the serotonin gene. They cited the previous studies emphasizing that a disproportionate sympathetic and vagal activation leads to the absence of heart rate variability and is associated with higher morbidity and mortality rates.

They also emphasized that the association between depression and CHD may also be mediated by changes in platelet activation. Platelets participate in the development of atherosclerosis and thrombosis by interacting with the subendothelial components of the vessels and with coagulation factors. An increased reactivity of platelets is common in depressed patients.<sup>4</sup>

Serrano et al.<sup>4</sup> noted that high cortisol levels in blood induce endothelial injury. The sympathetic adrenal activation leads to a significant catecholamine production and subsequent tachycardia, vasoconstriction, and platelet activation. Depressed patients have higher levels of C-reactive protein and inflammatory cytokines. It seems that depression can alter immune functioning and enhance inflammation.<sup>4</sup>

Cieřlik-Guerra et al.<sup>1</sup> noted that “studies of patients with posttraumatic stress disorder and



**FIGURE** Factors involved in the development of endothelial damage

affective disorders have provided the most reliable conclusions”, which is in line with the observations of Kreibig.<sup>5</sup> She discerns 6 negative emotions with some subtypes:

- 1 anger (eg, anger in defense of another person, anger in self-defense, indignation)
- 2 anxiety (eg, apprehension, consternation, fright, performance anxiety)
- 3 disgust (eg, repugnance, abomination, resentment)
- 4 embarrassment (eg, social anxiety, guilt, shame, social rejection)
- 5 fear (eg, threat, misgiving, dread, awe, panic)
- 6 sadness (eg, achievement failure, rejection, depression).

Kreibig<sup>5</sup> discusses, in detail, the empirical findings related to the symptoms of different activities of the ANS in individual types of emotions listed above. In light of her remarks, it seems that the most pathogenetic are mixed profiles of emotions, characterized by the coexistence of anxiety with feelings of social rejection, failure of achievements, and sadness.

Endothelial impairment probably occurs in the course of repeated situations characterized by the perception of stress evoked by self-accusation, self-condemnation, and dark self-portrait.

It seems that a detailed assessment of the psychological situations wherein an acute coronary syndrome had developed might allow to determine a potentially dangerous range of emotions.

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**Authors' reply** We thank Professor Brodziak<sup>1</sup> for his interest in our study and some insightful comments that inspired us to reply.

Professor Brodziak<sup>1</sup> wrote that our statement about the association between sympathetic activation and cardiovascular disease “should be explained more comprehensively by analyzing the interactions between etiological and pathogenetic factors and determining which emotions are the most dangerous.”

The famous quote of Charles Mayo says: “Worry affects circulation, the heart, the glands, the whole nervous system, and profoundly affects the heart. I have never known a man who died from overwork, but many who died from doubt”.<sup>2</sup> The INTERHEART study showed that 9 risk factors could account for more than 90% of the cardiovascular disease (CVD) risk.<sup>3</sup> Stress per se is one of those factors, but there are also other influences such as hypertension, physical activity, diet, smoking, alcohol consumption, and obesity. However, not all subjects who experience stress will develop acute cardiovascular syndromes in the future. There must be some kind of vulnerability, probably based on genetic factors that are still unknown. Apart from those considerations, almost all patients in our daily practice tell us about some stressful or traumatic events that preceded the occurrence of acute coronary syndrome (ACS). This observation prompted us to examine the correlation between endothelial function and the sympathetic nervous system (SNS) activity.<sup>4</sup> Three subjects in the study group reported the death of a child; 10, loss of work; 2, an accident; and others, conflict at home or at work.

