It's a Long Road to Heal a Heavy Heart:

a Century of Hypertrophic Cardiomyopathy

University of Texas Southwestern Medical Center

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This is to acknowledge that Dr Turer, has disclosed that he does have financial interests or other relationships with commercial concerns related indirectly to this program [Gilead Sciences (ongoing clinical research as a site PI)]. Dr. Turer will be discussing off-label uses in his presentation (beta-blockers, verapamil, disopyramide, ethanol)

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Dr. Turer received his undergraduate degree in biology from the University of California- Los Angeles in 1996 and his medical degree from the University of California- San Francisco in 2001. He completed internal medicine residency and general cardiology fellowship at Duke University in 2004 and 2008, respectively. During that time he worked on myocardial metabolism in the context of ischemia-reperfusion with Drs Mihai Podgoreanu and Christopher Newgard; during this interval, he also met his wife-to-be, Christy. He then completed an interventional cardiology fellowship and Masters in Health Sciences degree in 2009, also from Duke University. He has been on staff at UTSW since 2009 working in the cardiac catheterization lab and at SPUH on the wards and in the clinic. He started the UTSW Hypertrophic Cardiomyopathy Clinic in 2014.

At any one time, Dr Turer is only one of five Turers on the University Campus. His wife, Christy, is dual-appointed in the Departments of Medicine and Pediatrics and his younger brother, Emre, is a GI fellow currently trying to find a cure for murine inflammatory bowel disease. Two sons, Sebastian (3yrs) and Edison (9m), attend the Callier Center, where they are actively engaged in various academic pursuits, including fingerpainting, block-stacking and potty-training. Dr Turer would desperately like to have a daughter.

Purpose and Overview

The purpose of this presentation is to educate physicians on the history of HCM management and update them on current clinical guidelines. The presentation will focus on current imaging, medical and surgical options, ICD therapy and genetic screening. Potential future directions will also be highlighted.

Learning Objectives:

(1) To understand the current role of imaging in the management of HCM.

(2) To know the available medical and surgical options for management of the symptomatic patient with HCM.

(3) To understand the risk of sudden death associated with HCM and the role of ICD therapy.

(4) To understand the role of genetic testing in patients and families with HCM.

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Introduction

Hypertrophic cardiomyopathy (HCM) continues to fascinate cardiologists today as it did a century ago; despite all that has been learned about the disease, many fundamental questions remained tantalizingly unanswered. While often thought of as a disease of *extreme physiology*- massive ventricular hypertrophy, sudden cardiac death, and severe heart failure- perhaps it is better regarded as a disease of *extreme variability*. The heterogeneity of clinical presentation and ventricular phenotypes, even within the same family, can be striking. From the clinician's standpoint, managing HCM is interesting because it unites imaging, genetics, hemodynamics, and surgical and interventional procedures.

HCM is not a particularly rare disorder- estimated to affect 1 in 500 individuals(9)- but the many mild cases may go undiagnosed. The tendency to diagnose the most severe cases bolsters our preconceived notion that HCM is a highly symptomatic and uniformly fatal condition. Indeed, the symptomatic patients are only the tip of the proverbial iceberg; an estimated one quarter of patients with HCM are symptomatic.(10) Therefore, most patients

remained undiagnosed, and those who do present, usually do so in adulthood, not childhood, as is commonly believed.

These statistics notwithstanding, HCM can be a dramatic condition and is relatively common. When we juxtapose these facts with the recognition that HCM was only first characterized fifty years ago, the history of its elucidation becomes all the more compelling and interesting. To be sure, there remains much to learn and understand about HCM pathogenesis. This review will summarize what is known about HCM, how our understanding of HCM evolved and the future of HCM of research and clinical care.

The Past

First Case Reports and Anecdotes

Although we generally attribute our current understanding of HCM to the work done primarily in England and the United States during the middle of the 20th Century, in fact there were several case reports and descriptions of patients with probable HCM in the medical literature in the late 1800's and early 1900s. It is important to recognize that the inability to either image the heart or perform hemodynamic assessments hindered the recognition of this condition in the living patient, particularly in light of the fact that the first symptom was often sudden death and other causes of heart failure (e.g. rheumatic heart disease) were far more common than HCM in day-to-day clinical practice.

In 1907, the German pathologist Alexander Schmincke described two unrelated patients who had severe left ventricular hypertrophy (LVH).(11) He noted particular hypertrophy of the left ventricular outflow tract (LVOT) and postulated that the obstruction may be leading to secondary hypertrophy which, in turn, could result in more obstruction. This important insight would be expanded upon fifty years later.

In 1931, a case of a 15 year-old boy with heart failure was presented in the Case Records of the Massachusetts General Hospital in the *New England Journal of Medicine*.(12) The patient died after a year of medical attention. No clear clinical diagnosis could be made, but at autopsy, the heart was noted to be markedly hypertrophied and weighed 500 grams. Gross and microscopic pathology was unrevealing. The attending pathologist, Dr Mallory, commented that he had never seen anything like it before. The attendees at the clinicopathological case conference were left puzzled:

> Dr Cabot*: I should say this is a scandalous state of things. It does not fit anything at all, does it?*
> Dr Mallory*: Nothing we know of at the present time. Yet it is an entity, and is interesting in showing how little we really know of heart failure.*
> Dr Cabot*: I should think this was "idiopathic hypertrophy." That is where the scandal comes in, because neither before death nor after it was any cause for the hypertrophy found. It is one of the cases which has to go down for the future as a marplot, marring any future diagnosis because it does not fit anything known so far.*

This case, as suggested by Eugene Braunwald decades later, was probably an early reported case of HCM and remains important as it was perhaps the first description of the clinical course, physical exam, diagnostic findings, and *post-mortem* examination of a patient.

