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Antimitochondrial autoantibodies in myocardial hypertrophy: Comparison between hypertrophic cardiomyopathy, hypertensive heart disease, and athlete's heart

Antimitochondrial autoantibodies (AMA) were tested by indirect immunofluorescence in three groups of subjects with different types of myocardial hypertrophy: 35 patients affected with hypertrophic cardiomyopathy (HC), 20 patients with cardiac hypertrophy secondary to essential hypertension, and 35 active endurance athletes with exercise-induced left ventricular hypertrophy. Forty-two healthy subjects served as a control group. Left ventricular hypertrophy was considered a left ventricular mass (LVM) echocardiographically calculated (Devereux formula), exceeding 244 gm or a LVM index exceeding 122 gm/m² (greater than 2 SD from a previously studied normal population). AMA were found in 15 of 35 (43%) patients with HC and in 6 of 20 (30%) patients with hypertensive heart disease ($p < 0.01$); in contrast, AMA were not present in the sera of athletes or in the sera of controls. Although the significance of AMA in subjects with pathologic myocardial hypertrophy has not yet been established, their absence in the sera of athletes strengthens the opinion that cellular changes, as a compensatory response of the myocardium to a work overload, have a physiologic fashion in these cases. Moreover, identification of AMA in the sera of athletes with disproportionate severe left ventricular hypertrophy of uncertain origin may be helpful to ensure a single diagnosis. (Am Heart J 1988;116:496.)

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Klein et al.[1] have recently demonstrated the presence of organ-specific autoantibodies against heart mitochondria in patients with either dilated or hypertrophic cardiomyopathy, two pathologic conditions characterized by myocardial hypertrophy, regardless of their different etiology and pathogenetic aspects. In a previous study,[2] we found circu-

Table I. Left ventricular mass echocardiographically evaluated in the three groups of subjects

	Exercise-induced MH	*HC*	*Hypertensive heart disease*
Age (yr)	20 ± 4	49 ± 15	52 ± 10
LVM (gm)	298 ± 45	346 ± 72	282 ± 46
	$p < 0.01$	$p < 0.01$	
	p = n.s.		
LVM index (gm/m²)	145 ± 18	184 ± 41	147 ± 25
	$p < 0.001$	$p < 0.001$	
	p = n.s.		

MH = myocardial hypertrophy; HC = hypertrophic cardiomyopathy; LVM = left ventricular mass; LVM index = left ventricular mass corrected for body surface area; n.s. = not statistically significant. Values are expressed as mean ± standard deviation.

lating antimitochondrial autoantibodies in a group of patients with hypertrophic cardiomyopathy and, to a lesser extent, in the sera from patients with myocardial hypertrophy secondary to essential hypertension.

Cardiac hypertrophy in athletes has been widely studied from a morphologic and physiologic point of view by means of invasive and noninvasive cardiologic techniques; however, no report is available about the application of immunologic methods in investigating this condition. In view of our hypothesis that circulating antimitochondrial autoantibodies should be absent in subjects with supposed physiologic myocardial hypertrophy, we tested these autoantibodies in a group of highly trained athletes and we compared the results with those obtained in patients with hypertrophic cardiomyopathy and left ventricular hypertrophy secondary to essential hypertension.

METHODS

Preliminary study. An echocardiographic screening among a large series of athletes and patients with essential hypertension or hypertrophic cardiomyopathy (HC) was performed preliminarily to select subjects with cardiac hypertrophy (see below). Each subject was studied with either a VR12 Electronics for Medicine ultrasonograph for M-mode examinations (2.5 MHz transducer, Electronics for Medicine/Honeywell Inc., Pleasantville, N.Y.) and an ATL Ultramark 4 mechanical sector scanner (3 MHz transducer, Advanced Technology Laboratories, Inc., Bothell, Wash.) or a Hewlett-Packard phased array scanner (3.5 MHz transducer, Hewlett-Packard Co., Andover, Mass.). All standard echocardiographic views were done; left ventricular internal dimension (LVID), interventricular septal thickness (IVST), and posterior wall thickness (PWT) at end diastole (d) were measured on two-dimensionally guided M-mode recordings (at a paper speed of 50 mm/sec) at the peak of the R wave just below the tips of the mitral valve leaflets. The left ventricular mass (LVM) was calculated from the Penn convention measurement by the regression equation: Penn-cube $LVM^3 = 1.04$ $[(IVSTd + LVIDd + PWTd)^3 - LVIDd^3] - 13.6$ gm. To minimize the impact of variation in body size on LVM, the values were also corrected for body surface area. Measurements were made on three to five cycles and were averaged by two physicians on two separate occasions; the two values were then averaged if the difference did not exceed 10%, otherwise the parameter was recalculated.

