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論文内容要旨

Cerebral aneurysm, which is an abnormal expansion of the cerebral arterial wall, is a serious pathological condition because the rupture of an aneurysm is the most common cause of subarachnoid hemorrhage, well known for its very high mortality. It has been reported that between 3.6 and 6% of the population have cerebral aneurysms before rupture (called unruptured cerebral aneurysms). Recent advances in medical imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI) have increased the rate of detecting unruptured cerebral aneurysms. Surgery with clipping and endovascular treatment with coiling are the effective treatment options currently available for unruptured aneurysms. However, the morbidity of such treatments is not trivial. In contrast, the reported annual risk of the rupture of cerebral aneurysms is only about 1.9%. Consequently, determining whether a patient with an unruptured cerebral aneurysm, when it is detected, should undergo surgery or endovascular treatment is still difficult. To resolve this issue, one must better understand how cerebral aneurysms initiate and grow, as this may lead to the prevention of cerebral aneurysms or to other treatment options.

Cerebral aneurysms develop in several stages; initiation, growth, and rupture. It is widely accepted that blood flow-induced mechanical forces acting on the vessel wall, i.e. hemodynamics, plays a vital role at all the stages of the cerebral aneurysm development. To date, many animal models have been developed to investigate the initiation and growth of cerebral aneurysms. These experimental studies reported that the initiation of cerebral aneurysms was a result of the interaction between hemodynamics and structural degeneration of the arterial wall. A number of specific hemodynamic factors, such as wall shear stress (WSS), pressure and related mural stress, impingement force, flow rate, and residence time, have been proposed as candidates responsible for the pathogenesis of cerebral aneurysms. Among these several hemodynamic factors, however, WSS is the one which has received special attention in aneurysm studies, like hemodynamic studies on arteriosclerosis from the late

1960s onward. On the other hand, some studies recently focused on other hemodynamic factors such as spatial wall shear stress gradient (SWSSG), which is a hemodynamic quantity representing spatial nonuniformity of WSS, and some possible flow-related factors derived from disturbed flow. Although these studies regarding WSS, SWSSG, and other hemodynamic factors have provided useful insights into the initiation of cerebral aneurysms, the specific hemodynamic insults that lead to the arterial degeneration has not been clarified yet. Identification of specific hemodynamic factors responsible for aneurysm initiation may lead to the prevention of cerebral aneurysms.

Although the exact cause for the growth of cerebral aneurysms remains unclear, hemodynamics is believed to play a key role in the aneurysm growth as well and many experimental studies have been reported. These studies have provided useful information about the underlying mechanics. However, the growth of cerebral aneurysms is essentially a remodeling process that involves the arterial wall components. Thus, to better understand the growth of cerebral aneurysms, it is needed to address not only hemodynamics, but also the biological behavior of the arterial wall. Very few computational studies have focused on the growth of cerebral aneurysms. Although the results obtained from these computational studies was suggestive, the resultant aneurysms were fusiform, while most cerebral aneurysms are saccular. Thus, some other mechanism should be considered to represent saccular cerebral aneurysms. The development of a computational model for simulating the growth of saccular cerebral aneurysms can further our understanding in the mechanism of aneurysm growth, and this may lead to the prevention of aneurysm rupture or to advances in treatment of cerebral aneurysms.

To date, the bulk of investigations into aneurysm hemodynamics have been conducted in animal experiments and *in vitro* experiments. Although these experimental studies have provided valuable insights, each approach has some serious limitations. Computational biomechanics provide effective means for overcoming limitations in the biomechanical experiments, and it is appropriate for testing various hypotheses on biological events in the aneurysmal wall. That enables us to tackle the initiation and growth of cerebral aneurysms with a powerful tool.

With these backgrounds, the objectives of this thesis are summarized as follows: (1) to develop a computational model that can be used to test various hypothesis on the growth of saccular aneurysms, and to perform the simulation of saccular aneurysm formation based on a hemodynamic hypothesis, (2) to propose a novel possible hemodynamic factor responsible for the initiation of cerebral aneurysms, and (3) to demonstrate a realistic simulation of saccular cerebral aneurysm formation based on the distribution on the proposed hemodynamic index.

In Chapter 2, a computational model for the growth of saccular cerebral aneurysms was developed. This computational

model was designed to be able to take into account an arterial biological process, such as the cellular and extracellular matrix production of the wall. Using this model, we performed numerical simulations to examine saccular cerebral aneurysm growth at the outer curve of a bent artery. A U-shaped arterial geometry with torsion, which was modeled on part of the human internal carotid artery (ICA), was employed. The cellular and extracellular matrix production of the arterial wall was modeled by surface area expansion in high wall shear stress (WSS) region. Based on WSS distribution on the artery model, we investigated aneurysm formation for the following three conditions: (a) strength degradation of the wall, (b) cellular and extracellular matrix production of the wall, and (c) both strength degradation and cellular and extracellular matrix production of the wall. A saccular aneurysm shape was not observed when considering only arterial wall degradation up to 90%. However, the saccular shape formed when cellular and extracellular matrix production of the arterial wall was also taken into consideration. The resultant shape was consistent with clinical observations. From these results, it can be concluded that the strength degradation of the arterial wall is not sufficient to explain the formation of saccular cerebral aneurysms and the arterial wall growth due to biological process may play a vital role in the saccular shape formation.