In the subsequent twenty years, several small case series of patients with idiopathic hypertrophy, often associated with familial patterns of inheritance and sudden death were described. In 1958, a celebrated publication by the British pathologist, Donald Teare, appeared in the British Heart Journal.(6) It was entitled "Asymmetrical hypertrophy of the heart in young adults." Teare described nine patients with heart failure, most of whom had died suddenly, who were noted to have marked septal hypertrophy. Microscopic examination revealed "bizarre arrangements of muscle bundles…and considerable amounts of fibrosis." (**Figure 1**)

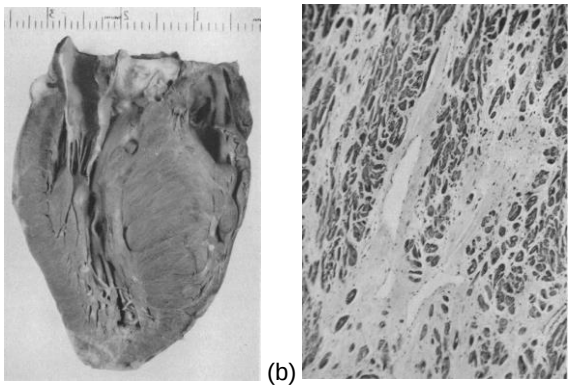


Figure 1: Teare's Landmark 1958 paper. (6) (a) Marked septal hypertrophy at autopsy in a patient who died suddenly; (b) marked interstitial fibrosis

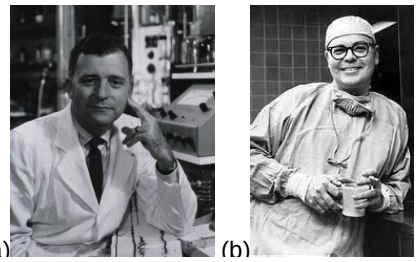
Over fifty years, scattered case reports and anecdotal descriptions had slowly given way to the more comprehensive, albeit still small, series of patients with idiopathic hypertrophy of the intraventricular septum. The obscure condition, as best as could be established at the time, was associated with heart failure, sudden death and a familial inheritance. What was lacking was an understanding of the etiology of the symptoms and the ability to identify patients with this condition *ante-mortem*.

The Celebrated Years at the NIH

The late 1950's and the first half of the 1960's saw tremendous progress in our understanding of HCM. This was certainly due in no small measure to rapid advancements in diagnostic modalities, most notably cardiac catheterization, and surgical techniques However, the catalyst for discovery was the appearance of a new brand of energetic physician-scientist who sought to understand the clinical observations they made by employing experimental techniques and detailed study. Without doubt, the most influential group in this field, was at the NIH led by a young Eugene Braunwald.

Eugene Braunwald arrived at the NIH (for the second time) as the director of the cardiac catheterization laboratory at age 28 after just having completing his medical residency at Johns Hopkins. By age 30 he had become the chief of cardiology at the National Heart Institute. Braunwald and his co-investigators at the NIH would go on to make a number of important contributions in cardiology. Notably, during this time, Braunwald would form a close working relationship to Andrew Glenn Morrow, a young cardiac surgeon (who would, ironically die of HCM-related complications 20 years later) (**Figure 2**). Together they formed the nucleus of the team which would go on to make some of the most celebrated discoveries in the clinical, hemodynamic and therapeutic characterization of HCM.

Figure 2: (a) Eugene Braunwald and (b) Glenn Morrow at the NIH



(a) (b)

The story began in 1958, when Glenn Morrow angrily summoned Braunwald to the operating room where a patient, sent by Braunwald to surgery for resection of presumed congenital subaortic stenosis, was on the table on cardiopulmonary bypass. Although Braunwald had documented a significant LV outflow tract gradient by cardiac catheterization, Morrow could find nothing wrong with the aortic valve, nor did he note any subvalvular ring. All he could see was that the ventricle was thicker than normal. While a despondent Braunwald returned to his office to call his mother, Morrow, at the request of Braunwald, rechecked the LV-aortic gradient once the heart was restarted. To his surprise, Morrow also noted a significant gradient.

The mysterious condition was to recur to months later, when another patient returned with the same hemodynamic and intra-operative findings. Morrow and Braunwald would conclude that the observed gradients were (1) real and (2) only seen in the working heart. Their first publication, entitled "Functional aortic stenosis: a malformation characterized by resistance to left ventricular outflow without anatomic obstruction," soon followed and detailed their first three cases of this obscure disease.(13) That same year in England, Sir Russell Brock, who had postulated the existence of this condition in the left ventricle based on his observations in the context of the right ventricle, published on his series of five patients with similar hemodynamic and clinical findings.(14)

Steadily, the number of cases and referrals increased, and by 1960, Morrow and Braunwald published the largest series of patients seen to date.(15) In that important work, they (1) emphasized that this condition can and should be identified based on clinical and hemodynamic grounds, (2) described their initial experience with the ventriculomyotomy, and (3) coined the condition idiopathic hypertrophic subaortic stenosis (IHSS). This term would be commonly used for another twenty years, and is still used today.[1]

One of the most fundamental features of IHSS would be the dynamic nature of the outflow tract gradient. Work at the NIH would go on to demonstrate the effects of those physiologic and pharmacologic manipulations which are often used today as diagnostic maneuvers. Administration of pro-contractility agents, such as isoproterenol or the digitalis glycoside ouabain, or dropping venous return to the heart (preload), such as with nitroglycerin or the Valsalva maneuver, were found to increase the gradient.(16-18) The group would also describe the hemodynamic finding of post-extrasystolic augmentation of the LVOT gradient which results in a drop in the aortic pulse pressure.(19) This finding could be used to differentiate the dynamic LVOT gradient from IHSS from the fixed gradient observed in e.g. aortic stenosis. This hemodynamic finding would later be given the eponym of the Brockenbrough-Braunwald-Morrow sign. (**Figure 3**)

[1] Since the 1970's the term IHSS is no longer favored, as subaortic stenosis is not a universal clinical feature and with elucidation of many causal genes, the etiology of the condition cannot strictly be considered idiopathic.

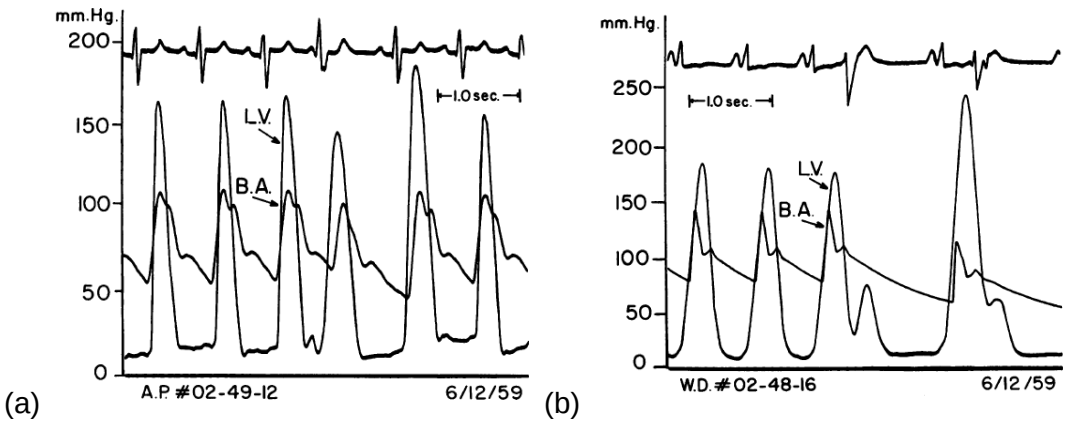


Figure 3: In (a) the post-PVC beat demonstrates no change or a slight increase in the pulse pressure, consistent with the patients's fixed LVOT obstruction from aortic stenosis. In (b) the post-PVC beat has a narrow pulse pressure from the increased obstruction from extra-systolic augmentation in the setting of IHSS- this is the Brockenbrough-Braunwald-Morrow sign. Figures from reference 11.

