Atrial and ventricular programmed electrical stimulation in patients with symptomatic hypertrophic cardiomyopathy[1]

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Hypertrophic cardiomyopathy is associated with a high incidence of sudden death. Eight patients with symptomatic hypertrophic cardiomyopathy were studied by atrial and ventricular programmed electrical stimulation in order to correlate the results with symptoms; with arrhythmias documented by continuous 24-hour electrocardiographic monitoring; and with electrocardiographic, echocardiographic, and hemodynamic measurements. Atrial stimulation induced sustained atrial tachyarrhythmias in 4 of 6 patients not having sustained atrial fibrillation prior to the study. Only 2 of these 6 patients had sustained atrial tachyarrhythmias documented by continuous 24-hour electrocardiographic monitoring. Ventricular stimulation induced sustained ventricular flutter-fibrillation in 1 of 8 patients—the patient with the longest run of unsustained ventricular tachycardia prior to our study. Atrial stimulation better identified patients who could sustain atrial tachyarrhythmias than continuous 24-hour electrocardiographic monitoring and demonstrated the hemodynamic consequences. Ventricular stimulation identified the patient most vulnerable to sustained ventricular tachyarrhythmias. Results of atrial and ventricular programmed electrical stimulation may guide patient-management decisions in an attempt to reduce sudden death due to hypertrophic cardiomyopathy.

Index terms: Cardiac pacing, artificial · Electric stimulation · Idiopathic hypertrophic subvalvular stenosis

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Hypertrophic cardiomyopathy, a disease of unknown etiology, is characterized by nonspecific symptoms, including exertional dyspnea, angina pectoris, lightheadedness, and syncope. It is associated with a high incidence of sudden death.[1,2] The best clinical predictors for sudden

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Table 1. Historical data

Patient No.	Age	Sex	Family history	Symptoms
1	24	M	Brother (patient 4) with hypertrophic cardiomyopathy	Palpitations, lightheadedness
2	51	M	Brother died suddenly (cardiac death) at a young age	Lightheadedness, worsening dyspnea on exertion, syncope (three times)
3	53	M	Twenty-one-year-old son died of hypertrophic cardiomyopathy	Lightheadedness, angina
4	28	M	Brother (patient 1) with hypertrophic cadiomyopathy	Syncope while driving
5	73	F	None	Syncope (three times), worsening dyspnea on exertion
6	56	M	None	Worsening dyspnea on exertion, episodic lightheadedness
7	58	F	None	Syncope, dyspnea on exertion, palpitations
8	64	F	None	Lightheadedness, palpitations, pulmonary edema

death are youth, strong family history of sudden death, and progression of symptoms.[3,4] Various reports have suggested dynamic outflow obstruction,[5] decreased ventricular diastolic compliance with inflow obstruction,[2,6,7] and cardiac arrhythmias[8,9] alone or in concert to be the underlying causes of symptoms and vulnerability to sudden death.

We describe our initial experience with atrial and ventricular programmed electrical stimulation in patients with hypertrophic cardiomyopathy and correlate the response with clinical symptoms, arrhythmias documented by 24-hour ECG, hemodynamic and anatomic data obtained by two-dimensional and M-mode echocardiography, and left heart catheterization.

Methods and materials

From May 1982 through January 1983, 85 patients with hypertrophic cardiomyopathy were seen in the Department of Cardiology at the Cleveland Clinic. Only those with progressive

Table 2. Initial ECG data

Patient No.	Rate (beats/min)	Rhythm	P width (sec)	PR interval (sec)	P axis	QRS duration (sec)	QRS axis
1	53	Sinus	0.14	0.18	−20°	0.11	+175°
2	65	Sinus	0.12	0.16	+30°	0.10	+30°
3	75	Atrial fibrillation	–	–	–	0.10	−30°
4	68	Sinus	0.12	0.18	+30°	0.11	−75°
5	53	Sinus	0.14	0.21	+120°	0.15 LBBB	−30°
6	76	Sinus	0.12	0.19	+50°	0.08	+30°
7	72	Atrial fibrillation, VVI pacer	–	–	–	0.11	−60°
8	75	Sinus	0.15	0.24	+75°	0.08	0°

