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A review on the reliability of hemodynamic modeling in intracranial aneurysms: why computational fluid dynamics alone cannot solve the equation

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Computational blood flow modeling in intracranial aneurysms (IAs) has enormous potential for the assessment of highly resolved hemodynamics and derived wall stresses. This results in an improved knowledge in important research fields, such as rupture risk assessment and treatment optimization. However, due to the requirement of assumptions and simplifications, its applicability in a clinical context remains limited.

This review article focuses on the main aspects along the interdisciplinary modeling chain and highlights the circumstance that computational fluid dynamics (CFD) simulations are embedded in a multiprocess workflow. These aspects include imaging-related steps, the setup of realistic hemodynamic simulations, and the analysis of multidimensional computational results. To condense the broad knowledge, specific recommendations are provided at the end of each subsection.

Overall, various individual substudies exist in the literature that have evaluated relevant technical aspects. In this regard, the importance of precise vessel segmentations for the simulation outcome is emphasized. Furthermore, the accuracy of the computational model strongly depends on the specific research question. Additionally, standardization in the context of flow analysis is required to enable an objective comparison of research findings and to avoid confusion within the medical community. Finally, uncertainty quantification and validation studies should always accompany numerical investigations.

In conclusion, this review aims for an improved awareness among physicians regarding potential sources of error in hemodynamic modeling for IAs. Although CFD is a powerful methodology, it cannot provide reliable information, if pre- and postsimulation steps are inaccurately carried out. From this, future studies can be critically evaluated and real benefits can be differentiated from results that have been acquired based on technically inaccurate procedures.

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KEYWORDS computational fluid dynamics; intracranial aneurysms; imaging; segmentation; uncertainty quantification

The assessment of patient-specific rupture risk for intracranial aneurysms (IAs) remains one of the most challenging quests for neuroradiologists and neurosurgeons.[8,40] Within the last decades, a tremendous effort has been undertaken to carry out research studies with respect to hemodynamics,[20,38,73] diseased vasculature,[11,50,65] and improvements in treatment techniques.[39,52] Specifically, investigations have focused on the interaction of hemodynamics (e.g., velocity, pressure, wall shear stresses) and luminal vessel walls (e.g., deformation, wall stresses) to understand pathological phenomena and evaluate the individual risks of existing therapies.

In this regard, the methodology of computational fluid dynamics (CFD), an established approach in traditional engineering disciplines, was applied to neurovascular research. Although clinically available modalities to assess personalized flow conditions exist (e.g., phase-contrast MRI or Doppler ultrasound), image-based blood flow simulations created high expectations for physicians. Ideally, the information on velocity, pressure, or every derived parameter could be available at an arbitrary point in space and time. Additionally, CFD-based investigations could improve approval procedures, speed up device design optimization, and reduce the number of animal studies.

ABBREVIATIONS CFD = computational fluid dynamics; IA = intracranial aneurysm; 3DRA = 3D rotational angiography.

