*Review Article*

Unruptured cerebral aneurysm risk stratification: Background, current research, and future directions in aneurysm assessment

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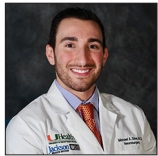
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ABSTRACT

Background: The optimal management of unruptured cerebral aneurysms is widely debated in the medical field. Rapid technology advances, evolving understanding of underlying pathophysiology, and shifting practice patterns have made the cerebrovascular field particularly dynamic in recent years. Despite progress, there remains a dearth of large randomized studies to help guide the management of these controversial patients.

Methods: We review the existing literature on the natural history of unruptured cerebral aneurysms and highlight ongoing research aimed at improving our ability to stratify risk in these patients.

Results: Landmark natural history studies demonstrated the significance of size, location, and other risk factors for aneurysm rupture, but prior studies have significant limitations. We have begun to understand the underlying pathophysiology behind aneurysm formation and rupture and are now applying new tools such as flow dynamics simulations and machine learning to individualize rupture risk stratification.

Conclusion: Prior studies have identified several key risk factors for aneurysmal rupture, but have limitations. New technology and research methods have enabled us to better understanding individual rupture risk for patients with unruptured cerebral aneurysms.

Keywords: Aneurysm, Cerebrovascular, Computational flow dynamics, Endovascular, Machine learning, Open vascular neurosurgery, Subarachnoid hemorrhage

BACKGROUND

Cerebral aneurysms [Figure 1] are relatively common in the general population. Several autopsy and radiographic studies have investigated the prevalence of these lesions, with estimates ranging between 2% and 5%[15,30,64] and exceeding 19% in high-risk populations.[9] Aneurysmal rupture can be a catastrophic event. Mortality after aneurysmal subarachnoid hemorrhage (aSAH) is as high 10–12% within the first 24 h,[28,59] 19–45% at 1 week,[2,60] and 25–60% at 3 months.[2,81]

The rate of repeat hemorrhage after aSAH rises steadily for the first 7 days and then tapers at 3 weeks.[24] For those who survive, rates of disability are extremely high, with only one-third of patients achieving favorable outcome (modified Rankin scale 1–3) at 1-year.[79] At long-term follow-up, just 62% of previously employed patients return to work,[72] and only half of elderly

patients with aSAH return to living at home.[88] The social and economic repercussions of aSAH are particularly problematic since patients tend to be young and healthy. Indeed, aSAH accounts for just 4.4% of stroke mortality, but 27.3% of years of life lost due to stroke.[35] Given the extremely poor natural history of aSAH, it is important to treat unruptured aneurysms that are at high risk for rupture while balancing rupture risk with the risk of aneurysm treatment. Identifying which aneurysms are high risk is challenging and actively debated.

NATURAL HISTORY OF UNRUPTURED INTRACRANIAL ANEURYSMS

A series of landmark studies describe the natural history of unruptured cerebral aneurysms. The best-known of these studies is the International Study of Unruptured Intracranial Aneurysms (ISUIA) which was published in several phases throughout the late 1990s and early 2000s.

The ISUIA I study was a hybrid retrospective and prospective study published in 1998. In the retrospective portion, 1449 patients with 1937 unruptured cerebral aneurysms with a mean duration of follow-up of 8.3 years were analyzed. The study described a 0.05% annual risk of rupture for aneurysms <10 mm (727 patients), which rose to 0.5% among patients with a prior history of ruptured aneurysm (722 patients). Rupture risk increased with aneurysm diameter, with aneurysms larger than 25 mm carrying a 6% annual risk of rupture.[31] In the prospective portion of the study, treatment related morbidity and mortality in 1172 patients with unruptured aneurysms was found to be 15.7% at 1 year. The authors concluded that the risks of surgery outweighed the annual risk of rupture for aneurysms <10 mm. However, the study is limited by short follow-up and is unable to capture the lifetime rupture risk that is saved by treatment, thus underestimating the full benefits of surgery. Although controversial, this study was an early demonstration of the importance of aneurysm size, personal history of aSAH, and age in estimating aneurysm rupture risk and the role of treatment.

