Systematic review

Aneurysm healing after endovascular treatment in the Helsinki sidewall aneurysm model: a systematic review

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ABSTRACT

Aims Intracranial aneurysms are treated with a variety of endovascular devices including coils, stents, and flow diverters. The mechanisms by which these devices result in aneurysm occlusion and subsequent healing have been the subject of significant research using various animal models. The murine Helsinki aneurysm model is a sidewall aneurysm created by the end-to-side anastomosis of a donor aortic graft onto the abdominal aorta of a recipient animal. The aim of this systematic review is to assess the efficacy of different endovascular devices for the treatment of the Helsinki model aneurysm.

Methods We performed a systematic review of Pubmed in accordance with PRISMA guidelines, yielding eight studies detailing the results of endovascular treatment of this preclinical aneurysm model. Studies were included if they provided rates of complete aneurysm occlusion after treatment.

Results In these studies, aneurysms were treated with coiling (n=81, 7 studies), stenting (n=67, 3 studies), stent-coiling (n=13, 1 study), and flow diversion (n=49, 2 studies). The results of each individual study are discussed with the goal of providing a measure of the relative efficacy of different endovascular devices for the treatment of this particular model aneurysm. We also pay special attention to insights into the mechanisms underlying aneurysm healing after different forms of endovascular therapy.

Conclusion The data presented here may be useful to investigators attempting to demonstrate superiority of novel endovascular devices relative to previous device iterations using this preclinical model.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The murine Helsinki aneurysm model has been used to study the mechanisms of aneurysm healing after endovascular treatment.

WHAT THIS STUDY ADDS

⇒ This study summarizes the reported rates of aneurysm occlusion after treatment of the Helsinki aneurysms with different types of endovascular devices.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ This study may aid researchers endeavoring to test endovascular devices in a preclinical setting with regard to selection of an apppropriate animal model.

INTRODUCTION

Over the past two decades, advances in endovascular technology have revolutionized the treatment of intracranial aneurysms, the majority of which are now treated via endovascular means.[1] Relative to surgical clipping, endovascular therapy is nevertheless associated with a higher rate of aneurysm recurrence after treatment.[2] To address this issue, numerous animal models have been developed to study the mechanisms underlying aneurysm occlusion and subsequent healing after endovascular therapy.[3] The Helsinki murine sidewall aneurysm model consists of suturing a ligated segment of thoracic aorta from a donor animal to the abdominal aorta of a syngeneic animal in end-to-side fashion, thereby creating a sidewall aneurysm (figure 1).[4] Sidewall aneurysms are amenable to multiple different endovascular treatment strategies, and thus the testing of endovascular devices in this aneurysm type has potential clinical applicability. Moreover, this model represents a relatively inexpensive and reproducible alternative to large animal aneurysm models, and importantly allows the placement of both standard and experimental endovascular devices within the created aneurysm at the time of aneurysm formation.[5–7] After an interval period, blood flow into the aneurysm can be assessed by fluorescence angiography,[8] and on animal sacrifice, histologic analyses can be performed to quantify the degree of aneurysm healing after endovascular treatment.[9 10]

We review the results of studies deploying endovascular devices in the Helsinki model, with the goal of characterizing current understanding of aneurysm healing mechanisms and obtaining a measure of relative efficacy between different endovascular devices regarding aneurysm occlusion.

METHODS

Literature search

We systematically reviewed the literature for studies detailing the results of endovascular treatment of the Helsinki sidewall aneurysm in accordance with PRISMA guidelines.[11] Pubmed/Medline was searched for articles written in English using all possible combinations of the keywords “Helsinki”,