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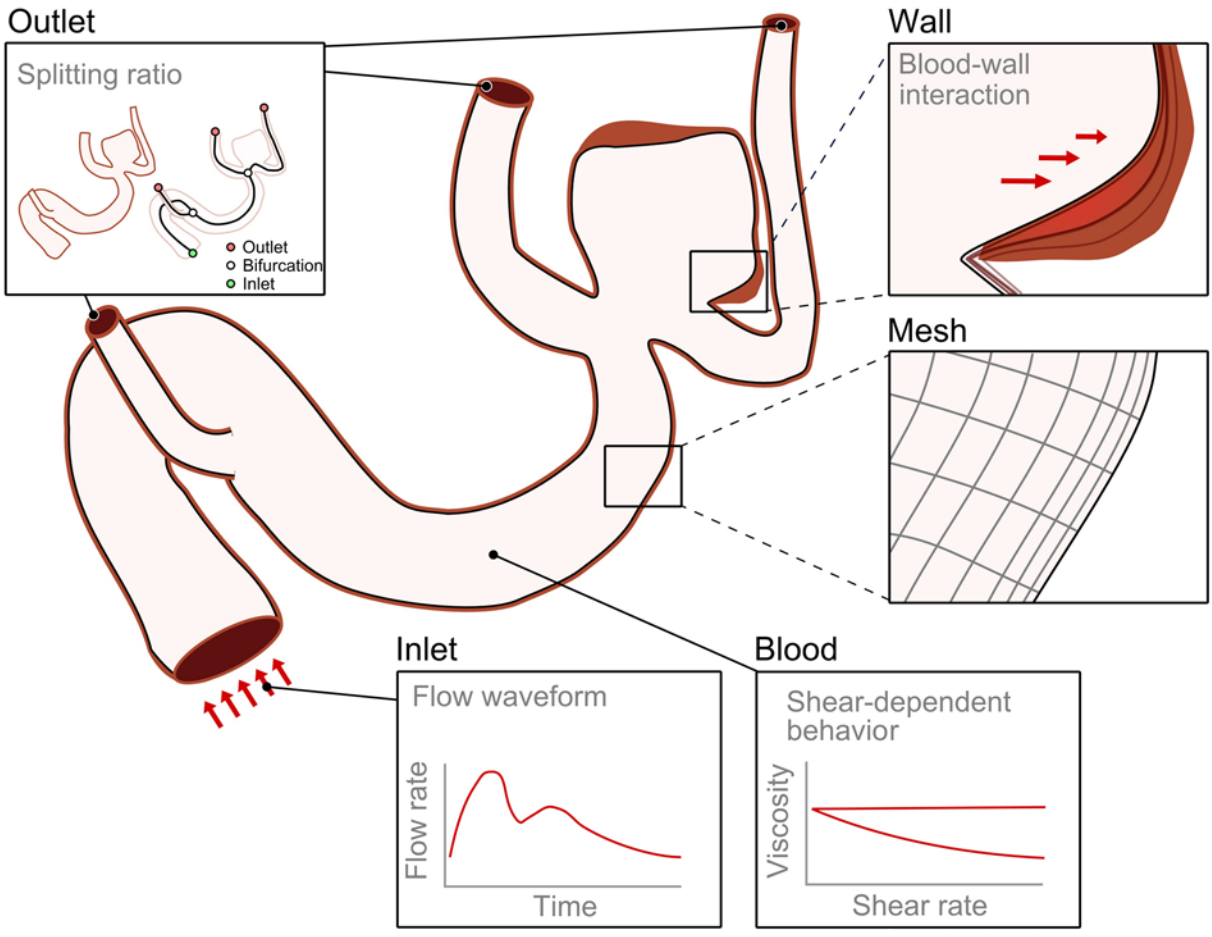

FIG. 1. Illustration of the relevant impact factors for hemodynamic simulations: spatial discretization of the flow domain using a volumetric mesh; (time-dependent) inlet and outlet boundary condition; wall treatment using rigid or flexible vessel walls; blood approximation based on Newtonian or non-Newtonian assumptions.

In reality, these expectations were hindered as simulations required individual information, particularly in the peripheral areas of the concerning spatial domain[26] (Fig. 1). However, this is not always available in a clinical context, and, thus, patient-specific blood flow simulations are only as accurate as their input data, the defined simulation setup, and the processing of acquired information.

This review article provides an overview of state-of-the-art simulation techniques to acquire reliable hemodynamic predictions in IAs. Relevant subtopics that affect the simulation outcome are addressed (Fig. 2). Furthermore, recommendations for specific aspects involving the interdisciplinary workflow are given to enable physicians to critically evaluate the quality of hemodynamic simulation results in the future.

