DEVELOPMENT OF A MODEL FOR THE INVESTIGATION OF BLOOD CLOTTING IN CEREBRAL ANEURYSMS FOLLOWING COILING

Andrew NARRACOTT[1], Patricia LAWFORD[1], Hao LIU[2], Ryutaro HIMENO[3], Rodney HOSE[1]

[1]Department of Medical Physics and Clinical Engineering,
I Floor, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF, U.K.
e-mail: a.j.narracott@sheffield.ac.uk

[2]Chiba University, Department of Electronics and Mechanical Engineering,
1-33 Yayoi-cho, Inage-ku, Chiba, 263-8522, Japan
e-mail: hliu@faculty.chiba-u.jp

[3]Computer and Information Division, Advanced Computing Center, RIKEN,
2-1, Hirosawa, Wako-shi, Saitama, 351-0198, Japan
e-mail: himeno@postman.riken.go.jp

Abstract *One of the methods of treatment of intracranial aneurysms involves packing of the aneurysm with small Guglielmi Detachable Coils (GDC). The purpose of this treatment is to induce clotting within the aneurysm thus preventing rupture. It is suggested that changes in haemodynamic flow patterns associated with the partial filling of the aneurysm with an inert material is responsible for initiating the clotting process and occlusion of the aneurysm. A residence time based clotting model, previously validated experimentally for a simple geometry, was applied to the CFD analysis of an idealized aneurysm geometry. Coil geometry was included in an idealized form to allow the interaction of the blood with the coil to be modeled. A novel approach was employed using a combination of fluid residence time and concentration of 'clottable' fluid to model the change in viscosity of the fluid during the clotting process.*

INTRODUCTION

One method of treating intracranial aneurysms involves filling the aneurysm with Guglielmi Detachable coils. This process aims to prevent flow within the aneurysm by filling the aneurysm with coils and thrombus [1]. The presence of the coil is thought to initiate clotting within the aneurysm, although the exact mechanisms behind this are unknown. Flow stasis caused by the presence of the coil geometry [2-4], thrombogenicity of the coil itself [5,6] and the effects of electrothrombosis during coil deployment [7] are all thought to play some part in the progression of clot formation. This study develops an experimentally validated residence time model to include the interaction of blood with the coil geometry. This model is then applied to an idealized aneurysm and coil geometry and the results are discussed in the context of observations of *in vivo* coil thrombosis. The aim of this work is to provide a model which allows initiation of clotting by the presence of a coil to be simulated.

VESSEL MODEL AND FLOW BOUNDARY CONDITIONS

The use of idealized or simplified 2d geometries has been proposed by many authors to allow detailed study of particular flow characteristics within aneurysms [8-10]. To allow development of the clotting model an idealized 3d aneurysm geometry was produced to allow the effects of aneurysm geometry on the solution to be investigated.

Three measures were used to specify the relation between aneurysm and vessel size: These parameters are illustrated in figure 1 (Vessel diameter, D_V, Aneurysm radius, R_A and height of the aneurysm above the vessel, H_A) and were estimated from a 512 x 512 pixel 2d CT image of a vessel which showed both the vessel and aneurysm clearly.

