

Infective Endocarditis in Hypertrophic Cardiomyopathy

Prevalence, Incidence, and Indications for Antibiotic Prophylaxis

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Background—The literature on infective endocarditis in hypertrophic cardiomyopathy (HCM) is virtually confined to case reports. Consequently, the risk of endocarditis in HCM remains undefined.

Methods and Results—We assessed the occurrence of endocarditis in 810 HCM patients evaluated between 1970 and 1997. Endocarditis was diagnosed in 10 patients, 2 of whom were excluded from analysis of prevalence and incidence because they were referred for acute endocarditis. At first evaluation, echocardiographic features consistent with prior endocarditis were identified in 3 of 808 patients, a prevalence of 3.7 per 1000 patients (95% CI, 0.8 to 11). Of 681 patients who were followed, 5 developed endocarditis, an incidence of 1.4 per 1000 person-years (95% CI, 0.5 to 3.2); outflow obstruction was present in each of these 5 patients and was associated with the risk of endocarditis ($P=0.006$). In the 224 obstructive patients, incidence of endocarditis was 3.8 per 1000 person-years (95% CI, 1.6 to 8.9) and probability of endocarditis 4.3% at 10 years. Left atrial size was also associated with the risk of endocarditis ($P=0.007$). In patients with both obstruction and atrial dilatation (≥ 50 mm), incidence of endocarditis increased to 9.2 per 1000 person-years (95% CI, 2.5 to 23.5). Analysis of all 10 patients with endocarditis identified outflow obstruction in each and atrial dilatation in 7.

Conclusions—Endocarditis in HCM is virtually confined to patients with outflow obstruction and is more common in those with both obstruction and atrial dilatation. These results indicate that antibiotic prophylaxis is required only in patients with obstructive HCM. (*Circulation*. 1999;99:2132-2137.)

Key Words: hypertrophy ■ cardiomyopathy ■ echocardiography

Infective endocarditis is a recognized complication of hypertrophic cardiomyopathy (HCM), and antibiotic prophylaxis is recommended by the American Heart Association in this disease.^{1,2} The literature on endocarditis in HCM, however, is scarce and virtually confined to reports of patients who developed this complication.³⁻⁵ Consequently, the risk of endocarditis in the overall HCM population remains undefined. In addition, because of the broad clinical spectrum of HCM,⁶⁻⁸ it is unclear whether antibiotic prophylaxis should be recommended to all patients or only to certain subgroups. In particular, it is unknown whether antibiotic prophylaxis is required in the increasing number of asymptomatic individuals with mild phenotypic expressions of the disease who are identified during routine echocardiographic and/or genetic screening of affected families.⁹⁻¹¹

In the present study, we have investigated the occurrence of infective endocarditis in a population of more than 800 patients with HCM. Our observations provide an estimate of the preva-

lence and incidence of infective endocarditis in this disease. Our findings also identify the clinical features associated with an increased risk of developing this complication and lead to specific recommendations for antibiotic prophylaxis in HCM.

Methods

Study Population

All the files of patients with HCM evaluated from 1970 to 1997 in the outpatient or inpatient services of the 6 institutions participating in the present investigation were reviewed. A total of 810 patients in whom a 2-dimensional echocardiogram had been obtained at initial evaluation or during follow-up (in those patients first seen in the pre-2-dimensional echocardiographic era) were identified and included in the study. In each patient, the diagnosis of HCM was based on the echocardiographic demonstration of a hypertrophied and nondilated left ventricle (wall thickness ≥ 15 mm in adults or the equivalent in children) in the absence of other cardiac or systemic diseases that could produce comparable left ventricular hypertrophy.^{6-8,12,13}

