Hypertrophic Cardiomyopathy: The Past, the Present, and the Future

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The Past

The Birth of HCM

Three patients with what now appears to have been HCM were described by French physicians in the late 1860s [1–3]. Perhaps of greatest interest is the case reported by Liouville. A 75-year-old woman developed worsening dyspnea and was found to have a systolic heart murmur and died shortly after presentation [2]. The autopsy report stated:

> The left ventricle is enlarged and very thick. It has considerable concentric hypertrophy measuring 3.5–4 cm in width. When I insert my index finger from the ventricle toward the aortic outflow tract, my finger becomes tightly pinched in the myocardium, 1 cm below the aortic valve. The aortic valve itself does not appear to be stenosed or calcified. When I try to insert my thumb backward through the aortic valve toward the ventricle, it cannot reach my index finger that I have inserted from the opposite direction. This is due to the obstruction that is caused by the myocardial thickening that is situated below the level of the aortic valve (my emphasis).

Liouville's description of the combination of left ventricular hypertrophy and muscular subaortic stenosis leaves little doubt that this patient suffered from HCM. She lived for 75 years, an age that exceeded double the life expectancy at the time, and her clinical course appeared to have been benign for many years. Seven decades before the measurement of intraventricular pressures in patients, Liouville clearly articulated the concept of intraventricular obstruction.

In 1907, Schmincke, a German pathologist, described the hearts of two women who had been in their 50s, both of which showed considerable left ventricular hypertrophy [4]. He wrote: "Diffuse muscular hypertrophy of the left ventricular outflow tract causes an obstruction. The left ventricle has to work harder to overcome the obstruction. So, the primary hypertrophy will be accompanied by a secondary hypertrophy causing an incremental (further) narrowing of the outflow tract." Thus, he proposed a vicious circle of ventricular hypertrophy leading to muscular obstruction, which stimulates more hypertrophy, leading to further obstruction, etc.

Sudden Death

The next key clinical-pathologic observation in the unfolding story of HCM was the association of ventricular hypertrophy of unknown etiology with sudden death in 1929 [5]. In 1944, Levy and von Glahn published an influential paper describing ten patients entitled "Cardiac Hypertrophy of Unknown Cause" [6]. This appears to have been the first series of patients with HCM observed clinically, studied by ECG and chest radiography and then at necropsy. Notably, three of their patients died suddenly. They wrote: "These cases appear to form a clinical group of which the chief features are: marked cardiac hypertrophy, symptoms of cardiac insufficiency and occurrence of various types of arrhythmia. The hearts, at autopsy, all show hypertrophy of the muscle fibers."

Familial Occurrence

An important milestone was the discovery of familial association in some patients with idiopathic left ventricular hypertrophy. In 1949, Evans reported five patients with idiopathic left ventricular hypertrophy who came from two families and termed the condition "familial cardiomegaly" [7]. In 1957, Teare, a London pathologist, described nine patients with massive hypertrophy of the interventricular septum, myocyte hypertrophy and disarray, as well as interstitial fibrosis. Little clinical information on these patients was

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provided except that eight of them had died suddenly and that two of them were siblings [8].

Thus, by the late 1950s, prior to the development of left heart catheterization, a syndrome was emerging which may be described as follows: idiopathic left ventricular hypertrophy, often severe and usually involving primarily the interventricular septum, which could cause intraventricular obstruction, was sometimes familial and could result in sudden death [9].

Elucidation of Pathophysiology

In 1955, Sir (later Lord) Russell Brock, a distinguished British cardiac surgeon, reported that congenital pulmonic valvular stenosis causes secondary subvalvular stenosis, and following successful pulmonary valvotomy, the obstruction moved from the valve to the subvalvular region [10]. He proposed that the same situation could occur in the left side of the heart and indeed reported on patients with aortic valvular stenosis and others with long-standing hypertension who came to operation with what he considered to be secondary muscular subaortic stenosis. He termed this condition "acquired aortic subvalvular stenosis" [11] and considered it to be analogous to the muscular subpulmonic obstruction that he had described previously in patients with congenital pulmonic stenosis.