Presimulation

Imaging Modalities

The initial step in obtaining patient-specific blood flow simulations is the selection of an appropriate imaging modality. MRA and CTA have been found to reliably and noninvasively diagnose most IAs.[15] In terms of spatial accuracy, however, Geers et al.[28] revealed that significantly larger aneurysm necks and unsuccessful reconstructions of vessels smaller than 1 mm occurred more often when using CTA compared to 3D rotational angiography (3DRA), which is acquired with DSA. Though main flow characteristics could be reproduced independent of the imaging modality, the hemodynamic parameters showed relatively large quantitative differences. In response to this, Kallmes emphasized the importance of this investigation but also raised the question of which modality can serve as ground truth.[41] To address this concern, different studies identified the advantages and disadvantages of existing techniques.[75] In this regard, 3DRA was identified to be the current gold standard for image-based hemodynamic simulations in IAs.

In the near future, the use of intravascular imaging such as neurovascular optical coherence tomography has huge potential, not only to precisely measure the vessel lumen, but also to assess local wall thicknesses and inhomogeneities.[31] Based on this valuable information, realistic advancement of recent fluid-structure simulation techniques is feasible. However, technical issues regarding the cerebrovascular access and the imaging depth have to be solved before the method becomes clinically applicable.

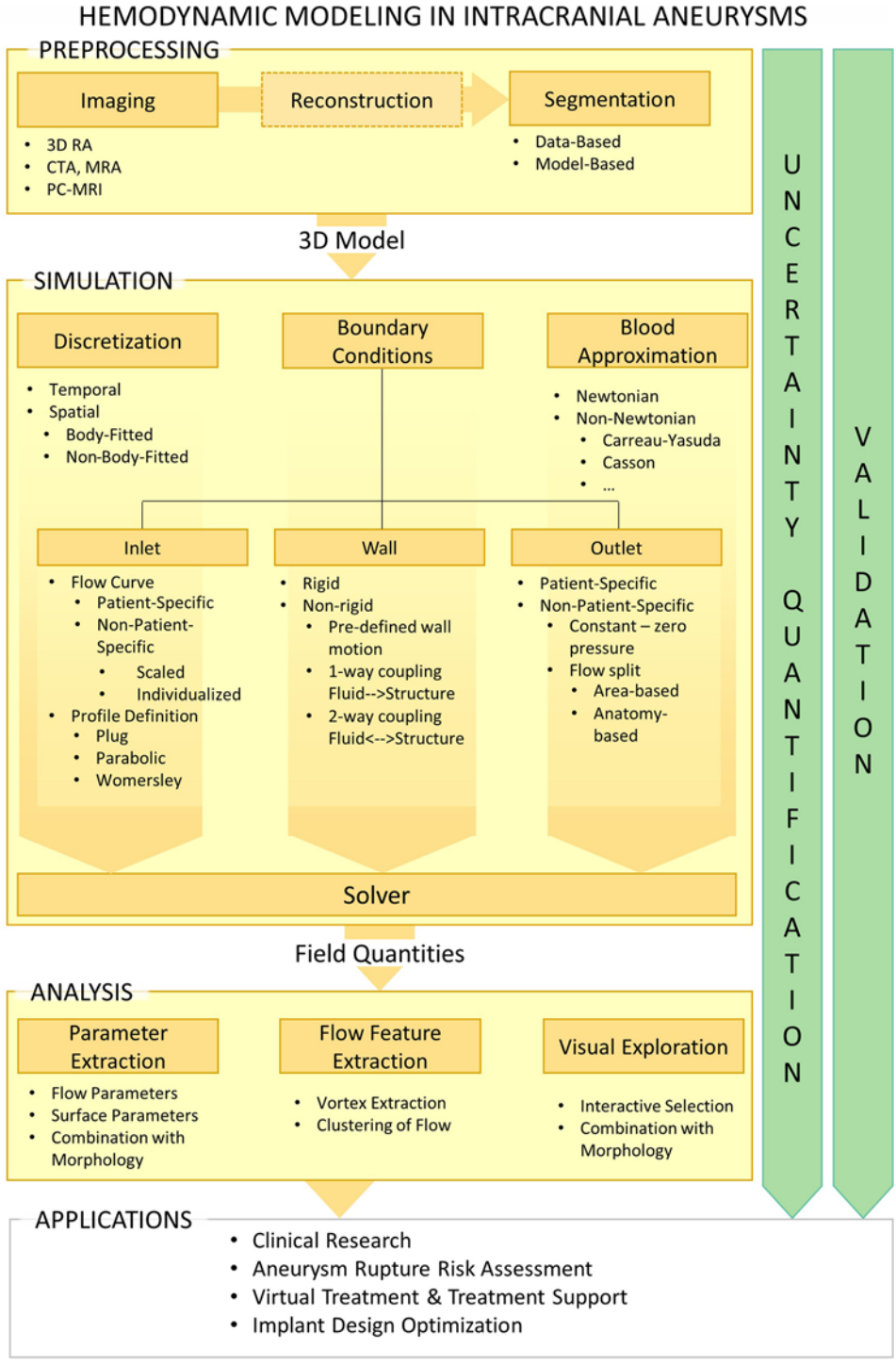

FIG. 2. Interdisciplinary workflow for the assessment of hemodynamics in patient-specific aneurysms. 1) Preprocessing containing the image acquisition, reconstruction, and segmentation. 2) Blood flow simulation based on an appropriate discretization, the definition of boundary conditions, a realistic approximation of blood, and the selection a of sufficient solver. 3) Analysis of the acquired field quantities either by extracting parameters and flow features or by visual exploration. This multistep workflow should be accompanied by both uncertainty quantification and validation to ensure that the variability of the evaluated quantities is known.

Recommendation

3DRA is the gold standard for image-based blood flow simulations. Low–spatial resolution images should not be used because they create geometrical inaccuracies that inevitably affect the results.

