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Intima-Media Thickness in Patients With Rheumatic Mitral Stenosis

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The aim of the study was to determine carotid artery intima-media thickness (IMT) in patients with rheumatic mitral stenosis (RMS). Between January 2001 and December 2003, 112 consecutive patients who had been diagnosed with RMS were screened. Patients with known cerebrovascular disease, coronary artery disease, diabetes, hypertension, left ventricular hypertrophy, hyperlipidemia, abnormal laboratory results, smoking, or age over 50 years were excluded. Forty-eight patients (43 women, 5 men, mean age 39.7 ±8.3 years) with RMS without risk factors were enrolled in the study. Age- and sex-matched healthy individuals (n = 48; 43 women, 5 men, mean age 39.6 ±8.6 years) with normal echocardiographic findings constituted the control group. Carotid IMT was determined by using a high-resolution ultrasound system equipped with a 7-MHz imaging probe (Acuson 128 XP CI) with a computer measurement software. The mean common carotid artery IMT thicknesses both in the right (0.604 ±0.112 mm vs 0.521 ±0.072 mm) and in the left side (0.581 ±0.097 mm vs 0.516 ±0.065 mm) were significantly higher in patients with RMS than in the control group ($p < 0.001$). Backward stepwise logistic regression analysis identified RMS as independent predictors of increased IMT (OR, 17.25 (CI, 3.99 to 76.28), $p < 0.001$). The present study demonstrated that RMS is associated with increased IMT. The findings indicate that in patients with RMS not only valvular but also systemic endothelium is damaged.

Introduction

The predominant cause of mitral stenosis, rheumatic fever,[1] is a sequela of throat infection group A streptococci. The pathogenic mechanisms involved in the development rheumatic mitral stenosis (RMS) are an abnormal humoral and cellular immune response.[2] In studies of antistreptococcal/antiheart monoclonal antibodies from rheumatic carditis the cross-reactive antibodies reacted with both myocardium and valvular endothelium.[3] It has been suggested that activated endothelium would obviously play a dramatic role in the initial development of rheumatic valvulitis

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and the progression of the disease throughout a lifetime.[4] High-resolution carotid ultrasonography has been used to obtain measurements of the thickness of the intima-media of the carotid arteries. Previous studies have shown cross-sectional associations between common carotid artery intima-media thickness (IMT) and cardiovascular risk factors,[5-7] the prevalence of cardiovascular disease,[6-8] and the involvement of other arterial beds with atherosclerosis.[9,10] Up to now, no study has been reported to determine carotid IMT in patients with RMS. Thus; in this study, we investigated the relation between RMS and IMT.

Materials and Methods

Patient Selection

Between January 2001 and December 2003, 112 consecutive patients who had been diagnosed with RMS were screened. Patients with known cerebrovascular disease, coronary artery disease, diabetes, hypertension, left ventricular hypertrophy, hyperlipidemia, abnormal laboratory results, smoking, or over 50 years were excluded. Forty-eight patients (43 women, 5 men, mean age 39.7 ±8.3 years) with RMS without risk factors were enrolled in the study. Age- and sex-matched healthy individuals (n = 48; 43 women, 5 men, mean age 39.6 ±8.6 years) with normal echocardiographic findings constituted the control group. Oral consent was obtained from all persons in the study.

Study Design

Age, sex, and history were recorded for all patients and control subjects. Weight, height, waist circumference, and hip circumference were measured for each subject, and body mass index was determined from these parameters. Waist circumference was measured with a soft tape on a standing subject midway between the lowest rib and the iliac crest. Laboratory studies (serum electrolytes, high-sensitive C-reactive protein, erythrocyte sedimentation rate, blood glucose, serum urea nitrogen, and serum creatinine concentrations, and a serum lipid profile) were performed. Echocardiographic determinations were performed for all patients and control subjects. We measured right and left common carotid artery IMT.

Echocardiographic Examination

Echocardiography was performed using an Acuson 128 XP CI. A 2.5- or 3.5-MHz transducer was used for M-mode, 2-dimensional, and Doppler echocardiographic examinations. Echocardiographic images were obtained from the parasternal and apical windows with the patients in the left lateral recumbent position. All recordings were obtained at the end of expiration to get good-quality images. M-mode measurements were performed according to the recommendations of the American Society of Echocardiography.[11]

Mitral valve area was measured by pressure halftime (PHT) method. Transmitral inflow velocities were recorded by continuous-wave Doppler echocardiography from the apical 4-chamber view. Spectral Doppler was traced and analyzed to determine peak and mean transmitral gradients. PHT was obtained as described by Hatle et al.[12] Doppler mitral valve area was estimated by 220/PHT formula.

