RELATIONSHIP OF CIGARETTE SMOKING TO ACUTE MYOCARDIAL INFARCTION. A CLINICAL-PATHOLOGICAL STUDY.

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Seventy-three autopsies of patients who died from an acute myocardial infarction (AMI) were reviewed. Thirty-eight chronic smokers were compared to 35 non-smokers No differences were found on age and sex distribution between both groups. The incidence of arrhythmias was significantly higher in the smokers group (36 of 38 vs. 26/35, $p < 0.025$), as well as that of conduction disturbances (24 of 38 vs. 12/35, $p < 0.05$). No relationship was found between smoking habit and left ventricular failure or cardiogenic shock. The percent of left ventricular mass infarcted, the degree of coronary stenosis and the incidence of recent coronary thrombosis were the same in both groups. The prevalence of recent coronary thrombosis were the same in both groups. The prevalence of confluent AMI was significantly higher in the smokers group (14 of 38 vs. 7/35, $p < 0.025$). Platelet thrombi were scarcely found.

This report confirms the higher incidence of arrhythmias in chronic smokers, but not that of recent coronary thrombosis and platelet thrombi, at least at the moment of death. The higher incidence of confluent AMI suggests a spastic mechanism.

Cigarette smoking (CS) has been linked to atherosclerosis since 1908 [1]. The Framingham Study data are representative of epidemiologic evidence on the association between CS and cardiovascular morbidity and mortality [2,3]. Heavy smoking doubles cardiovascular and overall mortality under age 65. Beyond this age, neither significant nor substantial gradients of risk can be demonstrated in either sex for cardiovascular morbidity. In men, significant associations of cardiovascular mortality and overall mortality are noted in relation to CS, even beyond age 65. Among women, in the 65-74 year age group, no significant relationship can be shown; but in younger age groups (25-65 years) the risks of dying from atherosclerotic heart disease is positively associated with CS [4]. Coronary mortality in general and sudden death are specifically related to CS and they increase progressively with the number of cigarettes smoked per day [5]. Autopsy studies have shown that the extent of atherosclerosis in aorta and coronary arteries increase with the amount of CS [6]. Accordingly [7], coronary arteriography has shown a correlation between chronic CS and the severity of coronary artery disease. Other studies have shown that CS leads to an increased rate or development of atherosclerosis, and to a higher risk of stroke [8] and sudden cardiac death.

Taking into account that cigarette smokers have twice the overall death rate of non-smokers in most of Western countries [9], we reviewed 73 autopsies from patients who had died from an acute myocardial infarction (AMI), trying to correlate the presence CS as a risk factor with other items such as percentage of infarcted left ventricular areas, previous myocardial infarction, age, cardiogenic shock, left ventricular failure, degree of coronary stenosis and cardiac rupture. We also tried to determine if recent coronary thrombosis (RCT) and/or platelet thrombi in the myocardial microcirculation were increased in chronic smokers when compared with non-smokers.

MATERIAL AND METHODS

Seventy-three patients who had died from an AMI were autopsied. Well known criteria for AMI diagnosis were used [10-11].

The patients were divided according to their post attack survival time as follows: a) “early-infarct”, 2 days; b) “acute infarct”, 3 to 10 days; and c) “recent infarct”, 11 to 30 days [10-11].

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There were 18 females and 55 males. There was no statistically significant difference concerning sex distribution between smokers and no smokers. There were 30 and 25 men and 8 and 10 women respectively (NS).

From the histologic standpoint, the type of infarction was defined as: 1) massive, when the cells of the infarcted zone, with a maximum diameter greater than 5 mm, were necrotic; 2) confluent, when multiple necrotic foci tended to join together with some separation of the foci by apparently viable myocardium; 3) focal, when the lesions appeared as small, unique or multiple microfoci of coagulation necrosis, scattered in the normal tissue [12].