Left ventricular hypertrophy (LVH) was judged a LVM exceeding 244 gm or a LVM index exceeding 122 gm/m², a value greater than 2 standard deviations from that obtained from a group of 54 healthy subjects (mean age 35 ± 14, range 5 to 6 years) previously studied by the same techniques and procedure. These values constitute the standard of reference of our laboratory to assess LVH and are quite comparable with those recently reported by Levy et al.[4] in the Framingham Heart Study.

Study group. *Athletes.* Thirty-five endurance athletes (all men, aged 16 to 28 years, mean 20 ± 4 years) were selected for echocardiographic evidence of myocardial hypertrophy. They were rowers at high level competition (23 national and Olympic athletes), and had been training for more than 4 years. None demonstrated any historical or clinical evidence of heart disease.

Hypertensive patients. Twenty subjects with essential hypertension (12 men and 8 women, aged 33 to 67 years, mean 52 years; clinical onset ranging from 1 to 21 years, mean 7 ± 7) were included in the study. All were receiving antihypertensive therapy and their blood pressure at the time of the study was between 135/80 and 230/120 mm Hg. None of them was taking any drug (i.e., methyldopa, hydralazine, or reserpine) that could affect immunologic tests. Patients with a history of angina, myocardial infarction, or valvular disease were excluded. No patient had a family history of HC or premature sudden death.

Patients with hypertrophic cardiomyopathy (HC). Thirty-five subjects with HC (27 men and 8 women aged 20 to 79 years, mean 49 ± 15 years; clinical onset ranging from 1 to 16 years, mean 5 ± 5) and adequate echocardiographic recordings for the assessment of the LVH were included in the study population. The diagnosis of HC was based upon the echocardiographic demonstration of a hypertrophied nondilated left ventricle in the absence of another cardiac or systemic disease capable of producing LVH.[5] Obstruction of the left ventricular outflow tract

Table II. Results of the immunologic study

Diagnosis	*No. of subjects*	*AMA*	*↑IgG*	*↑IgA*	*↑IgM*	*↑C3*	*↑C4*
Exercise-induced MH	35	—	—	—	2 (6%)	—	—
HC	35	15 (43%)	4 (11%)	4 (11%)	4 (11%)	17 (48%)	5 (14%)
Hypertensive heart disease	20	6 (30%)	—	4 (20%)	1 (5%)	13 (65%)	—

MH = myocardial hypertrophy; HC = hypertrophic cardiomyopathy; AMA = presence of antimitochondrial autoantibodies; ↑ = increased serum levels >2 SD from values obtained in 42 control subjects; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; C3 = third component of complement; C4 = fourth component of complement.

Table III. Hypertrophic cardiomyopathy and hypertensive heart disease; comparison between clinical and morphologic features of patients with and without AMA

	Hypertrophic cardiomyopathy		*Hypertensive heart disease*	
	AMA +	*AMA −*	*AMA +*	*AMA −*
No. of Patients	15	20	6	14
Age (yr)				
Range	28-69	20-79	33-67	38-67
Mean ± SD	46 ± 15	51 ± 16	52 ± 14	52 ± 8
	p = n.s.		p = n.s.	
Clinical onset (yr)				
Range	1-21	1-16	1-25	1-20
Mean ± SD	5.3 ± 5	5 ± 4	8.3 ± 10	6.7 ± 7
	p = n.s.		p = n.s.	
LVM (gm)				
Range	221-576	240-461	190-303	230-422
Mean ± SD	356 ± 94	316 ± 59	254 ± 38	277 ± 52
	p = n.s.		p = n.s.	

