NEW PERSPECTIVES IN HYPERTROPHIC CARDIOMYOPATHY

HYPERTROFISCHE CARDIOMYOPATHIE: NIEUWE DIAGNOSTISCHE EN THERAPEUTISCHE INZICHTEN

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Ter nagedachtenis aan mijn moeder

Voor Karin, Sander en Anne-Claire

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Chapter 1

Hypertrophic Cardiomyopathy: Update and New Perspectives

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SUMMARY

Hypertrophic cardiomyopathy is a primary cardiac disorder with a heterogeneous expression. Although relatively uncommon, the disease has been studied extensively as appears from the numerous studies that have explored specific facets of hypertrophic cardiomyopathy. This review will focus on the anatomic abnormalities, the prevalence, symptoms and clinical outcome, therapeutic interventions and genetic mutations responsible for the disease.

INTRODUCTION

Hypertrophic cardiomyopathy as a clinical entity was first described by Brock in 1957 (1). The diagnosis is based on the echocardiographic demonstration of a nondilated hypertrophied left ventricle in the absence of other cardiac or systemic disease that can produce left ventricular hypertrophy (2). During the last decades the understanding of this complex disease has grown substantially. However, several individual investigators have characterised hypertrophic cardiomyopathy on the basis of their experience in a particular cohort of patients. Consequently, controversy has arisen with regard to the pathology, natural history, management and aetiology of this heterogeneous disease. In this article, we summarise many of these issues and propose therapeutic strategies for these patients.

GENERAL CONSIDERATIONS

Pathology

The characteristic pathologic features of hypertrophic cardiomyopathy are asymmetric hypertrophy, especially of the interventricular septum (3,4), myocardial fiber hypertrophy and disorganisation of myocardial cells (5,6), abnormal thickened intramyocardial coronary vessels ("small vessel disease") (7-9) and interstitial fibrosis (10). In the majority of patients (approximately 90%), hypertrophy mainly involves the interventricular septum and anterolateral wall (11,12). The posterior segment of the left ventricular free wall is least affected. In a minority of patients myocardial hypertrophy is confined to the apical part of the left ventricle. However, in Japanese patients with hypertrophic cardiomyopathy the apical type represents up to 25 % of cases (13). Patients with apical hypertrophic cardiomyopathy seem to constitute a subset of patients with distinct manifestations: hypertrophy is limited to the left ventricular apex, the electrocardiogram is characterised by the presence of deep negative T-waves and the clinical course is more benign (13-15).

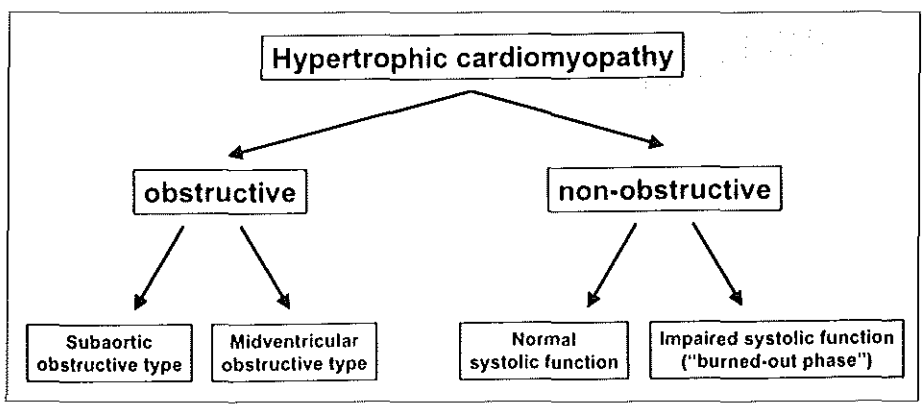
Myocardial hypertrophy is not the only hallmark of hypertrophic cardiomyopathy. Klues et al. have described anatomic alterations in the mitral apparatus which may be present in this disorder: an increase of the mitral valve area, in-

crease in length of the anterior leaflet, abnormal laxity and anterior displacement of the valve (16-19). Moreover, papillary muscles can be part of the disease process and may be displaced to anteriorly and inwards towards another (20), in some patients papillary muscles insert directly into the anterior mitral leaflet (21).

Obstructive versus non-obstructive hypertrophic cardiomyopathy
(Table I)
Obstructive hypertrophic cardiomyopathy can be divided in a subaortic and a midventricular obstructive type (figure I). Subaortic obstruction is present in approximately 25 % of patients with hypertrophic cardiomyopathy (4,22). The obstruction results from a combination of left ventricular outflow tract narrowing, due to basal septal hypertrophy and anterior displacement of the mitral valve, and systolic anterior motion of the mitral valve (23,24). Systolic anterior motion of the valve can be induced by several mechanisms: 1) Venturi forces: as a result of the narrowing of the outflow tract flow velocity increases and a pressure decrease develops above the valve. This cause the valve to be drawn towards the septum (25). 2) Flow drag: due to anatomic alterations in the mitral valve apparatus (increased length, laxity and valve area) and anterior displacement of the papillary muscles, the mitral valve protrudes in the outflow tract and is exposed to flow drag (26). As a result of the systolic anterior motion significant mitral insufficiency can develop (12) (figure II).

In a minority of patients, midventricular obstruction can be observed at the level of the papillary muscles when outspoken midventricular and apical hypertrophy is present. On echocardiography an apical chamber is visualized in systole. In this chamber an elevated systolic pressure is registered. The systolic pressure above the midventricular obstruction is normal, in contrast with the subaortic obstructive type where the systolic pressure in the whole left ventricu-

Table I



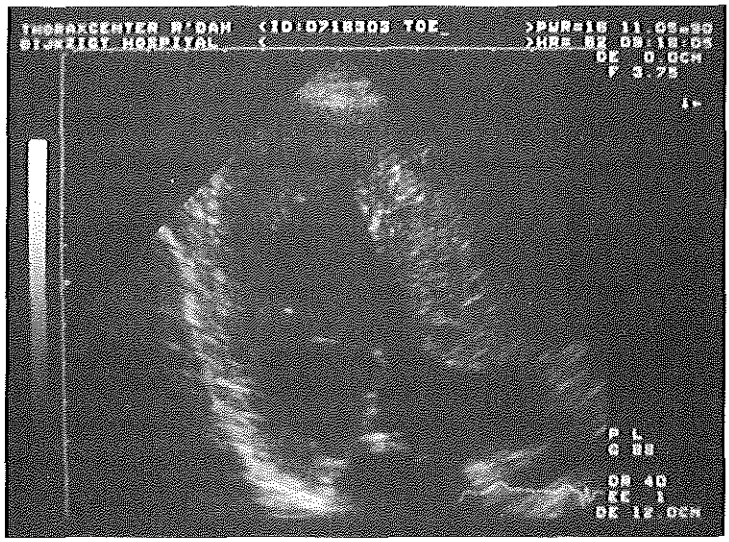


Figure Ia

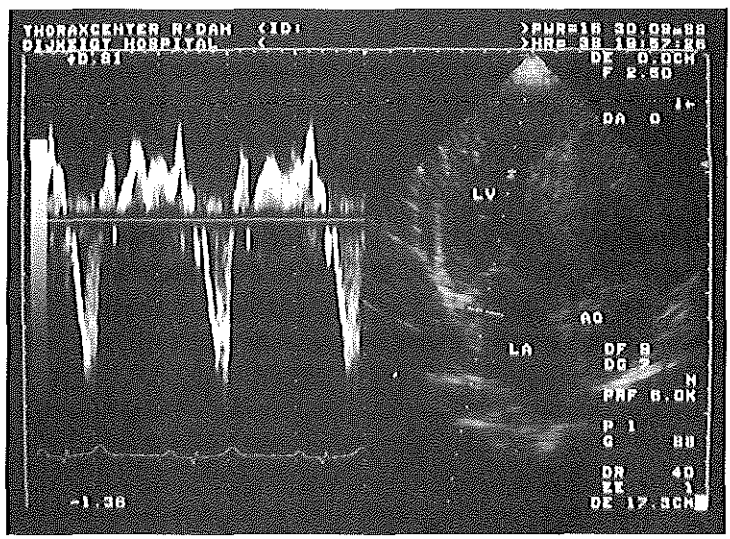


Figure Ib

Apical transthoracic three chamber echocardiographic presentation of a patient with hypertrophic cardiomyopathy and subaortic obstruction (upper panel) and of a patient with midventricular obstruction (lower panel). In the patient with midventricular obstruction, a maximal systolic gradient of 25 mm Hg was measured by pulsed Doppler echocardiography at the level of the obstruction.
Abbrevations: Ao=Aorta, LA= left atrium, LV= left ventricle.
*= level of the subaortic obstruction.

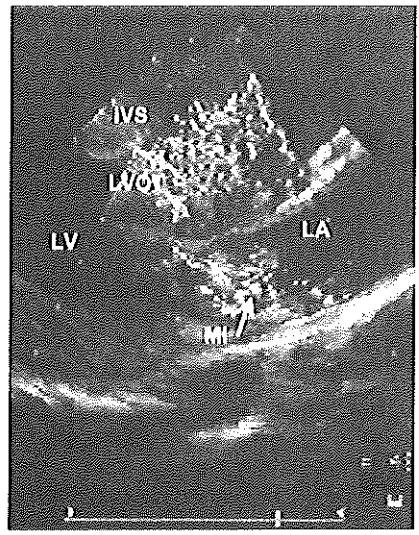


Figure II

Transthoracic long axis echocardiogram of a patient with hypertrophic cardiomyopathy and subaortic obstruction. Doppler colour flow reveals turbulent flow in the left ventricular outflow tract (LVOT), due to LVOT obstruction and turbulent flow in the left atrium (LA) as a result of mitral insufficiency (MI).
Abbrevations: IVS= interventricular septum, LV= left ventricle

lar cavity is elevated (25). Mitral insufficiency is generally absent in the midventricular obstructive type. Fighali et al. (27) and Ishiwata et al. (28) have shown a relation between this type of obstructive hypertrophic cardiomyopathy and apical myocardial infarction. Doppler recordings demonstrate peculiar apex to base flow patterns. As a result of the midventricular obstruction systolic apex to base flow suddenly stops. In the beginning of diastole flow from apex to base is registered (paradoxical diastolic flow), the apex just fills in the last part of diastole (29,30). In patients with midventricular obstruction and the presence of paradoxical diastolic flow, the incidence of cardiac events (systemic emboli, apical ischemia) is increased (29,30).

On both types of obstructive cardiomyopathy it has been shown that the obstruction is dynamic and its severity is dependent on left ventricular contractility, preload and afterload (12). In the subaortic type, the left ventricular outflow tract gradient will increase with positive inotropic stimulation (31), interventions which decrease left ventricular volume (administration of nitroglycerin, Valsalva manoeuvre) (31,32) and manoeuvres which decrease systemic vascular resistance (therapy with vasodilatating drugs) (31,32). Moreover, one should realise that the outflow tract gradient in the subaortic type of hypertrophic obstructive cardiomyopathy is unstable and may show a day-to-day variation not explained by changes in heart rate, blood pressure or left ventricular end-dias-

tolic dimension. Therefore, a single measurement of the pressure gradient is not adequate to define the severity of the dynamic outflow tract obstruction in hypertrophic obstructive cardiomyopathy (33).

Nonobstructive hypertrophic cardiomyopathy can be classified as a cardiomyopathy with normal systolic function or with impaired systolic function ("burned-out" or "end-stage" phase). Approximately 10 to 15 % of patients with the classical characteristics of hypertrophic cardiomyopathy (non-dilated, hypertrophied left ventricle with or without obstruction) will develop symptoms of congestive heart failure due to transformation of the disease in a condition that resembles dilated cardiomyopathy (32,34). On echocardiographic examination, the left ventricular wall thickness is only mildly increased or normal, left ventricular endsystolic- and enddiastolic dimensions are increased and ejection fraction is reduced. The depression of the left ventricular systolic function might well be the result of myocardial ischaemia and infarction, since in many of these patients extensive myocardial fibrosis is present (35,36).

Clinical presentation

It is important to realise that the majority of patients in unselected populations have no or little symptoms (37,38). When present, the main complaints are exertional angina, dyspnea and syncope or near-syncope (32,39,40). There are three different pathophysiologic processes known to contribute to symptoms: myocardial ischaemia, abnormal diastolic function and left ventricular outflow tract obstruction (4). Each of these can produce similar hemodynamic changes and symptoms. Myocardial ischaemia, through compromising left ventricular function and/or diastolic function, may result in a reduction in cardiac output, hypotension and elevation of the left ventricular end-diastolic pressure. These alterations will lead to complaints of angina, dyspnea and near-syncope. Abnormal diastolic function, by elevating left ventricular enddiastolic pressure and reducing left ventricular filling and left ventricular outflow tract obstruction through elevating systolic and diastolic left ventricular filling pressures leading to ischaemia, can produce identical complaints (4).

The contribution of each these mechanisms in the creation of the clinical picture differs from patient to patient. In order to reach benificial therapeutical results the most contributing pathophysiologic mechanisms must be clarified in each patient as much as possible.

PREVALENCE

Hypertrophic cardiomyopathy is the most common cause of sudden cardiac death in young people, including competitive athletes. Since the majority of these young individuals is free of symptoms their death is dramatic and unexpected. These tragic events have raised questions concerning the prevalence of the disease and the methods by which it is detected.

Screening for hypertrophic cardiomyopathy can be performed by echocardiography or genetic testing. The electrocardiogram is not appropriate as screening method for hypertrophic cardiomyopathy since many patients have a normal ECG (41).

Several echocardiographic studies have estimated the prevalence of hypertrophic cardiomyopathy in the general population. The frequency with which hypertrophic cardiomyopathy occurs in the general population is quite uniform according to these studies. Maron et al. (42) performed echocardiography in 4111 men and women 23 to 35 years of age as part of the Coronary Artery Risk Development in (Young) Adults (CARDIA) study, an epidemiological study of coronary risk factors. Hypertrophic cardiomyopathy was present in 7 subjects (0.17%). Only one subject had ever experienced cardiac symptoms, the electrocardiogram was abnormal in 5 of the 7 subjects. Hada et al. (43) surveyed 12000 adult Japanese workers initially with ECGs and subsequently with echocardiograms (in a subset of only about 12%): the prevalence for hypertrophic cardiomyopathy was 0.2%. In an other study by Savage et al. (44) over 3000 subjects (the offspring of the original Framingham cohort) were evaluated with M-mode echocardiography: 0.3% had evidence of hypertrophic cardiomyopathy. In an outpatient population referred for echocardiograpy because of suspicion of cardiovascular disease, Maron et al. reported a 0.5% prevalence of hypertrophic cardiomyopathy (45). Echocardiography may however underestimate the true prevalence of hypertrophic cardiomyopathy (46). The echocardiographic definition for hypertrophic cardiomyopathy is a nondilated hypertrophied left ventricle in the absence of another cardiac or systemic disease which may cause increased left ventricular mass (42). This definition, however, excludes patients who have inherited the disease gene for hypertrophic cardiomyopathy but have not developed left ventricular hypertrophy and excludes patients who do have hypertrophic cardiomyopathy but have another coexsisting disease that may contribute to left ventricular hypertrophy such as hypertension or valvular heart disease (46). Theoretically, it would be most appropriate to use the various genetic abnormalities as a basis for the analysis of prevalence, the description of the phenotypic expression and description of the clinical course of hypertrophic cardiomyopathy. Nevertheless, genetic testing is complex, expensive and probably more inaccurate to determine the prevalence of hypertrophic cardiomyopathy taken into account that a total of more than 70 gene mutations can create the phenotypical expression of hypertrophic cardiomyopathy and many additional genetic abnormalities remain to be documented (47,48).

In conclusion, echocardiography remains the most sensitive and specific tool to determine the prevalence of hypertrophic cardiomyopathy: it is non-invasive, relative cheap and the number of patients that is misdiagnosed is probably relative small (47,48).

PROGNOSIS

The natural history of hypertrophic cardiomyopathy is difficult to assess. Observational studies from tertiary referral centres have estimated the annual cardiac death to be 2-4% in adults (49-55) and as high as 6% in children (52,56,57). However the clinical outcome, derived from investigations performed at these centra, is profoundly influenced by referral bias (58). Hypertrophic cardiomyopathy is an uncommon, heterogeneous disease. Many patients remain free of symptoms during their lives, symptomatic patients may stay in a stable clinical

Table II

Prognosis of patients with hypertrophic cardiomyopathy. The upper panel represents patients from referral centra with the worst prognosis, the lower panel deals with studies in unselected populations of patients at the mild end of the disease spectrum.

	Patients (N)	Mean F/U (yrs)	Annual mortality (%)
Swan et al Br Heart J 1971	85	4.0	3.5
Hardarson et al Lancet 1973	119	4.6	3.5
Shah et al Circ Res 1974	190	5.2	3.4
McKenna et al Am J Cardiol 1981	254	6.0	5.9 (pts < 15 yrs) 2.6 (pts > 15 yrs)
Maron et al Am J Cardiol 1981	99	3.0	2.3
Romeo et al Eur Heart J 1990	125	7.6	3.4
Seiler et al J Am Coll Cardiol 1991	139	8.9	2.4 (surgery) 3.6 (pharmacologic)

	Patients (N)	Mean F/U (yrs)	Annual mortality (%)
Shapiro et al Br Heart J 1983	39	3.1	0.0
Spirito et al N Engl J Med 1989	25	4.4	0.0
Kofflard et al Am J Cardiol 1993	113	7.3	1.0
Cannan et al Circulation 1995	37	7.7	0.7
Cecchi et al JACC 1995	202	10.0	0.6

condition during many years and others have severe symptoms of heart failure or die suddenly. Patients who are referred to tertiary centres represent, for the most part, the segment of patients with severe symptoms, the ones who are candidates for surgical intervention or those who are at risk of sudden death. These patients with hypertrophic cardiomyopathy personify a selected minority and their clinical course seems to represent the worst end of the disease spectrum (58,59). Indeed, in unselected studies patients with hypertrophic cardiomyopathy have a more favourable prognosis and the annual mortality is 1 percent or less (37,38,59-61). Table II depicts studies concerning the prognosis of patients with hypertrophic cardiomyopathy.

Risk-factors for sudden death

The risk for the individual patient with hypertrophic cardiomyopathy for premature cardiac death is not easy to determine. However, there is agreement among investigators that there is a small subgroup of patients who are particularly at high risk for sudden death (62). Especially, patients who have survived cardiac arrest (63,64), young patients with a family history of multiple sudden deaths (52,65) and those with a "malignant" cardiac gene mutation seem to be at substantial risk for premature death (66-68), although the last two findings may reflect the expression of the same phenomenon. Several clinical characteristics have been described that are related with an adverse prognosis, they include: the onset of symptoms in childhood (52), syncopal attacks (69,70), the presence of non-sustained ventricular tachycardia on ambulatory Holter monitoring (53,71), atrial fibrillation (38), substantial left ventricular hypertrophy (72), a marked outflow tract gradient (73) and exercised induced hypotension (74). However other studies could not confirm the relationship between these characteristics and untimely death (48,52,54,56,75-77). Identification of the individual patient at increased risk for sudden death cannot be made on the basis of presence of one of these variables due to the low positive predictive accuracy. However, their negative predictive value is rather high (62). Therefore it seems justified to reassure patients with hypertrophic cardiomyopathy with respect to their prognosis if they have: (a) little or no symptoms, (b) no family history of premature death (c) sinusrithm on the electrocardiogram, (d) no ventricular tachycardia on 24-hour Holter monitoring and (e) lack a left ventricular outflow tract gradient (62). Our experience is that most patients with the disease are at low risk and require no other treatment than careful echocardiographic and clinical follow-up (37).

THERAPY (Table III)

Nonobstructive Cardiomyopathy

Pharmacological therapy

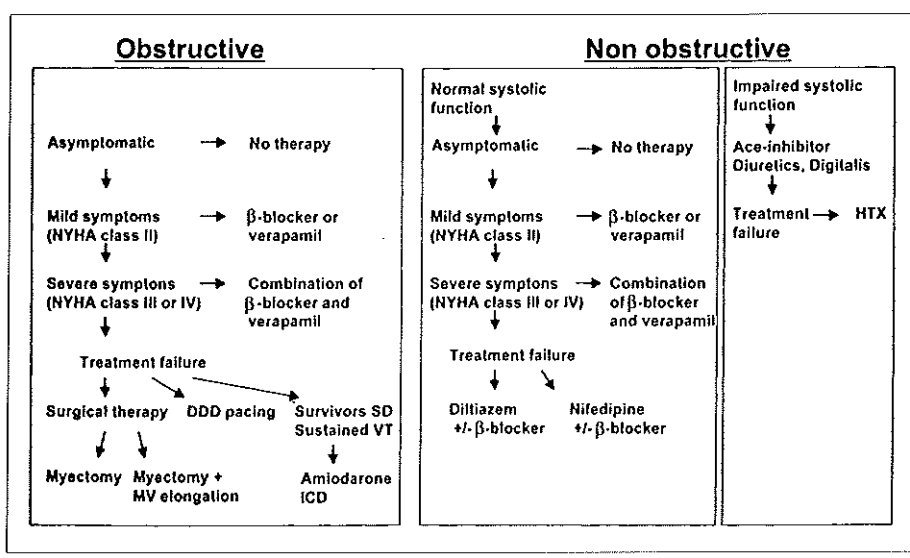
Since there are few controlled trials that have systematically compared the various forms of pharmacological therapy, treatment for hypertrophic cardiomyopathy is for the most part empirical and based on the experience of investigators familiar with this disease (4,62). Since the effectiveness of prophylactic treatment is unknown, patients who are asymptomatic and are not at high risk for sudden death probably need no treatment (62). Those who have complaints of angina and/or exertional dyspnea can be treated with beta-blockers or calciumantagonists. Beta-blockers reduce myocardial oxygen demand and relief symptoms of angina through lowering heart rate, left ventricular contractility and myocardial wall stress during systole (78). Due to the decrease in heart rate and reduction of myocardial ischaemia beta-blockers may improve left ventricular diastolic filling and consequently diminish symptoms of dyspnoe and near syncope during exertion (79,80).

Verapamil is the most prescribed calciumantagonist in hypertrophic cardi-

Table III

Diagram presenting the management of patients with hypertrophic cardiomyopathy in our clinic.

Abbrevations: HTX= heart transplantation, ICD= implantable cardiac defibrillator, MV= mitral valve, NYHA= New York Heart Association, SD= sudden death, VT= ventricular tachycardia



omyopathy, like beta-adrenergic blocking drugs verapamil reduces myocardial oxygen consumption by its negative inotropic and chronotopic effect. Moreover, verapamil decreases afterload through systemic peripheral vasodilatation. The benificial effect of verapamil on left ventricular filling and diastolic function, through lowering of the heart rate, reduction of myocardial ischaemia and shortening of the left venticular isovolumic relaxation period, also contributes to alleviate symptoms (81,82). There is no benificial effect of either beta-blockers or verapamil on the prevention of sudden death (4,73). Two other calciumantagonists, diltiazem and nifedipine, are less prescribed. Diltiazem produces a small reduction in heart rate and has a benificial effect on diastolic function: there is a reduction of the isovolumic relaxation time and early-diastolic filling velocities at rest and during exercise are increased (83,84). In a double-blind crossover study comparing diltiazem (180 mg daily) and verapamil (240 mg/daily), improvements in exercise duration and maximal oxygen consumption were more outspoken with verapamil therapy (85). There are only few studies that have studied the effect of nifedipine therapy in patients with hypertrophic cardiomyopathy. Nifedipine is a more potent vasodilatator than verapamil, however most of its action is improvement of diastolic function: reduction of the relaxation time and increasing left ventricular compliance (86). Nevertheless, Yamakado et al. could not confirm the beneficial results of nifedipine on the diastolic function (87).

In nonobstructive hypertrophic cardiomyopathy and impaired systolic function ("burned-out phase"), the therapeutic approach is similar to that applied for heart failure, including therapy with angiotensin-converting-enzyme inhibitors, diuretics and digitalis (4,62).

Pacemaker therapy

Cannon et al. studied the role of dual chamber pacing in nonobstructive hypertrophic cardiomyopathy. These investigators examined 12 symptomatic patients with nonobstructive hypertrophic cardiomyopathy treated with dual-chamber pacing (88). Although permanent dual-chamber pacing resulted in improvement in symptoms and exercise tolerance, there was absence of objective evidence of hemodynamic or myocardial perfusion improvement during exercise, and a common need to reinitiate medical therapy over time because of persistent or worsening symptoms. Cannon et al. concluded that dual-chamber pacing cannot be recommended for routine use in patients with nonobstructive hypertrophic cardiomyopathy with symptoms refractory to medical management.

Obstructive Hypertrophic Cardiomyopathy

Pharmacological therapy

With some exceptions medical therapy for obstructive hypertrophic cardiomopathy is equal to that for nonobstructive cardiomyopathy. Betablocking

agents are the most prescribed, because of their negative inotropic and chronotropic properties. Moreover, the agents can reduce the exercise generated increase in obstruction (89,90). The influence of beta adrenergic blockade on the basal outflow tract gradient is less significant (4,31). Verapamil can be used if therapy with betablockers is not succesfull: through its negative inotropic and chronotropic effects and benificial influence on diastolic function, the drug may lower the outflow tract obstruction and improve cardiac symptoms (91-93). However, in some patients the outflow tract gradient may increase through the vasodilatating properties of the drug and this may lead to serious complications as cardiogenic shock (94). Because of the outspoken reduction in systemic vascular resistance, therapy with nifedipine can not be recommended in patients with obstructive hypertrophic cardiomyopathy. Disopyramide has negative inotropic effects and especially this quality has been the reason to use this drug in the treatment of obstructive hypertrophic cardiomyopathy (95). It has been shown that dysopyramide reduces left ventricular outflow tract obstruction (96,97). In addition, dysopyramide can improve diastolic function (98). Therapy with disopyramide has resulted in improvement of symptoms and may be initiated if therapy with beta adrenergic blocking agents or verapamil fails (96,97). However, due to its anticholinergic activity and side-effects, patients may discontinue therapy.

Recently, Sherrid et al. (99) have studied the mechanism by which negative inotropic drugs cause elimination of the left ventricular outflow tract obstruction. These investigators concluded that negative inotropic drugs eliminate mitral-septal contact and obstruction by decreasing left ventricular ejection acceleration. By slowing acceleration, these drugs reduce the hydrodynamic force on the protruding mitral leaflet and delay mitral-septal contact. This, in turn, results in a lower final pressure gradient.

Pacemaker therapy

Haemodynamic studies have revealed that DDD pacing in patients with hypertrophic obstructive cardiomyopathy may lower the left ventricular outflow tract gradient. The mechanisms by which cardiac pacing results in haemodynamic and clinical improvement are not completely understood. First, apical stimulation of the right ventricular apex results in early activation of the left ventricular apical region. This leads to ejection of most of the left ventricular stroke volume before septal activation occurs. Second, due to the slower - non His-Purkinje system - spread of depolarisation, contractility and flow velocities are reduced and as a result the outflow tract gradient may be diminished. Third, since flow velocities are reduced and the contraction of the septum occurs late, systolic anterior motion of the mitral valve appears later and the duration of the septal-mitral valve contact will be shortened.

The timing of the AV interval is crucial in pacing for hypertrophic obstructive cardiomyopathy. The AV interval must be short enough to ensure ventricular

capture in every instance. On the other hand, the AV interval must be long enough to maintain atrial contribution to diastolic filling.

The first reports with respect to pacemaker therapy in obstructive hypertrophic cardiomyopathy were very promissing. Fananapazir et al. (100) studied 44 patients (mean age 49 ± 14 years) with left ventricular outflow tract obstruction (mean gradient 87 ± 43 mm Hg) who had symptoms of angina, dyspnea or syncope despite therapy with β–adrenergic blockers or verapamil. Patients were in New York Heart Association functional class III or IV. After DDD pacemaker implantation the left ventricular outflow gradient was reduced to 38 ± 38 mm Hg ($p<0.0001$) and the functional class was improved (1.7 ± 0.7 versus 3.4 ± 0.5, $p<0.00001$) In this study, follow-up evaluation was performed 1.5-3 months after implantation. Fananapazir et al. (101) showed in another study that these favourable results are maintained longterm: In 84 patients (mean age 49 ± 16 years) with obstructive hypertrophic cardiomyopathy the New York Heart Association functional class had improved significantly (1.6 ± 0.6 versus 3.2 ± 0.5, $p<00001$) 2.3 ± 0.8 years after implantation of a DDD device. In a subgroup of 74 patients with significant outflow tract obstruction at rest, the left ventricular outflow tract gradient was reduced significantly at follow-up (27 ± 31 versus 96 ± 41 mm Hg, $p< 0.00001$). Jeanrenaud et al. (102) reported equal long-lasting results in 8 patients with left ventricular outflow tract obstruction treated with DDD pacemaker therapy.

However, other authors did not present equal beneficial results. Nishimura et al. (103) studied 19 patients with obstructive hypertrophic cardiomyopathy with a baseline gradient of 76 ± 61 mm Hg who were symptomatic despite therapy with β–blockers and/or calcium antagonists. Patients underwent double-blind randomization to either DDD pacing for 3 months followed by backup AAI pacing for 3 months, or the same study arms in reverse order. In the DDD mode the left ventricular outflow tract gradient decreased significantly to 55 ± 38 mm Hg compared with the baseline gradient of 76 ± 61 mm Hg ($p<0.05$) and the gradient of 83 ± 59 mm Hg after AAI pacing ($p<0.05$). Symptomatic improvement was felt in 66 % of patients in the DDD-paced mode and in 42 % of patients in the backup AAI arm. Quality-of-life score and exercise duration were significantly improved from the baseline state after the DDD pacing but were not significantly different between the DDD and the AAI arm. These data show that dual chamber pacing results in modest reduction of the outflow tract gradient and that improvement in functional class can also occur from implantation of the pacemaker without its hemodynamic benefit (AAI mode), suggesting the role of a placebo effect. The same author warns for the deleterious effects of dual chamber pacing upon the diastolic function (104). Indeed, Nishimura et al. demonstrated that DDD pacing in obstructive cardiomyopathy had an adverse effect on the diastolic function: there was a significant decrease in peak positive dP/dT, an increase in mean left atrial presssure and a prolongation of τ, the time constant of relaxation. These results were confirmed by Betocchi et al. (105).

