

Original Paper

The Importance of Aortic Arch Plaque Characteristics in Patients with Ischemic Stroke

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REZUMAT

Importanța caracteristicilor plăcii de aterom aortice la pacienții cu accident vascular cerebral ischemic

Datele apărute în literatură în ultimii ani sugerează asocierea dintre ateroamele de arc aortic și AVC-ul ischemic, aterotromboza de arc aortic fiind considerată veriga lipsă, responsabilă de multe dintre accidentele vasculare ischemice de cauză necunoscută. Lucrarea de față își propune să studieze relațiile existente între ateroamele de crosă aortică și factorii de risc vasculari, markeri serici de inflamație, coafectarea mai multor teritorii vasculare în vederea identificării unui model al pacientului cu ateromatoză de arc aortic și boală vasculară cerebrală. Am studiat un lot de 30 de pacienți cu accident vascular cerebral ischemic având drept cauză cea mai probabilă ateromatoza de arc aortic, prin embolie arterio-arterială. S-au observat corelații statistice semnificative între grosimea plăcii de aterom și prezența elementelor mobile și unii factori de risc vasculari, markeri serici de inflamație și coafectarea coronariană, carotidiană și periferică.

Cuvinte cheie: ateromatoza aortică, accident vascular cerebral, factori de risc vasculari, markeri serici de inflamație

ABSTRACT

Recent data from the literature suggest that aortic atheromatosis may be the missing link, responsible for most of the cerebral infarctions of undetermined cause. The aim of this paper is to study the relations between aortic arch atheroma and vascular risk factors, inflammation biomarkers, impairment of other vascular territories in order to identify a model of patient with aortic arch atheromatosis and cerebral vascular disease. We studied 30 patients with ischemic stroke caused by arterio-arterial embolisation from aortic arch atheroma. We found statistically significant correlations between aortic plaque thickness and the presence of mobile elements and some vascular risk factors, seric inflammatory biomarkers and coronarian, carotid and peripheral vascular disease.

Key words: aortic atheromatosis, ischemic stroke, vascular risk factors, inflammation biomarkers

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INTRODUCTION

Stroke is the fourth leading cause of death in Unites States and the leading cause of adult morbidity and disability in Europe (1). Ischemic stroke represents approximately 88% of all strokes; however, in NINDS (National Institute of Neurological Disorders and Stroke) database almost 40% of ischemic strokes are listed as cryptogenic strokes (2). In the context of secondary prevention, establishing an etiological diagnosis is essential when it comes to prescribing the optimal treatment for every patient. Routine evaluation of a stroke patient includes evaluation of cervico-cerebral vessels and also cardiological evaluation in order to rule out an atrial arrhythmia with embolic potential in cerebral circulation (3,4).

Between the heart and the carotid and vertebral arteries lies the aorta, an area difficult to explore. Latest data from the literature suggest an association between aortic arch atheromas and ischemic stroke, thus aortic atheromatosis may be the missing link, responsible for most of the cerebral infarctions of undetermined cause (5,6).

This paper aims to study the relations between aortic arch atheromas and vascular risk factors, inflammatory and hemostasis biomarkers, the impairment of multiple vascular territories in order to identify a model of a patient with aortic arch atheromatosis and cerebral vascular disease.

MATERIAL AND METHOD

We studied a group of 30 patients with ischemic stroke, having aortic arch atheromatosis as the most likely etiology. These 30 patients were admitted in Neurology Department of Fundeni Clinical Institute between January 2008 and December 2012.

Inclusion criteria were: age above 60 years, identification of aortic arch atheromas using transesophageal echocardiography, clinical and para-clinical diagnosis of ischemic stroke (following clinical examination and cerebral CT or MRI).

Exclusion criteria were: present or past atrial fibrillation, presence of hypoechogenic plaques or stenosis of ipsilateral cervical vessels, presence of ipsilateral intracranial stenosis, acute cardiovascular disease within the last 2 months, chronic renal disease with creatinine clearance below 30 ml/min, B12 vitamin deficit, known autoimmune diseases or neoplasms, acute infectious diseases of known

chronic infections, known systemic coagulation disorder.