Carotid Ultrasound Protocol

A high-resolution ultrasound system equipped with a 7-MHz imaging probe (Acuson 128 XP CI) was used. All ultrasound scans were taken by the same person. The IMT of the common carotid artery was measured at the level of the middle cervical segment of the common carotid artery on the far wall. After acquisition of the echographic images, the M'ATH© software determined the mean IMT value. Several problems are associated with the ultrasonographic measurement of the carotid IMT, namely, resolution of the equipment, operator variability, and the definition of carotid IMTs. With advancement in technology and computer software, accurate measurement and the interpretation of the carotid IMT can be made with greater reliability and reproducibility. Computer software can now automatically define the IMT to within 0.01 mm.[13] We assessed carotid IMT by using computer software. Mean IMT obtained from all scans from the same subject were averaged, and the resulting mean IMT was used for statistical analyses.

Statistical Analysis

SSPS for Windows (version 9.05; SPSS, Inc, Chicago, IL, USA) was used for data management and statistical analysis. The numeric variables are given as means ± SD, the categorical variables, as percentage. Relations among different groups and

variables were analyzed with the Student's t test. Backward stepwise logistic regression analysis was performed to determine independent factors for increased common carotid artery intima-media thickness. All measurements of IMT higher than the 75% percentile were accepted as increased IMT. A p value <0.05 was considered statistically significant.

Results

Characteristics of patients with RMS are shown in Table I. The patients were free from traditional risk factors. Laboratory studies for all the patients and controls were within normal limits. Table II shows characteristics and the mean carotid IMT in patients and controls. The mean common carotid artery IMT thicknesses both in the right (0.604 ±0.112 mm vs 0.521 ±0.072 mm) and in the left side (0.581 ±0.097 mm vs 0.516 ±0.065 mm) were significantly higher in patients with RMS patients than in the control group ($p<0.001$).

According to mitral valve area, we separated the patients with RMS into 2 groups as follows: Group 1: patients with moderate and severe RMS, mitral valve area less than 1.5 cm^2; group 2: patients with mild RMS, mitral valve area more than 1.5 cm^2, as shown in Table III. Demographic characteristics (age, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, and body mass index) were similar between groups. In group 1 mean mitral valve area was less (1.11 ±0.24 cm^2 vs 1.95 ±0.27 cm^2), mean mitral valve gradient was more increased (15.8 ±7.9 mm Hg vs 7.0 ±3.0 mm Hg), and left atrial dimension was more enlarged (46.2 ±5.8 mm vs 40.5 ±5.1 mm) than in group 2, and the differences were statistically significant ($p<0.001$). Although in group 1 the carotid artery mean IMT was more increased than in group 2, the difference was not statistically significant. Backward stepwise logistic regression analysis identified RMS as an independent predictor of increased IMT (OR, 17.25 (CI, 3.99 to 76.28), $p<0.001$) Table IV. The dependent variable was increased IMT, and the independent

Table I. Features of mitral stenosis and control groups.

	Mitral stenosis (n: 48)	Control (n: 48)	p Value
Female/male, n	43/5	43/5	
Age, year	39.7 ±8.3 (18–50)	39.6 ±8.6 (20–50)	NS
Systolic blood pressure, mm Hg	120 ±8	119 ±7	NS
Diastolic blood pressure, mm Hg	69 ±6	68 ±6	NS
High-sensitive C-reactive protein, mg/L	3.83 ±0.91	4.04 ±0.97	NS
Erythrocyte sedimentation rate, mm/hr	13.19 ±3.13	12.73 ±2.57	NS
Total cholesterol, mg/dL	167 ±31	167 ±28	NS
HDL, mg/dL	47 ±10	46 ±7	NS
LDL, mg/dL	110 ±27	111 ±25	NS
Triglycerides, mg/dL	111 ±50	108 ±36	NS
BMI, kg/cm^2	26.3 ±4.6	25.2 ±4.8	NS
Ratio waist/hip	0.83 ±0.06	0.84 ±0.06	NS

BMI: body mass index, NS: nonsignificant.

Table II. Right and left carotid artery intima-media thickness measurements in patients with mitral stenosis and control group.

	Mitral stenosis (n: 48)	Control (n: 48)	p Value
R-IMT, mm	0.604 ±0.112	0.521 ±0.072	<0.001
(min-max)	(0.413–0.862)	(0.373–0.681)	
L-IMT, mm	0.581 ±0.097	0.516 ±0.065	<0.001
(min-max)	(0.369–0.853)	(0.378–0.663)	

R-IMT: right common carotid artery intima-media thickness, L-IMT: left common carotid artery intima-media thickness.

