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（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）
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論 文 内 容 要 約

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.