The following vascular risk factors were considered: arterial hypertension was defined as blood pressure $\geq 140/90$ mmHg based on the mean of 2 readings, documented history of hypertension, antihypertensive medication use; diabetes mellitus was defined as fasting glucose ≥ 126 mg/dl, documented history of diabetes, antidiabetic medication use; dyslipidemia was defined as seric cholesterol ≥ 200 mg/dl, seric triglycerides ≥ 150 mg/dl; smoking was taken into account when the patient smoke more than 7 cigarettes a day.

Carotid stenosis was defined as the vascular lumen narrowing more than 50%. Peripheral Atherosclerotic Vascular Disease (PVD) was defined based on clinical history, echographic examination, specific medication use. Coronary Artery Disease (CAD) – in this category were included patients with history of stable or unstable angina, myocardial infarction or revascularization procedures, patients which were using antiischemic medication.

We performed the following blood tests: leukocyte count (normal values between 4000-8000/mm³), blood sedimentation rate (normal values < 12 mm/h), C-reactive protein (CRP) (normal values < 2 mg/l), seric homocysteine (normal values < 12 mg/dl), seric fibrinogen (normal values 200-400 mg/dl), uric acid (normal values < 6 mg/dl). Blood was collected in the morning from patients in a supine position, in a fasting state, at least 8 days after onset. Duplex ultrasonography of cervico-cerebral vessels, cardiological evaluation with transthoracic echocardiography followed by transesophageal echocardiography were performed. The aortic arch was defined as the aorta segment comprised between the curve at the end of the ascending portion and the takeoff of the left subclavian artery. The aortic plaque was defined as a protrusion of the intimal surface with at least 2 mm in thickness. The thickest lesion was considered when multiple plaques were present. We also took into account the presence of calcifications or mobile elements.

Statistical Analysis

Statistical Analysis of data corresponding to the group of patients considered was performed using Microsoft Office EXCEL, as well as SPSS software package. In order to study the correlations between the considered medical parameters, the main statis-

tical tools were Pearson's correlation coefficient, with the corresponding p-value (defined as the probability that one would have found the current result if the correlation coefficient were in fact zero - null hypothesis). The correlation coefficient is called statistically significant if the p-value is lower than the conventional 5% ($p < 0.05$). Another statistical tool used in this paper is the Odds Ratio (OR).

RESULTS

Patient distribution by age and sex is:

- by sex: 13 men and 17 women (43.33% men and 56.67% women);
- by age see **Table 1**.

Table 2 presents some characteristics of the considered group of patients, in terms of average values, standard deviations and minimum and maximum values.

We analysed the correlations between aortic plaque thickness and the presence of vascular risk factors: smoking, arterial hypertension, diabetes mellitus, dyslipidemia (hypercholesterolemia). According to our results (presented in **Table 3**), the aortic plaque thickness is statistically significantly correlated with smoking, diabetes mellitus and hypercholesterolemia. The strongest correlation was observed between the aortic plaque thickness and the presence of diabetes mellitus (Pearson's correlation coefficient $r = 0.823$, $p\text{-value} < 0.001$). Another strong correlations were observed between aortic plaque thickness, hypercholesterolemia (Pearson's correlation coefficient $r = 0.761$, $p\text{-value} < 0.001$) and smoking (Pearson's correlation coefficient $r = 0.694$, $p\text{-value} < 0.001$). No significant correlation was found for arterial hypertension.

Table 1. Patient distribution by age

Age	No. of patients (%)
61-65 years	5 (16.67%)
66-70 years	5 (16.67%)
71-75 years	9 (30%)
76-80 years	9 (30%)
over 80 years	2 (6.66%)
Total number	30 patients

Based on the calculation of OR between aortic plaque thickness (binary value 0 associated to thicknesses < 4 mm and binary value 1 corresponding to thicknesses ≥ 4 mm) and vascular risk factors, yields the same conclusion: the strongest correlation was observed between aortic plaque thickness and presence of diabetes mellitus.