Image Reconstruction

An underestimated influence is associated with the reconstruction of raw 3DRA image data. In 2014, O'Meara et al.[51] revealed the imprecise assessment of anatomical characteristics using smooth reconstruction kernels. Two follow-up studies further emphasized the need to apply sharper kernels if quantitative morphology or hemodynamic measurements are of interest.[4] It was found that the use of smooth kernels can lead to pseudo-stenoses in side branches and inaccurate aneurysm neck representations. The latter was confirmed by Schneiders et al.,[60] who measured aneurysm neck sizes based on 3DRA and 2D DSA. Hence, it has to be emphasized that overestimations in the initial stages lead to error propagation and therefore may result in wrong conclusions.

Recommendation

The use of reconstruction kernels that contain smoothing algorithms should be avoided when quantitative analysis is desired.

Image Segmentation

Image segmentation represents the next crucial step toward realistic blood flow simulations. Due to multiple fields of application in medical imaging, a variety of segmentation tools and approaches, such as region growing or threshold-based techniques, exist.[61]

To assess the real-world variability of segmentation outcomes for IAs, Valen-Sendstad et al.[66] compared 28 data sets from different research groups containing segmentations of 5 middle cerebral artery aneurysms each. A wide variability occurred, which led to the suggestion that guidelines should be established.

The proposal is supported by the results of the most recent study, which compared aneurysm segmentation capabilities.[6] In the frame of the "Multiple Aneurysms Anatomy Challenge 2018," 26 research groups submitted segmentation results of 5 IAs. In general, an overestimation of the vessel domains occurred, while specific features, such as blebs, were underrepresented. In particular, the comparison with a 2D reference image revealed that an appropriate reconstruction of the aneurysm neck can be cumbersome, and a certain experience level with respect to aneurysm segmentation is required. The assessment of the impact of these segmentations on hemodynamic results demonstrates that unrealistic flow patterns and diverging flow parameter values can occur if insufficient segmentation is carried out.