Most recently, Kappenberger et al. (106) published the results of a multicentre, prospective, European study (PIC-study) which investigated the effects of adding cardiac pacing to normal medical treatment in hypertrophic obstructive cardiomyopathy. In total, 82 symptomatic patients with obstructive hypertrophic cardiomyopathy were randomized to receive pacemaker therapy. Programming the pacemaker in the DDD mode with optimal atrioventricular delay was considered to be pacemaker-activated; programming to AAI at 30 bpm was termed pacemaker non-activated. Programming in the active pacing arm during 12 weeks was followed by pacing in the non-activated arm in 50% of patients, or the same study arms in reverse order in the other half. After the second 12-week period the pacing mode preferred by the patient was programmed for long-term pacing. After 12 weeks of activated pacing the pressure gradient fell from 59 ± 36 mm Hg to 30 ± 25 mm Hg ($p<0.001$), New York Heart Association functional class improved from 2.4 to 1.4 ($p=0.001$) and 79 patients preferred active pacing over inactivation of the pacemaker at the end of the cross-over study.

In conclusion, dual chamber pacing will result in most patients in a modest reduction in the outflow tract gradient and will provide symptomatic improvement in selected patients. However, reduction of the left ventricular outflow tract obstruction with septal myectomy is much greater than with pacing, the diastolic function can deteriorate (especially important in patients with a combination of systolic and diastolic dysfunction) and the long-term outcome of dual-chamber pacing is still unknown. In our opinion, the long-term outcome of dual-chamber pacing has to be studied in multicentre, randomized trials before the ultimate role of pacing can be established.

Surgery

The largest experience in the invasive treatment of patients with obstructive hypertrophic cardiomyopathy is surgical therapy. Surgery for hypertrophic cardiomyopathy is generally performed in patients who have a significant left ventricular outflow tract gradient and severe symptoms despite maximal medical therapy (107-109). The classic approach is septal myectomy (the Morrow procedure), in which a portion of the basal septum is resected through an aortotomy (110). This procedure usually results in adequate reduction in the obstruction to outflow (111-116). Moreover, septal myectomy will in most cases lead to a reduction in the left ventricular systolic pressure, a decrease in the basal and peak myocardial oxygen consumption and a decrease in left ventricular end-diastolic pressure (117). The operation will result in a widening of the left ventricular outflow tract, thereby increasing the distance between the septum and the mitral valve and as a result this procedure reduces the high outflow tract velocity and Venturi forces that create systolic anterior motion of the mitral valve. Since mitral regurgitation results from systolic anterior motion of the valve, this phenomenon is also relieved by septal myectomy. The net result of the procedure is that

quality of life of the patients is improved as manifested by a reduction in symptoms of exertional dyspnea, angina and syncope or near-syncope (107). However, septal myectomy probably does not change the natural history of the disease (4,37,111,113,116). Septal myectomy has been performed since 1958 (118) and during early experience operative mortality was as high as 5-8% (107,111). However, with increasing surgical experience operative mortality is less than 2 percent at referral centers where the majority of the procedures are performed (113-116,119). Operative mortality is significantly higher when the myectomy procedure is combined with mitral valve replacement and/or coronary bypass surgery (115,116,120).

In selected patients septal myectomy is combined with mitral valve plication (121), extension of the anterior mitral leaflet by a pericardial patch (122) and mitral valve replacement (123). These additional procedures are performed if a suboptimal result is expected after septal myectomy alone, for instance in patients in which the basal septum is relatively thin and patients with intrinsic mitral valve disease (especially those with enlarged mitral valves which may predispose to residual systolic anterior motion after septal myectomy resulting in persisting outflow tract obstruction). Extended myectomy with partial excision and mobilization of the papillary muscles may be performed if the papillary muscles are hypertrophied and malattached to the lateral wall (124).

Mitral valve replacement is also performed without previous myectomy (125-127). In general, mitral valve replacement will result in a more significant reduction of the left ventricular outflow tract gradient and left ventricular end-diastolic pressure. However, the long-term risks of thromboembolism, prosthetic valve dysfunction and the need for anticoagulant therapy make valve replacement an unattractive option for many patients with hypertrophic obstructive cardiomyopathy.

Non-surgical septal myocardial reduction

This procedure was introduced by Sigwart and aims to reduce the septal mass by producing a septal infarction trough the injection of absolute alcohol in a septal branch of the anterior descending coronary artery (128). Knight et al. treated 18 patients with this technique and showed that it is a safe method of reducing left ventricular outflow tract obstruction (129). The new method has been tested and used by others with equal success (130-132). Further experience in prospective, randomized trials is needed to establish the role of this technique in treating patients with obstructive hypertrophic cardiomyopathy (133).

GENETICS

Hypertrophic cardiomyopathy can be caused by mutations in any one of several genes that encode proteins of the cardiac sarcomere: beta-myosin heavy chain, cardiac troponin T, alpha-tropomyosin, cardiac myosin-binding protein C, ven-

tricular myosin essential light chain, ventricular myosin regulatory light chain and cardiac troponin I (134). Mutations in the beta-myosin chain gene constitute most of the cases of familial hypertrophic cardiomyopathy (67,135). The beta-myosin heavy chain consists of 1936 amino acids and over 40 mutations in the genetic material encoding for these aminoacids have been described resulting in hypertrophic cardiomyopathy. For instance, in the most reported mutation $Arg^{403}Gln$, the aminoacid arginine is replaced by glutamine at coding position 403. Identification of the genetic defect has repercussions for clinical outcome. For example, the beta-myosin chain mutations $Arg^{403}Gln$ and $Arg^{719}Trp$ are associated with a high incidence of sudden death (136-139). Other mutations, like $Val^{606}Met$, $Leu^{908}Val$ and $Glu^{930}Lys$ are associated with a benign prognosis (67,138).

Generally, mutations in the gene encoding for cardiac troponin T will lead to left ventricular hypertropy that is substantially less than in patients with beta-myosin chain gene defect related hypertrophic cardiomyopathy, yet the incidence of sudden death is high in cardiac troponin T mutations and resembles the malignant beta-myosin mutations (66,140). Hypertrophic cardiomyopathy caused by alpha-tropomyosin mutations is usually associated with a benign prognosis (141). The estimated frequency with which a mutation on the corresponding gene cause hypertrophic cardiomyopathy is depicted in Table IV (62,67,136,140). It is likely that that numerous other mutations in other genes await identification (48,133).

Unfortunately, hypertrophic cardiomyopathy is a genetically heterogeneous disease and the same mutation will not always result in an identical phenotypical expression. For instance, the malignant beta-heavy chain $Arg^{403}Gln$ was not associated with poor outcome in a Korean family (139). Moreover, the degree of hypertrophy may vary in patients carrying the same mutation (68,142,143). These findings indicate that other factors, environmental as well as genetic, may

Table IV

Estimated percentages with which mutations on genes encoding for the proteins of the cardiac sarcomere cause hypertrophic cardiomyopathy.

	percentage
β-Myosin heavy chain	≈35 %
cardiac Troponin T	≈15 %
α-tropomyosin	< 5 %
myosin-binding protein C	≈15 %
Myosin light chain	< 1 %
Tropononin I	?
other genes	?

modify the phenotypic expression of the mutated gene. Lifestyle, riskfactors, exercise and modifier genes may play an important role in the presence, pattern and extent of hypertrophy in this disease (68). For instance, angiotensin II stimulates cardiac hypertrophy, and it is formed by angiotensin converting enzyme from angiotensin I. The ACE levels in the human heart are partly determined by the *I/D* polymorphism: subjects with the *DD* genotype have higher ACE levels than subjects with *II* or *ID* genotypes. In patients with hypertrophic cardiomyopathy, the ACE genotype *DD* has been associated with more extensive left ventricular hypertrophy (144,145). Angiotensin II exerts most of its known cellular actions trough the angiotensin II type 1 receptor (AT1-R) (146). Recently, it has been shown that the AT1-R *A/C* polymorphism is associated with the extent of hypertrophy: left ventricular mass was significantly higher in patients with hypertrophic cardiomyopathy carrying the C allele (147).

SPECIAL PROBLEMS

The athlete's heart

Hypertrophic cardiomyopathy is the most common cause of sudden death in young athletes (< 35 years), occurring in up to 50% of cases (148-150). The ma-

Table V

Criteria to distinguish the athlete's heart from hypertrophic cardiomyopathy.
Abbrevations: ECG= electrocardiogram, HCM= hypertrophic cardiomyopathy, LA= left atrium, LVED= left ventricular end-diastolic dimension, LVH= left ventricular hypertrophy, SAM= systolic anterior motion.

	Hypertrophic Cardiomyopathy	Athlete's heart
Unusual patterns of LVH	yes	no
Septal thickness >15 mm	yes	no
LVED < 45 mm	yes	no
LVED > 55 mm	no	yes
LA enlargement	yes	no
Female gender and abnormal septal thickness (>12 mm)	yes	no
Decrease of septal thickness with deconditioning	no	yes
Abnormal e/a ratio	yes	no
SAM of the mitral valve	yes	no
Family history of HCM	yes	no
Prominent q-waves on the ECG	yes	no

jority of these deaths occur during severe exertion (150). Athletic training leads to alterations in cardiac anatomy and these changes may resemble the anatomic features of hypertrophic cardiomyopathy. Athletic training leads to an increase in the left ventricular wall thickness, especially the septal wall, end-diastolic left ventricular dimension and left ventricular mass (151-153). However, it is important to distinguish the athlete's heart from hypertrophic cardiomyopathy, because identification of this disorder makes the athlete a patient with cardiovascular disease with increased risk for premature death and consequenses for health insurance. Besides, it disqualifies the athlete from competition and withholds the athlete from the health benefits of exercise. Echocardiography is an important tool to differentiate between the athlete's heart and hypertrophic cardiomyopathy. Table V showes the criteria to distinguish the athlete's heart from a patient with hypertrophic cardiomyopathy. Most important, in the majority of competitive athletes left ventricular wall thickness does not exceed 12 mm. In a study by Pellicia et al. (152), the left ventricular wall thickness was $\geq$ 13 mm in only 2% of 947 elite Italian athletes. Moreover, unusual patterns of hypertrophy involving other segments than the ventricular septum or heterogeneous distribution of myocardial hypertrophy favours hypertrophic cardiomyopathy. Second, the left ventricular end-diastolic cavity dimension is enlarged (> 55 mm) in more than one third of highly trained male athletes (152,154). In patients with hypertrophic cardiomyopathy the end-diastolic dimension is usually < 45 mm (4), unless the disorder has evolved to the end-stage phase where the end-diastolic dimension is increased and systolic function is diminished. Third, vigorous training in female athletes will not result in left ventricular thickness exceeding normal limits (152,155). Fourth, the ventricular wall thickness will show a substantial decrease with deconditioning . Maron et al. (156) showed that within 3 months of deconditioning left ventricular thickness was reduced to normal values in six highly trained athletes who had competed in rowing or canoeing at the 1988 Seoul Olympic Games. Fifth, the transmitral E/A ratio measured by pulsed Doppler echocardiography is normal in athletes (157-159) and may be altered in hypertrophic cardiomyopathy. Classically, the "E", due to rapid filling, is decreased and the "A", due to atrial contraction is increased in hypertrophic cardiomyopathy (160,161).

Atrial fibrillation

The onset of atrial fibrillation has an important impact on the clinical status of the patient with hypertrophic cardiomyopathy: most of the patients have worsening of symptoms, especially the patients with impaired diastolic function (4,12,76,162,163). From previous studies, atrial fibrillation is present in 10 - 15% of patients with hypertrophic cardiomyopathy (4,71,164).

The incidence of atrial fibrillation is highest in patients with obstructive hypertrophic cadiomyopathy due to concomitant mitral regurgitation and increased left atrial size (12,162,165). However, systolic and diastolic dysfunction in pa-

tients may also lead to enlargement of the left atrium and the onset of atrial fibrillation (166). Atrial fibrillation is associated with an increased risk of systemic tromboembolism (167,168) and prompt treatment with anticoagulant therapy is essential. There are controversial data concerning the presence of atrial fibrillation and the risk for cardiac death. Some authors have related atrial fibrillation with a poor prognosis (38,162,164), while others could not confirm this relation (37,76). The treatment of atrial fibrillation is aimed at restoration of sinus rhythm. Amiodarone is probably the most effective pharmacological agent to restore and maintain sinus rhythm (76,117,170). However, since patients are frequently young and side effects are not unusual with amiodarone therapy, sotalol may be attempted first to re-establish sinus rhythm (73). In patients with obstructive hypertrophic cardiomyopathy and atrial fibrillation, myectomy will lead to abolishment of mitral insufficiency and reduction of left atrial size and thereby restoration of sinus rhythm (172). If pharmacological conversion to sinus rhythm is not succesfull, electrical cardioversion has to be attempted. In chronic atrial fibrillation therapy with beta adrenergic blocking agents or verapamil is usually effective to control heart rate and alleviate symptoms (4,12,76).

Ventricular arrhythmias

It should be emphasized that there is no generally accepted strategy for the management of ventricular tachycardia in patients with hypertrophic cardiomyopathy. The prevalence of nonsustained ventricular tachycardia on Holter monitoring is between 20 and 50 % in these patients (37,38,53,63,71,75,164,173). Most reports indicate that nonsustained ventricular tachycardia on Holter monitoring has a benign prognosis in asymptomatic patients (63,75,173) and that these patients should probably not be treated with antiarrhythmic therapy (4,62,75). A more aggressive approach is warranted if ventricular tachycardia is sustained, associated with symptoms or when patients have survived cardiac arrest (4,62,73,173). Previous studies have shown that beta-blockers, verapamil and class I antiarrhythmic drugs do not diminish ventricular arrhythmias nor prevent sudden death (4,12,71,174,175). In contrast, amiodarone abolishes ventricular tachycardia during Holter monitoring in most patients with hypertrophic cardiomyopathy (174,176) and may prevent sudden death (176). However, other investigators could not confirm the finding that amiodarone prevents sudden death (12,173,177). Patients who survived cardiac arrest and who have a left ventricular outflow tract gradient may be successfully treated with myectomy (4,178). An implantable cardioverter-defibrillator may be implanted in patients with high risk for life-threatening tachyarrhythmias; for instance in survivors of cardiac arrest and patients with genetic risk of sudden death. The role of programmed electrical stimulation is questionable. Most reports do not identify patients at high risk for sudden death if sustained ventricular tachycardia is induced by programmed electrical stimulation (4,62,173,179,180).

CONCLUSION

Hypertrophic cardiomyopathy is a complex cardiac disorder with heterogeneity in pathophysiologic expression, clinical presentation, prognosis, management and genetic mutations that cause the disease. The knowledge about the various aspects of this disease is expanding continuously. However, the place of the newer treatment modalities (pacemaker therapy, septal myocardial ablation) has not been determined yet. The exact molecular pathogenesis of hypertrophic cardiomyopathy remains to be established and several factors that influence the phenotypic expression of the mutated gene are yet to be discovered. Elucidation of the molecular basis and the role of environmental factors will probably result in better understanding of the pathogenesis of this disease (143).

It is hoped that the application of molecular genetics will help to stratify and develop more definitive therapy, for instance inhibiting the transcription of the defective gene.

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Chapter 2

Prognosis in Hypertrophic Cardiomyopathy Observed in a Large Clinic Population

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ABSTRACT

Overall annual cardiac mortality in hypertrophic cardiomyopathy (HC) has been reported to be between 2 and 4%, although these numbers are primarily from retrospective studies of patients referred to large research institutions. A clinic population of 113 patients with HC was prospectively studied to assess cardiac mortality in the overall group and in selected subgroups commonly thought to be at high risk for sudden death. The mean age at diagnosis was 37 ± 16 years.

During follow-up, there were 11 cardiac and 2 noncardiac deaths. The annual cardiac mortality was 1% (95% confidence interval 0.2-1.8%). Because of the small number of deaths, relative risk for cardiac death was not significantly different in the presence of young age (≤ 30 years), family history of HC and sudden death, history of syncope or previous cardiac arrest, or both, ventricular tachycardia on 24-hour Holter monitoring, or septal myotomy/myectomy for refractory symptoms and outflow tract obstruction. It is concluded that HC has a relatively benign prognosis (1% annual cardiac mortality) that is 2 to 4 times less than that previously reported.

INTRODUCTION

Hypertrophic cardiomyopathy (HC) is notorious for an increased risk of untimely death (1-3), but its actual prognosis is poorly defined. Previous studies reported overall annual mortality rates between 2 and 4% (4-10). These rates for the most part are based on hospitalized patients referred to large research institutions and probably tell a bleaker story than actually exists for the general population of patients with HC, as suggested by a recent study by Spirito et al. (11).

These investigators followed a small number of outpatients with HC and found no case of sudden death or clinical deterioration over 3 to 6 years. Recent progress in electrophysiology (12,13) and genetics (14,15) has enabled investigators to identify selected patients with particularly high risk for sudden death. Before such highly technical and invasive tests are used in all patients with HC, a more accurate assessment of the overall prognosis in this disease is needed. Since 1970, we have followed a large number of patients at our HC clinic, representing the complete spectrum of the disease in regard to clinical presentations and treatment modalities. In our experience with these patients, we have found a remarkably low incidence of cardiac death.

METHODS

Patient selection

Patients in the HC clinic at the Thoraxcenter of Academic Hospital "Dijkzigt" generally are in 1 of the following 4 groups: (1) those diagnosed in our hospital or outpatients clinics, (2) those transferred from outlying hospitals for advanced

care, (3) outpatients referred from the community for advice and follow-up, and (4) self-referred family members of patients.

Patients with identifiable causes of left ventricular hypertrophy, such as valvular aortic stenosis and uncontrolled systemic hypertension, are not followed in the HC clinic and are not included in this study.

Between 1970 and 1990, 113 patients were examined initially and at yearly intervals. Before 1979, the diagnosis of HC was based on clinical parameters alone; after 1979, it as based on the echocardiographic finding of a nondilated, hypertrophied left ventricle (any wall thickness >15 mm) in the absence of known causes of left ventricular hypertrophy (16). For children, ventricular hypertrophy was diagnosed in relation to published standards for height and weight (17).

At the time of the initial visit, clinical characteristics including age at diagnosis of HC, family history of HC or sudden death in a first-degree relative, or both, history of syncope or sudden death, symptoms and New York Heart Association functional class were recorded. Physical examination and baseline laboratory studies were performed, including M-mode and 2 dimensional echocardiography (as well as Doppler echocardiography after 1985), and 24-hour ambulatory electrocardiographic monitoring when possible. Invasive hemodynamic and angiographic studies were performed only in patients with symptoms refractory to medical therapy who were potential surgical candidates. Surgery was recommended if a peak left ventricular outflow tract gradient >50mmHg at rest or with provocation was found.

Follow-up

Patients were assessed on a yearly basis or more frequently, as indicated. All patients were followed exclusively by 1 physician (FJtC).

Follow-up information on patients who moved out of Rotterdam was obtained from their private cardiologists. In cases of death, cause was determined by death certificate or autopsy when available, or by questioning of relatives or physicians involved in the patient's care. Cardiac death was defined as death from myocardial infarction, congestive heart failure or arrhythmia, or sudden death. Sudden death was assumed to be cardiac, and was defined as a witnessed death within 1 hour after the onset of symptoms or an unwitnessed death in a subject known to be alive and functioning normally 24 hours before (18). Episodes of successfully resuscitated cardiac arrest during follow-up were classified as cardiac death for the purposes of analysis.

Statistics

Survival estimates and 95% confidence intervals were calculated according to the Kaplan-Meier method. The yearly mortality rate was calculated on the basis of all available follow-up time. To assess risk factors for cardiac death, univariate analysis was performed using the Cox regression model. For each in-

dicator, the relative risk and 95% confidence interval are reported.

RESULTS

Baseline characteristics

Clinical characteristics of the 113 study patients (60 male and 53 female) at the time of the initial visit are presented in Table I. The mean age at presentation to our institution was 38 ± 15 years (range 12 to 76). Forty-three patients were aged ≤30 years, and 6 patients were >65 years at the time of diagnosis. Fifty-four patients reported history of HC in ≥1 first degree relative, of whom 40 patients also reported a family history of sudden death at a young age (<40 years). Seven patients reported multiple sudden deaths in the family. No patient had family history of sudden death in the absence of HC. Twenty-four patients had syncope at presentation. One patient had a witnessed cardiac arrest and was successfully resuscitated. Reported symptoms included dyspnea in 49 patients, exertional angina in 37, and palpitations in 34. Fifty-seven patients were asymptomatic or had trivial symptoms (New York Heart Association functional class I), 40 were mildly symptomatic (class II), and 16 were moderately symptomatic (class III). No patient had New York Heart Association class IV.

Baseline medications included β blockers in 49 patients, calcium antagonists in 17, both β blockers and calcium antagonists in 6, and antiarrhythmics in 4.

The diagnosis of HC was confirmed by 2-dimensional echocardiography in all patients (19). Mean left ventricular wall thickness was 22 ± 4 mm (range 15 to 40). Systolic anterior motion of the mitral valve was present in 64 patients.

Left ventricular outflow tract obstruction >50 mm Hg at rest or with provocation was present in 38 patients, as determined by Doppler echocardiography or cardiac catheterization, or both. Of 98 patients who had at least one 24-hour Holter monitor, 37 had ≥1 episode of ventricular tachycardia (≥3 consecutive ventricular beats) recorded; none of these had sustained (>30 seconds) ventricular tachycardia. Holter recordings were generally obtained without discontinuation of medications.

Follow-up data

No patient was lost to follow-up, and information was obtained in all surviving patients within 6 months of January 1990. Mean follow-up was 7 ± 6 years (range 1 to 19).

During the follow-up period, 32 patients underwent myotomy/myectomy. One patient underwent concomitant mitral valve replacement for significant mitral valve regurgitation, and 3 underwent concomitant coronary artery bypass grafting for significant coronary artery disease. No patient had intraoperative placement of a permanent pacemaker or automatic implantable cardioverter-defibrillator device; however, 4 patients needed permanent pacemakers after surgery. There was 1 perioperative death, a patient with a preoperative gradient

Table I

Baseline characteristics of patients with hypertrophic cardiomyopathy.

		Number (%)
Patients		113
Male/female		60/53
Mean age (years)		
First visit		38±15 (range 12 - 76)
Diagnosis		37±16 (range 5 - 71)
Family history		
HC	+	54 (48%)
	o	35 (31%)
	-	24 (21%)
HC and SD	+	40 (35%)
	o	52 (46%)
	–	21 (19%)
History		
Syncope		24 (21%)
Cardiac arrest		1 (1%)
Symptoms		
Dyspnea		49 (43%)
Angina		37 (33%)
Palpitations		34 (30%)
NYHA functional class		
I		57 (50%)
II		40 (36%)
III		16 (14%)
IV		0 (0%)
Therapy		
β blockers		49 (43%)
Calcium antagonists		17 (15%)
β blockers and calcium antagonists		6 (5%)
Antiarrhythmics		4 (3%)
LVOT gradient		
(at rest and/or provocation)		
≥ 50 mm Hg	+	38 (34%)
	o	68 (60%)
	–	7 (6%)

HC = hypertrophic cardiomyopathy; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; SD = sudden death; + = present; o = absent; – = unknown or not available.

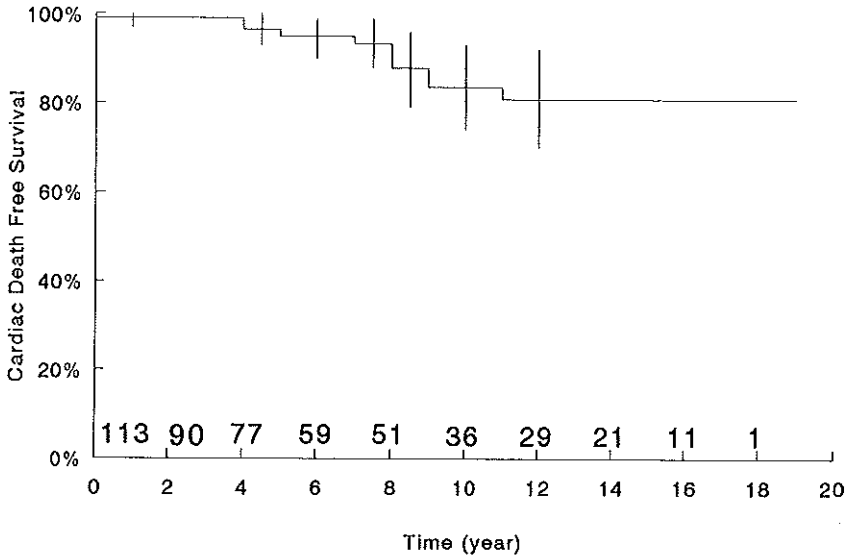

Figure 1

Cardiac survival of 113 patients with hypertrophic cardiomyopathy. Numbers above horizontal axis refer to numbers of patients at each follow-up period. Vertical bars indicate 95% confidence intervals.

of 145 mm Hg and class II symptoms, who died of intractable congestive heart failure 21 days after surgery. Three surgical patients died suddenly in late follow-up at a mean of 5 years after surgery.

During the follow-up period, 12 patients died and 1 was successfully resuscitated from cardiac arrest, which in this study is considered a cardiac death. Two patients died of noncardiac causes: 1 at age 53 years from carcinoma of the lung, and 1 at age 76 from a cerebro vascular accident. In the latter patient, a cardiac source of cerebral embolus was considered unlikely. The remaining 11 deaths were cardiac, of which 9 were sudden by defined criteria, including the 3 surgical patients and the 1 cardiac arrest survivor. One patient, the perioperative patient previously described, died from congestive heart failure. The remaining death was in an 80-year-old man who died at home of an undetermined but presumably cardiac cause. One patient who died had proven coronary artery disease.

The mean age at cardiac death was 47 ± 18 years (range 26 to 80). The annual cardiac mortality in this population was 1% (95% confidence interval 0.2 to 1.8%). Figure 1 shows the Kaplan-Meier survival curve for patients free from cardiac death.

For the purposes of analysis, patients were divided according to known or suspected risk factors for sudden death, including young age, family history of

both HC and sudden death, history of syncope or sudden death, or both, and presence of ventricular tachycardia on 24-hour Holter monitoring (8,13,20-23). No statistically significant difference in risk of cardiac death was found in any subgroup (Table II).

DISCUSSION

This study is the first to report a benign prognosis for a large, relatively nonselected population of patients with HC. In this population of 113 patients, only 11 died from cardiac causes during an average follow-up of 7 years, yielding an annual cardiac mortality rate of only 1%. Previous prognosis studies reported overall annual cardiac mortality rates of 2 to 4% (4-7,9,10), with annual

Table II

Cardiac death in selected subgroups of patients with hypertrophic cardiomyopathy.

Subgroup	Number	Cardiac Deaths	Follow-up (years)	RR (CI)
Total	113	11	7±5 (range 1-19)	
Age ≤ 30 years				
+	43	5	8±5	1.36 (0.44-4.18)
o	70	6	7±6	
FH of HC and SD				
+	40	3	7±6	0.65 (0.17-2.44)
o	52	6	7±5	
–	21	2	9±5	
Syncope and/or cardiac arrest				
+	31*	4	9±6	1.51 (0.48-4.81)
o	82	7	7±5	
VT on Holter				
+	37	2	8±5	0.55 (0.12-2.58)
o	61	6	8±6	
–	15	3	4±3	
Surgery				
+	32	4	8±6	1.45 (0.45-4.61)
o	81	7	7±5	

*includes 7 patients with syncope during follow-up.
CI = 95% confidence interval; FH = family history; RR = relative risk compared with patients in whom clinical feature is absent; VT = ventricular tachycardia; other abbreviations as in table I.

mortality rates up to 8.6% in selected high-risk subgroups (Table III) (7,8,13). In contrast to those previous studies, the present study is both prospective and all-inclusive; the analysis does not exclude patients who are asymptomatic, do not have outflow tract gradients or have had cardiac surgery.

All patients in this study were treated by the same physician to the following flexible guidelines: initial trial of β blockers for relief of symptoms, if present; switch to calcium antagonists if symptoms persist; and surgical therapy for those with medically refractory symptoms in whom a significant outflow gradient is shown at cardiac catheterization. Antiarrhythmic therapy was used very infrequently. We believe this therapeutic algorithm, although not unique to our institution, may have conferred a survival benefit in these patients.

Of 32 patients who underwent myotomy/myectomy during follow-up, there was only 1 perioperative death. Equally good surgical results were obtained by Seiler et al (10) who recently reported only 1 perioperative death in 79 surgical patients. This is in sharp contrast to previous surgical series that reported operative mortality rates as high as 31% (4-7) and to current estimated rates of 5 to 8% (1). The present data show a relatively good prognosis for patients surviving surgery, as do previous studies (6,7,10), although absolute protection against late sudden death does not occur.

Other investigators have reported favourable prognoses in specific subgroups of patients with HC, including the elderly (24), the nonobstructed (25), and those with apical hypertrophy (26). Only recently was the overall experience in a general HC clinic reported: Spirito et al (11) found no cases of cardiac death or deterioration in 25 outpatients, although the follow-up period was brief (mean 4.4 years) and the patient cohort small.

As Spirito et al (11) point out, and we believe correctly, selection bias has likely led to misrepresentation of the true prognosis in HC. They note that most patients in previous studies were hospitalized at 1 or 2 national referral centers. By inference, those patients are sicker and therefore have fatal complications more often than do those such as ours. However, it is difficult to prove the effect of selection bias, because a correlation between presenting clinical features and risk of subsequent death has not been shown in HC (4,6,20,23), with the possible exception of prior cardiac event (7,13), and class IV dyspnea (5). Although those 2 clinical features are rare in the present study, they are uncommon in other studies as well (Table III).

Because of the low incidence of cardiac death in this population, we were unable to delineate statistically significant risk factors for this outcome. The clinical features commonly believed to confer an increased risk of sudden death include young age, strong family history of sudden death, previous history of syncope or cardiac arrest, and ventricular tachycardia on 24-hour Holter monitor, especially when associated with symptoms (6-8,13,20-23). Recent genetic and electrophysiologic studies identified new risk factors for sudden death, including particular chromosomal abnormalities (14,15) and the presence of inducible

Table III

Comparison of clinical features of patients in different prognosis studies.

