Rupture prediction of intracranial aneurysms: a nationwide matched case-control study of hemodynamics at the time of diagnosis

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OBJECTIVE Hemodynamic rupture predictors in intracranial aneurysms (IAs) must be investigated in prerule aneurysms, because rupture might significantly alter aneurysm hemodynamics. Both clinical and aneurysmal factors influence hemodynamics, possibly confounding results in unmatched patient materials. The authors aimed to identify hemodynamic variables at the time of diagnosis that could be associated with IA rupture.

METHODS A nationwide matched case-control study of IA hemodynamics at the time of diagnosis was performed. Twelve IAs that later ruptured were matched 1:2 with control aneurysms that remained unruptured during a median follow-up time of 4.5 years (interquartile range 3.7–8.2 years). Cases and controls were matched by aneurysm location and size, and patient sex and age. Hemodynamic parameters were obtained from computational fluid dynamics simulations.

RESULTS The low shear area (LSA) was significantly higher in cases than in controls in univariate analysis ($p = 0.041$). Minimum logarithmic wall shear stress, averaged logarithmic wall shear stress, pressure loss coefficient, and inflow concentration index showed a tendency to be associated with later rupture ($p = 0.09, 0.14, 0.15$, and 0.18 , respectively). The LSA remained statistically significant in multivariable analysis ($p = 0.030$).

CONCLUSIONS Hemodynamics at the time of diagnosis are different in aneurysms that later rupture than in those that remain unruptured. Increased LSA might be an early predictor of rupture.

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KEY WORDS intracranial aneurysm; hemodynamics; computational fluid dynamics; subarachnoid hemorrhage; rupture; vascular disorders

SUBARACHNOID hemorrhage (SAH) is an important cause of premature death and socioeconomic cost.^{13,25} Saccular intracranial aneurysms (IAs) are the cause of 85% of SAH.³⁰ These IAs are found in approximately 2%–3.5% of the adult population, but the individual rupture risk is uncertain.^{21,31} Prophylactic surgical or endovascular treatment of aneurysms minimizes the chances of future rupture, but involves considerable risk. Wider use and availability of radiological imaging of the brain has increased the rate of incidentally discovered IAs. High-grade guidelines for the management of unruptured IAs

are lacking,²⁷ warranting improved methods for rupture risk assessment. Evaluation of aneurysm hemodynamics can possibly aid treatment decisions, because studies show that the hemodynamics of ruptured aneurysms are different from those for unruptured lesions.³ Frequently studied hemodynamic parameters include derivatives of wall shear stress (WSS), such as oscillatory shear index (OSI) and low shear area (LSA),⁵ and parameters related to the flow phenotype, such as pressure loss coefficient (PLC), inflow concentration index (ICI), and viscous dissipation ratio (VDR).^{4,28}

ABBREVIATIONS ACoA = anterior communicating artery; CFD = computational fluid dynamics; IA = intracranial aneurysm; ICA = internal carotid artery; ICI = inflow concentration index; IQR = interquartile range; LSA = low shear area; MCA = middle cerebral artery; OSI = oscillatory shear index; PCoA = posterior communicating artery; PHASES = population, hypertension, age, size of aneurysm, earlier SAH from another aneurysm, site of aneurysm; PLC = pressure loss coefficient; SAH = subarachnoid hemorrhage; VDR = viscous dissipation ratio; WSS = wall shear stress.

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Aneurysms are most likely to grow irregularly,¹ and there is increasing evidence that the rupture itself might significantly alter aneurysm geometry and hemodynamics.^{14,24,26} Therefore, only investigations of aneurysms before rupture can truly answer which factors predict rupture. Reports of up to 13 cases before rupture have emerged,^{6,18,24,28} in which aneurysms were evaluated at various time spans before rupture. None of these are matched on both clinical and aneurysmal factors, and are thus prone to confounding. The aim of this study was to identify hemodynamic factors at the time of diagnosis of unruptured aneurysms that are associated with subsequent rupture.

Methods

Study Design and Patient Selection

Norway has a 3-level hierarchical hospital structure. All university clinics (4 centers) with a neurosurgical department treating IA and SAH participated in the study, thus covering the whole population of Norway (5 million people).

The study is a matched case-control study, based on retrospective data collection in the time period from 2003 to 2013. For cases, we identified patients who presented with an unruptured saccular IA that subsequently ruptured. For controls, we identified matching patients with saccular IAs whose aneurysms did not rupture during follow-up.