Table 3. Initial 24-hour ECG data

Patient	Medications	Atrial arrhythmias	Ventricular arrthythmias
1	Verapamil (160 q.i.d.)	PACs	Single VPBs
2	Verapamil (120 q.i.d.)	Paroxysmal sustained SVT	Trebeled VPBs
3	Propranolol (40 q.i.d.)	Sustained atrial fibrillation	Paired VPBs
4	Verapamil (80 t.i.d.) Nadolol (80 q.d.)	None	Single VPBs
5	Verapamil (120 t.i.d.)	Paroxysmal sustained atrial fibrillation	Single VPBs
6	None	None	Six-beat unsustained VT
7	Propranolol (20 q.i.d.) Quinidine (200 q.i.d.)	Sustained atrial fibrillation	Single VPBs, VVI pacer
8	Verapamil (120 t.i.d.)	None	Five-beat unsustained VT

symptoms or a recent history of syncope were included in our study.

A careful history was obtained and a physical examination was performed. All patients underwent standard 12-lead and 24-hour ECG and M-mode and two-dimensional echocardiography, as well as left heart catheterization via the Sones technique. Pressure measurements from the left ventricular apex, left ventricular outflow tract, and ascending aorta were taken in sequence at rest and after provocation with isoproterenol (2 to 8 μg, administered intravenously) or nitroglycerin (0.4 mg, administered sublingually). All patients underwent selective coronary arteriography and left cine ventriculography (right anterior oblique and left anterior oblique projection).

Electrophysiologic studies

We performed electrophysiologic studies for all patients after sedating the patients with diazepam. Right atrial and right ventricular programmed electrical stimulation was conducted in all patients with the use of two or three multipolar catheters positioned in the high right atrium and right ventricular apex or in the high right atrium, right ventricular apex, and at the low right atrium-His bundle area. Intracardiac electrograms and surface electrocardiograms were simultaneously recorded via the Gould electrostatic recorder. Programmed electrical stimulation was performed with a Medtronic 5325 stimulator with 1.8-msec rectangular pulses at twice diastolic threshold.

Technique of atrial stimulation

The high right atrium was stimulated with atrial premature impulses at progressively shorter coupling intervals until atrial capture was lost. The high right atrium was next paced at a 600-msec cycle length, and a single premature extra stimulus was induced at progressively shorter coupling intervals until loss of capture. In the absence of an inducible sustained atrial arrhythmia, the atrium was ramp-paced down to 200-msec cycle length. Induced atrial fibrillation and atrial flutter were treated in a fashion best suited to the patient's hemodynamic status during the arrhythmia either by rapid atrial pacing, by observing spontaneous conversion to sinus rhythm, or by direct-current cardioversion.

Technique of ventricular stimulation

The right ventricular apex was paced at 600 msec (S1–S1). Premature stimuli (S2) were initi-

Table 4. Tachyarrhythmias

Supraventricular
- Paroxysmal
  - Unsustained (5–30 sec in duration)
  - Sustained (>30 sec in duration)
- Chronic (present throughout observation period)

Ventricular
- Paroxysmal
  - Unsustained (5–20 beats with spontaneous termination)
  - Sustained (>20 beats or requiring intervention)

Table 5. Echocardiographic data

Patient No.	Medications	Left atrium (mm)	Septal thickness (mm)	Resting SAM
1	Verapamil (160 q.i.d.)	53	32	+
2	Verapamil (120 t.i.d.)	46	20	+
3	Propranolol (40 q.i.d.) Quinidine SO_4 (300 q.i.d.)	47	22	+
4	None	44	24	–
5	Verapamil (120 t.i.d.)	50	25	+
6	None	44	20	+
7	Propranolol (20 q.i.d.) Quinidine SO_4 (200 q.i.d.)	51	20	–
8	None	42	30	+