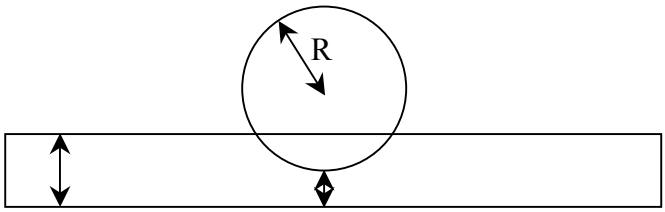


Figure 1 Parameters of idealized aneurysm geometry

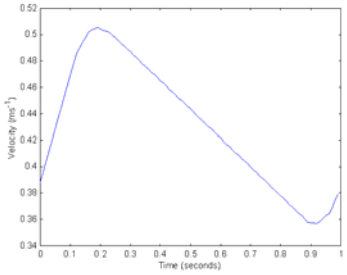


Figure 2. Inlet velocity variation as a function of time

The model was scaled to a typical value taken from the literature for cerebral artery diameter of 4mm [11]. The aneurysm was assumed to be spherical and the vessel to be a straight cylinder. The inflow and outflow lengths of the model were specified as 7*DV and 3*DV respectively to allow some development of the velocity profile prior to entry to the aneurysm. The fluid was specified as incompressible with viscosity 4mPas and density 1000kgm^{-3}. A zero pressure was specified at the outlet and a non-slip condition at the walls. At the inlet a flat periodic velocity profile was applied. The temporal velocity variation , (figure 2) was taken from published measurements [11] obtained from *in vivo* measurements in a 4mm diameter vessel.

MODELLING THE COIL GEOMETRY

Removal of fluid elements

An approach similar to that of Groden et al. [11] was initially used in the current study to model the coil using the removal of fluid elements. However, despite relatively fast convergence of the fluid terms the additional variables used to model residence time and clotting fluid concentration (described later) both suffered from poor convergence. Despite increasing the number of iterations at each fluid timestep, typical RMS residual values of 2-3*10^{-4} were observed for the additional variables at the end of each timestep, compared with RMS values of < 1*10^{-5} for the remaining fluid variables.

The poor convergence was attributed to the fact that the coil elements were selected at random from a previously meshed volume. Therefore the quality of the resultant mesh was poor, particularly as large elements were used to mesh the central areas of the ANSYS model. In order to improve the mesh it would be necessary to either refine the fluid mesh globally or produce the form of the coil within ANSYS prior to meshing. As the first approach would be likely to result in a restrictively large number of elements in the model, methods of explicitly modeling the coil were pursued.

Explicit coil modelling

An arbitrary geometry was chosen based on ease of producing the solid model and reproduction of features similar to a complex coil geometry. The model consisted of three cylinders of equal length and diameter, one at the aneurysm centre and two either side at equal intervals. The long axis of the central cylinder was parallel to the x direction the other cylinders were parallel to the y axis. The geometry of this model is shown in figure 3.

A mesh was produced using the smart-size command within ANSYS, due to the small elements required to resolve the coil geometry this resulted in a mesh of ~400,000 elements (fine mesh). In order to compare results with a different mesh density and reduce the number of elements around the coil itself, the areas of the model were meshed in 2d using user supplied element sizing and the FVMESH command was then used to produce a volume mesh of ~ 65,000 elements (coarse mesh).

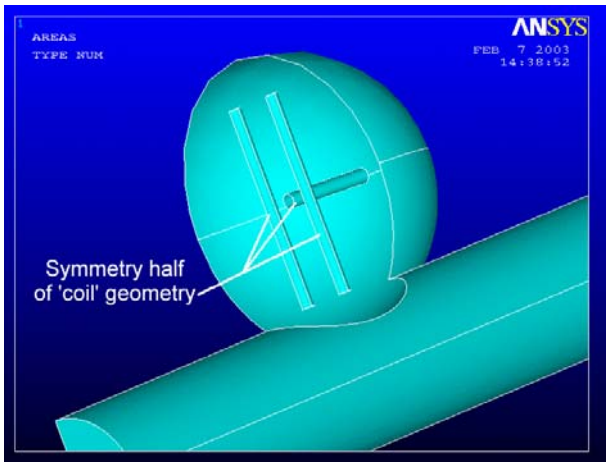


Figure 3 Idealised coil geometry within aneurysm model

RESIDENCE TIME BASED CLOTTING

A residence time based clotting model used by Friedrich and Reininger has been validated using experimental results of clotting in an *in vitro* system. The mathematical equation for the variation of blood viscosity with time was determined experimentally by Tippe et al. [12]. This equation was proposed by Friedrich and Reininger [13] as a means of modelling the clotting process.

Two steps were required to allow implementation of the clotting model within CFX:

- Calculate transient residence time in CFX throughout the fluid domain.
- Calculate the viscosity of the fluid based on residence time and the relationship given by the clotting model.

