ENDOTHELIAL DYSFUNCTION IN THE ANAESTHESIOLOGIST'S PRACTICE

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ABSTRACT — A detailed review offers an overview of the theoretical and practical aspects of endothelial functions and conditions for the endothelial dysfunction. It also covers the surgical and anaesthetic issues of the endothelial dysfunction formation.

KEYWORDS — endothelium, endothelial dysfunction, vasodilation, arterial hypertension.

Anaesthetic support is considered adequate for a given operation on a particular patient if it allows to maintain the compensatory abilities of the body in the course of an operative intervention without causing any pathological reactions at the same time (V.L. Vanevsky, 1983).

The purpose of the review is to study the possibility of influencing the processes of endothelial dysfunction as an adequacy factor of anesthesia.

THEORETICAL ASPECTS

The role of the endothelium in the regulation of body functions. Endothelium is a monolayer of epithelial cells that participates in the immune function, stabilisation of the vascular tone and structure of the vascular wall (1). In anaesthesia, the most important effects are those that affect the vascular tone. The importance of this function is confirmed by the fact that the degree of risk of occurrence of cardiovascular events is determined by the vasodilatation potential of the endothelium (2).

Endothelium executes its functions through the release of nitric oxide (NO) and the activity of the nitric oxide synthase (eNOS). Depending on the con-

ditions, they may have the opposite direction (dilation – spasm, hemostasis – antithrombotic activity, etc.).

Since the endothelium covers all the vessels, its functions are manifested in all parts of the channel, including microcirculation (MCR). With a uniform contribution to the total spectral activity (20% for the neurogenic, endothelial and myogenic links) (3), the endothelium integrates the effects of all effects on the vascular wall (4). In this sense, any changes in homeostasis are triggers in the formation of the endothelial dysfunction. Stress (including surgery), hypoxia, endotoxemia and other conditions lead to the degradation of the nitric oxide with the formation of peroxynitrite. The consequence is angiospasm and cytotoxic processes.

Conditions for the development of the endothelial dysfunction. The vascular endothelium, occupying a "strategic" position, accepts the action of the damaging factors (5). All processes, accompanied by a decrease in the synthesis and bioavailability of the nitric oxide, are manifested in violation of the vasodilation, the main mechanism of the endothelial dysfunction (6).

The endothelial dysfunction of the arteries is considered to be one of the integral mechanisms of the formation of hypertension. Excess production of free radicals overcomes the protective mechanisms of the antioxidant system as a result of changes in the endothelial function of the vessels: endothelium-dependent vasodilation; the synthesis of adhesive molecules and growth factors increases, the platelet aggregation and thrombosis grows and the apoptosis is accelerated (7). In response to stress, there is an imbalance between the depressor and pressor vascular influences with a predominance of the constrictor component (8).

The vascular endothelium, controlling the vascular tone, is influenced by the hemodynamics in its turn. In the normal condition, the pulse wave increases the shear stress (which in turn is inversely proportional to the viscosity and directly proportional to the blood flow velocity), increasing NO production and expanding the arteries. The resultant reverse rebound blood flow leads to the development of the main component of increased pulse blood pressure – isolated systolic hypertension; there is a violation of the rhythmic NO production, creating conditions for the development of the endothelial dysfunction (9).

ENDOTHELIAL DYSFUNCTION AS A RESULT OF THE DEVELOPMENT OF THE MAIN (SURGICAL) PATHOLOGY

During the development and treatment of the surgical pathology, the stress of the endothelial functions to the degree of the dysfunction occurs in cases associated with the development of endotoxemia and the use of antibiotics. Both processes are caused by the treatment of a surgical infection, an antibiotic therapy, intestinal microbiocinosis disorders and the surgical stress (10). As a result of the endotoxin aggression and the antibiotic-induced endotoxinemia, conditions are created for the manifestation of the endothelial dysfunction. A special place is given to the dysfunction resulting from the endotoxin aggression in developing peritonitis and the dysfunction that persists in the remote period (11).

ENDOTHELIAL DYSFUNCTION IN THE FORMATION AND CORRECTION OF A CONCOMITANT PATHOLOGY

Arterial hypertension is the most frequent concomitant pathology and one of the main factors of the cardiovascular risk. Doubling cardiovascular and fatal events, it is one of the main causes of death in Europe (12).

For the anesthetist, a hypertensive patient is a common situation in which it is necessary to assess the risk and depth of the cardiovascular system and select the pharmacological load and the anaesthesia/analgesia program (13). It is not only necessary to take into account the effects of the arterial hypertension on the perioperative period but also those of the corrective therapy and the methods of anesthesia. In this case, the severity of the arterial hypertension is associated with the intensity of its correction. It is believed that the inclusion of diuretics in pharmacological combinations is a factor which determines the severity of the arterial hypertension and the aggressiveness of its correction (14).