Most patients had more than one vascular risk factor: 7 patients had 2 risk factors, 6 patients had 3 risk factors and 7 patients had 4 risk factors. The growth of the aortic plaque thickness was statistically significantly correlated with the number of vascular risk factors (see **Fig. 1**), thus the Pearson's correlation coefficient $r = 0.762$, with $p\text{-value} < 0.001$.

Concerning the correlations between aortic plaque thickness and inflammatory biomarkers, we found statistically significant correlations with leukocyte count, blood sedimentation rate, seric fibrinogen and CRP (see **Table 4** and **Fig. 2-3**).

The aortic plaque thickness was also statistically significantly correlated with uric acid, seric homocysteine and triglycerides, as shown in **Table 5** and **Fig. 4**.

From the total of 30 patients, 13 patients had mobile elements associated to aortic plaque, especially those patients with plaques thicker than 4 mm.

Table 2. Data statistics of some characteristics of the patients group

Variable	Average	Standard deviation	Minimum value	Maximum value
Aortic plaque thickness [mm]	4.39	1.48	2.10	6.40
Leukocyte count /mm ³	6480.5	1840.6	4100	9300
Blood sedimentation rate [mm/h]	23.77	7.93	9	35
Fibrinogen [mg/dl]	423.4	49.5	328	489
CRP [mg/l]	4.23	2.89	0.8	8.5
Uric acid [mg/dl]	6.03	2.63	2.7	11.3
Homocysteine [mg/dl]	13.16	6.04	5.6	23
Cholesterol [mg/dl]	243.2	38.01	188	330
Triglyceride [mg/dl]	163.9	60.14	80	280

Table 3. Correlations between aortic plaque thickness and vascular risk factors

Risk factor	Pearson's correlation coefficient r	p -value	OR
Smoking	0.694	< 0.001	1.7
Arterial hypertension	0.231	0.218	2.2
Diabetes mellitus	0.823	< 0.001	21.2
Cholesterol	0.761	< 0.001	-

Table 4. Correlations between aortic plaque thickness and inflammatory biomarkers

Inflammatory biomarkers	Pearson's correlation coefficient r	p -value
Leukocyte count	0.920	< 0.001
Blood sedimentation rate	0.940	< 0.001
Fibrinogen	0.942	< 0.001
CRP	0.925	< 0.001

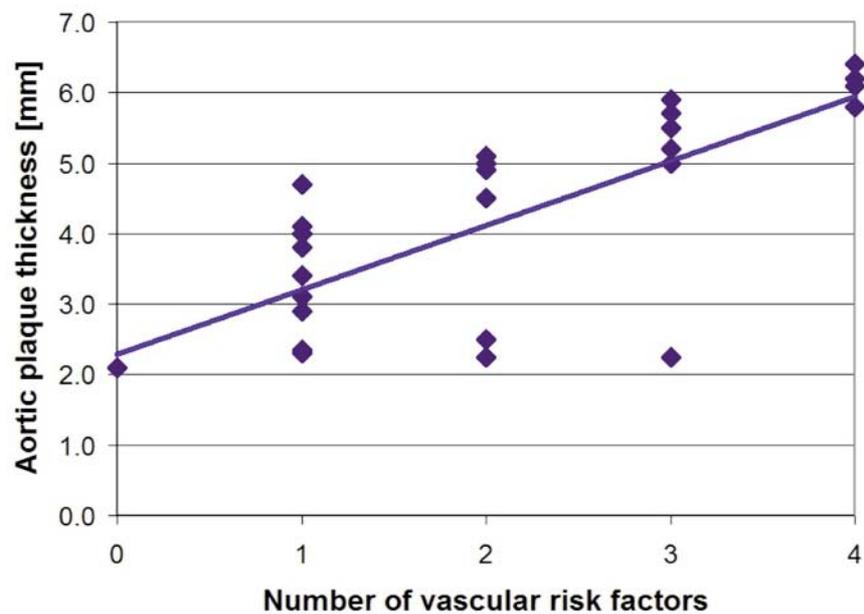


Figure 1. Correlation between aortic plaque thickness and the number of vascular risk factors

