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ORIGINAL ARTICLE

Methodologies to assess blood flow in cerebral aneurysms: Current state of research and perspectives

Approches méthodologiques de l'étude des flux dans les anévrismes intracrâniens : état de la recherche et perspectives

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Summary With intracranial aneurysms disease bringing a weakened arterial wall segment to initiate, grow and potentially rupture an aneurysm, current understanding of vessel wall biology perceives the disease to follow the path of a dynamic evolution and increasingly recognizes blood flow as being one of the main stakeholders driving the process. Although currently mostly morphological information is used to decide on whether or not to treat a yet unruptured aneurysm, among other factors, knowledge of blood flow parameters may provide an advanced understanding of the mechanisms leading to further aneurysmal growth and potential rupture. Flow patterns, velocities, pressure and their derived quantifications, such as shear and vorticity, are today accessible by direct measurements or can be calculated through computation. This paper reviews and puts into perspective current experimental methodologies and numerical approaches available for such purposes. In our view, the combination of current medical imaging standards, numerical simulation methods and endovascular treatment methods allow for thinking that flow conditions govern more than any other factor fate and treatment in cerebral aneurysms. Approaching aneurysms from this perspective improves understanding, and while requiring a personalized aneurysm management by flow assessment and flow correction, if indicated.

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Introduction

Cerebral aneurysms are pathological dilatations of arteries occurring mainly at bifurcations located in the vicinity of the

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circle of Willis [1]. Under the effect of a single or a combination of factors, the arterial wall is progressively thinned and ballooned out to create an aneurysm. Recognized cofactors contributing to intracranial aneurysm growth and risk of rupture are for example hypertension, atherosclerosis, smoking, excessive alcohol consumption and oral contraceptives. Increased risk exists among patients presenting hereditary deficiencies such as hereditary polycystic kidney disease, Ehlers–Danlos syndrome, Marfan syndrome, fibromuscular dysplasia or family history of aneurysm disease [2–4], and between 7 to 20% of people who underwent an aneurysmal rupture have a relative of first or second degree with a cerebral aneurysm diagnosed [5]. All this indicates that the biology and the resulting life cycle of a specific aneurysm is potentially influenced by a number of factors and coincidences, what allows for comparing the disease with a complex systems, where the variable factors want to be weighed and integrated according to their possibly varying role along the different periods of the aneurysm life cycle, i.e. initiation, growth and rupture.

Clinical studies reveal a prevalence of around 2% of the Western population having a cerebral aneurysm with a rupture incidence of only about 10 of 100,000 people per year [6]. Aneurysm rupture in these 10 people present mainly under the form of a subarachnoid hemorrhage (SAH), what results in high morbidity and mortality rates for the patients concerned [7], and this even under good medical care conditions. SAH conditions due to a ruptured aneurysm result for obvious reasons in high treatment cost. Treatment of unruptured cerebral aneurysm provides better results and at lower cost, however, not free of risk. With current diagnostic medical imaging methods, revealing increasingly such unruptured aneurysms as an incidental imaging finding, it seems of interest to search for criteria and methods that would allow for optimizing the rupture risk assessment and to weigh such risk against the risk of a potential treatment. To take into account the changing treatment risk, the assessment should be adjustable to the evolving treatment methods and standards. Such an educated approach may allow for reducing the stress conveyed to patients and may provide a useful support to the discussion and decision taking, while avoiding unnecessary treatment or supporting the decision on when and how to treat.

As outlined above, the multiple factors influencing the fate of a cerebral aneurysm require the use of a risk assessment model that perceives the condition as complex. Considering the roles of the different parameters in such a complex system, among others, the group representing biomechanical aspects is of special interest, because methods as developed in engineering and industry could be applied. Measurements or calculations of biomechanical factors include the intra-aneurysmal blood flow, the mechanical load on the arterial wall and the peri-aneurysmal environment in case appropriate boundary conditions can be defined. The aneurysmal shape reflects the wall quality and is the resultant of the aneurysm evolution, and depends from the physiological load, as well as from the contact with surrounding tissues [8], very much alike the riverbed, represents the resultant of the river and the land it runs through. Rupture mainly results from the progressive degeneration and weakening of the three arterial wall constituents, the elastin fibers, the vascular

smooth muscles and the collagen fibers. The last to go is the collagen network, which constitutes the major structural element of the aneurysmal wall. Contrary to the mainly flow driven degeneration, there have been observation of morphological changes associated with aneurysm wall remodeling representing inflammation or repair attempts.