SAM = systolic anterior motion of mitral valve.

ated after every eighth paced beat, starting in late diastole and repeating at progressively shorter coupling intervals until induction of a sustained ventricular tachyarrhythmia or loss of ventricular capture. When a sustained ventricular tachyarrhythmia could not be induced, a second extra stimulus (S3) was added. From the point of loss of capture of S2, S2 was moved outside the effective refractory period, and S3 was added at twice this S1-S2 interval. The S3 was moved earlier in diastole at 20-msec decrements until it failed to capture. Next, S2 was moved closer to S1 by 10-msec decrements until both S2 and S3 captured. This protocol was followed until either induction of a sustained ventricular tachyarrhythmia or failure of capture of S2 occurred. If premature stimuli S2 and S3 failed to induce a sustained ventricular tachyarrhythmia, rapid ven-

Table 6. Left heart catheterization data

Patient No.	Medications	CAD	MR	LVOT gradient (mm Hg)	
				Resting	Provoked
1	Verapamil (160 q.i.d.)	–	–	25	45 I
2	Verapamil (120 t.i.d.)	–	–	30	120 I
3	Propranolol (40 q.i.d.) Quinidine SO_4 (300 q.i.d.)	–	–	30	120 I
4	None	+25% right coronary artery	–	0	70 I
5	Verapamil (120 t.i.d.)	–	Severe	80	100 N
6	None	+30% right coronary artery +50% left coronary artery +40% left axis deviation	–	10	90 I
7	Propranolol (20 q.i.d.) Quinidine SO_4 (200 q.i.d.)	–	–	0	0 I
8	None	–	–	45	80 I

CAD = coronary artery disease, *I* = isoproterenol, *LVOT* = left ventricular outflow tract, *MR* = mitral regurgitation, and *N* = nitroglycerin.

Table 7. Electrophysiologic studies

Patient No.	Medications at time of study	Resting intervals (msec)			Atrial stimulation	Ventricular stimulation
		P–A	A–H	H–V		
1	Verapamil (160 q.i.d.)	35	130	55	Induced sustained atrial fibrillation with hypotension	–
2	None	40	70	55–60	–	Ventricular flutter-fibrillation with loss of consciousness
3	None	35	85	50	Pre-existing atrial fibrillation cardioverted to normal sinus rhythm	–
4	None	26	85	30	Induced sustained atrial flutter	–
5	Verapamil (120 t.i.d.)	55	140	40	–	–
6	None	45	80	45	Induced sustained atrial flutter with hypotension	–
7	Propranolol (20 q.i.d.) Quinidine (200 q.i.d.)	Not measurable			Pre-existing atrial fibrillation cardioverted to marked sinus bradycardia	–
8	Verapamil (120 t.i.d.)	25	125	45	Induced sustained atrial fibrillation	–

(–) = no arrhythmia induced.

tricular pacing at cycle lengths down to 300 msec, as tolerated by the patient, was performed. When encountered, the ventricular tachyarrhythmia was terminated by direct-current cardioversion.

Results

Five men and 3 women (age range, 24–73 years; average, 52 years) participated in the study group (*Table 1*). Two patients were less than 30 years old, and 6 patients were less than 60 years old. Four patients had a suspected or proved family history of hypertrophic cardiomyopathy. All patients complained of symptoms of cerebral hypoperfusion, and 4 had had syncope prior to this study. Underlying electrocardiographic rhythm was normal sinus rhythm in 6 patients and sustained atrial fibrillation in 2 patients. Electrocardiographic data are listed (*Table 2*), and 24-hour ECG data are summarized (*Table 3*).

