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Relation Between Temperature Extremes And Symptom Exacerbation In Patients With Hypertrophic Cardiomyopathy

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Abstract

Warm temperatures induce peripheral vasodilatation, decrease afterload, and may concurrently increase the left ventricular outflow tract (LVOT) gradient. We aimed to assess the impact of subjective ambient temperature on hypertrophic cardiomyopathy (HC) symptoms and determine whether they were associated with LVOT gradient, patient quality of life (QOL), and risk of sudden cardiac death (SCD). We identified consecutive patients with HC presenting to a tertiary referral center. Of the 173 patients in the study, 143 (83%) had HC symptoms, with ambient temperature change worsening symptoms for 72 patients (50%). Symptom exacerbation occurred only with heat for 57 (79%), whereas symptoms were exacerbated with cold only or with cold and heat equally for 15 (21%). Patients affected by any temperature exacerbation more commonly were women ($P=.009$), had a lower QOL ($P=.04$), had a family history of HC ($P=.007$), or underwent myectomy ($P=.01$). A greater proportion of patients with heat-only exacerbation had a family history of HC ($P=.005$) and SCD ($P=.05$). The presence of an LVOT gradient either at rest or with provocation was similar among all groups. In conclusion, although no appreciable difference in LVOT gradients were observed between patient groups, approximately half of the patients with HC reporting symptoms at baseline noted worsening of symptoms with temperature changes, with >75% describing heat-induced symptom exacerbation. Furthermore, affected patients more frequently were women, underwent surgical intervention and device implantation, and had an overall lower QOL.

Keywords

hypertrophic cardiomyopathy; quality of life; symptom manifestation

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Introduction

A subset of patients with hypertrophic cardiomyopathy (HC) report aggravation of symptoms in warmer temperatures. However, scientific investigations regarding the prevalence of this symptom and its bearing upon functional status and clinical outcome are lacking. Clinical history often shows exacerbation of symptoms in warm temperatures, with subsequent improvement upon moving to cooler environments. The proposed pathophysiology is that cooler temperatures induce peripheral vasoconstriction (1), thereby increasing afterload and ultimately decreasing the left ventricular outflow tract (LVOT) gradient. In contrast, warmer environments promote vasodilatation, decrease cardiac afterload, and increase the severity of LVOT obstruction. This present investigation had 2 objectives. First, we aimed to determine the prevalence of temperature-dependent symptom variation in patients with HC. Second, we aimed to characterize the association between subjective, temperature-dependent symptom change and clinical characteristics, particularly LVOT gradient, quality of life (QOL), and risk of sudden cardiac death (SCD). If significant correlations do exist, this study strives to be the foundation for further prospective work that examines real-time LVOT gradient changes in patients with HC, dependent upon variation of environmental temperature, or if not, it possibly will help determine future directions for physiologic investigations.

Methods

The Mayo Clinic Institutional Review Board approved the study. Written, informed consent was obtained from each patient. Consecutive patients with HC, evaluated at Mayo Clinic (Rochester, Minnesota) from January 1, 2002, through December 31, 2006, were eligible for this study. Exclusion criteria were age <18 years and lack of echocardiographic data before any surgical intervention for HC.

All eligible patients in the database were surveyed via telephone. All surveys were conducted by a single investigator (J.P.B.), who was masked to all patient variables except age and sex at the time the survey was conducted. The survey consisted of 3 questions:

1. Prior to having any therapeutic procedure performed for your HC, have you experienced any symptoms (shortness of breath, angina, presyncope, syncope, and chest tightness)? (Yes/No)
2. Prior to having any therapeutic procedure performed for your HC, on a hot day, have you felt that HC-related symptoms (shortness of breath, presyncope, syncope, angina, and chest tightness) were better, worse, or unchanged?
3. Prior to having any therapeutic procedure performed for your HC, on a cold day, have you felt that HC-related symptoms (shortness of breath, presyncope, syncope, angina, and chest tightness) were better, worse, or unchanged?