Residence time can be calculated by defining an additional scalar variable throughout the fluid domain. CFX solves the following transport equation for any additional variables:

$$\frac{\partial \phi}{\partial t} + \nabla \cdot (U\phi) - \nabla \cdot \left(\left[\rho D_\phi + \frac{\mu_t}{Sc_t} \right] \nabla \cdot \left(\frac{\phi}{\rho} \right) \right) = S_\phi$$

which, in the absence of turbulence or diffusion reduces to:

$$\frac{\partial \phi}{\partial t} + \nabla \cdot (U\phi) - \nabla^2 \cdot \phi = S_\phi$$

Previous authors [14] have modelled residence time as advection-diffusion with zero-order reaction kinetics, giving the equation for residence time as:

$$\frac{\partial r}{\partial t} = -u_i \frac{\partial r}{\partial x_i} + \frac{\partial r}{\partial x_i} \left(D_{ij} \frac{\partial r}{\partial x_j} \right) + 1$$

which, with no diffusion, is the same as the above equation with a source term of 1. Therefore, the residence time was calculated in CFX by specifying an additional variable labeled AGE with a uniform source term of 1.

CALCULATION OF CLOTTING FLUID CONCENTRATION

An appropriate model of clotting for cerebral aneurysms should include the following features:

- The uncoiled aneurysm does not clot.
- The role of coils is thought to be two-fold: i) To reduce flow within the aneurysm therefore increasing possibility of clot formation. ii) To act as a thrombogenic surface to initiate clot formation
- Treatment with coils has been successful in general terms if: i) The coil provides sufficient coverage of the aneurysm to reduce flow and promote clotting. ii) The coil is not forced towards the aneurysm wall by the flow, thus restoring flow to the aneurysm.

A model which uses residence time as the only variable for clotting requires either the entire fluid domain to be modelled or the residence time of fluid entering the domain to be applied as a boundary condition. This approach could prove difficult if the computational domain is large and the upstream flow is complex. There is also no sense of separate fluid species in this approach resulting in all fluid clotting after sufficient time. This would have dire implications in the circulation as there is no sense of a 'damage criterion' which must be initiated before clotting can take place.
In the experimental model of Friedrich and Reininger the event responsible for the initiation of the clotting process is the addition of thrombin to the solution. This takes place upstream of the domain of the computational model. Therefore, for the particular geometry and boundary conditions of their study, the residence time model performs well. However, the residence time approach also leads to a steady increase of the residence time at 'near-wall' areas, resulting in clotting along the outer wall of the model. This effect is not discussed by Friedrich and Reininger.
The current study focusses on the effects of the coil geometry on the flow within the aneurysm and the effect of the coil on the formation of clots. To allow the effects of the thrombogenic surface of the coil to be incorporated in the model, differentiation is necessary between:

- **clottable fluid**, which has been in contact with either the coil itself or fluid previously in contact with the coil

- **non-clottable fluid**, fluid newly entering the domain.

To include this effect, the concentration of clottable fluid was modelled using an additional variable labeled CONC with a source term defined only at the surface of the coil.

The effects of flow on clotting may exhibit themselves in several ways. Convective transport of any clottable fluid either toward or away from areas of clotting will affect clot build up. The effects of shear stress on the viscous behaviour of blood may also contribute to the clotting process. At low values of shear blood viscosity is greatly increased due to the aggregration of blood cells [15] and so distribution of shear rate of the fluid was examined during development of the clotting model. Initial analysis of the coiled aneurysm geometry were undertaken to investigate the distribution of the AGE and CONC variables and shear rate of the fluid.

Distribution of fluid variables
Solutions were obtained using both mesh densities of the explicit coil geometry. In both cases the additional variables converged within the allotted number of coefficient loops, unlike the results obtained using the mesh in which the coil geometry was created by removal of fluid elements. This result indicates that mesh quality is important to obtain convergence of these transport variables, even when an adequately converged fluid solution is obtained. The model was solved using a timestep size of 0.1 seconds, allowing reasonable resolution of the velocity variation without an excessive number of results over long timescales.

