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The impact of hypertension and nicotine on the size of ruptured intracranial aneurysms

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Background and Purpose

The goal of the present study was to analyze retrospectively the impact of risk factors for subarachnoid hemorrhage (SAH) on the size of ruptured intracranial aneurysms in order to identify variables which might influence the discrepancy between average sizes of ruptured and unruptured aneurysms.

Methods

The records and angiographies of 373 patients treated at our center due to aneurysmal SAH between 2004 and December 2008 were retrospectively analyzed. Modifiable and non-modifiable risk factors for SAH were correlated with exact measurement of aneurysm size using 3-dimensional rotational digital subtraction angiographies (3D-DSA).

Results

Average maximum aneurysm diameter in patients with combined history of hypertension and **cigarette smoking** was 5.47 ± 3.22 mm [95% CI 4.71-6.24], thus significantly smaller ($p < 0.001$) than in patients with hypertension only (6.27 ± 3.28 mm, 95% CI 5.75-6.78), with **cigarette smoking** only (7.61 ± 4.29 mm, 95% CI 6.43-8.79) and patients with no history for risk factors (8.08 ± 4.73 mm, 95% CI 6.96- 9.21). Odds ratio for aneurysm size less than 7mm in patients with combined hypertension and **cigarette smoking** was 3.63 [95% CI 1.78-7.42], 3.09 [95% CI 1.95-4.92] in patients with hypertension only and 1.02 [95% CI 0.64-1.62] in patients with **cigarette smoking** only.

Conclusions

The present analysis demonstrates a distinct correlation between hypertension, smoking and the size of ruptured aneurysms in SAH patients. Arterial hypertension and **cigarette smoking** appear to destabilize cerebral aneurysms growth. Our data strongly suggests that these factors should also be considered, when treatment indications for small unruptured aneurysms are discussed.

INTRODUCTION

Despite extensive, multimodal development of treatment strategies, aneurysmal subarachnoid hemorrhage (SAH) remains a disease with high morbidity and mortality, causing case fatality rates between 25 and 50%. ^[1] Due to the poor prognosis of aneurysmal SAH, the natural history of unruptured intracranial aneurysms (UIAs) and their treatment indications remain important questions. Prospective studies on UIAs have identified aneurysm size and location as key risk factors among others such as Japanese/Finnish descent, age and female gender. ^[2-4] Furthermore, retrospective studies have previously analyzed the impact of risk factors on the severity of SAH and it was found that hypertension and **cigarette smoking (i.e. nicotine use)** as well as age and gender are significant risk factors for SAH and correlate with unfavorable outcome after SAH. ^[5-10]

The goal of the present study was to retrospectively analyze the correlation of age, gender, location of the aneurysm, history of hypertension and/or **cigarette smoking** with the size of ruptured aneurysms in a large patient cohort.

ABBREVIATIONS:

ACA= Anterior cerebral artery; AComA= Anterior communicating artery; BA= Basilar artery; ICA= Internal carotid artery; MCA= Middle cerebral artery; PericA= Pericallosal artery; PComA= Posterior communicating artery; PICA= Posterior inferior cerebellar artery; VA= Vertebral artery

MATERIAL AND METHODS

We collected retrospectively data from patients suffering from SAH who were admitted to the Department of Neurosurgery at Düsseldorf University Hospital (Germany) between January 2004 and December 2008. The inclusion criteria comprised: 1) aneurysmal SAH and 2) digital subtraction angiography (DSA) to allow exact measurements. The exclusion criteria were defined as; 1) nonaneurysmal SAH, 2) inadequate diagnostic quality, 3) fusiform, traumatic or mycotic aneurysms, and 4) arteriovenous malformation associated aneurysms. SAH was verified by computerized tomography (CT), magnetic resonance imaging (MRI) or spinal tap.

Aneurysm size, configuration and location were assessed by reviewing the initial 3-dimensional rotational digital subtraction angiographies (3D-DSA). Exact aneurysm sizes were measured by an independent investigator and defined as the largest diameter, whereas aneurysm configuration was defined as even or lobulated. Aneurysm size was categorized in accordance to the classification of the International Study on Unruptured Intracranial Aneurysms (ISUIA) into A) less than 3 mm B) 3-7 mm C) 8-12 mm D) 13-25 mm and E) greater than 25 mm.^[4] If patients harbored multiple intracranial aneurysms, the most probable ruptured aneurysm with regards to SAH distribution, aneurysm size and configuration was included for further analysis.^[11,12] Furthermore, the major known risk factors for SAH, such as the history for hypertension and **nicotine use**, as well as the grading according to the Fisher and World Federation of Neurological Surgeons (WFNS) classification, were retrieved from the records.^[13,14] For statistical analysis patients were categorized into 4 different age groups: A) less than 30 years B) 31-50 years C) 51-70 years D) greater than 70 years.