Spontaneous arrhythmias and arrhythmias induced by programmed electrical stimulation were identically classified and defined. Supraventricular tachyarrhythmias, including atrial fibrillation, atrial flutter, and a regular tachycardia without visible atrial activity (supraventricular tachycardia), were categorized as paroxysmal and chronic. Paroxysmal supraventricular tachyarrhythmias were classified as unsustained and sustained. Ventricular tachyarrhythmias were classified as paroxysmal unsustained and paroxysmal sustained. These classes of tachyarrhythmias are defined (*Table 4*).

Echocardiographic data and left heart catheterization data are summarized (*Tables 5* and *6*).

Electrophysiologic studies

Resting P-A, A-H, and H-V intervals obtained during electrophysiologic study are shown (*Table 7*). Because of marked sinus bradycardia, no resting intervals were obtained for patient 7.

Atrial stimulation

Of the 6 patients not having sustained atrial fibrillation from the time of first examination, programmed atrial stimulation induced sustained atrial fibrillation in 2, sustained atrial flutter in 2 others, and no sustained atrial arrhythmia in the remaining 2, while receiving the medications listed in *Table 7*. The sustained atrial arrhythmias of all 6 patients, including patients 3 and 7 who

had sustained atrial fibrillation from the time of first examination, could be converted to sinus rhythm with atrial pacing, antiarrhythmic drugs, or direct-current cardioversion during or within two days of the stimulation study.

Ventricular stimulation

In patient 2, sustained ventricular flutter-fibrillation was induced by programmed ventricular stimulation with double extrastimuli (S1, S2, S3) that required direct-current cardioversion. Normal sinus rhythm promptly resumed with no untoward effects.

Surgery

Patients 2, 3, 5, and 8 underwent septal myectomy for control of symptoms refractory to medical management. The average preoperative left ventricular outflow tract gradient in these patients was 46 mm Hg at rest and 105 mm Hg after provocation. The resting and isoproterenol-stimulated postmyectomy gradient as measured in the operating room was zero in all 4 patients. The postoperative course was complicated by sustained atrial fibrillation in 3 of 4 patients and by unsustained ventricular tachycardia in 1. These arrhythmias were treated with either verapamil, propranolol, or amiodarone, after which atrial and ventricular programmed electrical stimulation were again conducted. No atrial or ventricular arrhythmias could be induced in these postmyectomy patients while being treated with antiarrhythmic drugs. A pathologic study of resected tissue showed marked myocyte disarray in all patients.

Discussion

Our study group was a selected series of 8 patients drawn from 85 patients with hypertrophic cardiomyopathy who were referred to our institution for evaluation of undiagnosed symptoms, a new heart murmur, or for treatment of previously diagnosed hypertrophic cardiomyopathy with progressively worsening symptoms.

Coronary artery disease did not play a role in their symptoms; in fact, the 1 patient who complained of angina pectoris had normal coronary arteries. Although a left ventricular outflow tract gradient was present in most patients, it did not always correlate with symptoms. Patient 7 had disabling symptoms, but no left ventricular outflow tract gradient at rest or after provocation.

Aside from heart rhythm, the electrocardiographic data contained in *Table 2* do not appear to correlate with specific symptoms or with vulnerability to a specific arrhythmia.

According to continuous 24-hour ECG, chronic atrial fibrillation was present in 2 patients, paroxysmal sustained supraventricular tachycardia was present in 1, and paroxysmal sustained atrial fibrillation was demonstrated in another. Unsustained ventricular tachycardia was present in 2 patients. Patients with hypertrophic cardiomyopathy were studied by Savage et al,[10] McKenna et al,[11] Canedo et al,[12] and Bjarnason et al[13] by continuous electrocardiographic monitoring. When consolidated, these studies comprise a group of 185 patients with hypertrophic cardiomyopathy. In this group, the average incidence of supraventricular arrhythmias, excluding patients with chronic atrial fibrillation, is 31%. The average incidence of unsustained ventricular tachycardia (defined as three or four or more consecutive ventricular beats) was 16%. By comparison, the incidence of paroxysmal sustained atrial fibrillation in our group, excluding patients with sustained atrial fibrillation, was two in six, and the incidence of unsustained ventricular tachycardia was two in eight.

