Elevated Erythrocyte Aggregation Rates in Smokers: An Impact on the Pathophysiology of Atherothrombogenesis

SİGARA İÇENLERDE ERİTROSİT AGREGASYON HIZLARINDA ARTIŞ: ATEROTROMBOGENEZİN PATOFİZYOLOJİSİ ÜZERİNDEKİ ETKİSİ

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Summary

Erythrocyte aggregation [EA] is one of the most important hemorheological parameters. It has been proposed that in patients with coronary heart disease [CHD], elevated EA is an independent risk factor. Smoking is also a major risk factor for the development of CHD. The exact mechanism of smoking in the pathophysiology of atherogenesis has not been established yet. We designed a study to show if smoking habits cause elevations in EA rates. On a total of 271 participants (140 non-smokers, 67 smoking <1 pack/day and 64 smoking >1 pack/day), EA rates were measured both at high (M) and low shear rates (Ml). It was seen that smoking had a significant effect on EA rates (p<0.0() 1). We suggest that atherogenic potential of smoking may be through its effects on altered red blood cell rheology.

Key Words: Erythrocyte aggregation, Rheology, Smoking

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Özet

Eritıvsit agregasyonu (EA) en önemli hemoreolojik parametrelerden birisidir. Koroner arter hastalığında (KAH) artmış EA 'nun bağımsız bir risk faktörü olabileceği öne sürülmüştür. Sigara içmek de KAH'nın gelişiminde majör bir risk faktörüdür. Sigara içmenin aterogenezin patofizyolojisindeki kesin mekanizması tam olarak gösterilememiştir. Biz sigara alışkanlığının EA 'mı artırıp arttrmadığını anlamak amacıyla bir çalışma planladık. Katılan toplam 271 kişide (140 sigara içmeyen, 67<1 paket/gün ve 64>1 paket/gün içen) yüksek (M) ve düşük (Mİ) akım hızlarında EA ölçüldü. Sigara içmenin EA üzerinde çok önemli etkisi olduğu görüldü (p<0.001). Biz sigaranın ateroj enik potansiyelinin kırmızı kan hücrelerinin reolojisini değiştirici etkisi yoluyla olduğunu düşünüyoruz.

Anahtar Kelimeler: Eritrosit agregasyonu, Reoloji, Sigara içme

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Hemorheology is an area of science concerned with the flow and deformation of blood and its relation to the vessel wall with which the flowing blood is in contact (1). It has long been known that hemorheological factors such as erythrocyte deformability, whole blood viscosity, fibrinogen, hematocrit and white blood cell count play important roles in the pathophysiology of atherothrombogenesis (2). One of the most important hemorheological determinants of microcirculation is erythrocyte aggregation (EA) (3). Elevated EA has been considered as an important risk factor for the development of vascular events, notably atherosclerosis (1,2).

In a previous study, we have shown that elevated EA is an independent risk factor especially for severe forms of coronary heart disease [CHD] (4). It is well known that cigarette smoking is a major risk factor for CHD. Since both EA and smoking are risk factors for CHD, we planned to compare EA rates in smokers and non-smokers.

Materials and Methods

Two hundred and seventy-one subjects with established CHD or no known health problem (191 CHD and 80 healthy controls; 155 men, 116 women, mean age: 54.4 ± 1.3, range: 33-80) were enrolled into the study. The participants were divided into 3 groups with respect to smoking; group

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1: non-smokers (n: 140), group 2: smoking <1 pack/day (n: 67) and group 3: smoking >1 pack/day (n: 64). Groups were age- and sex-matched. The distribution of CHD patients among 3 groups with respect to smoking were statistically similar (p>0.05).

For determination of EA, fasting venous blood samples were collected in the morning. EA was studied by a photometric rheoscope (Myrenne aggregometer) which measures EA in a 20 ul of blood anticoagulated with EDTA. Measurements were made at hematocrit adjusted to 45% by removing or adding autologous plasma, after shearing at 600 sec^{-1}, at stasis (M, high shear rate) and at 3 sec^{-1} (M1, low shear rate) (5). All other parameters (hematocrit, fibrinogen and cholesterol) were tested by routine methods. Student's t-test and analysis of variance were used for comparisons between groups where appropriate. The association of numeric variables with M and M1 were evaluated by Pearson's coefficient. Multivariate analysis was performed by using a multiple regression model. All values are expressed as mean ± standard error. A value of p<0.05 was accepted as statistically significant.

Results

As we have reported previously (4), when we compared EA rates at M and M1 between CHD groups and healthy controls, these 2 values were significantly higher in CHD group (p<0.05). In this study comparing EA rates with respect to smoking habits, we divided the subjects into 3 groups. Here we had the chance of examining the effect of smoking on EA independently since the distribution of CHD patients and healthy controls in 3 groups were similar.
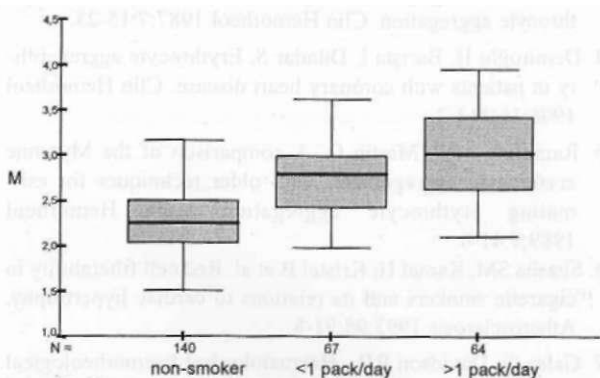
Biochemical and hemorheological results of the groups are shown in Table 1. Cholesterol and fibrinogen values were similar in all groups (p>0.05). Hematocrit was higher in group 3, than in the other groups (p<0.05). Although hematocrit was slightly higher in group 2 than in group 1, the difference was not significant (p>0.05). There were no statistically significant differences among groups (p>0.05) in age, sex and other parameters that may be important in blood rheology, such as arterial blood pressure and body weight, either. As seen in Figures 1 and 2, the effect of smoking on EA rates were significant (p<0.001). EA rates at M and M1 were higher in group 3 than group 2 (p<0.05) and group 1 (pO.OOl). M and M1 were also higher in group 2 than in group 1 (p<0.05). When we compare the EA rates with respect to smoking, separately inside CHD and healthy controls groups, the results are again similar i.e. with EA rates higher in those smoking more.