Information regarding the long-term history for hypertension and cigarette smoking was obtained from the patient or a surrogate.

In accordance to previous studies, hypertension was defined positive in patients with a definite long-term history of hypertension with systolic blood pressures (BP) greater than 160 mmHg and/or diastolic blood pressure greater than 95 mmHg. There was no differentiation between patients with medically treated primary or secondary hypertension or those with untreated hypertension. Patients with a history of borderline hypertension (160/95mmHg>BP>140/95mmHg) were not considered as hypertensive.^[15,16]

Cigarette smoking was included for further risk analysis only for those patients who were frequent and current smokers at the time of admission to our hospital. The individual amount as well as the duration of cigarette smoking were not differentiated due to the difficulty to obtain the history within this patient population and therefore patients were classified as ever or never smokers.

Patients were categorized according to their individual risk profile in one of the following risk groups:

1) no risk factor 2) nicotine alone 3) hypertension alone and 4) nicotine and hypertension.

The statistical analysis was performed using SPSS software v. 15.0.1 (© SPSS Inc. Chicago/Illinois, USA). Differences between groups were analyzed using Student's t-test for metric variables and

nonparametric tests for ordinal or nominal scaled variables. Analysis of variance (univariate ANOVA) was followed by Bonferroni post-hoc test to further determine individual differences between analyzed groups. Statistical significance was defined as $p < 0.05$ (CI 0.95).

RESULTS

Patient and vascular characteristics

Between January 2004 and December 2008 a total of 456 patients with aneurysmal subarachnoid hemorrhage were admitted to our department. Eighty-three (83) patients of this patient population were excluded retrospectively from further analysis due to the aforementioned exclusion criteria.

Table 1 Patients characteristics

Patients characteristics for n=373 patients

Age mean	53.55 ± 12.7 years, range 16 – 89 yrs		
Age groups (years)			
	<30	10	(2.7%)
	31 – 50	150	(40.2%)
	51 – 70	169	(45.3%)
	>70	44	(11.8%)
Gender			
	M : F	143 (38.3%)	: 230 (61.7%)

Grading upon admission for n=373 patients

WFNS			
	I	130	34.9%
	II	82	22.0%
	III	25	6.6%
	IV	47	12.6%
	V	89	23.9%
Fisher			
	0	12	3.2%
	1	28	7.5%
	2	33	8.9%
	3	127	34.1%
	4	173	46.4%

Risk factor incidence for n=352 †

No risk factors	70	19.9%
Nicotine only	53	15.0%
Hypertension only	159	45.2%
Nicotine + Hypertension	70	19.9%

†= 21 patients excluded due to incomplete risk factor profile

Among the entire cohort mean aneurysm size was 6.86 ± 4.26 mm (range 0.7 – 40 mm). Aneurysm sizes were distributed as follows: a) 3mm or less: 18.7 % b) 4-7 mm: 53.9 % c) 8-12 mm: 18.0 % d) 13-25mm: 8.8% e) larger than 25mm: 0.5%. Eighty-eight percent (87.7%) of the aneurysms smaller than 7 mm were localized in the anterior and 12.3% in the posterior circulation. Of the aneurysms larger than 7mm, 79.1% were localized in the anterior circulation versus 20.9% in the posterior circulation. Detailed distribution of aneurysm with regard to parent vessel and size is shown in Table 2. Aneurysm shape was lobulated in 59.1 %, whereas 40.9 % of the aneurysms were even. Fifty-six percent (55.6 %) of the patients were treated surgically and 44.4 % by- endovascular technique.

Table 2 Aneurysm size distribution

Aneurysm size	<7mm	>7mm	N=
Localisation			
AComA	107 (77.0%)	32 (23.0%)	139
BA	7 (25.9%)	20 (74.1%)	27
ACA	5 (100%)	0	5
PComA	29 (69.0%)	13 (31.0%)	42
PERICA	8 (57.1%)	6 (42.9%)	14
VA	6 (75%)	2 (25%)	8
ICA	15 (53.6%)	13 (46.4%)	28
MCA	51 (58%)	37 (42%)	88
PICA	14 (73.7%)	5 (26.3)	19
Else	2	1	3
Anterior circulation	214 (87.7%)	102 (79.1%)	316 (84.7%)
Posterior circulation	30 (12.3%)	27 (20.9%)	57 (15.3%)
N=	244	129	373

Risk group analysis

21 patients were subsequently excluded from the risk group analysis due to incomplete information on the history for hypertension or nicotine consumption.

