Mechanisms of Coronary Thrombosis in Cigarette Smoke Exposure

Rajat S. Barua, John A. Ambrose

Abstract—Acute rupture or erosion of a coronary atheromatous plaque and subsequent coronary artery thrombosis cause the majority of sudden cardiac deaths and myocardial infarctions. Cigarette smoking is a major risk factor for acute coronary thrombosis. Indeed, a majority of sudden cardiac deaths attributable to acute thrombosis are in cigarette smokers. Both active and passive cigarette smoke exposure seem to increase the risk of coronary thrombosis and myocardial infarctions. Cigarette smoke exposure seems to alter the hemostatic process via multiple mechanisms, which include alteration of the function of endothelial cells, platelets, fibrinogen, and coagulation factors. This creates an imbalance of antithrombotic/prothrombotic factors and profibrinolytic/antifibrinolytic factors that support the initiation and propagation of thrombosis. (Arterioscler Thromb Vasc Biol. 2013;33:1460-1467.)

Key Words: cigarette smoke exposure ■ coronary thrombosis ■ endothelial cells ■ plasminogen activator ■ von Willebrand factor

Hemostasis is a process that maintains integrity of a circulatory system after vascular injury and prevents the sequelae of uncontrolled hemorrhage. This process regulates the intravascular balance of antithrombotic/prothrombotic factors and profibrinolytic/antifibrinolytic factors via interrelated functions of endothelial cells (ECs), platelets, fibrinogen, and coagulation factors. Under normal physiological conditions, regulatory mechanisms contain thrombus formation temporally and spatially. When these regulatory mechanisms of hemostasis are overwhelmed by pathological processes, excessive quantities of thrombin form initiating pathological thrombosis. When a vessel wall is injured or when there is a rupture/erosion of an atheromatous plaque, collagen and tissue factor (TF) become exposed to the flowing blood. Exposed collagen triggers the accumulation and activation of platelets, whereas exposed TF initiates the generation of thrombin, which not only converts fibrinogen to fibrin but also activates platelets. All these initiate the formation of an intravascular thrombus.

Cigarette smoking (CS) is a major risk factor for acute coronary thrombosis leading to myocardial infarction and sudden cardiac death. Cigarette smoke exposure (CSE) seems to alter the balance of antithrombotic/prothrombotic factors and profibrinolytic/antifibrinolytic factors by affecting the functions of ECs, platelets, fibrinogen, and coagulation factors. A meta-analysis of 20 studies showed a 36% reduction in the crude relative risk of mortality for patients with coronary heart disease who quit smoking compared with those who continued smoking. Smoking cessation also leads to an exponential reduction in acute cardiovascular events, particularly in the first year after quitting. Furthermore, public smoking bans in Helena, Montana and Boulder, Colorado, as well as in Scotland and France, were associated with significant reductions in thrombotic cardiovascular events.

In the following sections, we review the existing data regarding the mechanisms of thrombosis in relation to CSE. The Table and Figure 1 summarize the effects and potential mechanisms of thrombosis in relation to CSE.

Smoking, Endothelium, and Thrombosis
ECs play a pivotal role in vascular homeostasis by maintaining a delicate balance between vasodilating (NO, prostacyclin [PGI2]) and vasoconstricting (endothelin-1) factors, thrombotic (TF) and antithrombotic (TF pathway inhibitor-1 [TFPI-1]) and thrombin activatable fibrinolysis inhibitor) factors, as well as fibrinolytic (tissue-plasminogen activator [t-PA]) and antifibrinolytic factors (plasminogen activator inhibitor-1 [PAI-1]). EC dysfunction precedes the thrombotic modification of an atherosclerotic plaque.