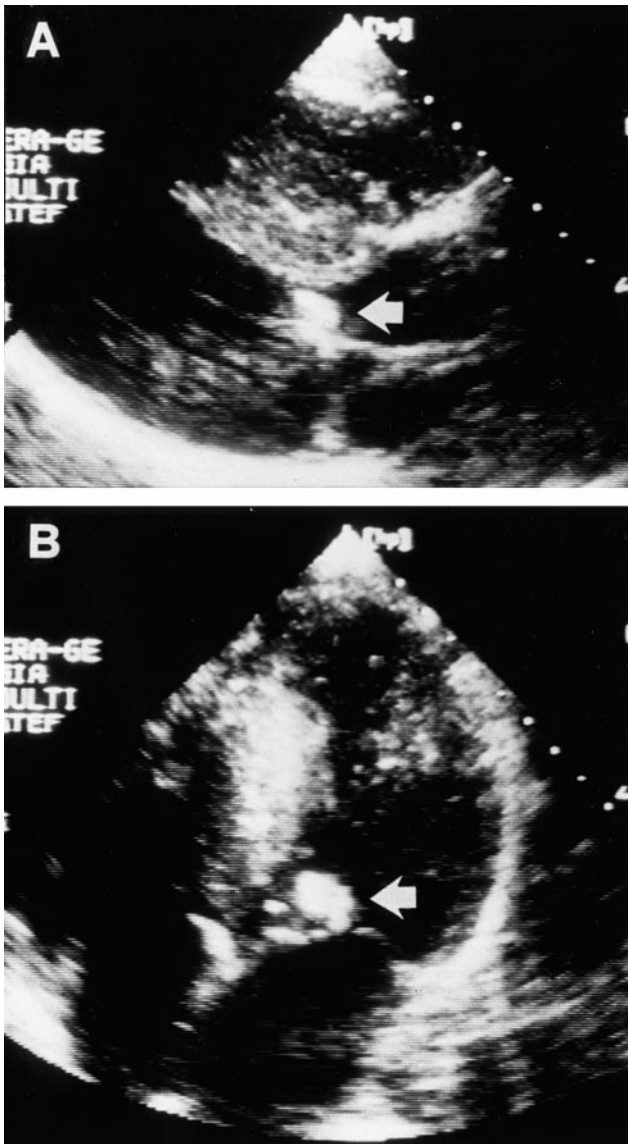
Received August 28, 1998; revision received February 1, 1999; accepted February 1, 1999.

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Stop-frames of a 2-dimensional echocardiogram obtained in a patient with HCM and infective endocarditis. A large vegetation (arrows) attached to anterior mitral leaflet is visualized in both the long-axis view (A) and the 4-chamber view (B).

Diagnosis of Infective Endocarditis

The frequency of infective endocarditis in the overall study population was assessed in terms of either evidence of prior endocarditis at the first 2-dimensional echocardiographic evaluation or occurrence of acute endocarditis during follow-up.

Prior endocarditis was diagnosed by 2-dimensional echocardiography as the presence of a mass that met all the following criteria: (1) was attached to an endocardial surface; (2) was visualized consistently throughout the cardiac cycle and in multiple views; (3) showed motion independent of that of the cardiac structures and/or echo-reflectivity distinct from that of the valve or endocardium^{14,15} (Figure). All the echocardiograms of the patients suspected of having vegetations were evaluated independently by 2 observers. In case of discordant interpretations, the echocardiogram was evaluated by a third observer and an agreement was reached regarding the final diagnosis.

Acute endocarditis was diagnosed on the basis of (1) 2 or more positive blood cultures in the presence of clinical features suggestive of endocarditis; or (2) bacteriologic evidence of active infection on valvular vegetations or embolic material obtained at surgery or necropsy.

Echocardiographic Evaluation of Left Ventricular Morphology and Function

Two-dimensional echocardiographic images were obtained in the parasternal long- and short-axis views and apical views with the use of standard transducer positions. Magnitude of left ventricular hypertrophy was assessed at end-diastole by use of criteria previously described and briefly summarized below.^{16,17} Left ventricular wall thickness was assessed primarily from the parasternal short-axis planes; the parasternal long axis and apical views were also used to integrate the observations obtained from the short-axis views. In the parasternal short-axis plane, the left ventricle was divided into 4 segments that identified the anterior and posterior portions of the ventricular septum and the lateral and posterior left ventricular free walls. Wall thickness was measured at the levels of both the mitral valve and the papillary muscles in each of the 4 ventricular segments. The segment of the wall with the greatest thickness was considered to represent the maximal left ventricular wall thickness.¹⁷ Left ventricular end-diastolic cavity dimension and left atrial size were assessed from the M-mode echocardiogram following the recommendations of the American Society of Echocardiography.¹⁸