The ISUIA 2 study assessed 4060 patients (1692 managed conservatively, 1917 with open surgery, 451 endovascular treatment) with unruptured aneurysms. Importantly, ISUIA investigated the impact of both size and location on 5-year cumulative rupture risk. The results corroborated earlier findings that larger size was associated with increased rupture risk, concluding that anterior circulation aneurysms <7 mm had a 0% rupture risk over 5 years. In contrast, posterior circulation and posterior communicating artery aneurysms of at least 25 mm had a 50% 5-year cumulative rupture rate.[91] However, patient selection and drop out are key limitations of this study. For instance, a significant number of patients were excluded from the study if their

perceived risk of treatment was low (i.e., young healthy patients) or if their perceived rupture risk was high (because they were treated and excluded from analysis).[16,80] The high rate of crossover, with over 500 patients excluded from analysis because they received treatment for their aneurysm, may have excluded high risk lesions from the final analysis, as it is not made clear why these aneurysms were treated.[63] In addition, selection bias may have favored lower risk aneurysms, as there were significant differences between the conservatively-managed cohort and the intervention cohort in aneurysm size, location, patient age, and presenting symptoms. An older patient population is particularly problematic because it leads to shorter follow-up times.[63] Despite these limitations, ISUIA was an important step toward a better understanding of the natural history of unruptured aneurysms.

Natural history studies out of Finland (Juvela *et al.*, 2000) and Japan (Unruptured Cerebral Aneurysm Study of Japan [UCAS], 2012) reported similar findings with additional nuances. Juvela *et al.* followed 2575 patients over nearly 20 years.[38] Their retrospective cohort consisted of mostly unruptured MCA (45%) and ICA (44%) aneurysms diagnosed before 1979 with follow-up. They found an overall annual rupture rate of 1.3%. Importantly, this study consisted predominantly of patients with a previously treated ruptured aneurysm and another unruptured aneurysm that was managed conservatively. Whether aneurysm multiplicity influences rupture risk of individual aneurysms remains to be elucidated,[43,52,65] but personal history of subarachnoid hemorrhage is associated with increased rupture risk[25] and calls to question the generalizability of their study. Compared to ISUIA, patients in the Finnish series were younger, had smaller aneurysms (mean 5 mm), and were followed for a longer period of time with fewer excluded patients. Even in their cohort of small aneurysms in young patients, larger aneurysm size was significantly associated with rupture. In several follow-up studies from Juvela *et al.*, they have demonstrated the association between smoking, young age, and aneurysm growth with rupture.[40] In one analysis of 111 aneurysms followed for over 20 years, all aneurysms that went on to rupture had increased in size by at least 1mm on preceding follow-up.[42] Like ISUIA, aneurysm size of 7 mm or greater was an independent predictor of rupture.[37,40] Female sex and smoking were associated with aneurysm growth and rupture, even when adjusting for other variables.[39,40]

The UCAS study was a prospective natural history study from Japan.[32] In their cohort of 5720 patients, they found an average 0.95% annual rupture risk that varied significantly with size, location, and morphology. Their location subgroup analysis differed from ISUIA in that they isolated posterior communicating artery (pcomm) aneurysms and anterior communicating artery (acomm)

aneurysms as being most strongly associated with increased rupture risk. In contrast, ISUIA classified pcomm aneurysms as posterior circulation and acomm as anterior circulation. Importantly, UCAS was the first large natural history study to find a significant association between aneurysm morphology and rupture risk, concluding that specifically presence of a daughter sac was associated with rupture. Interestingly, UCAS found that the previous SAH from another aneurysm, smoking, and family history were not a risk factor for rupture. Similar to other natural history studies, the UCAS study cohort may not represent the general population because patients who are deemed either low risk for rupture and/or high risk for treatment were followed over time.[80] Indeed, patients in the UCAS study were older (40% over the age of 70) and less likely to be smokers (15%). Moreover, many aneurysms (48% of initially included patients) were treated during the study and excluded from the final analysis. These higher-risk lesions excluded from analysis represents selection bias, likely underestimating overall rupture risk.