Table III. Determination of mitral stenosis patients features according to mitral valve area.

	Group 1 MVA <1.5 cm^2 (n: 21)	Group 2 MVA >1.5 cm^2 (n: 27)	p Value
Age, years	41.0 ±6.8	38.7 ±9.4	NS
Systolic blood pressure, mm Hg	119 ±8	121 ±8	NS
Diastolic blood pressure, mm Hg	69 ±6	69 ±7	NS
High sensitive C-reactive protein, mg/L	4.0 ±1.0	3.7 ±0.8	NS
Erythrocyte sedimentation rate, mm/hr	13.0 ±3.4	13.3 ±2.9	NS
Total cholesterol, mg/dL	160 ±30	173 ±30	NS
HDL, mg/dL	47 ±8	46 ±12	NS
LDL, mg/dL	107 ±25	113 ±29	NS
Triglycerides, mg/dL	108 ±53	113 ±49	NS
BMI, kg/cm^2	25.7 ±4.5	26.8 ±4.7	NS
Ratio waist/hip	0.82 ±0.06	0.84 ±0.05	NS
LA, mm	46.2 ±5.8	40.5 ±5.1	<0.001
MVA, cm^2	1.11 ±0.24	1.95 ±0.27	<0.001
MVMG, mm Hg	15.8 ±7.9	7.0 ±3.0	<0.001
R-IMT, mm	0.618 ±0.124	0.592 ±0.104	NS
L-IMT, mm	0.589 ±0.120	0.574 ±0.075	NS

BMI: body mass index, LA: left atrium, MVA: mitral valve area, MVMG: mitral valve mean gradient, R-IMT: right common carotid artery intima-media thickness, L-IMT: left common carotid artery intima-media thickness.

Table IV. Stepwise backward logistic regression analysis.

Determinants	p Value	OR	95% CI
Age	0.023	1.10	1.01–1.20
Gender	0.11	0.123	0.009–1.62
High-sensitive C-reactive protein	0.056	0.51	0.26–1.02
Triglycerides	0.085	0.99	0.98–1.0
Mitral stenosis	<0.0001	17.25	3.99–76.28

variables were age, gender, lipid profile, high-sensitive C-reactive protein, and systolic and diastolic blood pressure.

Discussion

This is the first study to report that RMS is associated with increased carotid IMT. Previous studies have demonstrated that several chronic infections are associated with accelerated atherosclerosis in the carotid arteries.[14-16] *Chlamydia pneumoniae, Helicobacter pylori,* herpes viruses, and hepatitis, have been most consistently associated with development of atherosclerosis.[14-16] Chronic infections may be accompanied by damage to endothelial cells, hypercoagulability, altered lipid profile, and enhanced autoimmunity, all of which might serve as mechanisms in the pathogenesis of atherosclerosis.[17] However Liuba et al[18] also showed that clinically manifest acute infections in children were accompanied by transitory proatherogenic lipid changes followed by thickening of carotid intima-media. These data provide support for a possible contribution of infection to the development of atherosclerosis, which may result from periodic spurts of vascular growth and incomplete healing due to repeated episodes of acute reinfections or reactivation of chronic infection. Our findings indicate that RMS is associated with increased carotid IMT. In our study, no patient had had an acute rheumatic fever attack for a long time.

Rheumatic mitral stenosis is a late complication of acute rheumatic fever; there is usually a long interval (10–20 years) between an episode of rheumatic carditis and the clinical presentation of symptomatic RMS. The pathogenic mechanisms involved in the development RMS are abnormal humoral and cellular immune responses.[2] Initial streptococcal infection with the activation of B and T lymphocytes by streptococcal antigens and superantigens in susceptible patients would lead to antibody and cytokine production.[19] The reaction of antistreptococcal/antimyosin antibodies from rheumatic carditis with the valve endocardium supports the hypothesis that cross-reactive antibodies may bind to endothelium and lead to inflammation, cellular infiltration, and valve scarring.[3] Roberts et al[4] found that the pathogenesis of rheumatic carditis involved the activation of surface valvular endothelium with the expression of vascular cell adhesion molecule-1 (VCAM-1) and the extravasation of $CD4^+$ and $CD8^+$ lymphocytes through the activated endothelium into the valve. They proposed that the mechanism of pathogenesis in rheumatic carditis begins at the valve surface endothelium.[4] We found that RMS in patients was associated with increased carotid IMT as a marker of systemic endothelial damage.

Conclusion

The present study demonstrated that RMS in patients was associated with increased IMT. Our findings indicate that in patients with RMS not only valvular but also systemic endothelium was damaged.

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