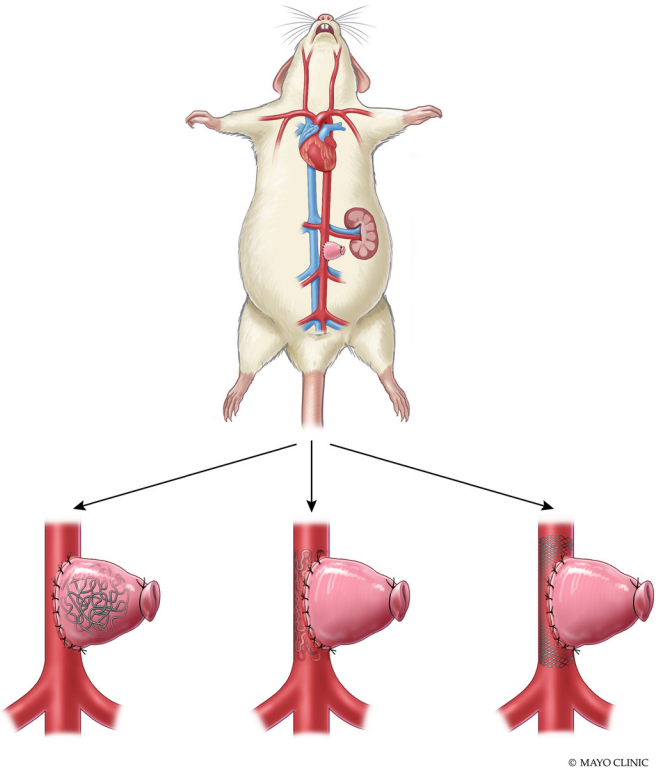

Figure 1 The Helsinki sidewall aneurysm model. The illustration shows the sidewall aneurysm after suturing the donor graft to the abdominal aorta distal to the origin of the renal arteries. The diagrams below depict the aneurysm after treatment with intrasaccular coils (left), an intravascular stent (middle), and an intravascular flow diverter (right).

'rat", "aneurysm", "sidewall", and "model". The reference lists of articles of interest were also reviewed for additional studies. Ethics approval was not required given the nature of the study.

Inclusion criteria and data extraction

Studies that reported the rate of complete aneurysm occlusion after endovascular treatment of the murine Helsinki sidewall aneurysm were included for analysis. Our search strategy yielded 1042 results, which were screened by the first author (LR), ultimately yielding 11 articles describing the results of endovascular treatment of the Helsinki aneurysm, all of which were retrievable. Three articles did not provide rates of aneurysm occlusion after treatment, yielding a total of eight articles (figure 2). Data extracted from each study included the type(s) of endovascular treatment performed and the rate of complete aneurysm occlusion after each type of treatment included in the study, which was reported as a frequency and percentage. We also noted whether aneurysms were decellularized prior to implantation and treatment, and when available rates of vital and decellularized aneurysm occlusion were reported separately. For studies reporting the outcomes after coiling, the loop diameter and length of coil in millimeters and centimeters, respectively, deposited into the aneurysm was reported and, when available, information on mean coil packing density was recorded.

Data analysis

Due to the heterogeneity between studies with regard to sample size and time after treatment at which complete aneurysm occlusion was determined, comparative statistics of rates of aneurysm occlusion after different types of endovascular treatment were not performed and only descriptive statistics were provided.

RESULTS

A total of eight studies reporting the results of endovascular treatment of the Helsinki sidewall aneurysm were found. In these studies, aneurysms were treated with coiling (n=81, 7 studies), stenting (n=67, 3 studies), stent-coiling (n=13, 1 study), and flow diversion (n=49, 2 studies; table 1). The results of each individual study and the associated conclusions regarding mechanisms of aneurysm healing after endovascular therapy, as well as implications for future research, are discussed below.

Aneurysm healing after endovascular therapy

An important consideration for aneurysm animal models is the aneurysmal patency rate after creation, particularly if the model is used to test the efficacy of endovascular devices. Unlike sidewall aneurysm models in swine which, for example, exhibit high rates of spontaneous thrombosis,[3] the Helsinki model exhibits long-term patency rates exceeding 90%.[6] Moreover, while the donor aortic segment can be immediately implanted in the recipient animal after harvesting, it is possible to 'decellularize' the graft by soaking it in sodium dodecyl sulfate prior to implantation.[12] The decellularized graft lacks mural smooth muscle cells (SMCs), which are thought to be critically important to the process of aneurysm healing after endovascular treatment.[13] Following endovascular treatment and initial aneurysm thrombosis, activated SMCs organize thrombus into fibrous tissue, which occurs concurrently with neointima formation across the aneurysm neck, ultimately excluding it from the circulation.[14] Relative to non-decellularized or vital aneurysms, Marbacher