Figure 4a and 4d show the distribution of the AGE variable at an analysis time of two seconds for the two meshes. It should be noted that, for comparable points in the flow waveform, the distribution of the AGE variable did not change significantly between flow cycles. The general form was very similar for both meshes, with a slightly higher overall residence time for the finer mesh and greater resolution of the change in residence time throughout the domain.
The distribution of the CONC variable after two seconds is shown in figure 4b and 4e. The concentration was seen to change little after the first second of the analysis. This was due to the constant source term from the coil and the fact that the convective terms dominate the solution. Once the initial flow field developed the concentration distribution only changed with variations of the flow waveform and not with the overall analysis time.
High gradients of concentration were captured well by the fine mesh, which produced values close to the boundary value near the coil surface. In contrast the coarse mesh did not resolve the distribution as well, and the value of concentration between the cylinders is a factor of five lower than the fine mesh result. This can be understood by examining the velocity vectors on the current viewing plane as shown in figure 4g and 4h. The no-slip boundary on the coarse mesh was very poorly enforced resulting in little deviation of the flow vectors by the cylinders. Therefore, the flow tended to convect the clotting fluid out of the aneurysm. Using a fine mesh the complex re-circulation of flow between the cylinders was well resolved and the stagnation of flow in this region led to a build up of clotting fluid between the cylinders.

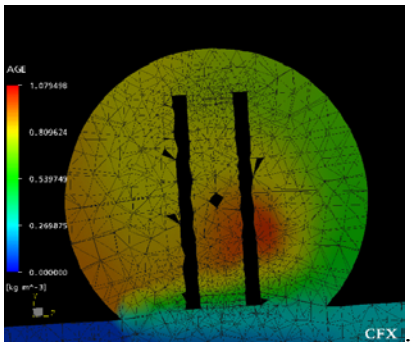
Figure 4c and 4f show the distribution of shear rate of the fluid, with the maximum contour value chosen as $100s^{-1}$. As expected, rapid changes in shear and the high shear that occurs close to the coil wall is not resolved well by the coarse mesh.
The distribution of the AGE and CONC variables is similar as the two variables are solved using the same transport equation. However, the high residence times that occur at the proximal side of the aneurysm (to the left of figures 4a and 4d) which are due to the slow moving fluid in these regions do not have a corresponding region of high concentration. This is because, as has been previously discussed, the fluid at these points was never 'clottable' to start with. Areas of low shear are also seen to occur in similar locations to areas of clotting fluid concentration.

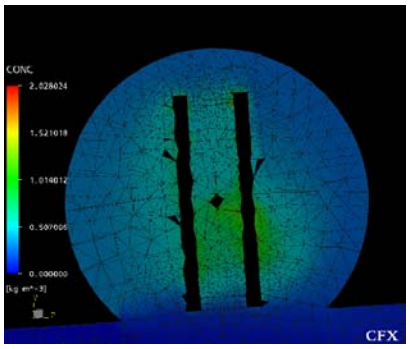
A COMBINED CLOTTING MODEL

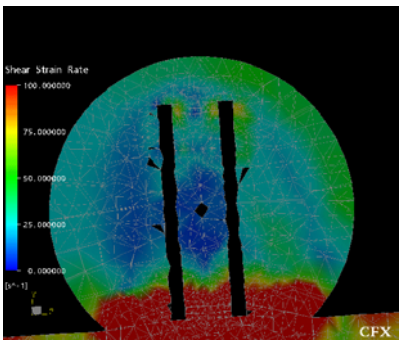
A clotting model was developed based on a combination of the concentration of clotting fluid in the domain and the residence time (AGE variable) calculated during the solution. In the proposed model the viscosity was defined to be of the form:

$$\text{Viscosity} = 0.004\ \text{kg.m}^{-1}.\text{s}^{-1} + S\ \text{kg}^{-1}.\text{m}^{5}.\text{s}^{-1} * \text{CONC kg.m}^{-3} * \text{AGE kg.m}^{-3} \quad 1)$$

This model produces a linear relationship between the viscosity, clotting fluid concentration and residence time. Thus, the viscosity of static fluid of uniform concentration would be expected to increase linearly with time. The scaling factor, S, was chosen as 0.004, to provide significant changes in viscosity within the relatively small time scale of the analysis. Experimental observations of blood clotting *in vitro* would be required to confirm the exact relationship between viscosity, concentration and residence time.

