SMOKING, PLATELET REACTIVITY AND FIBRINOGEN

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INTRODUCTION

It is universally accepted that smoking constitutes a major independent risk factor for the development of atherosclerosis as well as arterial thrombosis formation and its most serious consequences, i.e., coronary artery disease/acute myocardial infarction and stroke (A Report of the Surgeon General, 1983). Likewise, it is well recognized that platelets play an important role in the development of occlusive arterial disease (Schafer and Handin, 1979); there is indeed substantial evidence to suggest that abnormal platelet/vessel wall interaction is involved in the pathogenesis of the atherosclerotic lesion itself (Weksler and Nachman, 1981; Hoak, 1988). Also, a strong association between plasma fibrinogen concentration and platelet aggregability was reported by Meade et al. (1985). In atherosclerosis, lipids and fibrinogen accumulate in the subintimal layers of the arterial wall. Fibrinogen is an acute phase protein and plasma concentrations rise as a result of a wide range of stimuli many of which are of a non-specific nature, e.g., chronic inflammatory disorders, after surgery, in malignant disease and during pregnancy. Indeed, atheroma displays some of the characteristics of an inflammatory response. The present article attempts to review some of the concepts as to how smoking relates to platelet reactivity and plasma fibrinogen concentration, and thereby to arterial vascular disease.

PLATELET REACTIVITY

In their attempts to evaluate platelet reactivity in response to smoking, clinical investigators have employed a variety of laboratory tests thought to reflect in vivo platelet behaviour. Herein are included, e.g., measurements of platelet survival, the bleeding time, platelet aggregation in response to various agonists, platelet aggregation ratio, plasma concentrations of platelet-specific proteins, serum thromboxane B2 (TXB2) formation and serotonin (5-HT) release. However, only measurement of the standardized template bleeding time can be considered a true reflection of in vivo events. A carefully performed bleeding time yields a valuable measure of platelet participation in primary hemostasis with sufficient sensitivity and reliability to serve as the best clinical screening test of platelet function (Harker and Slichter, 1979).
Platelet survival studies

The results of studies obtained using $^{51}$Cr-labelled platelets have shown reduced platelet survival in habitual smokers (Fuster et al., 1981); further, significant lengthening of shortened survival toward normal occurred in smokers who discontinued smoking.

Measurement of bleeding time

The template bleeding time is a highly repeatable test when there is strict adherence to multiple technical points. The presence of a blood pressure cuff, which creates venostasis to insure adequate venous filling, and the direction of the incision are technical factors that influence the repeatability of the test (Mielke, 1982). The results may also be disturbed by the possible recent intake of aspirin or other non-steroidal anti-inflammatory drugs which necessitate additional caution whenever the test is performed.

Despite all these considerations having been taken into account, rather conflicting results emerged when the effect of acute smoking on the template bleeding time was investigated. Thus, one group of Danish workers demonstrated that the bleeding time became significantly shortened immediately after the smoking of two high-nicotine content cigarettes (Ring et al., 1983; Madsen and Dyerberg, 1984); no such shortening was recorded after smoking two nicotine-free cigarettes (Ring et al., 1983). However, in two other studies carried out on healthy habitual smokers, no such shortening in bleeding time was recorded after the acute smoking of two cigarettes (Davis and Davis, 1983; Kampman and Hornstra, 1988). Nor was there any difference as regards bleeding time in between steady state habitual smokers and non-smokers (Davis and Davis, 1983).

Platelet aggregation studies

Similarly, the results of in vitro platelet aggregation studies in response to various agonists have yielded conflicting results as regards the effect of smoking. Herein, it appears necessary to distinguish between results obtained from steady state chronic/habitual smokers and results obtained in the immediate response to acute smoking.

Chronic smoking. As regards in vitro platelet aggregation in response to a variety of agonists including adenosine diphosphate (ADP), epinephrine, collagen, thrombin and arachidonic acid (AA) as well as platelet aggregation ratio (Wu and Hoak, 1974) most authors appear to agree that platelet sensitivity does not differ between chronic smokers and non-smoking control subjects (Chao et al., 1982; Carlsson and Wennmalm, 1983; Dotevall et al., 1987; Rival et al., 1987; Berglund et al., 1988; Lassila and Laustiola, 1988). Indeed, in one study ADP-induced aggregability was even greater in non-smokers than smokers (Meade et al., 1985). More interestingly, it was demonstrated by Lassila and Laustiola (1988) that after exercise, smokers' platelets were desensitized to all doses of epinephrine and low doses of ADP and collagen and the levels of serum TXB$_2$ were lower than among non-smokers; this finding was supported by the decreased release of 5 HT and TXB$_2$ during aggregation induced with epinephrine. It was also shown that aggregation of platelets stimulated by epinephrine was significantly reduced in smokers after exercise and the refractoriness appeared to be maintained for 15 and 30 minutes afterwards (Lassila 1989).

In studies of chronic smokers at rest the plasma concentrations of $\alpha$-granule proteins, beta-thromboglobulin (BTG) and platelet factor 4