REVIEW ARTICLE
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The relationship between smoking and brain aneurysms: from formation to rupture

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INTRODUCTION

Cerebral aneurysms occur in 3–5% of the general population and are characterized by localized structural deterioration of the arterial wall, with loss of the internal elastic lamina and disruption of the media layer[1]. The most dreaded complication of a cerebral aneurysm is its rupture, which is likely related to several modifiable and nonmodifiable risk factors[2]. Subarachnoid hemorrhage (SAH), secondary to intracranial aneurysm (IA) rupture, has a high mortality, which approaches 50% in some studies[3].

Aneurysms deemed at low risk of rupture are typically kept under image surveillance, while endovascular embolization or surgical clipping is commonly offered to patients deemed to be at a higher risk of aneurysm rupture[4]. Although the exact underlying etiology that causes IA rupture is not clearly understood, cigarette smoking is considered to be the most significant modifiable risk factor[5].

Cigarette smoking is a major health hazard, with 5.4 million premature deaths worldwide every year and an average loss of 13–15 years of life expectancy[6]. Understanding how nicotine exposure impacts IA may have important implications for screening and counseling of patients. Therefore, the aim of this study is to evaluate the effects of smoking on the formation, growth, rupture, and even recurrence of IAs, by incorporating the data obtained from a review of the literature available.

METHODS

This is a descriptive study based on the literature available in the MEDLINE/PubMed database. The terms searched, all in English, were as follows: "smoking" AND "intracranial aneurysms," "pathophysiology," "aneurysms formation," "aneurysm growth," "aneurysms rupture," "subarachnoid hemorrhage," and "residual aneurysms." All articles that were considered relevant were included in this review, as were the studies referenced therein, to raise awareness about the method. Duplicate items were discarded.

DISCUSSION

The prevalence of intracranial saccular aneurysms is estimated to be 3.2–4% in a population without comorbidity, with a mean age of 50 years and with a 1:1 gender ratio[7]. Most IAs (approximately 85%) are located in the anterior circulation, predominantly on the circle of Willis arteries[8].

Aneurysmal SAH occurs at an estimated rate of 6–16 per 100,000 population, and its high morbidity and mortality rates are attributed mainly to brain damage that is caused by a severe initial hemorrhage, early rebleeding, and delayed cerebral ischemia[9]. As IAs are the major etiology of SAH, risk factors can be considered the same for both situations, which are mainly associated with hypertension, cigarette smoking, and alcohol consumption[10].

The pathogenesis of the formation of intracranial saccular aneurysms is multifactorial[11]. Usually, there is an endothelial dysfunction in response to turbulent flow and hemodynamic stress, which leads to compensatory responses that alter the endothelium. This results in functional and morphological changes that activate an inflammatory response in the vessel wall, leading to a proinflammatory local environment and an extracellular matrix remodeling by matrix metalloproteinases (MMPs)[12,13].

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When it comes to analyzing cigarette smokers, they have a significantly increased risk of SAH compared with the nonsmoker population. In the case–control study carried out by Bonita[14], the relative risk values of SAH for men and women were 3.0 and 4.7, respectively, and according to the number of cigarettes smoked, the risk increased. Those who smoked and those who had hypertension had a risk of SAH that is 15 times higher when compared with normotensive nonsmokers[14].

There are multiple hypotheses about the mechanisms through which smoking can lead to vascular inflammation, hemodynamic stress, endothelial dysfunction, and, ultimately, wall weakening and rupture[15] (Table 1). Cigarettes are composed of a mixture of chemical substances that release a bunch of harmful toxins when burnt, which can enter into the bloodstream and lead to many vascular adverse effects[16]. To understand it more clearly, we can analyze the impact of cigarette smoking on each stage of the development of aneurysms, such as its formation, growth, rupture, and, eventually, its recurrence (Figure 1).

Smoking and aneurysm formation

Hemodynamic forces play a key role in the development of the cerebral aneurysm, as they are highly associated with rapid degradation of the internal elastic lamina, followed by thinning of the media and outward bulging of the vessel wall[17]. Cigarette smoking contributes to this situation as it significantly increases the wall shear stress by raising the blood viscosity and the blood volume and also through the induction of cerebral vasoconstriction[18]. Similarly, nicotine may also raise wall shear stress as it inhibits nitric oxide synthase, which impairs the nitric oxide signaling pathway that is responsible for cerebral vasodilation[19].

Conjointly, smoking has shown to directly upregulate endothelin type B receptors in the cerebral arteries through the activation of key intracellular inflammatory signal molecules, such as mitogen-activated protein kinases and the NF-κB signal pathway, which plays a critical role in the pathogenesis of cerebral aneurysms[20].

Cigarette smoking also decreases the effectiveness of α1-antitrypsin, an inhibitor of proteases such as elastase (i.e., proteolytic enzyme), resulting in the vessel wall injury that can be associated with the hypoxemia-induced inflammation due to the smoke-related increased levels of carbon monoxide, proinflammatory cytokine tumor necrosis factor-α (TNF-α), and reactive oxygen species from cigarette combustion, which potentiates the possibility of development of the aneurysm[8,21].