AMA = antimitochondrial autoantibodies; + = presence; − = absence; LVM = left ventricular mass; SD = standard deviation; n.s. = not significant.

was estimated from the M-mode echocardiograms when both systolic anterior motion of the mitral valve and midsystolic closure of the aortic valve were present[6]; hypertrophic obstructive cardiomyopathy was then diagnosed in 11 of 35 cases. Asymmetric septal hypertrophy (septal to posterior wall ratio ⩾1.3) was found in 34 of 35 patients with HC.

Immunologic study. Sera from all study group individuals were analyzed; the athletes provided venous blood samples 24 to 36 hours after the last muscular effort. Serum levels of IgG, IgA, and IgM immunoglobulins and C3 and C4 complement fractions were determined by a simple radial immunodiffusion method[7] that used endoplate single radial immunodiffusion plates (Kallenstad, Austin, Texas). Values are expressed as milligrams per deciliter. Sera were examined for non-organ-specific circulating antimitochondrial (AMA), antinuclear (ANA), antismooth muscle (SMA), and antigastric parietal cell (PCA) autoantibodies by a routine indirect immunofluorescence test on cryostat sections; rat kidney and stomach were used as substrates.[8] Patients' serum samples were used at a dilution of 1:20; fluorescein conjugated burro antiserum to human total immunoglobulins (Kallenstad, Austin, Texas) was used at 1:40 dilution. Forty-two healthy subjects (mean age 30 ± 8 years) served as a control group.

Statistical analysis. Student's t test or the Mann-Whitney test for unpaired data were used to evaluate the significance of differences between two groups.

RESULTS

Preliminary study. LVMs of the three selected groups are listed in Table I. Patients with HC had a LVM greater than that of hypertensive patients (346 ± 72 gm vs 282 ± 46 gm; $p < 0.01$) and athletes (346 ± 72 gm vs 298 ± 45 gm; $p < 0.01$); no significative difference was found for LVM between hypertensive patients and athletes (282 ± 46 gm vs 298 ± 45 gm; p = n.s.).

Immunologic study. AMA were demonstrated in 15 of 35 (43%) patients with HC and in 6 of 20 (30%) hypertensive patients, whereas they were not seen in athletes or in the control group (Table II). AMA were found in 4 of 11 (36%) patients with obstructive HC and in 11 of 24 (46%) patients with the nonobstructive form ($\chi^2 = 0.024$; p = n.s.). The other

non-organ-specific autoantibodies tested (ANA, SMA, and PCA) were not found in any subject of the studied groups. Elevated C3 complement fraction serum levels (higher than 2 standard deviations from the control group) were measured in a high percentage of patients with HC and systemic hypertension (48% and 65%, respectively). Only in a small group of HC and hypertensive patients was an increase of serum immunoglobulin levels found; the four HC patients with increased IgM were also AMA-positive, while the sera with increased IgA and/or IgG were found in both patients with or without AMA. Increased C3 serum levels were detected in 12 of 15 (80%) AMA-positive patients with HC and in six of six (100%) AMA-positive patients with systemic hypertension. Furthermore, no relation was found between presence of AMA and age of patients, clinical onset of disease, or degree of myocardial hypertrophy (Table III).

DISCUSSION

In the present study, non-organ-specific AMA and elevated serum levels of C3 complement fraction were demonstrated in sera of patients with myocardial hypertrophy of pathologic type (primary and secondary to essential hypertension). By contrast, none of these immunologic abnormalities was detected in the group of athletes with myocardial hypertrophy secondary to chronic exercise (physiologic hypertrophy). The C3 protein belongs to the wide spectrum of acute phase reactants so that the increase of serum C3 concentration could be regarded as an expression of an active process, i.e., a nonspecific phenomenon as it occurs in ischemic heart disease.[9]