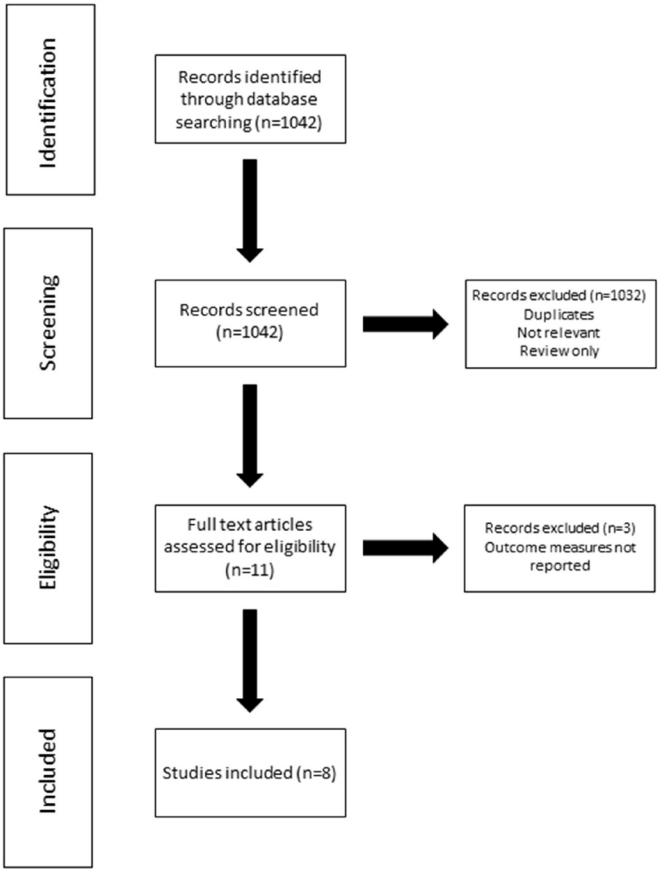

Figure 2 PRISMA flow diagram depicting selection of relevant studies.

Table 1 Aneurysm occlusion rates after endovascular treatment in the Helsinki rat model

Study	Devices	Decellularized aneurysms	Occlusion rates % (n)
Marjamaa 2009[6]	Platinum and PGLA-coated coils	No	PGLA: 88.9% (10/11) Platinum: 28.6% (2/7)
Marbacher 2014*[12]	–	Yes	Decellularized: 16.7% (2/12) Vital: 25.0% (3/12)
Zhang 2014[22]	Coils	No	100% (6/6)
Aquarius 2018[5]	Flow diverter	Yes	100% (36/36)†
Aquarius 2019[34]	Flow diverter	Yes	47.8% (11/23)†
Grüter 2019[31]	Bioresorbable stent, stent-coiling	Yes	Stent: 84.6% (22/26)‡ Stent-coiling: 100% (13/13)‡
Nevzati 2020[17]	Coils	Yes	Decellularized: 33.3% (2/6) Vital: 100.0% (7/7)
Grüter 2021[9]	Coils, stent	Yes	Coils: 42.8% (12/28)‡ Stent: 96.2% (25/26)‡
Wanderer 2022[10]	Coils, stent	Yes	Coils: 25.0% (4/16)‡ Stent: 93.3% (14/15)‡

*Aneurysms in this study were untreated, included to provide baseline values of aneurysm occlusion.
†All aneurysms were decellularized.
‡Includes both decellularized and vital aneurysms.
PGLA, polyglycolic-polylactic acid.

and colleagues observed increased amounts of disorganized intra-aneurysmal thrombus, mural degeneration, and inflammatory infiltration in decellularized aneurysms. Decellularized aneurysms were also found to grow (5/12, 41.7%) and even rupture (3/12, 25%) during follow-up, neither of which was observed in vital aneurysms.[12] Importantly, the degenerated mural phenotype was subsequently shown to be rescued by intra-aneurysmal SMC transplantation into decellularized aneurysms, which also prevented aneurysmal growth and rupture.[15] Spontaneous occlusion rates for vital and decellularized aneurysms were comparable at 25% (3/12) and 16.7% (2/12), respectively (table 1).

