	ふぇん　いいしゃん
氏　　名	馮　益祥
授与学位	博士（工学）
学位授与年月日	平成１８年３月２４日
学位授与の根拠法規	学位規則第４条第１項
研究科，専攻の名称	東北大学大学院工学研究科（博士課程）バイオロボティクス専攻
学位論文題目	A Model-Based Numerical Analysis on the Early Development of Intracranial Aneurysms Considering Solid Wall Mechanics and Fluid Dynamics (脳動脈瘤の発症および進展に関する計算力学シミュレーション)
指導教員	東北大学教授　山口　隆美
論文審査委員	主査　東北大学教授　山口　隆美　　東北大学教授　和田　仁
	東北大学教授　高橋　明　　東北大学助教授　和田　成生

論文内容要旨

Intracranial aneurysm is a vascular disease occurring at weakened areas of the cerebral arterial wall (Fig. 1). If it continues to grow large, it has a great risk of rupturing into the subrachnoid region, frequently causing immediate death. Despite of the increasing incidence of intracranial aneurysms and the threat of lives they put on the patients, little has been understood about the mechanism of the initiation and development of intracranial aneurysms. The treatment of intracranial aneurysms is limited to clipping, coiling and stenting, all of which by themselves are invasive and do harm to the patients. On many occasions neurosurgeons are faced with the dilemma of "to treat or not to treat".

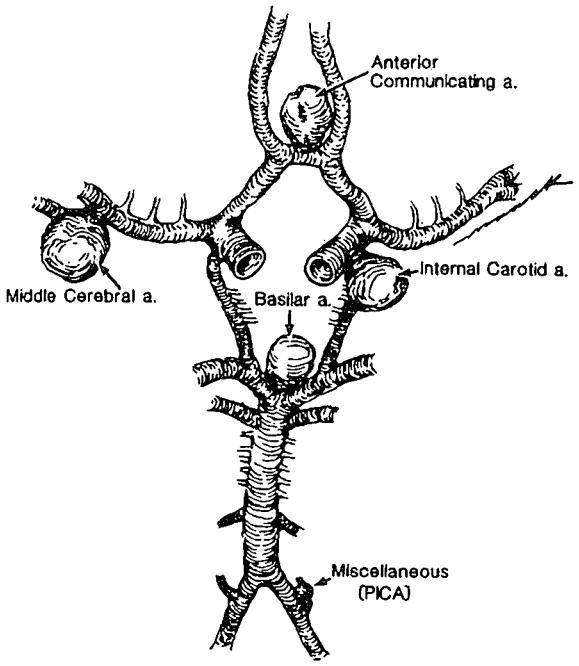
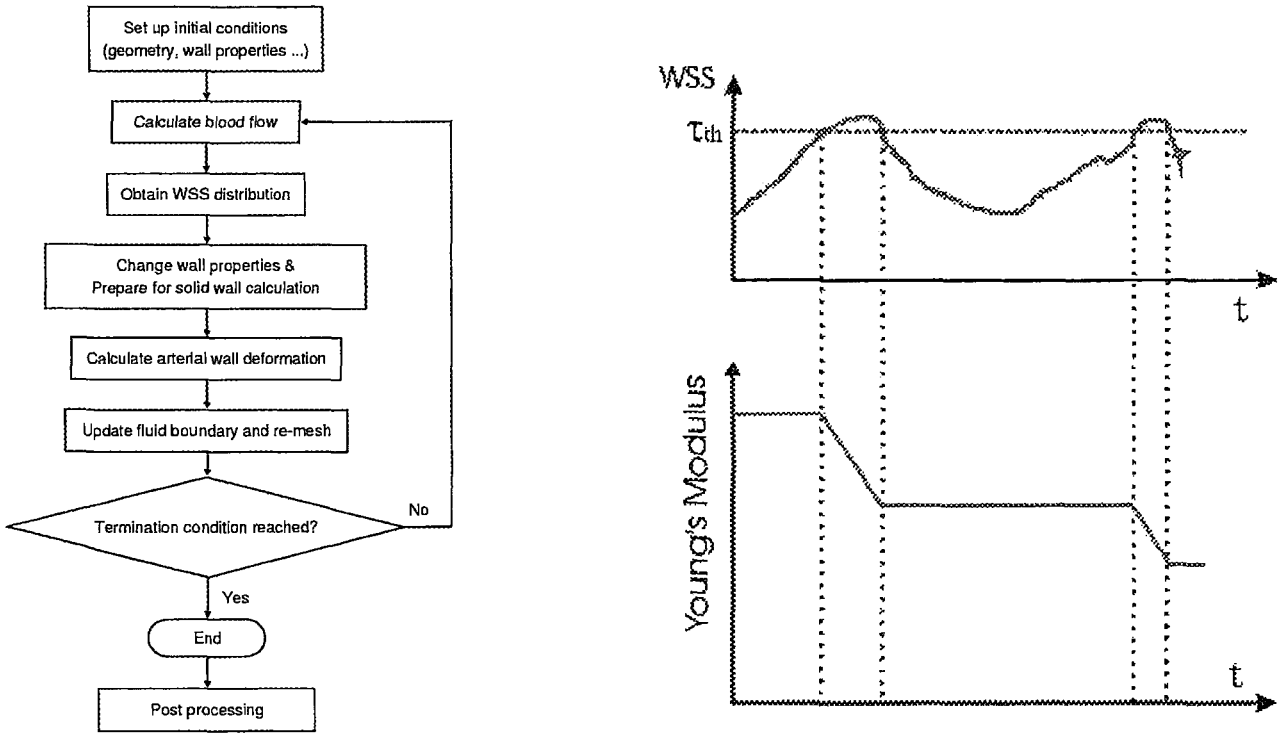