In Chapter 3, a novel possible hemodynamic index, the gradient oscillatory number (GON), for the initiation of cerebral aneurysms was proposed. The GON was designed to quantify the temporal fluctuations of hemodynamic tension/compression forces acting on endothelial cells, specifically temporal fluctuations of the spatial wall shear stress gradient (SWSSG) vector on the arterial wall. A patient-specific geometry of a human ICA with an aneurysm was employed. Based on this patient-specific geometry, we constructed an artery model without the aneurysm in the following manner to investigate the blood flow before aneurysm formation. First, we removed the segment of the parent artery near the aneurysm. Then, using the data for center positions and the mean diameters at several cross sections extracted from the original geometry, we roughly reconstructed the parent artery from both remaining parts. Finally, the wall was smoothed so that the elastic energy calculated by the spring network model was minimized. In this way the artery model of the ICA before aneurysm formation was successfully reconstructed. We calculated the proposed hemodynamic index and six other hemodynamic indices (WSS at peak systole, time-averaged WSS, oscillatory shear index (OSI), potential aneurysm formation indicator (AFI), SWSSG at peak systole, and time-averaged SWSSG) for the geometry before aneurysm formation using a computational fluid dynamics technique. By comparing the distribution of each index at the location of aneurysm formation, we discussed the validity of each. The results showed that only the proposed hemodynamic index had a significant correlation with the location of aneurysm formation. We investigated the sensitivity of the proposed hemodynamic index to the reconstructed surface geometry by performing additional flow calculations for other two different surface geometry. The result showed the similar distributions of the GON index among all cases. The GON was the highest at the location of aneurysm formation in all cases, and the differences of the maximum value was less than 5%. The influence of the inlet flow rate waveform on the GON was also discussed by

performing an additional flow calculation with a physiological inlet waveform. Again, the result showed the similar distribution of the GON index to the original case. These results have suggested that the proposed index, GON, may be useful as a hemodynamic index for the initiation of cerebral aneurysms.

In Chapter 4, we examined whether a saccular aneurysm could form in our aneurysm growth model for actual cerebral arterial geometry. Using aneurysm growth model in which the cellular and extracellular matrix production of the arterial wall was hypothesized, we performed an aneurysm formation analysis based on the GON index distribution for the patient-specific ICA geometry. It should be noted that, based on the findings in Chapter 3, the GON was taken to be a possible trigger to the aneurysm growth in Chapter 4. The result showed that a saccular cerebral aneurysm could appear based on our hypothesis for an actual cerebral arterial geometry. While a saccular aneurysm was not observed when assuming only strength degradation of the wall as with the result in Chapter 2, a realistic simulation of saccular cerebral aneurysm formation was successfully demonstrated when considering the cellular and extracellular matrix production of the wall.

In conclusion, it has been suggested that the formation of saccular cerebral aneurysms may require at least following two mechanisms: aneurysm initiation accompanied by arterial degenerative change due to hemodynamic stress, which would be marked by the high-GON index; and the subsequent aneurysmal wall remodeling and growth, specifically the arterial expansion due to persistent production of cellular and extracellular matrix of the wall, which can be modeled well by the growth model developed in this thesis.

論文審査結果の要旨

脳動脈瘤の発生と成長のメカニズムの理解は，瘤の予防や新しい治療選択肢の提供につながる重要な研究課題である。本論文では第一に，血管壁の生物学的反応を考慮した脳動脈瘤の成長に対する計算モデルを構築している。第二に，血流が及ぼす血管壁への力学的負荷の時間変動について考察し，瘤の発生リスクを評価するための新しい血行力学的指標を提案している。第三に，これらを統合することにより，脳動脈実形状における瘤のリアリスティックな形成シミュレーションに成功している。本論文は，これらの研究成果をまとめたものであり，全編5章からなる。

第1章は緒論であり，本研究の背景，目的および構成を述べている。

第2章では，壁の生物学的反応を考慮した脳動脈瘤の成長に対する計算モデルを構築している。当該成長モデルをヒト内頸動脈の走行を模擬したモデル形状に対して適用し，臨床で観察される脳動脈瘤の形態的特徴（嚢形状）を極めてよく再現することに成功している。これは初の成功例であり，瘤の成長メカニズムの解明に資する成果である。

第3章では，血流が及ぼす血管壁への力学的負荷の時間変動について考察し，瘤の発生リスクを評価するための新しい血行力学的指標を定式化している。また、瘤を発症した実際の患者の3次元脳動脈モデルから瘤発生前の脳動脈形状を再構築するアルゴリズムを開発している。再構築された脳動脈実形状において，脈動する血流の解析を行うことにより、前述の血行力学的指標が瘤の発生箇所と強い相関を有することを明らかにしている。これは，独創的かつ重要な成果である。

第4章では，第2章における成長モデルおよび第3章における血行力学的指標に関する研究を統合している。脳動脈実形状における提案指標の分布に対して，生物学的反応を考慮した成長モデルを適用することで，瘤のリアリスティックな形成シミュレーションに成功している。さらに，従来言われてきたような血管壁の強度低下による受動的拡張だけでは，嚢形状の形成を説明できないことを示し，瘤の成長において壁の生物学的反応が重要な役割を果たすことを明らかにしている。これらは，脳動脈瘤の形成メカニズムの解明のために有用である。

第5章は結論である。

以上要するに本論文は，脳動脈瘤の発生と成長に関して計算バイオメカニクスの手法を用いて独創的な研究を行ったものであり，バイオロボティクスおよび生体力学の発展に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。