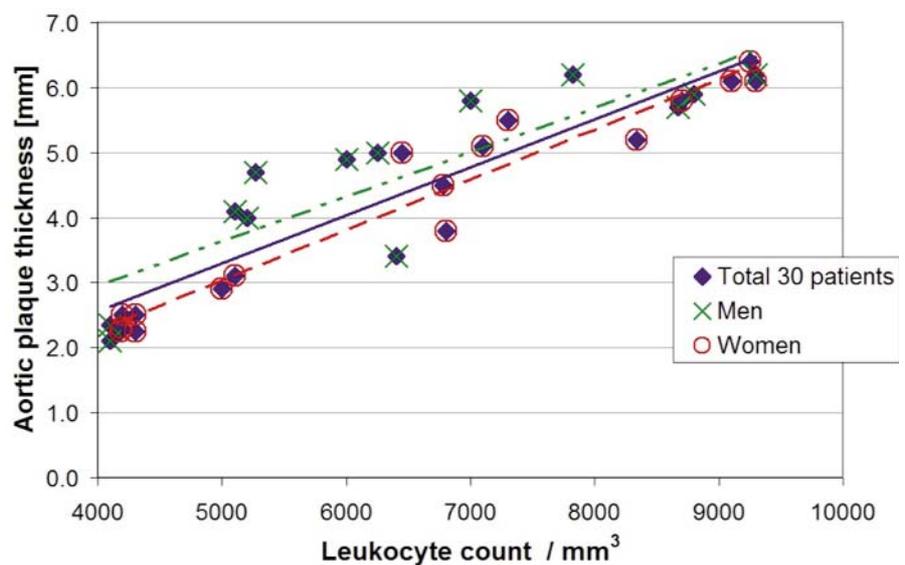


Figure 2. Correlation between aortic plaque thickness and leukocyte count.