We recorded the following: date of birth; date of diagnosis for unruptured aneurysm; aneurysm location and parent artery relation (bifurcation/sidewall aneurysm); date admitted with SAH for cases; the reason for the aneurysm being conservatively managed; and known risk factors for SAH—such as hypertension, ethnicity, smoking status, connective tissue disease, polycystic kidney disease, family history, or prior SAH. We also calculated the PHASES (population, hypertension, age, size of aneurysm, earlier SAH from another aneurysm, site of aneurysm) score.¹¹ Patients were excluded if they had undergone previous treatment of the aneurysm of interest, or if the image quality precluded segmentation. Furthermore, cases were excluded if there were multiple aneurysms of which the ruptured one was difficult to identify, and control patients were excluded if they died of an unknown cause during follow-up.

For each case we selected 2 controls who were matched on aneurysm location and size, as well as patient sex and age. The initial matching factor was location—if this factor could not be matched, the patient was excluded. Further matching was done in the order of the factors listed above.

The study was approved by the Northern Norway Regional Committee for Medical Research Ethics, which found the study to be exempt from patient consent. We report the findings according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.³²

Computational Simulation

We retrieved the first available cerebral angiography study for each patient to perform simulations using the data obtained at the time of diagnosis. Segmentation and meshing of the images was done using the Vascular

Modeling ToolKit (<http://www.vmtk.org>). All segmented models were inspected by an experienced neurosurgeon to ensure consistency with the original angiography.

We imposed a fully developed pulsatile Womersley flow profile at the model inlets.¹² At the outlets, we scaled the flow according to the principle of minimal work (Murray's law). In segmented models in which the posterior communicating artery (PCoA) was not merged to the posterior circulation, we assumed zero flux. Walls were assumed to be rigid and impermeable. We assumed blood to behave as a Newtonian fluid.⁸ The Navier-Stokes simulation equations were solved and postprocessed with the open source softwares cbcflow and cbcpost (https://bitbucket.org/simula_cbc/), based on the open source finite element library (i.e., FEniCS).¹⁹ To properly resolve the high-frequency flow dynamics, we resolved the simulations with a temporal resolution of 0.04 msec.

The engineering team conducting segmentation and simulation was blinded to the patients' status as case or control, and to any clinical data. The Supplementary Methods provide additional details about patient selection and computational simulation.

Parameter Definitions

The Supplementary Table specifies abbreviations, mathematical definitions, and pragmatic explanations for each studied parameter. The OSI and LSA are derivatives of WSS.⁵ The PLc, ICI, and VDR are related to the flow phenotype.^{4,28}

Statistical Analysis

Prior to analyses, the distribution of each continuous variable was assessed visually with Q-Q-plots and numerically with the Shapiro-Wilk test. Parametric variables were reported as means with SDs. Nonparametric variables were reported as medians with interquartile range (IQR). Balance between cases and controls was assessed using the Student t-test for parametric variables, and the Wilcoxon rank-sum test for nonparametric variables. Categorical variables were compared using the chi-square test.

Matched case-control analysis was performed using conditional logistic regression, which is appropriate for this study, with 2 controls for each case.²² For multivariable regression, backward stepwise elimination of independent variables with a threshold significance level of > 0.2 was used to select the final multivariable model. The data were analyzed with Stata for Mac (version 14, StataCorp LP). A p value of < 0.05 was assumed to be statistically significant.

Results

Study Population and Case Matching

The initial search identified 43 patients with confirmed aneurysmal SAH, originating from saccular aneurysms that were known prior to rupture and had been treated conservatively. Twenty cases were excluded because matching was not accomplished; of these, 18 had aneurysms larger than 10 mm. Eight cases were excluded because of insufficient image quality, and 3 were excluded because of in-

sufficient image quality in the available controls. Each of the remaining 12 patients were successfully matched to 2 control patients with a confirmed saccular IA that was neither treated nor ruptured during follow-up.

The cases consisted of 4 anterior communicating artery (ACoA; 33.3%), 7 middle cerebral artery (MCA; 58.3%), and 1 PCoA (8.3%) aneurysm. There were 4 (33.3%) men among cases, and 9 (37.5%) men among controls ($p = 0.81$). For cases, the median time from diagnosis to rupture was 3.4 years (IQR 1.6–6.3 years). For controls, the median time from diagnosis to death or end of follow-up was 4.5 years (IQR 3.7–8.2 years). The mean PHASES score was 6.4 (SD 3.0) for cases and 6.5 (SD 2.9) for controls ($p = 0.82$). Table 1 provides baseline characteristics of cases and matched controls.

Hemodynamic Parameters Associated With Future Rupture

In the univariate analysis, LSA was the only parameter statistically significantly associated with future rupture ($p = 0.041$) (Table 2). Minimum logarithmic WSS, averaged logarithmic WSS, PLc, and ICI showed a tendency to be associated with rupture ($p = 0.09, 0.14, 0.15$, and 0.18 , respectively). Figure 1 shows the distribution of these 5 parameters for cases and controls, and Fig. 2 visualizes WSS and LSA for all case and control aneurysms.

