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Thrombus mechanics: how can we contribute to improve diagnostics and treatment?

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This special issue aims to introduce the reader the most recent advances in the area of stroke treatment with an eye on the mechanical and modeling aspects.

Treatment of acute ischemic stroke (AIS) has gained interest in the recent years with the introduction, first of intravenous administration of thrombus-dissolving drugs, and more recently of endovascular thrombectomy (EVT) with stent retrievers and aspiration devices or a combination of the two. Mechanical aspects play a crucial role in various stages of the disease. The review by ***Ospel*** and colleagues (Ospel et al., 2021) introduces the reader to IAS and the treatment options, from the intravenous thrombolysis to the new EVT as the mechanical thrombectomy with both stent-retrievers and aspiration catheters. The authors provide from a clinical viewpoint a thorough overview of the mechanical factors that influence the EVT success, including factors on blood vessels, thrombus, procedure techniques, the interaction between devices and thrombus and vessels.

AIS research is devoted to study new technologies and treatment options by using in vivo, ex-vivo, in vitro and in silico tests. The important role of ex-vivo and in vitro modeling is comprehensively discussed in the review by ***McCarthy*** and colleagues (McCarthy et al., 2021) especially in light of the lack of in vivo measurements related to thrombus composition and shape. From a medical device developers' perspective, it is important to perform controlled experiments to qualitatively and quantitatively investigate clot mechanics. ***Luraghi*** and colleagues (Luraghi et al., 2021c) present an overview of the literature within the field of in vitro and in silico evaluation of EVT procedure. They categorized the studies based on the vessel, clot, device and procedure characteristics, geometries, and models. The use of animal and in vitro experiments is discussed in the work by ***Gounis*** and colleagues (Anagnostakou et al., 2022), who analyzed pre-clinical surrogate models of AIS treatment. They highlight the importance of the transition from preclinical tests to clinical applications as the former presents limitations, especially in satisfying the criteria established by the regulatory agencies. In this view, validation is usually proposed for a specific context of use and used to build credibility to the numerical model based on the ASME V&V40 protocol. The credibility refers to the level of trust of a computational test with respect to the context of the model use and is paramount when applying the results in safety-critical situations, as for the EVT application. ***Luraghi*** and colleagues (Luraghi et al., 2021a) proposed an applicability evaluation of a numerical thrombectomy model using a rigorous step-by-step method. Focusing on the credibility of the preclinical tests***,*** they demonstrated the reliability and validity of an in silico thrombectomy model based on validation evidence.

First and foremost, the mechanical properties of the thrombus under various loading conditions and how these are related to thrombus composition need to be established since they are essential data to better investigate optimization of AIS treatment. A novel computational model of microvascular thrombus formation is proposed by ***Masalceva*** and colleagues (Masalceva et al., 2022), based on 2D particle-based model of thrombus shell formation combined with platelet agonists kinetics. The strength of their model lies in its ability in analyzing the distribution of inter-platelet forces throughout the thrombus by coupling local biochemical cues to the inter-platelet interactions and granule secretion. Their study revealed multiple weak spots in the outer regions of thrombus, important issue in the thrombus formation process. On the same path, ***Rezaeimoghaddam*** and colleagues (Rezaeimoghaddam and Van de Vosse, 2022) present a mathematical model amenable to predict thrombosis and identify the risk of thrombus formation when devices are used. The developed method, which combines computational fluid dynamics with a set of convection-diffusion-reaction equations, is also compared to in vitro experimental results, aimining at identifying the most relevant equations by understanding signaling pathways. ***Teeraratkul*** and colleagues (Teeraratkul and Mukherjee, 2021) focus on the important phenomena of flow-mediated transport of biochemical species. They developed a microstructure model with a custom preconditioned fictitious domain formulation for thrombus-hemodynamics interactions and an advection-diffusion formulation for transport. They amied at demonstrating the formation of coherent flow structures around the thrombus which organize advective transport which plays an important role in the fundamental processes underlying flow-mediated transport around the thrombus, permeation into the thrombus, and subsequent intra-thrombus transport.

After the thrombus gets formed, the interaction between the thrombus and the blood flow is important to understand the relationship between the origin of the thrombus (left atrium, carotid bifurcation) and the location where the thrombus finally lodges in the intracranial circulation, and the consequences associated with the lodging location. The in vivo study presented by ***Georgakopoulous*** and colleagues (Georgakopoulou et al., 2021) analyses the effects of microemboli on the brain tissue. The objective of their study was to determine the extent of damage on brain tissue caused by microemboliby using rat models. They establish that microemboli, which individually may not always be harmful, could interact and result in local hypoxia or infarction in case of aggregation. ***Xue*** and colleagues (Xue et al., 2021) propose a numerical model to quantify the effects of cerebral microthrombi on oxygen transport to tissue in terms of hypoxia and ischemia. The implemented Green's function method was used to statistically represent the capillary networks in view of oxygen transport investigation. Quantifying the impact of microthrombi on oxygen transport and tissue death is believed to be extremely important in brain models of ischaemic stroke and thrombectomy.