In 1958, A. Glenn Morrow, the Chief of Cardiac Surgery at the NIH, and I studied two young men with severe dyspnea and angina who had high subaortic pressure gradients and who we thought had congenital membranous subaortic stenosis, a relatively rare congenital anomaly. When Morrow opened the heart at the time of open-heart surgery and potassium-induced cardioplegia, no subaortic obstruction was observed, although the left ventricle appeared to be hypertrophied. We reported these two patients and stated that: "with the delineation of its clinical, hemodynamic, angiocardiographic and anatomic features, HCM[1] emerges as a specific entity which can be distinguished preoperatively from discrete valvular and subvalvular aortic stenosis" [12]. At about the same time, Brock studied similar patients with hypertrophic subaortic obstruction but without muscular hypertrophy secondary to aortic stenosis or long-standing hypertension. He wrote, also in 1959: "That this is not an isolated case is made clear by the experience of Dr. Glenn Morrow who tells me he has operated on two similar cases in two young men in their early twenties; both survived. He has kindly allowed me to mention these prior to his own report of them (Morrow and Braunwald, Circulation, in press, 1959)" [13].

[1]In this report, we referred to the condition as "functional aortic stenosis" and subsequently as "idiopathic hypertrophic subaortic stenosis" (IHSS). The preferred term now is hypertrophic cardiomyopathy (HCM), which is used throughout this chapter.

Dynamic and Variable Obstruction

Thus, by 1959, HCM had entered a new era, in which hemodynamic studies were employed for both diagnosis and elucidation of the pathophysiology of the condition. An increasing number of patients were discovered and attention focused on the obstruction to left ventricular outflow. It soon became apparent that the obstruction in these patients differed from the fixed discrete obstruction produced by aortic valvular, subaortic, or supra-aortic stenoses. Instead, in HCM left ventricular outflow tract obstruction was both dynamic and variable [14], dynamic, in the sense that a variety of physiologic and pharmacologic stimuli altered its severity [15]. Interventions which reduce the size of the left ventricle (and, we presumed, the diameter of the outflow tract) were shown to increase the severity of obstruction [16]. Such interventions could also provoke obstruction in patients with HCM without obstruction in the basal state. These included (1) an increase in left ventricular contractility, such as exercise or the administration of a positive inotropic agent (isoproterenol), and (2) a reduction in ventricular preload, such as sudden standing, the strain phase of the Valsalva maneuver, or nitroglycerine administration. The opposite, i.e., transient reduction in severity or disappearance of obstruction, occurred with interventions that increased left ventricular volume, such as suddenly assuming the recumbent position, squatting, handgrip, or the infusion of a vasoconstrictor without inotropic properties (phenylephrine) [15].

The variability of the obstruction was evident in patients who had severe obstruction at one catheterization and far less or even no obstruction several days later [17]. In familial HCM, some affected individuals consistently exhibited obstruction, while others in the same family with left ventricular hypertrophy had obstruction only on provocation; in still other members of the same family, although left ventricular hypertrophy was noted, obstruction was not present at baseline and could not be provoked [18, 19].

Despite the obstruction, a large majority of patients had normal or even supranormal ejection fractions. Diastolic dysfunction was almost always present, with elevation of the left ventricular end diastolic pressure, while the left ventricular end-diastolic volume was normal. Reduced compliance of the hypertrophied left ventricle with increased interstitial fibrosis was thought to play a role [20–22]. The diastolic dysfunction could restrict inflow into either the left or right ventricle [23]. The unusual hemodynamic findings summarized above aroused widespread interest, and in the 1960s, HCM became something of a "poster child" of how the several newly developed techniques of left heart catheterization could provide a new understanding of cardiac pathophysiology. By the late 1960s, HCM was recognized with increasing frequency around the world, and a clinical picture emerged which remains pertinent today [15, 24].

The Present

Clinical Findings

Patients can be of any age between infancy and advanced age, and a family history with autosomal dominant inheritance is observed in about half; in others it appears to occur sporadically. In most patients the course is largely benign; indeed, many patients, particularly those detected in family studies (see below), or at the age of 60 or above, are asymptomatic, and they remain so for their entire lives [25].

Angina pectoris and exertional dyspnea are the most common symptoms and range from mild to severe. Presyncope and palpitations are common. The most common cause of death is sudden [8, 24], which may be preceded by syncopal episodes [26, 27]; less frequently, death results from severe obstruction leading to frank systolic and/or diastolic heart failure [28, 29].

On examination, patients with obstruction to left ventricular outflow have a rapidly rising arterial pulse. A left ventricular lift and a double apical impulse are frequently present. A fourth heart sound is usually audible. A loud (Gr $\geq$ 3/6) medium-pitched systolic ejection murmur may be heard along the left sternal border, where it may be accompanied by a thrill. The above-mentioned interventions which increase obstruction, such as sudden standing, increase the intensity and duration of this murmur, while those which reduce obstruction, such as sudden squatting, diminish or even abolish the murmur [15]. Most patients with obstruction also have a holosystolic murmur of mitral regurgitation at the cardiac apex. The ECG typically shows left ventricular hypertrophy and sometimes exhibits abnormally deep and wide Q waves, reflecting septal hypertrophy, rather than myocardial infarction [15]; atrial fibrillation which occurs not infrequently in patients with severe outflow tract obstruction is poorly tolerated. Since the ECG is occasionally normal, electrocardiography is not an adequate screening test to exclude HCM, although a routine ECG showing the characteristic changes can lead to the discovery of unsuspected HCM.