Through biology, all these mechanisms are influencing the aneurysm wall quality and therefore one could imagine addressing the disease and its evolution by pharmacological therapy influencing degeneration, inflammation or repair [9]. Although yet to explore further, in our view the most promising method to alter the biology of the aneurysm wall is acting on the fluid mechanic parameters, such as blood pressure, flow rates and patterns that may all, individually or in combination, alter the biological response of the wall constituents or of the endothelium, which in turn releases bioactive substances regulating the metabolism and matrix turnover of the aneurysmal wall [1]. If acting on the vessel lumen side to implement flow correction through medical devices like coils and stents seems increasingly feasible, acting on the outside of the aneurysm wall is less promising. Modification of the peri-aneurysmal environment is currently only possible by applying surgical wrapping methods [10].

Therefore blood flow modulation may constitute and increase its role as an efficient treatment principle, aiming either disconnection from the parent artery flow or restoration of a physiological flow in the parent artery. Neurosurgical treatment performed by placing a metallic clip around the aneurysmal neck is closing definitively the aneurysmal flow and may change the geometry of the parent artery. This could be seen as a therapy inducing flow modification in the aneurysm and the parent arteries. Although the surgical modality offers the advantage of a direct vessel repair, this is achieved with the effort of an open head surgery associated accordingly with patient discomfort and operative risk [7]. Less discomfort and procedural risk exists with endovascular repair, working minimally invasive through a small arterial puncture site and by using image guided treatment methods [11]. Endovascular treatment methods act by flow modulation in the aneurysmal cavity or in the parent vessel. The aneurysmal cavity can be filled with coils leading rapidly to aneurysmal thrombosis once enough coils have been introduced. Use of stents may act as a scaffold to help keeping coils in an aneurysmal cavity in case there is a large aneurysm neck and offering a higher vessel reconstruction success rate, with the stent acting as a scaffold for the vessel wall remodeling. The main difficulties of endovascular treatment are related to difficult access to the target area, intra-operative rupture risk and mainly a currently high peri-operative thromboembolic potential. Based on these facts, the decision for invasive treatment has to balance between the risks of treatment and the risks of natural disease course [12,13].

With this potential in mind, it is believed that stents alone will be able to redirect the flow in the parent artery and slow down the aneurysmal flow leading to a thrombus formation, stabilizing the aneurysm without the need to enter and to touch the fragile aneurysmal cavity. Prediction of intra-aneurysmal flow alterations after stent placement could be helpful to foresee the effect and to allow for choosing the most adequate stent capable of inducing alone or together

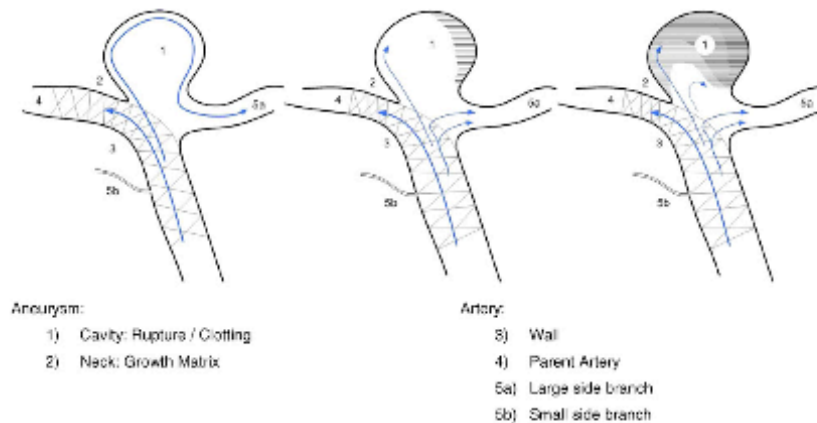


Figure 1 Illustration of the progression of clot formation in a bifurcation aneurysm model treated with an intracranial stent as seen in medical procedures.

with additional intra-aneurysmal flow modifiers (coils) a stable and safe clot formation (Fig. 1).

Such predictions could empower medical doctors to choose the most appropriate treatment. Medical imaging companies would have to integrate numerical simulation tools and medical device companies would have to develop and produce improved endovascular prostheses – processes that are currently well under way.

