	チャン　ミンズ
氏　　　　　名	張　明子　　Zhang　Mingzi
授　与　学　位	博士（工学）
学位授与年月日	平成２９年９月２５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	Haemodynamic Simulation and Optimisation for the Flow-Diversion Treatment of Cerebral Aneurysms（脳動脈瘤におけるフローダイバージョン術に対する血流シミュレーションと最適化）
指　導　教　員	東北大学教授　太田　信
論文審査委員	主査　東北大学教授　太田　信　　東北大学教授　早瀬　敏幸 東北大学教授　芳賀　洋一　教授　銭　逸 （マッコーリー大学）

論 文 内 容 要 旨

Intracranial aneurysms (IAs) make up a major proportion of cerebrovascular disorders, which likely lead to death of the patients due to aneurysm rupture. In the treatment of IAs, flow-diverting (FD) stent implantation has become a commonly adopted treatment mode, especially for wide-necked or fusiform aneurysms which previously went untreated. In the clinical practice of FD stent implantation, however, different kinds of post-treatment complications frequently occur, including notably incomplete aneurysm occlusion, delayed aneurysm rupture, and post-stenting in-stent stenosis. Research into those complications revealed their correlation with the local aneurysm haemodynamics, and suggest that the complications may be avoided by optimally designed FD devices, as well as optimally planned treatment procedures.

To meet this practical demand, the present thesis begins by reviewing a wider literature in Chapter I, in order to explore the current state of knowledge on underlying causes of those complications. Literature review suggests that successful treatment relies heavily upon sufficient "re-direction" of the aneurysm inflow; inadequate flow diversion generated by the implanted device would possibly account for incomplete aneurysm occlusion, and subsequently for the delayed aneurysm rupture. Furthermore, research into in-stent stenosis confirmed its relation to high levels of stent metal exposure; this is a serious condition which may activate platelets, and promote aggregation of platelets on the stent metal surfaces.

In view of this knowledge, important contributions can plausibly be made to the following two aspects: 1) a design optimisation strategy for FD stents, which attains efficient flow diversion with fewer stent metal filaments needed for a specific patient; and 2) a feasible approach for treatment individualisation via virtual deployment rehearsals and subsequent haemodynamic analyses, which ultimately support the determination of the best treatment plan for a patient.

To realise these objectives, three main studies are therefore included in the present thesis: 1) a structural optimisation study that pursues high flow diversion by accommodating FD wire configuration to a given patient aneurysm geometry, with the stent porosity fixed at a high level to protect against post-stenting stenosis; 2) a haemodynamic investigation of FD treatments with "stent compaction technique" applied to devices of various diameters, for successfully and unsuccessfully treated aneurysms; and 3) a haemodynamic study of dual-FD stent treatments with various combinations of device diameter following different deployment sequences, for successfully and unsuccessfully treated aneurysms. The detailed results were respectively reported in Chapters III, IV, and V, with the materials applied and methodologies adopted introduced in Chapter II.

In Chapter III of the present thesis, a practical optimisation approach was demonstrated for FD stents available on the market with initially homogeneous wire configurations. This optimisation approach is able to improve the flow-diversion efficacy of those conventional FD stents, by rearranging the starting phases of the helical metal filaments. The proposed method was applied to the structural optimisations of three FD stents, with each corresponding to one aneurysm geometry. Without altering the pre-assigned overall stent porosity of 80 %, optimisation respectively improved the flow-diversion efficacies by 5, 2, and 28 % for the S, C, and R aneurysm model. Observing aneurysmal flow patterns post-optimisation, we confirmed that a disruption of the bundle of inflow is of great importance for reducing the intra-aneurysmal average velocity. Furthermore, we tested the reliability of the optimised stent structures, and found that the structure for the R model exhibits the best performance in tolerating the longitudinal displacements incurred during stent deployment. The optimisation method developed can be used to identify the wire structure with the best flow-diversion efficacy for a given patient aneurysm geometry. By rearranging the helix wires' starting phases, a homogeneous FD stent can be tailored to an inhomogeneous one with maximal flow-diversion efficacy for a patient aneurysm. In addition, the developed approach does not alter a pre-assigned stent porosity after optimisation, which potentially protects patients against post-stenting in-stent stenosis.