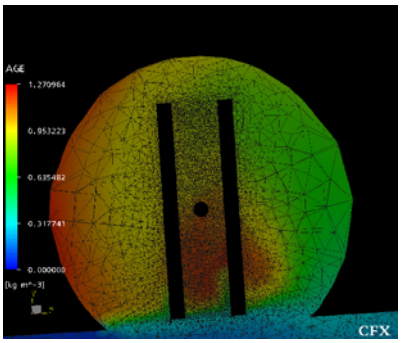


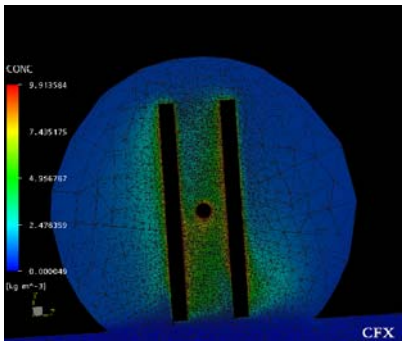
a)


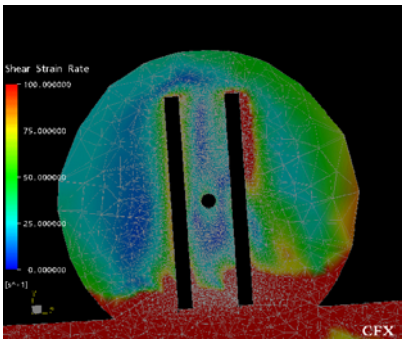
b)


c)

Fluid results using a coarse mesh: a) AGE variable b) CONC variable c) Fluid shear rate

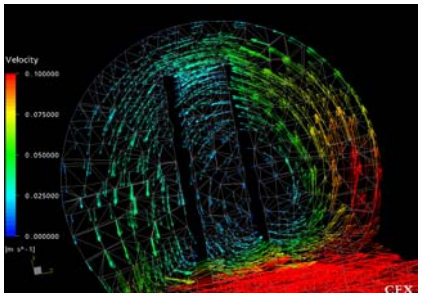


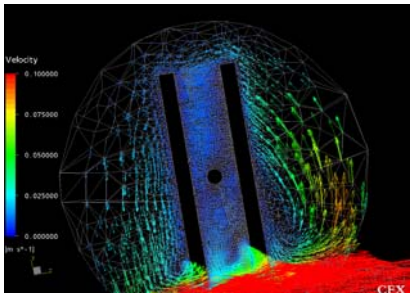
d)


e)


f)

Fluid results using a fine mesh: d) AGE variable e) CONC variable f) Fluid shear rate

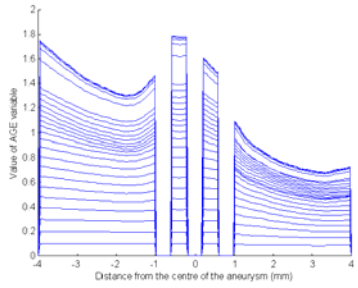


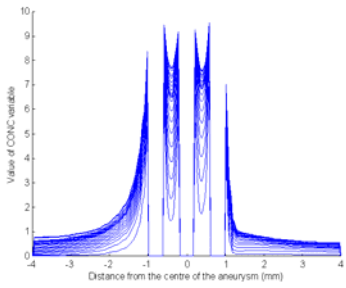
g)


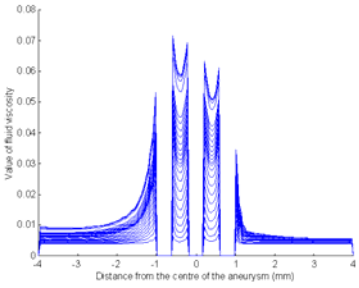
h)

Velocity vectors: g) with a coarse mesh h) with a fine mesh

Figure 4 Variation of fluid parameters within the aneurysm model geometry at a solution time of 2 seconds



a


b


c

Figure 5 Variation of variables at the centre of the aneurysm a) AGE variable b) CONC variable c) Fluid viscosity

Therefore this model was expected to produce the following effects:

- Fluid with high residence time but no concentration will never clot.
- Fluid with high concentration but low residence time will be unlikely to clot (however, this is unlikely as areas with low residence time will have high convective terms, reducing the concentration)
- Fluid that has both high concentration and high residence time will be likely to clot.

