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Risk for atrial fibrillation in patients with hypertrophic cardiomyopathy: Association with insulin resistance

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Summary
Background: We undertook a cross-sectional study to test the hypothesis that patients with hypertrophic cardiomyopathy (HCM) who have impaired left ventricular (LV) diastolic function are insulin resistant. We also evaluated the relation between the development of atrial fibrillation (AF) and insulin resistance (IR) in patients with HCM.
Methods and results: Eighty-eight patients with HCM (71 men, 17 women) were enrolled in the study. IR was estimated using the homeostasis model assessment (HOMA) index. Echocardiographically determined left atrial (LA) dimension was measured as a marker of LA size. The ratio of trasmitral early LV filling velocity to early diastolic mitral annulus velocity (E/e') was also measured as a marker of LV diastolic function. Twenty-seven patients (31%) had IR. Multivariate logistic regression analyses showed that independent determinants of AF were increased LA size [odds ratio (OR) 3.5, 95% confidence interval (CI) 1.2—9.8] and impaired LV diastolic function [OR 4.6, 95% CI 1.6—12.8]. The strongest determinant of LA size was the HOMA index ($p = 0.0005$). Similarly, the HOMA index ($p = 0.0019$) was an independent determinant of LV diastolic function.

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Conclusion: IR is highly prevalent among non-diabetic patients with HCM. A possible mechanism by which IR affects the development of AF is mediated through its association with increased LA size or impaired LV diastolic function. IR may be an important underlying mechanism for the genesis of AF in HCM.

Introduction

Atrial fibrillation (AF) is a particularly important arrhythmia in hypertrophic cardiomyopathy (HCM) [1—3]. AF develops in a substantial proportion of adult patients with HCM [1—4] and is associated with increased systemic thromboembolism, heart failure, and death [5,6]. In addition, AF contributes to a poor prognosis because of deterioration in cardiac function [7]. However, it is unclear how AF develops in patients with HCM. A number of mechanisms have been proposed, including neurohormonal alterations, oxidative stress, fibrosis, and maladaptive hemodynamic and barodynamic changes with resulting abnormalities in electrical conduction [8].

Insulin resistance has been associated with chronic heart failure independently of its etiology [9,10]. HCM is functionally characterized by impaired left ventricular (LV) diastolic function [11,12] and we have reported that patients with HCM without apparent diabetes mellitus or hypertension have insulin resistance [13]. The metabolic syndrome consists of a cluster of atherosclerotic risk factors, including insulin resistance, obesity, hypertension, and dyslipidemia. Many atherosclerotic risk factors are implicated in the pathogenesis of AF [14,15]. One recent study in Japan has shown the relation between metabolic syndrome and the development of AF [16]. Although insulin resistance plays an important role in the pathogenesis of metabolic syndrome, the precise relation between insulin resistance and the development of AF has not been assessed in patients with HCM.

We therefore undertook a cross-sectional study to test the hypothesis that patients with HCM who have impaired diastolic function are insulin resistant. We have also evaluated the relation between the development of AF and insulin resistance in patients with HCM.

Methods

Study patients

Eighty-eight patients with HCM (71 men, 17 women; mean age: 65 ± 11 years) participated in this study. They had normal findings on chemical screening battery and were non-diabetic by the criteria of the American Diabetes Association [17]. Coronary angiographic studies were performed in all study patients and none of them had coronary artery disease. The study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. All patients gave their informed consent prior to participation in the study.

Definitions of HCM and AF

HCM was defined as the presence of a hypertrophied, non-dilated ventricle in the absence of underlying cardiac or systemic secondary causes and was based on World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies [18]. Patients with HCM were subdivided into 2 groups: hypertrophic obstructive cardiomyopathy (HOCM) and hypertrophic non-obstructive cardiomyopathy (HNCM). HOCM was diagnosed when a patient had a LV pressure gradient greater than 30 mmHg without provocation in the LV outflow tract and/or mid-ventricle [19].

Documentation of AF was based on electrocardiography recordings obtained either after acute onset of symptoms or fortuitously during routine medical examination in asymptomatic patients. AF was defined as paroxysmal when it was either self-terminating or successfully cardioverted to sinus rhythm; AF was considered chronic when it became established.

Physical examinations

Physical examinations in study patients were supervised by the nursing staff. Weight and height were measured while the subjects were fasting overnight and wearing only underwear. Body mass index (BMI) was calculated as weight (kg) divided by height $(m)^2$. Blood pressure (BP) was measured in triplicate by a single physician with an appropriate arm cuff and a mercury sphygmomanometer after 5 minutes' rest in the sitting position. The arithmetic mean of the last two measurements was calculated. Korotkoff phase V was taken for diastolic blood pressure.