Furthermore, it is important to point out that in most studies, only comparisons among different modalities and techniques were carried out, as no ground truth was available.[41] Therefore, future investigations require highly precise references to demonstrate the applicability of specific segmentation techniques.

Recommendation

The aneurysm segmentation quality (e.g., avoiding vessel melting artifacts and over- or under-represented aneurysm necks) has a primary influence on subsequent simulation results. If possible, 3D models should be verified with the corresponding 2D images. However, important anatomical features such as blebs might not be visible in 2D images, and hence some uncertainty remains.

Simulation

Spatial and Temporal Discretization

The required spatial resolution of the computational domain highly depends on how the equations for conservation of mass and momentum are discretized (e.g., based on the finite volume or the finite-element method). Furthermore, the type of cell used (e.g., tetrahedral, hexahedral, polyhedral, prism) as well as the specific parameters of interest (e.g., direct variables such as velocity and pressure, or first/second derivatives) determine the mesh resolution. Alternatives to body conformal surface and volume meshes, such as the immersed boundary method, require an individual spatial discretization treatment.[62]

Regarding mesh refinement, Hodis et al.[33] concluded that each patient-specific model requires its own grid independence study to establish an accurate analysis. However, since studies with large case numbers are required to obtain significant results, this is not feasible in practice. According to Janiga et al.,[37] a fine discretization along the luminal wall is required to resolve the steep velocity gradients and achieve mesh-independent wall shear stress results. A landmark study by Valen-Sendstad et al.[70] emphasized the role of the solution strategy comparing high- and normal-resolution approaches. Their findings highlight the need to carefully select an appropriate simulation setup for the intended research question, which was confirmed by subsequent independent investigations.[7,23]

To identify an appropriate temporal resolution, Dennis et al.[19] demonstrated the requirement of small time-step sizes in combination with low residual errors to avoid discretization errors. However, high-order numerical schemes enable the use of coarser meshes and time-step resolutions and thus lead to shorter computation times. In consequence, image-based blood flow simulations are more applicable in a clinical context.[43]

Recommendation

For "common" hemodynamic simulations addressing time-dependent flow and shear phenomena, a cell size of at least 0.1 mm (or smaller) is mandatory. Regarding the time-step size, a value of 1 ms or lower with low residuals is recommended to ensure stable simulations and the ability to quickly resolve changing flow patterns.

Boundary Conditions

Inflow Boundary Conditions

Besides the importance of high-quality segmentations, the selection of appropriate boundary conditions is crucial.[47] At the inlet cross section(s) of the considered domain, time-dependent velocity or flow waveforms are commonly applied. Ideally, these curves were measured

in the patient (e.g., using Doppler ultrasound), but in most cases this information is missing. Therefore, flow rates are mostly taken from literature[34] and scaled according to the corresponding inlet area.[68] Nevertheless, it is clearly advised that, if possible, individual inflow conditions should be used or, at the very least, should be chosen from a predefined set of waveforms.[21]

Regarding the type of inlet boundary condition, plug (constant), parabolic, or Womersley profiles are defined. However, as pulsatile effects are clearly smaller in the cerebrovascular compared to cardiac arteries, the impact of the profile type is negligible (if an appropriate normal extrusion of the inlet was carried out).[3,32]

Finally, the setup of hemodynamic simulations should always be adapted to the clinical research question. For example, if only cycle-averaged flow fields are desired (e.g., mean aneurysmal velocities), time-saving, steady-state simulations may be sufficient.[27] However, advanced hemodynamic parameters such as the oscillatory shear index require time-dependent computations.[72]

Vessel Wall Conditions

Most computational studies assume rigid vessel walls, as contrast-enhanced imaging modalities such as 3DRA usually provide luminal information. However, as aneurysm motion can be observed and rupture occurs within the aneurysm wall, a consideration would be beneficial.[12] To account for fluid-structure-interaction simulation, additional vessel wall information is required (e.g., local wall thickness, material model, and parameters).[29,35] However, realistic values are difficult to acquire and few studies have managed the first assessments.[13,57]