We are aware of an important limitation of our study, namely, the lack of patients' assessment by means of parametric psychological tests. The knowledge about the levels of stress, depression, or anxiety might help explain the relation between the SNS and endothelium much more precisely. An important factor in such an analysis is the time elapsed from the event. In Poland, hospitalization after an ACS lasts merely 3 days, and it is a very intensive period for patients.<sup>5,6</sup> In many departments, such as ours, clinical psychologists try to help patients return to mental balance. The time of an acute event is not the best moment to perform deep psychological assessment because one-third of the patients showed spontaneous remission of symptoms within a month after discharge.<sup>7</sup> Usually, these types of

procedures are implemented during cardiac rehabilitation. Our study group only partly participated in cardiac rehabilitation. Tests of the endothelial function and SNS activity were performed before the rehabilitation program.

The available guidelines do not contain enough information about the psychological aspects of ACS. Recommendations about when, which types of tests to use, and, especially, how to help patients cope with psychological problems, are needed.

Professor Brodziak<sup>1</sup> stated that: “It is widely recognized that the etiology of atherosclerosis and coronary heart disease (CHD) is multifactorial. Any discussion of this etiology should include lipid and coagulation disturbances as well as inflammatory reactions in vascular walls. However, the question arises which of these pathogenic mechanisms are the most important.”

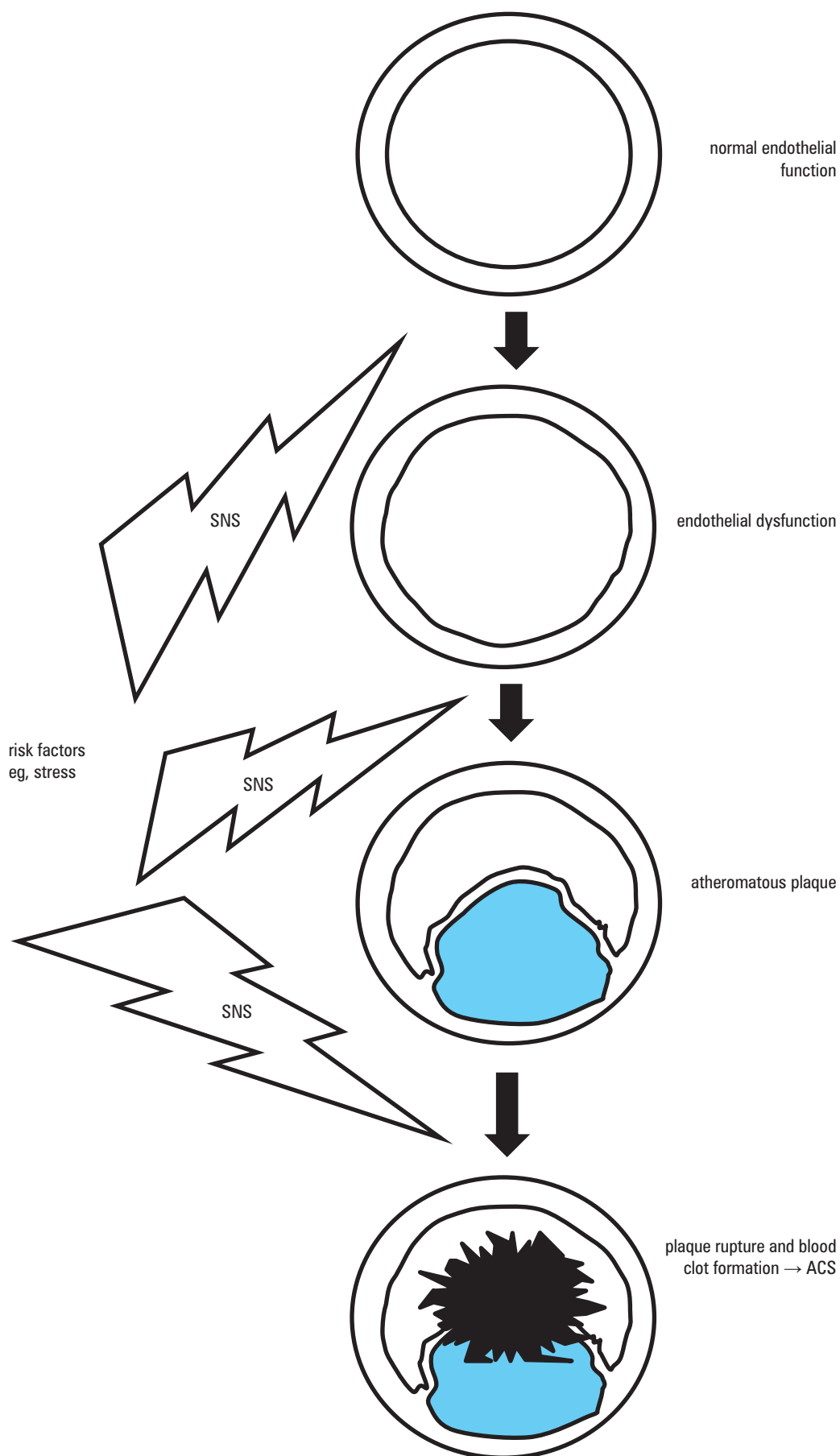
Since the discovery that the endothelium is not only a physical barrier between the blood stream and the vessel wall, but also a very active organ in maintaining homeostasis, the role of the endothelium and its function has become increasingly important. The endothelium plays a crucial role in the pathogenesis of atherosclerosis (FIGURE). We agree that so far the exact causes of atherosclerosis are unknown. However, chronic endothelial injury caused by a long list of diverse factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking, toxins, viruses, sedentary lifestyle, and, of course, stress may change the character of the blood flow from laminar to disturbed. Disturbed flow triggers a cascade of reactions, which leads to loss of atheroprotective functions by the endothelium.