Echocardiography

Until the development of echocardiography, left heart catheterization, with its accompanying discomfort, cost, and risk (albeit low), was necessary for the diagnosis of HCM with obstruction. Obviously, catheterization is not ideal for screening nor for regular follow-up examinations once the diagnosis has been established. Therefore, when echocardiography became available as a clinical tool, it was quickly applied to patients with known or suspected HCM and filled an important void by permitting safe, painless, and inexpensive noninvasive diagnosis [30]. This development ushered in what may be considered the "modern" era of HCM. Even the early M-mode echocardiograms provided a far more precise characterization of the severity of left ventricular hypertrophy than did the electrocardiogram and chest radiogram. Further, echocardiography demonstrated the characteristic asymmetry of ventricular hypertrophy; in most patients the ratio of the thickness of the septum to the posterior wall exceeded 1.3 [31]. An important echocardiographic finding, systolic anterior motion of the mitral valve (SAM), which made contact with the interventricular septum, was present in most HCM patients with obstruction [32], and the severity of obstruction correlated with the duration of this contact. Subsequently, two-dimensional echocardiography refined the localization of the hypertrophy [33] and allowed recognition of a variety of uncommon but important subtypes, including apical HCM (in which severe hypertrophy predominates at the left ventricular apex), patients with heart failure with preserved ejection fraction secondary to severe concentric hypertrophy, patients with severe diastolic dysfunction, and those with left ventricular dilatation and heart failure with reduced ejection fraction (usually patients who had previously had severe obstruction [28, 29, 34]). Subsequently, the development of Doppler echocardiography allowed determination of the outflow tract pressure gradient [35], detection of the presence and severity of mitral regurgitation, and more precise characterization of diastolic dysfunction with slowed relaxation and filling of the hypertrophied left ventricle as well as increased left atrial volume [36, 37].

Echocardiography is now universally used for screening persons suspected of having HCM, including adolescents who wish to participate in competitive sports, the relatives of patients with the clinical diagnosis of HCM, and of those with characteristic genotypes (see below). It is also employed in following patients with established HCM and in assessing the effects of therapy. Three-dimensional echocardiography with speckle tracking provides even more detailed analysis of structure and function.

During the past decade, cardiovascular magnetic resonance imaging (CMRI) has been employed with increasing frequency [38]. Although considerably more costly than echocardiography, CMRI provides tomographic imaging and greater spatial resolution. It is capable of detecting hypertrophy in the small fraction of patients in whom it cannot be detected by echocardiography and can demonstrate apical aneurysms, as well as abnormalities of the mitral valve apparatus. Contrast-enhanced CMRI may also show late gadolinium enhancement (LGE), representing myocardial fibrosis, which, if extensive, may be responsible for ventricular arrhythmias and sudden death [39].

Treatment

Two modes of therapy for obstruction to left ventricular outflow – one pharmacologic, the other surgical – were developed in the 1960s.

Pharmacologic Therapy

Given the provocation and intensification of obstruction by beta-adrenergic agonists [16], in the 1960s it was logical to test the then newly developed beta-blockers in patients with HCM, and we found the latter to be effective, both hemodynamically [40] and clinically [41]. These drugs also have been reported to reduce or prevent exercise-induced outflow tract obstruction [42]. Beta-blockers continue to be "first-line" pharmacotherapy in HCM and appear to reduce the severity of angina in about one half of patients [43, 44]. Other drugs that have also been reported to be useful in patients who do not tolerate or fail beta-blockers are non-hydropyridine calcium channel blockers (verapamil or diltiazem) and disopyramide [44, 45]. The former can be substituted for a beta-blocker, and the latter may be added cautiously.

Invasive Therapy

It is clear that outflow tract obstruction, when severe, is usually associated with symptoms and adverse clinical outcomes [40, 46, 47]. In 1961, Morrow and Brockenbrough [48] and Kirklin and Ellis [49] developed left ventricular myectomy, a surgical procedure that was quite risky in the first decades of its use and therefore was limited to patients with severe obstruction who were seriously symptomatic. More recently, the procedure has become more extensive and more efficacious in the abolition of obstruction, as well as in the reduction of the associated mitral regurgitation, with surgical mortality rates of 2% or less *when it is carried out by experienced surgical teams* [50, 51]. The indications for myectomy include the presence of severe obstruction (a systolic pressure gradient >50 mmHg at rest or with provocation) and the persistence of severe symptoms (angina, dyspnea, and/or syncope) despite pharmacologic therapy [26]. The majority of patients become asymptomatic or almost so, and the long-term prognosis of survivors is excellent [52]. However, the number of surgical centers with substantial experience is relatively small, and eligible patients must often be referred to a site at a distance from their homes.