Assessments of biochemical parameters and natriuretic peptides

Venous blood was taken in the morning after overnight fasting in the outpatient clinic. Plasma glucose was immediately determined by the glucose oxidase method. Plasma insulin was determined in duplicate by high specific and sensitive immunoradiometric assay (Abbott Japan, Tokyo, Japan; intra-assay coefficient of variation [CV] 1.6%, interassay CV 2.2%). Serum concentrations of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were assessed by standard enzymatic methods. Plasma levels of atrial and brain natriuretic peptides (ANP and BNP) were also measured in all patients, as previously reported [20].

Insulin resistance was assessed from fasting immunoreactive insulin (FIRI) and fasting plasma glucose (FPG) and the previously validated homeostasis model assessment (HOMA) [21], thus: HOMA index = FIRI (pmol/L) × FPG (mmol/L)/161. On the basis of FPG upper limit of normal of 6.1 mmol/L and our laboratory's upper limit of normal for FIRI of 71.0 pmol/L, a HOMA index of 2.69 was determined as the upper limit of normal. An individual

with the HOMA index $\geq$2.7 was considered to have insulin resistance [10].

Echocardiographic measurements

Two-dimensionally guided M-mode echocardiography was performed by standard methods, as previously outlined [5,13,22], using a Vivid 7 Dimension ultrasound machine (GE Healthcare, Milwaukee, WI, USA) with an M4S probe. Echocardiographic examinations were performed and interpreted by the same cardiologist, who was unaware of the patient's data. Left atrial (LA) dimension was measured at end-systole, according to the American Society of Echocardiography guidelines [23]. Interventricular septal thickness and LV posterior wall thickness were also measured in end-diastole at the level of the mitral valve. LV end diastolic and end systolic volumes (EDV and ESV), and ejection fraction (EF) were estimated by Simpson's rule from two-dimensional apical chamber view.

LV pressure gradient was measured from continuous-wave Doppler imaging of the LV outflow tract and/or mid-ventricle [19,24]. Early diastolic mitral annular velocity at the septal and lateral side (e') was obtained by tissue Doppler imaging, which reflects the time constant of isovolumic LV relaxation (tau) [25]. The combined assessment of peak early diastolic transmitral flow velocity (E) and e', E/e', was used as a surrogate of LV filling pressure [26].

Subgroup analyses

On the basis of cardiac rhythm, patients with HCM were distributed into the following three subgroups: HCM with sinus rhythm group (n = 54), HCM with chronic AF group (n = 22), and HCM with paroxysmal AF group (n = 12). To investigate the determinants of AF, patients with HCM were distributed into two subgroups: HCM with sinus rhythm (n = 54) and HCM with chronic AF or paroxysmal AF (n = 34), and subgroup analyses were performed.

Statistical analysis

All values are expressed as mean $\pm$ SD. One-way analysis of variance (ANOVA) was used to evaluate difference among groups, with Scheffe's correction for multiple comparisons. Categorical variables were compared with Fisher's exact and Chi-square tests. Univariate and multivariate logistic regression analyses were used to examine the effects of age, sex, BMI, insulin resistance, and echocardiographic variables on the risk of AF. These results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs).

Correlation coefficients were calculated according to Pearson's method. Multiple regression analysis was also performed to select appropriate independent variables producing the highest partial correlation with LA size or LV diastolic function. Probability values <0.05 were considered statistically significant in all analyses.

Results

The clinical characteristics of patients with HCM are presented in Table 1. There were no significant differences in age, pulse pressure, BP, and BMI among the three groups. Similarly, there was no significant difference in the prevalence of HOCM among the three groups. Plasma ANP levels in HCM patients with chronic AF were significantly higher than those in the other two groups. Plasma BNP levels in HCM patients with chronic AF were the highest, followed by HCM patients with paroxysmal AF, and HCM patients with sinus rhythm.

All of the 22 HCM patients with chronic AF received long-term anticoagulation with warfarin. Of the 12 HCM patients with paroxysmal AF, 7 patients (58%) received long-term anticoagulation with warfarin. Five HCM patients with paroxysmal AF, who did not receive warfarin, had pharmacological maintenance of sinus rhythm.

The biochemical and echocardiographic characteristics of the three groups are presented in Table 2. The HOMA index in HCM patients with chronic AF was significantly higher than that in HCM patients with sinus rhythm. In addition, the prevalence of insulin resistance in HCM patients with chronic AF or with paroxysmal AF was significantly higher than that in HCM patients with sinus rhythm. There were no significant differences in LDL-C, HDL-C, and TG among the three groups.