Figure 1. Intracranial aneurysms in the Circle of Willis

While experimental or *in vivo* measurements of the cerebral blood flow or wall properties are still extremely difficult, recent development in computer technology and its application to the biomedical field have become increasingly important. These computational studies have not only facilitated our understanding in the biomechanics of vascular diseases, but also provided us with a feasible approach to tackle the pathophysiology of these diseases.

Computational research on intracranial aneurysms has also developed rapidly for the last two decades. With modern medical imaging technologies such as digital subtractive angiography (DSA), computer tomography (CT) and magnetic resonance imaging (MRI), researchers are able to perform patient-specific simulations to obtain the blood flow field and its relative stresses. While the calculation time is still somewhat heavy to prevent its on-site use, with the current speed of hardware development, it should not be long before it becomes a routine tool for the clinicians.

The present study is an extension of the previous computational work on intracranial aneurysms. Different from most other studies in which an already-formed aneurysm model (virtual or realistic) is taken as object and the hemodynamic forces are calculated, in this study, we start from a normal artery with no aneurysm or only a small bump, and simulate the progression of aneurysms. This is based on the well-accepted theory that the hemodynamic stresses are key factors in the initiation and development of intracranial aneurysms. Growth of intracranial aneurysms can be viewed as a result of the remodeling process of the arterial wall triggered by the endothelial cells. Although the detailed remodeling process is still unclear yet, we adopt a macroscopic approach to study the wall remodeling process.



(a) (b)

Figure 2. (a) Flowchart describing the repeated process adopted in the simulation of aneurysm genesis

and development; (b) Illustration of the assumed relationship between the local wall Young's modulus and wall shear stress.

In this study, we focus on the interactive process between the blood flow, arterial wall property change, and the deformation of the vessel wall (Fig. 2a). It is hypothesized that there is a threshold in the wall shear stress (WSS), above which the arterial wall will become weaker (represented by the Young's modulus). The rate of decrease in the Young's modulus is defined as the degeneration ratio in this study (Fig. 2b). Numerical models are constructed to represent the solid wall domain and the blood flow domain. These two domains are linked by a boundary moving algorithm and both domains are solved separately. The change of geometry, WSS and Young's modulus are recorded in every calculation step.

We first investigate the development of aneurysm as influenced by the local hemodynamic field by applying our methods to a 90-degree curved artery model. Due to centrifugal force, the blood flow is skewed towards the outer wall, where higher WSS is observed. The elevated WSS leads to the decrease of the local Young's modulus and hence the deformation of the vessel wall. The arterial wall continues to grow as a result of the interaction between high WSS and the further weakening of the wall. Change of the wall geometry further complicates the flow and the WSS becomes fluctuated. The mean WSS decreases with the development of aneurysm, indicating that the enlargement of the vessel wall might be a conceptual self-protecting mechanism of the arterial wall. Finally all the WSS becomes lower than the threshold and a fusiform-like aneurysm is generated. Secondary flow is also observed in this study. To investigate its role in the development of aneurysm, we calculate the WSS in the circumferential direction. It is found that the circumferential WSS contributes greatly to the total WSS. Therefore, it is suggested that secondary flow is involved in the progression of aneurysm.

Since shape of the parent artery is one of the main factors to determine the hemodynamic field and the growth of intracranial aneurysms, we apply our method to a straight artery model and compare it with the curved one. In the straight artery model, a small bump is initially introduced to the artery to allow variation in the WSS. High WSS is initially found at the distal neck region of the existed bump and it triggers the weakening of the wall according to our hypothesis. High WSS continues for several steps while the distal neck region expands slightly. Finally all the WSS becomes lower than the threshold value and the aneurysm stops growing. This result shows that in a straight artery, the vessel is able to adapt itself with high WSS by deforming its shape (wall remodeling). If we can neglect other factors, an aneurysm arisen from a pure straight artery may be considered stable.

After comparison of aneurysm growth in the curved and straight artery models, we further investigate the influence of WSS threshold, Reynolds number of the blood flow, and the degeneration ratio of the arterial wall on the development of intracranial aneurysms using the curved model. It is found that with a decrease in the WSS threshold, more deformation in the wall accumulates and forms aneurysmal neck, which causes disturbance in the flow and fluctuations in the WSS distribution. Fluctuations in the WSS then lead to local

bumps of the wall and the aneurysm height increases without stabilization. An increase in the degeneration ratio also causes instability in the wall structure by forming local bumps in the wall. And when the Reynolds number of the flow increases, even if we fix the ratio between the WSS threshold and the baseline WSS, the development of aneurysm can accelerate due to the increased unsteadiness in the flow field. In all these studies, the interplay between the local hemodynamic field and the wall geometry change is key to determine the development of aneurysm.