Two EC-derived vasodilatory molecules, NO and PGI2, also have direct antithrombogenic effects because they inhibit platelet activation and aggregation by a cGMP-dependent mechanism. We have demonstrated that exposure to active smokers’ sera decreased NO availability from both human umbilical vein ECs (HUVECs) and human coronary artery ECs, by altering the expression and activity of the endothelial NO synthase enzyme. Similarly, using cigarette smoke extract or isolated components, such as nicotine, multiple studies have found that CS was associated with decreased NO availability. It is proposed that decreases in EC-derived...
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NO occur via 2 mechanisms. First, cigarette smoke contains high level of free radicals, and the scavenging activity of cigarette smoke-derived free radicals leads to reduced NO bioavailability. Second, altered endothelial NO synthase protein and its activity also decrease NO availability in relation to cigarette smoker exposure. Not only is NO a vasoregulatory molecule but also it helps regulate inflammation, leukocyte adhesion, platelet activation, and thrombosis. Therefore, an alteration in NO biosynthesis would cause both primary and secondary effects on the initiation and progression of thrombotic events.

Similarly, PGI₂ is also affected by CS. It was reported that aortas from rats that were chronically exposed to cigarette smoke showed a reduction in PGI₂ production. Reinders et al. showed that incubation of cultured HUVECs with cigarette smoke condensate impaired the basal and stimulated (phorbol myristate acetate) production of PGI₂. Ahlsten et al. reported that maternal smoking significantly decreased PGI₂ production in umbilical arteries from newborn infants. HUVECs isolated from mothers who smoke have also been shown to produce less PGI₂ in vitro.

The endothelium is a major source of both thrombotic (TF) and antithrombotic (TFPI-1) factors, as well as fibrinolytic (t-PA) and antifibrinolytic factors (PAI-1). We and others have demonstrated that CSE causes an imbalance in EC-derived antithrombotic and fibrinolytic factors, thus contributing to the generation of a prothrombogenic milieu leading to an acute thrombotic event. Existing data regarding these are discussed in more detail in a later section of this article.

### Smoking, Plaque Vulnerability, and Thrombosis

An atherosclerotic plaque may remain silent and stable for a long period of time. The vulnerability of a plaque for rupture depends on its lipid composition, fibrous cap, degradation of extracellular matrix proteins, recruitment of inflammatory cells, and intraplaque hemorrhage. It was

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CRP indicates C-reactive protein; EC, endothelial cell; IL-6, interleukin-6; PAI-1, plasminogen activator inhibitor; PGI₂, prostacyclin; TNF, tumor necrosis factor; t-PA, tissue-plasminogen activator; TF, tissue factor; and TFPI, tissue factor pathway inhibitor.
found that smokers have a higher extracellular lipid content in their plaques.27 CSE has also been reported to downregulate a key enzyme, n-prolyl-4-hydroxylase, in arterial wall collagen metabolism, which could contribute to development of a thin fibrous cap in the atherosclerotic plaques of smokers.28 Matrix metalloproteinases, which are involved in degradation of extracellular matrix proteins in plaque, were shown to have increased expression and activity in relation to CSE.29 Similarly, CSE or components of CS were suggested to increase intraplaque inflammation and intraplaque neovascularization.30–33 Intraplaque inflammation and intraplaque neovascularization lead to intraplaque hemorrhage and subsequent necrotic core enlargement.34 Furthermore, CSE was found to cause an increased sympathetic activity leading to a rise in blood pressure, pulse rate, and vasoconstriction, which might create a high-mechanical stress zone near a vulnerable plaque.35 All these together are likely to cause plaque instability that contributes toward plaque rupture. Once plaque rupture has occurred, its progression to pathological thrombosis depends on the local balance of platelet activation, antithrombotic/prothrombotic factors, and profibrinolytic/antifibrinolytic factors. Plaque erosion, the other major mechanism for coronary thrombosis leading to myocardial infarction, is highly dependent on prothrombotic forces and is increased in cigarette smokers.35,36