Presence of dynamic obstruction to left ventricular outflow under basal conditions was assessed by Doppler echocardiography in 793 patients and by M-mode echocardiography in the remaining 17 patients. Outflow obstruction was considered present when a maximal Doppler gradient ≥ 30 mm Hg and/or prolonged mitral-septal contact during systole on the M-mode echocardiographic tracing were identified.¹⁹⁻²¹

Statistical Methods

Data were expressed as mean \pm SD or median. Prevalence of infective endocarditis was estimated as the ratio between patients with a diagnosis of prior endocarditis at the initial 2-dimensional echocardiographic evaluation and total number of study patients. Incidence of infective endocarditis was estimated as the number of patients who developed infective endocarditis during follow-up divided by the total number of person-years of observation accumulated during follow-up in the study population (or in each patient subgroup). Incidence of infective endocarditis in different patient subgroups was compared by use of the Fisher exact test. All tests were 2-tailed. The 95% confidence limits of rates were calculated using the Poisson distribution. Follow-up times were calculated from the date of the first patient evaluation at 1 of the 6 participating institutions to the time of the most recent evaluation or to the time of diagnosis of infective endocarditis, whichever was first.

Results

During the period of time covered by the study, 2 patients with HCM were specifically referred for suspected acute infective endocarditis; positive blood cultures confirmed the diagnosis. To avoid a selection bias, these 2 patients were excluded from the analysis of prevalence and incidence of this complication in the overall study population. Clinical data of these 2 patients are reported separately (Table 1).

The remaining 808 study patients ranged in age from 1 to 89 years, mean 43; 520 (64%) were male. Of these patients, 738 (91%) were asymptomatic or had only mild symptoms (New York Heart Association functional class I or II) and 70 (9%) had severe symptoms (functional class III or IV); 262 patients (32%) had left ventricular outflow obstruction under basal conditions.

Prevalence of Infective Endocarditis

At the first 2-dimensional echocardiographic evaluation, features consistent with the diagnosis of prior endocarditis were identified in 3 of 808 patients. Therefore, prevalence

TABLE 1. Clinical, Morphological, and Functional Features at Time of Diagnosis of Either Prior or Acute Infective Endocarditis in 10 Patients With HCM

Patient	Sex (M/F)/ Age, y	NYHA Functional Class	LVOT Obstr	Max LVWT, mm	LVID, mm	LA, mm	Infective Agent	Affected Valves	Valve Replacement, n
1*	M/52	1	+	22	51	52	...	MV	0
2*	M/23	2‡	+	30	40	45	...	MV	0
3†	M/26	3	+	27	50	48	<i>Streptococcus sanguis</i>	MV	1§
4	F/31	4	+	17	49	46	<i>Staphylococcus aureus</i>	MV+ AoV	1
5	M/38	3	+	26	46	57	<i>Streptococcus fecalis</i>	MV	0
6	M/49	4	+	20	48	54	...	MV	1
7†	M/42	2	+	26	48	50	<i>Staphylococcus epidermidis</i>	MV+ AoV	0
8	F/48	2	+	28	43	53	<i>Streptococcus viridans</i>	MV	0
9	M/16	3	+	17	46	57	<i>Staphylococcus aureus</i>	MV+ AoV	1
10*	F/62	2	+	26	45	53	...	MV	0

AoV indicates aortic valve; LA, left atrial size; LVID, left ventricular internal diastolic dimension; LVOT Obstr, left ventricular outflow obstruction; Max LVWT, maximal left ventricular wall thickness; MV, mitral valve.

*Prior endocarditis; †referred for acute endocarditis; ‡died of heart failure during a second episode of infective endocarditis; §mitral valvuloplasty with associated septal myotomy-myectomy.

of prior endocarditis was 3.7 per 1000 patients (95% CI 0.8 to 11).

