Aneurysmal subarachnoid hemorrhage (aSAH) is bleeding into the subarachnoid space from a cerebral aneurysm, defined as a thin-walled outpouching on one of the cerebral arteries. SAH represents 0.8% to 15% of strokes and has a low incidence of 0.03 to 0.2 per 1000 person-years with a female preponderance. However, SAH usually occurs at a relatively young age and has a high 1-month case fatality rate (32%), leading to a high loss of potential life years. Subsequently, primary prevention of aSAH by identifying and addressing modifiable risk factors has been a focus of research for decades.

Although the main focus has been on identifying modifiable risk factors, less attention has been given to the underlying pathogenic mechanisms.

We, therefore, conducted a literature review to identify recognized modifiable risk factors for aneurysm development and aSAH and examined the pathogenesis by which these individual risk factors are suspected to contribute to aneurysm development and rupture.

Methods

We conducted MEDLINE searches using the PubMed database for relevant articles published between 1980 and 2012 in English. We used search words such as Cerebral Arteries [Majr], Subarachnoid Hemorrhage [Majr], or Intracranial Aneurysm [Majr] combined with Medical Subject Headings (MeSH) search words for different risk factors such as Alcohol drinking, Ethanol, Estrogens, Menopause, Hypertension, Smoking, Cholesterol, Diabetes Mellitus, and Cocaine. The first search was performed in June 2012 and the last in December 2012. Articles were screened by title and abstract, and if relevant the article was reviewed in its entirety. References lists in key publications were hand-searched to reveal additional relevant studies.

Initially, the focus was on epidemiological studies that helped establish the different modifiable risk factors for aSAH. Inclusion criteria comprised: (1) SAH analyzed as a separate stroke entity, although in some studies SAH was part of a hemorrhagic stroke group, and (2) diagnosis of SAH or aneurysm confirmed by CT, angiography, or at autopsy. The risk association is illustrated statistically with relative risk (RR), odds ratio (OR), and population-attributable risk.

Having established the individual risk factors, each was examined with a focus on the pathogenesis of aneurysm development and rupture. This was done by PubMed searches using the same search words as above. Books on vascular pathology were consulted for information on the effects of modifiable risk factors. We focused on studies investigating cerebral aneurysms or aSAH. Furthermore, relevant articles concerning pathological effects of ≥1 risk factors on cerebral arteries in general were also selected for review. Some findings were based on experimental data or observed general effects on the cardiovascular system.

To provide the reader with a more structured overview of the topic, the following section gives a description of the more general mechanisms of action related to aneurysm formation and rupture and subsequently a review of the current body of evidence concerning each known modifiable risk factor.

Results and Discussion

Modifiable risk factors predispose to aSAH by different mechanisms of action. The mechanisms could be classified as vessel wall injury, loss of ability to repair vessel wall injury, hemodynamic stress, and synergistic effects. The mechanisms are summarized in Figure 1 (vessel wall injury) and Figure 2 (hemodynamic stress) along with the risk factors associated with each mechanism.

Wall Injury

The vessel wall of cerebral arteries is made up of tunica intima, media, and adventitia, with endothelium lining the tunica intima. The tunica media consists of smooth muscle cells and extracellular matrix containing collagen, elastin, and glycosaminoglycans, whereas the adventitia consists of loose connective tissue, nerve fibers, and vas vasorum. An internal elastic lamina separates the tunica intima and media. Cerebral arterial vessels lack the external elastic lamina.

It is proposed that aneurysm formation is initiated by endothelial damage, followed by vessel wall inflammation, and finally completed by a defect in the inflammatory zone causing an outpouching.

Vessel wall injury has been associated with toxins and an increased amount of proteases (eg, elastase) in blood, causing wall injury by degrading the extracellular matrix of the vessel wall. This increased degradation can also be achieved by the inhibition of enzymes with an inhibiting effect on the proteases. Singh et al proposed α-antitrypsin deficiency and an imbalance between protease and protease inhibitor to be contributing causes for aneurysm formation, as have been corroborated by other studies. α-Antitrypsin is a protease inhibitor that has a significant inhibitory effect on elastase, a proteolytic enzyme. The role of α-antitrypsin is to maintain the integrity of connective tissue.
by keeping the balance with proteolytic enzymes. A lower affinity of \( \alpha \)-antitrypsin for elastase causes an increased proteolytic activity and consequently high levels of elastase in blood.

