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Anti-phospholipid antibodies and carotid-artery intima-media thickness in young survivors of myocardial infarction

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Summary

Background: Not all coronary events occur in young individuals with traditional risk factors. In recent years some authors have observed increased prevalence of elevated anti-phospholipid (aPL) antibodies in young patients with myocardial infarction. Also, thickening of the combined arterial intima-media thickness (IMT) of superficial vessels has been identified as an independent risk factor for both stroke and heart attack. The objective of our study was to assess possible association between aPL antibodies and carotid IM thickening in young survivors of myocardial infarction.

Material/Methods: In a case control study we determined IgG and IgM antiphospholipid antibodies by enzyme-immunoassay, and IMT by ultrasonography in 50 male survivors of myocardial infarction under the age of 50, and compared them to 50 healthy controls.

Results: Elevated aPL antibody levels (IgG>10 GPL; IgM>20MPL) were detected in 12 of 50 patients (24%) with MI and in 3 of 50 controls (6%). The mean level of aPL antibodies was significantly higher in the patients than in the controls (IgG 9.15±3.53 vs 7.69±2.98 GMP, $p=0.04$ and IgM 18.46±7.61 vs 12.14±5.05 MPL, $p<0.01$). Patients with MI had a significantly greater IMT than healthy controls (0.9 mm vs 0.6 mm; $p<0.01$). There was a correlation between aPL and IM thickening ($r=0.31$; $p=0.01$). Among coronary risk factors only hypertension ($r=0.28$; $p=0.01$) and smoking ($r=0.41$; $p=0.01$) showed a relationship with IMT.

Conclusion: The intima-media thickness of the carotid artery and elevated aPL antibodies are strongly associated with the risk of myocardial infarction in young patients.

key words: antibodies • intima-media thickness (IMT) • myocardial infarction • atherosclerosis

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BACKGROUND

Historically, atherosclerosis has been shown to be an ancient disease that existed at least 3500 years ago in Egypt and China. Today, we recognize that this arterial pathology is 'old' in another way as well. Autopsy studies have demonstrated that atherosclerosis begins early in life, and is present for years, if not decades, before clinical signs and symptoms occur. Despite this indolent time course and the prolonged period of clinical inactivity, the sequelae of atheroma, such as myocardial infarction, unstable angina or stroke, usually occur suddenly. Ischemic cerebral and myocardial events are the leading causes of adult mortality in most developed countries, and account for at least 10 million deaths per year [1]. Intravascular ultrasound studies have revealed widespread intimal thickening in patients with atherosclerosis, and indeed in many asymptomatic human adults [2–4]. B-mode ultrasound carotid artery imaging is a noninvasive method that can be used to visualize and measure the combined thickness of the arterial intima and media (IMT) of superficial vessels, where atherosclerosis originates [5–7]. Median population values for IMT range between 0.4 and 1.0 mm, while progression rates of 0.001 to 0.3 mm/y have been reported [8–12]. Thickening of the intima-media complex has been identified as an independent risk factor for both stroke and heart attack [13], while atherosclerosis is a risk factor for intima-media thickening. It has become increasingly clear that not all coronary events occur in individuals with traditional risk factors, and that in some individuals isolated abnormalities of hemostasis and thrombosis appear to play critical roles [14,15]. In recent years, some authors have observed an increased prevalence of elevated anti-phospholipid (aPL) antibody levels in young patients with myocardial infarction [16,17]. Furthermore, high titers of these antibodies appear to serve as a marker of risk for recurrent cardiovascular events [18]. Antibodies binding to anionic phospholipids, such as cardiolipin, are associated with a clinical syndrome characterized in particular by venous and arterial thrombosis, recurrent abortion, and thrombocytopenia [19]. Although the antiphospholipid (aPL) antibody syndrome was first described in patients with systemic lupus erythematosus (SLE), it is now generally accepted that there is a group of patients in whom high titers of aPL antibodies and thrombotic features occur without clinical manifestations of SLE [20]. The purpose of the present study, then, was to determine whether the presence of aPL antibodies entails a risk of CAD, and whether there is any relationship between aPL and carotid IM thickening in young survivors of myocardial infarction.