The model was solved with the same fluid boundary conditions as before but with a variable viscosity described by the relationship given in equation 1.

Results

Figure 5 shows the variation of the AGE and CONC variables and the fluid viscosity at the centre of the aneurysm parallel with the long axis of the vessel. These results are plotted at intervals of 0.1 seconds for the first 2 seconds of the analysis and then in intervals of 1 second for the next five seconds.

In figure 5a it is clear that there is a general decrease in residence time from the proximal to the distal side of the aneurysm. The residence time is increased by the presence of the coil geometry which results in re-circulation of the fluid. Initially the variation in AGE throughout the aneurysm is small as the flow within the geometry is yet to be established. The residence time increases steadily with analysis time and then starts to reach a maximum value as the analysis time exceeds the time for fluid to be convected from the inlet to the site of the coil. In figure 5b the CONC variable is seen to increase in value close to the coil where the variable source is located. However, this increase is seen to saturate as the change in concentration becomes small with increase in analysis time.

However, the viscosity of the fluid shown in figure 5c does not saturate as the concentration reaches its maximum value. This is due to the fact that the residence time between the cylinders of the coil model continues to increase, thus increasing the viscosity of the fluid in these regions. Eventually the viscosity also begins to reach a maximum value as the residence time becomes stable due to the convective transport. It is reassuring to see that although large values of residence time are observed at the proximal side of the aneurysm the low values of concentration in these areas ensure a low fluid viscosity is maintained.

It should be noted that the absolute values of viscosity in this analysis are much larger than those reported by Tippe et al [12]. In order to produce results in agreement with experimental blood clotting it will be necessary to modify the scaling factors of the model. The relationship between residence time, activated fluid concentration and fluid viscosity is likely to be more complex than the linear form used in these analyses. Experimental comparison will be necessary to provide appropriate data for model coefficients.

However, this model has produced results which contain the features expected to occur in the clotting of cerebral aneurysms. It should be noted that, although not obvious from figure 5, no areas of high viscosity were observed in the parent vessel, which would have been inevitable with the use of a residence time-only model.

CONCLUSIONS

The exact mechanisms for growth and rupture of aneurysms remain uncertain. Modifications to the pressure and flow within the aneurysm by the insertion of GDC coils are thought to be significant in reducing rebleeding [16]. However, the genesis of thrombus formation within the aneurysm is uncertain, although evidence that thrombus generation is initiated by the coil itself has been presented [1-3,5,7]. The model developed during the current study allows clotting to be modelled taking into account both the residence time of the fluid and the concentration of the fluid available for clotting. This is a novel approach which allows distinction between areas where clotting is unlikely to occur such as the parent vessel and areas prone to thrombus formation such as the surface of the coil. To improve the predictive capability of the model, tuning of the parameters will be necessary in comparison with experimental results of clotting mechanisms.

In order for such a model to be used as a predictive tool it is necessary to apply it to realistic aneurysm geometries. High quality fluid dynamics meshes of *in vivo* aneurysms have been obtained recently by other authors [17] and it is intended that similar methods will be applied to patient data to develop the clotting model further.

ACKNOWLEDGEMENTS

This work has been funded by RIKEN including research costs and software licenses. This work was also supported by a travel grant from the Royal Society of Engineering.

REFERENCES

[1] Dovey, Z., Misra, M., Thornton, J., Charbel, F.T., Debrun, G.M., Ausman, J.I. "Guglielmi detachable coiling for intracranial aneurysms." Archives of Neurology 58 : 559-564 ; 2001.

[2] Groden, C., Hagel, C., Delling, G., Zeumer, H. "Histological findings in ruptured aneurysms treated with GDCs: Six examples at varying times after treatment." American Journal of Neuroradiology 24 : 579-584 ; 2003.