In this paper, we present a review of the current state of research involving *in vitro* experiments and numerical simulations of intra-aneurysmal flow in presence of a stent.

Experimental methods developed to assess blood flow changes due to a stent in intracranial aneurysms: evolution of methods and transparent *in vitro* vascular models (phantoms, replicas)

One of the objectives of experimental methods is to assess blood flow changes in aneurysms induced by flow diverters such as may be produced by a stent deployed in the parent artery. Assessing the device effect on flow in *in vitro* vascular phantoms is done to estimate *in vivo* flow effects to be expected. This effort is aimed mainly at predicting the chance to obtain thrombus formation within an aneurysm after stent placement. The tests may include assessment of effects on flow in the parent artery and its branches. There are quantifiable flow effects, such as values of velocities and pressure and their related parameters, including vorticity (circulation), helicity (rotation), wall shear stress (WSS), and oscillatory shear index among others. Visualization and classification of altered blood flow patterns appears further of interest when it comes to estimating stent efficiency.

The materials of vascular replicas have evolved and spatial resolution of 3D data improved stepwise, giving today possibilities to a range of model production reaching from simple idealized shapes up to complex, patient-specific cerebral aneurysm replicas based on three-dimensional

rotational angiography (3D-RA) [14]. Using rapid prototyping (RP) technologies, 3D description of the aneurysm geometry serves to produce models made of transparent materials such as plexiglas (polymethyl-methacrylate), silicone or poly-vinyl-alcohol-hydrogel, (PVA-H). All such models are transparent and compatible with current medical imaging methods. Most used in our practice are silicone and PVA models. The low friction characteristics of PVA-H models and its elasticity close to soft tissue when compared to silicone models allow for more realistic simulation when it comes to study pulsatile flow effects.

The following flow measuring and visualization techniques have allowed for simple visualization up to a detailed mapping of the parameters defining flow within an aneurysmal cavity.

Slip stream visualization

Slip stream visualization without device

In 1992, flow patterns around human cervical carotid bifurcations were visualized using digital subtraction angiography by injecting contrast agents [15], allowing for direct visualization of flow. The authors hypothesized that high WSS could cause degenerative changes in the endothelial layer, initiating the formation of saccular and fusiform intracranial aneurysms. One year later, by injection of fluorescent particles in the blood stream, Nakatani et al. could visualize spiral blood flows *in vivo*, both proximal and distal to arterial bifurcations located at the base of rat brains [16]. This study led to hypothesize on aneurysms development, growth, and rupture. Chong et al. compared the flow patterns in a vertebrobasilar artery model using slip stream visualization and MR based flow measurements. Flow profiles were found to be consistent between both techniques [17].

Slip stream visualization with device

Lieber et al. visualized the pulsatile flow patterns in an experimental flow apparatus using a laser-induced

fluorescence of rhodamine dye. Various stents exhibiting four different porosities (comprised between 76 and 85%) were investigated and the results showed the difference of aneurysmal vortex reduction in large and small arteries [18]. Using a photochromic dye, Rhee et al. visualized the flow in sidewall and in fusiform aneurysms models, and velocity and WSS changes due to various stents could be calculated. The results reported in these two studies revealed different results with flow reduction being not similar in both kind of models and with stents of various porosities, a less porous stent reducing the intra-aneurysmal fluid motion significantly, and in the other, with stent porosity of less significant effect [19].

Particle illumination photography

Barath et al. studied 20 different stents of various ranges of porosity, permeability and filament diameter and quantified the reduction of the vortex displacement in two different neck-sized sidewall aneurysm models under unsteady flow conditions. Flow patterns were visualized by using glass particles and laser sheet transillumination. The method defines a vortex center path line method obtained by sequentially subtracting each image taken, followed by identification of the vortex center and by tracking the vortex center producing a center path line. The conditions were studied without and in presence of different stents [20]. The authors raised the question of stent positioning effects. In a second study [21], the authors studied the intra-saccular flow pattern changes and the vortex velocity reduction induced by a stent in a internal carotid artery model retrieved from human vascular casting.