To consolidate these findings Greving *et al.* performed a meta-analysis from 6 prospective natural history studies[32,33,38,78,90,91] and developed the PHASES aneurysm risk score, which attributes points to variables associated with aneurysmal rupture.[25] Their pooled analysis of over 8000 patients determined the following factors to be predictive of rupture risk: Age over 70, hypertension, aneurysm size, prior subarachnoid hemorrhage, location (anterior cerebral artery, pcomm, or posterior circulation as highest risk), and Finnish or Japanese background. The PHASES score has been validated in several retrospective and prospective studies[4,7,21] and may also be correlated with poor functional outcome after aSAH.[21] However, some studies have found that the majority of aSAH patients present with a low PHASES score, suggesting that the score may not fully capture rupture risk.[21,66]

A summary of the major natural history studies of unruptured cerebral aneurysms is shown in [Table 1].

ANEURYSM SIZE

The debate over the importance of aneurysm size in predicting rupture risk is ongoing. The natural history studies reviewed above consistently show that increased aneurysm size is a risk factor for rupture. ISUIA, which reported a 0% rate of rupture for aneurysms <7 mm in the anterior circulation,[91] is commonly cited as evidence against treatment of small anterior circulation aneurysms. However, 70% of the aneurysms that subsequently ruptured in the Finnish study were <6 mm,[38] and 72% of aneurysms in a large meta-analysis of 56,304 patients were <6 mm.[64] Median size of ruptured aneurysms in a large series of nearly 2000 patients was 7 mm.[45]

Reconciling this data is the subject of ongoing debate. It has been proposed that post-rupture aneurysm size may not represent the size of an aneurysm at the time of rupture, suggesting that perhaps the small ruptured aneurysms we see were actually larger at the time of rupture. However, Rahman *et al.* evaluated imaging of 13 patients who had pre- and post-rupture imaging and found that none had significantly decreased in size and in fact 53.8% increased in size after rupture.[61] Other studies have also demonstrated that aneurysms do not seem to shrink (and may even increase in size) after rupture.[93,94] Current evidence suggests that post-rupture size is similar to pre-rupture size.

The constancy of aneurysm growth has also been called to question. Aneurysm growth has been shown to be associated with rupture.[40,87] However, aneurysms may experience periods of growth followed by periods of stagnancy, and their rupture risk may depend on their growth phase.[44,55,69] Aneurysms that have been stable over time carry a different risk profile than newly discovered lesions.[47] A subset of small aneurysms grow with time,[10] and it has also been proposed that small aneurysms may be at highest risk of rupture shortly after formation.[47,55,69] Importantly, these lesions would not have been captured in most of the natural history studies because small symptomatic or growing aneurysms were typically treated. Moreover, these irregular growth patterns highlight the limitations of natural history studies with short follow-up periods, which may underestimate the lifetime rupture risk. Indeed, when aneurysms are followed for many years, lifetime rupture risk reaches nearly 30%.[46]

Moreover, it is impossible to know the true denominator when estimating the risk of rupture of small aneurysms. Autopsy studies, radiographic surveys, and meta-analyses have consistently shown a high percentage of small aneurysms. Dr. Housepian's autopsy data from the 1910s to 1950s found that 45% of the aneurysms found among his nearly 6000 brain autopsies were <6 mm.[30] More recent studies have corroborated his findings, showing that 50–72% of aneurysms are <6 mm.[1,64] Even if the rupture risk of small aneurysms is exceedingly low, with a large enough denominator there will inevitably be a reasonable number of small aneurysms that present ruptured.

The Small Unruptured Intracranial Aneurysm Verification Study out of Japan in 2010 sought to address this very issue. This prospective study of 374 patients with aneurysms <5 mm found a 0.5% overall annual rupture risk, further demonstrating the nonzero risk of rupture for small aneurysms.[78] Size remained an important risk factor in their study; size >4 mm was associated with increased rupture risk. Hypertension, young age, and aneurysm multiplicity were also identified as risk factors.[78]

In summary, the literature on small aneurysms suggests that they may have a very low rupture risk. However, given the

Table 1: Summary of major natural history studies.