Being one of the most common causes of the postponement of operations, arterial hypertension is not a strong independent risk factor for cardiovascular complications in a non-cardiac surgery (15). Changes in target organs is the event that translates arterial hypertension from the risk factor category into the category of cardiovascular complications (CCC). First, there are complications of the concomitant pathology, then there are complications of the postoperative period. The endothelial dysfunction is aggravated by a decrease in its ability to produce vasodilating substances; there are ischemic changes in the kidneys and the heart; blood rheology and tissue metabolism worsen (16).

The leading place in the normalisation of the endothelial function is the pharmacological correction. The positive effect on the endothelial function of most cardiological drugs – statins, calcium antagonists, angiotensin-converting enzyme inhibitors, diuretics, β-adrenoceptors, antiplatelet agents and so on (17), as well as antioxidants and NO donators (4) – has been proven.

Attention is drawn to the fact that the recommendations of the pharmacological strategies for the management of cardiac patients in the perioperative period include drugs that directly or indirectly affect the total dilution potential. The vast majority of the medically induced influences also have a vasodilatory orientation.

ENDOTHELIAL DYSFUNCTION UNDER OPERATIONAL STRESS

A high level of the neuroendocrinal tension, accompanied by a significant intensification of the metabolism, and pronounced shifts in hemodynamics – this is the essence of the body's reaction to the aggression during surgery (18). Under conditions of the operational stress, the endothelial response affects various systems.

The primary reaction of the peritoneum to the operating injury is a change in the functional state of its microcirculation (19). In this case, the greatest decrease in the rate of the local peritoneal blood flow to a standard operating injury is observed on the 2nd day of the postoperative period. The stress response of the *peritoneum* is associated with the development of the endothelial dysfunction of its vessels (20). The severity of the dysfunction directly depends on the volume of the operating injury and the timing of the recovery of the marker levels, which suggests their connection with the NO dynamics.

Surgical tissue damage with vegetative imbalance, deficiency in the volume of blood circulation, imbalance between prothrombotic and fibrinolytic factors and an increase in an intra-abdominal (pneumoperitoneum) and intrathoracic (Trendelenburg position) pressure are manifested by the neuroendocrine response of body systems (21). Stress and restriction of the functional capacity of the endothelium, without proper protection, are summarised in the hemodynamic and thrombotic changes.

THE IMPACT OF ANAESTHESIA ON THE DEVELOPMENT AND SEVERITY OF THE ENDOTHELIAL DYSFUNCTION

One of the important tasks of an anesthesiologist is to create emotional comfort in a patient. It is emotional stress that can serve as the first and provoking episode of the endothelial dysfunction. It has been established that pronounced disturbances in the endothelial function and psychoemotional status are present in patients with a combination of arterial hypertension and coronary heart disease – a frequently occurring group of patients (22). With the development of a hypertensive reaction to the emotional load, the formation of the endothelial dysfunction was not different from that of the arterial hypertension (23).

Since arterial hypertension is the most common concomitant pathology, when choosing an anesthesia program, it is necessary to take into account the combination of anesthesia and arterial hypertension (15) – with high individual sensitivity to drugs (24).

Electrolyte and cellular confirmations of the endothelial dysfunction as a result of the operational stress have been obtained in (25), despite the use of preparations with pronounced vasopligic action in the structure of anesthesia. The use of an antioxidant significantly reduced the manifestation of the endothelial dysfunction. It is hard to escape the conclusion that the influence of the means of anesthesia on the NO homeostasis is insignificant. However, in experimental studies, propofol has a direct vasodilating effect on coronary rats with stabilisation of the endothelial structures (26), mediated by NO release by the endothelium. In the process of the ischemia-reperfusion, propofol exhibits organoprotective properties (27). It is interesting to note that the protective effect of propofol can be disturbed by the use of nitroglycerin, which is manifested in the stimulation of the release of the tumor necrosis factor (28).

Most clearly the components of the anesthetic benefit affect the endothelial dysfunction when they are manifested by vascular reactions. In this case, the hemodynamic potential of anesthesia-analgesia techniques is different and should be taken into account when choosing tactics.

Thus, endothelium, participating in the formation of hemodynamic reactions at various stages of the perioperative period, regulates the vascular tone which is associated with the homeostasis of the nitric oxide produced by the endothelium. In this sense, the endothelium of the vessels is not only responsible for operational risks and the course of the intraoperative period but also for the provocation of pathological conditions of the distant postoperative period. Taking into account the main and concomitant pathology and surgical intervention, the total endothelial potential has a destructive orientation. An adequate anesthesia approach that provides a *hemodynamic corridor* has a protective character.

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