MATERIAL AND METHODS

We examined 50 men (age⩽50; range 37 to 50; mean 45.7±3.58) who had experienced an MI at least six months before the study. MI was diagnosed by clinical, electrocardiographic, and enzymatic criteria. In 32 patients the diagnosis was additionally confirmed by angiography. The control group consisted of 50 healthy men (age⩽50, range 35-50, mean 44.2±3.75 years) who had no history of CAD and completed an exercise stress test with negative result. Coronary risk factors were determined in both groups (table 1). Hypertension was diagnosed if the blood pressure was >140/90 mmHg or there was ongoing antihypertensive treatment. Cancer, severe liver or kidney disease, and peptic ulcer were exclusion criteria for this study. In all patients, IgG and IgM antiphospholipid antibodies were detected by a

Table 1. Intima-media thickness (IMT), aPL antibodies and clinical characteristics of the subjects studied.

Clinical data	MI patients	Control group	p values
Age, mean±SD (min-max)	45.7±3.58 (37–50)	44.2±3.75 (35–50)	NS*
Intima-media thickness (mm; mean)	0.9±0.02	0.6±0.01	<0.001*
Intima-media thickness ⩾0.1mm	25% (13)	4% (2)	0.001**
IgG aCL antibodies (GPL; mean)	9.15±3.53	7.68±2.98	0.04*
IgM aCL antibodies (MPL; mean)	18.45±7.61	12.13±5.05	<0.001*
aPL (IgG>10 GPL; IgM>20 MPL)	24% (12)	6% (3)	<0.001**
Carotid plaques (n)	24% (12)	2% (1)	0.01**
Carotid stenosis >50% (n)	4% (2)	0	–
Obstruction of carotid arteries	0	0	–
Coronary risk factors:			
Hypertension (n)	19	9	0.02**
Cholesterol mmol/L (mean)	6.09	5.39	0.01*
Triglicerides mmol/L (mean)	2.37	1.97	0.001*
Smoking (n)	44	30	0.01**
Diabetes(n)	5	0	0.06**
Obesity (BMI >30) (n)	10	9	NS**
Positive family history (n)	25	23	NS**

Mean values and standard deviations (SD) are given for continuous variables, % and (n) for coronary risk factors;

* P-values calculated by Mann-Whitney U test or Kolmogorov-Smirnov Two-Sample test;