Overall, it is important to emphasize that vessel wall modeling only adds knowledge if precise wall information exists. Simply assuming relevant parameters (e.g., constant wall thicknesses) may lead to erroneous conclusions.[71]

Outflow Boundary Conditions

With increasing computational resources, the region of interest increases and multiple outflow cross-sections occur. Initially, the zero-pressure boundary condition was the most favorable assumption due to unknown pressure waveforms, but several studies revealed its weaknesses.[18,54]

To avoid related inaccuracies, Chnafa et al.[17] introduced an advanced flow-splitting model that evaluates the blood flow distribution based on local vessel diameters and branches. The comparison with zero-pressure conditions and methods based on Murray's law[49] revealed the strong influence of outlet boundary conditions and the requirement of a careful model definition.

Furthermore, sophisticated 0D and 1D modeling approaches exist to further improve the quality of the numerical results.[16,45] Additionally, hybrid techniques are developed to combine flow information from different modalities,[1,46] and hence, constant pressure assumptions are avoidable.

Recommendation

1) If available, patient-individual flow rates acquired using Doppler ultrasound or phase-contrast MRI should be used.
2) Considering nonrigid vessel walls is only meaningful when precise wall information (e.g., local thickness, strength) is available.
3) Assuming constant pressures at outlet cross-sections should be strictly avoided, particularly for simulation domains containing larger numbers of outflows. Instead, advanced splitting techniques should be applied.

Solver Selection

After appropriate discretization and selection of valid boundary conditions, a comprehensive fluid solver must be chosen. Although several studies individually presented the usability of solvers for different applications, Steinman et al.[63] pioneered the intergroup simulation comparisons for IA research. Their study demonstrated that different solvers and solution strategies were capable of a consistent pressure and velocity calculation. Nevertheless, other hemodynamic quantities that are of clinical interest may differ depending on the solver. A follow-up challenge confirmed these findings by showing that cycle-averaged and peak-systolic velocity and pressure computations were in a good agreement among the groups—for example, with deviations of in-plane velocities lower than 20%.[3]

Different studies emphasize the importance of properly resolved simulations if researchers intend to investigate advanced flow features such as transitional phenomena or turbulent-like structures.[67] Dennis et al.[19] gradually refined several settings of a commercial solver and showed the nonnegligible effect on the suppression of flow instabilities. Therefore, high-frequency fluctuations occurring throughout the cardiac cycle can only be detected if appropriate solution strategies with respect to resolution, flow solver and numerical schemes are chosen.[24] This is particularly important when focusing on the methodological understanding of the relation of hemodynamics and rupture.[69,74]

Recommendation

The use of conventional flow solvers in combination with high-order numerical schemes (at least second order) is sufficient if global flow features are of interest. To capture flow instabilities that may occur in hemodynamically unstable IAs, higher-order solver algorithms are suggested.

Blood Treatment

Blood is a typical representative of a non-Newtonian fluid. Due to its shear-thinning behavior, existence of a yield stress, and its viscoelasticity and thixotropy, modeling remains challenging.[10] The acquisition of realistic model parameters is particularly demanding, as blood changes its properties in in vitro experiments. Moreover, variable viscosities appear with decreasing shear-rates which are associated with decreasing vessel calibers and blood flow velocity. As IAs mainly occur at the main cerebral vessels of the circle of Willis, representative vessel diameters vary between 2 and 7 mm. Therefore, Newtonian behavior is often assumed (e.g., with dynamic viscosities ranging from 3.5 to 4 mPa·s) or rheology is approximated using the Casson model, the power law model, or the Car-

reau-Yasuda model. To clarify whether the assumption of a constant viscosity is valid for the continuity approach, several experimental and numerical investigations were conducted. While some groups argue that significant differences between both assumptions exist,[22,25] others demonstrated that the non-Newtonian effects are negligible or have just a secondary impact.[42,48]

Recommendation

The non-Newtonian nature of blood becomes more prominent with decreasing vessel calibers. As shear rates in the circle of Willis are high enough to avoid agglomeration effects, the assumption of blood as a Newtonian fluid is acceptable.

