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Invited Review

Endothelial inflammation and thrombotic risk: From the leg to the pelvis and back

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Abstract

Pathological shear and stretch stress acting on the endothelium lining following venous reflux has been associated with an increased risk not only of thrombosis, but also of pan-endothelial inflammation. Indeed, varicose veins patients demonstrate an increased risk not only of deep venous thrombosis, but also of pulmonary embolism and peripheral arterial disease. Ex-vivo studies, including the ones on vascular endothelial cells, highlight the correlation between the physical forces and the biochemical related messaging triggering these clinical scenarios. Herein we report insights on the biosignaling following this mechano-transduction involving surface and cytoskeleton structures such as the glycocalyx, involved in endothelial permeability, protection, as well as in vessel tone and coagulation balance in a parallelism between lower limb and pelvic venous district venous thrombo-inflammation.

Keywords: Endothelial inflammation, thrombotic risk, pelvic veins, biosignaling, glycocalyx

INTRODUCTION

Vascular Biosignaling

Lower limb chronic venous insufficiency represents not only a pathology leading to chronic signs and symptoms of inflammation, but also to a related significant thrombotic risk.

Chang et al clearly demonstrated how the condition is associated with an increased deep venous thrombosis risk (5.30 (95% CI, 5.05-5.56)). Even more, the researchers demonstrated an increasd risk in pulmonary embolism (1.73 (95% CI, 1.54-1.94)) and, most interestingly, in peripheral arterial disease (1.72 (95% CI, 1.68-1.77)) [1].

These finding clearly reinforce the concept of the endothelium as an "organ", because of its multiple actions on vessel contraction, cells and nutrients trafficking, coagulation balance and permeability regulation [2].

The physical force of the different types of flow lead to different endothelial phenotype expression: laminar flow leads to an anti-inflammatory anti-thrombotic athero-protective expression, while turbulence is associate with pro-inflammatory, pro-thrombotic and athero-genic signaling [3].

"Biosignaling" can be defined as the translation of hemodynamic forces into biochemical cellular messages, involving different types of biomarkers [4].

In a previous publication of our group, we proved how Endothelial growth factor (EGF) , Platelet Derived Growth Factor (PDGF), and RANTES (regulated on activation, normal T cell expressed and secreted) are increased at the varicose vein site as compared to the general circulation, therefore identifying them as specific biomarkers of venous inflammation.

Following the surgical reflux suppression, their values normalized. Interestingly, in case of clinical recurrence 6 months

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after surgery, EGF, PDGF, and RANTES values increased again, confirming the correlation with the hemodynamic impairment [5].

This is of particular importance considering the possible role of PGDF in the coagulation balance and related thrombotic risk of the disease [6].

The endothelial glycocalyx is among the pivotal players in inflammation and coagulation balance. It is a complex of glycosaminoglycan and proteoglycans, constituting an electronically charged layer, responsible for regulation of endothelial permeability, protection, vessel contractility and coagulation balance [7].

The glycocalyx has been characterized in the venous as well as in the arterial system and ,nowadays, it is considered an innovative treatment target as its restoration following hemodynamics-induced alteration demonstrated benefits, both in peripheral arterial and chronic venous disease management [8].

A recent investigation demonstrated the presence of the glycocalyx also in the human lymphatics, paving the way for future investigations in vein-lymphatic edema formation [9].

In vitro clot formation studies confirmed the importance of the glycocalyx also in the coagulation balance. Flow alterations can act on the glycocalyx triggering thrombotic reactions [10].

All these pathophysiological considerations lead us to wonder what kind of parallelism can be found between the pathological pro-thrombotic biosignaling at the lower limb venous level and the pelvic venous system one.

Clinical Considerations

Recently, a fundamental work by Amin demonstrated that 3% of the women going to the gynaecologist for whatever reason present an incidental peri-uterine venous plexus thrombosis.

The study is extremely well designed and it involves 1383 participants, showcasing presence of varicose veins as risk factor (OR: 3.15, 95% CI: 1.32-7.49). This finding suggests a common leg-pelvic district endothelial inflammatory process that should be explored more in the thrombotic risk assessment of the same pelvic venous disorder patients [11].

This is particularly true when considering the periprocedural aspects.

Lower limb venous procedures present a still not strongly evidence-based management, with many experts around the world still prescribing just a single shot of heparin, without real risk score calculation [12].

At the same time, pelvic venous disorder is not usually included in the thrombotic risk factors, therefore representing an unmet need in the appropriate care of these patients.

A recently published work of Gavrilov looked at the thrombotic incidence following ovarian vein resection and embolization in pelvic venous disorders patients.

It's very important to notice how venous thrombo-embolism was reported in 19% of cases. More specifically, in the ovarian vein resection group, pelvic venous thrombosis was found in 9% and deep venous le thrombosis in 1%, with rates almost three times higher in the ovarian vein embolization group. The odds ratio for venous thrombo-embolism after coil was 10 times higher following embolization rather than resection (95% confidence interval: 2.35-56.43). Only 2.5% of the patients showed symptoms though [13].

The same Gavrilov described the post-embolization syndrome in pelvic venous disorder treatment, including increased pain, tenderness and hypothermia.

This phenomenon has been reported in 20% of patients and it could intersect the pathophysiology of venous inflammation and thrombosis, at the pelvic level, as already reported at the leg level [14].

CONCLUSION

Following these preliminary considerations, proper investigations and consequent clinical indications are mandatory on the topic of venous hemodynamics pathological biosignaling. The latter could trigger thrombosis at the pelvic as at the leg level. Consequent validated thrombo-prophylactic and therapeutic protocols are still needed.

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