Study	Years of enrollment	Patients	Major findings	Risk factors identified	Limitations
International Study of Unruptured Intracranial Aneurysms (ISUIA I) (Wiebers 1998)[31]	1991–1995 (prospective) 1970–1991 (retrospective)	2621	Aneurysms less than 10mm have low rate of rupture. Authors conclude that risk of intervention exceeds morbidity and mortality of unruptured aneurysms in patient with small aneurysms and no prior history of aSAH	Size; location	Short follow up period; partially retrospective
ISUIA (Wiebers 2003)[91]	1991–1998	4060	Largest prospective natural history study showed large size and posterior circulation to be major risk factors for rupture. Anterior circulation aneurysms <7 mm have extremely low rupture risk	Size; posterior circulation or pcomm location	Rate of conversion to treatment arm; selection bias; incomplete follow up
Juvela *et al.* 2000[38]	1956–1978	142	1.3% annual rupture risk with long follow-up period (mean 20 years) and few excluded patients. Smoking is a strong modifiable risk factor. Authors argue in favor of treatment especially in younger patients	Size; age (inversely); smoking	Homogenous and young study population; patients predominantly with history of prior aSAH
The Unruptured Cerebral Aneurysm Study of Japan 2012[32]	2001–2004	5720	1% annual rupture risk; corroborating prior evidence that size and location (pcomm and acomm) are important risk factors. Presence of a daughter sac is associated with rupture	Size; pcomm or acomm location; presence of "daughter sac"	High drop-out rate for aneurysms treated during the follow up period; homogenous study population; selection bias
Small Unruptured Intracranial Aneurysm Verification Study 2010[78]	2000–2004	374	Aneurysms <5 mm have a low but nonzero risk of rupture (0.54% annually)	Size; hypertension; age <50; aneurysm multiplicity	Homogenous study population; high rate of drop out due to treatment

high morbidity and mortality associated with rupture in combination with the high prevalence of small aneurysms (likely over 50%), further studies are necessary to weigh the risks and benefits of treatment versus observation.

HERITABILITY AND FAMILY HISTORY

As many as, 10–20% of patients with aSAH have a positive family history of aneurysmal rupture.[70,95] In addition, familial aneurysms (i.e., in patients with at least one direct relative with a ruptured aneurysm) have a higher rate of rupture compared to matched sporadic aneurysms.[8] Syndromic cases of intracranial aneurysms from, for example, autosomal dominant polycystic kidney disease (APCKD), have been well described. Patients with APCKD are more likely to develop aneurysms and tend to rupture earlier than patients with non-syndromic aneurysms.[23] Ehlers-Danlos syndrome and other connective tissue disorders have been proposed to be associated with increased risk of intracranial aneurysms; however, more research is needed to investigate the genetic basis of these associations.[29]

MODIFIABLE RISK FACTORS

Hypertension and smoking have been demonstrated by several studies to be associated with increased risk of aneurysmal rupture.[14,19,25,82] A large prospective study out of Norway with over 20 years of follow-up showed that systolic and diastolic blood pressure has a positive correlation with aneurysmal rupture risk.[68] Their data also demonstrated a strong association between current or former smoking and rupture risk. In fact, current smoking carried a higher risk of rupture compared to former smoking,[68] suggesting that this risk factor is modifiable with lifestyle changes. Epidemiologic studies suggest that these results are generalizable to broader populations; both smoking and hypertension have been consistently shown to be risk factors for aSAH.[14,19,25,82] Smoking is associated with both aneurysmal growth and rupture.[41] In patients with both cigarette smoking and hypertension, the size at which aneurysm rupture occurs is smaller than in those without these risk factors.[18] Indeed, the American Heart Association and American Stroke Association recommend

treatment of hypertension and decreased smoking to reduce the risk of aSAH.[14]

