



The clinical significance and reliability of self-reported smoking status in patients with intracranial aneurysms: A review



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ABSTRACT

Objective: Here we present a review of the pathophysiology of tobacco smoking on intracranial aneurysms, self-reported smoking status in these patients, screening tools and assays available for assessing active nicotine use, means of impacting smoking cessation rates, and the potential impact of smoking cessation on risk of rupture and recurrence of treated intracranial aneurysms.

Methods: A literature search using PubMed was done to identify all English language studies relating to tobacco use and intracranial aneurysms, smoking and subarachnoid hemorrhage, nicotine breakdown products, and smoking cessation in neurosurgery. Results from the studies were reviewed and summarized.

Results: Tobacco use is an independent risk factor for formation, growth, and rupture of intracranial aneurysms. The pathogenesis of aneurysm formation is complex, and related to increased wall shear stress, endothelial dysfunction, atherosclerosis, and altered gene regulation. Furthermore 80% of all aneurysmal ruptures occur in patients who have used tobacco products. It is suboptimal to rely on self-reported smoking status in order to determine patient risk. Use of objective metrics for ongoing tobacco use may be indicated in selected patients, and may increase smoking cessation rates in these patients. A variety of laboratory and point-of-care tests are available for measurement of nicotine and nicotine breakdown products. Most assays in clinical practice measure the nicotine breakdown product cotinine, which constitutes 75% of nicotine metabolites excreted in the urine and has a substantial half-life of 16 h, compared to nicotine's 2-h half-life. With proper identification, an astute physician may be able to assist in smoking cessation and foster improved patient care. By following recommended guidelines and prescribing pharmaceutical aid, a patient has a 2.5 times greater chance of smoking cessation compared with attempting to stop without physician assistance.

Conclusions: Smoking increases risk for intracranial aneurysm formation, rupture, re-rupture and need for re-treatment. Measurement of nicotine breakdown products may have clinical utility in the management of patients with intracranial aneurysms. Smoking cessation interventions may be effective, and use of established smoking cessation tools use may lead to improved clinical outcomes in these patients. The effects of smoking cessation efforts on smoking cessation and intracranial aneurysm outcomes is a fertile field for future investigation.

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1. Introduction

Tobacco smoking is an independent risk factor for intracranial aneurysm growth, rupture, recanalization following coiling, and

need for aneurysm retreatment [1–3]. The relative risk of aneurysmal subarachnoid hemorrhage for smokers is more than twice that of non-smokers [1,2], and tobacco smoking is the single most important modifiable risk factor for aSAH in patients with intracranial aneurysms [4–6]. Some 40% of all subarachnoid hemorrhages can be directly tied to smoking status [6]. Despite the fact that a relationship between smoking and subarachnoid hemorrhage has been firmly established, no studies have yet evaluated smoking cessation rates around the time of diagnosis of intracranial aneurysm, either ruptured or unruptured, using objective metrics

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of smoking cessation. This is in contrast to the situation with smoking and ischemic stroke, in which smoking cessation rates have been reported in a number of studies [7–9]. While smokers make up a higher percentage of patients with ruptured aneurysms than unruptured aneurysms, the benefit of smoking cessation on patients with already diagnosed intracranial aneurysms has not yet been established. The purpose of this review is to evaluate the current literature regarding smoking and aneurysm formation and rupture, as well as to discuss clinical tools for accurately assessing smoking status, and strategies for increasing smoking cessation rates in these high-risk patients that may allow a better understanding of the effect that smoking cessation may have on this population.

2. Methods

A systematic literature review was done using PubMed to identify studies published in the English language using the keywords “tobacco and intracranial aneurysms”, “tobacco and subarachnoid hemorrhage”, “nicotine breakdown products”, and “smoking cessation and neurosurgery”. References from papers published after 1985 were considered with preference to papers published after 1995. Over 150 references were reviewed and considered by each author for inclusion based on relevance to tobacco, aneurysms, nicotine breakdown products, and smoking cessation. References were excluded if the paper loosely fit the topics of interest. References cited by the relevant studies were also examined. Results from included studies were reviewed and summarized.

3. Results:

3.1. Overview of smoking and intracranial aneurysms

Tobacco smoking is associated with formation and growth of intracranial aneurysms [10–14]. Specifically, the hazard ratio for former smokers was found to be 2.7 (95% CI, 1.4–5.1) and 6.1 (95% CI, 3.6–10.4) for current smokers [15]. Additionally, smokers have greater incidence of multiple aneurysms compared to non-smokers [10,16]. Smoking is an independent predictor of aneurysm rupture [17], and family history of subarachnoid hemorrhage further increases the risk of aneurysmal SAH in smokers [18]. Smoking is associated with recurrent SAH after clipping of ruptured intracranial aneurysms [19], as well as recurrence following endovascular occlusion, especially in women [3]. Furthermore, smokers have increased incidence of symptomatic cerebral vasospasm after SAH resulting in increased morbidity and mortality [20,21]. Finally, smoking was found to increase all-cause mortality rates in unruptured intracranial aneurysm patients [22].