At autopsy, the heart was serially cross-sectioned in 0.5 cm thick slices. The areas of each slice and those of AMI were measured by a polar planimeter and the percentage of necrotic tissue calculated. To delineate accurately the areas of the infarct, slices were stained with nitroblue tetrazolium [13]. The coronary arteries were examined by serial cross sections at 2 mm intervals, and the percentage of lumen occlusion calculated with a micrometer. Each slice of myocardium was embedded in paraffin and sectioned by macromicrotome. These sections were stained with haematoxylin and eosin, the basic fuchsin stain and the Barbeito López Trichrome stain [14]. Histological mapping was made correlated with macroscopic planimetries, and all sections of coronary arteries were studied.

The following data were recorded: age, size, type and location of AMI, involved wall, previous infarction, degree and histological characteristics of coronary stenosis, RCT or chronic coronary thrombosis, external and internal cardiac rupture, and infarcted left ventricular areas. Correlative studies between these data and clinical features (heart failure, terminal cardiogenic shock, conduction disturbances and arrhythmias) were made.

Thirty-eight chronic smokers were compared with thirty-five non smokers. All subjects considered chronic smokers had smoked at least one pack of cigarettes a day for at least ten years, and no subject considered non-smoker had ever smoked cigarette for any length of time.

All data were statically evaluated using the chi square test id the Student "t" test for paired data.

RESULTS

The mean age for the whole group was 62.7 ± 11.6 years, the mean age for the smokers group being 62-44 = 14-4 years and 61.88 ± 10.9 years for the non smokers group (NS).

Male smokers (n = 30) had a mean age of 56.96 ± 16.19 years, and female smokers (n = 8) 74.5 ± 9-45 (NS). In the non smokers group, the mean male age was of 62.87 ± 12.27 years, and the females 66,1 =6,02 years (NS). Although a statistical significance was not evidenced, there was a trend in the male smokers group to die earlier. The prevalence of risk factors (determined following established criteria) [15-17] was as follows: smoking habit, 38/73 (52.0%); hypertension, 21/73 (28.8%); diabetes, 15/73 (20,5%); hyperlipemia 11/73 (15.1%).

The pathological study of the entire group revealed that the infarcted left ventricular area varied between 10 to 61%, with a mean of 25.4 ± 14.1%; 26,34% for the smokers group and 24,22% for the non-smokers group (NS). Infarction areas inferior to 30% of the left ventricular area (generally corresponding to a less than 10% infarcted area) was observed in 49 cases (24 in the smokers group and 25 in the non-smokers group); infarction areas between 30 and 50% in 17 cases (9 in the smokers and 8 in the non-smokers group); and 51 to 70% in 14 cases (4 in the smokers and 10 in the non-smokers group) (NS)

Massive transmural AMI (44 cases, 21 in the smokers and 23 in the non-smokers groups) was mainly observed in the patients deceased between 3 to 10 days of evolution. Conversely, confluent (21 cases, 14 in the smokers group vs. 7 in the nonsmokers group) or focal infarction (11 cases, 4 in the smokers and 7 in the non-smokers group), were observed in the early decreased group (2 days of evolution).

Our series showed a greater incidence of confluent myocardial infarction in the smokers group. From 38 smokers, 14 had confluent infarcts, while from 35 non-smokers, only 7 had evidence of a confluent AMI ($p < 0.025$).

There was a clear-cut relationship between the smoking habit and a higher prevalence of supraventricular and ventricular arrhythmias, and conduction disturbances. Of 35 non-smokers, 26 had cardiac arrhythmias and 12 showed conduction disturbances; while of 38 smokers, 36 had arrhythmias and 24 conduction disturbances, a statistically significant difference ($p < 0.015$ and $p < 0.05$, Graph 1 and 2).

The stenosis of the three major coronary arteries, considered together, was 86.6 ± 14.2% of their lumen in the whole group, 87.5 ± 15.3% in the smokers group and 84.76% ± 13.4% in the non-smokers group (NS).

The prevalence of RCT in the arteries corresponding to the infarct zone was of 17/38 (44.7%) in the smokers group and of 18/35 (51.4%) in the nonsmokers group (NS); the general frequency of RCT was 47.9%. It was generally associated with massive and transmural infarctions, deceased 3 to 10 days after admission. Infarct size less than 10% correlated with "early" and "focal" and mainly "subendocardial", while those with infarct size greater than 20% corresponded to acute, massive and transmural These data are similar to other reports [10,11,18,19].