LOCATION

The major natural history studies vary in their classification of aneurysm location, thus their cumulative results leave room for interpretation. ISUIA found that pcomm and posterior circulation aneurysms (as a group) had a higher rate of rupture than anterior circulation (which included acomm, MCA, and noncavernous ICA aneurysms).[91] UCAS, on the other hand, separated pcomm and acomm aneurysms from other locations and found a significantly higher rate of rupture at these two locations.[32] The link between aneurysm location and rupture risk begs the question of whether flow dynamics and wall stress play a role in determining rupture risk, which are discussed later in this review. The size of an aneurysm relative to its parent artery may be more important than the absolute size, which may explain why pcomm and acomm aneurysms have a higher rupture risk than similarly sized aneurysms of the larger ICA or MCA. Indeed, it has been shown that higher size ratio (i.e., the ratio of aneurysm sac diameter to parent artery diameter) is associated with higher rupture risk.[62]

MORPHOLOGY

The only major natural history study to find a significant association between a morphologic feature and aneurysm rupture risk is UCAS, which found that specifically the presence of a daughter sac in the aneurysm was high risk [Figures 2a and 2b].[32]

Certain morphologies have been associated with aneurysm growth, which we know is associated with aneurysmal rupture.[87] The ELAPSS study, which investigated risk factors for aneurysm growth and consolidated this data into a scoring system, found that three features were associated with rupture risk: blebs, wall protrusions, and multiple lobes.[3]

A recent study from China found that aneurysm sac irregularity (lobulation or blebs) and higher aspect ratio was associated with rupture.[89] Like many studies that assess aneurysm morphology, the authors compared pre-rupture to post-rupture morphology, and they acknowledge the limitations of making such a comparison. It is important to keep in mind that post-rupture morphology may not be fully representative of pre-rupture morphology, thus studies that draw conclusions about morphology based on post-rupture imaging may not fully capture the relationship. A prospective analysis from Juvela *et al.* demonstrated that post-rupture morphology differs significantly from pre-rupture morphology and thus cannot be used as a proxy.[37] Aneurysm volume and ratio of volume to neck size were independent predictors of aneurysm rupture in aneurysms that were imaged and subsequently ruptured.[37]

It has also been proposed that aneurysm size and morphology may be linked in that large aneurysms are more likely to develop blebs and other high-risk morphologies compared to small aneurysms, which become more regular with growth.[48] These findings suggest that perhaps the association between size and rupture risk may be related to evolution in morphology as an aneurysm grows.

FLOW DYNAMICS

Research has increasingly focused on flow dynamics as a possible explanation for why some aneurysms are more likely to rupture than others. Several parameters have been highlighted in the literature as important. In a matched case–control study, Skodvin *et al.* identified a straighter inflow angle as significantly associated with ruptured cases.[77] This is one of the few studies comparing pre-rupture morphology between aneurysms that did or did not go on to rupture, thus is of particular importance.

Higher aspect ratio [i.e., the ratio of aneurysm dome diameter to neck width, Figure 2c] has also been associated with increased risk of rupture.[85] In a study by Ujiie *et al.* 80% of ruptured aneurysms had an aspect ratio >1.6, compared to only 10% of unruptured aneurysms.[85] A major limitation of this study, however, is that it compares unruptured to ruptured morphology which, as discussed earlier, may not be reliable.

Higher size ratio [i.e., the ratio of the maximum diameter of the aneurysm sac to the diameter of the parent vessel, Figure 2d] is associated with high-risk flow dynamics.[62] The study also found an association with rupture status, but comparing unruptured to ruptured morphology may not be reliable. Complex flow patterns with vortices and areas of low wall shear stress (WSS) have been observed in aneurysms with higher size ratios.[83] Thus, absolute aneurysm size may not fully capture the rupture potential, and small aneurysms with higher size ratios may behave more like large aneurysms.