Smoking and aneurysm growth

The persistence of a proinflammatory environment is the main factor that contributes to the development of aneurysms as studies have shown that smokers have higher levels of interleukin-1β (IL-1β), TNF-α, and interleukin-6 (IL-6)[22], which are, respectively, associated with reducing the biosynthesis of collagen[23], activating MMP that remodels the extracellular matrix on the injured endothelium[24], and induction of gene polymorphisms[25].

Besides the proinflammatory status, Juvela et al.[26] observed that smoking habits and the number of cigarettes smoked daily seem to be more important in terms of aneurysm growth than the duration of smoking or age at which one began smoking, and those who gave up smoking did not present an increased risk for aneurysm expansion, as their growth rates were the same as in nonsmokers[26]. This suggests the importance of smoking control, even after the diagnosis of a cerebral aneurysm, as the risks appear to diminish rapidly within a few years of quitting[27].

Smoking and aneurysm rupture

Many studies have shown that cigarette smoking is a significant risk factor for the development of SAH. Anderson et al.[27] analyzed 432 incident cases of SAH that are compared with 473 controls, and the results showed that cigarette smokers have five times the risk of SAH compared with nonsmokers, and about one-third of all cases of SAH could be attributed to current smoking.

The risk of aneurysm rupture also seems to be higher in the initial three hours after smoking, due to the release of catecholamines stimulated by nicotine, with a greater risk ratio in women than in men[14,28]. Hence, synergistic mechanisms that increase the hemodynamic stress present a higher risk for its rupture when associated with smoking, such as hypertension, alcohol consumption, stimulant drugs (i.e., cocaine), and other factors associated with elevated blood pressure, uncompensated blood flow, or increased blood viscosity[29].

It is also known that inhalation of smoke from cigarettes irritates the lung tissue and causes an inflammatory reaction characterized by the elevated levels of white blood cells, which can secrete free radicals, elastase, and collagenase that may contribute to the injury of the endothelial cells[30].

There is also an association between cigarette smoking and thrombosis that can predispose aneurysm rupture, as nicotine increases plasminogen activator inhibitor-1 in human brain–derived endothelial cells, and it increases the levels of tissue factor, which is a key factor in thrombogenesis[31].

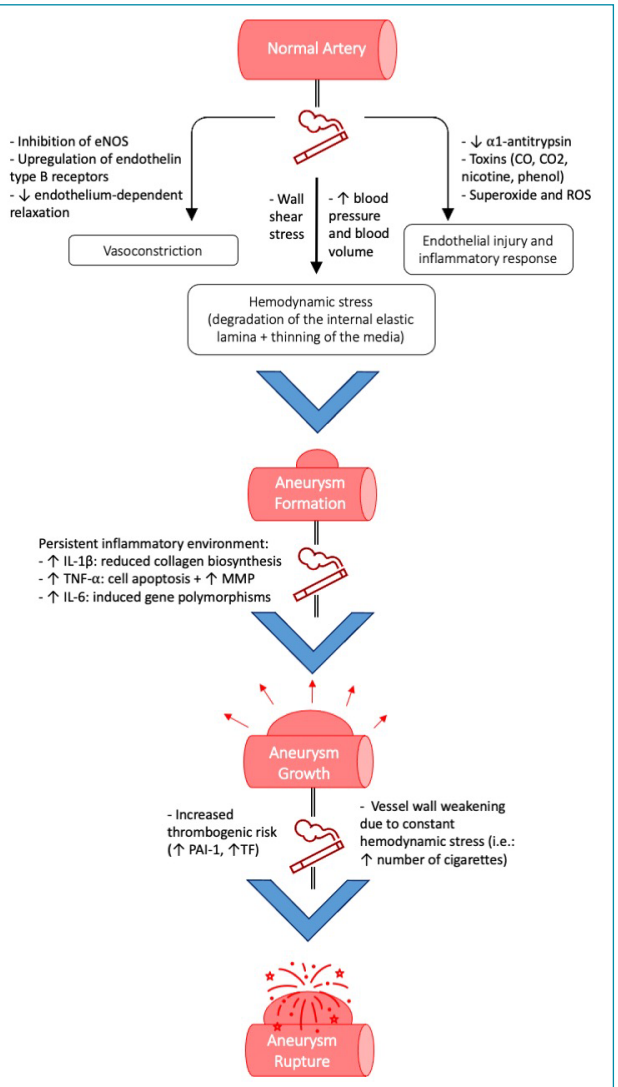
Smoking and aneurysm recurrence or residual

Patients who are smokers and who have undergone endovascular repair of cerebral aneurysms have shown an increased

Table 1. Smoking-induced mechanism described for the pathogenesis of aneurysms.