Vessel wall inflammation is mediated by several pathways associated with carbon monoxide and the proinflammatory cytokine tumor necrosis factor-\( \alpha \) (TNF-\( \alpha \)). Increased levels of carbon monoxide reduce the oxygen content of blood, thus causing hypoxemia-induced inflammation in the vessel wall. TNF-\( \alpha \) damages the endothelium, the smooth muscle cells, as well as the internal elastic membrane, which are all important structural components of the vessel wall. This is done by activating inflammation in the vessel wall with resulting migration of inflammatory cells such as monocytes. TNF-\( \alpha \) has also been found to inhibit cell proliferation as well as endothelial repair. Furthermore, TNF-\( \alpha \) is known to activate matrix metalloproteinases, which degrade structural components of the vessel wall, such as elastin and collagen.

Because of vessel wall injury combined with vessel wall inflammation, the vessel wall undergoes morphological changes, including endothelial cell swelling, subendothelial accumulation of fibrin, and cellular infiltration. The result is intimal thickening, which is thought to reduce the flow of nutrients to the intima as well as to the inner tunica media. Reduced nutrients then lead to deterioration of the internal elastic lamina and the extracellular matrix, which normally provide the elasticity and dynamic strength of the vessel wall, further potentiating the possibility of aneurysm development.

Loss of Ability to Repair Vessel Wall Injury
Impaired ability to repair vessel wall injury is thought to be a contributing factor in aneurysm formation, mainly because of impaired expression of proteins important for flow modulation and impaired collagen formation.

Collagen, elastin, and the elastin-to-collagen ratio along with the tunica media determine the mechanical properties of the vessel. The oscillations that stimulate the smooth muscle cells to produce collagen and elastin can be attenuated by intimal thickening. This could affect the metabolism of the connective tissue and leave the vessel wall less resistant to increased hemodynamic stress.

### Hemodynamic Stress
Hemodynamic stress is caused by elevated blood pressure, uncompensated blood flow, as well as increased blood viscosity.

Elevated blood pressure is an important contributor to hemodynamic stress and has its effect on aneurysm formation and rupture, suggested Vlak et al. who established several trigger factors (e.g., vigorous physical exercise) for aneurysm rupture, all causing a sudden rise in blood pressure.

Another cause of elevated blood pressure is oxidative stress, which increases levels of the potent vasoconstrictor endothelin in a dose-dependent manner.

The vasculature is nourished by the vasa vasorum, the presence of which was confirmed in 1996 in a study identifying vascular channels in the outer tunica media and adventitia. It is thought that elevated blood pressure could result in increased vascular resistance of the vasa vasorum, and that the tension could compress the vasa vasorum, causing an occlusion and subsequent ischemia and necrosis of the tunica media. This leaves the vessel thinned and bulging in response to increased intra-arterial pressure.

Uncompensated blood flow is mainly the consequence of disturbances in the cerebral autoregulation, resulting in an increased risk of aneurysm formation and rupture, because of the vasculature not being able to compensate or adapt to elevated blood pressure. A disturbance of the cerebral autoregulation has been described in relation to alcohol intoxication, with regulation of cortical neurons and lower medullary centers being depressed at high alcohol levels. This can lead to respiratory acidosis and build-up of carbon dioxide, that is, hypercapnia. A study by Blaha et al. examined the effects of ethanol and hypercapnia on cerebral autoregulation. The study found no significant effect on dynamic cerebral autoregulation by ethanol alone, but revealed that hypercapnia can cause an impairment of cerebral autoregulation, possibly resulting in uncompensated blood flow because of carbon dioxide being a potent vasodilator, increasing cerebral blood flow.

Finally, an increased blood viscosity, caused by increased fibrinogen and hematocrit levels in blood, has also been shown to exert increased hemodynamic stress on the vessel wall, contributing to possible aneurysm formation.

### Synergistic Effects
The combined pathological effect of hemodynamic stress and an injured vessel wall potentiates the risk of aneurysm formation by further increasing the level of shearing injuries.