Smoking, Proinflammatory Effects, and Thrombosis
Thrombosis and inflammation are interrelated and mutually reinforcing processes. Thrombosis is proinflammatory, and inflammation promotes thrombosis. These processes involve inflammatory mediators (eg, tumor necrosis factor-α and CD40 ligand), expression of adhesion molecules on ECs, platelets, and monocytes.2–4 An inflammatory response is also involved in TF expression on monocytes and the activated endothelium, as well as activation of circulating TF-bearing microparticles.7,37,38 In humans, chronic CSE was found to be associated with increased levels of multiple inflammatory markers, including peripheral leukocytosis, C-reactive protein, homocysteine, interleukin-6, and tumor necrosis factor-α.39–42 Studies have demonstrated that exposure of HUVECs to cigarette smoke condensate resulted in increased nuclear factor κB DNA binding activity, increased surface expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and platelet EC adhesion molecule-1.33–35 von Willebrand factor (vWF) is contained in EC Weibel–Palade bodies and is an important ligand of platelet binding. Multiple studies have demonstrated an increased level of circulating vWF in smokers.41

Smoking, Platelet Activation, and Thrombosis
During the process of thrombus formation, 2 distinct pathways acting in parallel or separately can activate platelets.5 In the first pathway, exposure of subendothelial collagen initiates platelet activation. The interactions of platelet glycoprotein VI with the collagen of the exposed vessel wall and of platelet glycoprotein Ib-V-IX with collagen-bound vWF result in adhesion of platelets to the site of injury.46 In the second pathway, platelet activation does not require disruption of the endothelium and is independent of vWF and glycoprotein VI.47 TF derived from the vessel wall or present in flowing blood initiates a proteolytic cascade that generates thrombin.48 Thrombin cleaves and activates protease-activated receptors on the surface of platelets. Protease-activated receptor-1 and -4 are particularly important for platelet activation. Once activated, platelets further stimulate thrombus formation and recruit additional platelets by releasing ADP and serotonin, producing thromboxane A2, and amplifying the signals for thrombus formation.46–48 CSE seems to activate platelets by both pathways.

Platelets isolated from smokers exhibited an increased stimulated and spontaneous aggregation.49 Platelet α-granule constituents, such as platelet factor-4, β-thromboglobulin, and platelet activating factor, are increased in the plasma of smokers, suggesting increased platelet activation.50–52 Using a modified prothrombinase method, Rubenstein et al53 compared the effects of sidestream and mainstream smoke on platelet function. Interestingly, the impact of sidestream smoke was as pronounced as that of mainstream smoke. Our group, using thromboelastography, demonstrated that acute CSE was associated with functional changes in platelets and these changes affected the dynamics of clot formation. These clots were more resistant to thrombolysis as compared with clots of nonsmokers.54,55 Smokers also have higher P2Y12 expression in platelet lysates than nonsmokers.56

Platelet activation and recruitment are partly regulated by products of the endothelium, including PGI2 and NO.14,15 NO inhibits platelet adhesion and aggregation; loss of platelet-derived NO promotes platelet recruitment.70 Furthermore, NO insufficiency combined with increased reactive oxygen species causes an increase in intracellular calcium levels in platelets. Increased intracellular levels of calcium induce cytoskeletal rearrangement, trigger α and dense granule release, and promote platelet activation. We and others have demonstrated that EC-derived NO, as well as platelet-derived NO, is decreased in relation to CSE.66–69,82–84 Impaired NO bioavailability also causes secretion of thromboxane A2 from the platelets, which, consequently activates additional platelets.14,15,57 These activated platelets show conformational changes in their cell surface integrin (glycoprotein IIB-IIIa [GP IIB-IIIa]) receptor that result in heightened affinity for its ligands (fibrinogen and vWF). Fibrinogen, vWF, and GP IIB-IIIa receptors cross-link these activated platelets, leading to platelet aggregation.14,15,57 CSE by affecting the levels of vWF and of fibrinogen contributes to increased cross-linking of platelets, which will further enhance the strength of a thrombus.7,39,54,55