The mainstay of current medical treatment for the labile LVOT obstruction, namely the β-blocker, was established by Braunwald and coworkers over these early years. Researchers at the NIH had early access to these drugs and when given to patients with IHSS, significant reductions in resting and exercise-induced gradients were observed. In an early placebo-controlled clinical trial, Cohen and Braunwald showed that propranolol treatment led to significant improvements in hemodynamics, exercise-capacity and angina.(7)

In 1968, prior to leaving the NIH for UCSD, Frank and Braunwald reported on the largest series of IHSS patients followed for up to 12 years.(20) This 30-page report carefully detailed the electrocardiographic, hemodynamic, and physical exam features of all patients seen at the NIH over the prior decade. Most importantly, a detailed, longitudinal assessment of the clinical course of HCM was made, which highlighted several important features we still recognize today. First, the clinical courses were highly variable- some patients being extremely symptomatic and others minimally so. Furthermore, the LVOT gradient itself did not necessarily correlate with the degree of symptoms. Finally, they reported that six of the patients (~5%) experienced sudden death, giving the first estimate of this previously anecdotal risk.

The decade between 1958 and 1968 was the most formative time shaping our current concepts of HCM, and we owe much to the investigative spirit and energy of Braunwald, Morrow and their colleagues at the NIH. The diagnostic maneuvers and therapeutic approaches they discovered 50-years ago are still used today. Their discoveries are perhaps even more impressive when considering that ultrasound technology still had not been adapted to cardiac imaging- they used only the physical exam, electrocardiography, and careful hemodynamics.

The Present

Imaging

Advent of M-mode and 2-Dimenstional Echocardiography

The echocardiogram revolutionized the field of cardiology by allowing assessments of cardiac structure and function in real-time and with relative convenience and low cost. This technology was applied to HCM in the 1970's and allowed visualization (although perhaps not full understanding of) what was occurring in the LV to generate the gradient to LV outflow. Although perhaps taken for granted today, it was actually a matter of significant debate whether there was actually any true LVOT gradient associated with HCM at all. It was argued (particularly by J. Michael Criley at Harbor-UCLA who had been a resident with Eugene Braunwald at Hopkins) that the observed gradients were simply a pressure artifact related to catheters becoming entrapped in the muscular hypertrophy/cavity obliteration.(21) Echocardiography was instrumental in helping to settle this issue by allowing for non-invasive assessments of the mechanism for obstruction, real-time visualization, and with the application of Doppler, estimating LVOT gradients without the use of catheters.

Echocardiography found an early role in detecting the asymmetric septal hypertrophy (ASH) typical of HCM. ASH referred to the disproportionate amount of subaortic hypertrophy in IHSS relative to the other walls, e.g. the posterior wall. Although most of the attention in IHSS in the 1960's focused on the influence of the subaortic hypertrophy as the cause of the outflow tract gradient, in the middle of the decade, the cardiothoracic surgeon Dr Viking O. Björk, first suggested the contribution the anterior leaflet of the mitral valve in generating the gradient. He proposed that the presence of ASH led to abnormal motion of the mitral valve. However, this theory was not widely adopted until M-mode echocardiography became available and used to systematically study patients with IHSS. It became clear that systolic anterior motion (SAM) of the mitral valve was a major component of the obstruction.(22) Even before the advent of Doppler echocardiography, which we more commonly use today, it was clear by M-mode alone that the duration and extent of mitral valve contact with the intraventricular septum during contraction closely correlated with the magnitude of the LVOT gradient.(23) During systole, the anterior leaflet of the mitral valve is pulled against the septum, forming a physical obstruction to blood as it exits the ventricle. (**Figure 4**)

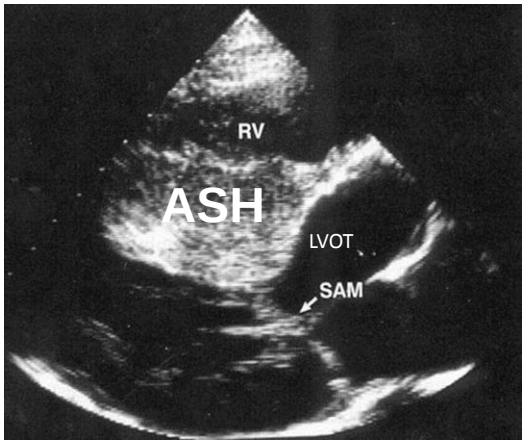
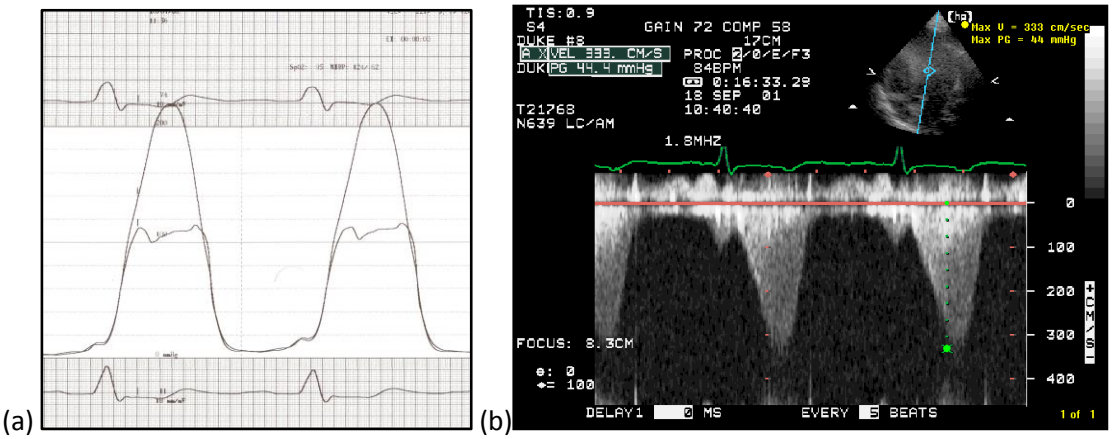


Figure 4: Transthoracic ECHO demonstrating the features of ASH and SAM obstructing the LVOT.

