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Research Article

**SIGNIFICANT EFFECT OF CIGARETTE SMOKING ON
PLATELET MORPHOLOGICAL INDICES BETWEEN
HEALTHY SMOKERS AND NON-SMOKERS**

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Abstract:

Cigarette smoking continues to be a major health hazard, and it contributes significantly to cardiovascular morbidity and mortality. Cigarette smoking impacts all phases of atherosclerosis from endothelial dysfunction to acute clinical events, the latter being largely thrombotic. Both active and passive smoking has been well established that cigarette smoking is a powerful risk factor for coronary artery disease. A number of epidemiological studies have shown a strong association between cigarette smoking and atherosclerosis, myocardial infarction and death from coronary artery disease. In addition to active smoking, passive smoking can also carry a risk of coronary artery disease. Although the detailed mechanism through which cigarette smoking is associated with cardiovascular disease has not yet been clarified. We sought to investigate whether plasma fibrin clot structure/function differ between healthy smokers and never-smokers.

Cigarette smoking in healthy individuals results in significant and considerable effects on platelet morphological indices. The mean platelet count is significantly increased, and platelet values are reduced, compared with non-smoking status.

Key Words: Platelets - plasma clot - Cigarette smoking (CS) - Atherosclerosis – predisposing factors.

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INTRODUCTION:

Background Smoking is associated with an increased risk of myocardial infarction and sudden death. Platelet activation and thrombosis at sites of vessel stenosis and injury or plaque disruption play a crucial role in these acute coronary events. Thus, the aim of this study was to determine whether cigarette smoking acutely increases platelet thrombus formation on an injured arterial surface at local shear rates typical of a stenotic artery.

Cigarette smoking is associated with an increased incidence of acute MI. Cessation of smoking significantly reduces this risk over a one- to three-year period with an exponential decline approaching the risk in ex-smokers within five years of cessation. Recent data indicate an immediate reduction in thrombotic events with smoking cessation. A preliminary, oral presentation study (presented by Sargent, Shepard, and Glantz at the 52nd Annual American College of Cardiology Conference in March 2003) reported that a citywide smoking ban in public places over a six-month period in Helena, Montana, reduced the incidence of acute MI by 60% during that time period. Furthermore, pathologic studies of sudden coronary death indicate that CS increased the risk of plaque rupture and acute thrombosis of a lipid-rich, thin-capped atheroma in men; in female smokers, the prevailing mechanism was plaque erosion with superimposed thrombosis. Acute cigarette smoke exposure may also increase coronary artery vascular resistance reducing coronary blood flow. Smoking may also be a risk factor for coronary vasospasm [1].

The prothrombotic effects of exposure to cigarette smoke have been repeatedly demonstrated to cause alterations in platelet function, antithrombotic/prothrombotic factors, and fibrinolytic factors. The following sections address the present knowledge regarding these effects. Platelets isolated from smokers exhibited an increased stimulated as well as spontaneous aggregation. After exposure to smokers' serum, platelets isolated from non-smokers demonstrated hyper aggregability. Cigarette smoking may decrease availability of platelet-derived NO and decrease platelet sensitivity to exogenous NO, leading to increased activation and adhesion [2]. Current smokers have higher fibrinogen levels that correlate with the number of cigarettes smoked. Ex-smokers have fibrinogen levels similar to non-smokers. Alterations of tissue factor (TF) and TF pathway inhibitor-1 (TFPI-1) and a consequent increase in thrombotic potential have also been documented. Human umbilical vein endothelial cells exposed to serum from chronic smokers showed a significantly decreased TFPI-1 level and relatively higher but non-significant increase in TF level in culture. An increased TF immunoreactivity

and an increase in TF activity were observed in atherosclerotic plaques isolated from APOE^{-/-} mice exposed to half of a non-filtered research cigarette five days a week, for eight weeks. In smokers 2 h after smoking two cigarettes, an increase in circulating TF activity has also been reported in human plasma [3]. Furthermore, higher red blood cell counts, hematocrits, blood viscosity, and an ongoing inflammatory process potentiate the prothrombotic process associated with smoke exposure [4,5,6].