Author	Smoking-induced mechanism described for the pathogenesis of aneurysms	Related outcome
Schievink WI et al.[8]	Decreased effectiveness of α1-antitrypsin and increased levels of proteolytic enzymes (i.e., elastase) contribute to the degeneration of the vessel wall, for example, through increased elastin degradation	Aneurysm formation
Price JF et al.[18]	Increased blood viscosity and blood volume and induction of cerebral vasoconstriction contribute to intensify the wall shear stress	
Gerzanich V et al.[19]	Inhibition of eNOS and impairment of the NO vasodilating pathway contribute to promote vasoconstriction of the cerebral arteries, which increases the pressure of blood against the walls of the vessel (increased wall shear stress)	
Hashimoto T et al.[17]	Hemodynamic forces cause rapid degeneration of the internal elastic lamina, followed by thinning of the media and outward bulging of the vessel wall	
Jayaraman T et al.[21]	Increased levels of TNF-α, CO, and ROS associated with hypoxemia-induced inflammation contribute to the inflammatory status that contributes to the injury of the vessel wall	
Xu CB et al.[20]	Upregulation of endothelin type B receptors in cerebral arteries induces cerebral vasoconstriction, which increases the pressure of blood against the walls of the vessel (increased wall shear stress)	
Juvela S et al.[26]	The greater the number of cigarettes smoked daily, the higher the risk of aneurysm growth due to constant inflammatory stimulus and progressive vessel wall weakening	Aneurysm growth
Jayaraman T et al.[24]	Higher levels of TNF-α can activate MMP that remodels the extracellular matrix on the injured endothelium and lead to the irreversible degradation of the vessel wall	
Aoki T et al.[23]	Higher levels of IL-1β can reduce the biosynthesis of collagen and promote apoptotic cell death, which contributes to vessel wall weakening	
McColgan P et al.[25]	Higher levels of IL-6 can act on the induction of gene polymorphisms, which suggests being relevant as some gene bases have recently been related to intracranial aneurysms development	
Juvela S et al.[28]	Nicotine stimulates the release of systemic catecholamines that can cause a transiently elevated blood pressure 2–3 h after smoking and can increase the risk of aneurysm rupture	Aneurysm rupture
Zidovetzki R et al.[31]	Nicotine can increase the levels of PAI-1 and TF, the key factors in thrombogenesis that can lead to thrombus formation, which can contribute to the proinflammatory environment and increase the hemodynamic stress against the walls of the aneurysms	
Kumar V et al.[30]	Elevated levels of white blood cells (i.e., neutrophils and monocytes) due to inflammatory reaction and consequent release of free radicals, elastase, and collagenases can contribute to endothelial cells injury and vessel wall weakening and increase in the risk of aneurysm rupture	
Tulamo R et al.[13]	Smoking-induced endothelial injury and de-endothelization with consequent hyperactivation of the coagulation cascade can contribute to the proinflammatory environment and further breakdown of the cerebral aneurysm wall	
Andreasen TH et al.[29]	Synergistic mechanisms (i.e., hypertensions, alcohol consumption, stimulant drugs, and hypercolestemia) can increase the risk of rupture as they can amplify the hemodynamic stress against the walls of the aneurysms	

CO: carbon monoxide; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; PAI-I: plasminogen activator inhibitor-1; ROS: reactive oxygen species; SAH: subarachnoid hemorrhage; TF: tissue factor; TNF-α: tumor necrosis factor-α; MMP: matrix metalloproteinase; IL-1β: interleukin-1β; IL-6: interleukin-6.



eNOS: endothelial nitric oxide synthase; ROS: reactive oxygen species; IL-1: interleukin-1; TNF-: tumor necrosis factor-; MMP: matrix metalloproteinases; TF: tissue factor.

Figure 1. The impact of smoking on aneurysms development.

risk of aneurysm recurrence as it was analyzed in the study conducted by Futchko et al.[32], in which the odds ratios (ORs) for aneurysm recurrence for current and former smokers were 2.739 and 2.698, respectively, compared with never smokers. In the same way, Aguiar et al.[33] also investigated this relationship based on the results obtained from 167 IAs treated by microsurgical clipping, from which 38 patients developed residual lesions, as 27 of them were current smokers compared with only 11 nonsmokers. Thus, it revealed an increased risk of residual aneurysms for current smokers (OR 3.38, 95%CI), possibly due to the effects of cigarette substances on the vessel well and on the blood flow of the brain as already described on the above mechanisms.

CONCLUSIONS

Cigarette smoking is still a very frequent habit among the general population, despite how much is known about its many harmful attributes, such as various ways that tobacco exposure can influence the pathogenesis of the cerebrovascular aneurysm as explored in this study. Therefore, it is of great importance to better understand the biological mechanisms of how it can lead to vascular inflammation, hemodynamic stress, endothelial dysfunction, and consequent vessel wall weakening to prevent the occurrence of IAs and to avoid further complications such as aneurysms ruptures and consequent SAH.

AUTHOR'S CONTRIBUTIONS

PB: Data Curation, Writing – original draft. **GBA:** Conceptualization, Writing – original draft. **RCS:** Conceptualization, Writing – review & editing.

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