Today, Doppler is typically used to measure the velocity of blood as it passes through the LVOT and estimate pressure gradients. Furthermore, using pulse wave Doppler, gradients can be sampled at specific locations from the apex out the LVOT to identify the specific level where obstruction may be occurring. In distinction to aortic stenosis, for instance, the typical Doppler signal for a dynamic LVOT obstruction from HCM has a so-called "dagger-shape," as it manifests

only as systole progresses, the ventricle contracts and SAM occurs. (**Figure 5**)

Figure 5: (a) Invasive hemodynamics and (b) ECHO Doppler demonstrating that the LVOT gradient of HOCM manifests as systole progresses. This results in the characteristic “dagger-shape” on Doppler.



MRI

The first published report of use of gated MRI to image HCM was in a series of patients from UCSF in 1985 using a 0.35 Tesla magnet.(24) Since that time, use of cardiac MRI has become commonplace in imaging HCM, particularly in specialized centers. The relatively widespread adoption of MRI stems in part from the fact that it allows for more accurate determination of wall thickness, location/pattern of hypertrophy, and papillary muscle anatomy (**Figure 6**). These features can be helpful when ECHO images are suboptimal (such as in detecting apical hypertrophy) or for pre-operative planning.

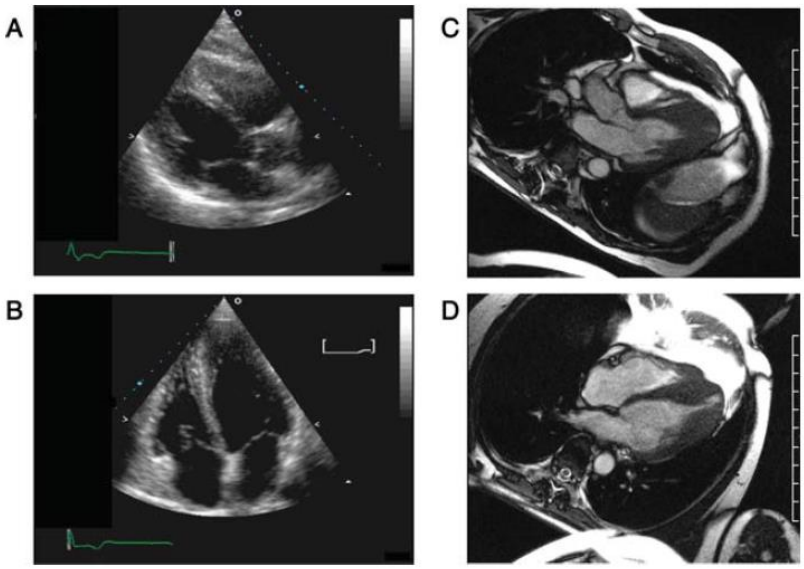


Figure 6: Example of apical HCM which is much more clearly delineated by MRI (c,d) than on ECHO (a,b). From ref (4).

In 2002, an important case series of HCM scans was published from Ray Kim’s MRI group. Extending their observations of myocardial infarct detection and quantification using late gadolinium enhancement (LGE) MRI, Choudhury *et al* reported that HCM was associated with the presence of LGE, even among asymptomatic or mildly symptomatic patients.(25) Scarring was common (found in 80% of patients), patchy, frequently mid-myocardial and often found at

the septum at the RV insertion site (**Figure 7**). A subsequent gross pathologic assessment of an explanted heart of a patient who received a heart transplant shortly after having had a cardiac MRI suggested that there was a close correlation between LGE on MRI and the presence of collagen at that location.(26) Because of these findings cardiac MRI became a new, non-invasive method to assist in the diagnosis of patients with possible HCM in the not-uncommon situations of clinical ambiguity.

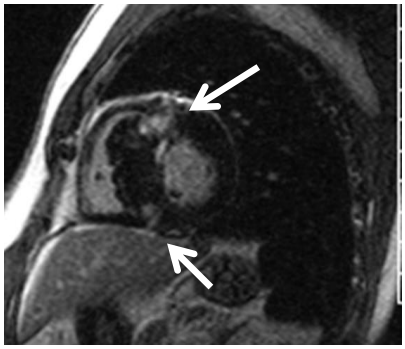


Figure 7: Cardiac MRI demonstrating prototypical RV insertion-site LGE

Since that time, we have gained new insight into the potential utility of LGE MRI in the management of HCM. While it had been established from autopsy studies that myocardial scarring was common among affected individuals suffering sudden cardiac death,(27) until recently it was unknown whether the presence of scar correlated with the burden of ventricular arrhythmias. Adabag *et al*,(28) demonstrated that the presence of LGE on MRI was associated with ventricular arrhythmias by 24-hour Holter, even in patients with no overt HCM-related symptoms. Although an initial follow-up study from that group was unable to show that this translated into a statistically significant difference in clinical events after two years of follow-up (5.5% with LGE vs 3.3% without),(29) subsequent series reports have linked the presence of LGE to a measurable increase in adverse clinical events on follow-up, including heart failure, arrhythmias and death.(30,31)

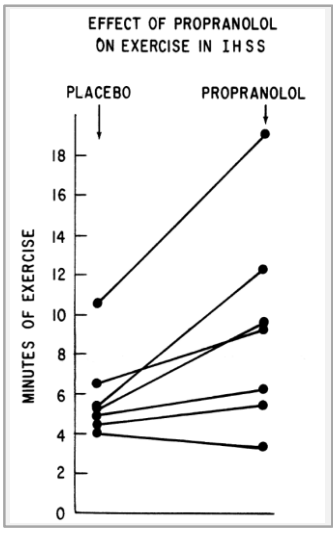


Figure 8: Effect of b-blockade on patient's ability to exercise on a treadmill before developing exhaustive fatigue or angina pectoris.(7)

Symptom Management

Medical Therapy

Since the early days at the NIH, it was recognized that patients felt better with negative inotropic drugs, while conversely, they did worse with digoxin and hypovolemia from diuretics (i.e. the standard of heart failure care in the 1960's). Since the initial studies by the Braunwald group, β-blockers have been the cornerstone of treatment. They have been shown to reduce angina and increase exercise tolerance.(7) (**Figure 8**) They have the additional theoretical benefit of reducing ventricular arrhythmia burden and atrial fibrillation rates.

In 1976, Kaltenbach and coworkers reported (in the German literature) on their experience with using verapamil in place of β-blockade. They concluded that verapamil appeared to be superior although their study was non-randomized.(32,33) Calcium channel blockers, like β-blockers are potent negative inotropes and may also have beneficial chronotropic and lusitropic properties. To date, there has been no randomized study comparing β-blockers, calcium channel blockers, or their combination in the initial treatment of HCM.