WSS is an important concept that is now being applied to aneurysm modeling to better understand rupture risk. WSS represents the frictional force on the wall per unit area and is dependent on blood viscosity and velocity.[22] Areas of high WSS occur at the apex of vessel bifurcations, regions of vessel stenosis, and the outer wall of curved vessel segments.[22] This concept correlates with areas of cerebral vasculature where we commonly see aneurysms develop, and intuitively makes sense when thinking of which vessel regions experience trauma and subsequently are more prone to aneurysm formation. WSS may additionally help predict which areas of the aneurysm are most at risk of rupturing.[53]

A similar concept called oscillatory shear index (OSI) measures the change in the vector of blood flow throughout the cardiac cycle, a more physiologic measure of WSS

in the vasculature.[11,58] Oscillatory shear stress promotes endothelial changes and triggers inflammatory pathways.[53] Unsurprisingly, higher OSI has been observed in ruptured aneurysms compare to unruptured aneurysms when matched by location and geometry.[58] The increased capability and wider use of computer simulations to model flow dynamics through different aneurysm positions, sizes, and morphologies have greatly facilitated our understanding of these parameters and their impact on rupture risk.[75]

ANEURYSM PATHOGENESIS

Cerebral arteries consist of several layers that are critical for understanding the pathophysiology of aneurysm formation. The innermost layer, the tunica intima, consists of endothelium, and basement membrane. The tunica intima is surrounded by an internal elastic lamina, which serves as a strength layer to withstand the repeated stretch forces from each cardiac cycle. This is followed by a thick tunica media of smooth muscle and then the thin adventitia (which is present in the proximal cerebral vessels but not distally); there is no external elastic lamina [Figure 1].[6] True aneurysms maintain all three layers of the vessel wall, unlike dissections or pseudoaneurysms which separate one or more layers of the vessel wall and are beyond the scope of this review. The key feature of true aneurysm development is the thinning of the tunica media and the internal elastic lamina, the two strength layers of the vessel.[53]

In vivo animal models and human histologic studies have facilitated our understanding of this process. Meng *et al.* used an *in vivo* dog model to surgically create artificial vessel bifurcations and subsequently measured hemodynamics, WSS, and histologic changes over time.[54] High WSS on the vessel wall was found to promote cellular hyperplasia in response.[53,54] Destructive remodeling ensues, whereby protease activity increases, and inflammatory cascades are triggered, leading to breakdown of the smooth muscle cells in the tunica media and degradation of the internal elastic lamina.[53] Macrophages, lymphocytes, and other inflammatory cells infiltrate the vessel wall, disrupting tight junction and producing reactive oxygen species which further increase vessel wall permeability.[73] Collagen and elastin in the vessel wall are degraded by proteases and replaced with more flexible type I collagen.[22] The now weakened vessel wall cannot tolerate the forces of arterial blood flow and a bleb is formed.

Once an early aneurysm sac has appeared, flow dynamics change dramatically [Figure 1]. Aneurysm sac growth is driven by two processes: high WSS and low WSS cascades. Areas of low flow within the aneurysm sac promote thrombus formation, which is highly inflammatory. This inflammation propagates a vicious cycle of vessel wall breakdown, weakening of the wall, aneurysm sac growth,
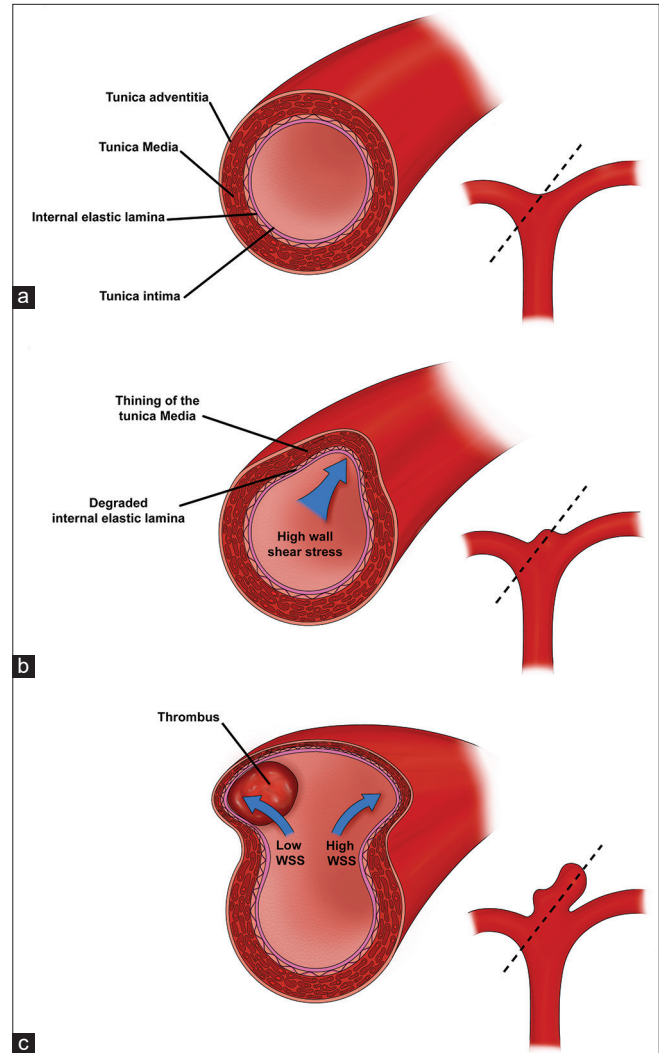