In 1995, alcohol septal ablation (ASA), another technique for the treatment of obstruction in HCM, was introduced by Sigwart [53] and has gained popularity as an alternative to surgical myectomy [51, 54–56]. Like myectomy, it appears to be effective in relieving obstruction, and its application should be limited to skilled interventionists, well trained in the performance of the procedure. Septal ablation is carried out by introducing a catheter into the first septal branch of the left anterior descending coronary artery, inflating a balloon, and injecting absolute alcohol distal to the balloon, thereby creating a septal infarction. Although the mortality from this procedure is low, atrioventricular block requiring a permanent pacemaker is required in up to 15% of patients, and in a small percentage of patients, ventricular tachyarrhythmias occur [55, 57, 58]. ASA has the distinct advantage of being percutaneous, with most patients discharged within 2 or 3 days and able to resume normal activities quickly. While a direct comparison between myectomy and ASA has not been carried out, operative and postoperative survival appear to be similar between the two techniques, but relief of obstruction is slightly less complete with ASA, and almost 10% of patients require a repeat procedure (ASA or surgical myectomy) [50].

For patients with HCM with intractable heart failure despite the successful relief of obstruction [28, 29], cardiac transplantation may be an option. In those who are not candidates for transplantation or for whom a donor heart is unavailable, the implantation of a left ventricular assist device, either as a bridge to transplantation or as destination therapy, may be considered [59].

Prevention of Sudden Death

In 1929, Whittle described an asymptomatic 20-year-old man who collapsed while riding a bicycle and died before reaching the hospital [5]. At postmortem examination, he had marked left ventricular hypertrophy of unknown etiology. As noted above, three of the ten patients with unexplained severe left ventricular hypertrophy reported by Levy and von Glahn died suddenly [6], and eight of the nine patients studied at necropsy by Teare with massive hypertrophy of the ventricular septum had died suddenly [8]. Among the patients whom we studied prospectively at the NIH and described in 1968, ten died of HCM; six of these were sudden and unexpected, and four were consequent to progressive heart failure [24]. Only one of the six sudden deaths occurred in a patient who had been symptomatic with severe obstruction in the basal state, while all four patients who died of heart failure had previously exhibited documented severe obstruction.

Sudden death is caused by ventricular fibrillation and remains the most common cause of death in HCM. Indeed, Maron has pointed out that it is the most common cause of non-violent death in the entire population of adolescents and young adults [26]. Because of the occurrence of this complication during competitive sports, this activity should be prohibited in patients with HCM [43].

The development of the implantable cardioverter/defibrillator (ICD) by Mirowsky et al. in 1980 [60] represents a major step forward in reducing the risk of sudden cardiac death in selected patients with HCM [26]. As pointed out by Maron et al., the availability of this device has challenged clinicians to identify patients with HCM who are at risk of

this usually fatal complication [61]. There is, of course, no argument about its use in secondary prevention, i.e. in patients who have survived an episode of cardiac arrest or sustained ventricular tachycardia. However, the ACC/AHA guidelines recommend that implantation of an ICD should also be considered in patients with HCM in whom sudden death has occurred in a first-degree relative, in patients with recent unexplained syncope as well as sustained and repetitive nonsustained ventricular tachycardia [43]. Other risk factors include failure of the blood pressure to rise on an exercise stress test and especially severe cardiac hypertrophy. Large areas of late gadolinium enhancement on CMRI are emerging as another risk factor for sudden death and may be an indication for ICD implantation as well [39, 61].

Genetics

A familial association with idiopathic ventricular hypertrophy, likely HCM, was described in 1949 [8, 62]. A large family of patients with familial HCM, of whom 77 were examined, was reported by Pare et al. in 1961 [63]. This family included six generations, and the transmission was in Mendelian autosomal dominant fashion. In our series, 40 of 126 (32%) patients were familial and demonstrated autosomal dominant inheritance [24]. C. Seidman and JG Seidman have pioneered the successful effort to uncover the genetic abnormality in HCM [64]. In 1990, they published a classic paper describing a mutation of a gene on chromosome 14 that encodes the beta-cardiac myosin protein [64, 65]. HCM has been shown to be a genetically heterogeneous disease, with more than 1500 mutations (largely missense mutations) on eight additional genes that encode other sarcomeric proteins (the myosin and actin proteins and the Z disc) associated with familial HCM and considered to be causal [65, 66]; mutations of six other genes are likely causal [62]. Such mutations have been found in about half of the patients with HCM; their expressivity is variable and the penetrance is age related.

