Hypertrophic cardiomyopathy (HCM) has historically been regarded as a complex and intellectually challenging cardiac disease (1–4). However, this disorder has also been a frequent source of frustration to clinicians and their patients. The therapeutic uncertainties of HCM are derived from its diverse pathophysiology and heterogeneous clinical spectrum (1–4). In addition, the striking morphologic and functional abnormalities characteristic of the disease, as well as certain dramatic features of its natural history (such as sudden death in the absence of prior symptoms), have conveyed a sense of urgency to develop novel and more effective treatments.

This complex interplay between investigative interest and therapeutic necessity has periodically exposed HCM patients to a broad range of innovative, but particularly bold or sometimes even questionable, treatment strategies. For example, massive doses of beta-adrenergic blocking drugs (e.g., up to one gram of propranolol per day) have been administered both to adults and children in an effort to improve symptoms and prevent disease progression (5). The argon ion laser has been proposed as an alternative to conventional surgical techniques for relieving outflow obstruction (6). More recently, dual-chamber pacemakers have been implanted in asymptomatic children without a subaortic gradient and with minimal left ventricular hypertrophy in an attempt to interfere with the powerful genetic forces that may lead to the development of outflow obstruction and the progression of hypertrophy during adolescence (7,8). Ultimately, these strategies have not been incorporated into the standard therapeutic armamentarium for the disease. The generally accepted treatment options currently available to clinicians include drugs (beta-blockers, verapamil and disopyramide) or surgery for the management of congestive symptoms, and the implantable cardioverter-defibrillator or amiodarone for those patients judged to be at high risk for sudden death (9–11).

NEW ALTERNATIVE THERAPEUTIC OPTIONS TO SURGERY

Currently, ventricular septal myotomy-myectomy (Morrow operation) represents the gold standard for the management of patients with a marked outflow gradient under basal conditions (≥50 mm Hg) and severe symptoms of heart failure refractory to medical therapy (New York Heart Association functional classes III or IV) (9–11). It should be emphasized, however, that patients with such clinical features represent only a minority of the overall HCM population (probably less than 5%) (10,11).

Considerable data assembled over more than 30 years from a number of centers indicate that about 70% of patients report substantial and persistent symptomatic improvement for five or more years after surgery, and that the basal outflow gradient is abolished or greatly reduced in more than 90% of patients (9–16). Because it is not known whether surgery prolongs survival or reduces the risk of sudden cardiac death in HCM (3,4,9–11), septal myotomy-myectomy is only offered to severely limited patients to improve their quality of life. However, to achieve maximal benefit with an acceptably low risk (≤2% operative mortality) (9,10,12,16), myotomy-myectomy must be performed by surgeons with extensive experience with this operation. Because such expertise is available only at a few centers in the world, there is ample justification for the development of therapeutic alternatives to the operation.

Indeed, the recent explosion in cardiovascular technology and interventional cardiology has in the process also generated new potential therapeutic options for patients with HCM. Proposed alternatives to surgery now include dual-chamber pacing and the induction of localized ventricular septal infarction by infusion of ethanol into a major septal perforator branch of the left anterior descending coronary artery. Although these therapeutic approaches may ultimately prove to have merit, certain important distinctions should be made between these two very different techniques.

Dual-chamber pacing has now been employed in HCM for about eight years, but its true efficacy remains uncertain. Pacing may impair diastolic function (17,18), and the reduction in the outflow gradient is greatly variable and generally much more modest than with surgery (19–24).
Indeed, objective evidence of improved functional capacity (such as increased exercise time and peak oxygen consumption) have not been convincingly demonstrated with pacing (19–24). Well-controlled, randomized studies indicate that the symptomatic improvement during pacing reported in observational investigations is consistent with a placebo effect in most patients (22,24,25). These persisting uncertainties regarding the role of dual-chamber pacing in the treatment of patients with obstructive HCM are also reflected in the recent ACC/AHA Guidelines for Implantation of Pacemakers and Antiarrhythmia Devices. Pacing was assigned to class IIb for those patients with obstruction and symptoms refractory to medical therapy, and to class III for patients with obstruction and symptoms responsive to drug treatment (26).