Glancy et al[14] found the incidence of atrial fibrillation to be 16 of 167 patients (10%) with hypertrophic cardiomyopathy. They found that atrial fibrillation occurred late during the disease process and was associated with severe clinical deterioration, not with the degree of left ventricular outflow tract obstruction or mitral regurgitation. In our small study, 2 of 8 patients presented with sustained atrial fibrillation, neither having a large left ventricular outflow tract gradient at rest nor mitral regurgitation.

Programmed atrial stimulation induced sustained atrial fibrillation or atrial flutter in 4 of 6 patients with normal sinus rhythm prior to stimulation. When all patients were studied by continuous 24-hour ECG and programmed atrial stimulation, 6 of 8 had sustained atrial fibrillation or atrial flutter. The remaining 2, who had no atrial arrhythmias during 24-hour ECG and no inducible sustained atrial arrhythmias with atrial stimulation, had sustained atrial fibrillation postoperatively. Postoperative pericarditis and its influence on atrial arrhythmias cannot be assessed in these patients. Therefore, all 8 patients had sustained atrial fibrillation or atrial flutter either during 12-lead or 24-hour ECG, after atrial stimulation, or postoperatively.

The predictive value of programmed atrial and ventricular stimulation has not been defined in patients with hypertrophic cardiomyopathy. Atrial stimulation resulted in atrial arrhythmias, such as atrial fibrillation and atrial flutter, in normal patients as described by Haft et al,[15] but these arrhythmias did not last for more than 23 seconds in the normal heart. Thus, stimulation resulting in sustained atrial arrhythmias implies an abnormal substrate. Patients with coronary artery disease who demonstrated sustained ventricular tachycardia on 24-hour ECG monitoring were studied by ventricular stimulation by Drew et al.[16] Similarly, Naccarelli et al[17] studied patients with noncoronary heart disease with sustained ventricular tachycardia on 24-hour ECG monitoring. In both groups, ventricular stimulation was more likely to induce sustained ventricular tachycardia in patients in whom ventricular tachycardia was sustained on 24-hour ECG recordings. In our study, no patient had sustained ventricular tachycardia by 24-hour ECG monitoring. However, in patient 2, in whom ventricular stimulation induced a sustained ventricular tachyarrhythmia, trebled ventricular premature beats occurred during a 24-hour ECG recording, as did longer runs of unsustained ventricular tachycardia prior to the study. Sustained ventricular tachycardia is more easily induced when more stimuli are used and when more sites are stimulated. Anderson et al,[18] in their study of epicardial ventricular pacing in patients with hypertrophic cardiomyopathy, induced sustained ventricular tachyarrhythmias in 14 of 17 patients. When two extrastimuli were used, a sustained ventricular tachyarrhythmia developed in only 3 of 17 patients. The remaining 11 patients required three extrastimuli for induction of sustained ventricular tachyarrhythmias. In our study, two extrastimuli induced sustained ventricular flutter-fibrillation in only 1 of 8 patients with hypertrophic cardiomyopathy. Our results are consistent with the Anderson study.

In the only other series of patients with symptomatic hypertrophic cardiomyopathy studied by atrial and ventricular programmed electrical stimulation, Kowey et al[19] found that two or less right ventricular extrastimuli could produce ventricular tachycardia in 3 of 7 patients, 2 of which had previously been resuscitated from cardiac arrest. In our study, during programmed electrical stimulation of patient 2 during the postmyectomy period, a sustained ventricular tachyarrhythmia could not be induced while he was receiving amiodarone. Amiodarone was used in 2 patients during the postmyectomy period. Our experience, similar to that of Goodwin et al,[2] is that amiodarone effectively controls both atrial and ventricular arrhythmias in patients with hypertrophic cardiomyopathy. This is further supported by the series described by Kowey et al[19] where ventricular tachycardia that could be induced with two extrastimuli without medication could no longer be induced while the patient was receiving amiodarone.