After stratification into the 4 different risk groups (no risk factors, **cigarette smoking** only, hypertension only and **cigarette smoking** combined with hypertension), the only significant difference between the risk groups with regards to patient characteristics was mean age. Patients suffering from hypertension alone, were significantly ($p < 0.001$) older (56.35 ± 12.75) than smokers alone (49.47 ± 10.08), patients with a combined **cigarette smoking** and hypertension history (52.23 ± 10.23) and patients with no risk factors (50.38 ± 13.93).

Gender-specific risk factor distribution did not differ significantly among males and females ($p = 0.355$). There was no significant difference regarding the distribution of initial WFNS ($p = 0.078$) and Fisher ($p = 0.338$) grading between the risk groups.

The correlation of aneurysm size, location and shape, with systemic risk factors revealed the aneurysm size being the most dependent parameter. Mean aneurysm size in patients with a combined history of hypertension and **cigarette smoking (i.e. nicotine)** was 5.47 ± 3.22 mm, [95% CI 4.71-6.24], thus significantly smaller ($p < 0.001$) than in patients with hypertension only (6.27 ± 3.28 mm, 95% CI 5.75-6.78). Patients with a history for **cigarette smoking** had only slightly smaller ruptured aneurysms (7.61 ± 4.29 mm, 95% CI 6.43-8.79), compared to patients with no risk factors (8.08 ± 4.73 mm, 95% CI 6.96- 9.21). The difference between average aneurysm sizes in patients with no risk factors and smoking history was not significant ($p = 0.56$) (Figure 1).

Figure 1

Table 3 Odds ratio for ruptured aneurysm size lesser than 7 mm

Odds ratio for ruptured aneurysm size < 7mm	OR	95% CI
Nicotine + hypertension	3.63	1.78 – 7.42
Hypertension alone	3.09	1.95 – 4.92
ACoMA	2.37	1.48 – 3.79
Male	1.08	0.69 – 1.67
Nicotine alone	1.02	0.64 – 1.62

OR=Odds ratio; CI= Confidence interval

Aneurysm configuration ($p=0.304$) and localization ($p=0.536$) was not significantly correlated to the presence of risk factors.

The correlation analysis of aneurysm location and size demonstrated a significant difference in mean aneurysm size only for the ACoMA as compared to BA, ICA and MCA (Figure 2).

Figure 2

Stratification of patients in age groups and correlation with risk factors demonstrated a possible trend:

Within the age groups, patients without risk factors had larger aneurysms than patients with hypertension. This difference was even more pronounced in patients with additional smoking history. Furthermore, within each risk group, older patients had larger ruptured aneurysms than their younger counterparts. Due to small group sizes and therefore large variance within each risk/age group, statistical significance with regard to the subgroups could not be obtained (data not shown).

DISCUSSION

The recommendation for treatment of UIAs currently relies to a great extent on the results of the ISUIA trial, which demonstrated that aneurysm size and location are the major predictive factors of rupture risk.^[4] For example, the rupture risk of UIAs in the anterior circulation smaller than 7mm was estimated as 0.2 percent per year. The risk of rupture and average sizes of UIAs are often challenged by retrospective studies on ruptured intracranial aneurysms, which illustrate that the majority of ruptured intracranial aneurysms in large SAH cohorts are significantly smaller than 7mm.^[17] Although prospective and retrospective studies must be compared carefully, the discrepancy between average sizes of unruptured and ruptured aneurysms remains striking and unexplained. Despite the currently accepted treatment strategies following the ISUIA trial controversies about the influence of systemic risk factors for rupture of UIAs such as age, gender, hypertension and **cigarette smoking** still exist.^[2,6,10,14,15] The goal of the present analysis was to provide data on the influence and importance of systemic risk factors for aneurysm growth and rupture.