RESULTS:

The biological mechanism linking smoking and clot features is complex and not fully understood. Besides clot features, proposed potential mechanisms by which smoking increases the risk of cardiovascular pathology include several other pathways: vascular endothelial dysfunction, systemic hemostatic and coagulation disturbances, and lipid abnormalities [7]. Many of these indexes including fibrinogen (marker of coagulation), fibrin d-dimer (a marker of cross-linked fibrin turnover), and tissue plasminogen activator antigen (t-PA, marker of endothelial dysfunction) have been identified as independent predictors of subsequent cardiovascular events in prospective studies conducted in healthy subjects. In addition, platelet hyper aggregation and activation, plasma viscosity, and plasminogen activator inhibitor (PAI) type I (marker of impaired fibrinolysis) levels have also been associated with cardiovascular morbidity and mortality in prospective studies. The effect of smoking on these variables has also been investigated in several cross-sectional studies, as will be discussed below. It has been demonstrated that the serum concentration of nitrate and nitrite, metabolic end-products of NO, is significantly decreased in smokers relative to that in nonsmokers. In cigarette smokers, low-density lipoprotein (LDL) is more prone to oxidation due to higher level of ROS and reactive nitrogen species [8,9]. Oxidatively modified LDL limits the bioactivity of endothelium-derived NO; and, in turn, the loss of NO bioactivity is associated with increased inflammatory cell entry into the arterial wall. Oxidatively modified LDL is taken up by macrophage scavenger receptors, promoting cholesterol ester accumulation and foam cell formation. Most recently, upregulation of the CD40/CD40L dyad and increased platelet/monocyte aggregation have been proposed as potential contributors to the atherothrombotic consequences of smoking [18]. CD40-CD40 ligand couples, members of TNF family, are co-expressed by all of the major cellular players in atherosclerosis. In particular, smokers appeared to have elevated plasma levels of soluble CD40 and increased surface expression of CD40 on monocytes together with

increased CD40 ligand on platelets. Furthermore, plasma cotinine concentrations correlated with CD40 and CD40 ligand expression, and with rate of platelet-monocyte aggregations. A recent study suggests that oxidatively modified LDL may play the role of initial trigger for CD40/CD40L expression in human endothelial and smooth-muscle cells. Dysfunctional endothelial cells lose their critical physiologic property of non-adherence to circulating immune effector cells (monocytes, macrophages, T-lymphocytes, platelets). Some adhesion molecules are known to be elevated in plasma of smokers. Several groups reported significantly higher levels of soluble intracellular adhesion molecule (ICAM)-1 and P-selectin and E-selectin in current smokers than in nonsmokers among healthy women. A dose-dependent relationship was observed between plasma ICAM-1 concentration and daily cigarette consumption, plasma cotinine level, and exhaled carbon monoxide level.⁸⁰ Generally, impaired endothelial function caused by cigarette smoking may lead to increased susceptibility of vasculature to atheroma formation and can be considered as a nearly feature of atherogenesis in humans. Furthermore, elevated levels of markers of fibrinolysis have been reported in healthy smokers [10-11]. t-PA, the main fibrinolytic activator, converting plasminogen to plasmin is synthesized by endothelial cells. In vivo studies⁸² have demonstrated major impairment of t-PA release from the vascular endothelium of smokers. The primary inhibitor of fibrinolysis is PAI-I, which inhibits plasminogen activation by binding with t-PA to form the PAI/t-PA complexes. Current smoking is associated with a significant increase in t-PA antigen, which represents mainly the circulating PAI/t-PA complexes and indicates impaired fibrinolytic activity in smokers. Supporting previous findings, plasma PAI-1 antigen and/or activity is significantly higher in smokers than in nonsmokers and is correlated with pack-years smoked. Plasmin promotes the degradation of fibrin within the thrombus, disintegrating clots, and hence maintains vascular patency. Fibrin d-dimer is a degradation product of cross-linked fibrin that is related to cardiovascular diseases risk. As been reported, smoking is positively associated with fibrin d-dimer [12-13]. The increased d-dimer in smokers probably reflects increased coagulation activation because this antigen is present in several degradation products from the cleavage of cross-linked fibrin by plasmin. Taking into account possible adverse effects of abnormal fibrinolysis and excess coagulation on vascular health, further studies are essential to evaluate the impairment of the fibrinolytic system in smokers [14-15].

There is a scarcity of studies that evaluate all of the platelet parameters including MPV, PDW, and PCT. In our study cigarette smoking in healthy men was accompanied by significant and considerable effects on platelet indices with a significantly increased mean PLT, and decreased PCT value in comparison with non-smokers. Further studies are required to explain these morphological changes in platelets following smoking. Some limitations of our study include the relatively small sample size and lack of investigation of women due to their denial of smoking.

DISCUSSION:

Smoking-enhanced platelet thrombosis may be an important contributory mechanism for acute coronary events in smokers that is not prevented by aspirin treatment. Catecholamine release and heightened platelet aggregation response to in vivo agonists may contribute to the prothrombotic effects of smoking.

Factors and mechanisms responsible for smoking-mediated vascular dysfunction

Human umbilical vein endothelial cells exposed to chronic smoker's serum have significant decreases in both basal and substance-P-stimulated t-PA release in culture with a significant alteration in t-PA/PAI-1 molar ratio. Similarly, decreased plasma t-PA antigen and activity were observed in smokers in samples isolated from brachial and coronary arteries after pharmacologic stimulation.