[3] Workman, M.J., Cloft, H.J., Tong, F.C., Dion, J.E., Jensen, M.E., Marx, W.F., Kallmes, D.F. "Thrombus formation at the neck of cerebral aneurysms during treatment with Guglielmi detachable coils." American Journal of Neuroradiology 23 : 1568-1576 ; 2002.

[4] Piotin, M., Mandai, S., Murphy, K.J., Sugiu, K., Gailloud, P., Martin, J-B., Rufenacht, D.A. "Dense packing of cerebral aneurysms: An in vitro study with detachable platinum coils." American Journal of Neuroradiology 21 : 757-760 ; 2000.

[5] Ishihara, S., Mawad, M.E., Ogata, K., Suzuki, C., Tsuzuki, N., Katoh, H., Ohnuki, A., Miyazawa, T., Nawashiro, H., Kaji, T., Shima, K. "Histopathologic findings in human cerebral aneurysms embolized with platinum coils: report of two cases and review of the literature." American Journal of Neuroradiology 23 : 970-974 : 2002.

[6] Stiver, S.I., Porter, P.J., Willinsky, R.A., Wallace, M.C. "Acute human histopathology of an intraccranial aneurysm treated using Guglielmi detachable coils: Case report and review of the literature." Neurosurgery 43 : 1203-1208 ; 1998.

[7] Padolecchia, R., Guglielmi, G., Puglioli, M., Castagna, M., Nardini, V., Collavoli, P.L., Guidetti, G., Dazzi, M., Zucchi, V., Narducci, P. "Role of electrothrombosis in Aneurysm treatment with Guglielmi Detachable Coils: An In Vitro Scanning Electron Microscopic Study." American Journal of Neuroradiology 22 : 1757-1760 ; 2001.

[8] Burleson, A.C., Strother, C.M., Turitto, V.T. 'Computer modeling of intracranial saccular and lateral aneurysms for the study of their hemodynamics'. Neurosurgery 1995 ; 37(4) : 774-782.

[9] Gongalez, C.F., Cho, Y.I., Ortega, H.V., Moret, J. 'Intracranial aneurysms: flow analysis of their origin and progression' AJNR Am J Neuroradiology 1992 ; 13(1) : 181-188

[10] Ortega, H.V. 'Technical report Computer simulation helps predict cerebral aneurysms' Journal of medical engineering and technology 1998 ; 22(4) : 179-181

[11] Groden, C., Laudan; J., Gatchell; S., Zeumer, H. 'Three-Dimensional Pulsatile Flow Simulation Before and After Endovascular Coil Embolization of a Terminal Cerebral Aneurysm' Journal of cerebral blood flow & metabolism 2001 ; 21 : 1464-1471

[12] Tippe, A., Muller-Mohnssen, H. 'Shear dependence of the fibrin coagulation kinetics in vitro.' Thrombosis Research 1993 ; 72 : 379-388.

[13] Friedrich, P., Reininger, A.J. 'Occlusive thrombus formation on indwelling catheters: In vitro investigation and computational analysis.' Thrombosis and Haemostasis 1995 ; 73 : 66-72

[14] Jozsa, J., Kramer, T. 'Modelling residence time as advection-diffusion with zero-order reaction kinetics.' Proceedings of the Hydrodynamics 2000 Conference, Cedar Rapids, Iowa, July 23-27, International Association of Hydraulic Engineering and Research.

[15] Gijsen, F. 'Modelling of wall shear stress in large arteries.' PhD Thesis.

[16] Sorteberg, A., Sorteberg, W., Turk, A.S., Rappe, A., Nakstad, P.H., Strotl, C.M. "Effect of Guglielmi Coil Placement on Intraaneurysmal Pressure: Experimental Study in Canines" American Journal of Neuroradiology 22 : 1750-1756 ; 2001.

[17] Steinman, D.A., Milner, J.S., Norley, C.J., Lownie, S.P., Holdsworth, D.W. "Image-based computational simulation of flow dynamics in a giant intracranial aneurysm." American Journal of Neuroradiology 24 : 559-566 ; 2003.