Only are, uneventful, platelet thrombi not are lated to necrotic zones were found in the microves-

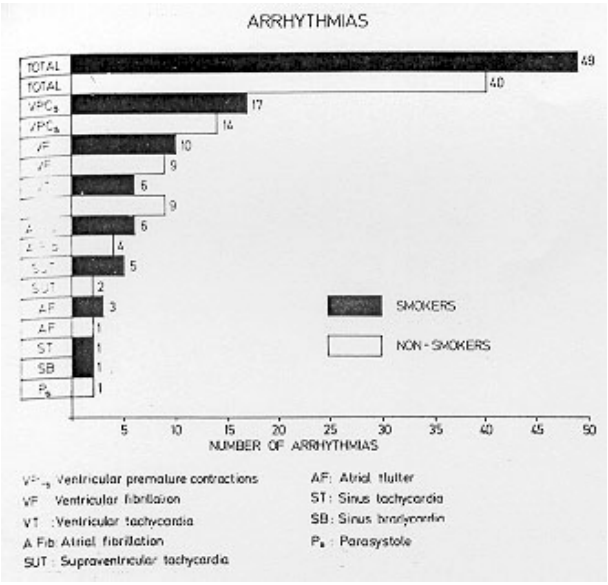

Fig. 1 - Arrthythtmias in smokers and non-smokers died from acute myocardial infarction.

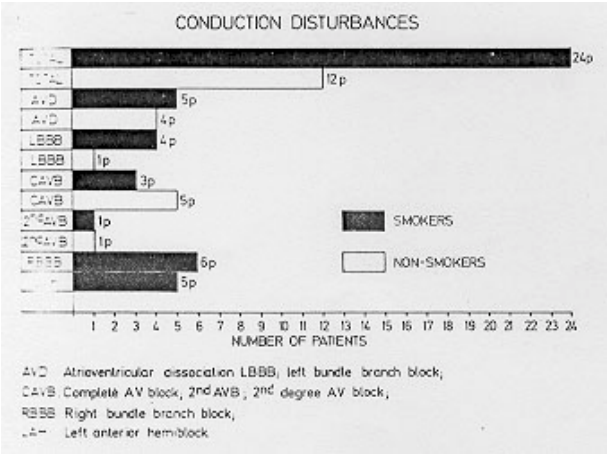

Fig. 2 - Conduction disturbances in smokers and non-smokers died from acute myocardial infarction.

sels of both groups, despite a careful search was undertaken in the macrosections of both ventricles.

A higher incidence of cardiac ruptures in the non smokers group ($p < 0.025$) was found. From 35 non-smokers, 16 showed rupture of the interventricular septum or the left ventricular free wall and, from 38 smokers, only 7 had evidenced cardiac rupture.

It was not possible to demonstrate any relation between smoking habit and left ventricular claudication.

Concerning previous myocardial infarction there was no difference between both groups (2/38, 52.6% in smokers vs. 16/35, 45.7% in non-smokers).

DISCUSSION

In this paper, it was shown that CS in patients who died from AMI clearly related to am Increase in cardiac arrhythmias and conduction disturbances and in the production of "confluent" myocardial infarctions; and that it does not increase the prevalence of heart failure, cardiogenic shock, RCT and platelet thrombi.

Smoking habit and age distribution - Even if there is no statistically significant difference concerning the mean age between both groups there is a trend in the male smokers group to die earlier, as compared to the non-smokers group. It is known that smoking habit doubles cardiovascular mortality rate in men aged less than 65 years. Our higher mean age in women may be attributed to the low number of individuals in the smokers group, and to the fact that most of the elderly women do not inhale the smoke. Conversely, in young women with a AMI, CS is generally found as a constant risk factor 4 and it enhances the risk of AMI in women taking oral contraceptives [20]. CS would cause vasoconstriction by altering the prostacyclin/tromboxane A2 ratio [21]. Thomboxane A2 is a stable prostacyclin metabolic that limits the extent of thrombus formation at sites of endothelial injury [23]; therefore, it is reasonable to suggest that the combination of tobacco and oral contraceptives may provide a strong stimulus for platelet aggregation, coronary spasm and RCT.