Figure 1: Aneurysm wall pathophysiology and progression. (a) The normal arterial vessel wall consists of an inner endothelial layer (tunica intima) followed by the two strength layers: internal elastic lamina and the smooth-muscle of the tunica media. Dotted line represents the region of the cross-sectional image displayed on the left (b) Regions of high WSS (blue arrow) (e.g., vessel bifurcations and outer wall of curved vessels) trigger an inflammatory cascade, increased protease activity, and breakdown of the tunica media and internal elastic lamina. Loss of integrity of the strength layers of the vessel wall cause outpouching of the vessel wall and formation of an early aneurysm bulge. (c) Enlargement of the aneurysm sac alters the flow dynamics, leading to areas of low WSS and high WSS (blue arrows). Areas of low WSS can develop thrombus, which trigger further inflammation and wall breakdown. Areas of persistent high WSS continue to experience protease activity and inflammation leading to continues degradation of the tunica media and internal elastic lamina.

and further thrombus formation.[22] Other regions of the aneurysm sac may experience persistent high WSS, which further traumatizes the weakened vessel wall, promotes protease activity, damages the endothelium, thins the tunica
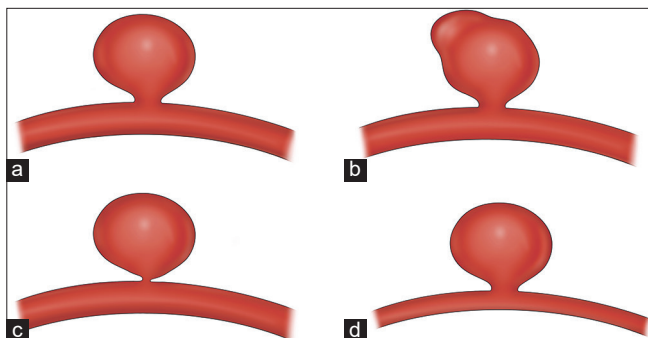
Figure 2: High-risk aneurysm morphologies. (a) Standard saccular aneurysm morphology. (b) Aneurysm with daughter sac. (c) Aneurysm with high aspect ratio. (d) Aneurysm with high size ratio.

media, and promotes aneurysm sac growth.[53] Aneurysm sac growth increases wall tension (a product of pressure, radius, and wall thickness) until the intramural stress reaches the point of failure and the aneurysm ruptures.[22]

RADIOGRAPHIC PREDICTION

MRI is increasingly being used to detect aneurysms at higher risk of rupture. It has been shown that gadolinium enhancement of the aneurysm wall on MRI is associated with areas of low WSS.[92] Given the results of prior studies showing the relationship between low WSS and aneurysm growth and rupture,[22] MRI enhancement may be a useful tool to identify high risk aneurysms. In fact, a prospective study by Vergouwen *et al.* found that 21% of aneurysms with gadolinium enhancement on MRI grew or ruptured over their follow up period (mean = 27 months), whereas 0% of non-enhancing aneurysms grew or ruptured.[86] Understanding that aneurysm growth is associated with higher risk of rupture,[87] one can conclude that MRI enhancement may be predictive of future rupture.