Inflammatory reactions in the endothelium and subendothelial regions cause the trapping of low-density lipoprotein (LDL) cholesterol, the oxidation of LDL, forming foam cells. This process initiates the generation of the atheromatous plaque in the inner layers of the arteries. Coagulation disturbances seem to be secondary to inflammation and lipid deposition.

Professor Brodziak<sup>1</sup> concluded that “It seems that a detailed assessment of the psychological situations wherein an acute coronary syndrome had developed might allow to determine a potentially dangerous range of emotions.”

Sympathetic activation by negative emotions, especially anger, mentioned in the comment of Professor Brodziak,<sup>1</sup> is like adding “fuel to the fire” in advanced atherosclerosis. It is the most commonly reported trigger for acute cardiovascular events. A recent meta-analysis of 9 studies conducted by Mostofsky et al.<sup>8</sup> reported that there was a higher rate of CV events during the 2 hours following outbursts of anger. The combined incidence rate ratio for ACS and myocardial infarction was 4.74 ( $P < 0.001$ ). The suggested pathomechanism, ie, sympathetic activation, causes an increase in the heart rate, blood pressure, and vascular resistance, and, as a consequence, disruption of the vulnerable atherosclerotic plaques.

**FIGURE** Stages of atherogenesis, including the role of the sympathetic nervous system  
ACS, acute coronary syndrome; SNS, sympathetic nervous system



Depression is independently associated with cardiovascular incidents and appears to be a new risk factor for heart diseases.<sup>9</sup> In patients with ACS, the occurrence of depression is associated with bad

prognosis and outcomes.<sup>10,11</sup> Depression affects a patient's motivation to control risk factors. Dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis in the course of depression causes

higher basic cortisol levels.<sup>12</sup> The central part of the autonomic nervous system consists of structures (anterior cingulate, prefrontal cortices, amygdala, hypothalamus) that are involved in depression, but also in the normal regulation of cardiac and emotional functions.<sup>13</sup> Depression activates—through mediators—coagulation and inflammation.<sup>14,15</sup> An elegant explanation of these relationships can be found on the scheme provided by Professor Brodziak.<sup>1</sup> An important question in the context of depression is how antidepressants would affect the cardiovascular system after ACS, and what type of an interaction we can expect.

We hope that our discussion will make it possible to put more emphasis on the control of negative emotions and depression in the daily prevention of cardiovascular events. It is important to remember that stress followed by sympathetic activation is one of the risk factors that initiate atherosclerosis and is the most important trigger of acute cardiovascular events.

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