Although not used as routinely, disopyramide, a class Ia (sodium-channel blocker) anti-arrhythmic has potent negative inotropic properties and has been shown to be very effective in reducing the LVOT gradient associated with HCM.(8) (**Figure 9**) Despite being a negative inotrope, this drug does not result in a decrease in cardiac output, presumably by increasing net forward flow out the aortic valve and reducing mitral regurgitation.(34) Although class I anti-arrhythmics are generally avoided in structural heart disease, disopyramide appears safe in observational studies and may improve functional status to the point that invasive treatments can be avoided.(35) It may be a helpful adjunct, particularly if there are additional arrhythmias which can be simultaneously addressed.

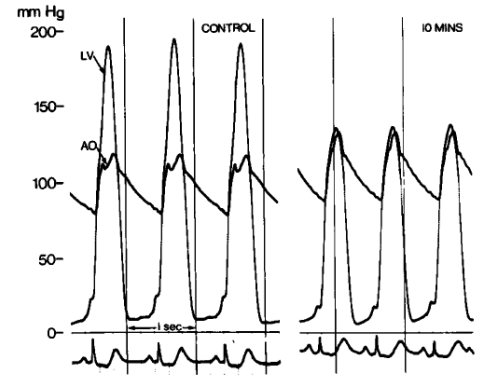


Figure 9: Disopyramide can significantly lower LVOT gradient in HOCM; baseline (left) and 10-min post IV administration (right).(8)

Current ACC/AHA guidelines recommend β-blockers or calcium channel blockers as Class I agents in the treatment of symptomatic HCM patients (with or without the presence of LVOT obstruction). Disopyramide can be added-on (IIa recommendation) for persistent symptoms. In the absence of symptoms, the benefits of medical treatment (e.g. with β-blockers) is uncertain (IIb recommendation).(36)

Septal Reduction Therapy

Some patients have persistent symptoms despite medical management. The guidelines suggest that septal reduction therapy can be considered for these patients *when resting or latent LVOT gradient ≥50mmHg is present*.

Surgical

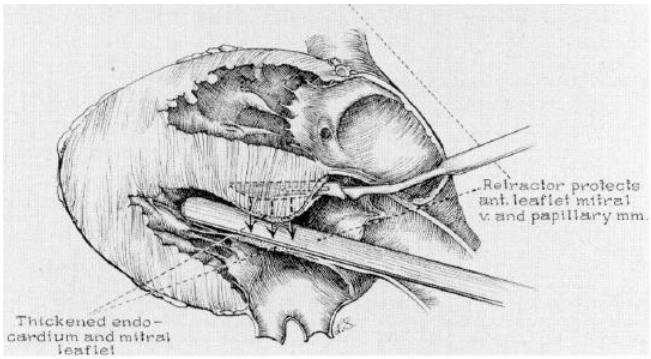
The septal myectomy (= myomectomy) was pioneered at the NIH by Glenn Morrow. The operation was described in early 1960's,(37,38) with the first case series having been reported in 1968,(39) with a follow-up series in 1975.(1) The procedure has since been named the Morrow Procedure in his honor. In essence, the surgeon approaches the septum from a retrograde approach; a retractor is placed across the aortic valve and protects the anterior leaflet of the mitral valve. A blade is used to carve out a channel (~4cm) through the hypertrophic septum and to improve LV outflow. (**Figure 10**) The results of the procedure can be amazing, with most patients having a dramatic improvement in their LVOT gradient and functional classification (**Figure 11**). Operative risk is generally low for this procedure, in part because most patients otherwise are generally healthy. Complications are summarized in **Table 1**.

Table 1: Complications from septal reduction therapies

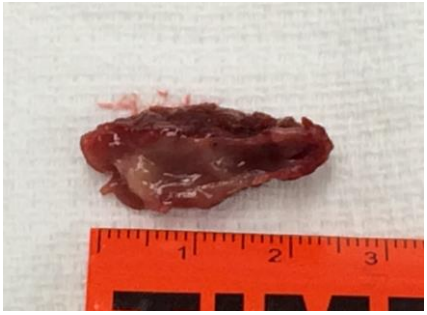
Myomectomy:
- -Mortality 2-3%
- -Heart Block <3%
- -VSD <1%
- -Aortic Regurgitation <1%

Septal Ablation:
- -Morality 2-3%
- -Heart Block 10-40%
- -VSD ?

Figure 10: (a) Schematic of the Morrow procedure(1) and (b) a sample of myocardium from a recent myomectomy performed at UTSW.



(a)



(b)

Although the improvements from myomectomy can be dramatic, it is important to recognize the potential caveats involved with surgical intervention. Generally speaking, the obstruction should be subaortic in order to achieve optimal results with surgery. The surgeon can (and should) extend the resection lower towards the papillary muscles in the case of more mid-cavitary obstruction. To date, however, surgical experience with apical forms of hypertrophy is limited, and although ventricular volume enhancement has been performed, the results have been less striking than those seen with traditional myomectomy.(40) Additionally, coincidental mitral valve abnormalities, very common in HCM, may play a considerable role in the obstruction; mitral valve repair or papillary muscle resection may be required. Sometimes, there is residual SAM after the initial procedure(s) and mitral valve replacement with a low profile mechanical prosthesis is required to alleviate the obstruction before separation from cardiopulmonary bypass.

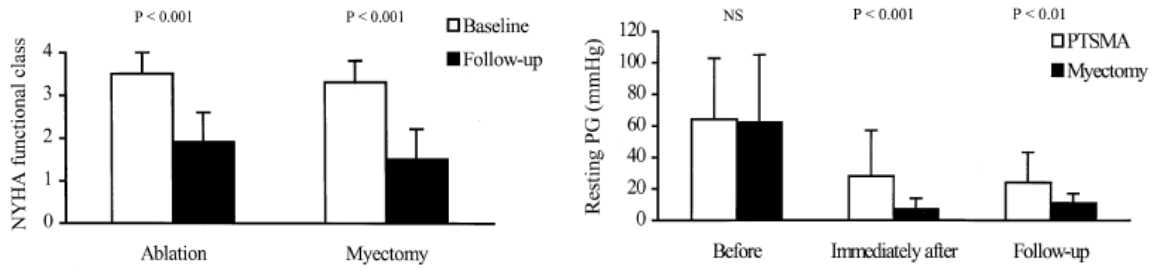


Figure 11: Effectiveness of septal reduction techniques in improving heart failure and LVOT gradients.(3)

Alcohol septal ablation

In 1995, Dr Sigwart at the Royal Brompton Hospital published in *The Lancet* the novel observation that the LVOT gradient in patients with HOCM could be reduced using catheter-based techniques.(41) He described a series of three patients with symptoms related to significant LVOT gradients. Initially he described a 30-minute balloon occlusion of the first septal perforator branch feeding the hypertrophic subaortic segment of myocardium with resultant improvement in hemodynamic parameters. After balloon deflation, the abnormal hemodynamics returned. He subsequently described the instillation of 5mL of absolute alcohol into the

ventricular myocardium served by the first septal perforator and noted a significant acute- and intermediate-term improvement in symptoms and hemodynamics.