Figure 3. Correlation between aortic plaque thickness and CRP

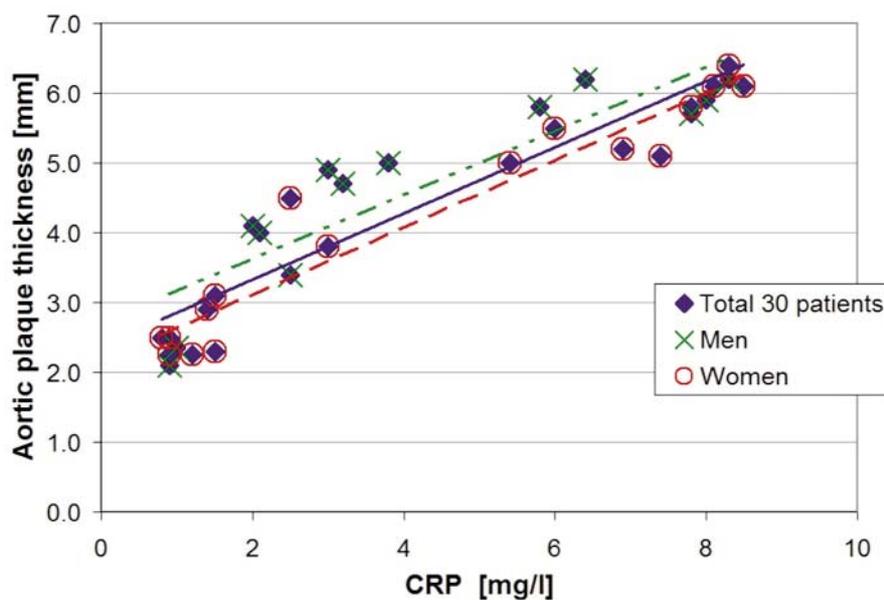
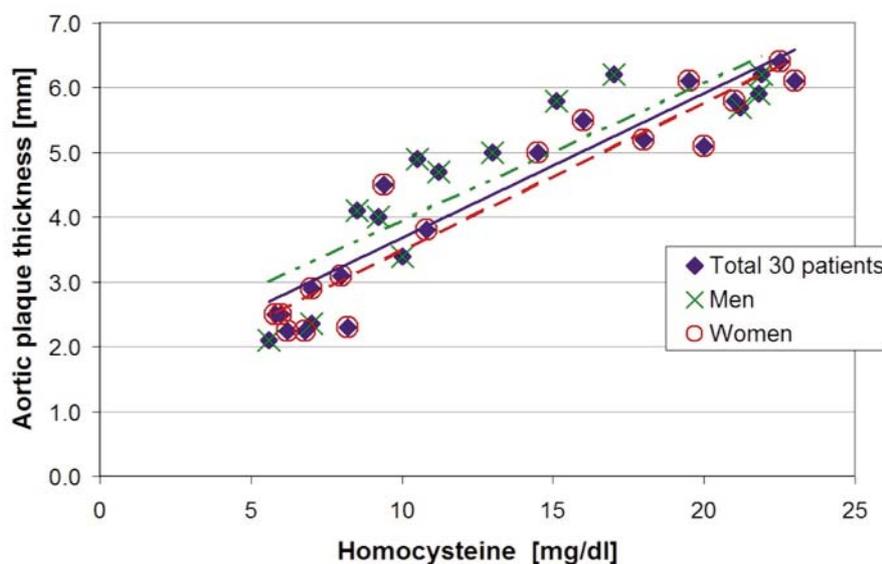


Figure 4. Correlation between aortic plaque thickness and seric homocysteine



There was a strong correlation between aortic plaque thickness and the presence of mobile elements, characterized by Pearson's correlation

coefficient $r = 0.8304$, $p\text{-value} = < 0.001$, $OR = 68.9$.

Table 5. Correlations between aortic plaque thickness and uric acid, seric homocysteine and triglycerides

	Pearson's correlation coefficient r	$p\text{-value}$
Uric acid	0.911	< 0.001
Homocysteine	0.913	< 0.001
Triglycerides	0.736	< 0.001

The presence of mobile elements was statistically significantly correlated with the number of vascular risk factors, especially with diabetes mellitus, as shown in **Table 6**.

Concerning the inflammatory biomarkers, we found statistically significant correlations between the presence of mobile elements and leukocyte count, CRP and blood sedimentation rate; strong correlations were found also with seric homocysteine and with uric acid (see **Table 7**). On the contrary, no correlation was found between the presence of aortic