All relevant clinical variables, including demographics, medical comorbidities, pertinent family and social history, and medications, were collected prospectively for all patients in the study.

All echocardiograms were performed at a single tertiary referral center, as described previously (2). Briefly, baseline echocardiographic features of the study population were compared. The echocardiographic parameters collected included structural measurements. Resting and provoked LVOT gradients were derived from the continuous-wave Doppler velocities.

The Minnesota Living With Heart Failure questionnaire was used to objectively measure the patients' QOL (3, 4). We compared patients with and without temperature-related symptom change to assess the effect of temperature on QOL.

Resting LVOT gradient was defined as >30 mm Hg and provoked obstruction was defined as a gradient >50 mm Hg (5). Provocative measures included either the Valsalva maneuver or administration of amyl nitrite.

The previously validated SCD risk score (6) was used to calculate the 5-year risk of SCD for each patient in the study. The risk score encompassed 7 features: 1) age; 2) maximum LVOT gradient; 3) severity of LV hypertrophy; 4) presence of nonsustained ventricular tachycardia; 5) unexplained syncope; 6) family history of SCD; and 7) left atrial diameter.

Data were summarized as mean (SD) for continuous variables and as number and percent for categorical variables. Categorical data were analyzed using the 2-tailed Pearson χ^2 or Fisher exact test. Association of continuous variables was examined using simple linear regression analysis. When indicated, nonparametric tests were used. Analyses were completed using SAS (version 9.2) and JMP (version 11.2.1) (SAS Institute Inc). Statistical significance was established a priori at P .05.

Results

We surveyed patients with HC regarding temperature and HC symptoms. We contacted 335 patients, and 173 (52%) were included in the study. Reasons for excluding 162 patients are shown in the Figure. HC symptoms were noted by 143 patients (83%), and of these patients, 72 (50%) noted symptom exacerbation in temperature extremes. The majority of these patients ($n=57$ [79%]) thought that their symptoms worsened only with heat, whereas the remaining patients ($n=15$ [21%]) thought that their symptoms were exacerbated either by cold temperature alone or by cold and heat equally (Figure). Clinical and echocardiographic characteristics of patients are shown in the Table.

We compared the 101 patients without any temperature-related HC symptoms against the 72 patients affected by cold and heat (Table). The 2 groups were similar in age, but there was a higher percentage of females in the group reporting temperature exacerbation. Furthermore, the group with temperature symptoms had a lower QOL and a family history of HC. They also had a greater proportion of patients who underwent surgical myectomy and placement of an implantable cardioverter-defibrillator (ICD) or pacemaker. Presence of LVOT obstruction at rest or with provocation was similar between both groups.

The 101 patients without HC temperature symptoms were compared with the 57 patients with heat exacerbation only (Table). The group with heat-exacerbated symptoms again had a

greater proportion of women. Whereas a family history of HC was higher in the group without temperature exacerbation in this subset, those with heat exacerbation had a higher rate of family history of SCD. A nonsignificant trend of a higher incidence of ventricular arrhythmia was noted in patients with heat exacerbation. Again, presence of LVOT obstruction either at rest or with provocation was similar between both groups.

Lastly, we compared the 101 patients without HC temperature symptoms with the 15 patients with cold exacerbation only or with equal heat and cold exacerbation (Table). Age and sex were similar between these groups, whereas QOL was markedly worse in those patients with temperature symptoms. Unlike patients with predominant heat exacerbation symptoms (Table), the groups showed no difference in family history of SCD or rate of ICD implantation. No difference in rate of LVOT obstruction at rest or with provocation was noted between the 2 groups.

Of the 143 patients with HC symptoms, 12 (8%) indicated improvement with symptoms in temperature extremes, with 10 of the 12 (83%) feeling better in colder environments and 2 (17%) feeling better in warm environments. Of the 10 patients who noted improvement in cold environments, 7 (70%) were men, with a mean (SD) age of 49 (16) years, and 70% had either a resting or dynamic LVOT gradient. Both patients who felt better in the warmer environment were women, ages 55 and 31 years, and both had a resting LVOT gradient.