Following this original publication, there has been a relatively widespread adoption of alcohol septal ablation (ASA) as a less-invasive alternative to surgical myomectomy. The technique is fairly simple. The left main coronary artery is intubated with a guiding catheter and the (generally first) septal perforator is wired and a balloon is inflated in it to occlude flow. Iodinated- and echo-contrast agents are injected through the balloon lumen to ensure that the coronary artery has been successfully occluded and to visualize the area of myocardium subtended by the target artery. An ideal septal perforator perfused the area of septal hypertrophy at the site where SAM is occurring. Once a suitable vessel has been confirmed, between 1-2mL of absolute alcohol is instilled into the septal perforator over ten minutes. (**Figure 12**)

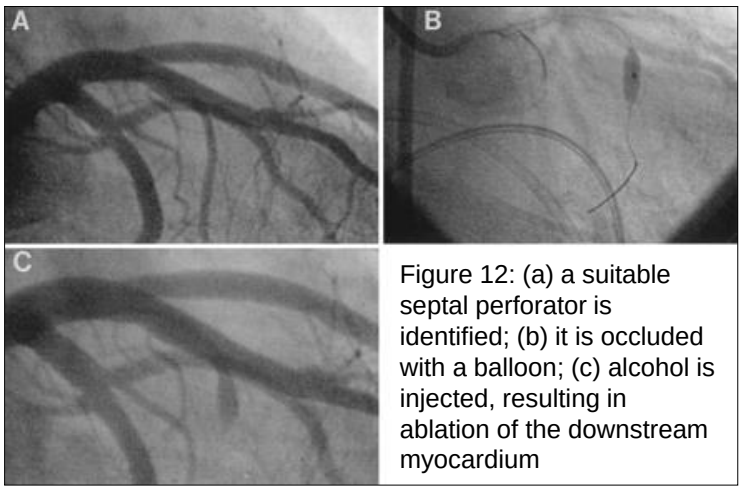


Figure 12: (a) a suitable septal perforator is identified; (b) it is occluded with a balloon; (c) alcohol is injected, resulting in ablation of the downstream myocardium

While ASA can be immediately effective (which is is associated with higher clinical success rates), it may take several weeks to see the maximal as the intraventricular septum remodels and regresses. While head-to-head comparator studies between surgical and catheter-based septal reduction methods is lacking, ASA can result in similar (although probably not as profound) reductions in gradients as myectomy (**Figure 11**).

Rates of complications are shown in **Table 1**. Whereas myomectomy is associated LBBB because of the location of the surgical resection (i.e. the left-side of the intraventricular septum), ASA is associated with a RBBB, probably owing to less redundancy in the blood flow serving this bundle. The nature of this procedure leads to scarring of the septum at the site of the controlled infarction (**Figure 13**). Although observational studies do not suggest an increase in mortality from ASA relative to myectomy, this remains a theoretical concern.(42,43)

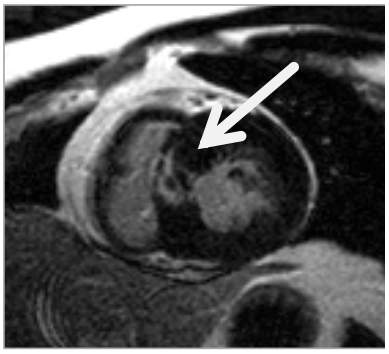


Figure 13: Septal scaring noted by MRI after ASA.

SCD Risk Stratification

Sudden death from arrhythmias is the most feared complication from HCM. The original reports, which described what we know today as HCM, emphasized unexplained and sudden death as the first (and perhaps only) clue that the patient had an underlying cardiac condition. It

was not until Braunwald's 1968 report on the natural history of IHSS that clinicians had an objective estimation of risk for SCD in this population. With the advent of implantable cardioverter-defibrillators (ICDs), there became a pressing need to understand in greater detail which patients were at risk for SCD.

Table 2: Risk factors for SCD in HCM

-Prior sustained VT/SCD
-First-degree family member with SCD
-Recent unexplained syncope
-Massive LVH (30mm+)
-Abnormal BP response with exercise
-Non-sustained VT on Holter

Risk of SCD

Not surprisingly, the risk of recurrent SCD events is high among survivors of previous arrests (~30-60% at 5 years),(44-46) and device therapy is warranted in this patient population. The challenge continues to be identifying appropriate candidates for primary prevention, i.e. balancing the risks of implanting an indwelling device in a young patient, who may have many decades of risk exposure, with the benefits from treating a potentially life-threatening arrhythmia with a small annual incidence. An additional hurdle has been our reliance on data from referral centers, which probably dramatically overestimate the risk of SCD and enhance the apparent benefit of primary prevention devices.

Over a number of years, several risk factors for SCD have been identified in cohort studies (**Table 2**). Historically, there had been no clear consensus as to the number of risk factors needed to recommend primary prophylaxis. In 2007, a multi-center cohort study of high-risk patients with HCM who had received ICD therapy was published.(5) The overall rate of ICD discharges was high, but significantly, post-hoc stratification by the number of pre-existing SCD risk factors did not help distinguish among patients at greatest risk for appropriate ICD shocks. Although the cohort was biased, these data suggested that we have a poor understanding of which patients are at highest risk for SCD and emphasized that patients with only a single traditional risk factor for SCD might need an ICD.(**Figure 14**)