	Number	Follow-up (years)	Mean Age (years)	NYHA class III or IV	LVOT Gradient present*	Syncope	FH of SD	Surgery	Annual Mortality (%)
Swan et al (4)	85	4.0	–	11	75	–	–	22	3.5†
Hardarson et al (5)	119	4.6	–	17	–	30	–	22	3.5†
Shah et al (6)	190	5.2	–	69	93	51	–	58	3.4
McKenna et al (7)	254	6.0	34	22	139	49	57	33	5.9‡ / 2.6§
Maron et al (8)	99	3.0	38	18	54	–	–	15	2.3
Spirito et al (11)	25	4.4	44	1	5	0	–	0	0.0
Romeo et al (9)	125	7.6	34	78	44	43	15	0	3.4
Seller et al (10)	139	8.9	37	–	–	–	–	79	2.4º/3.6¶
Present study	113	7.3	37	16	38	31	40	32	1.0

* Number of patients with a "significant" gradient (definition varies among investigators)
† Estimated from data
‡ Patients aged < 15 years
§ Patients aged = 15 years
º Surgical patients
¶ Medical patients
Abbreviations as in Table I and II.

sustained ventricular tachycardia (13). However, the present results suggest that applying genetic analysis and electrophysiologic testing to the general population of patients with HC is unjustified. With an annual cardiac mortality of 1% in HC, such expensive and invasive studies should be reserved only for the few patients known by history to be at exceptionally high risk of sudden death.

These findings also have important implications for the counseling of patients with HC. Although it is still necessary to inform affected patients and their relatives of the potential for sudden untimely death, physicians no longer need to paint an unduly bleak picture. The actual risk of dying in this disease is 2 to 4 times less than that previously reported. With further advances in the detection and treatment of patients at high risk for sudden death, true prognosis in HC can only be expected to improve.

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Chapter 3

Pregnancy in Hypertrophic Cardiomyopathy: Prospective Folllow-up in Nine Patiens

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ABSTRACT

Hypertrophic cardiomyopathy is a heterogeneous disease with a wide spectrum of clinical and haemodynamic manifestations. Pregnancy is generally considered a safe undertaking in patients with hypertrophic cardiomyopathy, nevertheless cardiac symptoms can develop or deteriorate during pregnancy. Studies that have investigated the clinical outcome of parturients with hypertrophic cardiomyopathy are for the most part retrospective. Hence, we prospectively followed 9 patients with hypertrophic cardiomyopathy during pregnancy and delivery between 1988 and 1998. Our population represented the clinical heterogeneity of the disease: Before pregnancy, syncopal attacks had been experienced by 4 patients, dyspnea or angina was present in 4 patients, septal myectomy because of left ventricular outflow obstruction had been carried out in 5 patients, on 24 hour Holter monitoring one or more episodes of ventricular tachycardia were documented in 6 patients. Nine women had 20 pregnancies. Cardiac symptoms worsened in 2 patients during pregnancy, in whom one patient was treated with diuretics for relief of signs of heart failure. Five pregnancies ended in a spontaneous abortion. From 15 births, thirteen children were born by vaginal delivery and two by cesarean section because of fetal distress. In the perinatal period, no child nor mother died. We conclude that pregnancy is well tolerated in patients with hypertrophic cardiomyopathy and that cardiological follow-up is necessary during pregnancy for the surveillance of the patients' clinical condition.

INTRODUCTION

Hypertrophic cardiomyopathy is a heterogeneous disease characterized by a diversity in anatomical, haemodynamic and clinical presentation (1-4). The clinical picture may differ from patient to patient: although the majority in unselected populations is asymptomatic, some patients have symptoms of angina, heart failure or syncope (5,6). Pregnancy and delivery is usually well tolerated in patients with hypertrophic cardiomyopathy (7,8). However, symptoms can worsen and venous pulmonary congestion may develop during pregnancy and delivery (7,9). Therefore, advise concerning pregnancy and delivery should be individualized in these patients. We report the outcome of nine pregnant women with hypertrophic cardiomyopathy and present general advice for management of pregnancy and delivery.

METHODS

Between 1988 and 1998, nine patients from the "Thoraxcenter hypertrophic cardiomyopathy clinic" were prospectively followed during pregnancy and delivery. The diagnosis of hypertrophic cardiomyopathy was based on the echocar-

diographic finding of a nondilatated hypertrophied left ventricle in the absence of known causes of left ventricular hypertrophy (10). At the time of the initial visit, clinical characteristics including age at diagnosis, family history of hypertrophic cardiomyopathy or presence of sudden cardiac death in a first degree relative, or both, history of syncope or sudden death, symptoms, New York Heart Association functional class and pharmacological therapy were recorded. Physical examination and baseline laboratory studies were performed, including twelve lead electrocardiography and echocardiography (M-mode as well as Doppler echocardiography). All patients had undergone 24 hour Holter monitoring before pregnancy. Clinical characteristics, physical and echocardiographic examination were reevaluated before pregnancy, at midterm pregnancy and after delivery. The gynecologist was responsible for the welfare of the parturients during pregnancy and delivery. When indicated, (worsening of cardiac complaints or signs of heart failure), cardiac evaluation was performed more frequently.

RESULTS

Baseline characteristics

The clinical characteristics of 9 study patients are listed in Table I. One patient (patient no 2) had given birth to 2 children before the diagnosis of hypertrophic cardiomyopathy was made. Since we included only patients who could be followed prospectively, we eliminated these pregnancies from our study. Nine patients were included with 20 pregnancies. The mean age at first presentation to our institution was 22 ± 6 years. Seven patients reported a family history of hypertrophic cardiomyopathy, of whom 6 patients also reported sudden death in a first-degree relative at a young age (< 40 years). Four women had experienced one or more syncopal attacks before pregnancy. Five women were asymptomatic prior to pregnancy, the symptoms recorded in the remaining patients included dyspnea in 4 patients and exertional angina in 3 patients. All symptomatic patients were in functional class II according to the New York Heart Association. Five women had undergone septal myectomy because of the presence of a left ventricular outflow tract of more than 50 mm Hg and complaints of angina or dyspnea despite therapy with betablockers and/or verapamil. In 4 patients this procedure took place before the first pregnancy. The left ventricular outflow tract gradients, as presented in Table I, were evaluated one to six months before the first pregnancy in 8 patients and before the third pregnancy in patient no 2. All patients were in sinusrythm during the study. On 24 hour Holter monitoring, five patients had one or more episodes of nonsustained ventricular tachycardia and in one patient an episode of sustained ventricular tachycardia was recorded without symptoms.

Table I

Clinical characteristics of pregnant patients with hypertrophic cardiomyopathy.

Pt. no	Year of birth	Family history SD	NYHA class	Medication pre	Medication during	LVOT gradient (mm Hg)	VT on Holter	Year of operation	Pregnancies
1	1962	+	I	-	-	15	+	1984	1988,1990
2	1966	0	II	-	-	25	0		1977*,1978*, 1991
3	1967	0	I	V	V**	5	+		1994,1995
4	1958	+	II	-	-	4	+	1985	1994
5	1967	+	I	-	D	10	+	1991	1988(A),1989 1989(A),1993,1995
6	1957	+	I	-	-	5	+		1992(A),1993,1995
7	1966	+	II	Dis	Dis**	50	+	1986	1988(A),1991,1994
8	1964	0	II	V	V,B	36	0		1997
9	1962	+	I	-	-	12	0	1995	1996(A),1998

Abbrevations:
A= spontaneous abortus, B= beta blocker, D= diuretic, Dis= disopyramide, LVOT= left ventricular outflow tract, NYHA= New York Heart Association, pre= medical therapy before pregnancy, SD= sudden death, V= verapamil, VT= ventricular tachycardia, + = present, 0 = absent, – = no therapy * = not included in the prospective study, **= therapy was stopped during the first trimester of pregnancy.

Follow-up during pregnancy

During pregnancy, four patients were treated with drugs, of whom 2 patients used verapamil (Table I). Patient no 3 discontinued verapamil at the first trimester of both pregnancies and restarted the drug after delivery. Patient no 8 continued verapamil troughout pregnancy. The outflow tract gradient had increased from 36 mm Hg before pregnancy to 90 mm Hg, at midterm evaluation. At 21 weeks gestation she was hospitalized under suspicion of an acute appendicitis. Laparascopy, however, did not confirm the diagnosis. Verapamil was discontinued at discharge, because of the increase in obstruction and was replaced by metoprolol. On echocardiographic examination, four weeks later, the left ventricular outflow tract gradient had decreased to 30 mm Hg. Pregnancy and delivery were uncomplicated afterwards. In patient no 7 disopyramide was stopped during the first trimester of both pregnancies and restarted after delivery. Two patients (no 2 and no 5) had worsening of symptoms during pregnancy. Patient no 2 was seen in our outpatient clinic at 38 weeks of her fourth pregnancy for progression of angina and dyspnea on exertion. At physical examination, there were no overt signs of heart failure and she fulfilled her term without pharmacological therapy. After delivery, cardiac complaints diminished and were comparable with the prepregnancy period . Diuretic therapy was indicated in one patient (no 5) at the end of the fourth pregnancy for relief of symptoms of heart failure.

Delivery

Nine women had 20 pregnancies, five of whom ended in spontaneous abortion. The first pregnancy of patient no 5 ended in the delivery of a stillborn child at 27 weeks. This patient was hospitalized because of excessive vaginal bleeding due to rupture of the placenta in the presence of placenta previa. Systolic blood pressure at admission was 75 mm Hg and was stabilized at 100 mm Hg after several blood transfusions. After delivery, the patients' recovery was uncomplicated. Autopsy of the female fetus of 640 grams did not reveal any cardiac abnormality. The characteristics of the 15 live-born infants are listed in Table II. There was no maternal nor neonatal death. Thirteen children were born by vaginal delivery, in one child vacuum extraction was needed because of fetal distress. Two intrauterine growth retarted children were born by cesarean section at 39 weeks because of fetal distress. These two neonates were monitored in the pediatric clinic. During their hospitalization no abnormalities were found and they were dismissed, 3 and 4 weeks after delivery respectively. The other newborns were discharged the same or the other day after routine examination and observation. Birthweight averaged 2868 ± 716 gram (range 1280 - 4160 gram) and apgar scores were 8.6 ± 1.3 and 9.5 ± 0.9 after 5 and 10 minutes respectively. Endocarditis prophylaxis was administered in 9 of sixteen deliveries.

Table II

Characteristics of the neonates of patients with hypertrophic cardiomyopathy.

Pt. no	Year of birth Gender	Birthweight (gram)	Apgar score 5 min-10 min	Mode of delivery	SBE
1	1988/F	3300	10 - 10	vaginal	+
	1990/M	4160	10 - 10	vaginal	+
2	1991/F	1280	8 - 8	sectio	0
3	1994/M	2030	9 - 9	vaginal	0
	1995/M	2430	9 - 10	vaginal	0
4	1994/M	3355	9 - 10	vaginal	0
5	1989/M	3340	8 - 9	vaginal	0
	1993/M	3200	10 - 10	vaginal	+
	1995/F	3205	9 - 10	vaginal	+
6	1993/F	2920	8 - 10	vaginal(vacuum)	+
	1995/F	2920	8 - 10	vaginal	+
7	1991/F	3055	6 - 9	vaginal	+
	1994/F	2990	10 - 10	vaginal	0
8	1997/M	3030	9 - 10	vaginal	+
9	1998/F	1800	6 - 7	sectio	+

Abbrevations:
min= minutes, sectio= sectio caesarea, SBE= endocarditis profylaxis, += present, 0= absent.

Follow-up after delivery

Uptill now, cardiac abnormalities are not found on echocardiographic examination in these children after maximal follow-up of nine years (range 0.1 - 9 years). During follow-up two women (no 4 and 7) had cardiac events. Both patients were admitted to local hospitals after resuscitation because of ventricular fibrillation, 5 and 8 months after the latest pregnancy respectively. Patient no 7 stayed comatose. Patient no 4 recovered without neurological injury, she was treated by implantation of an cardioverter defibrillator because of periods of sustained ventricular tachycardia despite antiarrhythmic drug therapy. In the other 7 patients clinical status was not different as compared to the prepregnancy period.

DISCUSSION

In this paper we report the outcome of 20 pregnancies in 9 patients with hypertrophic cardiomyopathy. Our cohort represented the heterogeneity in clinical presentation of this disease: while 5 patients were asymptomatic, 4 patients had complaints of angina or dyspnoe, 6 patients had ventricular tachycardia on 24 hour Holter monitoring and septal myectomy because of left ventricular outflow tract obstruction was performed in five patients. From 20 pregnancies, 15 children were born alive, 13 by vaginal delivery and two by caesarean section. Five pregnancies ended in spontaneous abortion. Our results are in agreement with previous reports and confirm that pregnancy is generally well tolerated in patients with hypertrophic cardiomyopathy.

Haemodynamic changes during pregnancy and its influence on hypertrophic cardiomyopathy

During pregnancy, important changes in the haemodynamic state take place. There is a reduction in the peripheral resistance beginning from the 12th week of gestation (11), nevertheless bloodpressure is unchanged in most patients since cardiac output is increased by 30-50% (12). In the last trimester, compression of the inferior caval vein by the expanding uterus can result in a decrease of venous return (13,14). During delivery, pain and stress causes sympathetic stimulation which leads to an increase in heartrate and contractility and furthermore the Valsalva manoeuvre may reduce venous return (13,14).

The increase in contractility and decrease in pre- and afterload can augment the obstruction in patients with hypertrophic obstructive cardiomyopathy, which in turn may lead to deterioration of the clinical condition (9,13,14). In patients with hypertrophic cardiomyopathy and diastolic dysfunction, the increase in intravascular volume and rise in heartrate is detrimental and may cause worsening of symptoms and pulmonary venous congestion (15).

Drug therapy during pregnancy
Beta adrenergic blocking agents are traditionally prescribed in symptomatic patients with hypertrophic cardiomyopathy. Beta-blockers reduce myocardial oxygen demand and relief symptoms of angina and dyspnea through lowering heart rate, reducing left ventricular contractility and reducing the exercise generated increase in obstruction (3,16,17). The use of these drugs in pregnancy is relatively safe. There are no reports indicating that therapy with beta-blockers results in fetal malformation (18). Intra-uterine growth retardation, neonatal bradycardia and neonatal hypoglycaemia are reported in a small number of patients (7,8,19,20). Verapamil is also widely used in the management of patients with hypertrophic cardiomyopathy, like beta-adrenergic blocking drugs, verapamil reduces myocardial oxygen consumption by its negative inotropic and chronotropic effect. Moreover, the drug may have a benificial influence on diastolic function (21,22). In patients with hypertrophic obstructive cardiomyopathy verapamil may increase the left ventricular outflow tract gradient through the vasodilatating properties of the drug (23). No teratogenic effects have been described in patients treated with verapamil for acute management of maternal supraventricular arrhythmias (24). The effects of chronic administration of verapamil on the course of pregnancy is still unclear.

Recommendations during labour and delivery
The use of betamimetic tocolytic drugs is contraindicated in patients with hypertrophic obstructive cardiomyopathy, because the left ventricular outflow tract gradient increases and symptoms may worsen (8). Analgesia during labour is useful to diminish sympathetic stimulation (13,14). Epidural analgesia is not contraindicated, however adequate volume-expansion and careful bloodpressure monitoring is necessary, to avoid hypotension specially in patients with hypertrophic cardiomyopathy and outflow tract obstruction (25,26). Haemodynamic monitoring by pulmonary artery catheterization should be considered in patients who are severely symptomatic or have signs of heart failure to guide drug therapy (9). According to the statement of the American Heart Association patients with hypertrophic cardiomyopathy are at moderate risk for acquiring endocarditis (27). In our institution, endocarditis profylaxis is recommended in patients with distinct systolic anterior motion of the mitral valve and obstruction, and in patients with considerable mitral insufficiency. Oxytocin has been administered safely in patients who require augmentation of uterine contraction after delivery (8,26). In general, vaginal delivery is considered safe and caesarean section is reserved for obstetretic indications.

General recommendations
Hypertrophic cardiomyopathy occurs both as a familial disorder, with an autosomal dominant pattern of inheritance, as well as in sporadic forms. The risk of inheritance in familial forms is 50%. However, it is important to note that pa-

tients with identical gene mutations display variable clinical manifestations or even fail to express the disease (28,30). In the prepregnancy consultation it is important to explain the potential risk of pregnancy with respect to maternal and fetal well-being. Cardiological controls are necessary during pregnancy for the surveillance of the patients' clinical condition, to start or change therapy if symptoms worsen or to hospitalize the patient if there are overt signs of heart failure. Postpartum blood loss should be replaced by intravenous fluids, specially in patients with hypertrophic obstructive cardiomyopathy, because of the potential aggravation of the pressure gradient across the left ventricular outflow tract. After birth, echocardiographic evaluation should be performed every 2 to 5 years in children (or sooner when cardiac symptoms develop) lasting until adulthood to recognize signs of hypertrophic cardiomyopathy.

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Chapter 4

Assessment of Left Ventricular Outflow in Hypertrophic Cardiomyopathy Using Anyplane and Paraplane Analysis of Three-Dimensional Echocardiography

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ABSTRACT

This study analyzes the alterations in size and geometry of the left ventricular (LV) outflow tract that occur in hypertrophic cardiomyopathy (HC) using transthoracic 3-dimensional echocardiography. Transthoracic 3-dimensional echocardiography was performed in 17 patients with HC (4 after myectomy) and in 10 normal subjects. Images were acquired with the rotational approach, with electrocardiographic and respiratory gating. From the 3-dimensional datasets, short-axis parallel slicing of the LV outflow tract at 1 mm distance was performed at the onset of systole. For each slice, cross-sectional area and maximal and minimal diameter were calculated. Reconstruction of the LV outflow tract could be displayed in 3 dimensions in all patients, allowing orientation and clear definition of the irregular geometry. In patients with HC, the minimal LV outflow tract cross-sectional area was smaller than in normal subjects (2.3 ± 1.0 cm^2 vs 5.0 ± 0.9 cm^2, $p<0.0001$). The ratio between maximal and minimal cross-sectional areas was higher in patients with HC than in normal subjects (2.6 ± 0.9 vs 1.4 ± 0.2, $p<0.0001$). The ratio between maximal and minimal diameter of the smallest cross-section of the LVOT was also significantly higher in patients with HC than in normal subjects (1.6 ± 0.3 vs 1.2 ± 0.1, $p<0.001$) and a value of 1.36 separated normal subjects from HC patients without previous myectomy. In conclusion, precordial 3-dimensional echocardiography allows detailed qualitative and quantitative information on the LV outflow tract. Patients with HC are characterized by a highly eccentric and asymmetric shape of the LV outflow tract, and by a smaller minimal cross-sectional area than seen in normal subjects.

INTRODUCTION

Postmortem studies and intraoperative findings indicate that 2-dimensional echocardiography may fail to give the full picture of the left ventricular (LV) outflow tract in patients with hypertrophic cardiomyopathy (HC) (1-6). Three-dimensional echocardiography is a new imaging modality which provides unique information on the spatial geometry of a given structure (7). Based on our experience in an unselected population (8,9), we believe that the alterations in size and geometry of the LV outflow tract in patients with HC could be more accurately analyzed with precordial 3-dimensional echocardiography. With these concepts in mind, we designed this study to gain further insight into the complex geometry of the LV outflow tract in patients with HC. With this aim, analysis of the LV outflow tract was performed using 3-dimensional datasets obtained after acquisition of precordial echocardiographic images.

METHODS

Study patients

We prospectively selected 17 patients (13 men and 4 women; mean ± SD age 39 ± 15 years, range 19 to 65) with HC referred to the outpatient clinic of our institution for routine transthoracic echocardiographic follow-up. High-quality images were a prerequisite for inclusion in this study. The diagnosis of HC was based on M-mode and 2-dimensional echocardiographic demonstration of a nondilated hypertrophic left ventricle in the absence of other cardiac or systemic disease that could produce LV hypertrophy (10). According to a previously established classification (11), the patterns of distribution of left ventricular hypertrophy were: type I, 1 patient; type II, 3 patients; type III, 12 patients; and type IV, 1 patient. Systolic anterior motion of the mitral valve was present in 12 patients and its severity was evaluated semiquantitatively from 0 = absence to 3+ = contact with the interventricular septum during systole (5). At the time of the echocardiographic study, a pressure difference was calculated from Doppler LV outflow tract velocity recordings, and obstruction (gradient >30 mm Hg under basal conditions) was detected in 4 patients. A septal myectomy had been performed in 4 patients. Ten asymptomatic subjects without evidence of LV hypertrophy were also studied for comparison. These controls were 20 to 49 years (mean 28 ± 8) and 8 were men.

Examination procedure

Two-dimensional echocardiographic studies were performed with a commercially available system (Vingmed CFM 750 [Horton, Norway] or Toshiba Sonolayer SSH-140A [Tokyo, Japan]) equipped with a 3.5 MHz transducer, while the patient was lying in the 45° left recumbent position. After the follow-up 2-dimensional echocardiographic study, the probe was positioned either at the left parasternal or apical window for acquisition of the tomographic images of the LV outflow tract for 3-dimensional reconstruction. Patient movement during the image acquisition can be prevented by thoroughly explaining the procedure before the study. The operator has to find the central axis of rotation so that the conical datasets encompass the LV outflow tract. During the acquisition, movements of the transducer holder must be avoided diligently. Mirror images of the first and the final cut-plane indicate a correct 180° rotation. All subjects gave informed consent.

Three-dimensional echocardiography

Image Acquisition. After the standard 2-dimensional examination, the video output of the echocardiographic system is interfaced to the acquisition system (Echo-scan, TomTec GmbH, Munich, Germany) and the transducer is fixed into a cylindrical holder. A step-motor mounted on this holder can rotate the probe around its longitudinal axis via a wheel-work interface. The step-motor is connected to the acquisition system which commands the rotation of the probe at 2°

intervals over a span of 180°. Respiratory and electrocardiographic gating are performed after the operator has selected the end-expiratory phase by thoracic impedance measurement and an adequate R-R interval. Thus, only those beats falling in the predetermined R-R interval and at the end-expiratory phase are selected by the steering logic of the system and acquired. Cycles that do not meet the preset ranges are rejected. Ninety sequential cross-sections are acquired, each during a complete heart cycle, encompassing a 3-dimensional conical volume. After distance calibration, images are stored in the computer memory for subsequent analysis.

Image Processing. The raw data are resampled off-line according to their temporal and spatial location. The coordinates of each point are converted from a polar to a rectangular system, and the space between contiguous points is electronically filled with a trilinear cylindric interpolation. Several algorithms are used to reduce noise and artifacts which can be created by patient and probe movements.

Image Display Analysis. Images were analyzed as follows:

1. After thourough examination of the 3-dimensional datasets with analysis of cardiac cross-sections in any desired plane ("anyplane echocardiography"), a cut-plane is selected where the LV outflow tract is visualized along its longitudinal axis.
2. The onset of ventricular systole is selected, as the first frame during the cardiac cycle in which the mitral valve appears closed.
3. Electronic parallel slicing ("paraplane echocardiography") of the LV outflow tract perpendicular to the vertical axis is performed at 1 mm intervals, from the hinge point of the anterior mitral leaflet to the point of coaptation of the mitral leaflets, and the corresponding 2-dimensional images (both the stop frame at onset of systole and the dynamic sequence) are displayed.
4. On the stop frame image at the onset of systole, the endocardial contour of the cross-section is manually traced for automatic area measurement, and maximal and minimal diameters are also measured.
5. Finally, reconstruction of the LV outflow tract at the onset of ventricular systole is displayed in wire frame mode and the representative image can be rotated on the screen for versatile 3-dimensional evaluation (Figure 1).

From the analysis of the 3-dimensional datasets, the following measurements of the LV outflow tract at the onset of systole were considered: 1) minimal cross-sectional area; 2) ratio between maximal and minimal cross-sectional area (max/min cross-sectional area), as an index of the "eccentricity" of the LV outflow tract (the higher the value, the greater the variations of the cross-sectional area throughout the length of the LV outflow tract); 3) ratio between maximal (latero-medial) and minimal (antero-posterior) diameter (max/min diameter) at the level of the cross-section with the minimal area, as an index of the "asymmetry" of the LV outflow tract (a ratio of 1 indicates a circular shape, with the highest values corresponding to the more elliptical shape of the cross-sections).

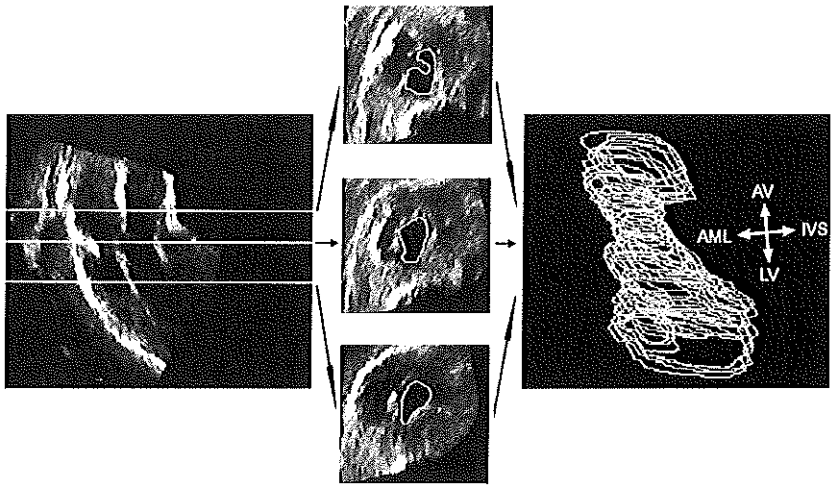

Figure 1

Analysis of left ventricular (LV) outflow tract in a patient with hypertrophic cardiomyopathy. From the 3-dimensional dataset, parallel slicing of the LV outflow tract perpendicular to the long-axis (paraplane echocardiography) is performed at 1 mm intervals, at the onset of ventricular systole. In the **left panel,** 3 representative cut-planes are indicated. The corresponding cross-sectional 2-dimensional images with the manually traced endocardial contours are shown in the **middle panels.** The final wire frame mode display represented in the **right panel** can be rotated on the screen along the 3 main axes for versatile qualitative 3-dimensional evaluation.
AML = anterior mitral leaflet; AV = aortic valve; IVS = interventricular septum.

Inter- and intraobserver reproducibility for the measurements of LV outflow tract with 3-dimensional echocardiography was assessed in all 27 patients. To assess interobserver variability, two observers (A.S. and Y.N.) independently measured the outflow tract area from the 3-dimensional datasets without prior knowledge of clinical data and without preselection of cut-planes. In addition, LV outflow tract cross-sectional area measurements were performed by 1 observer (A.S.) on 2 occasions (3 months apart, without preselection of cut-planes from the 3-dimensional datasets) to assess intraobserver variability.

Statistical analysis

Values are given as mean ± SD. Student's unpaired *t* test was used to compare the differences between HC and control subjects. Values of $p<0.05$ were considered to be significant. Reproducibility of the LV outflow tract measurements was expressed in terms of mean differences and the 95% confidence intervals (12).

RESULTS

Three-dimensional acquisition could be performed successfully in all patients. Echocardiographic acquisition of the image of the LV outflow tract for 3-dimensional reconstruction was performed either from the parasternal (n=20) or apical (n=7) windows, according to the image quality. The examination including the calibration procedure, selection of the optimal axis of rotation, a number of test runs, and the actual image acquisition required approximately 10 minutes in addition to the time required for the standard 2-dimensional echocardiogram. Three-dimensional reconstruction of the images was possible and of good quality in all patients. The time required for post-processing the raw data, and reconstruction and analysis of the images was approximately 20 minutes. Demographics, echocardiographic characteristics, and measurements of the LV outflow tract in each patient with HC are reported in Table 1.

Left ventricular outflow tract in patients with hypertrophic cardiomyopathy versus normal subjects

Cross-Sectional Area. The values of minimal cross-sectional area of the individual subjects are plotted in Figure 2. The minimal LV outflow tract cross-sectional area calculated with 3-dimensional echocardiography was significantly smaller in patients with HC than in the control group (2.3 ± 1.0 vs 5.0 ± 0.9 cm^2, $p<0.0001$). Thirteen of the 17 patients with HC had a value smaller than controls, and 2 of the 4 HC patients (nos. 6 and 17) with higher values were evaluated after myectomy. After correction for body surface area the values were 1.3 ± 0.5 and 2.7 ± 0.6 cm^2, respectively ($p<0.0001$).

Shape. From the 3-dimensional datasets, the reconstructed LV outflow tract could be displayed as observed from different viewpoints. This simplifies visualization of the geometry and shape as well as the localization of the narrowing of the LV outflow tract in patients with HC (Figure 3). A similar display in a normal patient is shown in Figure 4. Some examples of 3-dimensional reconstruction of the LV outflow tract in normal subjects and in patients with HC are shown in Figure 5.

Max/Min Cross-Sectional Area (Eccentricity Index). The max/min cross-sectional area of the LV outflow tract derived from the 3-dimensional datasets are displayed in Figure 6. From this figure, it is apparent that patients with HC had higher ratios (2.6 ± 0.9), with a broad range of values (from 1.5 to 4.2) indicative of many irregular different shapes of the LV outflow tracts. In contrast, normal subjects had smaller ratios (1.4 ± 0.2), with a narrow range of values (from 1.1 to 1.6). In particular, each of the controls had a ratio of ≤ 1.6, whereas 15 of 17 patients with HC had a ratio of >1.6. The 2 patients with max/min cross-sectional area of ≤ 1.6 (patients 16 and 17) were evaluated after myectomy. Thus, an outflow tract area ratio of 1.6 appeared to separate patients with from subjects without HC.

Table 1

Demographics, patient characteristics, and measurements of the left ventricular outflow tract in patients with hypertrophic cardiomyopathy.