Rupture is a desirable characteristic of preclinical aneurysm models for obvious reasons, and yet it is relatively rare with only 20 studies reporting spontaneous rupture of a model extracranial aneurysm.[16] Similar to decellularized Helskinki aneurysms, a majority of ruptured model aneurysms were either chemically or mechanically modified at the time of aneurysm creation, underscoring the importance of aneurysm wall biology to the pathophysiology of this process.[16] Importantly, the decellularized, but not vital, Helsinki model aneurysms exhibit histologic similarities to ruptured or growing aneurysms from human subjects, specifically mural hypocellularity, disorganized luminal thrombus, and inflammatory cell infiltrate, each of which is less common in unruptured aneurysms.[13] The Helsinki model may therefore allow for the testing of endovascular devices in two distinct physiologic settings, potentially simulating treatment of a ruptured or unruptured aneurysm depending on the cellularity of the implanted aneurysm. This model could therefore provide insight into the efficacy of particular endovascular devices for both unruptured and ruptured aneurysms. In the following sections we will review available data on mechanisms of aneurysm healing after endovascular treatment using different devices in both decellularized and vital aneurysms.

Endovascular coiling

Nevzati and colleagues compared the process of aneurysm healing after coil embolization between vital and decellularized aneurysms in Wistar rats.[17] Animals were randomly assigned to receive either vital or decellularized aneurysms, and aneurysms from both groups were coiled at the time of aneurysm creation prior to completion of the end-to-side anastomosis. For all aneurysms, 2 cm of 3 mm coils were introduced into the aneurysm, yielding mean (SD) packing densities of 6.5 (1.6)% and 6.7 (1.4)% for vital and decellularized aneurysms, respectively. Decellularized aneurysms demonstrated increased and persistent levels of mural inflammation and impaired neointima formation at multiple time points after aneurysm creation relative to vital aneurysms. At 90 days after treatment, 66% (4/6) of decellularized aneurysms demonstrated complete recanalization, with 33% (2/6) found to be completely occluded (table 1). Vital aneurysms demonstrated complete or near complete neointimal formation in all cases (7/7).[17] In vital aneurysms, SMC infiltration into and organization of luminal thrombus was found to progress inwardly from the aneurysm wall, whereas in decellularized aneurysms this process occurred primarily at the aneurysm neck and did not reach the aneurysmal dome.[17] Moreover, in experiments employing green fluorescent protein (GFP)-labeled donor and recipient animals, infiltrating SMCs were shown to originate primarily from the aneurysm wall and parent artery in non-decellularized and decellularized aneurysms, respectively.[17] These results reinforced the important role of SMCs in the organization of luminal thrombus. Relative to unruptured aneurysms, ruptured aneurysms are more often characterized by mural hypocellularity.[18] Future studies with larger sample sizes will be needed to determine whether mural hypocellularity significantly contributes to aneurysm recanalization after coiling, which occurs more frequently in previously ruptured aneurysms.[19]

Animal models have previously been employed to investigate the contribution of bone marrow-derived cells to neointima formation at the aneurysm neck.[20] In sidewall aneurysms created in mice with labeled bone marrow, Frösen and colleagues found that bone marrow-derived cells were infrequently found in neointima lining the aneurysm neck, suggesting that these cells may not be essential to neointima formation in this experimental setting.[21] The authors did note that these were not decellularized aneurysms, and thus bone marrow-derived cells may contribute more to the healing process