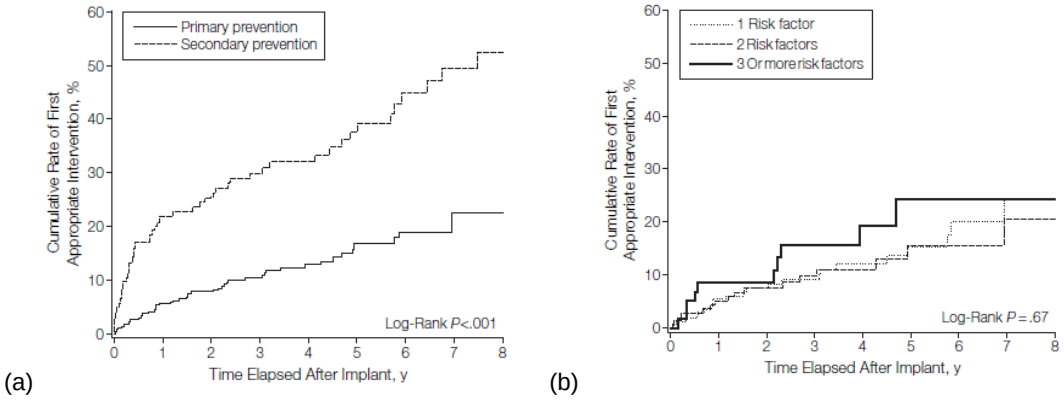


Figure 14: (a) Rates of discharge of ICDs in high-risk HCM populations and (b) primary prevention discharge rates stratified by number of traditional SCD risk factors.(5)

It is worth re-emphasizing that significant biases in the published literature are known to exist,(47) and this must be taken into account in interpreting a patient's individual risk of arrhythmic death. The annual risk of SCD among non-referral cohorts is <1%,(10,48) compared with the 4% annualized risk of appropriate device therapy in ICD cohorts. Furthermore,

appropriate ICD discharges are not necessarily synonymous with SCD. Lastly, the mechanism of sudden death may be embolic (i.e. a stroke); this is the most common cause of death among older HCM patients.(48)

Current Guidelines for ICD Therapy

The 2011 ACC/AHA guidelines for ICD therapy in patients with HCM are shown in **Figure 15**.(36) Outside of a secondary prevention, there are no Class I indications for ICD implantation, and the Level of Evidence for all primary prevention recommendations is Level C (i.e. "Very limited populations evaluated or consensus opinion of experts").

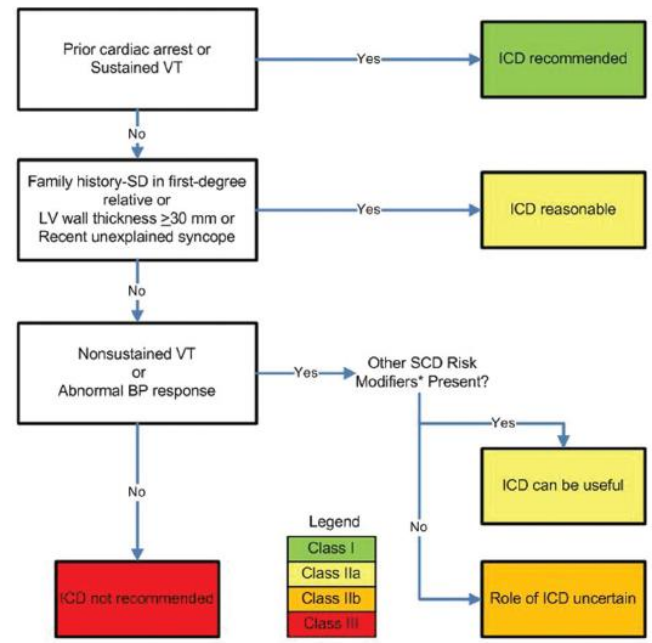


Figure 15: ACC/ACC HCM ICD implantation algorithm

Screening and the Genetic Evaluation of the HCM Patient

Early on, it was clear that HCM had a familial component. Paré *et al* described a large kindred of French Canadians- 30 of 87 of whom were clinically affected with HCM- and traced the lineage back >150 years and five generations back to the clan's original immigrant from France; the investigators were able to conclude that there was an autosomal dominant inheritance pattern.(49) This kindred would later be used to map the gene to chromosome 14q11-12 and subsequently identify beta-myosin (MYH7) as the first gene causing HCM (in this case, a missense mutation, R403Q).(50) It was quickly established that the causes for familial HCM were heterogeneous,(51) with innumerable reported mutations within MYH7 and other sarcomeric proteins. Currently, eleven genes have been firmly established as disease-causing (**Table 3**), with MYH7 and MYBPC3 being the most commonly encountered. More than 1400 mutations have been reported associated with HCM.

Table 3: Proteins (genes) with the strongest evidence for pathogenicity in human HCM.

Thick filament
-β-myosin heavy chain (*MYH7*)
-regulatory myosin light chain (*MYL2*)
-essential myosin light chain (*MYL3*)
Thin filament
-cardiac troponin T (*TNNT2*)
-cardiac troponin I (*TNNI3*)
-cardiac troponin C (*TNNC1*)
-α-tropomyosin (*TPM1*)
-α-cardiac actin (*ACTC*)
Intermediate filament
-Cardiac myosin-binding protein C (*MYBPC3*)
Z-disk
-α-actinin 2 (*ACTN2*)
-myozenin 2 (*MYOZ2*)

Guideline recommendations surrounding screening

The current HCM guidelines recommend as a Class I indication to clinically screen first-degree relatives of patients with HCM. This involves clinical consultation, EKG and echocardiography to assess for evidence of ventricular hypertrophy. If there is no evidence of HCM, periodic rescreening of the relatives is recommended, with intervals

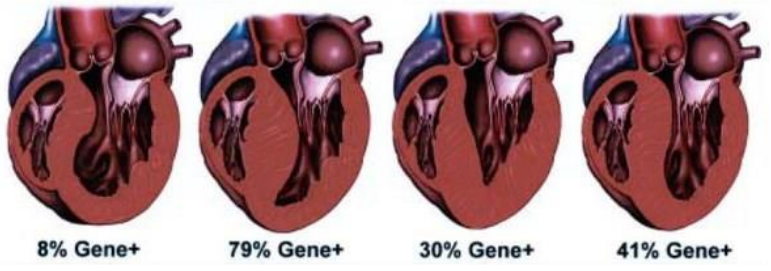
depending on the relative's age: <12 years screening is optional unless symptoms or high-risk familial features are present, or if the person being screened is playing competitive sports; between 12-21 years old (when puberty is occurring) screening is recommended every 12-18 months and after 21 years old, screening every five years is recommended unless interval symptoms develop.(36) The availability of genetic testing has streamlined this process; one-time screening to be possible in those cases when a genetic mutation in the proband is identified. This can potentially alleviate a lifetime of recommended screening and patient stress.