LA dimension and the E/e' ratio in HCM patients with chronic AF were significantly higher than those in HCM patients with sinus rhythm. There were no significant differences in LV pressure gradient and maximum LV thickness among the three groups. Similarly, there were no significant differences in EDV, ESV, and EF among the three groups of patients with HCM. Moreover, moderate to severe mitral regurgitation was presented in only a minority of HCM patients. There was no significant difference in the prevalence of moderate to severe mitral regurgitation among the three groups.

In univariate logistic regression analyses, insulin resistance, increased LA size, and impaired LV diastolic function were significant determinants of AF (Table 3). In multivariate logistic regression analysis, increased LA size and impaired LV diastolic function were significant determinants of AF, independent of insulin resistance. As shown in Table 4, the HOMA index, the E/e' ratio, EDV, ESV, and EF were significantly correlated with LA dimension. In multiple regression analysis, the strongest determinant of LA dimension was the HOMA index (p = 0.0005), independent of the E/e' ratio, EDV, ESV, and EF. Similarly, the HOMA index, natriuretic peptides, and LA dimension were significantly correlated with the E/e' ratio, as shown in Table 5. In multiple regression analysis, the HOMA index (p = 0.0019) and plasma BNP level (p = 0.0001) were independent determinants of the E/e' ratio.

Discussion

It is widely acknowledged that insulin resistance is a premier risk factor for cardiovascular disease [27] and this association is partly mediated by its effect on cardiac structure [28]. Consequently, we have examined the relations of

Table 1 Clinical characteristics, natriuretic peptides, and medical treatments in patients with HCM.

	HCM with sinus rhythm ($n = 54$)	HCM with chronic AF ($n = 22$)	HCM with paroxysmal AF ($n = 12$)
Age, years	64 ± 12	68 ± 9	63 ± 12
Pulse rate, beats/min	70 ± 15	68 ± 10	72 ± 12
BP, mmHg			
Systole	129 ± 17	135 ± 18	136 ± 16
Diastole	72 ± 12	77 ± 12	80 ± 14
BMI, kg/m^2	24.1 ± 2.7	23.6 ± 3.0	25.7 ± 2.5
HOCM, *n* (%)	13 (24)	5 (22)	4 (33)
Plasma ANP level, pg/mL	38 ± 32	109 ± 102[†]	58 ± 54
Plasma BNP level, pg/mL	146 ± 169	500 ± 447[†]	180 ± 151[*]
Medical treatments, *n* (%)			
Warfarin	1 (2)	22 (100)	7 (58)
Calcium antagonists	32 (59)	15 (68)	10 (83)
β-Blockers	33 (61)	12 (55)	7 (58)
Class Ia antiarrhythmic drugs	15 (28)	6 (27)	4 (33)

Vales are mean ± SD. HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; AF, atrial fibrillation; BP, blood pressure; BMI, body mass index; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.

[*] $p < 0.01$ vs. HCM with chronic AF.

[†] $p < 0.0001$ vs. HCM with sinus rhythm.

insulin resistance (assessed by the HOMA index) to LV pressure gradients and sudden death in patients with HCM [13]. The present study added to our previous study [13] by identifying the significant and independent relations of insulin resistance to echocardiograhically determined LA size and LV diastolic function. Furthermore, impaired LV diastolic function and increased LA size are important determinants of AF in patients with HCM.

Not only insulin, but also insulin-like growth factor-1 (IGF-1), is important in hypertrophic response of cardiac myocytes, by binding to the IGF-1 receptors because of the structural similarity between insulin and IGF-1 [28,29]. Mar-

Table 2 Biochemical and echocardiographic characteristics in patients with HCM.

	HCM with sinus rhythm ($n = 54$)	HCM with chronic AF ($n = 22$)	HCM with paroxysmal AF ($n = 12$)
Biochemical parameters			
FPG, mmol/L	5.6 ± 0.9	5.7 ± 0.8	5.3 ± 1.1
FIRI, pmol/L	60.3 ± 27.3	84.7 ± 48.8	84.7 ± 61.0
HOMA index	2.1 ± 0.9	3.1 ± 1.9[†]	2.7 ± 1.5
Insulin resistance, *n* (%)	11 (20)	10 (45)[*]	6 (50)[*]
LDL-C, mmol/L	2.87 ± 0.72	3.05 ± 0.55	3.08 ± 0.50
HDL-C, mmol/L	1.51 ± 0.47	1.23 ± 0.22	1.32 ± 0.33
Triglycerides, mmol/L	1.43 ± 0.58	1.34 ± 0.51	1.66 ± 0.76
Echocardiographic parameters			
LA dimension, mm	42.0 ± 6.4	51.2 ± 10.9[†]	46.1 ± 8.4
E/e' ratio	14.9 ± 4.9	23.6 ± 11.7[†]	19.7 ± 6.4
LVPG, mmHg	20.7 ± 31.4	18.7 ± 26.5	43.6 ± 61.4
Maximum LVT, mm	16.6 ± 4.1	15.7 ± 2.9	16.1 ± 3.5
EDV, mL	68.6 ± 21.0	76.6 ± 25.7	77.6 ± 26.7
ESV, mL	23.1 ± 11.9	29.6 ± 14.3	27.8 ± 17.4
EF, %	67.3 ± 10.5	61.8 ± 11.1	66.2 ± 12.4
Moderate to severe MR, *n* (%)	6 (11)	5 (23)	2 (17)