in aneurysms with mural hypocellularity. Nevertheless, Zhang and colleagues investigated the potential benefit of injecting bone marrow-derived endothelial progenitor cells (EPCs) derived from syngeneic donor animals into non-decellularized aneurysms treated with coiling.[22] In these experiments, 2 cm of 2 mm coils were placed into the aneurysm at the time of creation. Six weeks after aneurysm treatment, all aneurysms in animals receiving EPCs were noted to be completely occluded (6/6; table 1). EPCs were found to localize at the aneurysm neck, which relative to aneurysms in control-injected animals demonstrated a significantly thicker neointimal layer and more organized fibrous tissue.[22] These results suggested that better endothelialization across the neck of coiled aneurysms could potentially be mediated by EPCs. In a series of subsequent papers, this group investigated the effect of several interventions on the level of circulating EPCs and aneurysm healing after coiling using the Helsinki model. Liu and colleagues demonstrated increased levels of circulating functional EPCs and neck endothelialization and associated aneurysm occlusion in rats treated with the HMG-CoA reductase inhibitor rosuvastatin relative to control animals.[23] A similarly beneficial effect was observed in rats treated with erythropoietin, and this effect was potentially mediated by increased EPC expression of vascular endothelial growth factor.[24] Finally, Yu and colleagues showed that injection of microRNA-31a-5p also increased circulating EPC levels and improved aneurysm neck endothelialization relative to control animals. These effects were found to potentially be mediated by the effect of Axin on the Wnt/β-catenin molecular pathway.[25] In these studies, the degree of aneurysm occlusion was reported as a score quantifying both the degree of dome recanalization and neck endothelialization, with higher scores indicating more complete occlusion.[23–25] Absolute complete occlusion rates between intervention and control groups were not provided, nor were the diameter and length of coil inserted into the aneurysms. Taken together, these preclinical studies suggest that the modulation of circulating levels of EPCs holds promise as a possible adjunct to endovascular coiling.

There have been numerous clinical trials aimed at determining whether treatment with biologically active coils reduces the incidence of aneurysm recanalization relative to standard coils.[26] Marjamaa and colleagues compared the degree of aneurysm occlusion after coiling of non-decellularized rat sidewall aneurysms using platinum versus polyglycolic-polylactic acid (PGLA)-coated coils.[6] PGLA is believed to speed the process of luminal thrombus organization and scar formation, thereby facilitating aneurysm healing.[27] In an interesting experimental setup intended to simulate a commonly occurring clinical circumstance, aneurysms in both groups were incompletely coiled to intentionally leave a small neck remnant. Coil diameter and length inserted into the experimental aneurysms was 2 mm × 2 cm for both PGLA-coated and bare platinum coils. Aneurysms were serially imaged with high-resolution time of flight magnetic resonance angiography, with particular attention paid to the size of the neck remnant. While there was no initial difference in neck remnant size between groups, serial imaging demonstrated a progressive decrease in size and eventual occlusion of neck remnants in most PGLA-coiled aneurysms, whereas neck remnants in the platinum coiled groups either remained stable or increased in size. There were no instances of overt aneurysm recanalization in either group. On the final imaging session 28 days after aneurysm creation, a residual neck remnant was observed in 11.1% (1/9) and 71.4% (5/7) of PGLA- and platinum-coiled groups, respectively (table 1). Animals were then sacrificed to allow for endoscopic aneurysm inspection and subsequently histologic analysis of aneurysm healing. Importantly, there was excellent correlation between the endoscopic assessment of aneurysm occlusion and the previous radiographic results. Histologically, PGLA-coiled aneurysms exhibited more dense fibrosis and a significant degree of inflammatory cell infiltrate, the latter of which was not observed in platinum-coiled aneurysms.[6] These data demonstrate the feasibility of testing novel coiling technology using the Helsinki model.

Stenting

Intracranial stenting is frequently used as an adjunct during endovascular coiling of cerebral aneurysms, particularly for wide-necked aneurysms.[28] Interestingly, a large-scale meta-analysis did not show differences in initial aneurysm occlusion rates after stent-assisted versus simple coiling, yet stent-coiled aneurysms were more likely to show progressive occlusion and less likely to recanalize on follow-up analysis.[28] Although they are relatively porous, intracranial stents typically used for stent-assisted coiling may partially function as flow diverters, redirecting blood flow away from the aneurysm and serving as a scaffold for endothelial cell formation across the aneurysm neck, particularly for sidewall aneurysms such as the Helsinki model.[29] Interestingly, in an analysis of stent-coiled aneurysms, coil packing density was not independently associated with subsequent aneurysm occlusion, suggesting the benefits of stenting may extend beyond the facilitation of denser aneurysmal packing.[30]