Genotype-Phenotype Correlation

Over the past decade there has been considerable interest in correlating specific genotypes with phenotypes in HCM. Despite some initial data suggesting particular genotypes may be more pathologic than others, it has subsequently become clear from other studies that clinical courses cannot be predicted by particular genotype. This conclusion is supported by the current ACC/AHA HCM guidelines which do not advocate using genotype data to predict disease course (e.g. whether to place an ICD).(36) Part of the issue is the clear influence of additional (unknown) modifier genes on phenotypic expression, and the fact that for any particular gene, there can be dozens (or more) of different mutations. There clearly are more molecularly pathologic mutations within a particular gene, but cohort studies have been underpowered to detect clinically-meaningful differences.

Published data do demonstrate that compound (i.e. multiple) mutations, which may affect up to 5% of HCM patients,(52,53) typically result in more symptomatic clinical courses, and these patients may be more likely to go on to develop a dilated phenotype. Genotype+ patients are more likely to have particular clinical characteristics (younger age at presentation, a family history of HCM or SCD, and greater wall thickness).(54) Finally, although ventricular morphology cannot be predicted by genotype (indeed, multiple ventricular morphologies can coexist within the same family), the likelihood of finding a genetic mutation is dependent on ventricular morphology (**Figure 16**).(2,55) In this way, imaging and basic demographics can be helpful to decide on the potential yield of genetic testing.(56)

Figure 16: Relationship between ventricular morphology and yield of genetic testing.(2)



Genetic Testing

The first commercial vendor for genetic testing in HCM appeared in 2003 and currently there are several available for physicians to choose from. The cost of testing is in the range of $4000-5000, but vendors work with the patient's insurance and the out-of-pocket expense, e.g. with Familion and GeneDx, for patients with private insurance is often only between $50-100. Ordering commercial genetic testing for uninsured or Medicare patients will likely be probably cost-prohibitive to the patient. The turn-around time is generally 8-16 weeks (depending on the

number of panels ordered), but results are available within a month for follow-up testing when a known genetic mutation has been identified in a family member. The yield of genetic testing is generally between 30-60%, largely depending on whether a family history is present.(53)

The genotype-positive, phenotype negative patient

The availability of genetic testing has given rise to a new classification of HCM patient: one who has who has a positive genetic screen but no clinical evidence of HCM. Long-term follow-up of this patient population is limited, so management is generally done on a case-by-case basis. Guidelines recommend clinical screening intervals similar to those used when genetic data is unavailable. This is important because there appears to be an age-related phenotypic expression of HCM. MRI may identify myocardial abnormalities which never (or only later) become evident on echocardiography(57) and is more sensitive in detecting more subtle degrees of LV hypertrophy in previously-regarded phenotype negative patients.(58)

The Future

Despite significant advances in our understanding of HCM over the past century, clinical care and treatment options have not changed substantially the past 50 years. A recent working group of the NHLBI has outlined several of the research priorities for HCM, and has highlighted the particular need for high quality clinical trials and novel therapeutic agents.(59)

Medical Therapy

GS-6615

In the Spring of 2014, Gilead announced that it was starting a clinical trial entitled, “A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of GS-6615 on Exercise Capacity in Subjects with Symptomatic Hypertrophic Cardiomyopathy” that will evaluate the utility of GS-6615, a novel selective inhibitor of the late sodium current, in the symptomatic management of patients with hypertrophic cardiomyopathy. Key study inclusion criteria for the study are HCM with a maximal septal wall thickness ≥15mm, exertional symptoms of chest pain or dyspnea, and a peak oxygen consumption (VO_2) <75% predicted at screening. The main outcome measure will be a change in peak VO_2 at 12 weeks. Several clinically-meaningful secondary endpoints will also be studied

Rationale for the Study

Under normal conditions, the sodium channels are activated during the upstroke of the action potential, leading to sodium flux into the cell. These channels are quickly inactivated, so the residual amount of late sodium current is low. Under several pathological states, including HCM, late sodium current is increased. This leads to consequent calcium-overload through activation of the Na^+/Ca^{2+}-exchanger. These effects lead to an increase in early- and late after-depolarizations, which are markers of arrhythmogenic potential, and lead to elevated intracellular diastolic calcium concentrations. High intracellular calcium levels presumably result

in persistent Ca^{2+}-activated cross-bridging of the contractile apparatus and lead to sustained activation of Ca^{2+}/calmodulin kinase II further potentiating this process. These molecular events may be linked to diastolic dysfunction. These abnormalities could be reversed with ranolazine, a commercially available, non-selective sodium-channel blocker.(60)

Randomized Clinical Trials

In addition to novel therapeutic agents, randomized clinical trials of medical management strategies are needed. Relatively simple questions, such as whether β-blockers or calcium channel blockers or both should be first line treatments have not been adequately answered. Similarly, we do not know whether medical treatment of the asymptomatic patient is useful. To address these questions, larger networks of clinical trial sites will need to be established.

Lifestyle Modification

We know that most patients with HCM will perform below expected on cardiopulmonary exercise testing, and despite the potential benefits of fitness training, many HCM patients purposely avoid exercise. This has been, in part, because of a lack of clarity regarding whether exercise is safe in this population. Although this has partially been addressed in the latest ACC/AHA guidelines which lists allowable activities, considerable ambiguity remains. Furthermore, it has been demonstrated that obesity is associated with a higher degree of LV mass,(61) suggesting that improving patient's activity level may impact their hypertrophy. An important question is whether exercise training is safe and effective in impacting symptoms in HCM.

UTSW HCM Clinic

What about HCM and the future of UTSW?

In 2014, we began a dedicated HCM clinic in the Clinical Heart Center in Professional Office Building 2 as part of a broader cardiovascular genetics initiative within the Division of Cardiology. Here in North Texas, we are probably the largest U.S. metro area without a dedicated HCM center. The goals of the clinic are to improve and standardize the care of patients living with HCM by providing comprehensive clinical, imaging, and procedural services, familial screening and genetics counseling. In addition, industry-sponsored and local research activities are high priorities. An immediate goal is to achieve HCM Association accreditation as a Center of Excellence to enhance regional visibility and referrals.

Conclusions

HCM continues to fascinate physicians because of the variety of its presentations- from entirely asymptomatic to the most dramatic. It is common enough that practitioners need to be aware of the basics of management. Despite a relatively high level of research interest, much of the management is largely unchanged over the past 40-50 years, in distinction to other areas of

cardiovascular care. This is, paradoxically, precisely of the features which make it interesting in the first place- its relative rarity and the variability in its clinical presentations. Research priorities for HCM have been laid out. *Present day* HCM clinicians need to reflect on the teamwork, inspiration and dedication that characterized the clinician-researchers of the *past* to ensure clinically meaningful advancements in the field in the *future*.

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