On average, the ruptured aneurysms of the actual sample measured 6.86 ± 4.26 mm (range 0.7-40mm). 73% of all ruptured aneurysms measured less than 7mm in diameter, and 88% of the anterior circulation aneurysms measured less than 7mm. Similar results have been described before.^[18]

With regard to risk factors for aneurysm rupture, mainly patient age and female gender have been reported in the literature as non-modifiable risk and smoking status and hypertension as additional modifiable risk factors.^[3] Our analysis investigated possible correlations of these factors with the size of ruptured aneurysms. Multivariate correlation analysis did not show such a correlation for age or gender, but a **significant correlation for cigarette smoking** and hypertension. Hypertensive patients had significantly smaller ruptured intracranial aneurysms (6.27 ± 3.28 mm) than normotensive, non-smoking patients (7.61 ± 4.29 mm). Furthermore cigarette smoking in combination with hypertension significantly amplified the effect of hypertension on aneurysm size (5.47 ± 3.22 mm).

Consequently, the probability of harboring an aneurysm less than 7mm was significantly higher in smoking patients suffering from hypertension (OR 3.63, 95% CI 1.78-7.42) and also non-smoking hypertensive patients (OR 3.09, 95% CI 1.95-4.92) in comparison with normotensive smoking patients (OR 1.02, 95% CI 0.64-1.62) or normotensive non-smokers (OR 1). The amplifying

tendency of concomitant hypertension and nicotine consumption on the reduction of aneurysm size was observed also within the age groups. However, due to the small subgroups and large variation statistical analysis did not reach significance level.

This finding is in contrast with a previous report demonstrating that that smoking is associated with the development of large middle cerebral artery aneurysms.^[19] On the basis of the current available data, it cannot be excluded that middle cerebral aneurysms have different dynamics than aneurysms of other locations, as a corresponding subgroup analysis is impossible because of insufficient numbers of data.

The prevalence of hypertension of 45.2 % in our patient population is very similar to the figures of comparable studies.^[20,21] However, the impact of hypertension on aneurysm size has not been further characterized in these previous analyses.

Although deduction from our results to UIAs must be made cautiously, one could conclude that UIAs in hypertensive patients and smokers might have an increased risk of rupture below the critical size as defined by ISUIA, which could suggest that treatment of UIAs smaller than 7mm in hypertensive patients and smokers may be beneficial. Whether medical treatment of hypertension and/or cessation of smoking could also lead to restabilization of UIAs is currently a matter of speculation. The pathophysiology of an increased rupture risk of cerebral aneurysms due to risk factors such as hypertension and/or nicotine remains incompletely understood at present. A hypertension-induced damage of the aneurysmal wall has been described due to occlusion of the vasa vasorum and a disturbance in the synthesis of elastin and collagen.^[22] Furthermore, hypertension was described to cause a misbalance of the arterial vessel wall homeostasis due to impaired nitric oxide and prostacyclin production resulting in a loss of elasticity and increased exposition of the aneurysm to wall shear stress.^[23] Smoking, on the other hand, affects vascular homeostasis and structural integrity. Inactivation of α -1-antitrypsin and subsequent impact on aneurysm formation may be a possible mechanism.^[24-26]

We observed that older patients had larger aneurysms, which could be explained through a selection effect: On average, aneurysms appear to grow during lifetime.^[27,28] It cannot be excluded, however, that aneurysms in older patients enlarge faster.^[28]

Lastly, our data demonstrated that AComA aneurysms were significantly smaller than aneurysms of other parent arteries. This phenomenon has been previously described in other studies.^[29,30] There is no generally accepted explanation. One could only speculate that the average aneurysm diameter at the time of rupture is related to the diameter of the parent artery.

The major limitation of the current study to be mentioned is its retrospective nature. In addition, we did not differentiate between medically treated and untreated hypertension.^[15,31] Despite these limitations the present study has, to the best of our knowledge, demonstrated a correlation of the size of ruptured aneurysms and systemic risk factors for the first time.

SUMMARY

The present retrospective analysis demonstrates that hypertension and smoking have a significant influence on the size of ruptured aneurysms in patients suffering from SAH. For patients presenting with a ruptured aneurysm, the size of that ruptured aneurysm is almost 4 times more likely to be less than 7 mm, in those patients that have a history of hypertension and for smoking. As a consequence our data strongly suggests that patients with these risk factors have a lower threshold of aneurysm rupture than patients without risk factors. Therefore the history of hypertension and cigarette smoking should be considered in the assessment of treatment of small unruptured intracranial aneurysms.

FIGURE LEGENDS

Figure 1 Impact of risk factors on ruptured aneurysm size. (** p<0.001)

Figure 2 Ruptured aneurysm size variation

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COMPETING INTERESTS:

None declared

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