Pt.	Age(yrs)/Sex	type LVH	Therapy	Gradient	SAM	CSA(cm2)	Max/Min CSA	Max/Min diameter
#1	19 M	III	V	58	3+	2.9	2.0	1.9
#2	21 M	III	-	< 10	2+	2.4	2.5	1.7
#3	22 M	I	-	< 10	1+	3.0	1.8	1.4
#4	24 M	IV	-	< 10	2+	2.9	2.4	1.6
#5	25 M	III	V	< 10	2+	2.7	2.4	1.6
#6	31 F	III	S,V	50	3+	1.3	4.2	2.0
#7	38 F	II	V	< 10	0	2.4	2.7	1.7
#8	39 F	III	V	< 10	0	3.2	2.1	1.6
#9	41 M	III	V	20	1+	1.9	1.7	1.8
#10	46 F	II	A,V	< 10	2+	0.7	4.1	1.4
#11	53 M	III	-	< 10	1+	1.5	3.8	1.9
#12	63 M	II	M	100	3+	1.5	3.0	2.6
#13	65 M	III	V	35	3+	2.0	3.0	1.6
Mean±SD	37±15					2.2±0.7	2.7±0.8	1.75±0.3
#14	31 M*	III	-	< 10	0	2.1	2.4	1.3
#15	34 M*	III	S	< 10	1+	0.9	3.9	1.2
#16	44 M*	III	S,V	< 10	0	4.7	1.5	1.3
#17	59 M*	III	V	< 10	0	3.0	1.6	1.3
Mean±SD	42±12					2.7±1.6	2.3±1.1	1.27±0.05
Mean±SD (overall)	39±15					2.3±1.0	2.6±0.9	1.6±0.3

*Patients evaluated after myectomy

A = amiodarone; CSA = cross-sectional area; LVH = left ventricular hypertrophy; M = metropolol; Max./Min. = maximal/minimal; S = sotalol; SAM = systolic anterior movement; V = verapamil.

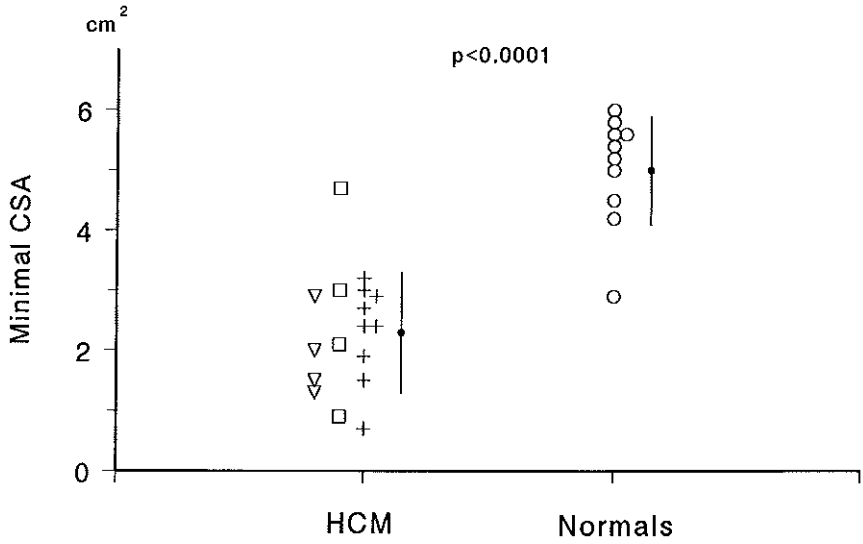

Figure 2

Minimal cross-sectional area (CSA) of the left ventricular outflow tract in patients with hypertrophic cardiomyopathy (HCM) and in normal subjects (○).
+ = patients without obstruction; □ = patients after myectomy; ▽ = patients with obstruction.

Max/Min Diameter (Asymmetry Index). The individual values of max/min diameter of the LV outflow tract cross-section are displayed in Figure 7. This ratio was significantly higher in patients with HC than in normal subjects (1.6 ± 0.3 vs 1.2 ± 0.1, p=0.001). Of interest, patients evaluated after myectomy had the lowest values; conversely, the highest values were found in patients with HC and LV outflow tract obstruction. An index of 1.36 appeared to separate normal subjects from patients with HC who did not undergo operation.

Reproducibility analysis of three-dimensional echocardiography:

Interobserver Variability. The difference between the 2 observers for measurements of the LV outflow tract was compared with the average of the 2 measurements for each patient. The mean difference between the measurements of the 2 observers was 0.04 cm^2 (95% confidence interval - 0.08 to 0.12 cm^2) for cross-sectional area.

Intraobserver Variability. The difference between the 2 measurements made by the same observer was compared with the average of the 2 measurements for each patient. The mean difference between the 2 measurements was 0.13 cm^2 (95% confidence interval - 0.01 to 0.25 cm^2) for cross-sectional area.

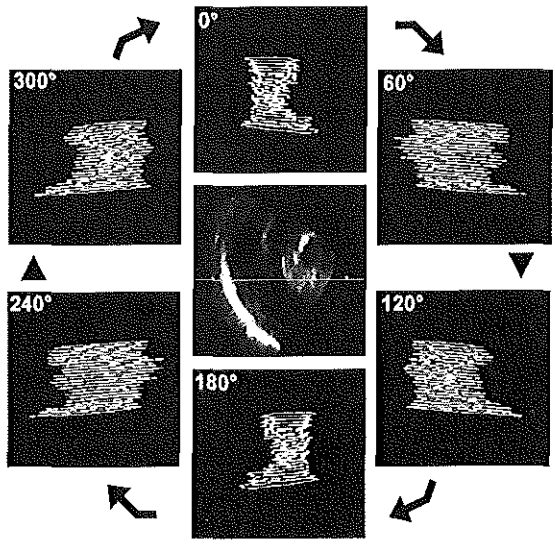

Figure 3

In this patients with hypertrophic cardiomyopathy, the wire frame display of the reconstructed left ventricular (LV) outflow tract is represented as observed from different viewpoints. The view at 0° corresponds to the cut-plane represented in the **central panel.** The images obtained after incremental 60° clockwise rotation are displayed in the corresponding panels. There is an eccentric and asymmetric shape of the LV outflow tract. From these images it is also apparent that the narrowing is localized at the middle-caudad part of the LV outflow tract and is mainly related to a reduction in the anteroposterior diameter.

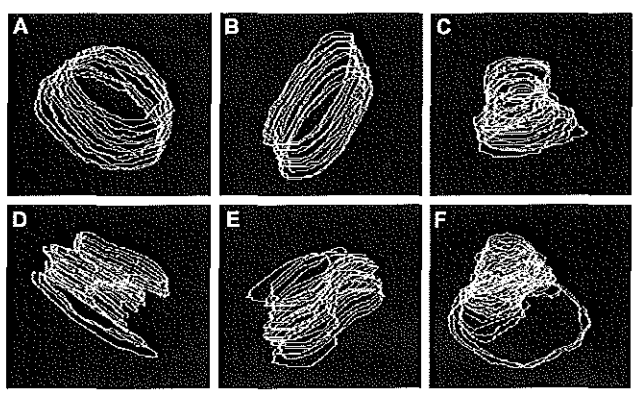

Figure 4

Three-dimensional reconstruction of the left ventricular (LV) outflow tract in a normal subject, with the same display as in Figure 3. Note the uniformity (indicated by the minimal variations of the diameters throughout the lenght of the LV outflow tract) as well as the symmetry (indicated by the similar diameters of individual cross-sections from different viewpoints) of the LV outflow tract.

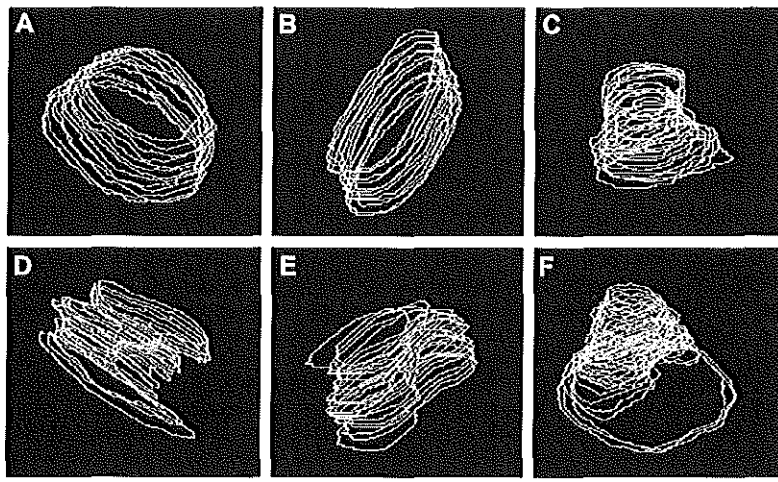

Figure 5

Three-dimensional reconstruction of the left ventricular outflow tract with wire frame display in normal subjects (A to C) and in patients with hypertrophic cardiomyopathy (D to F). The different irregular configuration of the left ventricular outflow tract in patients with hypertrophic cardiomyopathy can be evaluated.

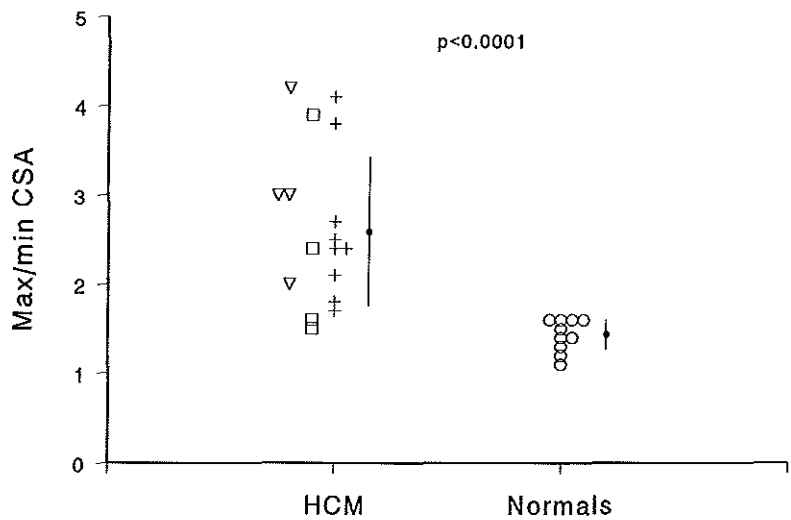

Figure 6

Ratio between maximal and minimal cross-sectional area (max/min CSA) of the left ventricular outflow tract in patients with hypertrophic cardiomyopathy (HCM) and in normal subjects. A high ratio indicates an eccentric shape of the left ventricular outflow tract. Symbols as in Figure 2.

DISCUSSION

Hypertrophic cardiomyopathy is a disease with a great individual variability and "no two hearts are alike" (13). The results of the present study indicate that 3-dimensional echocardiography allows visualization of the varied complex geometry of the LV outflow tract in patients with HC. With quantitative analysis of the 3-dimensional datasets, we demonstrated that in patients with HC the minimal cross-sectional area is smaller than that in normal subjects. In addition, most patients with HC have an irregular shape of the LV outflow tract as demonstrated by an eccentricity index of ≥ 1.5. In normal subjects, this index is always ≤ 1.6, indicating a uniform shape of the LV outflow tract, without significant variation of the cross-sectional area throughout its length. We have also demonstrated that the cross-sectional shape of the LV outflow tract is more elliptical in patients with HC than in normal subjects, as indicated by a higher ratio of max/min diameter measured at the plane of the minimal cross-sectional area. This finding is in agreement with the concept that in HC the hypertrophic ventricular septum narrows the LV outflow tract mainly along its anteroposterior diameter. Of interest, this asymmetry index was highest in patients with HC and obstruction of the LV outflow tract at rest. In contrast, in HC neither the minimal cross-sectional area nor the eccentricity index of the LV outflow tract separated this subgroup. This finding indicates that for similar cross-sectional area the asymmetry of the LV outflow tract plays an important role in determining the presence of significant obstruction at rest.

Patients who had undergone myectomy had a minimal cross-sectional area similar to other patients with HC, including those with obstruction (Figure 2). However, from Figure 7 it is clear that after myectomy the asymmetry index was lowest, indicating that the surgical remodelling of the LV outflow tract was adequate for the relief of the obstruction despite the finding that the cross-sectional area remained small compared with that in normal controls, and remained in the same range as that of the other HC patients without previous myectomy. Thus, in patients with HC, precordial 3-dimensional echocardiography has the potential to play a major role in tailoring the standard surgical resection of the interventricular septum to the individual patient's anatomy, which is crucial for safe and efficacious performance of myectomy, and also for evaluation of the results of surgery.

Evaluation of left ventricular outflow tract using three-dimensional echocardiography

Previous experience with 3-dimensional echocardiography for the evaluation of the LV outflow tract was based on morphologic analysis with volume-rendered display (14). In contrast, for quantitative analysis of the LV outflow tract performed in the present study, we selected a multitude of cut-planes ("anyplane echocardiography") and performed a parallel scanning of the LV outflow tract at

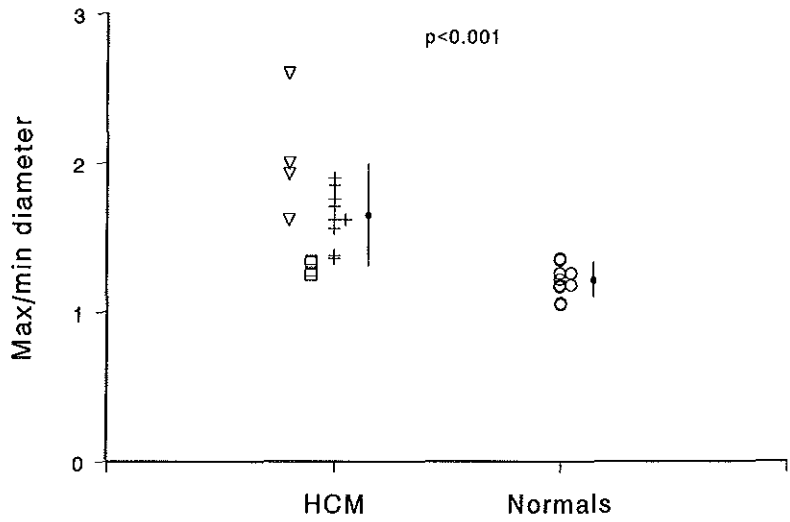

Figure 7

Ratio between maximal and minimal diameter (max/min diameter) measured at the cross-section of the left ventricular outflow tract with the minimal area in patients with hypertrophic cardiomyopathy (HCM) and in normal subjects. A high ratio indicates an asymmetric shape of the left ventricular outflow tract. Symbols as in Figure 2.

1 mm intervals ("paraplane echocardiography"). This rate of sampling of the dataset is similar to the analysis done with magnetic resonance imaging or computed tomography, and allows detailed spatial information (15). While some display modalities, such as volume rendering, are indicated more for representation of anatomical details (16-18), the wire frame display format appears particularly suited to 3-dimensional reconstruction of the cardiac cavities, where areas, volumes, size and shape can be adequately evaluated.

Limitations of three-dimensional echocardiography

In this study, patients were selected on the basis of high-quality images at 2-dimensional echocardiography, which yielded a success rate of 3-dimensional reconstruction of 100%. The same results cannot be expected from an unselected population where poor quality precordial images may prevent adequate quality of the reconstruction.

Echocardiographic images were acquired by an experienced technician and reconstruction was performed by a cardiologist after a learning period of > 50 studies. This previous experience of 3-dimensional echocardiography prevented artifacts in the 3-dimensional datasets, limited the time required both for acquisition and reconstruction, and resulted in a minimal variability for the measurements.

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Chapter 5

Spark Erosion Myectomy in Hypertrophic Obstructive Cardiomyopathy

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ABSTRACT

The design features of the cutting electrode and the electrical characteristics of a monopolar electrosurgical device were specially adapted for performing a septal myectomy in patients with hypertrophic obstructive cardiomyopathy. Both the cutting behavior and electrode design were found to facilitate myectomy.

INTRODUCTION

Septal myectomy is effective in relieving the symptoms of hypertrophic obstructive cardiomyopathy refractory to medical treatment. Although many procedures have been advocated for the surgical treatment of hypertrophic obstructive cardiomyopathy, most surgeons approach the septum through an aortotomy, but some surgeons add a ventriculotomy to improve exposure (1-16). A conventional myectomy can be technically demanding because of the midventricular location of the obstruction and the risk of disrupting septal integrity. The monopolar electrosurgical device called *spark erosion* was originally designed for intravascular applications (17). Impressed by its cutting characteristics, we constructed a modified device for use in septal myectomy.

MATERIAL AND METHODS

The cutting electrode is a quadrangular monopolar electrode composed of a metal foil (Fig 1). The electrode is covered with an electrically insulating synthetic resin, except for the cutting front side, which is 50 µm wide. The insulation is able to withstand temperatures up to 400°C. The cutting electrode is connected to a pencil with a malleable connection to allow the electrode to be adjusted with respect to the orientation of the handle. The width and depth of the myectomy depend on the dimensions of the electrode. Currently available (but not commercially) electrode sizes are 10 x 6.5 mm, 11 x 9 mm, and 14 x 9 mm (width x depth) (Fig 2). After an initial resection, the width and depth of the myectomy can be adjusted further. Because of the cutting characteristics, additional resections then can be done easily without fragmentation of the muscle tissue.

The generator is battery operated, with an output impedance of 60 ohm delivering an alternating square-wave voltage at a frequency of 500 kHz, with an effective value of 700 V (18). Direct current is blocked at both output terminals by capacitors to minimize stimulating side effects (19). Energy is applied during short pulses of 1.5 ms at a repetition rate of 12 Hz. These characteristics make possible a cutting speed through heart muscle of approximately 2 mm/s. Transparent Perspex (methacrylic acid) retractors were constructed in several sizes to optimize visibility and probe orientation during the procedure and to protect the aortic valve cusps, the mitral valve, and the anterior papillary muscle (Fig 3).

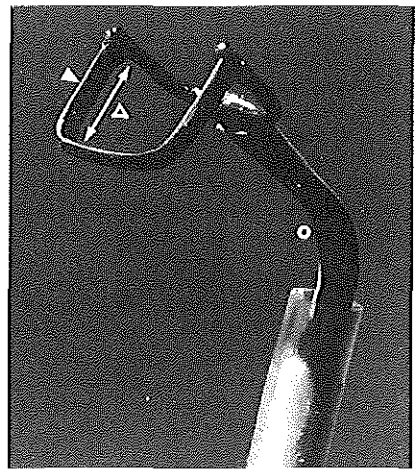

Figure 1

The electrode, showing some of the special features. The cutting front side (solid arrowhead) can be distinguished easily from the insulated part of the electrode. The electrode support (open arrowhead) limits the depth of the myectomy. The malleable connection (open circle) is shown here in a heavily bent position, but can be positioned to any angle from +90 degrees to -90 degrees.

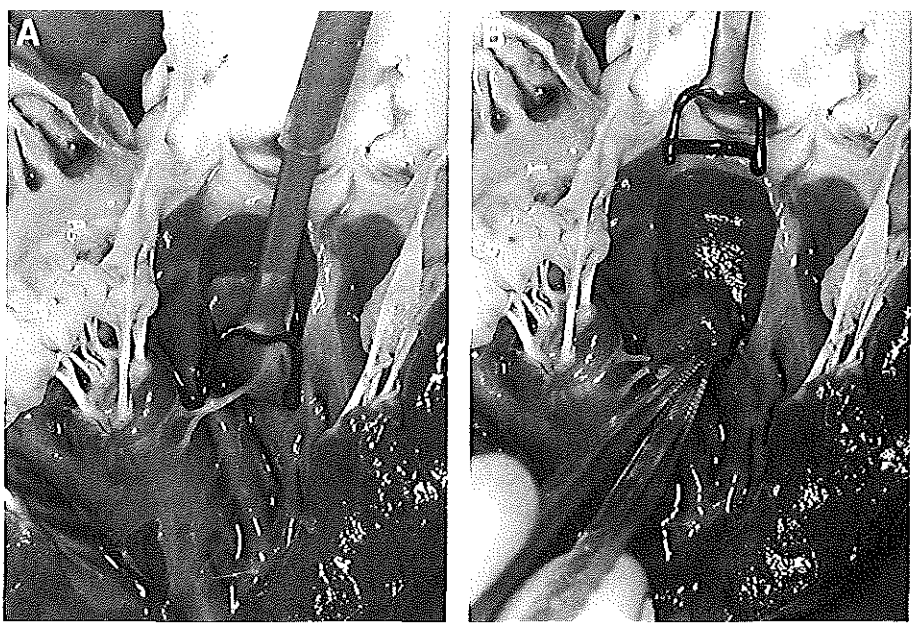

Figure 2

The myectomy procedure in a pig heart. (A) The electrode has been advanced a few centimeters. (B) The electrode is withdrawn. The surface of the trough is very smooth and no coagulation effects can be observed on visual inspection.

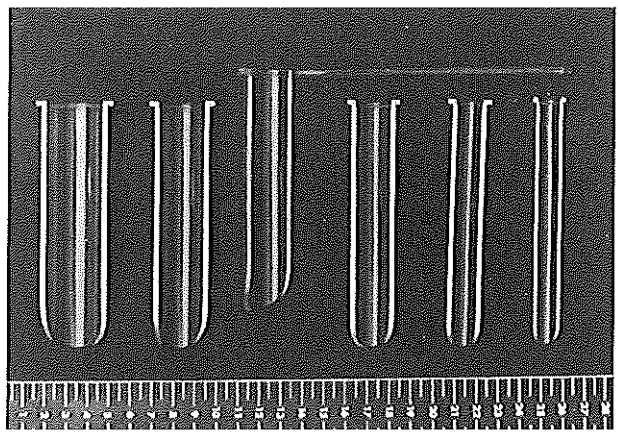

Figure 3
The set of transparent Perspex (methacrylic acid) retractors.

Between February 1987 and March 1993, spark erosion septal myectomy was performed in 18 patients with hypertrophic obstructive cardiomyopathy. All these patients were symptomatic despite optimal medical treatment. The demographic data, preoperative and postoperative pressure gradients, and preoperative and postoperative New York Heart Association functional class are summarized in Table 1. The peak systolic left ventricular outflow tract gradient was measured with continuous-wave Doppler echocardiography and expressed in millimeters of mercury. In 17 patients, the pattern of hypertrophy was graded as type III according to the classification scheme of Maron and colleagues (20). Patient 9 was classified as having type II hypertrophy.

Patients were operated on with cardiopulmonary bypass and moderate hypothermia. Cardiac arrest was induced by topical cooling and aortic root cardioplegia (St. Thomas' Hospital solution). The ventricular septum was approached via the ascending aorta through a hockey-stick incision.

Septal exposure and visualization were improved by passing the appropriate-sized transparent retractor through the aortic valve toward the left ventricular apex. Further improvement of exposure was obtained by exerting counterpressure on the external left ventricular wall. In 3 patients, there was an important mitral insufficiency that was not caused by systolic anterior motion of the anterior mitral valve leaflet.

Patient 3 had been treated for bacterial endocarditis 5 years preoperatively. After the myectomy, the valve was successfully repaired (closure of a tear in the anterior leaflet and commissuroplasty). Patient 9 had a destroyed anterior mitral valve leaflet as the result of recent bacterial endocarditis. At the time of operation, reconstruction of the valve seemed impossible and, in addition to the myectomy, the valve was replaced with a mechanical prosthesis (St. Jude Medical,

Table 1
Preoperative and postoperative characteristics.

Patient No.	Sex	Age (y)	Peak Gradient[a] (mm Hg)		NYHA Class		Additional procedures
			Preop	Postop	Preop	Postop	
1	F	51	36	8	III	II	...
2	F	61	80	6	III	II	...
3	F	19	62	?	III	I	Mitral valve repair
4	M	38	36	10	III	II	...
5	M	32	125	25	II	I	...
6	F	30	10	5	III	III	...
7	M	58	81	5	III	I	...
8	M	44	38	8	III	II	...
9	M	40	36	8	IV	I	Mitral valve prosthesis
10	F	36	100	50	II	I	...
11	F	36	108	36	III	I	...
12	F	61	100	8	III	I	Mitral valve prosthesis
13	F	24	80	10	III	I	Mitral valve patch
14	M	29	74	8	III	I	Mitral valve patch
15	M	67	92	6	III	I	Mitral valve patch
16	M	55	200	4	III	I	Mitral valve patch
17	M	43	148	7	III	I	...
18	M	31	140	16	III	I	Mitral valve patch

[a]Peak systolic left ventricular outflow tract gradient measured by continuous-wave Doppler echocardiography.
F = female; M = male; NYHA = New York Heart Association

St. Paul, MN). Patient 11 had severe mitral insufficiency stemming from a heavily calcified posterior mitral valve leaflet and annulus. After myectomy, the systolic anterior motion of the mitral valve decreased considerably but the mitral insufficiency persisted. An attempt to repair the valve failed, so this valve was also replaced with a mechanical valve (St. Jude Medical).

More recently, a patch technique has been used in selected patients in addition to the myectomy. Figure 4 shows the epicardial echocardiograms from a patient obtained before and after spark erosion myectomy and mitral valve patch placement.

The removed tissue was cut into 5-mm sections after formalin fixation, paraffin embedding, and staining with hematoxylin-eosin and elastic van Gieson. All specimens were evaluated by one pathologist and one surgeon. The depth of thermal injury was measured by multiplying the number of injured cells by the diameter of the hypertrophied myocytes.

RESULTS

Our clinical experience, spanning February 1987 to March 1993, consists of septal myectomy performed in 18 patients. There were no perioperative deaths. Two patients received a permanent pacemaker: in 1 patient, because of a newly formed atrioventricular conduction block; in the other, because of conduction abnormalities preoperatively, which was followed by periods of abnormal atrioventricular conduction postoperatively. Damage to the aortic or mitral valve was not encountered during or after the procedure, and no ventricular septal defects were created.

Light microscopic evaluation of the surgical specimens from the 18 patients revealed an uniform pattern (Fig 5). The depth of complete cell destruction by thermal energy was two to three cell layers; complete destruction of four or more cell layers was never seen. Between this zone and the "normal" myocardium was a zone of five to eight cell layers that showed hypereosinophilia, increased vacuolization, and, in some cells, contraction bands. The cross-sectional diameter of myocytes in the setting of hypertrophic obstructive cardiomyopathy is between 25 and 35 μm (normal, 10 to 15 μm). The maximum depth of the thermal injury is thus between 175 and 385 μm if the damage to the hypereosinophilic zone is irreversible. Otherwise, the depth of the thermal injury is between 50 and 105 μm.

Patient 5 died suddenly 8 months after the operation, and autopsy revealed a recent myocardial infarction. The surface of this patient's myectomy was covered with a thin and smooth connective tissue layer. His initial postoperative course had been uneventful.

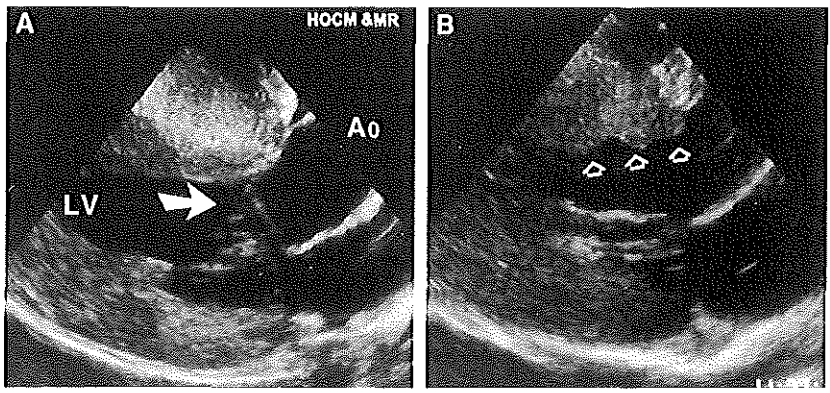

Figure 4

Epicardial echocardiograms in the left ventricular long axis, before (A) and after (B) spark erosion myectomy and patch plasty of the mitral valve. Systolic frames with an open aortic valve. (A) The closed arrow points to the area of systolic anterior motion of the anterior mitral valve leaflet. (B) The open arrows point to the site of myectomy. Systolic anterior motion has completely disappeared. (Ao = aorta; LV = left ventricle; HOCM = hypertrophic obstructive cardiomyopathy; MR = mitral valve regurgitation).

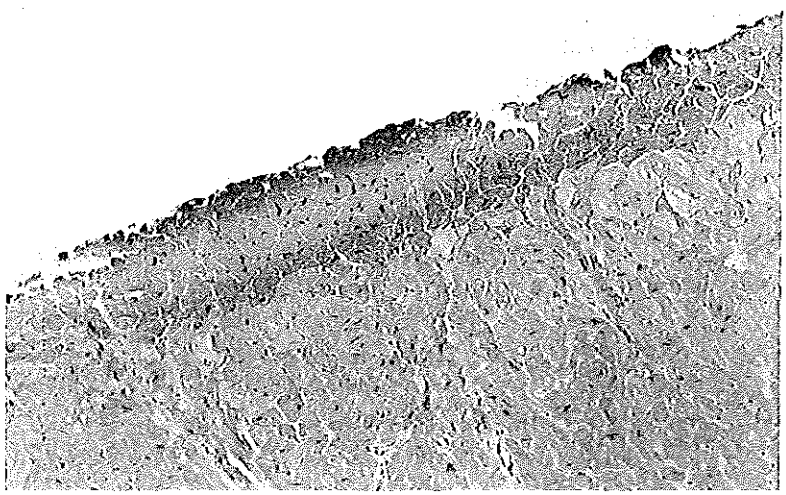

Figure 5

Representative photomicrograph of a resection specimen. The surface layer contains destroyed cells; the hypereosinophilic zone and the "normal" myocytes can be recognized easily. (Elastic van Gieson stain; x180).

COMMENT

Treatment of hypertrophic obstructive cardiomyopathy with an electrosurgical device is not new. A wire-loop electrode, connected to a standard electrosurgical device, was used by Dobell and Scott in 1960 (4). Cooley and colleagues (9) also used a loop cautery device in 1 patient. To our knowledge, none of these devices stood the test of time and most surgeons use a surgical scalpel or a scalpellike device for myectomy or myotomy. However, the depth of the myectomy is not precisely controlled with this instrument, and the fear of septal perforation may cause the depth of the septal resection to be inadequate. In performing a resection with a scalpel, small myocardial fragments and a rough myocardial surface may be a source of concern. Therefore, a more controlled way of performing septal myectomy is desirable.

In our opinion, the uncontrolled depth of thermal injury accomplished with traditional electrosurgical devices makes them unsuitable for use in septal myectomy. The coagulating properties of electrosurgical devices depend on the so-called crest factor (voltage peak divided by the voltage root mean squared).
We developed a dedicated electrosurgical unit and electrodes for septal myectomy possessing minimal coagulation effects. Compared with the properties of readily available electrosurgical units, our device has a much lower output impedance in combination with a high effective voltage. This minimizes the warm-up time needed to form a steam envelope around the electrode, which is required before sparking and cuttings can commence.