Alcohol septal ablation must still be regarded as an experimental procedure, but it seems to have a more substantial influence than pacing on the outflow gradient of patients with HCM (27–30). At present, studies assessing the efficacy of this technique on symptoms are short-term and objective evidence of improved exercise capacity is still limited. The rate of complications, including death, is also unresolved and seems to differ considerably amongst individual practitioners, being closely related to the level of expertise with the procedure. For example, septal ablation not uncommonly necessitates permanent pacemaker implantation due to the creation of high-grade atrioventricular block (27,28,30). Also, because the period of follow up is brief, the long-term safety of septal ablation is unresolved. This is of concern because it is possible that the alcohol-induced scars in the ventricular septum could ultimately increase the arrhythmogenicity of a left ventricle already prone to complex and potentially life-threatening arrhythmias. This applies particularly to patients undergoing septal ablation relatively early in life who would be exposed to this risk for a large portion of their life span. Because of these difficult issues, septal ablation at an acceptably low risk requires a high level of expertise, which is available only at those few referral centers that perform a sufficiently high number of procedures.

Other uncertainties are a natural consequence of the fact that most specialists in interventional cardiology, despite their considerable cardiovascular expertise, may not have extensive experience with HCM. Such a mismatch could translate into misleading perceptions that newly proposed therapies (such as septal ablation or pacing) prolong survival and prevent sudden death and thus represent appropriate treatment approaches for all HCM patients with an outflow gradient, including those with no or only mild symptoms.

Therefore, it may be appropriate to re-examine our understanding of the pathophysiology and clinical course of HCM in order to draw attention to certain specific issues, including appropriate patient selection, that could be overlooked in the enthusiasm for new treatment strategies. As experience grows, these general considerations can serve as a platform upon which to establish the most prudent use of these therapies throughout the broad clinical spectrum of HCM.

**NATURAL HISTORY**

Until a few years ago, the literature projected a rather dismal clinical picture of HCM, in which most patients experienced either progression to incapacitating symptoms of heart failure or premature and often sudden cardiac death. More recently, however, we have come to appreciate how profoundly the overall perception of this disease has been influenced by biases in patient referral (31,32). Indeed, most of the published studies on HCM have emanated from a small number of tertiary institutions focused on the study and management of this disease (31). Because patients with severe symptoms, or those at high risk for sudden death, have been preferentially referred to these centers, the image of HCM projected in the literature has been based primarily on the most extreme expressions of the disease spectrum (31,32).

In recent years, a number of studies have described the clinical course of HCM in largely unselected patient cohorts that were more representative of the overall disease spectrum (31,33–38). Such studies have shown that many patients have a favorable clinical course and may achieve normal life expectancy, often without important symptoms, and even in the presence of substantial subaortic obstruction at rest (31,33–38). Indeed, many HCM patients have only mild symptoms that are usually controlled by medications and do not, per se, justify aggressive interventions (10,11,31,33–38). Furthermore, during the last few years, systematic clinical and genetic screening of HCM pedigrees has identified many affected but asymptomatic family members of all ages who might otherwise have gone undetected (10,39–42). Therefore, after four decades of intense investigation, a less pessimistic and more balanced view of HCM is emerging, in which the disease may often be associated with little or no disability and a favorable prognosis.

**PATHOPHYSIOLOGY**

Our understanding of the determinants of clinical course in HCM has also evolved substantially. The dynamic left ventricular outflow gradient initially captured the attention of investigators in the early 1960s and continues to be the most visible and quantifiable hemodynamic alteration of the disease. Indeed, before the advent of echocardiography, clinical identification of HCM was virtually confined to those patients with a loud heart murmur (associated with the outflow gradient). Consequently, at that time, the
obstructive form seemed to represent virtually the entire clinical spectrum and the subaortic gradient was often identified with the disease itself (43). We now realize that most HCM patients have the nonobstructive form (9–11) and, in many patients, the outflow gradient is compatible with normal longevity in the absence of significant symptoms (10,11,31,33–38).