Smoking, TF, and Thrombosis
TF is proposed to be a major initiator of thrombin generation and fibrin formation.6 TF is constitutively expressed on fibroblasts and pericytes in the adventitia and medial smooth muscle cells of the vessel wall. Its expression on monocytes and ECs can be induced by various stimuli.60–61 TF is also present in circulating blood in association with micro particles. These vesicular structures (microparticles), which are <1000 nm in diameter, are derived from leukocytes, platelets, ECs, smooth muscle cells, and monocytes.5,52–54 Microparticle-associated TF is thought to exist in a latent
(or encrypted) form that lacks coagulant activity. Currently, it is unclear how microparticle-associated TF becomes active. It has been hypothesized that activated platelets and ECs secrete protein disulfide isomerase, and this enzyme converts the inactive microparticle-associated TF to its active form. CS seems to affect TF expression and activation in cells, as well as in the circulation. Atherosclerotic plaques isolated from ApoE−/− mice exposed to nonfiltered research cigarettes showed an increased TF immunoreactivity and an increase in TF activity. In smokers, 2 hours after smoking 2 cigarettes, an increase in circulating TF activity has also been reported in human plasma. In vitro, HUVECs exposed to serum from chronic smokers showed a relatively higher increase in TF level after 12 hours. However, it was not statistically significant.

In the same cell culture supernatant, there was a significant decrease in EC-derived TFPI-1 secretion in the smoking group. TFPI-1 is a potent regulator of TF factor VIIa-dependent activation of the TF pathway. In the same study, EC culture supernatant in smokers group had a relative increase of the TF/TFPI-1 ratio, and this alteration conceivably denoted an increase in thrombotic potential. Additionally, TFPI-1 showed a significant positive correlation with NO. This suggested that the prothrombotic alteration in TF/TFPI-1 could be partially mediated by decreased NO bioavailability. Similarly, an increase in TF-containing microparticles in the circulation was reported in multiple studies in relation to CSE.

Smoking, Fibrinogen, and Thrombosis
Fibrinogen, a bivalent molecule, augments platelet aggregation by linking GPIIb/IIIa receptors between activated platelets. The structural support of a thrombus is provided by a matrix of cross-linked fibrin. Dotevall et al found that plasma fibrinogen levels were significantly higher among smokers. Factor XIII covalently cross-links and stabilizes fibrin clots. It was reported that factor XIII A-subunit levels were significantly increased in smokers. Our group, using thromboelastography, demonstrated that acute CS was associated with functional changes in fibrin, which increased the kinetics of clot formation, the rapidity of fibrin buildup, and clot strength. In the same study by using electron microscopy, we found these effects were partly mediated by changes in fibrin clot architecture. CS was associated with thinner and denser fibrin fibers that were resistant to thrombolysis (Figure 2).

A timely dissolution of the fibrin matrix is essential to inhibit pathological propagation of a thrombus. The lysis of fibrin is mediated by plasmin. Plasminogen is activated to plasmin by t-PA. On the contrary, t-PA is inhibited by PAI-1. Smokers have higher PAI-1, which correlated with the estimated pack-years of cigarettes smoked. It has been suggested that the t-PA/PAI-1 molar ratio is a useful indicator of fibrinolytic balance. Newby et al have shown that, in smokers, substance P-stimulated t-PA antigen and activity are decreased with no change in PAI-1 antigen or activity in both the peripheral and coronary circulation. Using HUVECs and smokers serum, we demonstrated that substance P-stimulated t-PA release was decreased in smokers with no change in basal and stimulated PAI-1 antigen. Additionally, basal t-PA production and t-PA/PAI-1 molar ratio were also significantly reduced in smokers.

Figure 2. Electron microscopic image of fibrin clots from a smoker (A and B, pre- and postsmoking samples from the same subject) at 20K magnification.

All these suggest that endogenous fibrinolytic activity is impaired in smokers.