The greatest effect is apparent in the age group with the lowest incidence of cardiovascular disease, the association decreasing as the disease incidence increases. The weakening of the effect of CS with age may be due to a marked increase in the impact of other risk factors. Because of this, the relative effect of CS may appear less pronounced. It is also possible that those persons particularly susceptible to the adverse effects of CS have been removed at an earlier age from the population at risk, leaving a remaining sample of less susceptible persons.

Smoking habit and AMI type - Our greater prevalence of "confluent" AMI in the smokers group may be due to a spastic mechanism. As "confluent" infarction are multiple necrotic foci tending to join together but separated by apparently viable myocardium [10], neither associated to RCT [11] nor to platelet thrombi, an irreversible spasm lasting only for 20 minutes may account for the production of necrotic cells surrounded by viable ones [23]. Furthermore, "contraction-bands", considered [24] as reperfusion lesions, were commonly found scattered throughout the neighboring normal myocardium. Besides, Klein et al [25] demonstrated that coronary vascular reserve is significantly decreased in heavy chronic smokers as compared with non-smokers. In this sense, Moanad [26], demonstrated the vasoconstrictive effect of CS in human coronary arteries. Therefore, transient spasm might cause patchy ("confluent") myocardial necrosis in the smokers group.

Smoking habit, RCT and platelet thrombi - The issue of whether RCT precedes and initiates AMI is a major r controversy [27]. There is no dispute about the importance of advanced coronary atherosclerosis in predisposing to an AMI, but its existence is also evident with patent coronary arteries [28]. Many authors have suggested that RCT appears to follow the AMI [10,11,19] based on the clear correlation between the frequency of RCT and the time of survival from tile of myocardial ischemia [29,30].

RCT was scantly found even in transmural AMI [18]. Thus, it seemed that adequate conditions allowing RCT are transmural, massive, large (size more than 20%) and recent (3 to 10 days old) AMI [10-12,29-13].

Our data confirmed these findings, as RCT in the whole group was 47.9%, generally associated with massive and transmural AMI deceased 3 to 10 days after admission. RCT was not increased in the smokers group (17/38 vs. 18/35). Thus, even in this group RCT was not a prerequisite for AMI. In fact, although CS stimulates catecholamine release and wild epinephrine stimulates platelet aggregation and thrombus formation by an alpha-adrenergic mechanism [34,35] a major incidence of RCT and platelet thrombi the microcirculation has not been demonstrated in our study.

In addition to these acute effects there may also be a chronic atherogenic effect of CS, by interfering with the endothelial barrier function. The of carbon monoxide would lead to endotelial hipoxia allowing the passage of lipids cowards the intimal and inducing smooth muscle cell proliferation at the intimal level [36,37]. Besides, increases in collagen contents of systemic and pulmonary of smokers 38 and an increased stiffens in femoral arteries of dogs 39 exposed to chronic been shown.

Even though the coronary arteries of heavy cigarette smokers were found to have approximately 50% more intimal surface involved with fibrous plaques other advanced lesions than those of non-smokers [38], those findings were not corroborated by us. The percentage of coronary lumen occlusion and the type of atherosclerotic lesions was similar in both groups.

Smoking habit and cardiac arrhythmias - A scandard cigarette contains about 20 mg of nicotine, of which 2 mg are inhaled on the average. This produces a small but consistent increase in heart rate, arterial blood pressure and cardiac output [40] through neutrally mediated mechanisms [41,42]. Also, free fatty acids are, mobilized and may interfere with metabolism across the capillary wall and induce cardiac arrhythmias [43].Accordingly, a prolonged reduction of the threshold for ventricular fibrilation was experimentally demonstrated [40] Long-term hemodynamic alterations in chronic smokers have not been observed.

Besides, the build-up of carboxihemoglobin reduces oxygen carrying capacity of the blood, which is further aggravated by impaired tissue utilization of oxygen at the myoglobin level [44,45]

Both, the decrease in the coronary flow reserve [25], and the increase in carboxihemoglobin may account for the higher prevalence of arrhythmias in the smokers group.