Vales are mean ± SD. HCM, hypertrophic cardiomyopathy; AF, atrial fibrillation; FPG, fasting plasma glucose; FIRI, fasting immuno-reactive insulin; HOMA, homeostasis model assessment; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; LA, left atrial; LVPG, left ventricular pressure gradient; LVT, left ventricular thickness; EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction; MR, mitral regurgitation.

[*] $p < 0.05$ vs. HCM with sinus rhythm.

[†] $p < 0.01$ vs. HCM with sinus rhythm.

Table 3 Determinants of AF in patients with HCM.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age ≥ 60 years old	1.0 (0.4–2.6)	0.92	NI	
Male sex	0.4 (0.1–1.2)	0.39	NI	
Obesity (BMI ≥ 25 kg/m^2)	1.9 (0.8–4.6)	0.17	NI	
Insulin resistance (HOMA index ≥ 2.7)	3.5 (1.4–8.9)	0.0097	2.3 (0.8–7.0)	0.12
Increased LA size (LA dimension ≥ 45 mm)	5.7 (2.2–14.6)	0.0003	3.5 (1.2–9.8)	0.018
Impaired LV diastolic function (E/e' ratio ≥ 18.0)	6.9 (2.6–17.8)	<0.0001	4.6 (1.6–12.8)	0.0037
Maximum LV thickness ≥ 20 mm	1.0 (0.3–3.3)	0.99	NI	
LV outflow obstruction (gradient ≥ 30 mmHg)	0.8 (0.3–2.3)	0.70	NI	
Moderate to severe MR	2.1 (0.6–6.8)	0.23	NI	

NI indicates not included in multivariate analysis. AF, atrial fibrillation; OR, odds ratio; CI, confidence interval; HCM, hypertrophic cardiomyopathy; BMI, body mass index; HOMA, homeostasis model assessment; LA, left atrial; LV, left ventricular; MR, mitral regurgitation.

ian [30] reported the possibility that IGF-1 was up-regulated in patients with HCM due to decreased cardiac contractility, resulting in the pathologic manifestations of HCM. Despite the structural similarity to IGF-1, the relationship between insulin and HCM, which is another cause of LV hypertrophy and diastolic dysfunction, is incompletely understood. Our previous study [13] disclosed that interventricular septal thickness and LV pressure gradient without provocation were significantly associated with the HOMA index, and that these associations were independent of age, sex distribution, and blood pressure in patients with HCM. In the present study, we have chosen this simple HOMA index and have found that insulin resistance is highly prevalent (31%) among non-diabetic patients with HCM. Insulin resistance has been associated with chronic heart failure independently of its etiology [9,10]. Exact mechanisms for the development of insulin resistance in chronic heart failure are not known. A number of mechanisms have been proposed, including the loss of skeletal muscle bulk and skeletal blood flow, sympathetic overactivity, pro-inflammatory cytokines, altered adiponectin and leptin levels, and endothelial dysfunction [31].

We found in the present study that greater HOMA index was strongly associated with echocardiographic LA size in patients with HCM, concordant with the findings in our previous study [22] which took hypertensive patients as objects. In addition, it has been shown that increased LA size and LA dysfunction are risks for AF [32,33], these observations support that higher insulin resistance in patients with HCM is related largely to the development of AF. Furthermore, it has been reported that metabolic syndrome is associated with increased LA size in patients with non-valvular AF [34]. Another possible mechanism by which insulin resistance may predispose to AF is inflammation and oxidative stress. Although not measured in our study, C-reactive protein and oxidants were elevated in patients with AF [35,36]. Insulin resistance is also associated with a systemic chronic inflammatory response characterized by altered cytokine

Table 4 Correlation of LA size with natriuretic peptides, demographic and echocardiographic variables in patients with HCM.