When diagnosing patients with intracranial thrombus, the extraction of additional information like the thrombus mechanical properties and perviousness is of fundamental importance. **Cahalane** and colleagues (Cahalane et al., 2021), in their review study, stressed particularly the usefulness and feasibility to quantitatively assess compositional and mechanical properties of thombi with imaging. They present a scoping review detailing associations between thrombus composition, mechanical behaviour and radiological imaging characteristics. They point out the importance of correctly identifying with imaging techniques if a thrombus is fibrin-rich or red blood cell-rich, which have different mechanical properties, to choose the best thrombectomy approach. The work by ***Santos*** and colleagues (Santos et al., 2021) studies the link between perviousness detected by thrombus attenuation measurements and functional outcome. They state that thrombus perviousness measurements from entire thrombus segmentation have a stronger impact on functional patient outcome compared to the current clinical approach of manual assessments.

In the majority of the case, the first treatment of AIS involves the administration of intravenous recombinant-tissue plasminogen activator (r-tPA) as soon as the patient arrives at the hospital. A perspective paper on thrombolysis with particular emphasis on numerical modeling is presented by **Petkantchin** and colleagues (Petkantchin et al., 2022). The authors point out the difficulties to have a complete picture of the thrombolysis problem and they present the steps to build a numerical model describing the evolution of a patient's clot under the action of t-tPA. ***Dwivedi*** and colleagues (Dwivedi et al., 2021) quantified the effect of r-tPA on clot analogs' mechanical behavior in view of its impact on the mechanical thrombectomy. They concluded that the red blood cell content, platelet retraction and exposure time to r-tPA independently affect the mechanical properties of the clots. The dose of r-tPA on the contrary, was not a significant factor in reducing clot mass or changing mechanical properties of the clots.

Today, the preferred treatment of ischemic stroke is the rapid restoration of blood flow by means of EVT. The treatment consists of the mechanical removal of a blood clot by a stent retriever and/or an aspiration catheter. A major shortcoming of EVT is that in 20% of the cases the occluding thrombus cannot be removed from the artery by a stent retriever. Recent studies (Dutra et al., 2019; Ospel et al., 2019; Pérez-Garciá et al., 2020; Zhang et al., 2020) have demonstrated that large fragments of thrombus may be left behind after EVT in stroke patients. This aspect of EVT, which impacts the procedure outcome by incomplete restoration of blood flow, re-occlusion or distal embolization, is presently difficult to predict and control. Incomplete removal of the thrombus is assumed to result from a poor match between the highly variable mechanical properties of the thrombus and the design of the stent retriever. In the paper by ***Moerman*** and colleagues (Moerman et al., 2021), a costumized and automated platform for the generation of high-resolution patient-specific models of cerebral arteries directly from clinical images was developed. It is the first step in the pre-processing phase to have a patient-specific virtual representation of the EVT procedure. In the study by ***Luraghi*** and colleagues (Luraghi et al., 2021b), the first finite element simulations on patient-specific thrombectomy were carried out by comparing virtual results with real patient outcomes. The simulations showed, as in reality did happen, that two attempts of stent-retriever passes were necessary to remove the clot with no fragmentations to follow.

Finally, the removal of the thrombus is often done by direct aspiration as a first-line option. How the **thrombi behave during aspiration**, and how they **might fail** during such a procedure is of crucial importance. ***Fereidoonnezhad*** and colleagues (Fereidoonnezhad and McGarry, 2021) and ***Oyekola*** and colleges (Oyekole et al., 2021) investigated the aspiration procedure by means of in silico models. The former mainly focuses on the development of a new constitutive model that incorporates the unrecoverable plastic deformation of clots, calibrated with experiments. The new model which links the plastic deformation and cross-link formation/dissociation in blood clots was used to simulate the aspiration procedure. The latter proposes a viscoelastic solid model and a viscoelastic cohesive interface between the clot and the artery to virtually reproduce the EVT. Their results indicate the likelihood of the clot to be pushed outward against the artery, close to the catheter tip.

From the collection of the papers presented in this special issue, it is clear that mechanics plays a crucial role in the treatment of AIS. It is our hope that deepening our knowledge of thrombus mechanics will help us to optimize treatment strategies and devices.

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