More advanced imaging modalities have shown promise in identifying unstable aneurysms and predicting future rupture. Given the known role of inflammation in the development of the aneurysm sac,[13,73] it is thought that inflammation in the aneurysm wall may indicated instability and is thus the target of new imaging technology.[84] 7T MRI has been shown to identify thinning of the aneurysm wall where WSS and thus rupture risk might be highest.[5] Similarly, high resolution quantitative susceptibility mapping has been used to identify micro hemorrhages from sentinel bleeding that may predict future hemorrhage.[56]

Ferumoxytol is an FDA-approved iron oxide used for iron deficiency anemia, which appears hyperintense on T1 and hypointense on T2 gradient echo sequences. It is cleared by macrophages and is, therefore, useful for identifying regions of active inflammation.[12] Early uptake of the molecule in the aneurysm wall on ferumoxytol-enhanced MRI has been

associated with aneurysm instability and increased risk of rupture.[27]

MACHINE LEARNING (ML)

Due to the complexity of risk stratification for aSAH, some groups have turned to novel data analytics tools to better understand aneurysm rupture risk. ML algorithms, of which there are many types, have revolutionized high throughput data analysis because of their ability to detect patterns in data that traditional statistics may not.[36] ML algorithms are fed either labeled or unlabeled data and iteratively test the algorithm on new input data. ML can be supervised (i.e., trained on labeled input and output data to optimize the algorithm to predict the output of new data) or unsupervised (i.e., trained on unlabeled input data to allow the algorithm to detect new patterns or associations).[51] The model is trained and optimized on a training data set until the parameters that achieve the best performance are determined. The algorithm is validated on external data and can then be easily applied to new data. The iterative nature of ML algorithm training allows for the simulation of large quantities of input data which would otherwise be difficult to achieve with traditional statistics.[51] Furthermore, the unsupervised or partially supervised nature of many algorithms allows ML to detect novel associations without being explicitly programmed with a particular hypothesis in mind.[36,57]

ML is increasingly used throughout medicine, neurosurgery, and has even integrated itself into many aspects of our daily life.[36,71] After being trained on one dataset, it can be applied to new data, making implementation of ML algorithms straightforward and easily scaled. ML algorithms have been shown to identify features associated with rupture that closely match the findings of the landmark natural history studies.[76] Similar to ISUIA and UCAS, random forest and support vector machine models highlighted pcomm, acomm, and posterior circulation aneurysms as most strongly associated with rupture, and also found size to be a clear risk factor.[76] The consistency of these results supports the validity of ML as a reliable tool for analyzing big data. Other studies have shown that ML can predict rupture status based on hemodynamic, clinical, and morphologic parameters[74] and even identify aneurysms on digital subtraction angiography.[26] Additional research is needed to identify a clinical role for ML in the management of patients with unruptured aneurysms.

CONCLUSION

Our understanding of unruptured cerebral aneurysms and their risk of rupture has improved over the past several decades. However, it remains challenging to identify aneurysms at high risk for rupture and to individualize risk

stratification for unruptured aneurysms. Natural history data tells us that size, location, and family history, among other variables, are important for estimating rupture risk. Newer tools such as flow dynamics analysis, *in vivo* aneurysm models, and ML have improved our ability to predict which aneurysms are at higher risk of rupture. Despite significant progress, there remains uncertainty and debate regarding the natural history of unruptured cerebral aneurysms, even among cerebrovascular specialists.[17]

As the cerebrovascular field continues to evolve, we will continue to see the expansion of endovascular treatment options[50,67] and aneurysm treatment availability.[20] For both open and endovascular treatment of aneurysms, complications rates and length of stay have steadily decreased over the past two decades.[34,49] Nonetheless, it is important that we continue to hone our ability to identify which patients warrant treatment in the context of the natural history of unruptured aneurysms and taking into account the new tools that are being developed to stratify risk in these patients.

Disclosures

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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