Although it was hoped that the identification of these mutations could aid in risk stratification and become useful in guiding therapy, this now appears to be possible in only a small minority (approximately 5%) of patients who present with double or compound mutations and who are at high risk of adverse outcomes [67–71]. It has been suggested that HCM patients with a sarcomeric gene mutation exhibit more derangement of left ventricular function than do patients without a detectable myofilament mutation [72].

Genetic testing, now carried out by automated whole-exome DNA sequencing, should be carried out in patients in whom the clinical diagnosis of HCM has been established as well as in close relatives of patients with a specific sarcomeric mutation. Such testing can now be carried out rapidly and is becoming progressively less expensive. It has been found to be useful in identifying two groups of individuals [67–72]. The first are the relatives of patients with a sarcomeric mutation who are without the mutation, so-called "gene-negative" (G−) patients, who can be reassured that they will not develop HCM and who therefore do not need to be followed for this condition nor modify their lifestyles. The second group are the relatives of patients with HCM who harbor the mutation, i.e., gene positive (G+), and if these persons show no evidence of HCM by both clinical appraisal and imaging, they constitute a relatively new category of patients, so-called genotype positive and phenotype negative (G+/P−) [72]. Such patients should be screened by echocardiography at yearly intervals until their mid-20s and at 3–5-year intervals thereafter to detect overt disease.

The Future

Pathobiology

A number of challenges regarding a more complete understanding of HCM remain. The first is to understand better the effect of the causal mutations on myocardial function at the molecular level. Actomyosin cross-bridge cycling, variations in Ca++ sensitivity of the troponin complex, and reduction of tension development per unit of ATP hydrolyzed have been suggested [62].

The second is to ascertain the natural history of G+/P− subjects referred to above [72]. The identification of this group has enlarged dramatically, perhaps as much as doubling the total number of persons with an HCM mutation [73]. How many of them are likely to become P+ during their lives and at what age can routine follow-ups of G+/P− patients be discontinued? What is the first sign of P positivity in G+/P− persons? Is it ventricular hypertrophy or diastolic dysfunction [62], or is it LGE on contrast-enhanced CMRI? Additional questions include whether there are any clinical risks associated with G+ persons in the absence of any abnormalities by echocardiography [74]. Should such patients avoid participation in competitive sports? How should their genetic counseling be managed?

A third challenge is to learn more about G−/P+ patients [72]. How many have familial HCM whose mutations simply have not yet been discovered? How many have new mutations? How many are truly "sporadic?" Importantly, what are the natural histories of patients in each of these groups?

Therapy

There are many challenges for selecting and improving treatment. Although the drugs employed to reduce obstruction

(beta-blockers, non-dihydropyridine calcium blockers, and disopyramide) are considered to be beneficial [44] and are widely used, they have not been subjected to rigorous, placebo-controlled double-blinded, randomized trials [45]. Such trials should not be too difficult to perform because using a crossover technique, each patient can be his/her own control with placebo periods alternating with various drugs and combinations. The end points could be changes in symptoms, in exercise capacity, and in outflow tract obstruction as well as adverse drug effects.

Similarly, there have been no rigorous comparisons between the two mechanical interventions – myectomy and ASA [51, 55]. While it would be optimal to conduct a randomized trial, this is probably not possible because of the large sample size required and the necessity of having well-trained operators in both techniques available. Instead, consideration might be given to developing *prospective* registries in which detailed baseline characteristics are obtained to allow meaningful comparisons between similar groups of patients receiving the two interventions.

Finally, as the molecular consequences of the mutations responsible for the development of HCM become clearer, it is possible that tailored therapy could be developed that actually improves the natural history of HCM [73–77]. Drugs that inhibit myosin ATPase activity may modify genetically induced alterations in myocyte Ca^{2+} cycling, the Ca^{2+} sensitivity of contractile proteins, or the enhanced production of extracellular matrix. These actions might delay or even prevent the development of HCM in G+/P− persons or retard the progression of patients with clinically evident HCM.

HCM was first recognized almost 150 years ago. We have learned an enormous amount about this fascinating condition, but the story is still incomplete. Future progress is likely to require the continued collaboration of scientists and clinicians with expertise in many fields, including molecular and clinical genetics, biophysics, pathology, electrophysiology, interventional cardiology, and cardiac surgery.

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