As an example, Singh et al. suggested that hemodynamic stress, also referred to as wall shear stress, on the vessel wall...
Table 1. Relative Risk (RR) and Odds Ratio (OR) of Aneurysmal Subarachnoid Hemorrhage (ASAH) Associated With Modifiable Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Teunissen et al21: 1.9 (1.5–2.3); Ruigrok et al22: 1.9 (1.5–2.3); Juvela et al25: 2.1 (1.2–3.6); Feigin et al4: 2.2 (1.3–3.6); Feigin et al4: 2.4 (1.8–3.4); Bonita et al3: 3.3 (2.0–5.3); Bonita et al4: 5.4 (3.0–9.7); Sandvei et al26: 6.1 (3.6–10.4); Juvela et al25: 7.3 (3.8–14.3)†</td>
<td>Feigin et al4: 3.1 (2.7–3.5); Ohkuma et al22: 3.12 (2.05–4.77); Teunissen et al25: 3.5 (2.9–4.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Feigin et al4: 2.0 (1.5–2.7); Feigin et al4: 2.5 (2.0–3.1); Teunissen et al21: 2.8 (2.1–3.6); Ruigrok et al22: 2.8 (2.1–3.6); Sandvei et al26: 3.3 (1.7–6.3); Bonita et al3: 3.4 (2.3–5.7)</td>
<td>Ohkuma et al22: 2.29 (1.66–3.16); Isaksen et al26: 2.46 (1.52–3.97); Feigin et al4: 2.6 (2.0–3.1); Teunissen et al21: 2.9 (2.4–3.7)</td>
</tr>
<tr>
<td>Heavy alcohol consumption (&gt;150 g/wk)</td>
<td>Feigin et al4: 2.1 (1.5–2.8); Teunissen et al21: 4.7 (2.1–10.5)</td>
<td>Feigin et al4: 1.5 (1.3–1.8); Teunissen et al21: 1.5 (1.3–1.8)</td>
</tr>
<tr>
<td>Estrogen preparations</td>
<td>n/a</td>
<td>Longstreth et al23: 0.47 (0.26–0.88); Feigin et al4: 0.6 (0.4–0.8); Mhurchu et al30: 0.64 (0.41–0.98)‡</td>
</tr>
<tr>
<td>Cocaine</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>n/a</td>
<td>Ohkuma et al22: 0.41 (0.24–0.71); Feigin et al4: 0.6 (0.4–0.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Feigin et al4: 0.3 (0–2.2)</td>
<td></td>
</tr>
</tbody>
</table>

n/a indicates not available.
*For ≤20 cigarettes/d.
†For >20 cigarettes/d.
‡For hormone replacement therapy.
§For stimulant drugs in the week preceding SAH.

day), and an OR of 1.8 (95% CI, 1.0–3.2) for former smokers. The risk of developing aSAH associated with smoking seems to be highest in the initial 3 hours after smoking.31 Also, a higher RR in women than in men has been established.25

The formation of carbon monoxide and release of cigarette toxins into the blood stream link smoking with aneurysm formation and rupture.9,33 Smoking also promotes increased blood levels of proteases such as elastase. Inhalation of smoke from cigarettes irritates the lung tissue and causes an inflammatory reaction with migration of neutrophil granulocytes to the site of inflammation, causing release of elastase.1

Inhibition of α1-antitrypsin could increase elastase activity. Gaetani et al7 showed that cigarette smoking reduces the inhibitory effectiveness of α1-antitrypsin on proteases such as elastase. Furthermore, oxidative stress by smoking was found to inactivate the methionine site in the inhibitory active site of α1-antitrypsin, causing a lower affinity of α1-antitrypsin to elastase.8 Smoking also elevates levels of fibrinogen in blood, causing increased blood viscosity and thus hemodynamic stress.11

Table 2. Population-Attributable Risk and Dose–Response Relationship for Aneurysmal Subarachnoid Hemorrhage and Their Associated Modifiable Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Population-Attributable Risk</th>
<th>Dose–Response Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>20% to 40%²⁸,²⁹,³⁰,³¹</td>
<td>Yes²⁹,³⁰,³¹</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17% to 28%²⁸,²⁹,³⁰,³¹</td>
<td>n/a</td>
</tr>
<tr>
<td>Heavy alcohol consumption (100–299 g/wk); (≥300 g/wk)²¹</td>
<td>11% (100–299 g/wk); (≥300 g/wk)²¹</td>
<td>Yes²²,²²</td>
</tr>
<tr>
<td>Estrogen preparations</td>
<td>n/a</td>
<td>Yes²⁴,²⁵</td>
</tr>
<tr>
<td>Cocaine</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

n/a indicates not available.
Additionally, blood pressure has been shown to be elevated transiently 2 to 3 hours after smoking,23 with nicotine stimulating the release of catecholamines and thus increasing hemodynamic stress.9 This transient elevation of blood pressure has been associated with aneurysm rupture.27

Finally, smoking has been associated with antiestrogenic properties, diminishing the beneficial effects of estrogens,10 which we will discuss later in this article.