Smoking, Oxidative Stress, and Thrombosis
Cigarette smoke contains >4000 identified and >100000 unidentified components, of which only a few components have been examined in isolation, such as carbon monoxide (CO), nicotine, and particulate matter. An earlier study suggested that CO could be responsible for smoking-related atherothrombotic events. However, more recent data suggest that CO from cigarette smoke has been shown to exhibit antithrombotic properties. Nicotine is the only known addictive substance in cigarette smoke, and it is also its most studied component. Although the role of nicotine in the hemodynamic effects of smoking is well accepted, its effect on thrombohemostatic factors, such as platelets, fibrinogen, t-PA, or PAI-1, seems to be small and probably plays only a minor role in atherothrombotic events directly. Current data suggest that particulate matter contributes to atherothrombotic events by increasing the inflammatory response and oxidative stress. Regardless of the components of CS, current available data suggest that free radical–mediated oxidative stress and the loss of the protective effect of NO are the key steps in the prothrombogenic modification of the ECs, platelets, fibrin, and prothrombotic factors in the vessel wall, as well as in the circulation. These 2 processes are interrelated. In a setting of CSE, free radicals could potentially arise from the following: (1) cigarette smoke directly, (2) circulating or in situ-activated macrophages and neutrophils, and (3) endogenous sources of reactive oxygen species, such as uncoupled endothelial NO synthase, xanthine oxidase, and the mitochondrial electron transport chain. A reaction between free radicals, such as superoxide and NO, not only decreases NO availability but also generates peroxynitrite, which further potentiates the oxidative stress. Increased oxidative stress with the loss of the protective effect of NO tips the
Passive Smoking and Thrombosis

Like active CS, passive smoke exposure is also associated with an increase in the incidence of myocardial infarction.82,83 The risk of death attributable to cardiovascular disease increases by 30% in nonsmokers who live together with smokers. It is estimated that >50,000 deaths annually from ischemic heart disease are associated with passive smoking.82,83 A meta-analysis of large cohort studies showed that, in active smokers, the risk for ischemic heart disease with 5 cigarettes per day was not a quarter but about half that associated with 20 cigarettes per day.84 More importantly, it has been estimated that with environmental smoke exposure, even though the exposure to tobacco smoke was <1% of the exposure from smoking 20 cigarettes per day, the excess risk for ischemic heart disease was ≈33% of that experienced by a person who smoked 20 cigarettes per day.85,86

All these epidemiological data suggest a nonlinear dose–response relationship in the intensity of exposure to passive smoking.85 These findings are consistent with experimental data showing a nonlinear effect on platelet activation and aggregation.82,86–88 Public smoking bans in multiple countries were associated with rapid and significant reductions in thrombotic cardiovascular events.9–11 In a study in France, it was reported that smoke-free legislation led to a 40% reduction in fibrin-rich clot stiffness coupled with a drop in clotting time and fiber density among exposed subjects. This change in fibrin structure led to a 22% reduction in the clot lysis-time.12 These results were similar to the change in fibrin architecture seen by our group in relation to active smoking.54,55 Similarly, vWF, TF-containing microparticles, fibrinogen, and inflammatory markers were reported to be elevated in passive smokers.82–89

Smoker’s Paradox

Although thrombosis is the main mechanism for smoking-related cardiovascular mortality, in a seemingly contradictory observation, it has been reported that there is a reduced mortality for smokers with ST-elevation myocardial infarction, and it was proposed that based on higher thrombolysis in myocardial infarction-3 (TIMI-3) flow after t-PA, thrombolysis was enhanced in smokers.90,91 Furthermore, post hoc analyses of pivotal clinical trials (Clopidogrel for the Reduction of Events During Observation [CREDO], Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance [CHARISMA], Clopidogrel as Adjunctive Reperfusion Therapy [CLARITY]-TIMI 28), comparing dual antiplatelet therapy consisting of aspirin and clopidogrel versus aspirin alone, showed that clopidogrel therapy may be more effective in current smokers compared with nonsmokers.92–94 These findings have been suggested to reflect a smoker’s paradox. One of the hypotheses is that thrombus in smokers may be more fibrin-rich and, therefore, more amenable to fibrinolytic therapy.90,94 However, in an experimental study, our group demonstrated that clots from smokers were significantly more resistant to lysis when exposed to t-PA compared with nonsmokers. This seems to contradict this hypothesis.55