In the multivariable analysis, LSA ($\beta = 8.72$ [95% CI

TABLE 1. Comparison of baseline characteristics between cases and matched controls

Characteristic	Cases, n = 12	Controls, n = 24	p Value*
Patients			
Male sex	4 (33)	9 (38)	0.81†
Mean age in yrs	64.4 ± 9	63.5 ± 10	0.80†
Current smoker	6 (50)	10 (42)	0.64
Medical Hx			
Hypertension	9 (75)	19 (79)	0.78
Family Hx of aneurysms or SAH	1 (8)	3 (13)	0.71
Previous SAH	1 (8)	0 (0)	0.15
Multiple aneurysms	3 (25)	8 (33)	0.61
Treatment of another aneurysm	1 (8)	1 (4)	0.61
Aneurysms			
Location			
ACoA	4 (33)	8 (33)	1.0†
MCA	7 (58)	14 (58)	
PCoA	1 (8)	2 (8)	
Mean max diameter in mm	8.34 ± 3.41	8.15 ± 3.40	0.87†
Mean vol in mm ³	177.9 ± 219.4	168.8 ± 250.8	0.92†
Mean PHASES score	6.4 ± 3.0	6.5 ± 2.9	0.82

Hx = history; max = maximum.

Continuous, parametric variables are reported as the mean ± SD. Dichotomous and categorical variables are reported as number (%).

* Statistical significance was set at $p < 0.05$.

† Matched variables.

TABLE 2. Univariate analysis of hemodynamic parameters in cases and controls

Parameter	Mean Value (± SD)		p Value
	Cases	Controls	
Min WSS	0.62 (0.66)	0.84 (0.69)	0.39
Time- & space-avg WSS	6.33 (4.70)	7.50 (3.42)	0.41
Max WSS	39.6 (23.5)	55.2 (54.1)	0.39
Min logarithmic WSS	-1.17 (1.39)	-0.47 (0.79)	0.09
Avg logarithmic WSS	0.96 (1.01)	1.37 (0.53)	0.14
OSI	0.046 (0.039)	0.039 (0.025)	0.47
LSA	0.15 (0.16)	0.06 (0.07)	0.041
PLc	1.25 (0.31)	1.48 (0.45)	0.15
ICI	2.28 (1.12)	1.90 (1.17)	0.18
SCI	4.07 (2.38)	4.31 (2.44)	0.76
VDR	0.31 (0.23)	0.46 (0.63)	0.49

Avg = averaged; min = minimum; SCI = shear concentration index.

Boldface type indicates statistical significance ($p < 0.05$).

0.85–16.59], $p = 0.030$) and ICI ($\beta = 1.13$ [95% CI -0.30 to 2.55], $p = 0.12$) were retained in the conditional logistic regression model. Their p values remained almost constant when adjusting for the matching variables patient sex, age, aneurysm location and size, as well as smoking status, previous SAH, hypertension, and PHASES score (data not shown).

Discussion

This study indicates that, already at the time of diagnosis, unruptured aneurysms that later ruptured had statistically significantly higher LSAs than aneurysms that did not rupture. To our knowledge, this study is one of very few to investigate hemodynamics in prerule aneurysms, and the first that matches cases and controls on both patient and aneurysmal characteristics.

Isolating Hemodynamic Properties

Unmatched studies reporting WSS differences between ruptured and unruptured aneurysms might simply observe the effect of other factors on hemodynamics. Lauric et al. observed a strong negative correlation between WSS and aneurysm volume ($R^2 = 0.97$).¹⁶ The importance of matching based on clinical factors is illustrated in a prospective study that estimated the joint hazard ratio for aneurysm rupture associated with smoking and hypertension to be 13.3 (95% CI 6.9–25.4).¹⁷

Future tools to aid patient-specific treatment choices must probably encompass both clinical and aneurysmal factors to increase predictive power.⁷ However, to understand the contribution of hemodynamics to the overall rupture risk, a matched study reducing possible confounding from aneurysm size and location, and patient sex and age is essential.

Prerule Hemodynamics

Our study shows that larger areas of low WSS and a concentrated inflow jet might constitute some of the ear-

FIG. 1. Boxplot showing graphic representation of the distribution of selected hemodynamic parameters in cases and controls. LnWSS = averaged logarithmic WSS; MinLnWSS = minimum logarithmic WSS.

liest detectable hemodynamic patterns in an aneurysm's natural history from formation to rupture.