Therefore, CS is associated with dysfunctional thrombo-hemostatic mechanism(s) that promote the initiation and/or propagation of thrombus formation and limit its effective dissolution [16].

Cigarette smoke contains over 4,000 known components, of which only a few components have been examined in isolation. Carbon monoxide (CO) is one such component, but its effects on atherothrombotic disease have been equivocal. An earlier study suggested that CO could be responsible for smoking-related cardiovascular alterations. However, more recent data suggest that CO from cigarette smoke was an unlikely cause for atherosclerosis or thrombus. Polycyclic aromatic hydrocarbons found in the tar fraction of cigarette smoke have also been studied, and these components, at least in experimental models, accelerate atherosclerosis [17].

Nicotine in cigarette smoke is probably the most studied component. Although nicotine plays a major role in smoking-related increases in cardiac output,

heart rate, and blood pressure, its role in CS-related atherothrombotic disease remains controversial [18]. Nicotine exposure alone had been reported to cause no change, a decrease, or an increase in EDV or NO availability. In various models, although high doses of nicotine favor atherogenic changes, the majority of current evidence suggests that nicotine, at concentrations similar to a smoker's blood level, has a minor effect on the initiation or propagation of atherosclerosis. Similarly, the effect of nicotine on thrombo-hemostatic factors such as platelets, fibrinogen, or t-PA, PAI-1 appears to be insignificant in the setting of smoking. As mentioned earlier, nicotine is the known addictive substance in cigarette smoke, and its addictive qualities likely perpetuate exposure to the other more detrimental components [19].

Currently, free radical-mediated oxidative stress is emerging as the pivotal step for the development of atherosclerosis. In a setting of CS, free radicals could arise from: 1) the gas or tar phase of cigarette smoke; circulating or in situ-activated macrophages and neutrophils; and endogenous sources of reactive oxygen species such as uncoupled eNOS, 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 enhances the cellular oxidative stress [20]. Increased oxidative stress with the loss of the protective effect of NO tips the cellular balance towards a proatherogenic and prothrombotic milieu. Many of the abnormalities described above, including endothelial dysfunction, proinflammatory effects on the vessel wall, prothrombotic effects such as increased platelet reactivity, reduced endogenous fibrinolysis, and lipid peroxidation, can largely be explained by the effects of increased oxidative stress. Furthermore, antioxidants or agents that reduced the oxidative stress or increased NO availability have been shown to either improve or reverse the proatherogenic, proinflammatory, and prothrombotic attributes associated with CS.

Nonlinear dose effect of smoking on cardiovascular function

Although the association between CS and cardiovascular risk has clearly been demonstrated, an unanswered question is whether or not there is a linear dose effect. Several recent large epidemiologic studies showing a trend for more cardiovascular events in heavier active smokers have failed to find a significant dose-dependent correlation between cardiovascular risk and the number of cigarettes smoked or the pack-years of exposure. More recently, heavy and light active smokers had a similar decrease in brachial artery EDV and similar abnormalities of NO biosynthesis.

Similarly, even with passive smoking, certain atherothrombotic markers such as a reduced EDV and increased platelet activation were similar to that of active smoking. The data presented above suggest that the underlying biochemical and cellular processes may become saturated with small doses of toxic components from cigarette smoke causing a nonlinear dose-response on cardiovascular function. The exact mechanisms require further studies [21-22].

CONCLUSIONS:

Despite strong epidemiological evidence linking tobacco smoking to an increased risk of ischemic heart disease and vascular mortality, the precise mechanisms involved are not fully elucidated. Suggested causal mechanisms in chronic smokers include increased atherosclerosis, enhanced platelet aggregation and thrombosis, hyper coagulability, increased fibrinogen, and decreased fibrinolytic activity in the blood. Because smoking is particularly associated with an increased risk of myocardial infarction and sudden death, it is likely that smoking influences the terminal occlusive and thrombotic event. This is further supported by the rapid decrease in risk of myocardial infarction and coronary death among ex-smokers. Although the precise mechanisms responsible remain undetermined, free radical-mediated oxidative stress appears to play a central role in CS-mediated atherothrombotic diseases. These free radicals could potentially arise directly from cigarette smoke and indirectly from endogenous sources as well. Furthermore, potentiated by multiple prothrombotic and antifibrinolytic effects, intravascular thrombosis is the predominant cause of acute cardiovascular events. An increasing body of epidemiologic, clinical, and experimental data also suggest that the pathophysiologic effects of cigarette smoke exposure on cardiovascular function may be nonlinear.

Cigarette smoking is a major risk factor for cardiovascular morbidity and mortality and is a leading cause of death. The effect of cigarette smoking on coronary risk factors is pervasive. Unfavorable effects include enhancement of platelet function. Platelet activation by cigarette smoking is linked to thrombosis formation, including onset of myocardial infarction. In light of the adverse effects on platelet function, cessation of smoking should be encouraged.

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