Variables	Univariate analysis		Multivariate analysis	
	r-Value	*p*-Value	β	*p*-Value
Age	0.028	0.7968	NI	
BMI	0.125	0.2449	NI	
HOMA index	0.431	<0.0001	0.358	0.0005
Systolic BP	0.055	0.6100	NI	
Diastolic BP	0.061	0.5709	NI	
Plasma ANP level	0.161	0.1333	NI	
Plasma BNP level	0.200	0.0615	NI	
E/e' ratio	0.316	0.0027	0.150	0.1490
LV pressure gradient	0.048	0.6599	NI	
Maximum LV thickness	0.001	0.9957	NI	
EDV	0.347	0.0009	0.190	0.5447
ESV	0.340	0.0012	0.190	0.5447
EF	0.227	0.0331	−0.128	0.6938
			Multiple $R^2 = 0.323$, $p < 0.0001$	

NI indicates not included in multivariate analysis. LA, left atrial; HCM, hypertrophic cardiomyopathy; BMI, body mass index; HOMA, homeostasis model assessment; BP, blood pressure; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; LV, left ventricular; EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction.

Table 5 Correlation of the E/e' ratio with natriuretic peptides, demographic and echocardiographic variables in patients with HCM.

Variables	Univariate analysis		Multivariate analysis	
	r-Value	*p*-Value	β	*p*-Value
Age	0.143	0.1837	NI	
BMI	0.087	0.4184	NI	
HOMA index	0.387	0.0002	0.309	0.0019
Systolic BP	0.149	0.1668	NI	
Diastolic BP	0.128	0.2329	NI	
Plasma ANP level	0.325	0.0020	−0.201	0.2036
Plasma BNP level	0.465	<0.0001	0.631	0.0001
LA dimension	0.316	0.0027	0.102	0.2895
LV pressure gradient	0.094	0.3817	NI	
Maximum LV thickness	0.008	0.9423	NI	
EDV	0.181	0.0911	NI	
ESV	0.024	0.8255	NI	
EF	0.069	0.5236	NI	
			Multiple $R^2 = 0.430$, $p < 0.0001$	

NI indicates not included in multivariate analysis. HCM, hypertrophic cardiomyopathy; BMI, body mass index; HOMA, homeostasis model assessment; BP, blood pressure; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; LA, left atrial; LV, left ventricular; EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction.

production and activation of inflammatory signaling pathway [37].

A relation between systolic blood pressure and LA size has previously been reported in the Framingham Heart Study [38]. Our previous study [22] has shown that obesity is highly associated with increased LA size. Unfortunately, systolic blood pressure, pulse pressure, and body mass index were not identified as independent determinants of LA size in patients with HCM. Therefore, a mechanistic link between blood pressure or obesity and LA size is unclear in patients with HCM.

HCM is functionally characterized by normal or supernormal LV systolic function and impaired LV diastolic function, and the severity of LV diastolic dysfunction is related to exercise capacity, clinical symptoms, and even prognosis [11,12,39]. Although transmitral LV filling velocity values recorded by Doppler echocardiography are widely used to assess LV diastolic function, conventional Doppler indices and the severity of LV hypertrophy, exercise capacity, clinical symptoms, or the mean LA pressure were not related in patients with HCM [40]. The ratio of trasmitral early LV filling velocity to early diastolic Doppler tissue imaging velocity of the mitral annulus (E/e') has recently been reported to be a preload independent index for evaluating LV diastolic function [41] and predicting objective exercise capacity [42] in patients with HCM. In the present study, the E/e' ratio was an independent association with the development of AF. Mechanical and pressure stress in the left atrium may stretch the atrial wall around the pulmonary veins, which may trigger the onset of paroxysmal AF [43]. In addition, the association between the HOMA index and the E/e' ratio seen in this study was independent of the parameters of LV hemodynamics and structure, suggested that direct, hemodynamic-independent effects of insulin resistance on myocardium might play a significant role for the development of LV diastolic impairment in HCM.

We also found that higher plasma BNP levels predicted the presence of HCM and AF, even after accounting for systolic impairment. Furthermore, plasma BNP levels were independently associated with impaired LV diastolic function evaluated by the E/e' ratio in HCM. These observations also support that although LV systolic function is normal, plasma BNP levels are elevated in the presence of impaired LV diastolic function [44,45].

In conclusion, insulin resistance is highly prevalent among non-diabetic patients with HCM. A possible mechanism by which insulin resistance affects the development of AF is mediated through its association with increased LA size or LV diastolic impairment. Insulin resistance may be the underlying mechanism for the higher prevalence of AF in HCM.

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