Incidence of Acute Infective Endocarditis

The 3 patients with evidence of prior endocarditis at the first 2-dimensional echocardiographic evaluation were excluded from the analysis of the incidence of this complication. Of the remaining 805 study patients without evidence of prior endocarditis, 681 (85%) were subsequently followed at the participating institutions. The period of follow-up ranged from 1 to 320 months (mean 55, median 46 months). At the initial evaluation, these 681 patients ranged in age from 1 to 88 years, mean 42; 438 (64%) were male. Of these patients, 620 (91%) were asymptomatic or had only mild symptoms (New York Heart Association functional class I or II) and 61 (9%) had severe symptoms (functional class III or IV); 224 of the 681 patients (33%) had left ventricular outflow obstruction under basal conditions. During follow-up, 5 patients developed acute infective endocarditis. Therefore the incidence of endocarditis was 1.4 per 1000 person-years (95% CI 0.5 to 3.2).

Variables Associated With Increased Risk of Endocarditis

The morphological, functional, and clinical features at initial evaluation in the 681 study patients who were followed, and the relation between these features and the risk of developing endocarditis are reported in Table 2. In particular, left ventricular outflow obstruction was present in each of the 5 patients who developed acute infective endocarditis during follow-up, and the association between outflow obstruction and infective endocarditis was statistically significant ($P=0.006$). In the 224 patients with outflow obstruction, the incidence of endocarditis was 3.8 per 1000 person-years (95% CI 1.6 to 8.9) and the cumulative probability of developing endocarditis was 4.3% at 10 years.

Left atrial size was also significantly associated with the risk of developing endocarditis ($P=0.007$), and 4 of the 5

patients who developed endocarditis during follow-up had a markedly dilated left atrium at initial evaluation (≥ 50 mm). In patients with both outflow obstruction and marked left atrial dilatation, incidence of endocarditis increased to 9.2 per 1000 person-years (95% CI 2.5 to 23.5). Other clinical and morphological features, including age, sex, functional class, left ventricular end-diastolic cavity dimension, and wall thickness were not significantly associated with the risk of developing endocarditis (Table 2).

Clinical Features of all the 10 Study Patients With Endocarditis

The morphological, functional, and clinical features of the 2 patients primarily referred for acute endocarditis, the 3 patients with diagnosis of prior endocarditis at the first 2-dimensional echocardiographic evaluation, and the 5 patients who developed acute endocarditis during follow-up are summarized in Table 1. At the time of diagnosis of either prior or acute endocarditis, age ranged from 16 to 62 years, mean 39. Left ventricular outflow obstruction under basal conditions was present in each of the 10 patients. The left atrium was markedly dilated (≥ 50 mm) in 7 of the 10 patients. Vegetations were localized on the mitral valve in 7 patients and on both the mitral and aortic valves in 3.

One of these 10 patients was a heroin addict. None had ever received antibiotic prophylaxis for endocarditis. Within the 3 months before the infection, 4 of the patients with acute infective endocarditis had undergone dental or other procedures considered to be a likely cause of endocarditis.

Clinical Course of the 10 Study Patients With Infective Endocarditis

After identification of either prior or acute endocarditis, the 10 patients were followed for a period of 20 to 213 months (mean 88). Severe symptoms of heart failure (functional class III or IV) developed at the time of acute endocarditis in 5 patients; 2 of these 5 patients underwent both mitral and aortic valve replacement, 1 underwent mitral valve replace-

TABLE 2. Relation Between Incidence of Infective Endocarditis and Clinical, Morphological, and Functional Features at Initial Evaluation in 681 Study Patients Who Were Followed