To investigate the biological contribution of stenting to aneurysm healing, Grüter and colleagues examined patterns of neointima formation after stenting versus simple coiling using a rat sidewall aneurysm model.[9] Both stenting within the aorta across the aneurysm neck and coiling were performed at the time of aneurysm creation, with a coil diameter and length of 2 mm × 2 cm and stent diameter and length of 2.5 mm × 6 mm. To investigate the relative contributions of neointimal-forming and thrombus-organizing cells from the aneurysm wall and parent artery, aneurysms from wild-type (decellularized) and GFP-labeled (vital) donors were sutured onto GFP-labeled and wild-type recipient animals, respectively.[9] Complete aneurysm occlusion after stent treatment was observed in 96.2% of cases (25/26), with a single decellularized aneurysm remaining patent. All stented aneurysms (3/3) analyzed at the latest follow-up time (28 days) were occluded. In contrast, only 42.8% (12/28) of coiled aneurysms were occluded, with 25% (1/4) found to be occluded at 28 days. Among decellularized coiled aneurysms, 30% (3/10) were occluded, with 0% (2/2) occluded at the latest follow-up (table 1). A single decellularized aneurysm that was initially coiled ruptured during follow-up.[9] Histologically, aneurysms treated with stenting generally had a thin but continuous neointimal layer across the neck along with dense fibrous tissue and minimal residual hematoma in the aneurysm sac, whereas coiled aneurysms often demonstrated disorganized luminal thrombus and incomplete neointimal formation, particularly in decellularized aneurysms. In wild-type animals with GFP-labeled aneurysms, while there was no difference in fluorescence signal within the aneurysm wall and luminal thrombus between stented and coiled aneurysms, a greater proportion of cells comprising the neointima of coiled aneurysms were GFP-labeled, indicating that neointimal forming cells migrated predominantly from the aneurysm wall in coiled but not stented aneurysms. A hypothesized corollary to this result is that parent artery cells play a greater role in neointima formation after stenting, and that stents may provide scaffolding to facilitate cell migration to the aneurysm neck.[9] Considering the superior degree of observed neointimal formation in stented relative to coiled aneurysms, these findings may explain the superior rates of sustained aneurysm occlusion after stent coiling noted in clinical studies.[28] In a follow-up study by the same group, Wanderer and colleagues investigated the effect of aneurysm decellularization on the relative contributions of mural and parent artery cells to neointima formation after coiling versus stenting.[10] Similar to prior experiments, 2 mm × 2 cm coils and 2 mm × 6 mm stents were implanted. Endothelial cells within

the parent artery were labeled with a fluorescent marker at the time of aneurysm creation and treatment, and the fluorescence signal within the neointima of decellularized and vital aneurysms was subsequently analyzed. Complete aneurysm occlusion was observed in 93.3% (14/15) and 25% (4/16) of stented and coiled aneurysms, respectively (table 1).[10] Somewhat in contrast to the results of Grüter and colleagues, no difference in neointimal fluorescence signal was observed in vital aneurysms treated with coiling versus stenting.[9 10] In decellularized aneurysms, however, greater neointimal signal was observed in stented compared with coiled aneurysms,[10] suggesting that mural cellularity may influence the need for parent artery cell contribution to neointimal formation.

There are important disadvantages associated with stenting, particularly the need for initial dual antiplatelet and potentially lifelong monotherapy. Given this important disadvantage, there has been considerable interest in developing biodegradable stents that resorb after aneurysm occlusion, obviating the need for sustained antiplatelet therapy. Nevzati and colleagues demonstrated the feasibility of implanting a magnesium bioresorbable stent following aneurysm creation in standard fashion, although rates of aneurysm occlusion in this study were not reported.[7] In a follow-up study, Grüter and colleagues examined aneurysm healing after treatment with bioresorbable versus non-resorbable cobalt-chromium stents, with or without concomitant placement of coils.[31] Bioresorbable stent placement resulted in complete aneurysm occlusion in 84.6% (22/26) of cases (table 1), which was comparable to occlusion rates with cobalt-chromium stents. Regardless of composition, stent placement resulted in robust neointima formation at the aneurysm neck much more frequently than aneurysms treated with coiling only. Treatment with aspirin was found to reduce periadventitial inflammation and intraluminal inflammatory cell infiltrate and to improve neointima formation relative to animals not receiving aspirin. The addition of coils did not affect deleteriously the magnesium stents, which were found to progressively involute over a 6-month period without any associated morbidity. Notably, 100% of aneurysms (13/13) treated with stent-coiling, regardless of stent composition, were completely occluded at last follow-up evaluation (table 1).[31] The coil diameter and length was 2 mm × 2 cm for all aneurysms treated with coiling regardless of stent placement. Future studies will undoubtedly be aimed at providing further comparisons between bioresorbable stents and standard endovascular devices.