With our device, the crest factor reaches its theoretical minimal value of 1, rather than the usual 1.4 to 2 seen in conventional electrosurgical devices, by applying an unmodulated square-wave alternating voltage. These specifications allow application of a brief cutting pulse, and this plus the low repetition rate maintain highly effective cutting with a minimal accumulation of thermal energy. In addition, the electrical insulation of the electrodes improves the cutting behavior by minimizing the cutting area and preventing the backward arcing of sparks to areas already passed. Smoke and vapor production during cutting are negligible. The low cutting speed of 2 mm/s allows the electrode to be accurately guided during the procedure. Compared with a wire-loop electrode, the quadrangular electrode is much stronger.

The height of the electrode supports limits the depth of the myectomy to the electrode size selected, thereby reducing the risk of creating a ventricular septal defect. The malleable connection of the electrode to the pencil allows for the electrode to be precisely adjusted with respect tot the orientation of the handle.
No patient in the present series died and no ventricular septal defect was caused by the procedure. In the study group, 1 patient (5.5%) suffered a new atrioventricular conduction block. This does not seem excessive in light of the experience described in the literature (21-23). Light microscopic reevaluation revealed there was no difference between this patient and the other patients with respect

to the depth of thermal injury. Most likely this complication was related to a surgical technical imperfection, rather than to the electrical device.

In conclusion, both the design features and the cutting characteristics of the spark erosion device facilitate the performance of myectomy in patients with hypertrophic obstructive cardiomyopathy.

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Chapter 6

Initial Results of Combined Anterior Mitral Leaflet Extension and Myectomy in Patients With Obstructive Hypertrophic Cardiomyopathy

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ABSTRACT

Objectives. The purpose of this study was to describe the clinical and functional results of combined anterior mitral leaflet extension and myectomy in patients with hypertrophic obstructive cardiomyopathy.

Background. Septal myectomy is the most commonly performed surgical procedure in patients with hypertrophic cardiomyopathy and left ventricular outflow tract obstruction. Because of the role of the mitral valve in creating the outflow tract gradient, mitral valve replacement or plication is performed in selected cases in combination with myectomy, often with better haemodynamic results than those of myectomy alone. Mitral valve leaflet extension, in which a glutaraldehyde-preserved autologous pericardial patch is used to enlarge the mitral valve along its horizontal axis, is a novel surgical approach in patients with hypertrophic obstructive cardiomyopathy.

Methods. Eight patients with hypertrophic obstructive cardiomyopathy were treated with mitral leaflet extension and myectomy. Pre- and postoperative data (New York Heart Association functional class, number of drugs prescribed, width of the interventricular septum, severity of the mitral valve insufficiency, severity of the systolic anterior motion of the mitral valve and the outflow tract gradient) were compared with 12 patients undergoing myectomy alone.

Results. Preoperative evaluation demonstrated that mitral insufficiency and systolic anterior motion of the mitral valve were more severe in the group undergoing mitral valve extension ($p<0.001$ and $p<0.05$ respectively). There were no deaths associated with surgery. Two patients, both treated by myectomy alone, died during the follow-up period. Postoperatively, patients treated with mitral valve extension had less mitral insufficiency ($p<0.005$), less residual systolic anterior motion ($p<0.01$), greater improvement in New York Heart Association functional class ($p=0.05$) and greater reduction in the number of drugs ($p<0.005$) and in septal thickness ($p<0.05$).

Conclusions. Mitral leaflet extension in combination with myectomy is a promising new surgical approach that may provide superior results to those of myectomy alone. Further studies are needed to determine the clinical value of this procedure.

INTRODUCTION

Surgery for hypertrophic cardiomyopathy is generally performed in patients who have a significant left ventricular outflow tract gradient and severe symptoms despite maximal medical therapy (1-4). The most commonly performed procedure is septal myectomy (the Morrow procedure) (5), which usually results in an adequate reduction in the obstruction to outflow (6-9). Because of the contribution of the mitral valve in generating the outflow tract gradient (10-13), mitral valve replacement alone or in combination with myectomy is also per-

formed, often with better hemodynamic results than those of myectomy alone (8,9,14,15). However, the long-term risks of thromboembolism and hemorrhage associated with prosthetic valves and the need for anticoagulant therapy make mitral valve replacement an unattractive option for many patients with hypertrophic cardiomyopathy, who are frequently young and physically active (1,16).

Mitral leaflet plication in combination with myectomy has recently been proposed (17) as a successful alternative to mitral valve replacement in hypertrophic cardiomyopathy. Another alternative procedure is anterior mitral leaflet extension, one of several valve repair techniques developed by Carpentier (18) and Chauvaud et al.(19), in which a glutaraldehyde-preserved autologous pericardial patch is used to enlarge the mitral valve along its horizontal axis. The application of mitral leaflet extension in patients with obstructive hypertrophic cardiomyopathy has not been reported previously. In this report we present the immediate results and early follow-up data (up to 4 years) in 8 patients treated with combined anterior mitral leaflet extension and myectomy. Results are compared with those of 12 patients undergoing myectomy alone. The possible mechanisms of action of mitral leaflet extension are also discussed.

METHODS

Indications

Indications for surgery in our Hypertrophic Cardiomyopathy Clinic include a rest or provokable left ventricular outflow tract gradient ≥50 mmHg and persistent symptoms despite an adequate trial of medical therapy, consisting of beta-adrenergic blocking agents, calcium channel blocking agents, or both. Preoperative echocardiography and cardiac catheterization for invasive hemodynamic measurements and angiography are performed in all patients for whom surgery is proposed. Postoperative assessment includes repeat echocardiography 1 week and again several months after operation. Repeat cardiac catheterization is not routinely performed unless clinically indicated.

The decision to perform anterior mitral leaflet extension in conjunction with myectomy is made at the time of operation if, in the surgeon's view, myectomy alone is likely to yield a suboptimal result. Conditions that favor inclusion of a valve procedure include atrial fibrillation, limited septal hypertrophy, marked systolic anterior motion of the mitral valve and significant mitral regurgitation (1,4,5).

Patients

Between 1986 and 1988, the myectomy procedure was performed by two surgeons (L.A.H. and an older colleague who taught L.A.H. the myectomy procedure). From 1988 on, all operations, including all mitral valve procedures, were carried out by a single surgeon (L.A.H.). A total of 20 patients underwent septal myectomy; 8 of whom underwent concomitant anterior mitral leaflet extension.

The primary reason for performing mitral leaflet extension was mitral regurgitation and systolic anterior motion of the mitral valve of particular severity; one patient had chronic atrial fibrillation associated with significant mitral regurgitation.

Surgical technique

Open chest epicardial echocardiography is used extensively during the procedure for ongoing assessment of septal thickness, systolic anterior motion of the mitral valve and detailed structure of the mitral leaflets. Continuous wave and Doppler color echocardiography are used to quantify the outflow tract gradient and mitral regurgitation and their responses to physiologic manipulation such as volume infusion and administration of inotropic agents. The images are registered on video-tape for off-line analysis. Patients are operated on with standard techniques of cardiopulmonary bypass with moderate hypothermia and crystalloid cardioplegic arrest (St. Thomas's solution). An autologous pericardial patch is harvested, trimmed of fat and extraneous tissue, immersed for 10 min in 0.62% glutaraldehyde and then placed in a normal saline bath. The aorta is opened by an oblique incision and septal myectomy is performed to the left of an imaginary line through the nadir of the right aortic cusp, with a locally designed electrocautery device, described in detail elsewhere (20). In brief, the cutting electrode of the device is a quadrangular monopolar electrode composed of a metal foil. The cutting electrode is connected to a pencil with a malleable connection to allow the electrode to be adjusted with respect to the orientation of the handle. The width and depth of the myectomy depend on the dimensions of the electrode. Currently, three different electrode sizes are available: 10 x 6.5, 11 x 9, and 16 x 9 mm (width x depth). The procedure is guided by intraoperative echocardiography with the removal of additional septal myocardium if necessary.

Next, anterior mitral leaflet extension is performed according to the method described by Chauvaud et al.(19), with the following modifications: the pericardial patch harvested at the beginning of the procedure is cut to an oval shape approximately 3 cm wide and 2.5 cm long. The anterior mitral leaflet is incised longitudinally from its subaortic hinge point to the rough zone. The patch is sewn onto the ventricular surface of the leaflet at the site of the incision by using three running polypropylene monofilament sutures (Fig.1). Immediate results are assessed by intraoperative echocardiography after weaning from cardiopulmonary bypass, with particular attention to residual systolic anterior motion, mitral regurgitation and the left ventricular outflow tract gradient. Reinstitution of bypass for the purpose of modifying the surgical result was not required in this cohort of patients.

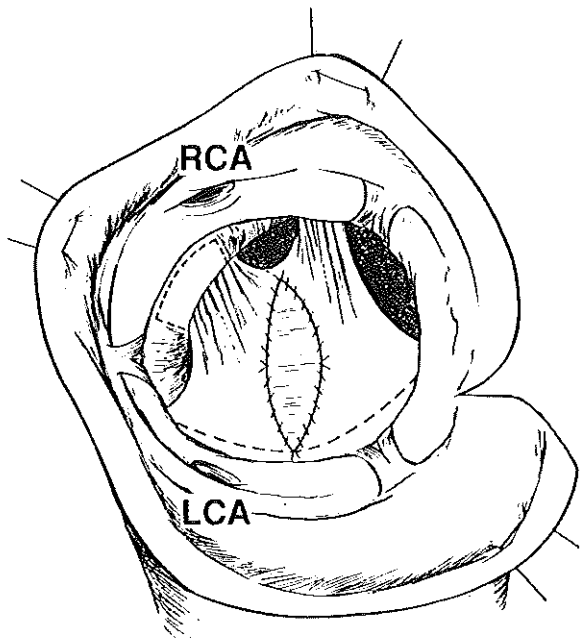

Figure 1

Schematic representation of mitral leaflet extension. The pericardial patch is clearly seen in the middle of the drawing, within the anterior mitral leaflet. The area of the myectomy is seen in the interventricular septum, demarcated by dots. The ostia of both the left (LCA) and right (RCA) coronary arteries are indicated for orientation purposes.

Data collection and analysis

All patients were assessed clinically preoperatively and postoperatively by the same physician (F.J.T.C.), who was also responsible for their medical management. Transthoracic echocardiographic data were reviewed by two physicians who had access to data on the patients' histories and surgical procedures. Interventricular septal thickness was determined by two-dimensional echocardiography in the parasternal short axis view at the site of the myectomy. Mitral regurgitation was assessed by color Doppler echocardiography and graded on a scale of 0 to 4+. Systolic anterior motion of the mitral valve was assessed from the two-dimensional images and graded as 0 (absent), 1+ (mild: minimal mitral-septal distance >10 mm during systole), 2+ (moderate: minimal mitral-septal distance ≤10 mm during systole) or 3+ (marked: brief or prolonged contact between mitral valve and septum) (21). Peak left ventricular outflow tract gradient at rest or with provocation was estimated with Doppler echocardiography by using the modified Bernoulli equation, $P = 4V^2$, where P is pressure gradient and V is Doppler-determined blood velocity. When echocardiographic data were inadequate or unavailable, catheterization data were used. Intraoperative epicar-

dial echocardiograms were performed in all patients before and after cardiopulmonary bypass. The recordings of those patients who underwent anterior mitral leaflet extension were available for futher analysis.

The left ventricular outflow tract and mitral valve leaflet areas were calculated according to previously described methods (21,22). In brief, the left ventricular outflow tract area is calculated in the short axis view at the level of the mitral valve at the onset of systole. The first frame in the cardiac cycle (onset of ventricular systole) when the mitral valve appears closed is taken for analysis.

On the stop frame the innermost margins of the outflow tract are traced on the screen and the demarcated area is calculated by utilizing an off-line computer and a dedicated software program (23). The mitral valve leaflet area is derived from the mitral valve opening area (MVOA). The latter is measured by tracing the innermost margins of the mitral valve in the parasternal short-axis view at the point of maximal opening. The mitral valve leaflet area (MLA) is then calculated by using the formula MLA = 2.19 + 3.06 x MVOA validated by Klues et al. (22).

Statistics

Data were expressed as mean value ± SD. The Wilcoxon test was used to compare clinical characteristics before and after operation of the patients with combined myectomy and anterior mitral valve extension and those with myectomy alone. The characteristics compared were age, New York Heart Association functional class, number of drugs prescribed, width of the interventricular septum, severity of systolic anterior motion, severity of mitral insufficiency and left ventricular outflow tract gradient.

RESULTS

Patient characteristics and surgical outcome

Preoperative and postoperative clinical and transthoracic echocardiographic characteristics of the 8 patients undergoing myectomy combined with anterior mitral valve extension and the 12 patients undergoing myectomy alone are presented in Table 1. The postoperative clinical and echocardiographic data refer to the latest patient follow-up. There were no deaths or serious complications associated with the surgical procedures. Patients 4 and 6 in the group with myectomy alone died during follow-up: Patient 4 died of congestive heart failure 6 years after operation and Patient 6 died suddenly 2 years after the procedure.

Statistical differences between the two groups are presented in Table 2. Preoperative mitral regurgitation and systolic anterior motion of the mitral valve were worse ($p<0.001$ and $p<0.05$, respectively) in the patients who underwent combined myectomy and mitral valve extension than in patients who underwent myectomy alone. Nonetheless, postoperative residual mitral regurgitation and systolic anterior motion were significantly better ($p<0.005$ and $p<0.01$, respec-

Table 1

Preoperative and postoperative clinical and transthoracic echocardiographic data of patients with hypertrophic obstructive cardiomyopathy treated with either combined myectomy and mitral valve extension or myectomy alone.

Patient	Age/Sex	OK-Date	NYHA		Med.		IVS (mm)		MR		SAM		Peak LVOT-gradient(mmHg)	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
MM/MLE														
#1	57 M	5/91	3	1	A,C,D,W	C,W	27	20	3+	1+	3+	0	92	5
#2	25 F	9/91	3	1	B	-	30	20	3+	1+	3+	1+	58	25
#3	29 M	2/92	3	1	B,C	-	35	25	3+*	0	3+	0	74	9
#4	54 M	1/93	2	1	B	-	22	15	3+	0	2+	0	100	9
#5	31 M	3/93	3	1	C	-	22	15	2+	1+	3+	0	112	36
#6	35 F	6/94	2	1	C	C	29	20	2+	0	3+	0	121	16
#7	59 M	6/94	3	1	B	-	22	18	2+	0	3+	0	100	6
#8	44 F	6/94	2	1	C	C	20	15	3+	1+	3+	1+	100	36
MM alone														
#1	54 M	3/86	3	1	C	C,W	28	24	2+*	1+	2+	2+	80*	16
#2	29 F	8/86	3	2	C	A	30	26	2+*	3+	3+	3+	60	50
#3	52 F	2/87	3	2	C,W	B,D,W	27	18	1+*	1+	2+	0	100	7
#4	61 F	12/87	3	2	B,C	A,D,I,W	26	21	1+	0	1+	0	80*	5
#5	38 M	7/88	3	2	C	B	30	25	1+	0	3+	1+	81*	7
#6	32 M	11/88	2	1	C	-	24	18	2+	1+	3+	3+	160	41
#7	30 F	5/89	3	3	C	B,C,D	25	19	1+	0	1+	0	36	4
#8	38 M	7/89	2	1	C	C	20	20	0	0	1+	1+	81	5
#9	44 M	3/90	3	2	B	B	33	30	0	0	2+	1+	50	12
#10	36 F	6/90	2	1	C	A	30	22	0	0	3+	0	100	36
#11	35 F	4/91	3	2	B	B	20	18	1+	2+	3+	3+	70	64
#12	44 F	2/93	3	1	B,C,W	B,C,W	31	27	0	1+	1+	1+	147	25

*assessed by angiography. A = antiarrhythmic agents; B= beta-adrenergic blocking agents; C = calcium channel blocker: D = diuretic drug, F = female, I = angiotensin-converting enzyme inhibitor; IVS = interventricular septum; LVOT = left ventricular outflow tract; M = male; MM = myectomy; MM/MLE = myectomy and mitral valve extension; MR = mitral regurgitation, NYHA = New York Heart Association functional class; Post = postoperative; Pre = preoperative; Pt = patient; SAM = systolic anterior movement; W = warfarin; - = none.

Table 2
Baseline and postoperative characteristics in patients treated by myectomy and mitral valve extension and in patients treated by myectomy alone.

	MM/MLE	MM	p value
Baseline			
Age (yr)	42 ± 10	41 ± 10	0.94
NYHA class	2.6 ± 0.5	2.8 ± 0.5	0.59
Number of drugs	1.5 ± 1.1	1.3 ± 0.7	0.96
IVS width (mm), (range)	26 ± 5, (20-35)	27 ± 4, (20-33)	0.56
MR* (grade)	2+/3+	0/2+	< 0.001
SAM** (grade)	2+/3+	1+/3+	< 0.05
LVOT gradient (mm Hg)	95 ± 20	87 ± 36	0.33
Postoperative			
NYHA class	1	1.7 ± 0.7	0.05
Number of drugs	0.5 ± 0.8	1.8 ± 1.2	< 0.005
IVS width (mm), (range)	19 ± 4, (15-25)	22 ± 4, (18-30)	< 0.05
MR* (grade)	0/1+	0/3+	< 0.005
SAM** (grade)	0/1+	0/3+	< 0.01
LVOT gradient (mm Hg)	18 ± 13	23 ± 20	0.35

* Range of mitral regurgitation observed in the two respective patient groups.
** Range of systolic anterior movement observed in the two respective patient groups.
Data are presented as mean value ± SD, range or grade. IVS = width of the interventricular septum; other abbrevations as in Table 1.

tively) in the group with the combined procedures. Moreover, this group had greater improvement in functional class ($p=0.05$) and a greater reduction in both the number of drugs prescribed ($p<0.005$) and the width of the interventricular septum ($p<0.05$).

Mitral valve measurements
The mitral valve leaflet and left ventricular outflow tract areas of patients undergoing combined myectomy and mitral valve extension were calculated from intraoperative epicardial echocardiographic data according to previously descibed methods. The mean mitral valve leaflet area of 15.9 ± 2.0 cm^2 is considerably above mean values for the general population (< 12 cm^2). All patients belonged to a subset of patients with hypertrophic cardiomyopathy, as described by Klues et al. (24), with enlarged mitral leaflets, relatively large left ventricular outflow tract area (≥2.0 cm^2 [mean 2.9 ± 0.7 cm^2]) and a distinctive sharp-angled bend of the anterior mitral leaflet.

By transthoracic echocardiography, the anterior mitral valve extension procedure did not induce obvious changes in the length or thickness of the anterior

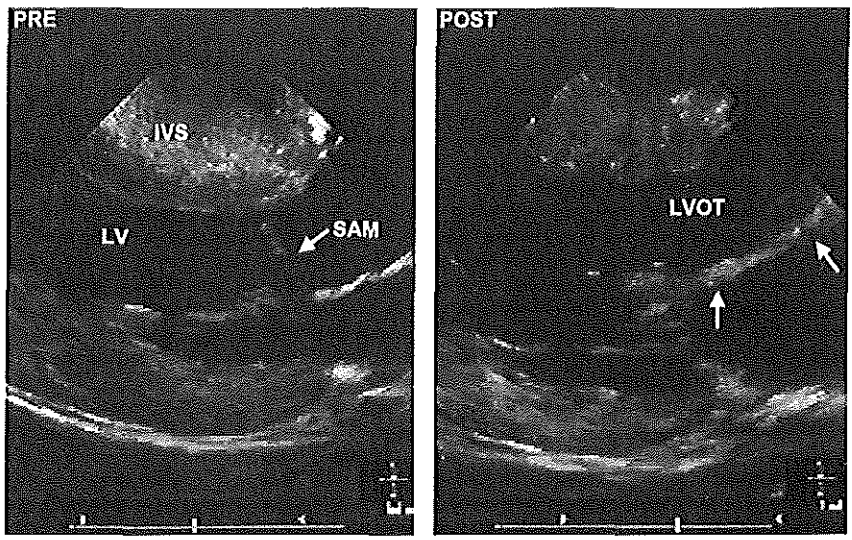

Figure 2

Two-dimensional, long-axis transthoracic echocardiograms from the same patient before and after combined anterior mitral leaflet extension and myectomy. Both are systolic frames from the same point in the cardiac cycle. **Left,** Preoperative image, demonstrating marked systolic anterior movement of the distal anterior mitral leaflet (SAM, single arrow). **Right,** Postoperative image, showing no significant systolic anterior movement of the valve. Note also the widened outflow tract after myectomy and the probable position of the pericardial patch (double arrows). The mitral valve itself is not demonstrably longer or thicker, although differences in technical quality prevent direct comparison. IVS = interventricular septum; LV = left ventricle; LVOT = left ventricular outflow tract.

mitral leaflets, although subjectively they appeared somewhat less flexible. Figure 2 shows a typical postoperative transthoracic echocardiogram without any residual systolic anterior motion of the mitral valve and a widened left ventricular outflow tract.

DISCUSSION

Anterior mitral leaflet extension is a novel surgical approach to the treatment of obstructive hypertrophic cardiomyopathy. The procedure entails grafting a patch of autologous pericardium onto the center portion of the anterior mitral leaflet, effectively increasing the size (mainly the width) of the leaflet. In the eight patients who underwent anterior mitral leaflet extension in combination with septal myectomy, the extension procedure was safe and effective in abolishing or greatly reducing systolic anterior movement of the mitral valve and mitral regurgitation and in lessening symptoms. Patients undergoing the combined procedure had significantly greater improvement in functional class and required

fewer number of drugs postoperatively than did the 12 patients undergoing myectomy alone.

The reduction of septal thickness in both groups is not in contrast with the results of other institutions (25-27). Nevertheless, our approach may not be as agressive as the double myotomy-myectomy procedure reported by Morrow (28). However, overzealous septal myectomy must be avoided, because it may cause complete haert block, septal defect or increased mortality (29-31). The optimal myectomy procedure reduces septal thickness to a minimum without augmenting morbidity and mortality. Starting in 1972 we performed myectomy with or without mitral valve extension in 46 patients with only 1 in-hospital death. We cannot exclude that these good results were obtained because of a less agressive septal myectomy.

Although the principal benefit of anterior mitral leaflet extension appears to be the abolition of systolic anterior movement and mitral regurgitation, the precise mechanism of this effect is not clear. In fact, the idea of enlarging the anterior mitral leaflet is counterintuitive, given the awareness of the role that the mitral valve plays in producing the systolic anterior movement.

Mechanisms of outflow tract obstruction

Outflow tract obstruction in patients with hypertrophic cardiomyopathy results from a combination of left ventricular outflow tract narrowing, due to basal septal hypertrophy, and systolic anterior motion of the mitral valve (1,11,32). Several mechanisms for systolic anterior motion have been proposed: 1) the Venturi mechanism, by which the hypertrophied septum and anterior displacement of the mitral valve create outflow tract narrowing, increased flow velocity, decreased pressure above the valve and, consequently, the development of systolic anterior motion, partly due to the abnormal laxity of the mitral valve (10,12-14,22,24,32-35). 2) Anatomic alterations in the mitral valve apparatus. These may predispose to systolic anterior motion due to flow drag, the combination of increased mitral leaflet area, length and laxity and anterior displacement of the papillary muscles allowing the mitral leaflets to protrude into the left ventricular outflow tract and thus exposing them to flow drag. 3) Inward displacement of the papillary muscles toward one another. This displacement can produce relative chordal slack in the central leaflet portions; consequently, the systolic anterior motion will be greatest in the center of the valve (36).

Recently a combined pathologic and echocardiographic review by Klues et al. (24) confirmed that an enlarged mitral valve is present in a subset of patients with hypertrophic cardiomyopathy. These investigators classified patients with obstructive hypertrophic cardiomyopathy into two categories: 1) patients with an enlarged mitral valve, relatively large left ventricular outflow tract area and distinctive sharp-angled bend of the anterior leaflet (typical systolic anterior motion) and 2) patients with a normal-sized mitral valve, small outflow tract area and "atypical" systolic anterior motion. All of our patients treated by the com-

bined myectomy-mitral valve extension technique belonged to the subset of patients with an enlarged mitral valve. This finding is important because an enlarged mitral valve may predispose to residual systolic anterior motion of the valve after myectomy, resulting in a suboptimal outcome with persisting outflow tract obstruction.

Possible mechanisms of action of mitral leaflet extension

How, then, does further increasing the size of the anterior mitral leaflet with a pericardial patch abolish the systolic anterior motion? Both the Venturi mechanism and the flow drag of the leaflets described earlier may be counteracted by anterior mitral leaflet extension. The distal end of the patch lies in the proximity of the bending point of the anterior leaflet. The patch may merely serve to stiffen the leaflet, making it less lax and less likely to buckle in the presence of Venturi forces or flow drag forces. Subjectively, the anterior mitral leaflets after combined myectomy and mitral valve extension did appear less "floppy" by two-dimensional echocardiography, without compromise in leaflet mobility or coaptation.

The mitral valve extension technique increases the width (horizontal dimension), not the length (vertical dimension), of the anterior leaflet. Conceivably, increasing the width of the anterior mitral leaflet could erect the relative lax chordae attaching central portions of the mitral leaflet and thus prevent buckling of central parts of the valve.

Currently we perform the mitral valve elongation procedure in patients undergoing surgery who are likely to have suboptimal results from myectomy alone. These may include patients with particulary severe systolic anterior motion of the mitral valve and mitral regurgitation, as well as patients with chronic atrial fibrillation or limited septal hypertrophy. In retrospect, all of our patients who underwent combined myectomy and anterior mitral valve elongation belonged to the subset of patients with an abnormally enlarged anterior mitral leaflet surface area. Whether equal results can be achieved in patients with a normal-sized mitral valves is unknown.

SUMMARY

Adequate and predictable relief of outflow tract obstruction is the primary goal of surgery for hypertrophic cardiomyopathy. Multiple techniques, including simple septal myectomy, extended myectomy using intraoperative echocardiography and multiple periods of cardiopulmonary bypass (31), mitral valve replacement (1,8,9) and mitral leaflet plication (17), are currently available to the cardiac surgeon. Anterior mitral valve extension is a promising new surgical approach to obstructive hypertrophic cardiomyopathy that may provide more satisfactory results than those of myectomy alone. The mitral valve extension procedure is known to be a safe and reliable therapy in other conditions such as rheu-

matic valve disease and bacterial endocarditis with perforation (19). Further experience needs to be gained in obstructive hypertrophic cardiomyopathy before its widespread use can be recommended.

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Chapter 7

Decreased Coronary Flow Reserve in Hypertrophic Cardiomyopathy Is Related to Remodelling of The Coronary Microcirculation

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ABSTRACT

Background. Ischemia occurs frequently in hypertrophic cardiomyopathy (HCM) without evidence of epicardial stenosis. This study evaluates the hypothesis that the occurrence of ischemia in HCM is related to remodelling of the coronary microcirculation.

Methods and Results. End-diastolic septal wall thickness was significantly increased in patients with HCM (25.8 ± 2.9 mm) in comparison with cardiac transplant recipients (control subjects: 11.4 ± 3.0 mm; $p< 0.05$). Although the diameter of the left anterior descending coronary artery (LAD) was similar in both groups (3.0 ± 0.8 versus 3.0 ± 0.5 mm, p= NS), the coronary resistance reserve ($CRR= CRR_{basal}/CRR_{hyperemic}$), corrected for extravascular compression (end-diastolic left ventricular pressure), was reduced to 1.5 ± 0.6 in HCM ($p< 0.05$; control, 2.6 ± 0.8). Arteriolar lumen (AL) divided by wall area was lower in HCM (21 ± 5% versus 30 ± 4%; $p< 0.05$), and capillary density tended to decrease (from 1824 ± 424 to 1445 ± 513 mm^2, p= 0.11) in HCM. CRR was linearly related to normalized AL according to the formula: CRR = 0.1 AL - 0.45 ($r=0.57$; $p< 0.05$). Further analysis revealed that CRR, AL, and capillary density were all linearly related to the degree of hypertrophy.

Conclusions. Decrements in CRR were related to changes of the coronary microcirculation. Both the decrease in CRR and these changes in the coronary microcirculation were related to the degree of hypertrophy. All these factors might contribute to the well-known occurrence of ischemia in this patient group.

SELECTED ABBREVIATIONS AND ACRONYMS

AL	=	normalized arteriolar lumen
CFR	=	coronary flow reserve
CRR	=	coronary resistance reserve
HCM	=	hypertrophic cardiomyopathy
HTx	=	cardiac transplant
LAD	=	left anterior descending coronary artery

INTRODUCTION

Anginal symptoms and signs of ischemia occur frequently in patients with HCM without detectable lesions of the major epicardial arteries (1-5), suggesting that the presence of ischemia is the result of abnormalities of the coronary microcirculation. Indeed, postmortem analysis of HCM hearts showed the existence of arterioles with abnormally thick walls (6,7). Furthermore, in experimentally induced hypertrophy, it has been shown that the hypertrophic process is accompanied not only by decrements in coronary flow reserve (CFR) but also by structural changes in the coronary microcirculation (coronary remodelling), including

a decreased capillary density (8-10). The resulting increased diffusion distances for oxygen and the disturbed perfusion of the capillary bed have been forwarded as an explanation for ischemia (8-10).

Although the CFR is decreased in HCM, in accordance with the findings of experimentally induced hypertrophy (9,10), it is unknown at present whether the decreased CFR is related to the abnormal arterioles and whether a decrease in capillary density accompanies this decrease in AL. To that end, we measured CFR in combination with a quantitative analysis of AL, wall area and capillary density in myocardial tissue obtained during surgery (HCM) and obtained from endomyocardial biopsies (HTx).

METHODS

Subjects and Protocol

Studies were performed in a group of patients with hypertrophic obstructive cardiomyopathy (HCM; n= 10) who were referred for cardiac catheterization. The control group consisted of asymptomatic cardiac transplant recipients (HTx group; n= 8) undergoing follow-up coronary angiography after transplantation. Informed consent was obtained from all patients. Patients in the HCM group were symptomatic, New York Heart Association (NYHA) class II or III, despite β-blockade therapy (n= 5) or therapy with calcium antagonists (n= 5). These patients were considered candidates for surgery (myotomy/myectomy). Medical therapy was continued in both groups. Right heart catheterization was performed with a 7F balloon-tipped flow-directed thermodilution catheter. A 7F temporary pacemaker was positioned into the right atrium. Left heart catheterization was carried out, after which left ventricular angiography and coronary arteriography were performed with standard techniques. A 0.014-in Doppler guidewire with a floppy distal end (Cardiometrics,Inc) was introduced through a 8F guiding catheter and positioned at the midsegment of the LAD to measure Doppler flow velocity at rest and after hyperemia. In both groups, hearts were paced at a constant heart rate of 100 bpm to avoid metabolic vasodilatation during determination of the CFR. After optimization of the settings of the velocity signal and 3 to 5 minutes after intra coronary injection of a bolus of 2 to 3 mg isosorbide dinitrate, baseline recordings of flow velocity and perfusion pressure were collected and digitized at a sample rate of 125 Hz, for off-line analysis. Maximal hyperemia was induced by an intracoronary bolus injection of 18 μg adenosine (10).