As for the increased effectiveness of clopidogrel in smokers, CS is a known inducer of cytochrome P450 1A2 (CYP1A2), and its activity increases relative to the number of cigarettes smoked per day.95 CYP1A2 is the predominant isoenzyme responsible for the first of the 2 oxidative steps required for clopidogrel to be metabolized into its active metabolite. However, contradictory data exist and, additionally, a smoking paradox was not demonstrated in trials with newer antiplatelet agents, such as prasugrel (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel [TRITON]-TIMI 38) and ticagrelor (Platelet Inhibition and Patient Outcomes [PLATO] trials).96,97 Furthermore, other studies proposed that smokers have a lower mortality after myocardial infarction because of their younger age and lower rates of other coexisting cardiovascular risk factors compared with nonsmokers.98,99

Future Direction

Although CS is very hazardous, not all smokers seem to be affected similarly from their addiction.100 For example, 50% of lifelong smokers die prematurely from smoking-related diseases, but the other 50% do not.100 The sources of variability are partly attributable to the presence of other risk factors and partly attributable to genetic predisposition. It was reported that there is a differential effect of smoking on cytochrome P450 system polymorphism.100,101 Current smokers and ex-smokers with uncommon endothelial NO synthase 4a gene polymorphism have been reported to have severe coronary stenosis.101 Several studies have reported that smokers with the A-455 allele (G-455A b-fibrinogen gene promoter polymorphism) experienced a greater rise in fibrinogen than those lacking this allele.102 Similarly, the presence of the glycoprotein IIIa P1(A2) polymorphisms are associated with increased risk of acute ST-elevation myocardial infarction in smokers.103 Polymorphisms of factor XIII genes are also reported to affect fibrin architecture and fibrinolysis.55 The combination of the FXIII L34-allele and nonsmoking status increased the risk of nonreperfusion and worse outcomes.55 The mechanisms of gene CSE interactions in atherothrombotic disease have not been well studied. Future focus studies examining the interaction between CSE and these genetic variations will be needed to further understand the differential effect of genetic polymorphisms in CSE-related atherothrombotic diseases, which will potentially allow improved targeted therapies in these individuals.

Biomarkers can be used as indicators for certain biological states, pathogenetic processes, or responses to pharmacological treatments. An ideal biomarker would show a dose–response relationship with smoking and a change with cessation or reduced exposure. So far, no existing biomarkers have been demonstrated to be predictive of smoking-related atherothrombotic disease, which highlights a need for research.
in this field. MicroRNAs are involved virtually in every cellular process, and aberrant expression is associated with cellular dysfunction and disease.\(^{104}\) Recently, evaluation of microRNAs showed some promise as potential biomarkers for atherothrombotic diseases, as well as CSE-related diseases.\(^{105,106}\) Additional research in these areas will be needed if one is to develop effective diagnostic or prognostic tools in CSE-related atherothrombotic diseases.

The most effective prevention for CSE-related atherothrombotic diseases is to avoid all exposure to CS. However, for those who have previously been exposed to CS or continue to be exposed, whether actively or passively, there is further need for a mechanistic understanding of molecular pathways linking individual smoke constituents or classes thereof to the process of atherothrombotic diseases and their outcome. Improved mechanistic understanding in this area might support the development of novel products that would help for the general prevention, diagnosis, and therapy, in CSE-related atherothrombotic diseases.

**Conclusions**

Epidemiological studies have established that CSE is an important cause of cardiovascular morbidity and mortality worldwide. Clinical and experimental studies indicate that either active or passive cigarette exposure promotes thrombosis in multiple vascular beds by affecting the function of ECs, platelets, fibrinogen, and coagulation factors. Although the precise mechanisms responsible for these alterations remain to be confirmed, a growing body of evidence supports free radical–mediated oxidative stress and loss of the protective effect of NO playing a central role in CSE-mediated thrombotic diseases. However, future studies with a multidisciplinary approach will be needed to further define these mechanisms.

**Disclosures**

None.

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