Postsimulation

Analysis Standardization

Many studies that relate morphological or hemodynamic discriminants with rupture risk and treatment outcome are based on a clear definition of the ostium. However, it has been noticed that for the separation between a parent vessel and aneurysm sac, only cut-planes are used. As IAs are highly individually and complexly shaped malformations, this approach often leads to insufficient predictions (even if the presimulative steps and the computations were performed with high precision). To avoid inaccuracies due to user-dependent analysis techniques, verified standardization is claimed using (semi)automatic evaluation methods.[56] In this regard, one of the few open-source software packages specifically designed for vascular applications is the Vascular Modeling Toolkit.[53] This toolkit provides several substeps of the descripted simulation workflow and is also applicable in a clinical context.

Besides automatization, clear definitions of commonly used phrases such as "parent vessel" (how far from the aneurysm?) or "low shear area" (based on which threshold?) are required to avoid distraction due to diverging specifications.[14] Only then can a comparability of the findings from different groups be realized. In this regard, normalizations are strongly encouraged in order to reduce the influence of boundary conditions.

Recommendation

Aneurysm analysis should become standardized. For instance, cut-planes for the separation of parent vessels and aneurysms should be avoided. Instead, verified neck-curve or ostium reconstruction techniques are recommended.

Advanced Flow Analysis

With increasing computational resources, the amount of flow information in individual IAs increases as well. However, most of this information is discarded in practice and only temporal and/or spatially averaged values remain. To further quantify advanced flow structures and extract more knowledge, several attempts exist already. This includes clustering-based approaches to visualize vortical flows, vortex classifications, combined visualization of hemodynamic and structural information, and explorative blood flow visualization.[2] Furthermore, methods from proper orthogonal decomposition are applied to aneurysmal flow to enable the comparison of 4D flows and identify dominant flow features.[36] Spatial complexity and temporal stability were further addressed by Byrne et al.,[9] who compared vortex core lengths and aneurysm entropy for the assessment of rupture risk.

So far, the applicability of these techniques is rather limited in clinical practice as they are based on individual workflows or depend on local research projects. To allow for deeper insights into aneurysmal flow on a larger scale, the described methods would also benefit from standardization.

Recommendation

As simplified evaluations of hemodynamic properties were not successful in explaining aneurysm growth, remodeling and rupture, advanced flow analysis may be beneficial in improving the knowledge in aneurysm research.

Uncertainty Quantification

Other important research activities relate to the assessment of simulation errors using uncertainty quantification methods. Tangible knowledge about the individual impact is required, especially due to the highly interdisciplinary and multistep workflow. Goubergrits et al.[30] assessed the uncertainty of complex aneurysm morphology metrics. They demonstrated that the uncertainty of 2D and 3D size parameters was significantly higher than the uncertainty of 1D parameters. Sarrami-Foroushani et al.[59] found that variations of the flow waveforms in the internal carotid artery have limited influence on cycle-averaged parameters. However, multidirectional flow structures are strongly affected by changes at the inlet. In a follow-up study, the authors further claim that there is a strong need to extend deterministic computational simulations with strategies for uncertainty mitigation, uncertainty exploration, and sensitivity-reduction techniques.[58]

In addition to variations of the aforementioned technical aspects, individual factors such as age, sex, ethnicity, or family history are often not considered. Systemic hemodynamic parameters should be evaluated (e.g., using ensemble simulations), while existing examples from cardiovascular research could be transferred to cerebrovascular questions as well.

Recommendation

Profound uncertainty quantification of clinically relevant parameters is required to objectively assess the impact of specific error sources.