Doppler measurements

The sample volume of the Doppler wire was positioned at a distance of 5.2 mm from the transducer and was ≈2.25 mm wide. After power spectral analysis based on a fast Fourier transform algorithm, the maximal Doppler shift (kHz) was automatically tracked and converted to the instantaneous velocity values

(cm/s). CFR was defined as hyperemic devided by basal velocity (V_{cor}). Coronary Resistance was defined as $(P_{ao}- P_{ed})/V_{cor,}$ where P_{ao} is aortic pressure and P_{ed} is end-diastolic pressure. P_{ed} was subtracted to account for increments in extravascular compression. CRR was defined as the ratio of basal divided by over hyperemic resistance.

Quantitative Angiographic Measurements
A validated on-line analysis system operating on digital images [ACA-DCI, Philips (11)] was used during the catheterization procedure. With this system, the end-diastolic diameter of the LAD was determined in the segment of the LAD in which the sample volume of the Doppler wire was located.

Echocardiographic measurements
Two-dimensional echocardiographic studies were performed (HP Sonos 1500) with the heart being visualized from standard cross-sectional planes while images were recorded on videotape (VHS) for off-line analysis. Septal wall thickness was measured in diastole from both the parasternal short-axis and long-axis views. From the recordings on videotape, representative stop-frames from the various cross-sectional planes were acquired to determine septal wall thickness with the aid of a computer and a dedicated software program. To obtain an average for septal wall thickness the various cross-sectional planes were pooled. One patient from the control group was not analysed due to insufficient image quality. Thickness of the septal wall for the HCM and the control groups was defined as the degree of hypertrophy.

Histological measurements
The myocardial tissues from the HCM group (n= 9) and from the control group (n= 8) were obtained from surgical myectomy (left ventricular septal tissue; weight, 0.3 to 1 g) and myocardial biopsies (right ventricular septal tissue; weight, 0.5 to 1 mg), respectively. During catheterization, one HCM patient presented without a subvalvular pressure gradient and was not operated on. The tissue was fixed with paraldehyde and immersed in 10% buffered formalin. van Gieson staining was used for identification and analysis of intramyocardial small arteries. Arterioles were identified on the basis of the appearance of a layer of media and diameter < 100 µm. Only arterioles with round cross sections and without side branches were analysed. Capillaries were identified with specific antibodies (CD34) against endothelium. Quantitative morphometric analysis of the histological sections occurred with an in-house-developed software program applied to a morphometric system (Clemex Techn Inc) that calculated density of capillaries (capillaries per square millimeter), taking tissue shrinkage into account. Five cross sections per patient (≈1000 capillaries) were analysed. In addition, software was available that allowed us to trace the arteriolar lumen-intima and adventitia-media borders, which defined the lumen and wall thick-

ness regions. The areas of these regions were obtained from the number of pixels in the two regions. Normalized wall area is given by circular wall area/(lumen area +wall area). This value was calculated for 10 arterioles per patient. Data are presented as mean ± SD. Regression analysis, ANOVA and *t* tests were performed with standard statistical software (SPSS). A value of $p< 0.05$ was considered significant.

RESULTS

The HTx recipients, who served as control subjects, had no cardiac complaints, and all of them had normal coronary arteriograms. The time interval of catheterization after transplantation was 4 ± 2 years. Medication of HTx-patients at the time of catheterization was imunosuppresion (n= 8) Ca^{2+} antagonists (n= 8); aspirin (n= 5) and dipyridamole (n= 4). No member of the control group had signs of rejection on the basis of the biopsies. Age distribution between the HCM (45.5 ± 14.6 years) and control (48.7 ± 6.0 years) groups were similar. HCM patients were symptomatic (NYHA class II or III), whereas all members of the control group were symptom free (NYHA class I). HCM patients had a subvalvular gradient of 88 ± 31 mm Hg and a lower aortic pressure (103 ± 14 versus 120 ± 15 mm Hg, $p< 0.05$), a higher end-diastolic left ventricular pressure (22 ± 1 versus 12 ± 6 mm Hg, $p< 0.05$), a lower cardiac index (2.7 ± 0.5 versus 3.5 ± 0.7 L/m^2, $p< 0.05$) and a lower heart rate during baseline conditions (70 ± 13 versus 97 ± 13 bpm, $p< 0.05$) than the control group.

End-diastolic septal wall thickness was significantly increased in patients with HCM (25.8 ± 2.9 mm) compared with members of the control group (11.4 ± 3.0 mm; $p< 0.05$). All HCM patients had normal angiograms. The diameter of the LAD was similar in both groups (3.0 ± 0.8 versus 3.0 ± 0.5 mm). Coronary velocity during baseline conditions was higher for HCM-patients (34 ± 11 versus 20 ±11 cm/s, $p< 0.05$), whereas velocities during hyperemia were similar (49 ± 20 versus 53 ± 22 cm/s). As a consequence the CFR was reduced from 2.6 ± 0.8 in the control group to 1.8 ± 0.9 in HCM group ($p< 0.05$). Coronary resistance values, corrected for extravascular compression (see above), were lower (3.7 ± 2.1 versus 6.5 ± 2.2 mm $Hg.s.cm^{-1}$, $p< 0.05$) during baseline conditions and were similar during hyperemia (2.6 ± 1.5 versus 2.6 ± 1.0, p= NS) in HCM. Consequently, the CRR was lower (1.5 ± 0.6 versus 2.6 ± 0.8, $p< 0.05$) in HCM than in the control group. Arteriolar wall area was similar (5720 ± 2130 versus 7107 ± 3544 μm^2; p= NS), but lumen area (1273 ± 688 versus 2260 ± 1165 μm^2; $p< 0.05$) and diameters were significantly lower (19.6 ± 4.5 versus 25.9 ± 4.3 μm; $p< 0.05$) in HCM compared with control values. Consequently, AL was lower in the HCM (21 ± 5%) than in the control group (30 ± 4 %; $p< 0.05$), and capillary density tended to decrease from 1824 ± 424 to 1445 ± 513 per square millimeter in HCM (p= 0.11). In addition, both the CFR and the CRR were linearly related to AL according to the formula CFR = 0.1 AL - 0.45 (r= 0.57; p<

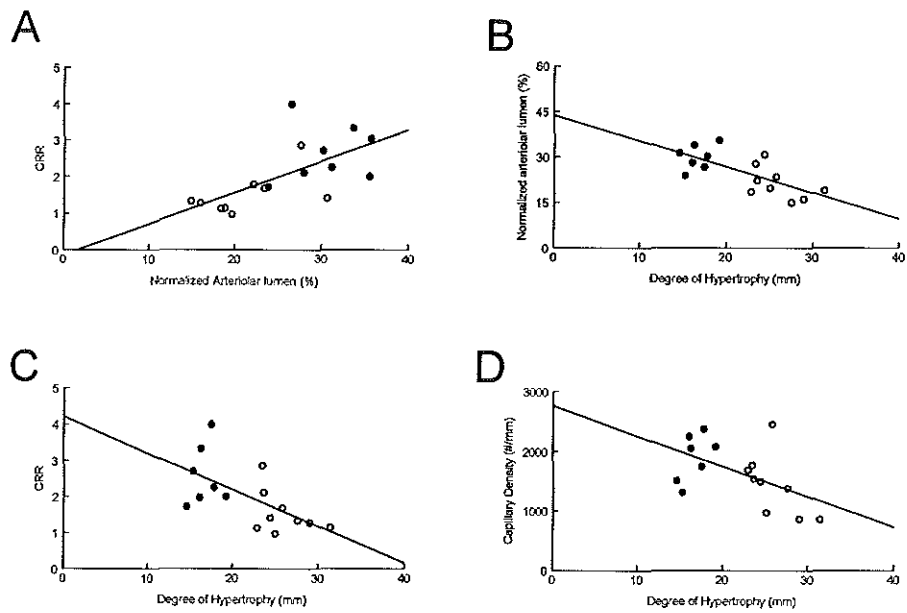

Figure 1

Relationship of CRR with AL (A); AL and degree of hypertrophy (B); CRR and degree of hypertrophy (C), and capillary density and degree of hypertrophy (D).

0.05) and CRR = 0.07 AL + 0.35 ($r = 0.50$; $p < 0.05$; Fig 1A). Further analysis revealed that the degree of AL (AL = -0.85 Hyp + 43.7; $r = 0.71$; $p < 0.05$; Fig 1B), the CFR (CFR = -0.17 Hyp + 5.9; $r = 0.80$; $p < 0.05$), the CRR (CRR = -1.2 Hyp + 4.7; $r = 0.7$; $p < 0.05$; Fig 1C) and the capillary density (CD = -51 Hyp + 2750; $r = 0.53$; $P < 0.05$; Figure1D) were all inversely related to the degree of hypertrophy (Hyp). In addition, a linear relationship between AL and capillary density was measured (AL = 42 CD + 577, $r = 0.54$; $p < 0.05$).

DISCUSSION

In symptomatic patients with HCM without evidence of a functional stenosis of the epicardial vessels, decrements in CFR were detected, confirming earlier studies (1-5). Similar decrements in CRR were measured, implying that these findings could not be explained by increments in extravascular compression (9,10). Abnormal arterioles with decreased lumen were detected in HCM patients, suggesting that a structural change in the coronary arterial vascular tree might be related to this finding. Indeed, a positive relationship between both CFR and CRR and AL, corrected for tissue shrinkage by normalization to the wall area (7), was detected. Furthermore, an inverse relationship was noted be-

tween AL and the degree of hypertrophy, confirming earlier postmortem studies (7). Because of this relationship, an inverse relationship between CFR and the degree of hypertrophy could be measured. Again, a similar relationship was found between CRR and degree of hypertrophy, implying that extravascular compressive forces were not essential for these findings. In large-animal models of pressure-overload induced left ventricular hypertrophy, vascular medial hypertrophy has been observed only when the coronary circulation was exposed to high perfusion pressures. The present arteriolar abnormalities were obtained at normal to low aortic pressures and might imply that hypertrophy of the arterioles, in parallel to the hypertrophy of the myocardium, is an independent process (7).

A decreased capillary density has been measured in several animal studies with experimentally induced secondary hypertrophy and recently in humans with secondary hypertrophy (12,13). Although differences between the groups in capillary density did not reach levels of statistical significance, there clearly was a an inverse relationship between capillary density and degree of hypertrophy. Furthermore, the decrements in capillary density and decrements of AL are related in HCM. These findings may imply that the decreased AL induces periods of ischemia, which results in increased angiogenesis. This angiogenesis normalizes the decrements in capillary density. However, because we did not analyse HCM myocardial tissue without hypertrophy, we cannot exclude the possibility that the occurrence of changes in the coronary microcirculation in HCM is a more independent phenomenon and not directly related to the degree of hypertrophy (6,7).

In conclusion, septal hypertrophy is associated with decrements in CFR and CRR in HCM patients. Arterioles of HCM patients exhibited a smaller lumen at similar wall thickness, which correlated well with decrements in CFR and CRR. These findings suggest that abnormal arterioles might contribute to the perfusion abnormalities found in these patients, resulting in recurrent myocardial ischemia.

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Chapter 8

Mechanisms Determining the Reduction in Coronary Flow Reserve In Hypertrophic Obstructive Cardiomyopathy

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submitted

ABSTRACT

Objectives. The purpose of this study was to investigate which haemodynamic, echocardiographic and morphometric data are responsible for the reduction in coronary flow reserve in patients with hypertrophic obstructive cardiomyopathy.

Background. Anginal symptoms and signs of ischaemia are frequently present in patients with hypertrophic cardiomyopathy despite the presence of normal coronary arteries. It has been postulated that periods of ischaemia are related to the reduction in coronary flow reserve in these patients. Although single haemodynamic, echocardiographic and morphometric variables have been related to the decrease in vasodilatory capacity, the relative contribution of each of these factors is not known.

Methods. In 10 patients with hypertrophic obstructive cardiomyopathy, mean [±SD] age 44 ± 14 years and 8 cardiac transplant recipients, mean [±SD] age 51 ± 6 years (control group), coronary flow reserve was calculated at the proximal or mid-segment of the left descending coronary artery. In all subjects we determined the New York Heart Association functional class, medical therapy, width of the interventricular septum and left ventricular posterior wall, indexed left ventricular mass, cardiac index, left ventricular end-diastolic pressure, left ventricular outflow gradient, systolic and end-diastolic diameter of the left descending coronary artery and first septal branch, lumen to wall ratio of the arterioles and capillary density in septal endocardial myocardium. We then evaluated the relationship between these variables and the coronary flow reserve by linear regression analysis.

Results. Coronary flow reserve was reduced in patients with hypertrophic obstructive cardiomyopathy compared to cardiac transplant recipients, 1.6 ± 0.7 vs. 2.6 ± 0.8 respectively (p=0.009). An increase in the thickness of the left ventricular septal myocardium (p=0.005), indexed left ventricular mass (p=0.005), left ventricular end-diastolic pressure (p=0.0002) and left ventricular outflow tract gradient (p=0.03) and a decrease in percentage lumen of the arterioles (p=0.04) were all related to the reduction in coronary flow reserve.

Conclusions. Several haemodynamic, echocardiographic and morphometric variables are responsible for the reduction in coronary flow reserve in patients with hypertrophic obstructive cardiomyopathy. The importance of each of these variables in reducing the vasodilatory reserve may differ from patient to patient.

INTRODUCTION

Chest pain is frequently present in patients with hypertrophic cardiomyopathy, despite the presence of normal epicardial coronary arteries (1). Anginal symptoms can be triggered by exercise and atrial pacing, usually in combination with reversible perfusion defects detected by Thallium-201 imaging and abnormali-

ties in lactate metabolism (2-4). These objective signs of ischemia occur preferentially in patients with a reduction in coronary vasodilatory capacity and it has been postulated that a reduced coronary flow reserve induces periods of ischemia in patients with hypertrophic cardiomyopathy (3,5). A number of independent mechanisms are associated with this decrease in coronary flow reserve: 1) elevation of left ventricular end diastolic pressure (6), 2) systolic compression of the septal branches (7,8), 3) the existence and degree of the left ventricular outflow gradient (9), 4) "small vessel disease" of the intra myocardial arterioles (10,11) and 5) lack of compensatory growth of the coronary microcirculation (4). Although all mechanisms have a role in creating an imbalance between oxygen supply and demand, their relative contribution to the decrease of coronary flow reserve has not yet been evaluated in hypertrophic cardiomyopathy. The aim of the study was to investigate to which extent each of the separate variables mentioned above contribute to the reduction of coronary flow reserve in a group of patients with hypertrophic obstructive cardiomyopathy. To that end, haemodynamic and echocardiographic variables and histological data of the coronary microcirculation were obtained in patients with hypertrophic cardiomyopathy and compared with a control group consisting of asymptomatic cardiac transplant recipients undergoing routine follow-up coronary angiography 1 to 5 years after transplantation. To evaluate changes in the coronary vascular bed we investigated septal myocardial tissue specimen of patients with hypertrophic cardiomyopathy, cardiac transplant recipients and a control group of victims of car accidents without cardiovascular disease. In each subject we determined the degree of small vessel disease and capillary density.

To our knowledge, this study is the first to describe the influence of a combination of heamodynamic, echocardiographic and morphometric data on the reduction of coronary flow reserve in patients with obstructive hypertrophic cardiomyopathy.

METHODS

Patient population

To study haemodynamics and changes in the coronary vascular bed in hypertrophic cardiomyopathy, patients with obstructive hypertrophic cardiomyopathy (N=10, mean age 44±14, range 20-63 years) were compared with a control group of asymptomatic cardiac transplant recipients (N=8, mean age 51±6, range 40-61 years) undergoing routine follow-up coronary angiography 1 to 5 years after transplantation. Patients with hypertrophic cardiomyopathy were symptomatic, New York Heart Association Class II or III, despite therapy with β-blockers and/or calciumantagonists and were candidates for surgical treatment (myectomy-myotomy according to Morrow) (12). The left ventricular outflow tract gradient was assessed by cardiac catheterisation and was > 30 mm Hg at rest in all patients with hypertrophic cardiomyopathy. Nine of 10 patients with

hypertrophic cardiomyopathy underwent septal myectomy-myotomy, the left ventricular outflow tract gradient in one patient was considered to low to expect considerable improvement of symptoms after surgery. The myocardium obtained at surgery was used for morphometric analysis of the intramyocardial arterioles and capillaries. Cardiac transplant patients were studied 1 to 5 years after cardiac transplantation. These patients were asymptomatic. We obtained myocardial material by right ventricular septal biopsy in these patients to determine the presence of rejection. Part of this material was used for the morphometric analysis of the coronary bed. These data were compared with myocardial tissue from left ventricular septal endocardium collected from victims of traffic accidents (N=10, mean age 38±19, range 8-58 years) without apparent cardiovascular disease.

Cardiac Catheterization

Cardiovascular therapy was continued during the study for both patients with hypertrophic cardiomyopathy and cardiac transplant recipients. After intravenous administration of 10 000 IU heparin and 250 mg acetylsalicylic acid right heart catheterization was carried out with a 7F balloon-tipped flow-directed thermodilution catheter. Left heart catheterization was performed with a 8F double-sensor high fidelity pig tail catheter (Cordis 811-180, Roden, the Netherlands). At baseline the following parameters were evaluated: Mean central venous pressure, mean pulmonary wedge pressure, left ventricular systolic and end-diastolic pressure, peak left ventricular-aortic gradient, cardiac output and cardiac index. In addition, left ventricular and coronary angiography was performed according to standard techniques. The end-systolic and end-diastolic diameters of the left descending coronary artery and the proximal part of the first septal branch were calculated by quantitative angiographic measurement at the site of the Doppler sample volume (CAAS-system) (13).

Coronary flow velocity measurements and analysis

After right and left cardiac catheterization, coronary flow velocity was measured in patients with hypertrophic cardiomyopathy and cardiac transplant recipients by use of a 0.014" Doppler guidewire with a floppy shapable distal end (Cardiometrics,Inc.) (14), which was advanced through a 8F guiding catheter and positioned at the proximal or mid-segment of the left descending coronary artery. The sample volume from the Doppler wire is positioned at a distance of 5.2 mm from the transducer and has an approximated width of 2.25 mm due to a divergent ultrasound beam. After real-time processing of the quadrature audio signal, a fast-Fourier algorithm is used to increase the reliability of the analysis (15). The flow velocity measurements obtained with this system have been validated in vitro and in an animal model using simultaneous electromagnetic flow measurements for comparison (14). Before the assessment of the coronary flow reserve, the hearts were paced from the right atrium at 100 beats/minute and this

rate was kept constant during the remainder of the protocol. After optimization of the settings of the velocity signal and 3 to 5 minutes after intra coronary injection of a bolus of 2 to 3 mg isosorbide dinitrate, baseline flow velocity was measured. Maximal flow velocity was acquired by measurement of the peak effect of an intra coronary bolus injection of 18 μg adenosine. The dose of adenosine used has been shown to produce maximal vasodilation in humans (16). Coronary flow reserve was defined as the ratio between maximal flow velocity at the peak effect of the adenosine injection and that under baseline conditions.

Quantitative Angiographic Measurement

The guiding catheter, filmed devoid of contrast medium, was used as a scaling device. A previously validated on-line analysis system operating on digital images (ACA-DCI, Philips, Eindhoven, The Netherlands) was used during the catheterization procedure (17). With this system we calculated the end-diastolic and end-systolic diameter of the left anterior descending coronary artery and the proximal part of the first septal branch. Care was taken to select the portion of the segments in the LAD where the Doppler catheter was located. The derived vessel diameters at the tip of the Doppler quidewire were used to calculate the vessel lumen area assuming a circular shape of the vessel. This vessel area was multiplied with the spatially averaged Doppler velocity (assuming a parabolic profile) to obtain coronary flow (ml/min).

Echocardiography

Two-dimensional echocardiographic studies were performed with commercially available equipment (Toshiba Sonolayer SSH-140A). The heart was visualised in a number of cross-sectional planes using standard transducer positions and images were recorded on videotape for off-line analysis. Septal and posterior left ventricular wall thickness was measured in diastole from both the parasternal short axis and long axis views (18,19) In the short axis view, the magnitude of left ventricular hypertrophy was assessed at the levels of both the mitral valve and papillary muscles (19,20). For the ventricular septum, two segments were evaluated: the cephalad position, which extended from the cardiac base to the distal margins of the mitral leaflets, and the caudal position, which included the portion of the left ventricle imaged below the mitral leaflets (21). From the recordings on videotape representative stop-frames from the various cross-sectional planes were acquired to determine septal and posterior left ventricular wall thickness with the aid of a computer and a dedicated software program (22). Mean septal thickness was calculated by averaging the data for the width of the septum, mean posterior wall thickness was calculated in the same way. Left ventricular mass was calculated according to the method developed by Devereux et al.(23): LVmass (g) = $0.8\{1.04[(IVS + LVED + LVPW)^3 - LVED^3]\} + 0.6$ g, where IVS and LVPW are enddiastolic thickness of the interventricular septum and posterior wall respectively and LVED is the left ven-

tricular enddiastolic diameter. Left ventricular mass was indexed by body surface area (g/m^2).

Morphometric analysis of arterioles

The myocardial specimen from patients with hypertrophic cardiomyopathy (N=9), cardiac transplant recipients (N=8) and victims of car accidents (N=10) were fixed by immersion in 4% phosphate-buffered formaldehyde. The group of victims of car accidents consisted of subjects without detectable signs of cardiovascular disease. Care was taken that only specimen from the endocardial septal site was utilised for analysis in all three groups. After fixation, the myocardial tissue was processed for paraffin sectioning and staining. For identification and analysis of intra myocardial small arteries an elastic von Giesson staining was used according to Tanaka et al.(10). In brief, each preparation was magnified with a light microscope (Zeiss, Germany) and digitized for further analysis with a quantitative morphometric system (IBAS system, Kontron, Germany). Only round appearing vessels without side branches were studied. For each arteriole, the wall (intima plus media) and total vessel area were traced and the areas were, via appropriate gain settings, converted to square micrometers. The adventitia was not included in the measurements since the distinction between adventitia and perivascular fibrosis was difficult. Percent lumen area was calculated from the ratio of Lumen area (L), and Wall area (W) plus Lumen area (L) as L/(W+L)x100%. The external diameter (D) of the intramyocardial coronary arterioles was calculated by the formula: $D= 2x \sqrt{wall + lumen\ area/\pi}$. In each subject at least 10 arterioles were identified and used for analysis.

Morphometric analysis of capillaries

In order to elucidate the capillary density in the above mentioned myocardial specimens, sections (4μ) from formalin fixed, paraffin embedded tissue were stained with antibodies directed against the CD-34 epitope (Biogenex, San Ramon, MO) as described below. After deparaffinization and rehydration sections were rinsed with phosphate-buffered saline and incubated with normal goat serum (DAKO, Glostrup, Denmark), antibodies directed against the CD-34 epitope, biolinylated secondary antibodies (Multilink, Biogenex, San Ramon, MO) and peroxidase labelled streptavidin (Biogenex), respectively. The subsequent immunoproduct was visualised with 3.3' diaminobenzidine . In negative controls the primary antibody was replaced by normal mouse serum (DAKO, Glostrup, Denmark). The CD-34 antibody demonstrated endothelial cells from capillaries in human myocardium most consistently, whereas CD-31 antibodies and the lectin Ulex Europeaus (in general more specific endothelial markers) left some capillairies uncoloured. In our experience, staining by Jones' silver methanamine, which was used by Rakusan et al. (30) to analyse capillary density in human myocardium, provided suboptimal results: discrimination of individual capillaries was more difficult and moreover, this staining method left

some capillaries uncoloured. Quantitative morphometric analysis of the sections with an area of 62.500 μm^2 was performed with a specially developed software program applied to a morpometric system (Clemex Techn Inc., Quebec, Canada). We payed special attention that cross-sections were originating from the endo- or midmyocardium, only regions were selected where the cardiomyocytes were cut transversely and no or only minimal fibrosis was present. For each patient at least five different regions were selected. The number of cardiac myocyte, and therefore the capillary-myocyte ratio was not determined because of the inability to outline myocytes correctly. Figure 1 shows an example of capillary density in a patient with hypertrophic cardiomyopathy and a victim of a car accident respectively.

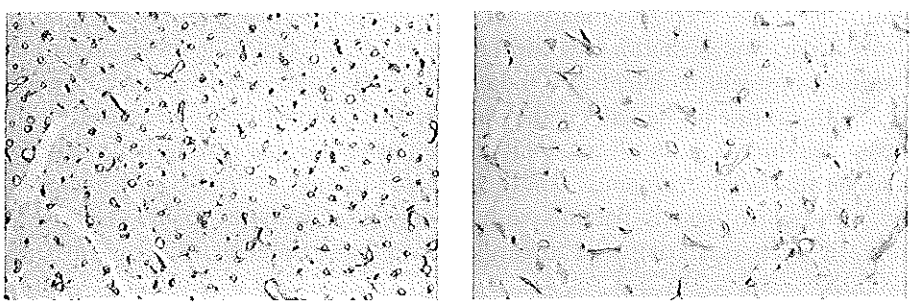

Figure 1

The capillary density of a victim of a car accident is represented at the left panel. At the right panel, the capillary density of a patient with hypertrophic cardiomyopathy is displayed. Note the decrease in number in capillary vessels in hypertrophic cardiomyopathy (magnification 40 x).

Interobserver variability

The percentage lumen of the arterioles and the capillary density was independently quantified by two different observers. The variance of percentage lumen and capillary density was <3% and < 5% respectively.

Statistical analysis

Data are presented as mean ± SD. To evaluate differences between groups unpaired student *t*-test was utilized. The relationship between coronary flow reserve and haemodynamic, echocardiograhic and morphometric variables was evaluated by linear regression analysis. A value of $p< 0.05$ was considered to be significant.

RESULTS

Patient characteristics

Demographic information, haemodynamic and morphometric data are presented in Table 1. Patients with hypertrophic cardiomyopathy (N=10) were all symptomatic: nine from ten patients had complaints of angina and/or dyspnoe, syncopal attacks as sole expression of the disease was present in one patient. Cardiac transplant recipients (N=8) were free of symptoms. Beta-blockers and/or calciumantagonists were prescribed in nine from ten patients with hypertrophic cardiomyopathy, one patient did not use medical therapy. Statistical differences in patient characteristics between the two groups are displayed in Table 2. Patients with hypertrophic cardiomyopathy had increased thickness of the interventricular septum (2.3±0.3 cm, range 2.0-3.0 cm) and posterior wall (1.3±0.3 cm, range 1.1-1.8 cm), compared with thickness of septal- (1.1±0.1 cm, range 1.0-1.2 cm) and posterior myocardial wall (1.1±0.1 cm, range 0.9-1.1 cm) of cardiac transplant recipients; p= 0.0001 and p= 0.005 respectively. At baseline, resting heart rate for patients with hypertrophic cardiomyopathy averaged 70±13 beats per minute, which was significantly lower than the resting heart rate for cardiac transplant recipients (97±13 beats per minute, p= 0.005). The indexed left ventricular mass in patients with hypertrophic cardiomyopathy (187±41 g/m^2) was increased compared to cardiac transplant recipients (89±15 g/m^2), p= 0.0001

Cardiac index was depressed in patients with hypertrophic cardiomyopathy; this finding could mainly be attributed to the lower heart rate in patients with hypertrophic cardiomyopathy, since stroke volume was not statistically different in both groups. Left ventricular end-diastolic pressure was significantly higher in the patients with hypertrophic cardiomyopathy (21±8 mm Hg vs. 9±3 mm Hg, p= 0.0007).

Selective coronary angiography did not show epicardial coronary artery disease in the two groups. Systolic and enddiastolic lumen-diameters of the left anterior descending artery and first septal branch were comparable in patients with hypertrophic cardiomyopathy and cardiac transplant recipients. Septal perforator artery compression, defined as a disappearance of part of the septal artery during systole (8) was not observed in patients with hypertrophic cardiomyopathy nor in cardiac transplant recipients.

Morphometric and histological analysis

The external calibre of the intramyocardial arterioles in patients with hypertrophic cardiomyopathy (42.0±7.8 μm) and cardiac transplant recipients (46.1 ±12.7 μm) were not significantly different from the external calibre of victims of car accidents (49.9±13.4 μm), p= 0.14 and p= 0.45 respectively (Table 2). In contrast, the percentage lumen was reduced in patients with hypertrophic cardiomyopathy (21.3±5.2%) compared to cardiac transplant recipients (30.4±3.3%)

Table 1

Baseline, echocardiographic, haemodynamic and morphometric data of patients with hypertrophic cardiomyopathy and cardiac transplant recipients.

	AGE/SEX	NYHA	Therapy	IVS (mm)	LVPW (mm)	LVmass/ BSA (g/m²)	Cardiac Index (l/min/m²)	LVEDP (mm Hg)	LVOT-gradient (mm Hg)	% lumen IMSA	Capillaries (n/mm²)	CFR
HCM												
# 1	45 F	II	-	20	11	168	2.8	12	32	-	-	3.10
# 2	59 M	III	B	23	13	202	2.4	28	100	14.9	1379	1.33
# 3	35 F	II	V	30	18	276	3.1	23	124	18.9	849	1.12
# 4	27 F	III	B	25	12	205	2.9	26	100	16.0	864	1.20
# 5	44 F	II	V	20	11	122	3.2	14	100	22.1	1541	2.10
# 6	20 M	II	V	23	11	182	2.9	23	58	27.6	1768	1.22
# 7	41 F	III	B,V	24	18	199	1.8	37	124	19.7	969	0.97
# 8	63 M	III	B	17	13	147	2.3	16	74	18.4	1686	1.13
# 9	62 M	III	V	22	12	184	3.4	20	88	30.7	1496	1.41
# 10	43 M	III	B	22	12	186	2.0	13	84	23.4	2451	1.68
HTX												
# 1	49 M	I	A,C,N,P	11	10	91	3.4	9	-	26.1	1308	3.38
# 2	61 M	I	C,D,N,P	12	10	88	3.2	6	-	26.6	1747	4.01
# 3	40 M	I	A,C,N,P	11	10	82	4.8	10	-	35.3	2079	2.00
# 4	57 M	I	C,D,N,P	11	11	119	4.1	11	-	31.2	2373	2.70
# 5	51 M	I	C,D,N,P	11	10	84	3.4	5	-	31.2	1511	2.25
# 6	55 M	I	A,C,N,P	10	10	73	3.2	7	-	33.7	2050	3.13
# 7	50 M	I	A,C,D,V	10	9	71	2.6	11	-	28.0	2245	1.97
# 8	52 M	I	A,C,N,P	11	10	100	3.9	13	-	31.5	1279	1.72

Therapy: A=aspirin, B=β-blocker, C=cyclosporin, D=dipyridamole, N=nifedipin, V=verapamil. CFR=coronary flow reserve, IMSA=intramyocardial small arteries, IVS=interventricular septum, LVEDP=left ventricular enddiastolic pressure, LVmass=left ventricular mass, LVOT-gradient=left ventricular outflow tract gradient, LVPW=left ventricular posterior wall, NYHA=New York Heart Association functional class.