A known correlate of sustained atrial fibrillation is left atrial enlargement as determined by echocardiography.[20] Echocardiographic measurement of left atrial size averaged 47 mm in this group. Spontaneously and/or induced sustained atrial fibrillation or atrial flutter was seen in all study patients. James and Marshall[21] studied the hearts of 22 patients with hypertrophic cardiomyopathy who died suddenly. In 12, the sinus node was fibrosed to the point of almost certain malfunction during life. Theorizing that loss of the sinus pacemaker in these patients could contribute to atrial fibrillation, they suggested that paroxysmal atrial fibrillation is more frequent in patients with this disease than has been documented.

Several authors have documented that development of atrial fibrillation rapidly leads to clinical deterioration in patients with hypertrophic cardiomyopathy.[15,21,22] Our study supports this finding. Patients 3 and 7 with atrial fibrillation were symptomatic at rest at the beginning of the study. Patient 3 was cardioverted electrically to normal sinus rhythm postoperatively with improvement from New York Heart Association (NYHA) functional class 3 to functional class 1. He returned to work. The other, patient 7, had sick sinus syndrome requiring a VVI pacemaker prior to referral for evaluation. She had no resting or provocable left ventricular outflow tract gradient, but she was near syncopal with minimal exertion and had a history of syncope with a normally functioning VVI pacemaker in place. When electrical cardioversion to normal sinus rhythm and A-V sequential pacing were achieved in the laboratory, her cardiac index increased by 53%. After a DDD permanent pacemaker was inserted, she could walk without assistance and her NYHA functional class improved from 4 to 2. Atrial contribution to filling of this hypertrophic left ventricle is an important factor in

maintaining cardiac output. Accordingly, when atrial fibrillation induced by atrial stimulation developed in patients 1 and 6, they became markedly hypotensive and near syncopal in the supine position until normal sinus rhythm was reestablished. Similarly, in the series described by Kowey et al,[19] 2 of the 7 patients had their symptoms reproduced by the atrial stimulation induction of supraventricular tachycardia.

Although much emphasis has recently been placed on ventricular arrhythmias during 24-hour ECG studies as indicators of a poor prognosis involving hypertrophic cardiomyopathy, less has been written about the role of supraventricular arrhythmias. McKenna et al[23] recently reported a case of syncope in a woman with hypertrophic cardiomyopathy. She had frequent, documented asymptomatic paroxysms of unsustained ventricular tachycardia, but while wearing an ambulatory electrocardiographic monitor, sinus tachycardia developed (up to 130 beats per minute). She lost pulse and heart murmur, and she was unconscious for 90 seconds. In a long-term follow-up of patients who had had septal myectomy for hypertrophic cardiomyopathy, Beahrs et al[24] found that atrial fibrillation occurring late postoperatively was associated with increased frequency of late death or continuing poor functional class status.

Atrial stimulation uncovered the vulnerability to sustained atrial arrhythmias in patients with hypertrophic cardiomyopathy better than resting ECG and continuous 24-hour ECG recordings. Atrial stimulation in these patients is predictive of susceptibility to sustained atrial arrhythmias and their hemodynamic consequences in the individual patient under controlled circumstances. In addition, ventricular stimulation can be used to identify patients with hypertrophic cardiomyopathy at high risk for sustained ventricular tachycardia and ventricular fibrillation and to test the efficacy of drug therapy and surgery in these patients.

Atrial and ventricular stimulation studies were conducted safely 11 times in 8 patients with symptomatic hypertrophic cardiomyopathy. We believe this laboratory evaluation of such patients can be a useful adjunct to their management. How the incidence of sudden death in hypertrophic cardiomyopathy is influenced by management decisions based on atrial and ventricular stimulation studies will require long-term follow-up of a larger study group and control population.

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