Discussion

This study examined the role of temperature exacerbation in patients with HC. Approximately half the patients with HC symptoms at baseline noted worsening of symptoms with temperature changes. Greater than 75% of affected patients described symptom exacerbation in warm temperatures. Furthermore, these patients had a lower QOL ($P=.04$), and compared with patients without symptom exacerbation, a greater proportion of patients with symptom exacerbation had undergone surgical myectomy ($P=.01$). Symptom improvement in temperature extremes was rare (8%), but when documented, they more often occurred in colder temperatures. Of note, the prevalence of coronary artery disease, with ischemic thresholds previously demonstrated to lower in colder temperatures (7), was similar among all groups.

This study revealed clinical insights that are hypothesis generating. For instance, one can postulate that temperature-related peripheral vasodilatation with resultant decreased afterload and increased LVOT gradient may be the pathophysiologic mechanism responsible for increasing an already-elevated resting gradient, resulting in symptom manifestation. Indeed, physiologic studies have shown that 10% of cardiac output transverse cutaneous arteriole-venous shunts and that constriction or dilation of these shunts in response to hot or cold temperatures may alter systemic blood pressure by up to 15 mm Hg (8). An alternative explanation may relate to heat-induced volume depletion and the resultant decrease in preload and LV cavity size. Although no difference between patient groups was observed in resting or provoked LVOT, the gradient was tested at typical room temperature, and a gradient provoked by temperature fluctuations therefore may have been missed. Ideally, future investigations would include echocardiographic measures of LVOT gradients at

average ambient room temperature and then again in cold and warm environments to examine any dynamic gradient changes. Given the high proportion of patients who noted symptoms worsening in temperature extremes, better understanding and possible preventive interventions ultimately are needed.

Of particular interest was that patients with temperature exacerbations, particularly heat-related, appeared to show higher rates of ventricular arrhythmia (21% vs 11%) and 5-year risk of SCD (5% vs 2%), although the differences were not statistically significant. One possible explanation for these findings is autonomic dysfunction or instability in the HC population. A prior study showed ventricular arrhythmias arising when parasympathetic activity is impaired and sympathetic activity is enhanced (9). Further investigations showed that patients with HC have increased catecholamine levels (10), reduced in β -adrenergic receptors (10), and impaired heart rate recovery after exercise (11), suggesting autonomic dysregulation. Furthermore, temperature regulation is tightly integrated with autonomic function (12), suggesting a possible association between autonomic dysfunction in patients with HC and the inability to tolerate warmer temperatures.

Women more frequently reported temperature-related symptoms, particularly heat exacerbation, compared with men ($P=.009$). This observation supports findings of a prior investigation noting that women with HC were more symptomatic than men (13). Prior studies, however, did not specifically investigate temperature-related symptomatology. Women have less autonomic support of arterial blood pressure than men (14), and they therefore may be predisposed to heat-induced peripheral vasodilation and subsequent symptom exacerbation, as shown in the current study.

Nonresponse bias is a limitation of the study, given that 46% of the original patient cohort did not respond to the study inquiry or were excluded for other reasons (Figure). Using all available telephone numbers in the patient record, we made at least 3 separate attempts to contact each nonresponder. Compared with the study cohort, the nonresponder cohort was younger (mean age, 45 vs 54 years) but had a similar sex distribution (60% vs 61% men).

In any survey study, recall bias can affect the patient's response to the inquiry. This limitation was addressed by not revealing the study hypothesis to the patient at the time of the survey. Furthermore, the survey conductor (J.P.B.) was masked to all clinical data other than age and sex at the time of the survey to limit possible bias while the survey was being conducted.

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Figure.
Overview of Study Population. HC indicates hypertrophic cardiomyopathy; temp, temperature.