Table 2

Comparison of patient characteristics between subjects with hypertrophic cardiomyopathy and cardiac transplant recipients.

	HCM(N=10)	HTX(N=8)	p-value
Age (years)	44±15	51±6	0.13
IVS (mm)	26±3	11±1	0.0001
LVPW (mm)	15±4	10±1	0.005
LVmass/BSA (g/m^2)	187±41	89±15	0.0001
Cardiac Index (l/min/m^2)	2.7±0.5	3.5±0.7	0.009
LVEDP (mm Hg)	21±8	9±3	0.0007
LADed (mm)	3.29±0.96	3.12±0.48	0.48
LADes (mm)	3.14±0.92	3.05±0.51	0.63
SAed (mm)	1.49±0.43	1.25±0.22	0.09
SAes (mm)	1.34±0.41	1.15±0.20	0.24
External Diameter of IMSA (µm)	42.0±7.8	46.1±12.7	0.46
L/W+L(%) of IMSA	21.3±5.2	30.4±3.3	0.0007
Capillary density (N/mm^2)	1445±514	1824±425	0.11
Coronary flow reserve	1.6±0.7	2.7±0.8	0.009

Data are presented as mean values ± SD. L=lumen area, LADed=enddiastolic diameter of the left descending coronary artery, LADes=endsystolic diameter of the left descending artery, SAed=enddiastolic diameter of the septal artery, SAes=endsystolic diameter of the septal artery, W=wall area. Other abbreviations as in Table 1

and the normal control group (30.9±5.7%), p= 0.0007 and p= 0.001 respectively.

The capillary density was diminished in patients with hypertrophic cardiomyopathy (1445±514/mm^2) compared to cardiac transplant recipients (1824±425/mm^2), however this difference was not significant (p= 0.11). In victims of car accidents the number of capillaries (3883±798/mm^2) was larger compared to patients with hypertrophic cardiomyopathy (p= 0.0001) and cardiac transplant recipients (p= 0.0001).

Coronary flow reserve

The coronary flow reserve in patients with hypertrophic cardiomyopathy was reduced compared to cardiac transplant recipients, 1.6±0.7 vs. 2.6±0.8, p= 0.009. Since this decrease in coronary flow reserve may be due to different mechanisms we performed univariate regression analysis to determine which factors contributed to the variance in the vasodilatory reserve. We evaluated the following parameters: left ventricular septal thickness, left ventricular posterior thickness, indexed left ventricular mass, left ventricular end diastolic pressure, left ventricular outflow gradient, cardiac index, systolic and enddiastolic lumen of the left anterior descending coronary artery and first septal branch, the percentage lumen of the intramyocardial small arteries and the capillary density. An increase in the thickness of the left ventricular septal myocardium (p= 0.005), indexed left ventricular mass (p= 0.005) (Figure 2), left ventricular enddiastolic

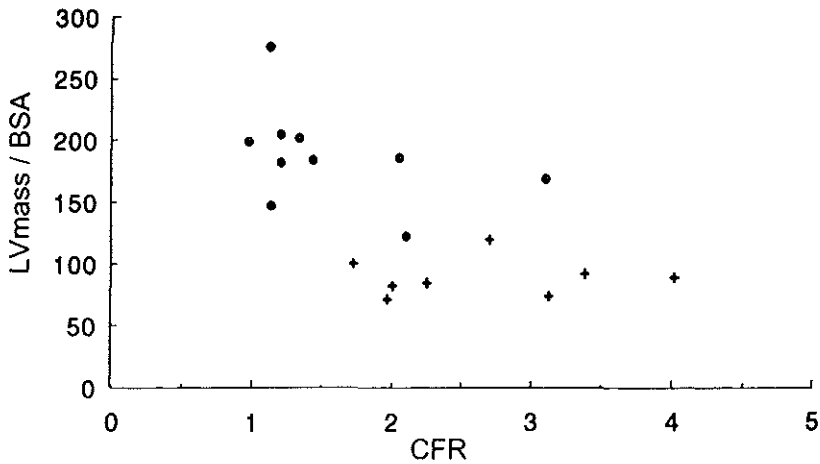

Figure 2

The relation between the coronary flow reserve (CFR) and left ventricular mass corrected for body surface area (LVmass/BSA, g/m^2) in patients with hypertrophic cardiomyopathy (●) and cardiac transplant recipients (+).

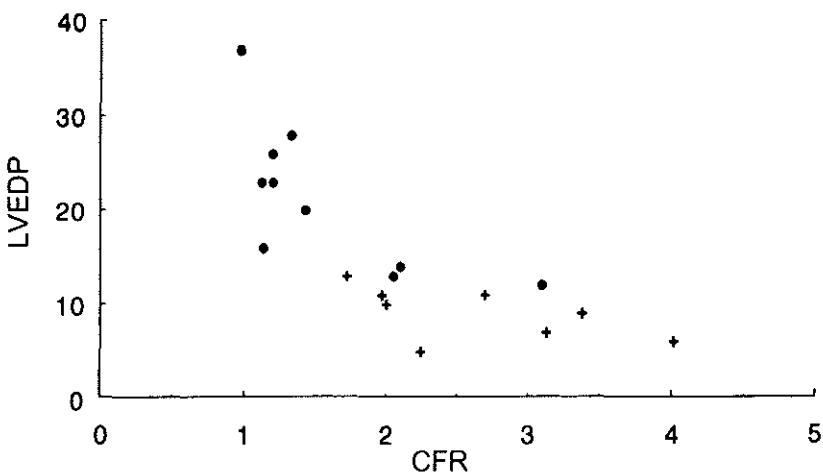

Figure 3

The relation between the coronary flow reserve (CFR) and left ventricular enddiastolic pressure (LVEDP, mm Hg) in patients with hypertrophic cardiomyopathy (●) and cardiac transplant recipients (+).

pressure (p= 0.0007) (Figure 3) and the left ventricular outflow gradient (p= 0.03) and a decrease in percentage lumen of the arterioles (p= 0.04) were all related the reduction of coronary flow reserve. The reduction in capillary density

in patients with hypertrophic cardiomyopathy was not significantly related to the reduction in the vasodilatory reserve (p= 0.10). Multivariate analysis was not performed because of the small patient numbers.

DISCUSSION

Previous studies have described the role of coronary flow reserve in hypertrophic cardiomyopathy and have related the reduction of the vasodilatory reserve in these patients with single echocardiographic, haemodynamic and morphometric alterations. This is the first study to relate a combination of clinical (increase in indexed left ventricular mass, increase in left ventricular enddiastolic pressure, the degree of the left ventricular outflow gradient) and pathologic factors (decrease of the percentage lumen of the arterioles) with the reduction in coronary flow reserve.

Morphometric analysis of myocardial tissue: the role of small vessel disease
In patients with hypertrophic cardiomyopathy post-mortem histologic analysis of left ventricular myocardium has revealed the presence of abnormal intramyocardial arterioles with markedly thickened walls and narrowed lumens (24,25). The presence of abnormal intramyocardial small arteries has been considered as one of the possible mechanisms for reduction in coronary flow reserve in these patients (10,11). Indeed, in our study we could find a positive relationship between the degree of arteriolar dysplasia and the decrement in the vasodilatory reserve. Since myocardial tissue was obtained from different sites (left ventricular septal endocardium for patients with hypertrophic cardiomyopathy, right ventricular septal endocardium in cardiac transplant recipients), this could have affected the present results. Nevertheless, Tanaka et al. (10) demonstrated that the percentage lumen of the intramyocardial arterioles was identical in the right, middle and left thirds of the ventricular septum in hearts with hypertrophic cardiomyopathy and normal hearts. To evaluate the role of small vessel disease in cardiac transplant recipients we compared the percentage lumen of intramyocardial arterioles in this group with that of normal hearts: no significant differences were found.

Morphometric analysis of myocardial tissue: the role of the capillary density
Although the small arteries and arterioles mainly control the blood flow of the coronary circulation, the capillary density and distribution are of crucial importance in the process of exchange between blood and tissue (26). In patients with hypertrophic cardiomyopathy ischaemia might be due to an increased oxygen diffusion distance caused by an inadequate growth of the capillaries. The existence of this phenomenon has been confirmed in studies with mature animals with pressure-overload hypertrophy (27,28). However, there are only few studies that have investigated the coronary vascular microcirculation in the normal

human population and in patients with pressure-overload hypertrophy. Rakusan et al. (29) showed that the left ventricular capillary density is similar to other mammalian species, and that pressure-overload left ventricular hypertrophy in children demonstrates proportional capillary angiogenesis, whereas in adults, hypertrophy appears to be associated with failure of compensatory angiogenesis.

To our knowledge, there are no studies concerning the role of capillary angiogenesis in hypertrophic obstructive cardiomyopathy. In our study, we showed that there was a clear reduction in capillary density in patients with hypertrophic cardiomyopathy compared with patients without cardiovascular disease and cardiac transplant recipients, however the decrease in capillary density did not reach statistical significance in patients after heart transplantation ($p= 0.11$). There was only a weak relation between the reduction in coronary flow reserve and the decrease in capillary density ($p= 0.10$). However, the patient population could have been to small for differences to appear. In comparison with the study by Rakusan et al. (29), the capillary density in normal subjects was higher in our study (3883 vs. 2249 per square mm). An explanation for this difference may be found in the staining-method we used for the detection of the capillaries. Indeed, we tried to colour capillary vessels with the Jones' silver methanamine method used in study by Rakusan et al, however in our experience this method presented suboptimal results.

Limitations of the study

First, in our study we used cardiac transplant recipients as a control group. To use cardiac transplant recipients as a "control"-group is debatable, nevertheless Vassali et al. showed that coronary flow reserve is comparable with the normal population 1 to 6 years after transplantation (30). The group of cardiac transplant recipients had no signs of acute allograft rejection or epicardial coronary artery disease, conditions which are known to diminish the coronary vasodilatory reserve (31,32). Although coronary flow reserve is comparable with the normal population, patients after heart transplantation can not be considered "normal". From the parameters we studied which could influence coronary flow reserve, the reduction in capillary density in cardiac transplant recipients was the most striking difference in comparison with the normal situation. Second, the sample size of the patient populations we studied was relatively small, as a consequence: 1) Only univariate analysis could be performed 2) Only very clear differences in patient characteristics will show significancy. A larger sample size might reveal other factors, like capillary density, being responsible for a decrease in vasodilatory reserve in patients with hypertrophic obstructive cardiomyopathy. Moreover, in our study, the contribution of systolic compression of the septal artery could not be studied since this phenomenon was not present in either patients with hypertrophic cardiomyopathy or cardiac transplant recipients. Third, the medical therapy was maintained throughout the study. This could have affected coronary flow reserve. However, since all patients with hy-

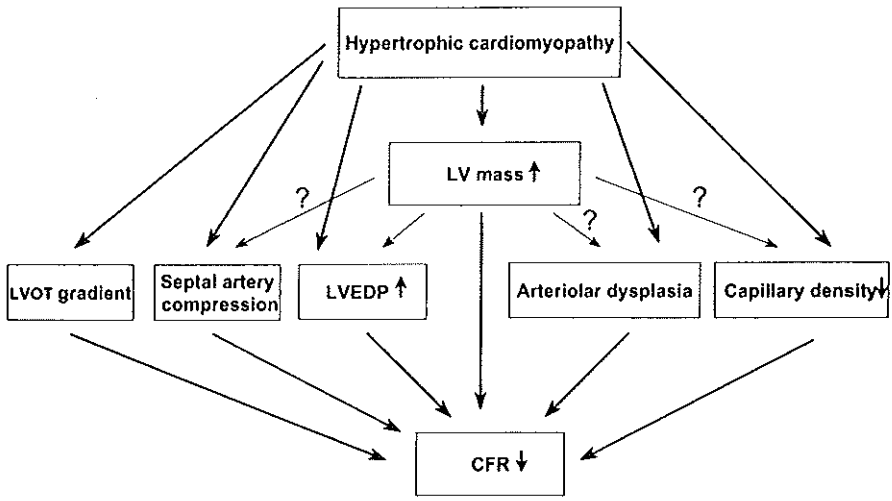

Figure 4

Mechanisms underlying the reduction in coronary flow reserve in hypertrophic cardiomyopathy.

pertrophic cardiomyopathy had serious complaints of angina and/or dyspnea, it was not considered ethical to discontinue medical therapy.

Conclusions

Many patients with hypertrophic cardiomyopathy manifest evidence of myocardial ischaemia. Myocardial ischaemia is often the result of a reduction in coronary flow reserve in these patients. Figure 4 gives an update from what we and others found concerning the role of clinical and pathological variables with relation to the coronary flow reserve in patients with hypertrophic cardiomyopathy. Some interrelations are yet unknown: especially this accounts for the relation between the left ventricular mass and variances in the microcirculation. Moreover, the importance of each of the variables in reducing coronary flow reserve may differ from patient to patient.

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Chapter 9

The Angiotensin II Type 1 Receptor A/C^{1166} Polymorphism Contributes to Cardiac Hypertrophy in Patients with Hypertrophic Cardiomyopathy

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ABSTRACT

The development of left ventricular hypertrophy (LVH) in subjects with hypertrophic cardiomyopathy (HCM) is variable, suggesting a role for modifying factors such as angiotensin II. We investigated whether the angiotensin II type 1 (AT1-R) A/C^{1166} polymorphism, the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism and/or plasma renin activity influence LVH in HCM.

Left ventricular mass index (LVMI) and interventricular septal thickness (IVS) were determined by two-dimensional echocardiography in 104 genetically independent subjects with HCM. Extent of hypertrophy was quantified by a point score (Wigle score). Plasma prorenin, renin and ACE were measured by immunoradiometric or fluorimetric assays, and ACE- and AT1-R genotyping were performed by polymerase chain reactions.

The ACE D allele did not affect any of the measured parameters except plasma ACE ($p< 0.02$). LVMI was higher ($p< 0.05$) in patients carrying the AT1-R C allele (190 ± 8.3 g/m^2) than in AA homozygotes (168 ± 7.2 g/m^2), and similar patterns were observed for IVS (23.0 ± 0.7 vs. 21.6 ± 0.7 mm) and Wigle score (7.0 ± 0.3 vs. 6.3 ± 0.3). Plasma renin was higher ($p< 0.05$) in carriers of the C allele than in AA homozygotes. Multivariate regression analysis however revealed no independent role for renin in the prediction of LVMI. Plasma prorenin and ACE were not affected by the AT1-R A/C^{1166} polymorphism, nor did the ACE- and AT1-R polymorphisms interact with regard to any of the measured parameters.

We conclude that the AT1-R C^{1166} allele modulates the phenotypic expression of hypertrophy in HCM, independently of plasma renin and the ACE I/D polymorphism.

ABBREVIATIONS AND ACRONYMS

ACE	=	angiotensin-converting enzyme
Ang	=	angiotensin
AT1-R	=	angiotensin II type 1 receptor
BSA	=	body surface area
HCM	=	hypertrophic cardiomyopathy
IVS	=	interventricular septal thickness
LVH	=	left ventricular hypertrophy
LVM	=	left ventricular mass
LVMI	=	left ventricular mass index
MI	=	myocardial infarction
PCR	=	polymerase chain reaction
SAM	=	systolic anterior motion

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is characterized by idiopathic myocardial hypertrophy. HCM occurs as a familial disorder, with an autosomal dominant pattern of inheritance, as well as in sporadic clinical presentation. Currently, six genes (β-myosin heavy chain, cardiac troponin T, α-tropomyosin, cardiac myosin binding protein-C, essential light chain-1, regulatory light chain) have been identified that may cause HCM (1-5). Patients with identical gene mutations display variable clinical manifestations or even fail to express the disease (6-8). Other factors, genetic as well as environmental, may therefore modify the phenotypic expression of the mutated gene.

It is now generally believed that angiotensin (Ang) II, formed by ACE from Ang I, is not only a potent vasoconstrictor, but also an important modulator of cardiac hypertrophy (9,10). ACE inhibition induces regression of cardiac hypertrophy, independent of load, and prevents dilatation and remodeling of the ventricle after myocardial infarction (MI) (11-14). Cardiac ACE levels are increased following MI (11,15,16), as well as during pressure overload-induced left ventricular hypertrophy (17). The ACE levels in the human heart are in part determined by the so-called insertion/deletion (I/D) polymorphism, subjects with the DD genotype having higher tissue ACE levels than subjects with II or ID genotypes (18). According to some (19-21), but not all (22,23) studies the frequency of the D allele is higher in patients with HCM. Moreover, the extent of hypertrophy in subjects with HCM is influenced by the ACE I/D polymorphism (20,22,23), suggesting that Ang II may modify the phenotypic expression of hypertrophy in HCM. The latter association may depend upon the underlying gene mutation, since it was found only in subjects with mutations in the Arg 403 codon of the β-myosin heavy chain gene (23).

Ang II exerts most of its known cellular actions through the angiotensin II type 1 receptor (AT1-R) (24). Recently, the C allele of a polymorphism located in the 3' untranslated region of the AT1-R gene (corresponding to an adenine/cytosine (A/C) substitution at the 1166 position) has been shown to increase synergistically the risk of MI in subjects carrying the ACE D allele (25).

It was the aim of the present study to investigate whether the AT1-R C allele influences the extent of hypertrophy in HCM, for instance through an interaction with the ACE D allele. Since cardiac angiotensin generation depends largely on kidney-derived (pro)renin taken up from the circulation (26-28), we also studied the relationship between plasma (pro)renin, cardiac hypertrophy and the AT1-R C allele in subjects with HCM.

METHODS

Patients

One-hundred and sixteen patients with HCM (age 21-81 years; median 47 years)

visiting the Hypertrophic Cardiomyopathy Clinic at the Thorax Center of the Academic Hospital "Dijkzigt" between December 1994 and January 1997 for a routine follow-up were included in the study. HCM had been diagnosed on the basis of echocardiographic criteria showing a nondilated, hypertrophied left ventricle (any wall thickness >15 mm) in the absence of known causes of left ventricular hypertrophy such as systemic hypertension or valvular disease (29). From each patient a peripheral venous blood sample was collected for measurement of plasma prorenin, renin and ACE, and for the extraction of genomic DNA. Patients using ACE inhibitors (n=7) were excluded from the study because of interference with the measurement of plasma ACE. Of the remaining 109 subjects, forty-one had a sporadic form of HCM and fifty had at least one other affected first degree family member. The family history of HCM was unknown in eighteen patients. To avoid potential bias introduced by the presence of genetically dependent samples (relatives), we randomly selected one patient per family. This resulted in a final cohort of 104 genetically independent patients, of whom 30 were receiving a beta-adrenergic antagonist, 44 a calcium-channel blocker and 8 a diuretic.

The study was approved by the internal review board and patients gave informed consent.

Echocardiographic methods

Two-dimensional echocardiography was performed with commercially available equipment (Toshiba Sonolayer SSH-140A System, Tokyo, Japan). The heart was visualized in a number of cross-sectional planes, using standard transducer positions, and images were recorded on videotape for off-line analysis. Echocardiographic analysis was performed by two physicians who were blinded to the results of the genotyping studies.

Interventricular septal thickness (IVS) was measured in diastole from the parasternal short-axis view at the level of the papillary muscles. The magnitude of LVH was determined by calculating left ventricular mass (LVM, g) according to the method described by Devereux et al.(30): $LVM = 0.8(1.04[(IVS+LVED+LVPW)^3 - LVED^3]) + 0.6$ g, where LVED is the left ventricular end-diastolic diameter, and LVPW is the end-diastolic thickness of the posterior wall. LVM was indexed (LVMI, g/m^2) to body surface area.

Systolic anterior motion (SAM) of the anterior leaflet of the mitral valve was assessed from the two-dimensional images and graded 0 (absent), 1+ (mild [minimal mitral-septal distance >10 mm during systole]), 2+ (moderate [minimal mitral-septal distance ≤10 mm during systole]) or 3+ (marked [brief or prolonged contact between the mitral valve and septum]) (31).

Peak left ventricular outflow tract gradient at rest was estimated using the modified Bernoulli equation, $P=4V^2$, where P is the pressure gradient and V is the velocity determined by Doppler echocardiography.

Since the echocardiographic measurement of LVMI may not truly reflect the

extent of hypertrophy and the involvement (or lack thereof) of the distal (apical) half of the septum or lateral wall, the extent of hypertrophy was also assessed by a semi-quantitative point score method developed by Wigle et al.(32). A maximum of 10 points are given: 1 to 4 points for septal hypertrophy based on magnitude of thickness, 2 points for extension of hypertrophy beyond the level of the papillary muscles (basal two-thirds of septum), 2 points for extension of hypertrophy to the apex (total septal involvement), and 2 points for extension of hypertrophy into the lateral wall.

Biochemical measurements

Five mL blood was collected into tubes containing trisodium citrate (final concentration in blood: 0.026 mol/L). The blood was centrifuged at 3000g for 10 minutes at room temperature, and plasma was stored in 1 mL aliquots at -70°C. Shortly before assaying, the samples were rapidly thawed and kept at room temperature. All assays were performed in duplicate.

Immunoreactive renin was quantified in 200 µL plasma using an immunoradiometric assay kit (Nichols Institute, Wychen, The Netherlands), following the methods proposed by Derkx et al.(33). Prorenin was activated non-proteolytically, by incubation with the renin inhibitor remikiren, and its concentration was calculated by subtracting the results obtained before activation of prorenin (i.e., renin) from those obtained after activation (i.e., renin + prorenin). The renin and prorenin levels are expressed as mU/L, using the international human kidney renin standard MRC 68/356 (Medical Research Council, National Institute of Biological Standards and Control, London, U.K.) as a reference. The normal range in plasma is 8 to 55 mU/L for renin and 88 to 390 mU/L for prorenin (33).

ACE activity was measured with a commercial kit (ACE Color, Fujirebio, Tokyo, Japan); its normal range in plasma is 7 to 20 U/L (34).

Genetic analysis

Peripheral leukocytes, obtained after centrifugation of 5 mL blood (see under Biochemical Measurements), were used to isolate genomic DNA in H_2O using the QIAamp Bloodkit (QIAGEN Inc., Santa Clarita, CA). DNA concentrations varied from 25-50 ng/µL.

The determination of the ACE gene I/D polymorphism was based on the triple primer method described by Evans et al.(35). This method, which avoids mistyping of ID as DD (36), was modified into two separate polymerase chain reactions (PCR). The first PCR encompassed the entire insertion/deletion region. Using the sense oligonucleotide primer 5'gctggagaccactcccatcctttct3' and the anti-sense primer 5'tagacctccacgagtcccctgcat3', two fragments of 493 base pairs (bp) and 781bp were amplified corresponding to the D- and I allele respectively (Figure 1). In the second PCR an insertion-specific sense primer, 5'tgggattacaggcgtgatacag3', was used with the above mentioned anti-sense

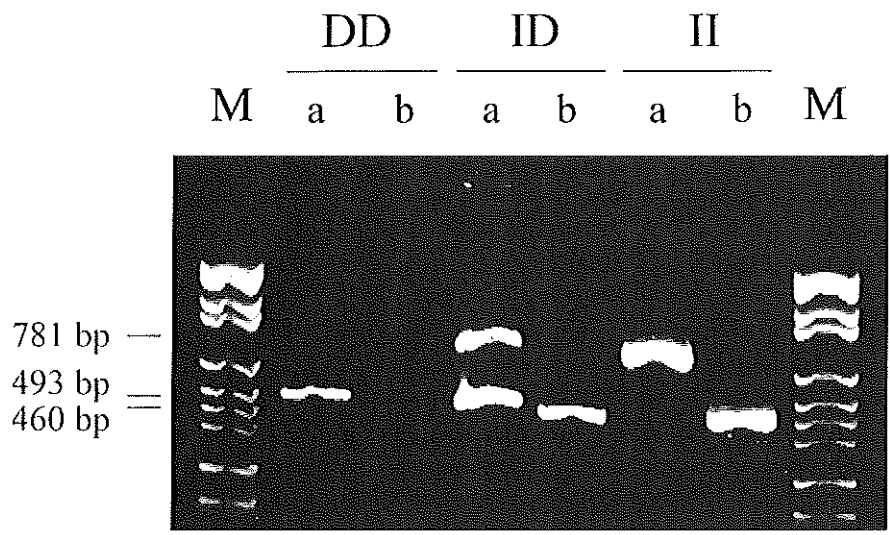

Figure 1

Agarose gel electrophoresis of PCR products in the region of the ACE insertion (I)/deletion (D) polymorphism in three patients with the DD, ID and II genotype, respectively. A triple primer method (see 'Methods' section) was used to avoid mistyping of ID as DD[20]. Lane a, obtained with primers adjacent to the insertion site, shows the presence of a 493bp and/or a 781bp band, representing the D- and the I allele, respectively. Lane b, obtained with an insertion-specific primer, shows the presence of a 460bp band, representing the I allele. Lane M shows the size marker, which is a mixture of digestion products of pBR328 by Bgl II and Hinf I.

primer. This PCR amplified a 460bp fragment (Figure 1). PCR reactions were performed on 2 µL genomic DNA in a final volume of 25 µL containing 0.4 nmol/L of each primer, 1.5 mmol/L $MgCl_2$, 75 mmol/L Tris-HCl (pH9.0), 20 mmol/L $(NH_4)_2SO_4$, 0.01% (w/v) Tween 20, 0.2 mmol/L of each dNTP, and 0.5 U Goldstar DNA polymerase (Eurogentec Inc., Seraing, Belgium). The amplification profile included an initial denaturation at 96°C for 3 minutes and 35 cycles of denaturation at 96°C for 30 seconds, annealing at 60°C for 15 seconds, and extension at 72°C for 60 seconds with a final extension time of 10 minutes. The PCR products were separated by electrophoresis on 3% agarose gels and visualized by ethidium bromide staining (Figure 1).

The AT1-R gene A/C[1166] polymorphism was determined using a PCR, spanning the polymorphic site, and subsequent fluorescent sequence analysis of the PCR product (Figure 2). The sense primer in the PCR was extended at the 5' site, with a nucleotide stretch homologous to the sequence analysis primer (-28M13Rev) shown in bold, 5'**aggaaacagctatgaccat**gacatgttcgaaacctgtcca taaag3', and the anti-sense primer was 5'cggttcagtccacataatgc3'. These primers allowed the amplification of a genomic DNA segment of 139bp which con-

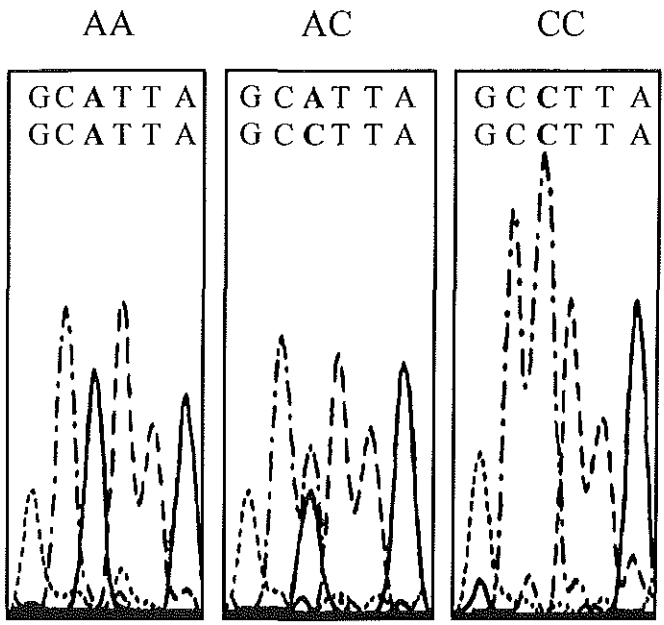

Figure 2

Fluorescence plots representing the DNA sequence of the PCR product in the region spanning the AT1-R A/C[1166] polymorphic site in three patients with the AA, AC and CC genotype, respectively. Each peak represents a different nucleotide [------- : Guanine (G), – . – . – : Cytosine (C), ——— : Adenine (A), and - - - : Thymidine (T)]. The nucleotide sequences of both alleles are depicted above the plots. The polymorphic site is indicated in bold.

tained the polymorphic site 88bp downstream the sequencing primer. Reactions were performed on 1 µL genomic DNA in a final volume of 15 µL containing 0.2 nmol/L sense primer, 0.4 nmol/L anti-sense primer, 1.5 mmol/L $MgCl_2$, 75 mmol/L Tris-HCl (pH9.0), 20 mmol/L $(NH_4)_2SO_4$, 0.01% (w/v) Tween 20, 0.2 mmol/L of each dNTP, and 0.5 U Goldstar DNA polymerase (Eurogentec Inc., Seraing, Belgium). The amplification profile included an initial denaturation at 96°C for 3 minutes and 35 cycles of denaturation at 96°C for 30 seconds, annealing at 50°C for 15 seconds, and extension at 72°C for 60 seconds with a final extension time of 10 minutes. After completion of the PCR, 6 µL was used to perform sequence analysis reactions using the fluorophore-labeled '28M13Rev DYEnamic ET-primer' and the 'DYEnamic direct cycle sequencing kit with 7-deaza dGTP' according to the instructions of Amersham Int. (Little Chalfont, U.K.). The sequence reaction products were separated by electrophoresis in polyacrylamide gels and analyzed in an ABI PRISM 377 automatic DNA sequencer (Perkin-Elmer Corp., Foster City, CA) using the accompanying software.