Hypertension

Hypertension has been associated with an increased risk of aSAH in several studies (Table 1) with a reported RR as high as 3.4 (95% CI, 2.3–5.7).25

Inci et al12 have proposed 3 mechanisms by which hypertension predisposes to aneurysm formation:

1. Endothelial damage
2. Occlusion of the vasa vasorum
3. Disturbance in the synthesis of elastin and collagen by smooth muscle cells

Hypertension may also damage the vessel wall by affecting endothelial production of several mediators, such as matrix metalloproteinase-13 and NO.6 Additionally, mechanical damage may be inflicted by increasing hemodynamic stress on the vessel wall of cerebral arteries.6,27

Alcohol Consumption

An increased risk of aSAH has been shown with a weekly consumption of >150 g of alcohol (Table 1). The risk of aSAH grows with increasing amounts of alcohol, as illustrated by a dose–response relationship in Table 3. Conversely, a protective effect of light drinking has also been established.21

Heavy alcohol consumption is thought to damage the endothelium11 by inducing oxidative stress10,11 and has also been associated with induction of TNF-α as well as increased NO production.11 Also, a breakdown product of alcohol, acetaldehyde, has been shown to cause cell damage through the generation of reactive oxygen species.20

Heavy alcohol consumption has been associated with elevated blood pressure22,23 and increased hematocrit, plasma osmolarity, and fibrinogen levels in blood.11,19 Together, these are synonymous with increased hemodynamic stress.6

Subsequent alcohol withdrawal, however, is associated with increased levels of catecholamines, causing elevated blood pressure.23

On the contrary, light to moderate alcohol consumption has been inversely associated with the risk of aSAH, suggesting a protective effect, in some studies. Alcohol shows an effect on lipid profiles, with moderate amounts of alcohol reported to increase serum levels of high-density lipoprotein cholesterol, and heavy consumption reported to lower the serum levels of high-density lipoprotein cholesterol.1,17 The protective effect of light to moderate drinking could be associated with higher high-density lipoprotein serum levels, acting as an effective antioxidant.11 Similarly, moderate drinking has been associated with decreased TNF-α activity and antioxidant effect.11 Overall, these effects are beneficial to the vessels by acting against vessel inflammation.

Table 3. Relative Risk (RR) for Aneurysmal Subarachnoid Hemorrhage (aSAH) in Relation to Alcohol Consumed Within 24 Hours Preceding aSAH

<table>
<thead>
<tr>
<th>Amount of Alcohol Consumed &lt;24 h Preceding aSAH</th>
<th>RR</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light drinking 1–40 g</td>
<td>0.3 (95% CI, 0.1–0.8)</td>
<td>Reduced risk of aSAH</td>
</tr>
<tr>
<td>Moderate drinking 41–120 g</td>
<td>2.5 (95% CI, 1.1–5.5)</td>
<td>Increased risk of aSAH</td>
</tr>
<tr>
<td>Heavy drinking &gt;120 g</td>
<td>4.5 (95% CI, 1.5–12.9)</td>
<td>Increased risk of aSAH</td>
</tr>
</tbody>
</table>

The results depict male population only. In women, RR was higher in all categories of drinking, but light drinking was still associated with a reduced risk for aSAH. Data are from Juvela et al.23

Oral Contraceptive Pills and Hormone Replacement Therapy

Estrogens are used in oral contraceptive pills and hormone replacement therapy for postmenopausal women.1 A meta-analysis on the use of oral contraceptives and the risk of subarachnoid hemorrhage found a trend toward greater risk when using high-estrogen preparations compared with low-estrogen preparations, although the difference was not statistically significant.32 Because estrogen has been shown to promote hypertension,1 older oral contraceptive compounds, with larger amounts of estrogens, may have led to elevated blood pressure and increased risk of aSAH.29,32 The mechanism by which estrogens elevate blood pressure is unknown, but it is speculated that estrogens induce retention of sodium and plasma, increasing blood volume and affecting the actions of renin, angiotensin, and aldosterone.9

Despite the fact that estrogens promote hypertension, a beneficial effect has been established for the use of estrogen compounds. Estrogen hormone replacement therapy has shown a risk-reducing effect in regard to aSAH.4,29,30 as well as a risk-reducing effect for premenopausal women in regard to aSAH.30 Estrogens have been shown to have protective effects by having a direct effect on blood vessel integrity. Using transthoracic Doppler technique imaging, the effect of estrogens on cerebral blood vessels was investigated,34 revealing a decrease in pulsatory index in postmenopausal women receiving hormone replacement therapy. This indicates decreased vessel reactivity, suggesting an increased elasticity of blood vessels and thus lower risk of aneurysm formation.29,32,34 Similarly, it has been shown that estrogen deficiency leads to reduced amounts of collagen and elastin in skin,29 which might also be true for collagen and elastin of vessel wall.