Table

Patient Characteristics, Stratified by Presence or Absence of Temperature-Associated Symptom Exacerbation

Variable	No Temperature Symptoms (n=101)	Any Temperature- Associated Exacerbation (n=72)		Heat-Associated Exacerbation Only (n=57)		Cold or Equal Exacerbation (n=15) ^d	
		Value	P Value ^b	Value	P Value ^b	Value	P Value ^b
Age, mean (SD), years	55±16	52±14	.16	51±5	.12	55±12	.92
Male sex	69 (68%)	35 (49%)	.009	31 (54%)	.005	9 (60%)	.52
Quality of life score (mean [SD]) ^c	26±26	36±26	.04	33±25	.20	48±27	.01
Angina class III/IV	9 (9%)	3 (4%)	.23	0 (0%)	.02	3 (20%)	.19
Dyspnea class III/IV	38 (38%)	32 (44%)	.37	25 (44%)	.44	7 (47%)	.50
Presyncope	49 (49%)	40 (56%)	.36	32 (56%)	.36	8 (53%)	.73
Syncope	19 (19%)	12 (17%)	.72	11 (19%)	.94	1 (7%)	.25
Heart failure	5 (5%)	6 (8%)	.37	4 (7%)	.59	2 (13%)	.20
Coronary artery disease	15 (15%)	7 (10%)	.32	5 (9%)	.27	2 (13%)	.87
Diabetes mellitus	6 (6%)	2 (3%)	.33	2 (4%)	.50	0 (0%)	.33
Hypertension	49 (49%)	26 (36%)	.10	23 (40%)	.32	3 (20%)	.05
Family history of HC	24 (24%)	21 (29%)	.007	26 (46%)	.005	5 (33%)	.43
Family history of SCD	14 (14%)	18 (25%)	.06	15 (26%)	.05	3 (20%)	.53
Ventricular septum 30 mm	8 (8%)	1 (1%)	.06	1 (2%)	.11	0 (0%)	.26
LVOT obstruction at rest or with provocation.	68 (67%)	50 (69%)	.77	39 (68%)	.89	11 (73%)	.64
LVOT obstruction at rest	47 (47%)	36 (50%)	.65	28 (49%)	.75	8 (53%)	.62
LVOT obstruction with provocation	21 (21%)	14 (19%)	.83	11 (19%)	.82	3 (20%)	.94
5-Year SCD risk, mean (SD)	3±2	5±5	.20	5±6	.14	4±3	.95

Variable	No Temperature Symptoms (n=101)	Any Temperature- Associated Exacerbation (n=72)		Heat-Associated Exacerbation Only (n=57)		Cold or Equal Exacerbation (n=15) ^a	
		Value	P Value ^b	Value	P Value ^b	Value	P Value ^b
β-blocker	67 (66%)	49 (68%)	.81	37 (65%)	.86	12 (80%)	.29
Calcium channel blocker	24 (24%)	21 (29%)	.43	16 (28%)	.55	5 (33%)	.52
Disopyramide	6 (6%)	5 (7%)	.79	3 (5%)	.86	2 (13%)	.29
Ventricular septal ablation	10 (10%)	11 (15%)	.29	8 (14%)	.44	5 (33%)	.42
Septal myectomy	24 (24%)	30 (42%)	.01	20 (35%)	.13	10 (67%)	.002
Pacemaker	9 (9%)	14 (19%)	.04	12 (21%)	.03	2 (13%)	.63
Internal cardioverter defibrillator	10 (10%)	15 (21%)	.04	13 (23%)	.03	2 (13%)	.69
NSVT/VT	11 (11%)	15 (21%)	.08	12 (21%)	.07	3 (20%)	.39

Abbreviations: HC, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; NSVT/VT, nonsustained ventricular tachycardia/ventricular tachycardia; SCD, sudden cardiac death.

^a Symptom exacerbation occurred with cold only or with cold and heat equally.

^b Compared with patients who had no temperature symptoms.

^c Higher scores indicated a lower quality of life.