Flow diversion

Since their introduction to clinical practice, flow diverters have greatly impacted the endovascular treatment of intracranial aneurysms. These devices are now arguably the standard of care for paraclinoid aneurysms and show promise for the treatment of complex aneurysms at other locations in both the anterior and posterior circulations.[32] Flow diverters are less porous than traditional intracranial stents, which facilitates the redirection of blood flow away from the aneurysm and down the parent artery. Stagnant blood within the aneurysm sac precipitates aneurysm thrombosis; however, sustained aneurysm occlusion may depend primarily on endothelialization of the device across the aneurysm neck.[33] Aquarius and colleagues demonstrated the feasibility of flow diverter deployment in the rat Helsinki model.[5] Custom-made flow diverters were deployed across the neck of decellularized aneurysms at the time of aneurysm creation. Rats were maintained on dual antiplatelet therapy and subsequently sacrificed at different time points to allow for histologic assessment. Notably, regardless of the time from aneurysm creation, 100% of aneurysms (36/36) treated with flow diversion were found to be thrombosed (table 1) although, importantly, there were no instances of flow diverter thrombosis.[5] In a follow-up study using the same model, Aquarius and colleagues investigated the relative importance of device porosity and wall apposition to ultimate aneurysm occlusion.[34] Flow diverters with low (10 pores/mm^2) and high (23 pores/mm^2) pore density were deployed across decellularized aneurysms, which were later harvested at 1 or 3 months following implantation. Complete aneurysm occlusion rates were 33% (2/6) and 66% (4/6) at 1 and 3 months after deployment of low pore density flow diverters and 20% (1/5) and 66% (4/6) at 1 and 3 months after deployment of high pore density flow diverters, with no significant difference between groups at either time point. The overall total occlusion rate was 47.8% (11/23) (table 1).[34] Notably, the average percentage of aneurysm occlusion, defined as the percent aneurysm volume occupied by organized thrombus, was 93.5%, indicating that incomplete occlusion was secondary to a small neck remnant in all cases. The authors did find a significantly greater number of malposed device struts, as well as a greater distance between malposed struts and the parent artery, in incompletely occluded aneurysms, suggesting that wall apposition may be more important to flow diverter efficacy than pore density.[34] These studies clearly demonstrate feasibility of flow diverter deployment in the Helsinki model, however comparative analyses of efficacy between different flow diverter devices may be limited due to the high degree of aneurysm occlusion after flow diverter placement.

CONCLUSION

The results presented in this systematic review provide a measure of aneurysm occlusion rates after endovascular treatment of the Helsinki sidewall aneurysm with different devices (table 1), which may be useful information for future studies attempting to demonstrate improved efficacy of one device over another. Endovascular coiling, particularly of decellularized aneurysms, was consistently associated with low rates of aneurysm occlusion,[9 10 17] and thus the Helsinki model appears to be an excellent model for testing and improving emerging coiling technology. It should be noted, however, that coil packing density in the presented studies was quite low, which may have contributed to the low rates of aneurysm occlusion after coiling. In contrast, regardless of aneurysm cellularity, both stent and flow diverter placement across the aneurysm neck were associated with fairly high rates of aneurysm occlusion (table 1),[5 9 10 34] which may complicate comparative analyses of different devices. Ultimately, modifications to the model may be necessary to test the relative efficacy of different stent technologies.

Contributors LR: study conceptualization, drafting manuscript, critically reviewing manuscript, final approval of manuscript, accountable for all aspects and guarantor of this study. JLAL: study conceptualization, critically reviewing manuscript, final approval of manuscript, accountable for all aspects. RK: study conceptualization, critically reviewing manuscript, final approval of manuscript, accountable for all aspects. DFK: study conceptualization, critically reviewing manuscript, final approval of manuscript, accountable for all aspects.

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