Particle image velocimetry (PIV)

PIV is a non-intrusive technique which allows reconstructing the velocity vectors fields in a flowing fluid seeded with particles. This technique, which is widely adopted in a variety of liquid and gas flows, has been used by Lieber et al. to quantify the effects of the strut size of three helical stents on flow [22], and by Canton et al. to measure the intra-aneurysm flow dynamics and mechanical stresses changes resulting from the placement of neuroform stents in bifurcating intracranial aneurysms models [23]. Measurements of the circulation demonstrated a reduction of the vortex magnitude due to the placement of one, two or three stents. PIV was also used by Yu et al. in sidewall aneurysm models under steady flow conditions, where the Reynolds number varied from 200 to 1600. They noticed that for Reynolds number higher than 700, a large recirculating vortex would be formed. The insertion of two different stents damped the flow movement, the mean velocity and reduced consequently the WSS [24].

Laser Doppler velocimetry (LDV)

Other techniques, such as LDV are also used to assess flow and WSS in patient-specific geometries. LDV is an accepted

method in velocity measurement investigations based on the cross of two beams of collimated, monochromatic, and coherent laser light in the flow of the fluid being measured.

Validation and comparison with numerical simulations and clinical data without device. Liou et al. compared tri-dimensional flow fields with computational fluids dynamics (CFD) simulations in idealized, lateral and rigid cerebral aneurysm models and found that the inflow angle into the lateral aneurysm, the maximum WSS acting on the distal lip of the lateral aneurysm and the intra-aneurysmal vortical motion increased with decreasing aneurysm size, underlining the potential critical aneurysm geometrical configuration leading to rupture [25]. Tateshima et al. measured and evaluated the alternation and distribution of WSS in two aneurysm models (middle cerebral artery and basilar tip, both with blebs at their domes). They noticed that both aneurysm models blebs were exposed to high WSS, region where the arterial wall is the finest in vivo [26]. Hollnagel et al. used LDV to validate phase-contrast magnetic resonance angiography (PC-MRA) in a patient specific aneurysm model under steady flow conditions. They found only minor differences in velocity field distribution and mean velocity values between both techniques, the accuracy depending on the artery size and the measurement plane positioning [27].

Our group measured the aneurysmal flow, qualified and quantified the flow reduction due to the insertion of an endovascular prosthesis using PIV. Fig. 2A to D present the aneurysm flow in a lateral aneurysm placed on a curved parent artery model without (A and C) and with (B and D) a commercial stent (Neuroform II, Boston Scientific, Fremont, CA) under a steady flow of 100 ml/min. The corresponding Reynolds number is 70.2 and the stent effective porosity defined to be the ratio of the free surface area over the stent area is calculated to reach 82%. For this specific case, we quantified the mean velocity magnitude reduction within the aneurysm to reach 69%; in other words, only 31% of the flow is remaining; 78% reduction in vorticity.

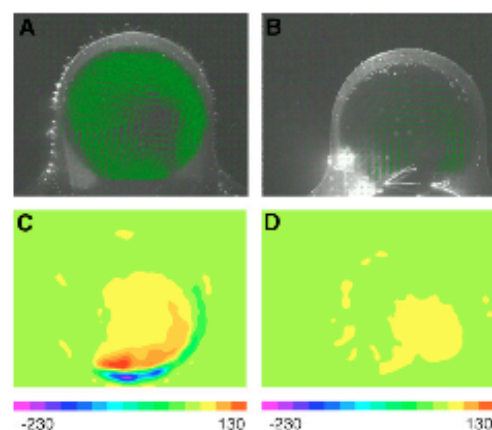


Figure 2 Velocity vector fields without (A) and with a stent (B); vorticity magnitudes without (C) and with stent (D) are presented.

Prediction of hemodynamical changes due to a stent in aneurysms models using computational fluids dynamics: numerical models

Simulation without stent

With the improvement of computer power and the evolution in computational fluid dynamics, numerical simulations gained in speed and precision. Nowadays, an up-to-date laptop or small cluster of computers has enough power to compute the flow in a patient specific aneurysmal geometry under unsteady flow conditions within a few hours. The quality of medical images permits the reproduction of the cerebral geometry very precisely, so that intra-aneurysmal flow can be simulated accurately. The combination of advanced image processing and geometrical modeling techniques with computational fluid dynamics enhanced the generation of detailed hemodynamical aneurysmal flow in patient-specific geometries [14,28]. Cebral et al. developed a CFD pipeline allowing for the computation of the arterial and aneurysmal flow based on CTA and 3D rotational angiography image data. The morphological boundaries of the vessel lumen were obtained through 3D reconstruction, segmentation and meshing. Physiological flow boundaries were set based on ultrasound measurements. Subsequent computation provided blood flow patterns, WSS, oscillatory shear and pressure data. Their results enhanced the understanding of intra-aneurysmal flow patterns and their relation to aneurysmal rupture risk [29]. Four flow pattern categories were defined: simple stable, complex stable, simple unstable and complex unstable. Aneurysms of the first group were less at risk of rupture whereas aneurysms presenting a complex unstable flow were more likely to be associated with rupture. The additional evaluation of the jet type entering into the aneurysmal cavity showed it to be a potential indicator of aneurysmal rupture. Indeed, geometries aiding the creation of a fluid jet impinging on a small aneurysmal wall area belonged mainly to ruptured groups. Conversely, geometries where flow was more diffused and entered less canalized into the aneurysms were less at risk of rupture [30].