**Chi-square test (Yates' correction)

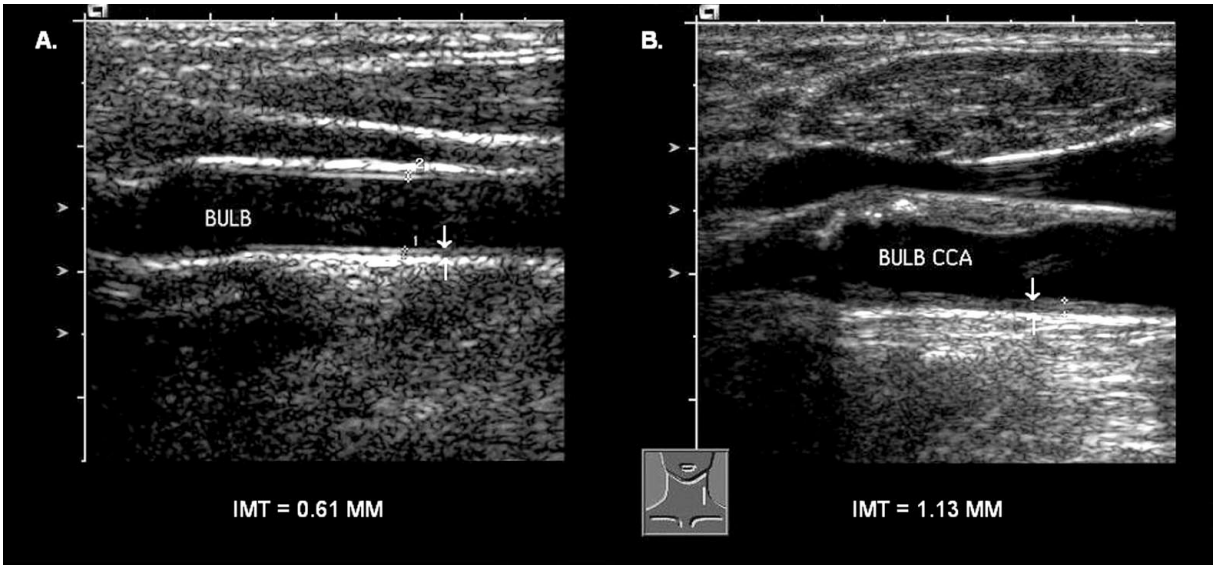

Figure 1. Measurements of the intima-media thickness (IMT) of the common carotid artery (CCA) using ultrasonography (arrows). **A.** MI patient with IM thickening. **B.** Healthy subject with normal IMT.

standard ELISA technique (Sigma; Daco), as previously described [21]. The results for aPL were expressed as GPL or MPL-Units (GPL-U or MPL-U). Results above 10 GPL and 20 MPL were considered positive.

B-mode ultrasound quantification of carotid artery intima-media thickness was obtained in all patients (Sequoia 512C sonograph; Acuson Corp, Mountainview, USA; linear probe 6÷Hz). Intima-media thickness (IMT) was measured in the left and right carotid arteries and expressed as a mean of the maximum value in the common carotid, bifurcation and internal carotid artery (Fig. 1). Values in the range 1–1.3 mm were regarded as indicative of IM thickening. Plaque was defined as local IM thickening ⩾1.3 mm. Carotid artery stenosis was identified and quantified by analyzing the Doppler velocity spectrum in combination with measurement of the stenosis area in all patients with severe lesions.

Statistical analysis

All statistical analyses were performed with the STATISTICA data analysis software system, version 5 (StatSoft, Inc, Tulsa, Oklahoma, USA). The aPL antibody levels and IMT were compared between groups using the Mann-Whitney U test (the Kolmogorov-Smirnov Two-Sample test for mean values of age, total cholesterol and triglycerides). IM thickening, elevated aPL antibodies, carotid plaques, and other coronary risk factors in patients and controls were compared with the Yates' corrected chi-square test. The non-parametric Spearman R correlation test was applied to analyze associations between aPL antibody levels, IMT and classic risk factors. All results are expressed as means ± standard deviation (SD). The significance level was set at $p<0.05$.

Results

Elevated aPL antibody levels (IgG >10 GPL; IgM >20 MPL) were detected in 12 of 50 patients with MI (24%) and in 3 of 50 control subjects (6%); cf. Table 1. The differences were statistically significant at the level of $p<0.001$. The mean level of aPL antibodies was significantly higher in patients with MI (the IgG mean was 9.15±3.53 GMP, the IgM mean was 18.46±7.61 MPL) than in the control group (IgG mean 7.69±2.98 GMP, $p=0.04$; IgM mean 12.14±5.05 MPL, $p<0.01$). The MI patients had significantly greater carotid IMT than healthy controls (mean 0.9±0.02mm vs 0.6±0.01mm; $p<0.01$). IM thickening was detected in 13 cardiac patients (25%) and only 2 controls (4%; $p<0.001$). Carotid plaques were found in 12 MI patients (24%) and in 1 control subject (2%, $p<0.001$). Stenosis exceeding 50% of the carotid arteries was recorded in 2 patients (4%). None of the patients or healthy subjects showed total obstruction of carotid arteries. There was a correlation between IM thickening and aPL ($r=0.31$; $p=0.01$). Among coronary risk factors only hypertension ($r=0.28$; $p=0.01$) and smoking ($r=0.41$; $p=0.01$) correlated with IM thickening.

Discussion

In the present study, elevated aCL antibody levels were significantly more common in patients with MI than in control subjects. Our data indicates that an elevated level of aPL antibodies may carry an additional risk of atherosclerosis, which supports previous observations [22,23]. The association between aPL antibodies and valvular lesions had been described previously in several case reports and studies [24,25]. Some authors also suggest that aPL antibodies contribute to the pathogenesis of systemic and pulmonary hypertension [26]. Because aPL antibodies in healthy subjects have been shown to predict myocardial infarction [27], it is possible that at

least in some instances they could be directly involved in the pathogenesis of thrombotic events.