Estrogens promote increased endothelial NO production and collagen strengthening, contributing to the integrity of vessel wall.35 This may indicate a beneficial effect of NO in low amounts. Furthermore, estrogens have been associated with lowered TNF-α activity, thus protecting against vascular inflammation.10

Both alcohol and smoking are associated with antiestrogenic effects, inhibiting the beneficial effects of estrogens in regard to collagen strengthening and lowering TNF-α levels.
Other Risk Factors

Stimulant drugs such as cocaine have been associated with an increased risk of aSAH (Table 1). Cocaine inhibits the reuptake of norepinephrine at the presynaptic neuron, resulting in elevated blood pressure.36 Cocaine also induces vasoconstriction by promoting intracellular calcium release from the sarcoplasmic reticulum in cerebral vascular smooth muscle cells and disturbs cerebral autoregulation, with the vasculature being unable to compensate for high blood flow at high blood pressures as a consequence, that is, an uncompensated blood flow.17

Hypercholesterolemia is inversely associated with the risk of aSAH,4,27 although not all studies have found such an association.21 It has also been shown that low serum cholesterol increases the risk of hemorrhagic strokes.37 The risk-reducing effect of hypercholesterolemia could partly be explained because of the fact that lipids are required by most cells for the maintenance of plasma membranes.9 Also, smooth muscle cell necrosis has been shown to be inhibited by a high cholesterol diet in experiment with rats,26 thus protecting blood vessel integrity.

Diabetes mellitus seems to be associated with a reduced risk of SAH.4 However, insulin resistance (type 2 diabetes mellitus) has been shown to be associated with endothelial dysfunction, inflammation, and oxidative stress.11 Nevertheless, the reduced risk was only statistically significant in case-control studies in a review, leading the authors of the review to conclude that these findings may have been biased and explain the results by considering an increased mortality caused by diseases other than SAH, or that these patients had access to better medical treatment or different and healthier lifestyles.

Synergistic Effect

A synergistic effect of smoking and hypertension in regard to increased risk of aSAH has been shown in both sexes,25,35,40 whereas the risk of cerebral hemorrhage (including aSAH) due to alcohol consumption has been shown to be increased in individuals with hypertension.41 This suggests that the harmful effects of one modifiable risk factor can amplify the effects of another, increasing the overall risk of aSAH.

Difference Between Sexes

Alcohol, smoking, and hypertension have been found to have a more hazardous effect on women than on men,2,47,42 explaining the increased incidence of SAH in women.45

The fact that women, compared with men, often experience earlier hazardous effects of heavy alcohol consumption could be attributed to the fact that women have lower total body water mass, lower activity of alcohol dehydrogenase, and that alcohol has been associated with inhibiting the otherwise beneficial effects of estrogen on endothelial cells.11

A second reason could be differences in the force of hemodynamics on the vessels. Lindekleiv et al44 showed that women have smaller blood vessel diameters compared with men, and that this contributes to a higher hemodynamic force acting on female cerebral vessel bifurcations.

In addition, fluctuations in estrogen levels are also thought to play an important role, because the highest number of aSAH in women is observed in perimenstrual and postmenopausal period.29

Conclusions

Cigarette smoking, hypertension, heavy alcohol consumption, cocaine abuse, estrogen compounds, hypercholesterolemia, and diabetes mellitus are associated with aneurysm formation and rupture by mechanisms involved in vessel wall injury, inhibition of wall injury repair, and increased hemodynamic stress. The synergistic effect of these mechanisms would result in a higher degree of shearing injuries, increasing the risk of aneurysm formation and rupture.

The different modifiable risk factors, once identified, may be avoided so as to reduce the risk of aSAH. Knowledge about the pathogenesis behind aneurysm build-up and rupture gives a better understanding of why exposure to the risk factors should be reduced. Because none of the risk factors have been fully explored, acquisition of more data is warranted.

Disclosures

None.

References


KEY WORDS: aneurysm ◦ etiology ◦ risk factors ◦ subarachnoid hemorrhage