Discussion

Cigarette smoking adversely affects blood fluidity by increasing blood and plasma viscosity and by causing abnnonnalities of eiythrocyte deformability (6). Alterations in blood rheology might influence blood flow and play a role in the develop-

Table 1. Laboratory values of the groups

	Group 1	Group 2	Group 3
Hematocrit (%)	44.4 ± 0.6	44.8 ± 0.3	45.7 + 0.5
Cholesterol (mg/dl)	192 ±4	201 ±6	204 + 7
Fibrinogen (mg/dl)	218+12	225+ 16	230+ 10
M	2.29 ± 0.03	2.73 ± 0.04	3.03 + 0.06
M1	6.85 ± 0.09	7.84 ±0.12	8.43 ± 0.15

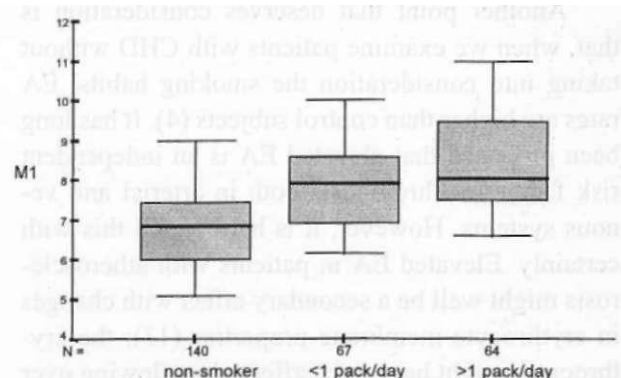**Figure 1.** Effect of smoking on EA at high shear rate

Figure 2. Effect of smoking on EA at low shear rate

merit of atherosclerosis (7,8). It was shown that rheologic properties of blood improves with the cessation of smoking (9).

The mechanism of atherogenesis due to cigarette smoking is not clear. The risk is reduced when smoking is stopped. In the Framingham Study, it was shown that the risk of smoking was independent of other major risk factors for CHD (10). Smoking may also aggravate other risk factors such as hypertension and may also reduce high density lipoprotein cholesterol which is protective against atherosclerosis. One of the mechanisms of increased tendency towards atherogenesis may be through its effect on the behaviour of erythrocytes, such as increased EA, decreased filterability of erythrocytes and elevated blood viscosity as a result of increased hematocrit (6,7,11). The results presented in this study confirm positive correlation between smoking and disturbances of red blood cell rheology. According to the results of our study, it is apparent that smoking (more packs/day) causes higher EA rates. The mechanism(s) of smoking on the increased rate of EA is not exactly known. In general, elevations in EA rates go in parallel with increase in fibrinogen concentrations (12). However, in our patient groups, fibrinogen concentrations were similar. The only difference in hemorheological parameters between heavy smokers (group 3) and the other groups was the hematocrit values. Elevated hematocrit causes increase in EA rates (1). Thus higher hematocrit might partly explain the difference between group 3 and other groups; however why in group 2, EA rates were higher than group 1 despite similar hematocrits could not be explained.

Another point that deserves consideration is that, when we examine patients with CHD without taking into consideration the smoking habits, EA rates are higher than control subjects (4). It has long been proposed that elevated EA is an independent risk factor for thrombosis both in arterial and venous systems. However, it is hard to tell this with certainty. Elevated EA in patients with atherosclerosis might well be a secondary effect with changes in erythrocyte membrane properties (13); the erythrocytes might have been affected by flowing over and in contact with arteriosclerotic plaques on inti-

mal walls, subjected to turbulence in narrowed lumens. In the current study, we however, examined the independent role of smoking on EA rates and found higher values in smoking subjects. Even in CHD patients, smoking increased EA rates further. The question here is that if the potential role of smoking on the pathophysiology of atherogenesis is through its effects on elevated EA. To definitely answer this question, further studies are required. We believe that the atherogenic potential of smoking might be at least partly explained by its effect on blood rheology.

Pharmacologic approach to the elevated EA is a subject of investigation in recent years. Beta blockers, calcium channel blockers and ticlopidine are only a few drugs shown to decrease elevated EA (14-16). These drugs are currently used in the treatment of CHD. The exact mechanism(s) of elevated EA in the pathogenesis of thrombotic disorders have not been fully established yet and further studies are required to elucidate them. Thus, pharmacological management can not be justified for otherwise healthy individuals. Modification of factors known to affect flow behaviour of blood like stress, cigarette smoking and abnormal lipid profile must be preferred over drugs to prevent vascular diseases until more about pathophysiology of blood rheology is learned (17).

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