In Chapter IV, I studied FD treatment with "stent compaction technique" applied to stents of various diameters, through 24 virtual stenting scenarios for two patient-specific aneurysm cases — one was clinically categorised as a successful treatment and the other unsuccessful. By contrasting the haemodynamics in the successful and the unsuccessful treatment scenarios, the results indicate notably the following findings: 1) with stent compaction technique applied, the flow-diversion efficacy in the unsuccessful case can be improved to a level similar to that in the successful case without compaction; 2) the change of flow-diversion efficacy with respect to the compaction level follows a linear trend ($R^2 > 0.85$), regardless of the selection of stent diameter or the morphology of a recipient aneurysm; 3) the same level of compaction applied to different FD sizes (*i.e.* the stent diameter, *etc.*) could result in different treatment outcomes (with a maximum difference of about 10% in flow-diversion efficacy); and 4) the virtual stent deployment techniques developed in this study could be used to perform treatment rehearsals, to predict the treatment outcomes. These findings could plausibly be referred to by clinicians in many circumstances: For example, in the unsuccessful case, if a level-IV compaction had been applied, the treatment outcomes could be improved significantly (a further reduction of inflow by more than 30% of the untreated condition); moreover, clinicians may realise the importance of paying additional attention in dealing with aneurysms located at highly-curved parent arteries, *etc*. While the main purpose of this study is to help improve the understanding of stent compaction technique, under the influence of different device diameters, the 1) FD modelling technique, 2) stent compaction classification, and 3) virtual stent deployment method established in this study, on the other hand, will certainly contribute to the simulation methodologies used in future FD-related research and developments.

In Chapter V, virtual stent deployments and haemodynamic simulations were performed for a total of 18 dual-FD treatments, with different combinations of stent diameter considered for two clinically observed aneurysms — one successfully treated with an FD and the other unsuccessful after two FDs were implanted. Using a virtual deployment technique, we first implanted FD stents of respectively three sizes — 4.0, 4.5, and 5.0 mm — into both aneurysms; and then deployed a second device at each of those three sizes into each of the earlier deployed ones. Finally, we compared the stent wire configurations across the 18 treatment scenarios, and investigated the post-stenting haemodynamics by computational fluid dynamics (CFD) simulations. Results indicate that, attributable to the second device, 1) the stent porosity can be further decreased by approximately 20 % and the pore-density doubled; 2) an additional reduction of aneurysmal inflow (around 20%) occurred; and 3) diameter of the later-deployed device has limited effects on post-treatment aneurysmal haemodynamics, with standard deviation of less than 5%. Despite a greater flow-diversion improvement resulting from the second device, the final haemodynamic status in the unsuccessful case was only comparable to that with one FD implanted in the successful case, suggesting that FD stents might be an unsuitable choice for the unsuccessful aneurysm. This illustrates that haemodynamic simulation is helpful in the estimation of treatment outcome, so as to assist clinicians in choosing a favourable treatment plan.

To discover the differences between the extra flow diversions generated by the "stent compaction" technique and by implantation of an "additional device", representative results from Chapters IV and V were respectively selected and contrasted in Chapter VI, qualitatively and quantitatively. Results suggest that: 1) both the stent compaction technique and multi-stent implantation could effectively reduce the aneurysmal inflow; 2) the treatment strategy, as well as the FD device size, may considerably affect the treatment outcome; and 3) a treatment rehearsal prior to the real treatment may assist neuroradiologists in determining a favourable treatment plan. If computer simulation can be applied to quantify the haemodynamic consequences of a variety of prospective treatments that may plausibly be used in the real treatment, neuroradiologists may have something more than experience in deciding a favourable treatment plan.

The focus of the present thesis is related to the developments of a novel optimisation approach for FD designs and a feasible treatment planning method that could simulate those commonly adopted treatment strategies using FD stents available on the market. Results of the present thesis indicate several new findings, which have been listed and discussed in each Chapter in detail. But it would be remiss not to mention here again the following:

- ❖ the flow-diversion efficacy of a FD device depends not only on its porosity, but also on its structural design in relation to a patient aneurysm geometry, suggesting the importance of design optimisation of future FD wire configurations (*Chapter III*);
- ❖ the flow-diversion efficacy would be drastically improved when the "bundle of inflow" of an aneurysm has been effectively blocked, or disrupted (*Chapter III*);

- ❖ the change of "flow-diversion improvement" with respect to "stent compaction ratio" follows a linear trend ($R^2 > 0.85$), suggesting that stent compaction should be encouraged where applicable (*Chapter IV*);
- ❖ a 25% increase in compaction ratio leads to a further flow-diversion improvement of 10 % on average, whereas the same level of compaction applied to stents of different sizes yields a maximum difference of around 10 % in flow diversion (*Chapter IV*);
- ❖ if an additional FD stent is implanted, the porosity finally achieved could be decreased further by around 20% and pore density doubled (*Chapter V*); and
- ❖ the effects of the second FD stent's diameter on haemodynamics are modest, with a standard deviation less than 5 %. (*Chapter V*).