Statistical analysis

Data are expressed as mean ± SEM or as median and range. Statistical analysis was performed with the SPSS 7.0 statistical package. Because of non-normal distribution, plasma renin and prorenin data were logarithmically transformed prior to analysis. The Hardy-Weinberg equilibrium was tested by a χ^2 test. Differences between groups (AC+CC vs. AA and ID+DD vs. II, respectively) were tested by two-tailed Student's *t*-test. The probability (p) values for statistical significance are reported without correction for multiple comparisons. Univariate and multivariate regression analyses were conducted to determine the percentage of explained variance in LVMI that is accounted for by the genotypes of the candidate modifier genes and other variables. Both polymorphisms were tested as codominant 0,1, or 2 ordinal variables (presence of 0,1, or 2 C or D alleles). In the multivariate regression analysis the two polymorphisms, sex (male=0, female=1), age, peak left ventricular outflow tract gradient and plasma renin concentration were considered independent variables. Plasma prorenin, plasma ACE, and SAM were excluded from this analysis because of their respective high correlation with plasma renin ($r= 0.680$, $p< 0.001$), ACE genotype ($r= 0.389$, $p= 0.003$) and peak left ventricular outflow tract gradient ($r= 0.766$, $p< 0.001$).

RESULTS

The distribution of the ACE I/D- and the AT1-R A/C^{1166} genotypes in 104 genetically independent HCM patients are shown in Table 1. The frequencies of the ACE I- and D alleles (0.50 and 0.50, respectively) and the AT1-R A- and C alleles (0.74 and 0.26, respectively) were similar to previously reported numbers in normal Caucasian populations (18,25,37,38). Genotype frequencies were in agreement with Hardy-Weinberg equilibrium.

Table 2 lists the characteristics of the HCM patients according to ACE I/D genotype. No differences with regard to gender, age, BSA, or any of the cardiac parameters were found between carriers of the D allele and subjects with the II genotype. Plasma renin and prorenin (Table 2), as well as the percentage of patients taking beta-adrenergic antagonists, calcium-channel blockers or diuretics (data not shown), were also similar in II and ID+DD patients. In accordance with previous studies (39,40) plasma ACE activity was highest in DD subjects and intermediate in ID subjects. Regression analysis showed that the ACE genotype accounted for 15.1 % of the variability in plasma ACE activity ($r= 0.389$, $p= 0.003$).

Table 3 lists the characteristics of the HCM patients according to AT1-R A/C^{1166} genotype. The percentage of patients taking beta-adrenergic antagonists, calcium-channel blockers or diuretics did not differ between AA and AC+CC

Table 1

Genotype Frequencies of the ACE- and AT1-R Genes in HCM Patients.

		AT1-R Genotype (n)			Sum (%)
		AA	AC	CC	
ACE Genotype	II	15	6	3	24 (23%)
	ID	33	21	3	57 (55%)
	DD	9	12	2	23 (22%)
	Sum (%)	57 (55%)	39 (38%)	8 (8%)	104 (100%)

Table 2

Characteristics of HCM Patients According to ACE I/D Genotype

	ACE Genotype			*P*
	II (n=24)	ID (n=57)	DD (n=23)	ID + DD vs II
Men/Women	14/10	36/21	15/8	NS
Age, y	49.8±3.3	46.2±2.0	48.0±2.8	NS
BSA, m^2	1.80±0.05	1.85±0.02	1.88±0.04	NS
IVS, mm	22.0±0.9	22.3±0.7	22.3±1.1	NS
LVM, g	326.5±22.2	331.1±14.1	315.2±18.4	NS
LVMI, g/m^2	182.5±11.9	180.3±8.1	167.0±8.3	NS
Wigle score, 1-10	6.8±0.4	6.6±0.3	6.5±0.6	NS
SAM, 0/1+/2+/3+	4/1/7/9	11/9/11/22	5/4/8/4	NS
Gradient, mmHg	55.8±9.4	47.6±5.4	36.1±7.9	NS
Prorenin, mU/L	156(86-1339)	173(47-813)	141(28-299)	NS
Renin, mU/L	20.7(7.8-202)	21.0(3.0-85)	20.3(3.0-54)	NS
ACE, U/L	8.7±0.5	9.9±0.4	11.2±0.5	0.036

Values are mean ± SEM or median(range). Student's *t*-test was used to compare the mean values in the ID+DD vs. the II subjects. NS = non significant. Gradient = peak left ventricular outflow tract gradient; Wigle score = semi-quantitative point score assessing the extent of hypertrophy.

Table 3

Characteristics of HCM Patients According to AT1-R A/C^{1166} Genotype.

	AT1-R Genotype			*P*
	AA (n=57)	AC (n=39)	CC (n=8)	(AC+CC vs AA)
Men/Women	33/24	29/10	3/5	NS
Age, y	48.6±2.1	45.7±2.1	47.4±6.9	NS
BSA, m^2	1.84±0.03	1.88±0.03	1.75±0.06	NS
IVS, mm	21.6±0.7	22.9±0.7	23.4±2.3	NS
LVM, g	306.2±12.5	350.1±16.2	356.5±49.3	0.025
LVMI, g/m^2	167.9±7.2	186.5±8.1	205.4±30.3	0.048
Wigle score, 1-10	6.3±0.3	6.9±0.3	7.3±0.8	NS
SAM, 0/1+/2+/3+	7/8/14/23	12/5/8/10	1/1/4/2	NS
Gradient, mmHg	53.1±5.5	37.8±6.4	43.6±16.6	NS
Prorenin, mU/L	161(28-741)	147(48-1339)	228(86-813)	NS
Renin, mU/L	17.0(3.0-55)	22.7(3.0-202)	24.6(10.2-85)	0.049
ACE, U/L	10.2±0.4	9.6±0.4	9.9±0.8	NS

Values are mean ± SEM or median (range). Student's *t*-test was used to compare the mean values in the AC+CC vs. the AA subjects. NS = non significant. Gradient = peak left ventricular outflow tract gradient; Wigle score= semi-quantitative point score assessing the extent of hypertrophy.

patients (data not shown). Gender, age, BSA, SAM, and peak left ventricular outflow tract gradient were not associated with the AT1-R A/C^{1166} polymorphism. LVM, LVMI and plasma renin were however significantly higher in subjects carrying one or two C alleles than in AA homozygotes, and similar patterns were observed for IVS (p= 0.162) and Wigle score (p= 0.108). Regression analysis showed that the AT1-R genotype accounted for 4.3% of the variability of LVM (r= 0.208, p= 0.034), 4.5% of the variability of LVMI (r= 0.213, p= 0.031) and 4.6% of the variability in plasma renin (r= 0.214, p= 0.029). Using a two factor ANOVA, no interaction was observed between the ACE D allele and the AT1-R C allele with regard to any of the measured parameters.

Plasma renin, plasma prorenin, and the sum of plasma renin and plasma prorenin (plasma total renin) did not correlate with LVM, LVMI or any of the other cardiac parameters (data not shown).

Multivariate regression analysis showed that age, peak left ventricular outflow gradient and the AT1-R A/C^{1166} polymorphism, but not sex, plasma renin

Table 4

Multivariate Regression Analysis of Factors with Potential Effect on LVMI

	ß	SE	*P*
Sex, male=0, female=1	4.715	11.043	NS
Age, y	-0.891	0.351	0.013
ACE Genotype, no. of D alleles	-8.819	7.912	NS
AT1-R Genotype, no. of C alleles	22.412	8.332	0.010
Log Renin, mU/L	-26.842	17.998	NS
Gradient, mmHg	0.276	0.132	0.040

SE = standard error; NS = non significant. Gradient = peak left ventricular outflow tract gradient.

or the ACE I/D polymorphism, were significant predictors of LVMI (Table 4).

DISCUSSION

The present study shows that the AT1-R genotype influences the magnitude of LVH in subjects with HCM. LVM and LVMI were significantly higher in patients carrying the C allele than in AA homozygotes, and a similar pattern was observed for IVS and Wigle score, the latter being a semi-quantitative score reflecting the extent of cardiac hypertrophy (32). No relationship with SAM or peak left ventricular outflow tract gradient was observed. Interestingly, plasma renin, but not plasma prorenin, was higher in subjects carrying the C allele than in AA homozygotes.

The AT1-R A/C^{1166} polymorphism is located at the 5' site of the 3' untranslated region of the gene. This polymorphism is probably not functional but might be in linkage equilibrium with an unidentified functional variant affecting the structure or function of the AT1-R (or adjacent unknown genes). Tiret et al.(25) have speculated that the downregulation of the AT1-R gene in response to Ang II is altered in subjects with the C allele. Such altered down regulation, which is most likely tissue-specific (41-44), would not only offer an explanation for our findings on cardiac hypertrophy but it might also explain the increased renin levels in patients carrying the C allele, since Ang II stimulates cardiac hypertrophy (9,45) and regulates renin release (46,47) via AT1-receptors. In line with our findings, Hein et al.(48) recently showed that overexpression of the AT1-R in the mouse leads to an increase in cardiac mass and myocyte hypertrophy.

The C allele has been associated with hypertension (38,49), aortic stiffness

(50), the development of coronary artery stenosis (51), and coronary artery vasoconstriction (52). The frequency of the C allele in the HCM subjects of the present study was similar to that reported previously in the general population (25,50). Thus, the AT1-R A/C^{1166} polymorphism is not associated with HCM as such, but rather modulates the phenotypic expression of hypertrophy in subjects with HCM. Such modulation might explain why individuals with the same HCM mutation show a significant variability in the magnitude of LVH (6-8).
The ACE I/D polymorphism has also been reported to account for some of the variability of LVMI in HCM subjects (20,22). This could not be confirmed in the present study, although our data do support the previously described (39,40) association between plasma ACE and ACE genotype. It is possible that the influence of the ACE genotype in HCM subjects depends on the specific disease gene mutation (23). We did not determine the underlying gene mutations in our HCM patients. The presence of different sarcomeric gene mutations in our population might however offer an explanation for the lack of association between ACE genotype and LVH in the present cohort. It might also explain why Brugada et al. did not find an association between the AT1-R C allele and cardiac hypertrophy in their patients (53). In addition, the HCM patients selected by Brugada et al. (53) had a less severe form of HCM (wall thickness ≥13mm) than those selected in the present study (wall thickness >15mm). This may have enhanced our chance of finding a significant association between hypertrophy and the AT1-R C allele (23).

Theoretically, the high tissue ACE levels found in DD subjects (18) might lead to high tissue Ang II levels and thereby enhance the AT1-R C allele-related effects on hypertrophy. Such synergy has been described for the risk of MI (25). Any interaction between the AT1-R C allele and the ACE D allele will however be obscured by the elevated plasma renin levels found in HCM patients carrying the C allele. High plasma renin levels will, via uptake of renin by the heart (26,27,54), also lead to high cardiac Ang II levels. Thus, cardiac Ang II levels may already be high in AC and CC subjects independently of the ACE gene polymorphism, and this could explain the lack of interaction between the two gene polymorphisms of the renin-angiotensin system in the present study.
Recently, plasma renin activity was found to correlate positively with LVM in healthy young adults (10). One may therefore argue that the elevated plasma renin levels in subjects carrying the C allele are the underlying reason for the relationship between the C allele and cardiac hypertrophy. However, plasma renin did not correlate with either LVM or LVMI in the present study, and multivariate regression analysis revealed no independent effect of plasma renin after correction for AT1-R genotype. Thus it appears that, in HCM subjects, other factors related to the AT1-R A/C^{1166} polymorphism (e.g., cardiac AT1-R density) are more important determinants of cardiac hypertrophy than plasma renin.

In addition to the AT1-R A/C^{1166} polymorphism, age and peak left ventricular outflow gradient were also independent predictors of LVMI. Both associations

have been reported before (55-59). LVMI decreases with age, most likely because progressive wall thinning occurs gradually over time in HCM patients (55,56). Mitral leaflet-septal contact determines the magnitude of the pressure gradient in the left ventricular outflow tract, and more marked SAM of the mitral valve is associated with an augmentation of LVH (55-59).

In conclusion, the results of this study support a modulating role for the AT1-R A/C[1166] polymorphism in the development of LVH in patients with HCM, independently of age, sex, peak left ventricular outflow gradient, plasma renin and the ACE I/D polymorphism.

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Summary

Hypertrophic cardiomyopathy is an intriguing disease that puzzled many investigators due to the heterogeneity in clinical presentation, natural history, aetiology and management.

In this thesis, we have discussed new conceptions concerning prognosis, imaging modalities, surgical therapy, coronary flow reserve and modifier genes in patients with this disease.

In Chapter 1, a review of the recent literature is presented focusing on the pathology, prevalence, symptoms, clinical outcome, therapeutic interventions and alterations in the genetic material responsible for the development of hypertrophic cardiomyopathy.

In Chapter 2, the annual cardiac death is assessed in an unselected outpatient population of 113 patients with hypertrophic cardiomyopathy. Mean age at diagnosis was 37 ± 16 years (range 5 - 71 years). During a mean follow-up of 7 ± 5 years, there were 11 cardiac and 2 noncardiac deaths. The annual cardiac death was 1% (95% confidence interval 0.2 - 1.8%). Previous prognosis studies from tertiary referral centres have reported an annual cardiac mortality of 2 - 4%. It is believed that investigations performed at these centres were profoundly influenced by referral bias. Patients who are referred to tertiary centres represent, for the most part, the segment of patients with severe symptoms or those who are at risk of sudden death. It is concluded that hypertrophic cardiomyopathy has a relatively benign prognosis.

In Chapter 3, we report the clinical outcome in 9 parturients with hypertrophic cardiomyopathy. These women characterize the clinical heterogeinity of this disease: Before pregnancy, complaints of dyspnea and/or angina were present in 4 patients, septal myectomy because of left ventricular outflow tract obstruction had been carried out in 5 patients, episodes of ventricular tachycardia were documented in 6 patients and in 6 patients sudden death was reported in a first-degree relative. Nine women had 20 pregnancies. During pregnancy, cardiac symptoms worsened in only 2 patients, one of whom had to be treated with diuretics for relief of heart failure. Five pregnancies ended in spontaneous abortion. From 15 births, thirteen children were born by vaginal delivery and two by cesarean section because of fetal distress, In the perinatal period, no mother nor child died. We conclude that pregnancy is well tolerated in patients with hypertrophic cardiomyopathy and caesarean section can be reserved for obstretic indications only.

In Chapter 4, we study the alterations in size and geometry of the left ventricular outflow tract which occur in hypertrophic cardiomyopathy. To this end, transthoracic 3-dimensional echocardiography was performed in 17 patients with hypertrophic cardiomyopathy and in 10 normal subjects. Both the ratio between maximal and minimal cross-sectional areas and the ratio between maximal and minimal diameter of the smallest cross-section were significantly higher in patients with hypertrophic cardiomyopathy than in normals (2.6 ± 0.9 vs. 1.4

$\pm$ 0.2, $p< 0.0001$; 1.6 $\pm$ 0.3 vs. 1.2 $\pm$ 0.1, $p< 0.001$, respectively). Patients with hypertrophic cardiomyopathy are characterized by a highly eccentric and asymmetric shape of the left ventricular outflow tract, and by a smaller minimal cross-sectional area compared to normal subjects.

In Chapter 5, we describe the design features and electrical characteristics of a monopolar electrosurgical device called spark erosion for use in septal myectomy in patients with hypertrophic obstructive cardiomyopathy.

In Chapter 6, we assess the clinical and functional outcome of combined anterior mitral leaflet extension and myectomy in 8 patients with hypertrophic obstructive cardiomyopathy. The results were compared with 12 patients undergoing myectomy alone. Postoperatively, patients treated by mitral valve extension had less mitral insufficiency ($p< 0.005$), less residual systolic anterior mortion ($p< 0.01$), greater improvement in New York Heart Association functional class ($p= 0.05$), and greater reduction in the number of drugs ($p< 0.005$). We conclude that mitral leaflet extension in combination with myectomy is a promising new surgical approach that may provide superior results to those of myectomy alone.

In Chapter 7, we measure the coronary flow reserve (CFR) and coronary resistance (CRR) (CRR= CFR corrected for the enddiastolic pressure) in 10 patients with hypertrophic cardiomyopathy and in a control group of 8 asymptomatic cardiac transplant recipients. Both CFR and CRR were reduced in hypertrophic cardiomyopathy (1.8 $\pm$ 0.9 vs. 2.6 $\pm$ 0.8, $p< 0.05$; 1.5 $\pm$ 0.6 vs. 2.6 $\pm$ 0.8, $p< 0.05$, respectively). End-diastolic interventricular septal wall thickness was significantly increased, arteriolar lumen divided by wall area (AL) was lower and capillary density tended to decrease in patients with hypertrophic cardiomyopathy (25.8 $\pm$ 2.9 vs. 11.4 $\pm$ 3.0 mm, $p< 0.05$; 21 $\pm$ 5% vs. 30 $\pm$ 4%, $p< 0.05$; 1824 $\pm$ 424 vs. 1445 $\pm$ 513 per mm^2, respectively). The decrease in CRR was linearly related to a reduction in AL. Further analysis revealed that CRR,AL and capillary density were all linearly related to the degree of hypertrophy. It is concluded that decrements in CRR are related to changes in the microcirculation and that both the decrease in CRR and changes in the coronary microcirculation are related to the degree of hypertrophy.

In Chapter 8, we investigate which other haemodynamic and echocardiographic factors, besides changes in the microcirculation, are responsible for reduction in coronary flow reserve in patients with hypertrophic obstructive cardiomyopathy. For this study, we calculated CFR in patients with hypertrophic obstructive cardiomyopathy (N=10) and in cardiac transplant recipients (controlgroup, N=8). As seen before, CFR was reduced in patients with hypertrophic cardiomyopathy. An increase in the thickness of the septal myocardium ($p= 0.005$), indexed left ventricular mass ($p= 0.005$), left ventricular enddiastolic pressure ($p= 0.0002$) and the left ventricular outflow tract gradient ($p=0.03$) were are related to the reduction in CFR. We conclude that both haemodynamic and echocardiographic factors and changes in the microcirculation may contrib-

ute to the occurence of ischaemia in patients with hypertrophic cardiomyopathy.

In Chapter 9, we have analysed whether the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism, the angiotensin II type 1 (AT1-R) A/C^{1166} polymorphism and/or plasma renin activity influenced left ventricular hypertrophy in patients with hypertrophic cardiomyopathy. Left ventricular mass index (LVMI) and interventricular septal thickness (IVS) were determined by two-dimensional echocardiography in 104 genetically independent subjects with hypertrophic cardiomyopathy. The ACE D allele and the plasma renin activity were not associated with more extensive left ventricular hypertrophy. However, LVMI was higher in patients carrying the C allele than in AA homozygotes (190 ± 8.3 vs. 168 ± 7.2 g/m^2, $p< 0.05$). A similar pattern was observed for IVS thickness (23 ± 0.7 vs. 21.6 ± 0.7 mm, $p= 0.162$). Statistical analysis showed that the AT1-R C^{1166} allele modulated the phenotypic expression of hypertrophy in hypertrophic cardiomyopathy independently of plasma renin and the ACE I/D polymorphism.

Samenvatting

Hypertrofische cardiomyopathie werd als ziektebeeld voor het eerst beschreven door Brock in 1957. De ziekte wordt veroorzaakt door een mutatie in een van de genen welke coderen voor eiwitten van de cardiale sarcomeer. Hypertrofische cardiomyopathie is een fascinerende aandoening mede door de variatie in presentatie, natuurlijk beloop en behandeling.

Het doel van de in dit proefschrift beschreven studies is de evaluatie van het natuurlijk beloop van de ziekte, de evaluatie van nieuwe beeldvormende en chirurgische technieken en het onderzoek naar pathofysiologische processen die de klachten van de patient kunnen verklaren.

Hoofdstuk 1 is een overzichtsartikel betreffende hypertrofische cardiomyopathie en behandelt de meest recente opvattingen betreffende de pathologie, prevalentie, symptomatologie, natuurlijk beloop, behandeling en veranderingen in het genetische materiaal welke verantwoordelijk zijn voor de ziekte.

In hoofdstuk 2, wordt het natuurlijk beloop van de ziekte beschreven in een populatie van 113 patienten met hypertrofische cardiomyopathie. De gemiddelde leeftijd bij aanvang van de studie van de patienten was 37 ± 16 jaar (spreiding 5 - 71 jaar). Na een periode van gemiddeld 7 (± 5) jaar, waren er 13 patienten overleden; elf ten gevolge van een cardiale en twee ten gevolge van een niet cardiale oorzaak. De cardiale mortaliteit was 1% per jaar (95% betrouwbaarheidsinterval 0.2 - 1.8%). De cardiale mortaliteit in deze studie was beduidend lager dan de mortaliteit van 2 tot 4% per jaar welke in eerdere prognose studies werd gerapporteeerd. Het verschil in cardiale mortaliteit kan worden verklaard door de uiteenlopende samenstelling van de patienten-populaties. De populatie in onze studie was als volgt samengesteld: (a) patienten die primair poliklinisch of klinisch in het "Dijkzigt ziekenhuis" werden gediagnostiseerd (b) patienten die werden verwezen door cardiologen uit perifere centra ten behoeve van gespecialiseerde zorg (c) patienten waar tijdens keuring of routine cardiologische evaluatie de diagnose hypertrofische cardiomyopathie werd gesteld (deze patienten hadden in het algemeen geen cardiale klachten) (d) familieleden van patienten; deze personen werden op eigen verzoek onderzocht op aanwezigheid van de afwijking. De eerdere prognose studies waren voornamelijk afkomstig van zogenaamde tertiare klinieken; de patienten populatie werd hier voornamelijk gedomineerd door patienten met ernstige symptomen, patienten met een verhoogd risico op plotse dood en patienten die werden verwezen voor chirurgische interventie. Het is aannemelijk dat de prognose in deze patienten aanzienlijk wordt beinvloed door de zogenaamde "referral bias". De patienten in onze studie waren minder geselecteerd en wij concluderen dat patienten met een hypertrofische cardiomyopathie een relatief goede prognose hebben.

In hoofdstuk 3, wordt het beloop van de zwangerschap beschreven bij 9 patienten met een hypertrofische cardiomyopathie. Vier vrouwen hadden reeds voor de zwangerschap cardiale klachten (angina en/of dyspnoe), vijf patienten

hadden reeds een myectomie ondergaan vanwege een linker ventrikel uitstroombaan obstructie en bij 2 patienten werd er middels Doppler echocardiographie een belangrijke gradient (> 35 mm Hg) over linker ventrikel uitstroombaan gevonden. De 9 patienten maakten 20 zwangerschappen door. In 2 patienten namen de cardiale klachten toe tijdens de zwangerschap; een van deze patienten moest worden behandeld met diuretica wegens tekenen van hartfalen. Vijf zwangerschappen eindigden in een spontane abortus. In dertien van de 15 zwangerschappen vond er een vaginale bevalling plaats, in 2 gevallen werd de zwangerschap beeindigd middels een keizersnede wegens foetale nood. In de perinatale periode hebben zich zowel bij de patienten als de neonaten geen cardiale complicaties voorgedaan.

De resultaten van deze studie tonen dat patienten met een hypertrofische cardiomyopathie een zwangerschap goed kunnen doorstaan mits adequate cardiologische en obstretische begeleiding gewaarborgd is. Een keizersnede is alleen aangewezen bij een obstretische indicatie.

In Hoofdstuk 4, worden de veranderingen in vorm van de linker ventrikel uitstroombaan bij patienten met een hypertrofische cardiomyopathie beschreven. Met transthoracale driedimensionale echocardiografie werd de linker ventrikel uitstroombaan bestudeerd in 17 patienten met een hypertrofische cardiomyopathie en in 10 patienten zonder cardiale afwijkingen. Zowel de verhouding tussen de oppervlakte van de grootste en de kleinste dwarsdoorsnede als de verhouding tussen de maximale en minimale diameter van de kleinste dwarsdoorsnede was duidelijk toegenomen in patienten met een hypertrofische cardiomyopathie in vergelijking met de controle patienten (respectievelijk 2.6 ± 0.9 versus 1.4 ± 0.2, $p< 0.0001$ en 1.6 ± 0.3 versus 1.2 ± 0.1, $p< 0.001$). Patienten met een hypertrofische cardiomyopathie worden gekenmerkt door een asymmetrische vorm van de linker ventrikel uitstroombaan en door een afname van de oppervlakte van de kleinste dwarsdoorsnede in vergelijking met de controle patienten.

In hoofdstuk 5, worden de eigenschappen van een instrument besproken welke gebruikt wordt voor de chirurgische behandeling (septale myectomie) van patienten met een hypertrofische obstructieve cardiomyopathie. Dit instrument, ontworpen in het Thoraxcentrum-Rotterdam, bewerkstelligt resectie van het septale myocard middels vonkerosie.

Hoofdstuk 6 beschrijft de resultaten van een nieuwe chirurgische therapie voor patienten met een obstructieve hypertrofische cardiomyopathie. Bij deze behandeling wordt naast de klassieke myectomie een plastiek van de voorste mitralisklep slip uitgevoerd met pericard van de patient. In totaal werden er 8 patienten volgens de nieuwe techniek behandeld. De resultaten van gecombineerde myectomie en mitralis klepplastiek worden vergeleken met de resultaten van de klassieke myectomie welke plaatsvond in 12 patienten. Na operatie blijkt er in patienten die met de gecombineerde techniek zijn behandeld minder mitralisklep insufficientie te bestaan ($p< 0.005$), is de kenmerkende

beweging van het voortse klepblad ("systolic anterior mortion") meer teruggebracht ($p< 0.01$), is er een grotere verbetering in de functionele klasse ($p=0.05$) en is er een grotere afname van de hoeveelheid voorgeschreven medicamenten ($p< 0.005$) in vergelijking met patienten die alleen behandeld zijn met myectomie. De combinatie van myectomie en plastiek van het voorste mitralisklepblad is een nieuwe, veelbelovende chirurgische benadering voor patienten met een obstructieve hypertrofische cardiomyopathie. Een studie met grotere patienten aantallen zal de plaats van de nieuwe techniek moeten bepalen.

Hoofdstuk 7 beschrijft de coronaire bloedstroom reserve ("coronary flow reserve" (CFR)) en coronaire weerstand reserve (CRR) (CRR= CFR gecorrigeerd voor de einddiastolische druk) bij 10 patients met een hypertrofische cardiomyopathie en bij een controle groep van 8 asymptomatische patienten na een harttransplantatie. Zowel de CFR als de CRR waren afgenomen in patienten met een hypertrofische cardiomyopathie (respectievelijk 1.8 ± 0.9 versus 2.6 ± 0.8, $p< 0.05$ en 1.5 ± 0.6 versus 2.6 ± 0.8, $p< 0.05$). De eindiastolische septale interventriculaire ventrikel wanddikte was aanzienlijk toegenomen bij patienten met een hypertrofische cardiomyopathie (25.8 ± 2.9 versus 11.4 ± 3.0, $p < 0.05$). Tevens werd vastgesteld dat het lumen van de arteriolen gecorrigeerd voor de oppervlakte van de vaatwand (AL) afgenomen was en dat er een tendens was tot afname van de capillaire dichtheid bij patienten met een hypertrofische cardiomyopathie (respectievelijk $21 \pm 5\%$ versus $30 \pm 4\%$, $p< 0.05$ en 1824 ± 424 versus 1445 ± 513 per mm^2, p=NS). De afname van de CRR was rechtevenredig gerelateerd met de reductie van de AL. Bij verdere analyse bleek dat zowel de CRR,AL als de capillaire dichtheid rechtevenredig gerelateerd waren met de mate van hypertrofie. Op grond van deze resultaten concluderen wij dat de afname van de CRR gerelateerd is aan veranderingen in de microcirculatie en dat zowel de afname van de CRR als de veranderingen in de coronaire microcirculatie samen hangen met de mate van hypertrofie.

In hoofdstuk 8 wordt onderzocht welke haemodynamische en echocardiografische factoren naast veranderingen in de microcirculatie verantwoordelijk zijn voor de afname van de coronaire bloedstroom reserve bij patienten met een hypertrofische obstructieve cardiomyopathie. In deze studie werd de coronaire bloedstroom reserve (CFR) berekend in patienten met een hypertrofische obstructieve cardiomyopathie (N=10) en in een controle groep van 8 patienten na een harttransplantatie. Zoals reeds eerder geconstateerd, was de CFR afgenomen in patienten met een hypertrofische cardiomyopathie. Zowel een toename van de dikte van de septale interventriculaire ventrikel wanddikte ($p= 0.005$), een toename van de linker ventrikel massa gecorrigeerd voor de lichaamsoppervlakte ($p= 0.005$), een toename van de linker ventrikel einddiastolische druk ($p= 0.0002$) als de mate van de uitstroombaanobstructie ($p=0.03$) waren gerelateerd met de afname van de CFR. Deze haemodynamische en echocardiografische bevindingen kunnen naast veranderingen in de coronaire microcirculatie verantwoordelijk zijn voor het optreden van ischaemie bij

patienten met een hypertrofische cardiomyopathie.

In hoofdstuk 9, wordt bestudeerd of het "angiotensin-converting enzyme" (ACE) insertie/deletie (I/D) polymorfisme, het angiotensine II type 1 (AT1-R) A/C^{1166} polymorfisme en/of de plasma renine activiteit de linker kamer hypertrofie beinvloedt bij patienten met hypertrofische cardiomyopathie. Hiertoe werd de linker ventrikel massa gecorrigeerd voor de lichaams-oppervlakte (LVMI) en de dikte van het interventriculaire septale myocard (IVS) berekend met behulp van twee-dimensionale echocardiografie in 104 patienten met een hypertrofische cardiomyopathie. Het ACE D allele en de plasma renine activiteit waren niet gerelateerd met de mate van linker kamer hypertrofie. Echter zowel de LVMI als de IVS waren toegenomen in patienten die het C allele bezaten in vergelijking met de AA homozygoten (respectievelijk 190 ± 8.3 versus 168 ± 7.2 g/m^2 , $p< 0.05$ en 23 ± 0.7 versus 21.6 ± 0.7 mm, $p= 0.162$). Na statistische analyse blijkt het AT1-R C^{1166} allele de fenotypische expressie van linker kamer hypertrofie onafhankelijk van het plasma renine of het ACE I/D polymorfisme te beinvloeden.

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Curriculum Vitae

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