Figure 5. Correlation between aortic plaque thickness and cholesterol

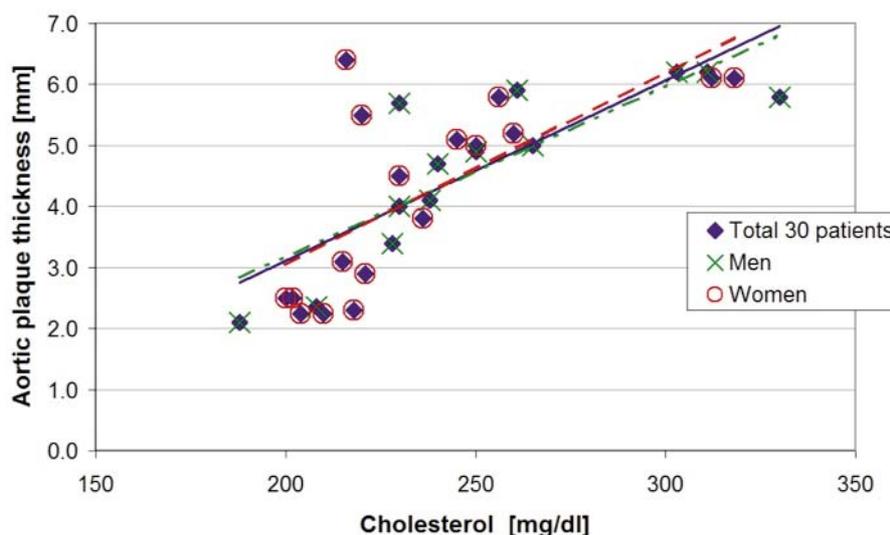


Table 6. Correlations between the presence of mobile elements and vascular risk factors

	Pearson's correlation coefficient <i>r</i>	<i>p</i> -value	OR
Presence of 2 or more risk factors	0.780	< 0.001	-
Smoking	0.665	< 0.001	2.5
Arterial hypertension	0.384	0.035	3.9
Diabetes mellitus	0.800	< 0.001	89.5
Cholesterol	0.631	< 0.001	-

Table 7. Correlations between the presence of mobile elements and leukocyte count, CRP, blood sedimentation rate, seric homocysteine and uric acid

	Pearson's correlation coefficient <i>r</i>	<i>p</i> -value
Leukocyte count	0.851	< 0.001
CRP	0.940	< 0.001
Blood sedimentation rate	0.837	< 0.001
Homocysteine	0.912	< 0.001
Uric acid	0.873	< 0.001

plaque calcifications and inflammatory biomarkers.

17 patients (56,67%) had also Coronary Artery Disease (CAD). The correlation between the presence of mobile elements and the presence of CAD was statistically significant (Pearson's correlation coefficient $r = 0.493$, p -value = 0.005, OR= 8.6).

Only 7 patients in our group (23.33%) had Peripheral Vascular Disease (PVD); no correlation was found between the presence of mobile elements and the presence of PVD (p -value= 0.092 > 0.05, Pearson's correlation coefficient $r = 0.313$, OR=1.4), while the correlation between PVD and aortic plaque thickness was strong (Pearson's correlation coefficient $r = 0.498$, p -value= 0.005, OR=2.1).

As expected, 63.33% of patients (19 patients) had also carotid atheromatosis, which was statistically significantly correlated with the aortic plaque thickness (Pearson's correlation coefficient $r = 0.852$, p -value < 0.001, OR= 11.3), as well as with

the presence of mobile elements (Pearson's correlation coefficient $r = 0.665$, p -value < 0.001, OR=25.7).

Table 8 shows that aortic plaque thickness was statistically significantly correlated with CAD, PVD and carotid atheromatosis, while the presence of mobile elements was strongly correlated only with CAD and carotid atheromatosis.

DISCUSSIONS

Our study concerned patients with ischemic stroke for whom the investigations performed have revealed that the most probable etiology was aortic arch atheromatosis by arterio-arterial embolism. Therefore, our attention was focused on the correlations between aortic plaque thickness and different variables: vascular risk factors, inflammatory and hemostatic biomarkers, coexis-

Table 8. Correlations between aortic plaque thickness/presence of mobile elements and CAD, PVD and carotid atheromatosis

	Aortic plaque thickness			Presence of mobile elements		
	Pearson's correlation coefficient r	p-value	OR	Pearson's correlation coefficient r	p-value	OR
CAD	0.532	0.002	5.5	0.493	0.005	8.6
PVD	0.498	0.005	2.1	0.313	0.092	1.4
Carotid atheromatosis	0.852	< 0.001	11.3	0.665	< 0.001	25.7

tence of other locations of atherosclerotic vascular disease. These correlations were also studied in what concerns the presence of mobile elements, mostly represented by thrombi with high embolic potential. For our group of patients, we observed that mobile elements are present especially when the aortic plaque is thicker than 4 mm (statistically significant correlation). This result suggests the high probability of occurrence of ischemic stroke by arterio-arterial embolism in these patients.