3.2. Pathophysiology of tobacco smoke and intracranial aneurysms

The interaction between the thousands of chemicals comprising tobacco smoke and intracranial aneurysms remains incompletely understood. Several interdependent mechanisms appear to contribute to aneurysm formation and rupture in smokers, including increased wall shear stress, endothelial dysfunction, atherosclerosis, and altered gene regulation. Tobacco smoke seems to increase wall shear stress. The Haagen–Poisuille equation can be used to calculate shear stress within a vessel, in which shear stress (τ) = $8 \times \mu \times u/d$, where μ = viscosity, u = mean flow, and d = diameter of the vessel. Thus, wall shear stress is proportional to the viscosity, proportional to the flow and inversely proportional to the diameter of the vessel. Tobacco smoke has been found to increase both blood viscosity and blood volume [23–25]. Tobacco

smoke also causes vasoconstriction via the inhibition of eNOS and impaired nitric oxide signaling [26–29]. Therefore, as the viscosity, volume (and flow) increase and as the diameter of the vessel decreases, wall shear stress increases.

Tobacco smoking is also associated with endothelial dysfunction. Via a complex interplay of gene alterations and other processes, vascular smooth muscle cells are converted into a proinflammatory and dedifferentiated type, causing matrix metalloproteinases to remodel the extracellular matrix [30]. This remodeling leads to a loss of the internal elastic lamina and a reduction in the size of the tunica media, resulting in a fragile vessel wall more susceptible to aneurysm formation. The reactive oxygen species produced from tobacco smoke also accelerates the inactivation of nitric oxide, which is a key signaling molecule required for endothelial homeostasis [31].

Atherosclerosis also appears to contribute to the formation, growth and rupture of intracranial aneurysms [30]. Free radicals present in tobacco smoke play an integral role in atherosclerosis. These particles increase proinflammatory cytokines that recruit and assist with the transendothelial migration of leukocytes. The free radicals also oxidize LDL particles that are then phagocytized by roaming macrophages, causing their transformation into lipid-rich foam cells and the progression of atherosclerotic plaques. These areas may serve as a nidus for aneurysm formation.

Yet another pathway to the formation and rupture of aneurysms by tobacco smoke is via alterations in gene expression. Tobacco smoking is associated with an imbalance in the elastase/ α 1-antitrypsin ratio, leading to increased elastase activity [32]. This may contribute to the destruction of the internal elastic lamina. Additionally, tobacco smokers have increased expression of IL-1 β , TNF α and IL-6, cytokines that contribute to aneurysm formation [33,34]. IL-1 β works via the NF- κ B pathway and vascular smooth muscle cells (VSMC) by reducing collagen formation and causing apoptosis of the VSMC [35,36]. TNF α was similarly shown to promote apoptosis of VSMC, yet also activates matrix metalloproteinases with resultant extracellular matrix remodeling [37]. IL-6 gene polymorphism is likewise associated with cerebral aneurysm formation [38]. Active, ongoing research continues to identify other changes in gene expression associated with aneurysm formation.

In combination, interdependent gene expression, inflammation, atherosclerosis, increased wall stress, and endothelial dysfunction transform the large cerebral arteries into weak vessels in which aneurysms are more easily formed. Some of these same processes occur as part of the natural aging process, but are accelerated by exposure to tobacco smoke, leading to a higher rate of aneurysm formation.

3.3. Nicotine metabolism

Inhalation of tobacco smoke leads to the absorption of up to 90% of the nicotine in the smoke drawn into the lungs. Nicotine intake is affected not only by the number of cigarettes smoked each day, but also volume, depth, dilution, rate, and intensity of intake, as well as the nicotine content of each cigarette [39]. Nicotine is primarily metabolized in the liver in an extensive and complex manner. Many nicotine metabolites have been identified with cotinine representing 75% of urinary excretion. The minor metabolites and their excreted urinary percentages are: 4-oxo-4-(3-pyridyl)butanoic acid and 4-hydroxy-4-(3-pyridyl)butanoic acid 11%, nicotine N'-oxide 5.5%, nicotine glucuronide 4%, nornicotine 0.6%, other 3.9% [39]. Nicotine is converted by liver enzyme CYP P450 2A6 to cotinine, the principal metabolite. Levels of cotinine begin to rise 4–5 min after inhalation and exceed nicotine levels 60 min after inhalation [40].

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