Smoking habit and cardiac ruptures - The incidence of rupture of the heart complicating all AMI was reported as varying from 4% to 13% of fatal cases [46,47]. It occurs most frequently during the first week after the AMI, the infarction often having been the patient's first (71% in our series). Before operative repair was introduced [48], cardiac rupture was almost always fatal: 80% of patients died within 2 months and 93% within one year [49].

Hypertension before and after AMI has been postulated to be important in its pathogenesis [50]. Roberts et al. 51 found that all of their 41 patients who died of post-infarction septal or free wall rupture had left ventricular thickening consistent with a history of hypertension. But our findings and those of others 52 suggest that the relationship between cardiac rupture and hypertension, if it exists, is not a close one. Only 28.57% of our patients were hypertensive.

Our data agree with the concept that cardiac rupture has an increased frequency in patients over 60 [53], our mean age being 68.14 years for the smokers group and 63.35 years for the non smokers group.

We do not know the reason for the statistically greater incidence of cardiac rupture in the non smokers group. One may theorize that there is an earlier degradation of collagen after AMI [54] in the non-smokers as compared to smokers as a result of a smoking-induced less collagen degradation mediated by inflammatory cell proteases. In other words, CS might protect the collagen fibroskeleton from leucocyte-induced proteolysis by decreasing normal inflammatory proteases.

Final appreciations

Heavy cigarette smokers are more prone to suffer from an AMI [2,3]. This higher incidence could depend to some extent on alterations in blood flow due to various mechanisms, but neither entirely on the degree of sclerosis of the coronary arteries not on the production of RCT. Platelet thrombus formation occurring in the stenosed human coronary arteries, likely to be exacerbated by CS could mot be demonstrated in this study.

Because of this the question is open as to whether or not there may have been lysis of the thrombi prior to examination. It has mot been shown in animals [55] and a reduced fibrinolytic and anticoagulant activity has been reported in human coronary atherosclerosis [56]. It is too difficult to accept that

lysis occurs specially in hearts with subendocardial AMI, in which RCT are significantly less. Therefore, post-mortem total dissolution of a RCT does not seem acceptable.

Conversely, Roberts [57] and Baroldi [12] demonstrated that. in patients with a transmural AMI or cardiogenic shock, blood stasis associated with increased coagulability , viscosity following tissue necrosis, and decreased fibrinolytic activity of the fibroatheromatous artery wall, produce secondary RCT. In this sense, smokers did not seem to be different from non-smokers.

The data from the Framingham Study [2,3] are consistent with the concept that on those patients with a coronary risk profile compatible with an accelerated pace of atherogenesis, CS can trigger a coronary attack or sudden death. The effect of CS on the incidence of AMI is independent of all the major risk factors, but the risk is greater in those predisposed by one or more of them. Although CS effects are mixed with those provoked by other risk factors, the reduced oxygen carrying capacity of the blood, furtherly aggravated by impaired myocardial utilization of oxygen. appears as the main action of tobacco.

RESUMO

Foram revistas 73 autópsias de pacientes que faleceram por infarto agudo do miocárdio (IAM); 38 eram fumantes crônicos e 35 não fumantes, constituindo dois grupos, que foram comparados. Não houve diferença entre ambos quanto a sexo e idade. A incidência de arritmias foi significativamente maior no grupo de fumantes (36/38 vs. 26/35, $p < 0,025$), assim como os distúrbios de condução (24/38 vs. 12/35, $p < 0,05$). Não houve correlação entre o hábito de fumar e a falência ventricular esquerda ou choque cardiogênico.

A massa infartada, o grau de estenose coronária e a incidência de trombose coronária recente foram similares nos dois grupos. A prevalência de IAM subendocárdico foi significativamente maior no grupo de fumantes (14/38 vs. 7/35, $p < 0,025$). Raramente se encontraram trombos plaquetários.

O presente relato confirma a incidência maior de arritmias nos fumantes crônicos, mas não as de trombose coronária recente e trombos plaquetários, pelo menos no momento da morte. A maior incidência de infarto subendocárdico sugere um mecanismo espástico.

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