According to our results, aortic plaque thickness and the presence of mobile elements were statistically significantly correlated with the presence of diabetes mellitus (the strongest correlation), with dyslipidemia (hypercholesterolemia) and thirdly with smoking. No correlation was found between aortic plaque thickness and arterial hypertension. Furthermore, aortic plaque thickness and the presence of mobile elements were statistically significantly correlated with the number of risk factors in a patient.

The variations of inflammatory biomarkers can be taken into account if one can rule out other physiopathological mechanisms that can also alter the values of those biomarkers. The considered inflammatory biomarkers were: leukocyte count, blood sedimentation rate, CRP, seric homocysteine, fibrinogen. Statistically significant correlations were observed between aortic plaque thickness and the presence of mobile elements and the following inflammatory biomarkers: leukocyte count, blood sedimentation rate, fibrinogen and CRP. On the contrary, no correlation was found between the presence of aortic plaque calcifications and inflammatory biomarkers.

An interesting finding concerns the correlation between seric homocysteine and aortic plaque thickness in our study. Several authors (7,8) have already suggested the association between slightly

or moderated increased values of seric homocysteine and coronary artery disease. The possible mechanisms of vascular risk mediation by seric homocysteine are: increased oxidative stress, proliferation of vascular smooth muscle cells, activation of factor V, inhibition of protein C, platelet aggregation (9). It has still not been demonstrated if homocysteine is a risk factor or just a marker of atherosclerotic vascular disease.

Atherosclerosis is a disease affecting large and medium vessels. There are also studies associating the increase of carotid intima-media thickness and the presence/severity of coronary artery disease (10). On the other hand, Framingham study described an association between aortic calcifications radiologically revealed and the development of coronary artery disease. The aortic plaques revealed by transesophageal echocardiography have been correlated with coronary artery stenosis revealed by angiography (11,12,13). In our study, a significant number of patients presented either coronary disease (56.67%) or carotid disease (63.33%), statistically significant correlations being observed with aortic plaque thickness, as well as with the presence of mobile elements. Concerning peripheral vascular disease, a statistically significant correlation was observed with aortic plaque thickness, no correlation being found with the presence of mobile elements.

CONCLUSIONS

Atherosclerosis is a systemic arterial disease affecting mainly coronary vessels, carotid arteries, peripheral vessels and aorta. Up to now, the most studied vascular territories were coronary and carotid arteries. In our study, a significant number of patients presented either coronary or carotid disease associated to aortic atheromatosis and ischemic

stroke, especially for patients with aortic atheromas thicker than 4 mm. The occurrence of ischemic stroke in patients with aortic arch atheromatosis was influenced by the following vascular risk factors: age, diabetes mellitus, dyslipidemia and smoking.

The following inflammatory and hemostatic biomarkers were correlated with high risk of ischemic stroke: fibrinogen, blood sedimentation rate, CRP, seric homocysteine. All these biomarkers had increased values in patients with stroke and with aortic plaque thicker than 4 mm.

In order to quantify the risk of occurrence of ischemic stroke in patients with aortic arch atheromatosis, the following variables can be taken into account:

- aortic plaque thickness, measured by transesophageal echocardiography (high risk for plaques thicker than 4 mm) and also the presence of mobile elements on the aortic plaque;
- age (increased risk for patients over 70 years);
- presence of diabetes mellitus and dyslipidemia;
- increased values of certain inflammatory and hemostatic biomarkers (e.g., CRP value greater than 3 mg/l);
- presence of coronary artery disease or carotid atheromatosis.

Since our study concerned a relatively small number of patients, further studies should comprise a greater number of patients, in order to verify the results and conclusions of this study.

Further studies should also concern other markers (so far associated mainly with coronary artery disease) correlated with inflammation and atherosclerotic disease (14). The purpose of such studies would be to introduce to clinical practice new indicators for better classification of embolic risk in patients with aortic arch atheromas and thus for improving therapeutic protocols.

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