Smoking Out the Cause of Thrombosis

Robert A. Campbell, PhD; Kellie R. Machlus, BS; Alisa S. Wolberg, PhD

Cigarette smoke exposure (CSE) is known to increase the risk of arterial thrombosis; almost 40% of smoking-related deaths are associated with cardiovascular disease. Most research has focused on the direct cellular effects of CSE, demonstrating that increased risk of thrombosis is linked to oxidative damage to cardiomyocyte mitochondria, increased smooth muscle cell proliferation, and increased platelet aggregation. Studies examining the effects of CSE on hemostasis have documented decreased expression of tissue factor pathway inhibitor on endothelial cells exposed to serum from chronic smokers and increased plasma fibrinogen levels in smokers compared to nonsmokers. Few studies have examined the effects of acute CSE on clotting, but increased levels of circulating tissue factor activity have been demonstrated after short-term exposure to cigarette smoke. Thus, CSE appears to increase prothrombotic biomarkers and may directly promote thrombosis.

See accompanying article on page 75

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Barua et al. strengthen the argument for a direct functional effect of CSE in thrombosis by demonstrating abnormal fibrin clot dynamics and structure in plasma from individuals exposed to acute CSE. Whereas baseline fibrin clot dynamics and structure in platelet-rich and platelet-poor plasma in nonsmokers and smokers is similar, acute CSE exposure shortens the onset and increases the rate of fibrin formation and development of fibrin clot strength as measured by thrombelastography. The authors suggest the increase in clot strength is attributable to changes in platelet function as well as changes in fibrin structure. Acute CSE effects are observed in platelet-rich plasma in the presence and absence of the platelet antagonist, Abciximab. Visual evidence using scanning electron microscopy shows decreased fibrin diameter and increased fibrin fiber density in clots formed from platelet-poor plasma isolated after acute CSE. Whereas the authors did not explicitly examine fibrinolysis, previous studies have demonstrated dense fibrin networks composed of thin fibers are associated with abnormally high resistance to fibrinolysis. These findings suggest alteration in fibrin clot structure attributable to acute CSE plays a central role in the etiology of smoking-associated thrombosis.

Although these data suggest a novel, independent means by which acute CSE contributes to the pathology of thrombosis, the findings are currently limited because they lack a specific, biochemical mechanism explaining the effects of acute CSE on clotting. Because high thrombin concentrations were added to platelet-poor plasma to induce fibrin formation in the microscopy studies, the fibrin structural abnormalities seen in this assay likely reflect fibrin(ogen) abnormalities and not contributions of endogenous thrombin generation. Thus, these data support the idea of a direct functional modification to fibrinogen. The authors suggest oxidative stress from CSE directly modifies fibrinogen and, therefore, fibrin formation and structure. Cigarette smoke contains free radicals (reactive oxygen species) and may downregulate endogenous antioxidants. Moreover, fibrinogen is susceptible to oxidation in vitro, and oxidative stress has been implicated in abnormal fibrin structure and stability in acute coronary syndrome. However, further studies are necessary to determine whether acute CSE modifies fibrinogen through oxidation or another mechanism in vivo, and whether this modification affects fibrin formation and structure. Although these data suggest direct functional effects on fibrinogen, the data do not rule out additional effects of acute CSE on plasma proteins or endogenous procoagulant activity. Because Abciximab not only inhibits platelet integrin/fibrin interactions but also reduces platelet procoagulant activity, the relative contributions of fibrinogen abnormality and effects of altered thrombin generation are difficult to ascertain from these experiments. Moreover, the authors initiate fibrin formation in the thrombelastography experiments through contact activation rather than tissue factor. Given previous reports of increased tissue factor expression in atherosclerotic plaques and its role in arterial thrombosis, additional studies are necessary to determine whether and how acute CSE affects tissue factor-induced fibrin formation.

Although abnormal fibrin structure and stability were first reported for dysfibrinogenemia-associated coagulopathies, abnormal fibrin quality (formation, structure, or stability) can be detected in plasmas from patients with a variety of disorders (Figure). The present study complements an increasing number of reports correlating abnormal fibrin quality with hemostatic and thrombotic pathologies, including hemophilia, idiopathic venous thromboembolism, chronic thromboembolic pulmonary hypertension, cryptogenic ischemic stroke, myocardial infarction, and diabetes. Findings that acute CSE modulates fibrinogen/fibrin quality suggest a similar situation occurs in thrombosis associated with environmental toxins, as well. For example, studies showing the incidence of acute thrombotic events
peaks on days after increased air pollution\textsuperscript{21,22} provide an intriguing parallel to the effects of acute CSE observed by Barua et al. Overall, these studies suggest abnormal fibrin quality is a pathological mechanism common to a number of coagulopathic disorders. Further studies are warranted to fully elucidate the contributions of altered fibrin quality to hemostatic and thrombotic diatheses, and to identify novel therapeutic targets to reverse or prevent abnormal fibrin formation.

**References**


Smoking Out the Cause of Thrombosis
Robert A. Campbell, Kellie R. Machlus and Alisa S. Wolberg

Arterioscler Thromb Vasc Biol. 2010;30:7-8
doi: 10.1161/ATVBAHA.109.198051

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/30/1/7

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/