Validation

A mandatory step associated with numerical simulations is the methodological validation of either in vitro (based on comparisons in phantom models)[44,55] or in vivo (using noninvasive imaging)[5] measurement techniques. Here, several attempts with enormous differences regarding accuracy and depth were already carried out. Overall, it was demonstrated that good qualitative agreement between well-conducted numerical and experimental methodologies can be achieved, but quantitative discrepancies remain.

Nevertheless, many validation concepts are mainly

limited to single cases and restricted flow conditions. Furthermore, the applied measurement modalities possess certain technical limitations and may not be capable of detecting flow structures that can be identified by means of numerical approaches.[55] Hence, generalizable conclusions regarding a global validity are not yet possible. As a result, dedicated study collections are organized that are aimed at the identification of robust verification and validation studies.[64]

Recommendation

Validation is mandatory for hemodynamic simulations, but limitations regarding appropriate validation concepts remain. Therefore, in vitro and in vivo measurement techniques should be improved.

Conclusions

Open questions still remain regarding the growth, remodeling, and rupture of IAs. Although it has been shown that the assessment of detailed hemodynamic properties using image-based simulations can provide helpful information, the clinical applicability has been limited until now. Various international studies, which compared the simulation results from multiple research centers, demonstrated that considerable differences with respect to final simulation results occur. Specific analysis of the individual procedures revealed particular weaknesses during imaging and image processing, in the context of the simulation setup or after the simulation along the postprocessing. Hence, there is a need to rely on certain methodological quality thresholds and standardized procedures. In this regard, it is important to raise the awareness of these sources of error and how they can propagate:

1) The quality of the underlying images is of primary importance. Highly resolved image data, as well as sufficient reconstruction and segmentation, is mandatory. As clinically acquired images are subject to inconsistencies, (semi)automatization can be cumbersome. Because of this, manual adjustment (e.g., removal of imaging artifacts) by experienced personnel is sometimes unavoidable.
2) On the other hand, hemodynamic simulations can (and should) be automatized in order to guarantee reproducibility. However, a sufficient setup with respect to the spatial discretization, the selection of boundary conditions, the numerical solver, and the modeling of blood is expected. The level of accuracy that this setup must be defined to strongly depends on the research question.
3) Even when the first and second aspect are realized with high fidelity, insufficient processing of the raw simulation results produces a considerable variability of relevant hemodynamic parameters and, therefore, may lead to incorrect conclusions. Thus, standardization is advised after careful uncertainty analyses in the context of cerebrovascular research have been carried out.
4) Finally, an important aspect regarding the modeling of hemodynamics in IAs is the fact that people work in interdisciplinary teams. Specifically, physicians and experts from medical imaging, bio-medical engineering, and computer sciences collaborate and must find a common language for the overall tasks. When domain experts cover working steps, which are outside of their actual expertise, user-induced errors are likely to happen.

Overall, image-based simulations for IA hemodynamics can add value to the existing knowledge of physicians, if these steps along the multidisciplinary workflow are carried out carefully. For the investigation of complex flow structures or advanced biochemical reactions such as thrombosis, other conditions are clearly required in comparison to the assessment of rather simple flow metrics. Nevertheless, a combination with other relevant disciplines such as morphometry, biomechanics, or histology (and not CFD alone) is crucial to obtain an improved understanding of this neurovascular disease.

In summary, this review article condenses relevant elaborations and findings related to the computational flow modeling in IAs. Furthermore, it emphasizes the need for accompanying verification and validation studies, as well as a multi-institutional consensus of best practices, for cerebral blood flow simulations.

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Disclosures

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Author Contributions

Conception and design: Berg, Saalfeld, Voß. Drafting the article: Berg. Reviewed submitted version of manuscript: Berg. Critically revising the article: Saalfeld, Voß, Beuing, Janiga. Approved the final version of the manuscript on behalf of all authors: Berg. Administrative/technical/material support: Berg, Saalfeld, Voß. Study supervision: Berg, Janiga.

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