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A NEW INTRAVASCULAR COMPARTMENT: ENDOTHELIAL GLYCOCALIX. ARE THERE CONSEQUENCES FOR THE CLINICAL PRACTICE?

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The glycocalix was first described in 1963 by Bennett as a polysaccharidic layer, which covers the endothelial cells [1]. Long time it was hard to evidence this anatomical structure and it was mainly supposed by its functional consequences. These difficulties are related to the fragile nature of this layer being rapidly destroyed by tissue preparation and to the flow dependency, cultured endothelial cells displaying poor glycocalix. Modern *in vitro* or *in vivo* techniques allowed glycocalix visualization and research.

Today glycocalix is considered a bulky, intravascular compartment, which plays an important role in the homeostasis of the vascular wall, blood flow and tissue exchange regulation. It is the first barrier between the intravascular space and cells. Thus, the intravascular space consists of 3 compartments: cellular volume (mainly erythrocytes), plasma volume and the glycocalix volume.

The glycocalix structure is complex. It may be described as a gel with a negative electrical charge that "lubricates" the internal side of vessels. At electron microscopic view it looks like a "brush" with a height of 60-110 nm lining the vascular endothelium inside [1]. It is composed of an array of macromolecules anchored to the endothelial cells: glycoproteins, proteoglycans and glycosaminoglycans, but also contains plasma proteins (albumin, fibrinogen), enzymes (e.g., lipoprotein lipase, superoxide dismutase) and growth factors (e.g. vascular endothelial growth factor). This entire structure is soaked with water. Glycocalix and endothelial cells form together a morpho-functional structure that is called "*endothelial glycocalix layer"* [1].

The glycocalix physiology was extensively studied in last decades and new and complex functions are recently described. The main functions described so far are regulation of vascular permeability, mediation of shear stress and prevention of leukocytes and platelets adhesion [1].

The glycocalix pathology is uncovered parallel to its physiology. Several injury factors result in anatomical and/or functional impaiment. Partial alteration (compaction, fragmentation and shedding) consists of selective enzymatic cleavage by heparinase or hyaluronidase. This phenomenon is

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accompanied by increased plasma level of heparan, condroitin and other glycocalix constituents [2,3]. Injury factors are ischemia / reperfusion, hypoxia / reoxygenation, inflammatory cytokines and proteases and atrial natriuretic peptide [4]. Consequences of glycocalix injury are increased capillary permeability (capillary leak syndrome), tissue edema, enhanced inflammation, hypercoagulability, loss of vascular tone regulation [1].

The revised Starling theory

According to the "classical" Starling theory the capillary water exchange is governed by the difference between hydrostatic and colloid-osmotic pressure of the intravascular and the interstitial space. Water shifts out at the arteriolar and in at the venular end of capillaries. A small part of the interstitial fluid is drained to the lymphatic circulation.

Anatomical and functional glycocalix description resulted in the review of the Starling theory [5]. The barrier to the interstitial space is represented not only by the endothelial cells, but by the morpho-functional complex called "*endothelial glycocalix layer"*. According to the revised theory water exchange is governed by the difference between hydrostatic and colloid-osmotic pressure between the vascular lumen and subglycocalix space devoided of protein [1,5,6]. Colloid-osmotic pressure of the interstitial space does not play a role in the water movements. Thus, the rate of water filtration at capillary level is lower than predicted by the classical Starling theory and the major route for water return into intravascular space is lymph circulation [5].

Perioperative volume therapy and glycocalix theory

The intraoperative permissive administration of volume solutions is based on the concept of "third space" formation by water shift from the intravascular to interstitial space. But modern research showed that "third space" does not exist. Then the interstitial edema is the cause or the consequence of "vigorous2 volume administration?

According to glycocalix theory, there are two types of water movements during and after major surgery [6]. *Type I*, always present, is physiological water and electrolyte shift devoided of proteins from the intravascular to the interstitial space by an intact vascular barrier. Excessive intraoperative administration of cristalloid solutions will increase the volume of water passing into interstitium. *Type II*, inconstantly present, is pathological water, electrolytes and macromolecules (proteins or colloids) shift through an altered vascular barrier. It depends on the location, extent and duration of surgery. It is a result of glycocalix degradation with two major iatrogenic causes. On one hand, surgery induces the glycocalix injury by mechanical stress, endotoxin exposure, ischemia / reperfusion. On the other hand, anesthesia is commonly associated with excessive volume administration. Hypervolemia stimulates the secretion of atrial natriuretic peptide, which causes glycocalix degradation with several clinically significant consequences: increased vascular permeability, tissue edema, increased platelet aggregation [6].

This new theory of perioperative water movements provides a logical basis for volume therapy. Thus, minimizing type I water shifts may be accomplished by intraoperative cristalloid administration to replace urinary and insensible losses and colloid administration to replace blood loss [6].

Minimizing type II shifts may result from prevention of glycocalix degradation. To accomplish these goals surgery should be minimally invasive, with gentle visceral manipulation, mechanical sutures, atraumatic dissection and anesthesia may include a neuraxial block and avoid hypervolemia [6].

In **conclusion**, perioperative volume therapy should not be governed by the cristalloid / colloid or restrictive / liberal controversy, but by the cristalloids and

colloids administration in optimal amounts with optimal timing to minimize side effects and to preserve the integrity of the glycocalix.

CONFLICT OF INTERESTS

None to declare.

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