The present discussion is focused on obstructive HCM because the new treatment modalities under consideration here are confined to this hemodynamic form of the disease. Therefore, it is worth summarizing the significance of the outflow gradient in HCM as follows. It is not usually appropriate to intervene with operation (or potential surgical alternatives) based solely or largely on the presence of a gradient. On the other hand, when the outflow gradient is believed to be a major determinant of severe symptoms unresponsive to medical therapy, then its reduction by such interventions is justifiable and desirable.

CLINICAL TRIALS IN HCM: THE IMPORTANCE OF PROPER PATIENT SELECTION

These evolving views on the natural history and pathophysiology of HCM serve as a reference point upon which to formulate patient selection criteria for trials testing new treatment strategies. A comparison with coronary artery disease may help to clarify the unique problems traditionally associated with establishing consistent and reliable approaches to the management of HCM. Because ischemic heart disease is a common and relatively homogeneous disorder, advances in treatment have been based on the vast clinical experience accumulated by many clinicians and investigators throughout the world with a large number of patients. Conversely, because HCM is an uncommon and particularly heterogeneous condition, new treatment strategies have often been proposed on the basis of limited experience derived from small, highly selected patient cohorts, and subsequently extrapolated to the overall disease spectrum.

These considerations raise the possibility that some HCM patients destined to experience a favorable clinical course will, nevertheless, be exposed to unnecessary interventions as a consequence of well-intentioned enthusiasm for innovative therapeutic approaches. For example, in less than three years, alcohol septal ablation has been performed in a total of more than 300 HCM patients at two centers in Germany that have been rapidly accumulating a large experience with this technique (44–47). In contrast, it has taken about 20 years to perform a similar number of septal myotomy-myectomy operations at two major surgical referral centers for HCM in North America (12,15,16). Such demographics raise the possibility that the generally accepted patient selection criteria for surgery, i.e., a marked outflow gradient under basal conditions and severe symptoms (New York Heart Association functional classes III or IV) refractory to drug treatment (9–16) may have been softened. Indeed, recent trials evaluating the efficacy of pacing or septal ablation in HCM have included many mildly symptomatic patients, as well as patients in whom subaortic obstruction was not present at rest but was evident only under provocative conditions (23,27–30), including some in whom gradients were induced solely with dobutamine (30,48). It is well-documented that such dynamic subaortic gradients can be induced not only in patients with HCM, but also in normal subjects, using a variety of agents or maneuvers (including dobutamine) (49,50). Unless caution is exercised, gradients generated artificially in nonobstructive patients may be inappropriately used as an indication for invasive procedures. Indeed, the application of anything less than strict patient selection criteria and study designs will make it exceedingly difficult to discern whether these potential alternatives to surgery are truly effective in treating patients with HCM.

CONCLUSIONS

Current approaches to developing and testing new treatment strategies for obstructive HCM should be consistent with the evolution in our understanding of the natural history and pathophysiology of this challenging disease. There is now convincing evidence that many patients with HCM experience a favorable clinical course in the absence of important disability. Although we do not wish to inhibit the well-intentioned efforts of many investigators we, nevertheless, believe that a note of caution is warranted regarding new invasive treatment strategies in this disease. Appropriate patient selection is crucial to designing clinical trials that assess the efficacy of these innovative interventions on the hemodynamics and clinical course of HCM. Only by enrolling patients with marked outflow obstruction under basal conditions and severe symptoms refractory to drug therapy (who would otherwise be regarded as candidates for surgery), will the interests of both clinical investigation and patient care be fully preserved.

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