We further explore the application of our model by applying it to a double-curvature model and a bifurcation model are developed to. In the double-curvature model, fusiform-like aneurysm is developed between the two curvatures. In the bifurcation model, it is found that aneurysm develops near the bifurcational area. These examples further demonstrate the key role of local hemodynamics in determining the progression of intracranial aneurysms.

Finally, the extensibility of this model as a rule-based tool to study the growth of aneurysm is explored by incorporating the effect of wall thinning into our hypothesis. Decrease of the wall thickness by a constant ratio is assumed as a response to elevated WSS. It is found that thinning of the wall itself is able to cause initiation and development of aneurysm. Continuous thinning of the wall can cause more instability of the wall structure and may be related to aneurysm rupture. The development of aneurysm is further complicated by the combination of wall thinning and decrease in the Young's modulus.

In summary, we have constructed a rule-based computational model to study the initiation and development of intracranial aneurysms. It is based on the hypothesis that high WSS above a threshold can degenerate the vessel wall. The interactive nature of the blood flow and wall deformation is captured in this study by solving the fluid and solid wall models iteratively. Results are obtained in curved artery models, straight artery models, double curvature models, and bifurcational models, which represent various characteristics of the cerebral arterial geometry. The influence of WSS threshold, degeneration ratio, and Reynolds number is also studied. These results reveal the complicated pattern of aneurysm growth due to the interaction between the geometrical changes, re-distribution of the hemodynamic stresses, and the degeneration of the arterial wall. The capability of our model to study the progression of aneurysm is further demonstrated by incorporating the wall thinning effect into our hypothesis. These results suggest the potential utility of this rule-based numerical model in the investigation of development of cardiovascular diseases.

論文審査結果の要旨

本論文は、脳動脈瘤の発症および進展のメカニズムを、流体力学的計算と構造力学的計算を併用して検討した結果について述べるもので全文７章からなる。

第１章は緒言であり、本論文の背景と目的を述べる。

第２章においては、本論文に述べる研究全体の方法論を論じる。まず、数値計算に用いた方法を、血管壁の構造解析に用いた有限要素法、および、血流の解析に用いた有限体積法のプログラムについて述べ、次きに、モデルの作成のためのプレおよびポスト処理システム、さらに、流体および固体の運動と変形を相互連結して解析する方法を述べる。本研究全体の基礎をなす重要な基礎的知見を示す。

第３章においては、壁せん断応力に適当な閾値を仮定し、それがこの閾値を越える場合に血管壁のヤング率が低下するという仮説を提示する。この仮説に基づき、実際の脳動脈形状を理想化した曲がり管モデル内部における流れ場を計算し、壁せん断応力の分布により、壁のヤング率を変化させ、血管壁を変形させ、これを繰り返すことにより、動脈瘤が発生するメカニズムを再現する結果を述べる。次ぎに、同じ手法を、あらかじめ、僅かな損傷部位を仮定する直管の血管モデルに適用し、この場合は動脈瘤が生じないことを示し、脳動脈瘤の発生には、複雑血管形状がもたらす２次流れが支配的な複雑流れ場およびその結果生じる局所的な壁せん断応力の分布が重要であることを示す。これは、これまで、脳動脈瘤の発症について明らかにされたことのない計算結果であり、非常に有用な知見である。

第４章においては、いくつかの流体力学的および病態生理学的パラメタを変化させてその影響を検討している。まず、壁せん断応力の閾値について検討し、これが大きい場合は動脈瘤の発達が少ないことを示す。次ぎに、壁が脆化する速度を変更することにより、これが最終的な形状に大きく影響することを示す。最後に、血流のレイノルズ数を変化させることにより、ある値以下のレイノルズ数では動脈瘤が発生しないことを示す。この結果は、脳動脈瘤の局在、個人差を説明するもので重要な知見である。

第５章においては、さらに複雑な形状の影響を検討する。とくに、分岐血管では、分岐角度の大きい枝の側に脳動脈瘤が発生することをしめし、かつ、これが破綻しやすいことを示しているが、この結果は、臨床脳血管医学における知見を説明するものであり、特に、脳動脈瘤の破裂に至る過程をコントロールする因子についての重要な知見である。

第６章は、壁せん断応力の分布によって壁の菲薄化が生じるという仮説を導入して、脳動脈瘤の発達を検討したもので、今後の病態生理学的および病理学的検討の方向性を示す極めて重要な知見である。

第７章は、結論である。

以上要するに本論文は、高齢化に伴い、社会的重要度を増している脳動脈瘤の発症および進展の機構をこれまでの静的な解析とは異なり、動的な発達過程として解析する計算力学的手法を開発し、計算生体力学および臨床脳血管医学に対して寄与するところが少なくない。

よって，本論文は博士(工学)の学位論文として合格と認める。