Variable	No. (%) of Patients	Median (Range) of Follow-up, mo	No. of Patients With Infective Endocarditis	Incidence of Infective Endocarditis (per 1000 person-years), n	<i>P</i>
Men	438 (64)	48 (1–320)	3	1.23	0.67
Women	243 (36)	45 (1–245)	2	1.64	
Age, y					
<20	88 (13)	70 (2–278)	0	...	
20–40	229 (34)	50 (1–320)	3	2.28	0.99
41–60	243 (36)	51 (1–273)	2	1.43	
≥60	121 (17)	20 (1–176)	0	...	
NYHA functional class					
I–II	620 (91)	47 (1–320)	5	1.51	1.00
III–IV	61 (9)	42 (1–273)	0	...	
LVOT obstruction					
Yes	224 (33)	45 (1–319)	5	3.83	0.006
No	457 (67)	50 (1–273)	0	...	
Max LV wall thickness, mm					
<20	322 (48)	39 (1–320)	2	1.27	1.00
≥20	350 (52)	59 (1–273)	3	1.45	
LA size, mm					
<40	175 (31)	52 (1–278)	0	...	
40–50	270 (47)	43 (1–267)	1	0.70	0.007
>50	125 (22)	44 (1–320)	4	5.38	
LVIDd, mm					
<40	122 (21)	64 (2–278)	0	...	
40–50	366 (65)	42 (1–273)	5	2.51	0.22
>50	77 (14)	32 (1–319)	0	...	

LA indicates left atrial; LVIDd, left ventricular internal diastolic dimension; LVOT, left ventricular outflow tract; Max LV, maximal left ventricular.

ment, 1 mitral valvuloplasty with associated septal myotomy-myectomy, and 1 showed gradual clinical improvement to functional class II on medical treatment. The patient who was a heroin addict had only mild symptoms of heart failure (functional class II) after the first episode of endocarditis but experienced a second episode of endocarditis that led to acute heart failure and death; at necropsy, large vegetations on the mitral valve and a perforated anterior mitral leaflet were found.

With regard to the clinical sequelae of endocarditis, systemic embolic events occurred in 1 of the 10 patients at the time of acute endocarditis. A second patient had an embolic event 5 years after the echocardiographic diagnosis of prior endocarditis. At the time of the embolic event, this patient was in normal sinus rhythm but had a markedly dilated left atrium (56 mm). Therefore, the embolus may not have originated from the valvular vegetations but from the left atrium.

At the most recent evaluation, 8 of the 9 surviving patients were asymptomatic or had mild symptoms (New York Heart Association functional class I or II), and 1 had severe symptoms (functional class III). This latter patient showed

only moderate mitral valve incompetence but had evolved toward end-stage disease with left ventricular wall thinning, cavity dilatation, systolic dysfunction, and loss of dynamic outflow obstruction. Therefore, in this patient, the severity of symptoms was primarily due to the progression of the disease rather than the previous episode of endocarditis.

Review of the Literature

In view of our finding that each of the 10 study patients with endocarditis had left ventricular outflow obstruction, we also verified the frequency of outflow obstruction in the 33 HCM patients with infective endocarditis reported in the English language literature during the last 20 years^{3–5,22–30}; each had outflow obstruction under basal conditions.

Discussion

Infective endocarditis is a known complication of HCM and has been reported to be associated with substantial morbidity and mortality in this disease.^{3–5} The frequency of endocarditis in the overall HCM population, however, remains unknown and the features of the disease associated with an increased risk of developing this complication have never been systematically investigated. Therefore it is not clear whether all

patients or only certain subgroups, within the broad clinical spectrum of HCM, require antibiotic prophylaxis for infective endocarditis.

In the present study, we have assessed the occurrence of infective endocarditis in a large HCM population of >800 patients, and we have determined the morphological, functional, and clinical features of HCM associated with an increased risk of developing this complication. Antibiotic prophylaxis was not routinely recommended in the patients included in the present investigation because of the widespread perception that infective endocarditis is uncommon in this disease. Therefore the occurrence of endocarditis in the study population was virtually free from the potential influence of antibiotic prophylaxis.

Prevalence and Incidence of Infective Endocarditis

At the first 2-dimensional echocardiographic evaluation, features consistent with a previous episode of infective endocarditis were identified in 3 patients, representing a prevalence of 3.7 per 1000 patients. Incidence of endocarditis was assessed in almost 700 study patients who were followed at the participating institutions. Acute infective endocarditis occurred in 5 of these patients, an incidence of 1.4 per 1000 person-years. Two additional patients were primarily referred for suspected acute endocarditis and the diagnosis was confirmed by positive blood cultures. In all, either prior or acute endocarditis was diagnosed in only 10 of more than 800 patients.