Some studies used such CFD simulations to propose flow-based indices for the prediction of aneurysmal rupture risk or even the rupture location [31,32]. It has been shown that flow features are strongly dependant on aneurysm geometry. It has been further hypothesized that flow, having a strong relation to geometrical aspects, could be the principal equivalent of a surrogate biomarker of aneurysmal rupture [29].

Valencia et al. pointed out the relationship between WSS and aneurysm area index. In fact, by defining the aneurysm surface index as the ratio between the aneurysm surface area and the arterial lumen cross-sectional area, they found a correlation between the mean WSS on the aneurysmal sac and the aneurysm surface. Aneurysms presenting a higher surface with low mean WSS were more likely to rupture [33]. Numerical simulations matched to clinical observation allowed to correlate the high fluid-induced WSS with ruptured areas [34].

Simulation with stent

Due to complex problem of representing a patient-specific geometry and due to the huge computational load numerical simulations are requiring, blood flow was simulated in two-dimensional idealized geometries. Ohta et al. investigated the hemodynamical flow patterns in intracranial aneurysms bifurcations models before and after stent placement over a cardiac cycle. As blood was modeled to be a non-Newtonian fluid, the lowered values of peak velocities and WSS due to stent placement allowed to localize the region of increased dynamic viscosity [35].

Numerical simulations were also performed to assess how stents can be optimized to enhance their ability at diverting the flow and, consequently, reduce the risk of rupture. Stent effects on aneurysmal flow, WSS, pressure and oscillatory shear were quantified. Aenis et al. [36] investigated the flow patterns in a sidewall aneurysm under physiological pressure and flow conditions. The stent altered the local hemodynamics and substantial differences in flow patterns and pressure values were observed and quantified. Stuhne et al. developed mesh generation tools to manage the difficulties encountered with the meshing of stented aneurysm geometries. More detailed flow patterns description could be provided [37]. Cebral et al. present an adaptive grid embedding technique to manage the mesh difficulties due to scales differences between artery and stent strut sizes [38]. The modeling of stent deployment in a patient-specific geometry is currently achieved by morphing technique. Appanaboyina et al. developed a method that deforms a straight stent model and fits it in a patient-specific geometry. Basically, a cylindrical surface composed of shell elements is generated along the skeleton of the parent vessel of the patient-specific geometry and is considered as an elastic material. This surface is expanded under the action of internal smoothing forces and external attractive forces to the wall. The resulted deformation of the cylindrical surface is performed interactively and the expansion is stopped when most of the points on the cylinder touch the wall [39]. This methodology is successfully used to model patient-specific anatomies with different stents allowing for the exploration of different stent designs efficiency.

Other numerical simulation techniques, such as Lattice-Boltzmann method (LBM), were developed to avoid the mesh generation difficulties encountered with finite element and finite volume methods [40]. An LBM-based clotting model for stented intracranial aneurysms has been developed [41] and a direct clotting metric measuring the percentage of clotting of aneurysm impacted by different stents have been compared with indirect metrics measuring both velocity and WSS reductions inside the aneurysm [42].