The friction between blood and endothelial cells induces mechanobiological signaling essential for normal arterial wall proliferation. Low or stagnant flow causes an inflammatory response in the vascular wall, promoting atherogenesis and leukocyte infiltration.²⁰ In histological analyses of ruptured and unruptured aneurysms, Frösen et al. found that ruptured aneurysms were characterized by inflammatory infiltration as well as apoptosis and degeneration of the wall matrix.¹⁰ However, alterations in blood–endothelial signaling cannot serve as a complete explanation. Frösen et al. also found that 62% of ruptured aneurysms lacked endothelium, compared with 30% of unruptured aneurysms. In addition to shear stress, cyclic pressure induces stress in the vascular wall sensed by the deeper smooth muscle. In computational fluid dynamics (CFD) studies, this mechanotransduction is not subject to study because walls must be assumed rigid. Other methods, such as fluid structure interaction analyses, can investigate forces other than shear stress, because they are not limited to the rigid wall assumption. However, fluid structure interaction analysis introduces additional assumptions into the model, and has higher computational resource requirements.

Our findings are in accordance with other studies indicating that hemodynamic parameters might predict rupture. Takao et al. found significantly lower PLc among 13 internal carotid artery (ICA) and MCA aneurysms that later ruptured, compared with 87 control aneurysms. The 7 ICA aneurysms in the study also had lower minimum

WSS.²⁸ However, the authors did not report patient characteristics, and although the aneurysms belonged to the same size category, the mean size was larger for aneurysms that later ruptured than for those that did not. Duan et al.⁶ matched 6 patients with PCoA aneurysms that later ruptured to 4 controls each, based on clinical factors. The aneurysms that later ruptured showed larger LSA and lower normalized WSS. Case and control aneurysms were not matched for size, and the mean size was significantly larger for the aneurysms that later ruptured (mean 7.8 mm) than for those that did not (mean 4.7 mm).⁶

Aneurysm growth and aneurysm rupture are considered to be closely related. Importantly, Brinjikji et al. also found statistically significantly larger LSA in 12 aneurysms that grew for at least 1 year, compared with 12 matched, stable aneurysms.²

Limitations of the Study

Because all patients in this study were treated conservatively, they can be assumed to be older or to have more comorbidities than the general population of patients with aneurysms, or the aneurysms may have seemed more benign to the responsible clinicians. Matching can further decrease generalizability, but increases internal validity and statistical power.⁹ Of note, the matching caused large aneurysms to be underrepresented, because patients with such aneurysms are quickly treated and not readily available as controls. However, this selection bias caused a relative emphasis on small- and moderate-sized aneurysms, in which decision support is needed the most. We also be-

FIG. 2. Visualization of WSS and LSA for all case and control aneurysms, grouped by location. The WSS is represented by a color scale ranging from *blue* for $WSS < 1.0$ Pa, to *red* for $WSS > 10$ Pa. Areas of low shear are colored *gray*, and represent areas of the dome where the average WSS is below 10% of the average WSS in the parent artery. ACOM = ACoA; PCOM = PCoA.

lieve that the matching design is highly warranted to control for known confounders of hemodynamic parameters. More study patients are needed to allow for definite conclusions. Conservatively managed aneurysms that are followed until rupture or with a long follow-up time without rupture are rare, but the statistical power of the present

study is increased because we managed to match 2 controls to each case. Whether any of the control aneurysms would eventually rupture during further follow-up is unknown. If that were the case, the findings of this study suffer from a dilution bias in which effect sizes are larger in a general group of patients with aneurysms than in our study

sample. None of the clinical risk factors such as previous SAH, multiple aneurysms, and smoking status were statistically significantly different between cases and controls. The retrospective nature of the study reduces the accuracy of the patient risk factors recorded, and we cannot rule out any selection bias from these factors.

Previous CFD studies have revealed partially conflicting results.¹⁴ The segmentation process introduces uncertainty, and the computational simulation depends on assumptions of given boundary conditions, fixed walls, and rheology model, as well as the numerical methods used.²⁹ Still, CFD is increasingly used within the field of biomechanics, and adds to a growing knowledge about the role and importance of hemodynamic forces in vascular pathophysiology.

Follow-up of conservatively managed aneurysms is still required, because our findings are insufficient for a conclusive rupture prediction at the time of diagnosis. Future studies investigating the hemodynamic trends at several points from diagnosis to rupture can shed light onto which hemodynamic changes are causal to later hemodynamic differences. Furthermore, improved simulation methods incorporating more patient-specific input variables might minimize simulation setup uncertainties. Despite limitations, however, this study presents long-awaited data on the association between prerule rupture hemodynamics and future rupture risk.

Conclusions

The hemodynamics of unruptured aneurysms at the time of diagnosis are different in aneurysms that later rupture than in those that remain unruptured, even with rigorously matched case and control aneurysms. Increased LSA might be an early predictor of rupture.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Skodvin, Isaksen. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Skodvin. Statistical analysis: Skodvin. Administrative/technical/material support: all authors. Study supervision: Skodvin, Isaksen.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Methods and Table. <https://thejns.org/doi/suppl/10.3171/2017.5.JNS17195>.

Previous Presentations

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