Along with these key findings, the present thesis may certainly have favourable impacts on future clinical practice of FD stent intervention, as well as the future research and development of FD stents:

Firstly, we worked out an automated design optimisation method, which is the first feasible approach that can be readily applied to design optimisation of commercially available stents; this is because our optimisation algorithm retains the filament braiding structure of those FD stents on the market. *Secondly*, performing virtual stent deployment, we noticed a dangerous morphological characteristic that deserves special attention from the treating clinicians — a highly-curved parent artery with the aneurysm located at the curvature 'apex'. FD stents deployed along highly-curved arteries can result in a considerable compromise of the metal coverage ratio achieved, compared to those deployed along less-curved parent arteries. *Thirdly*, based upon our haemodynamic analyses, we recommend that additional attention should be paid to those cases with 'gaps' existing between the parent artery wall and the FD stent wires; the main stream of blood flow in the parent artery may have a chance to enter the aneurysm sac through the 'gap', causing treatment failure. *Furthermore*, we demonstrated a feasible approach for treatment rehearsals, and found that the flow diversion achieved in the unsuccessfully treated case may be improved to a level similar to that in the successful one, either with a Level-IV compaction applied or with an additional FD stent deployed. If the treating clinicians could have performed such treatment rehearsals, or had had access to predictive modelling results illustrating the wire configurations of a virtually deployed FD stent and its subsequent haemodynamic outcomes, it is possible that they could have better treated the patient by a more favourable plan determined by haemodynamic simulation. *Finally*, the FD stent modelling technique, the classification of stent compaction, and the in-house programs developed for virtual stent deployment *etc*. would certainly contribute to the future studies of FD stent design and treatment planning.

論文審査結果の要旨

くも膜下出血の主原因である脳動脈瘤の破裂を予防するために，血流の遮断効果を考慮したフローダイバータ（FD）ステントと呼ばれる医療機器が近年開発されている。FDステントは，これまで治療が困難であった瘤の頸部が広い形状の疾患に有効であるとされている。しかしながら，臨床ではしばしば合併症や遅発性破裂を引き起こすことが報告されるなど，問題が多発している。これらの問題の原因は，瘤内の血流状態が治癒に至る状態に達していないことと考えられ，FD ステントの血流遮断効果が低いことや，臨床において治療指針が未確立なことがあげられる。これらの問題を解決するためにステントが留置された状態での瘤内の血流状態の解明が重要であるとされ，数値流体力学解析がこれまでにも多く用いられている。一方で治療を有効に行うためには，血流遮断効果を最適化したFDステントの開発が重要である。さらには，治療方針を設計するために，ステントの留置，展開および血流の数値流体力学解析を行う一連のプロセスを確立することが不可欠である。本論文は，これらの研究成果をまとめたものであり，全7章からなる。

第1章は序論であり，本研究の背景，目的および構成を述べている。

第2章では，本研究で用いる脳動脈瘤の形状，数値流体解析手法，およびFDステントの留置と展開の方法に関する一般的な知見を述べている。

第3章では，FDステントの空げき率を保持しながら血流遮断効果を最適化する形状の探索解析を行っている。特に，形状探索を行う際に FD ステントの形状の特徴を考慮し計算を行うことにより，FDステントの最適化設計が可能であることを示している。さらに，血流遮断効果が最適な形状の特徴を発見し，FDステントの設計指針を考案している。これらは重要な成果である。

第4章では，術式の変化を考慮したFDステントの留置および展開について計算を行っている。術式を 24 通り変化させた FD ステントの留置状態における血流の数値流体力学的解析を行うことにより，FD ステントをコンパクションし，空げき率を低下させる手法の再現を試みている。この再現により，空げき率の低下と血流遮断効果には高い相関性があることを示している。本章で得られた知見は有益である。

第5章では，さらに術式を考慮し，様々な直径のFDステントを2つ重ねる留置および展開を18例示し，瘤内の血流速度の計算を行い，FD ステントを2つ重ねた状態においても，必ずしも血流遮断効果が高くない例もあることを発見している。この知見は，治療の方針を立てる上で有益で重要な成果である。

第6章では，第4章と第5章までの成果を踏まえ，FDステントのコンパクションと2つ重ねる手法を比較し，血流工学の観点から治療方針を考案している。これは治療方針を工学的視点から考案できることを示した重要な成果である。

第7章は結論である。

以上要するに本論文は，血流の数値流体力学解析技術により，FDステントの最適形状の探索を行い，その設計指針を考案し，工学的視点から治療方針を構築しているものであり，バイオロボティクスおよび医工学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。