Our group measured the aneurysmal flow, qualified and quantified the flow reduction due to the insertion of an endovascular prosthesis using the techniques described above. Fig. 3 shows the results of blood flow simulation in a patient specific geometry under unsteady flow conditions. The aneurysm geometry was retrieved using 3D-RA and the volume was processed to be finally meshed. Blood flow was measured in the internal carotid artery of a healthy volunteer using PC-MR technique [43]. This physiological flow waveform was applied at the inlet by defining fully spatial

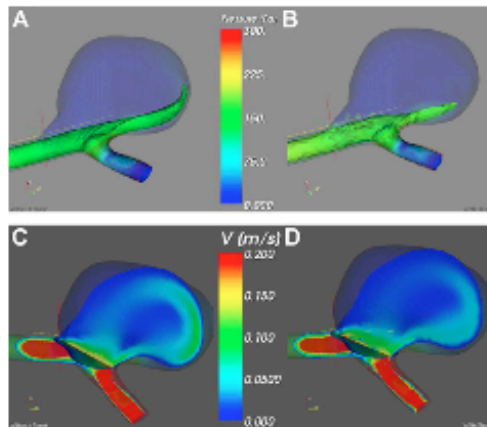


Figure 3 Isovelocity surface (0.1 m/s) colored in pressure without device (A) and with device (B), velocity magnitude in cross-sectional and neck planes, without device (C), and with device (D).

and temporal developed velocity profiles (Womersley profiles). A virtual stent was further inserted in the parent artery and flow was computed. The efficiency of the stent to reduce flow and vorticity within the aneurysm was assessed. Although a residual flow remains inside the aneurysm, a reduction of the jet entering the aneurysmal cavity can be observed (Fig. 3B). It can be noticed that the Z-like stent, presenting in this case an open-cell design and a rather large porosity of 82%, is still able to reduce somewhat the entry of flow from the parent artery. This reduction is small because stent porosity is high (82%). Stents currently under development aim at much lower porosities so as to increase much greater flow entry impediment.

In order to demonstrate the clinical value of numerical simulations of the effects of stent on intra-aneurysmal flow, the Virtual Intracranial Stenting Challenge (VISC'07, [44]¹) was launched and discussed at the 4th Intracranial Stent Meeting (ICS'07, Kyoto). Its objectives were to compare state-of-the-art numerical approaches for solving flow in a stented human cerebral aneurysm model and to illustrate the ability of academic groups and leading CFD companies in providing a description of changes in aneurysmal blood flow patterns for a given stent design. The adopted methodology, as well as simulation parameters, software and hardware choices, simulation times, stent performances were compared. Although some differences in the magnitude of the computed WSS and the velocity field were reported, it was demonstrated that numerical simulations were reproducible among teams. The VISC'07 reinforced the potential role of CFD simulations in providing a description of patient-specific blood flow information in clinical settings, enabling the virtual evaluation of stent performances. The ultimate goal is to use such methods for the selection of an appropriate stent prior to intervention. Also, the same methodology can be used by stent manufacturers for performance analysis and development of novel stent designs.

Discussion/conclusion

Flow is believed to be a major actor in the initiation, growth and rupture of cerebral aneurysms, hence, the interest for the development of methodologies allowing for the assessment of blood flow within the aneurysm and the flow-driven biomechanical effects.

The modeling of such complex systems must be further improved by including wall motion, wall stress, mechanotransduction at the endothelial and medial cell level and clot formation mechanics.

Due to the complex modeling of patient-specific aneurysm geometries and endovascular prosthesis representations, experimental setups allowed for the understanding of aneurysmal hemodynamical effects due to a stent or a coil prior to numerical approaches.

The most common methodologies to assess blood flow in cerebral aneurysm models are PIV and numerical simulations. Patient specific numerical simulations approaches have the potential to become the method of choice for planning, treatment and follow-up decisions. Numerical simulations have proved to be reproducible among teams and to be quite similar to experimental observations and measurements and may therefore become a post-processing path-empowering personalized treatment strategies. However, in order to increase their impact and general acceptance, further efforts are needed to reach agreement between experimental and virtual worlds. Should numerical analysis of blood flow in aneurysms reach the level of being precise and fast enough to be seamlessly integrated with the imaging procedures, physicians would possess a valuable tool for assessing the effects of flow and the impact of their gestures on local hemodynamics in a quantitative way. We may imagine that numerical simulations could be carried out at the moment a patient enters in a hospital and integrated in the medical image acquisition modalities. Results would arrive in time allowing treating physicians to decide on treatment modality. A personalized treatment could be subsequently proposed.

This objective in mind, a sixth framework programme (information society technology, FP6-IST), @neurIST² is aiming at developing the required IT for supporting a management that can integrate the complexity of data made available with modern medicine of cerebral aneurysms.

Conflict of interests

No potential conflict of interests relevant to this article was reported.

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¹ <http://www.cilab.upf.edu/visc06/>.

² www.aneurist.org.

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