Speculation on cause-and-effect based on statistical relationships is of course a highly questionable procedure. However, in light of the accumulated experimental and clinical data, this circumstantial evidence could be interpreted to support a role for aPL antibodies in thrombinogenesis, rather than in the pathogenesis of atherosclerosis. Musiał et al. reported increased thrombinogenesis in patients with antiphospholipid syndrome [28,29]. In particular, the interactions between aPL antibodies and smoking, leukocyte count, or triglycerides support this conclusion, since all of these coronary risk factors are known to be associated with hypercoagulative stages [30–32]. Although the pathogenic mechanism leading to thrombosis in patients with aPL remains unclear, it is known that aPL can bind to endothelial cells [33] and activate them [34,35]. Activated endothelium may change its properties from antithrombotic towards prothrombotic [36,37]. Another possibility is impaired function of the protein C system [38], with an important role played, among others, by acquired free protein S deficiency. The most consistent finding in a large number of studies reviewed by de Groot [39] is the inhibition by antiphospholipid antibodies of the inactivation of factor Va by activated protein C. Thus, an important feedback mechanism inhibiting thrombin formation could be impaired. The unopposed activity of prothrombinase complex would then lead to increased thrombin generation. Endothelium and other phospholipid membranes may be involved. Antiphospholipid antibodies can interfere with the activation of protein C by the thrombomodulin-thrombin complex or by the inhibition of the assembly of the protein C complex on such surfaces.

Several different mechanisms have been proposed for the involvement of aPL antibodies in thrombinogenesis [40]. For example, aPL antibodies may bind not only to the membranes of endothelial cells, but also to thrombocytes. Infections may also play a role in the pathogenesis of coronary heart disease [41]. A transient aPL antibody response takes place in a variety of bacterial and viral infections, and elevated levels can persist in many chronic infections. Perhaps aCL antibodies rise in response to chlamydial infection, which has been associated with coronary heart disease [42–44].

We have shown significant thickening of the intima-media complex in patients with MI. Also, the number of atherosclerotic plaques was greater in these patients in comparison to healthy subjects. We observed a relationship between aPL and IM thickening. Consistent with other reports, we have shown that the IMT of the carotid artery is strongly associated with the risk of cardiovascular events [45,46]. Some authors have found a significant correlation between IM thickening and several cardiovascular risk factors, including age, hypertension, diabetes, total cholesterol, and smoking [47,48]. In our study only hypertension and smoking correlated with increased carotid IMT. Although the levels of total cholesterol and triglycerides were significantly higher in survivors of MI, they did not show such a relationship with IMT. The effect of lipids on IMT may have been masked by the absence of women and the relatively young age of the study groups. Additionally, the patient population distribution was highly skewed, and most of these patients were on lipid-lowering treatment. B-mode ultrasound carotid artery imaging is a noninvasive, safe and inexpensive method that can be used to visualize and measure the combined arterial IMT of superficial vessels [49]. This technique, which has been proven to be reproducible in numerous studies (range of absolute differences in replicate scans and readings 0.06–0.15 mm), yields information on atherosclerotic wall changes that cannot be obtained by conventional contrast angiography or MRI [49]. Increased carotid IMT has been demonstrated to be predictive of ischemic stroke and myocardial infarction [50–52]. Clinical trials that have used carotid IMT as an endpoint in treatment of asymptomatic subjects with known hypercholesterolemia or hypertension have shown that such treatment reduces IMT progression rates and stabilizes or regresses pre-existing atherosclerosis [53–55]. Carotid IMT is a direct method of measuring the extent, severity and evolution of atherosclerosis, and helps to estimate the efficacy of preventive medical treatment.

CONCLUSIONS

Our results indicate that measuring IMT and detecting aPL antibodies can be used as a screening tool to identify asymptomatic subjects who are at risk of developing atherosclerosis-related cardiovascular events.

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