Klein et al.[1] demonstrated AMA in 33% of patients with HC and pointed out that an immune mechanism may be operative in at least some forms of cardiomyopathies. In the present work, as in our preliminary study,[2] we found circulating AMA in both patients with HC and essential hypertension but no association with the age of patients or the clinical onset of illness. These results suggest that although a pathogenetic role of these autoantibodies cannot be excluded, their presence might be related to the exposure of new antigens in conditions of myocardial hypertrophy leading to cellular lesions and ultrastructural changes, particularly mitochondrial damage and increased number of small, immature mitochondria.[10] It is worthy of note that disproportionate cellular biosynthesis of organelles and the inability of mitochondria to increase in number proportionate to energetic demands occur in the evolution of pathologic hypertrophy.[11] Concerning the presence of such immunologic abnormalities, only in a subgroup of patients with pathologic hypertrophy may we suppose that this factor may be related to a genetically determined disregulation of the immune response probably existing in some individuals, as suggested also by HLA typing studies on HC.[12] The characteristics and specificity of the putative antigen involved in the immune response in the course of pathologic myocardial hypertrophy remain obscure, and an attempt to clarify them is beyond the scope of the present study. However, we can observe that the absence of AMA in the group of highly trained athletes with echocardiographically documented myocardial hypertrophy strengthens the opinion that cellular changes, as a compensatory response of the myocardium to a work overload, may have a physiologic fashion in athletes.

Our results may also account for the diagnostic relevance of testing circulating AMA in athletes. In some cases, myocardial hypertrophy of athletes may have morphologic features intermediate between the normal athletic heart and nonobstructive hypertrophic cardiomyopathy, and it can fall into an equivocal "gray zone" between these two diagnostic possibilities, as defined by Maron.[13] In such circumstances while the absence of AMA cannot rule out HC, their presence in sera of those athletes with disproportionate left ventricular hypertrophy may be helpful to ensure a single diagnosis. Prospectively, testing circulating AMA in a large series of athletes in the "gray zone" and comparing the results with those obtained in each case from family echocardiographic studies and from deconditioning will better assess the clinical significance of these autoantibodies in myocardial hypertrophy.

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Clinical significance of radionuclide angiographically-determined abnormalities following acute blunt chest trauma

Abnormalities of right and left ventricular ejection fraction and segmental wall motion may be detected by radionuclide angiography (RNA) following blunt chest trauma. Of 111 patients with blunt chest trauma who were admitted to a large regional shock trauma center and underwent combined first-pass and equilibrium gated RNA, abnormalities were present in 40 (36%). These abnormalities were confined to the right ventricle in 33 patients. There was a positive association between RNA abnormalities and the presence of right bundle branch block (10 of 40, $p < 0.05$) and a negative association between RNA abnormalities and the finding of rib fractures (6 of 40, $p < 0.05$). The in-hospital death rate of these patients was low (3 of 40 patients with an abnormal RNA and 2 of 71 patients with a normal RNA). Follow-up RNA was performed at 10 ± 4 days in 26 of the 40 patients with initially abnormal scans, and 22 (85%) of the 26 had reverted to normal. Thus although RNA abnormalities appear common following blunt chest trauma, among patients who survive for more than 24 hours and who undergo subsequent RNA, the complication rate is low despite an abnormal scan. We conclude that routine RNA adds little to clinical management following acute blunt chest trauma. (Am Heart J 1988;116:500.)

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Over the past several decades, a growing body of literature has accumulated attempting to define the incidence and natural history of cardiac injuries that result from blunt chest trauma. Early studies consisting primarily of autopsy series[1-3] suggested that the incidence was low, but this has been revised upward more recently as the techniques available for diagnosing myocardial injury and dysfunction have become more sensitive. Electrocardiography, serum cardiac enzyme determinations, technetium pyrophosphate scanning, echocardiography, and radionuclide angiography (RNA) have all been used in an attempt to detect cardiac injury following trauma.[4-8] The incidence of abnormalities has varied from 26%[5] to 75%,[8] depending on the technique employed. In general, the ECG, serum enzymes, and technetium scanning have been found to be nonspecific,[9-11] and the experience with echocardiography has been limited.[7,12] RNA is a relatively easily obtainable test that allows for the noninvasive determination of right ventricular ejection fraction (RVEF), left ventricular ejection fraction (LVEF), and regional wall motion abnormalities. Previous

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