Patient Subgroups at Higher Risk for Infective Endocarditis

Although our observations show that infective endocarditis is an uncommon complication in the overall HCM population, our analysis of the clinical features of the 10 study patients with endocarditis clearly identifies an HCM subgroup at increased risk for developing this complication. Each of the 10 patients with endocarditis had left ventricular outflow obstruction under basal conditions. In the patient subset with the obstructive form of the disease, the incidence of endocarditis was 3.8 per 1000 person-years and the likelihood of developing this complication was \approx 4% at 10 years. These findings prompted us to verify the functional profile of the HCM patients with infective endocarditis previously reported in the literature. During the last 2 decades, 33 HCM patients with endocarditis were reported in the English language literature^{3-5,22-30}; each had the obstructive form of the disease. Therefore, on the basis of our findings, as well as our focused analysis of the literature, HCM patients with left ventricular outflow obstruction under basal conditions would appear to be the ones at significant risk for developing endocarditis and thus the subgroup that requires antibiotic prophylaxis. This higher risk of endocarditis may be due to damage of the mitral and aortic valve endocardium caused by the high velocity and turbulence of blood flow during ejection and by the mitral-septal contact during systole, as well as by mitral valve regurgitation, which is often present in patients with outflow obstruction.

Our results also indicate that patients with the nonobstructive form of HCM, including those with an outflow gradient

induced only under provokable conditions, are at negligible risk for endocarditis. Therefore these patients, who represent the great majority of the HCM population,⁶⁻⁸ do not require prophylaxis for endocarditis. This latter conclusion is reinforced by the fact that antibiotic prophylaxis is indicated only in cardiac patients known to be at either moderate or high risk for this complication, since the efficacy of antibiotic prophylaxis in the prevention of infective endocarditis has been demonstrated in animal models but has not been proved in humans.^{1,2} Patients with HCM and significant mitral valve regurgitation due to intrinsic abnormalities of the valve apparatus, such as prolapse, are candidates for endocarditis prophylaxis also in the absence of left ventricular outflow obstruction.

We also identified a significant correlation between left atrial size and the risk of developing endocarditis. In patients with both left ventricular outflow obstruction and marked left atrial dilatation, incidence of endocarditis increased to 9.2 per 1000 person-years. It is unclear why a markedly dilated left atrium should be associated with a higher risk of endocarditis. A possible explanation is that a dilated left atrial cavity may reflect more severe hemodynamic impairment, with a higher outflow gradient, more important mitral valve regurgitation, and thus, greater damage to the valve endocardium.

Other clinical and morphological variables, including age, sex, functional class, left ventricular end-diastolic cavity dimension, and wall thickness were not significantly associated with the risk of developing endocarditis. A recent dental or other procedure considered to be a potential cause of endocarditis was reported by approximately half of the patients with acute endocarditis. None of these patients was taking antibiotic prophylaxis at the time of the procedure.

Although infective endocarditis remains a potential cause of severe and acute congestive heart failure in HCM, this complication had a relatively benign clinical course in a significant proportion of our patients, with less than half requiring cardiac valve surgery for severe symptoms of heart failure due to valve regurgitation. The only patient who died was an intravenous drug user who had a second and fatal episode of endocarditis. These observations suggest that this complication is not invariably associated with an unfavorable short-term prognosis in HCM. Indeed, the degree of incompetence of the damaged valve, which is the principal determinant of clinical course in endocarditis, is not necessarily severe in all patients. The particularly high morbidity and mortality generally reported for endocarditis in HCM is probably due to the fact that the literature is based on case reports^{3-5,22-30} and thus is probably skewed toward those patients posing the most challenging clinical problems.

Conclusions

Our results show that infective endocarditis in HCM is virtually confined to patients with left ventricular outflow obstruction under basal conditions and that the risk of this complication is highest in patients with both outflow obstruction and marked left atrial dilatation. Therefore our observations indicate that antibiotic prophylaxis for infective endocarditis is required only in patients with the obstructive form

of HCM and particularly in those with a markedly dilated left atrium.

Acknowledgments

This study was supported in part by grants from the Consiglio Nazionale delle Ricerche and from Telethon-Italy (to Dr Spirito).

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Circulation. 1999;99:2132-2137

doi: 10.1161/01.CIR.99.16.2132

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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